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ORIGINAL

Clinical features, ventilatory management, and outcome of ARDS caused by COVID-19 are similar to other causes of ARDS

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Abstract

Purpose: The main characteristics of mechanically ventilated ARDS patients affected with COVID-19, and the adherence to lung-protective ventilation strategies are not well known. We describe characteristics and outcomes of confirmed ARDS in COVID-19 patients managed with invasive mechanical ventilation (MV).

Methods: This is a multicenter, prospective, observational study in consecutive, mechanically ventilated patients with ARDS (as defined by the Berlin criteria) affected with with COVID-19 (confirmed SARS-CoV-2 infection in nasal or pharyngeal swab specimens), admitted to a network of 36 Spanish and Andorran intensive care units (ICUs) between March 12 and June 1, 2020. We examined the clinical features, ventilatory management, and clinical outcomes of COVID-19 ARDS patients, and compared some results with other relevant studies in non-COVID-19 ARDS patients.

Results: A total of 742 patients were analysed with complete 28-day outcome data: 128 (17.1%) with mild, 331 (44.6%) with moderate, and 283 (38.1%) with severe ARDS. At baseline, defined as the first day on invasive MV, median (IQR) values were: tidal volume 6.9 (6.3–7.8) ml/kg predicted body weight, positive end-expiratory pressure 12 (11–14) cmH_2O. Values of respiratory system compliance 35 (27–45) ml/cmH_2O, plateau pressure 25 (22–29) cmH_2O, and driving pressure 12 (10–16) cmH_2O were similar to values from non-COVID-19 ARDS patients observed in other studies. Recruitment maneuvers, prone position and neuromuscular blocking agents were used in 79%, 76% and 72% of patients, respectively. The risk of 28-day mortality was lower in mild ARDS [hazard ratio (RR) 0.56 (95% CI 0.33–0.93), $p = 0.026$] and moderate ARDS [hazard ratio (RR) 0.69 (95% CI 0.47–0.97), $p = 0.035$] when compared to severe ARDS. The 28-day mortality was similar to other observational studies in non-COVID-19 ARDS patients.

Conclusions: In this large series, COVID-19 ARDS patients have features similar to other causes of ARDS, compliance with lung-protective ventilation was high, and the risk of 28-day mortality increased with the degree of ARDS severity.

Keywords: Acute respiratory distress syndrome, Coronavirus, Mechanical ventilation, Outcome

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Introduction

In late December 2019, the Chinese Center for Disease Control and Prevention (Chinese CDC) reported a series of cases of unknown pneumonia which was subsequently termed Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. The health, social, and economic impact of this disease is unprecedented in our life-time. The COVID-19 pandemic has collapsed health care systems and led to an overwhelming pressure on Intensive Care Units (ICUs), since many patients developed profound hypoxemia and extensive pulmonary infiltrates requiring intubation and ventilatory support [2].

Recent publications from China and Italy have described the epidemiology, clinical characteristics, and prognostic factors of patients who developed acute respiratory distress syndrome (ARDS) caused by COVID-19 [3–5]. A number of editorials and anecdotal points of view have suggested that COVID-19 ARDS has an atypical behavior, since a number of patients with profound hypoxemia had normal or close to normal respiratory system compliance (Crs) [6–8]. However, data confirming this assumption are scarce, and the view that severe COVID-19 causes an "atypical" ARDS has generated debate. Consequently, there is controversy as to what are the most appropriate oxygenation and ventilation strategies without increasing ventilation-induced lung injury or multi-organ damage.

It has long been known that patients with ARDS have markedly varied clinical presentations, and the Berlin definition did not include a threshold value for respiratory compliance as a diagnostic criterion for ARDS, because it did not add to predictive validity [9]. As well, it can be difficult to measure accurately in non-passive patients.

The clinical features of patients with SARS-CoV-2-induced ARDS, and the ventilatory management, and patient outcomes have not been well described [4]. The main objective of this large observational study was to describe the physiologic characteristics over time, the ventilatory management, and outcomes in a large cohort of confirmed ARDS COVID-19 patients. A secondary objective was to compare respiratory parameters and outcomes of ARDS COVID-19 patients with ARDS of other causes, where possible.

Methods

Study design

This is a prospective, multicenter, observational, cohort study that enrolled patients with COVID-19 ARDS admitted into 36 hospitals from Spain and Andorra (participating centers are listed in the Supplementary file).

Take-home message

The COVID-19 pandemic has collapsed health care systems and led to a critically overwhelming pressure on Intensive Care Units (ICUs), since many patients developed profound hypoxemia and extensive pulmonary infiltrates requiring intubation and ventilatory support. COVID-19 patients with ARDS predominantly presented a typical moderate-to-severe ARDS. Ventilatory management, and 28-day outcome did not differ from other causes of ARDS.

During the pandemic, there were no specific hospitals that were designated as COVID-19 centers, and thus the distribution of patients among centers was similar to that observed pre-COVID-19. The study was approved by the referral Ethics Committee of Hospital Clínic, Barcelona, Spain (code number: HBC/2020/0399). According to Spanish legislation, this approval is valid for all participating centers. The informed consent was waived, except in three centers where the institutional review boards requested oral informed consent from patient's relatives. This study followed the "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" statement guidelines for observational cohort studies [10].

Study population and data collection

Data from patients' electronic medical records were reviewed and collected by physicians trained in critical care, according to a previously standardized protocol. Each investigator had a personal username and password and entered data into a specifically pre-designed online data acquisition system (CoVid19.ubikare.io). Patient confidentiality was protected by assigning a de-identified patient code. All consecutive COVID-19 patients included in the dataset from March 12 to June 1, 2020 were enrolled if they fulfilled the following criteria: $\geq$ 18 years old, intubated and mechanically ventilated, confirmed SARS-CoV-2 infection from a respiratory tract sample using PCR-based tests, and had acute onset of ARDS, as defined by the Berlin criteria [9], which includes a new or worsening respiratory symptoms due to COVID infection, bilateral pulmonary infiltrates on chest imaging (X-ray or CT scan), absence of left atrial hypertension or no clinical signs of left heart failure, and hypoxemia, as defined by a ratio between partial pressure of oxygen in arterial blood (PaO_2) and fraction of inspired oxygen (PaO_2/FiO_2) $\leq$ 300 mmHg on positive end-expiratory pressure (PEEP) $\geq$ 5 cmH_2O, regardless of FiO_2. Exclusion criteria were patients with non-confirmed SARS-CoV-2 infection according to WHO guidance [11], patients with no data at baseline, patients with no information on ventilatory parameters, or non-intubated patients.

Recorded data included demographics [age, gender, body mass index (BMI), comorbidities], vital signs [temperature, mean arterial pressure (MAP), heart rate], laboratory parameters (blood test, coagulation, biochemical), ventilatory parameters [tidal volume (VT), inspiratory oxygen fraction (FiO_2), respiratory rate (RR), PEEP, plateau pressure (Pplat), driving pressure (DP), respiratory system compliance (Crs)], the use of adjunctive therapies [recruitment maneuvers (RM), prone position, neuromuscular blocking agents (NMBA), extracorporeal membrane oxygenation (ECMO)], pharmacological treatments, disease chronology [time from onset of symptoms and from hospital admission to initiation of mechanical ventilation (MV), ventilator-free days (VFDs) during the first 30 days, ICU length of stay (LOS)]. Sequential Organ Failure Assessment (SOFA) and APACHE II scores, patients discharged from ICU, patients who had died or still being treated in the ICU on June 1, 2020 were also reported.

A full data set was obtained on the first day on invasive MV which was defined as baseline. We also collected the "worst" values during the period of invasive respiratory support (maximum or minimum, depending on the parameter). Site investigators collected what they considered to be the most representative data of each day from admission to ICU discharge, alive or dead. Prior to data analysis, two independent investigators and a statistician screened the database for errors against standardized ranges and contacted local investigators with any queries. Validated or corrected data were then entered into the database.

Statistical analysis

For the main objective of the study, two descriptive analyses including clinical characteristics, mechanical ventilation data, respiratory parameters, and adjunctive measures were performed. First, we describe patients stratified as mild, moderate, and severe ARDS based on the Berlin criteria. Second, we describe patients stratified as having normal Crs (≥ 50 ml/cmH_2O) or low Crs (<50 ml/cmH_2O) according to baseline values [12]. Patients were considered as having low Crs if <50 ml/cmH_2O on day 1 of invasive MV. Descriptive variables are expressed as percentage, mean and standard deviation (SD), or median and interquartile range (IQR), as appropriate. Then, we compared variables across groups using Student's *t* test or Mann–Whitney test and one-way ANOVA or Kruskal–Wallis test for numerical variables, and Chi-squared test or Fisher exact test for categorical variables. Second, to assess the relationship among ARDS severity and discontinuation from mechanical ventilation, ICU discharge and mortality at day 28 time to event curves were plotted using the Kaplan–Meier method and analyzed with log-rank test and univariable Cox regression analysis. The same analysis was performed for Crs. Time to discontinuation from mechanical ventilation/mortality/ICU discharge was described using Kaplan–Meier plots across categories of ARDS severity, Crs, plateau pressure and driving pressure. For the Kaplan–Meier analyses, patients with the complementary outcome were right-censored at the longest recorded length of stay. Additionally, to test differences between groups, we used log-rank test and univariable Cox regression model due to the absence of imbalances between groups at baseline (or multivariable, adjusted for ARDS, in the case of plateau pressure and driving pressure). As a sensitivity analysis, we reported results using competing-risks approach. Results were consistent across methods [12]. We compared our results for Crs, Pplat, and driving pressure to five studies in the literature [13–17] using one sample Student's *t* test. For the largest study (LUNG SAFE), we estimated median Crs from Supplemental Figure e2, since it was not explicitly reporter in the study. When mean values of the whole cohort were not reported, we calculated it from the mean values of the study groups.

As this was an observational study with no harm or benefit to patients in the study, we aimed to recruit as many patients as possible, with no pre-defined sample size. All time to events were defined from day 1 of invasive MV. Missing data were not imputed. Analyses were performed in a complete case analysis basis. All tests were two-sided, and a p-value <0.05 was considered statistically significant. We have applied the Benjamini–Hochberg corrections procedure, and have marked with an asterisk the *p* values that were <0.05 after the correction. All analyses were performed with STATA version 16.

Results

Characteristics

Over a period of 81 days (between 12 March and June 1, 2020), 742 mechanically ventilated patients admitted to 36 ICUs were included in the study and followed for at least 28 days (Fig. 1). The distribution of included patients among the different participating hospitals is shown in Table S1. The enrollment and follow-up of patients are still ongoing, and as of June 29 2020, 100 (13%) patients were still in the ICU. Demographics, APACHE II and SOFA scores, vital signs and laboratory findings at baseline are shown in Table 1 and Table S2. The percent of patients with severe, moderate and mild ARDS was 38.1%, 44.6% and 17.2%, respectively (Table 1); the percentage of severe ARDS patients was higher than a number of other large observational studies in non-COVID-19 ARDS patients.

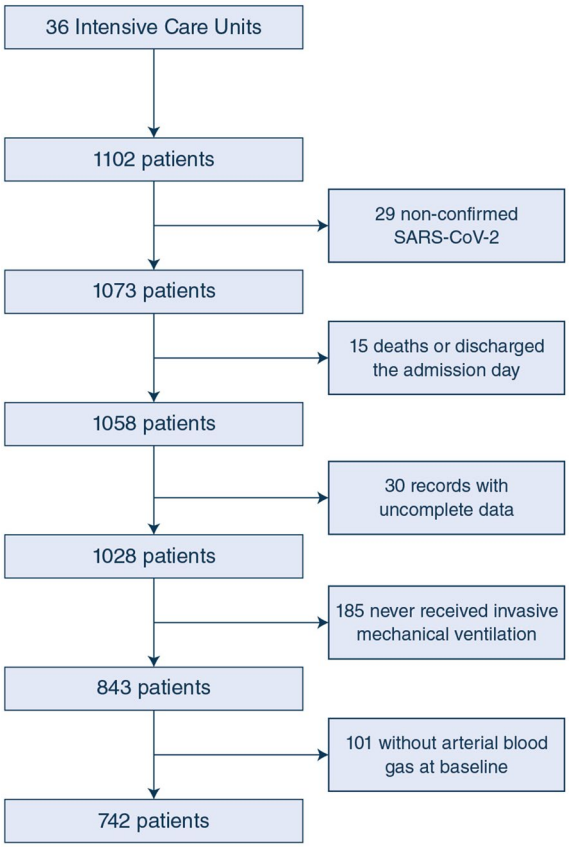


Fig. 1 Patients flowchart. A total of 742 patients were followed-up for 28 days and stratified as mild, moderate and severe ARDS based on baseline PaO_2/FiO_2. *ARDS* acute respiratory distress syndrome, *PaO_2/FiO_2* partial pressure of arterial oxygen to inspiratory oxygen fraction ration

The percent of patients with severe ARDS decreased markedly from Day 1 to Day 2 and remained at this lower level from day 2 onwards (Fig. 2). This was paralleled by an increase in the percentage of patients with mild ARDS. From the 296 patients (40.8%) with compliance data, 78% (231) were classified as having low Crs (Tables S2, S3 and Figure S1). From these 296 patients, 35.7% were classified as severe, 44.4% as moderate and 18.9% as mild.

Mechanical ventilation and respiratory parameters

Median time from the onset of symptoms to initiation of invasive MV was 12 (IQR: 9–16) days, and from hospital admission to initiation of invasive MV was 5 (IQR: 2–8) days. The median VT at baseline was 6.9 (IQR: 6.3–7.8) ml/kg predicted body weight (PBW); in 23% of patients the VT never exceeded 6 ml/kg PBW. The median highest VT, including during the weaning process with assist modes, was 8.4 (IQR: 7.3–9.5) ml/kg PBW. The median PEEP at baseline was 12 (IQR: 11–14) cmH_2O, similar to the highest collected values of 14 (IQR:12–15) cmH_2O (Table 1). Mean VT and PEEP during MV are shown in Figures S2 and S3. The ventilation strategy (VT and PEEP) did not vary with the degree of lung severity or with Crs (Table 2 and S3). The median PaO_2/FiO_2 at baseline was 120 (IQR: 83–177) mmHg. The lowest values reported during the patient´s evolution was 84 (IQR: 65–114) mmHg.

At baseline, median values for Crs, Pplat and driving pressures were 35 (IQR: 27–45) ml/cmH_2O, 25 (IQR: 22–29) cmH_2O, and 12 (IQR: 10–16) cmH_2O, respectively (Table 2). These values were not statistically different from values obtained from a number of large relatively recent observational and randomized studies of ARDS patients (Table S4).

The worst values during the MV period were 29 (IQR: 22–37) ml/cmH_2O, 28 (IQR: 23–31) cmH_2O, and 15 (IQR: 12–19) cmH_2O, respectively. Figures S4 and S5 show mean values during controlled MV. There were no differences in oxygenation (PaO_2/FiO_2) between patients with normal or low Crs (Table S3). Although the distribution of patients with normal or low Crs showed significant differences in driving pressure, both at baseline [8 (IQR: 6–9) vs 14 (IQR: 12–17) cmH_2O, $p<0.001$] and at maximum values [10 (IQR: 8–13) vs 16 (IQR: 13–20) cmH_2O, $p<0.001$], these differences were not associated with ARDS severity (Table 2 and Figure S5).

Adjunctive measures

Continuous NMBA were used in 72% of patients, prone position in 76%, and RM in 79%. Degree of ARDS severity was associated with significant differences in the use of prone position ($p<0.001$) and NMBA ($p=0.01$), but not RM (Table 2, Figure S6). No differences were observed in patients with normal vs low Crs (Table S3 and Figure S7). The pharmacological treatments received by the patients is shown in Table S5.

Clinical outcomes

Mean VFDs (to day 30) was 14 [IQR: 3–20] days. As of June 29, 2020, 401 (54%) patients were discharged from the ICU with an ICU LOS of 19 [IQR: 11–37] days. All-cause 28-day mortality was 32% (241 patients) distributed as 39% in severe, 29% in moderate and 24% in mild ARDS (Table 2). These mortality values were similar to those from four observational studies from the past 10 years (Table S6). The probability of discontinuation of MV was not significantly affected by ARDS severity (Fig. 3). The probability of ICU discharge was higher in mild [hazard ratio (RR) 1.49 (95% CI 1.08–2.04), $p=0.014$], but not in moderate when compared to severe ARDS (Table 2 and Fig. 3). The risk of 28-day mortality was lower in mild ARDS [hazard ratio (RR) 0.56 (95% CI 0.33–0.93),

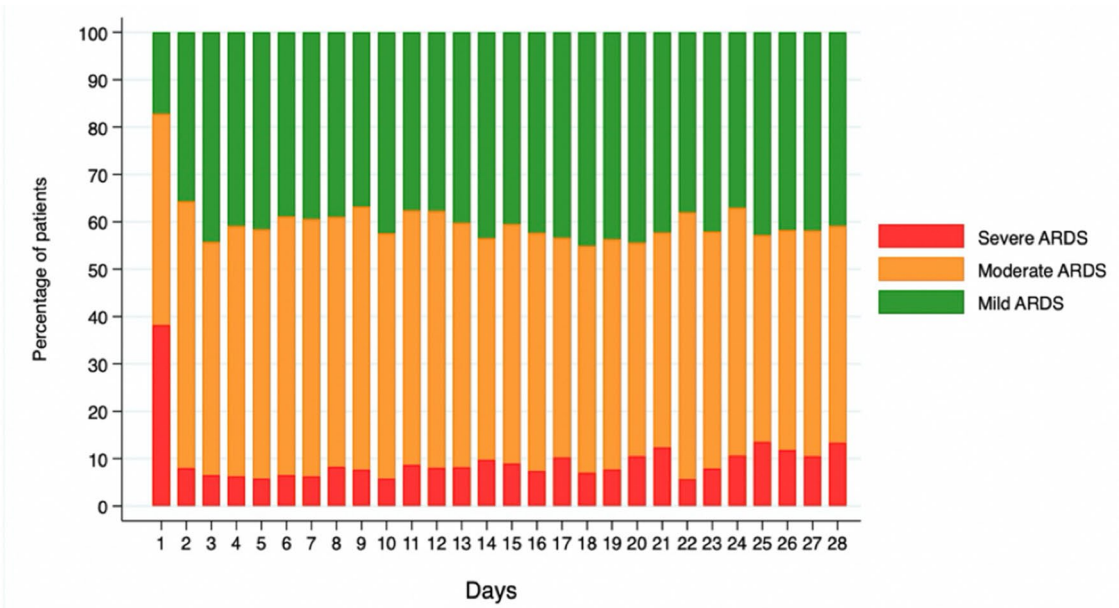
Table 1 Patient characteristics according to ARDS severity

	All ($n=742$)	Severe ARDS ($n=283$)	Moderate ARDS ($n=331$)	Mild ARDS ($n=128$)	p value
Patients demographics and comorbidities at baseline					
Age (*n*)	64 [56–71] (737)	64 [56–71] (280)	64 [56–71] (329)	64 [55–71] (128)	0.859
Gender, male	504/740 (68.1%)	185/281 (65.8%)	238/331 (71.9%)	81/128 (63.3%)	0.118
Body mass index, kg/m^2 (*n*)	29 [26–33] (480)	29 [26–34] (169)	28 [26–32] (223)	29 [26–31] (88)	0.035
Arterial hypertension	364/742 (49.1%)	143/283 (50.5%)	161/331 (48.6%)	60/128 (46.9%)	0.779
Diabetes mellitus	180/742 (24.3%)	76/283 (26.9%)	77/331 (23.3%)	27/128 (21.1%)	0.397
Chronic cardiac failure	13/742 (1.8%)	3/283 (1.1%)	7/331 (2.1%)	3/128 (2.3%)	0.459
Chronic renal failure	36/742 (4.9%)	9/283 (3.2%)	19/331 (5.7%)	8/128 (6.2%)	0.219
Asthma	19/742 (2.6%)	13/283 (4.6%)	6/331 (1.8%)	0/128 (0%)	0.009
COPD	35/742 (4.7%)	15/283 (5.3%)	18/331 (5.4%)	2/128 (1.6%)	0.167
Obesity	262/681 (38.5%)	112/262 (42.7%)	111/302 (36.8%)	39/117 (33.3%)	0.161
Dyslipidemia	131/742 (17.7%)	57/283 (20.1%)	52/331 (15.7%)	22/128 (17.2%)	0.351
Scores					
APACHE II (*n*)	13 [10–18] (513)	14 [10–18] (203)	13 [9–17] (230)	12 [8–19] (80)	0.110
SOFA (*n*)	6 [4–8] (393)	7 [4–9] (131)	6 [4–7] (193)	6 [4–8] (69)	0.023
SOFA maximum (*n*)	9 [7–12] (619)	9 [7–12] (241)	9 [7–11] (275)	8 [7–11] (103)	0.158
Vital signs					
Temperature, °C	36.6 [36–37.5] (708)	36.8 [36–37.5] (269)	36.5 [36–37.5] (316)	36.6 [36.0–37.1] (123)	0.083
Temperature max, °C	38 [37.4–38.7] (740)	38 [37.5–38.8] (283)	38.0 [37.4–38.7] (330)	38.1 [37.4–38.9] (127)	0.337
Mean blood pressure, mmHg	82 [73–93] (718)	83 [73–95] (270)	82 [75–91] (324)	80 [73–90] (124)	0.281
Mean blood pressure min, mmHg	67 [61–74] (739)	67 [61–73] (280)	68 [60–75] (331)	67 [61–74] (128)	0.974
Heart rate, bpm	80 [68–96] (722)	86 [70–100] (275)	80 [68–95] (322)	78 [63–90] (125)	< 0.001*
Heart rate maximum, bpm	110 [95–120] (740)	110 [99–123] (281)	108 [92–120] (331)	110 [94–120] (128)	0.025
Laboratory findings					
Ferritin, ng/mL (*n*)	1401 [741–2315] (271)	1405 [767–2400] (93)	1330 [677–1999] (125)	1452 [793–2993] (53)	0.574
Ferritin maximum, ng/mL (*n*)	1674 [881–2919] (578)	1738 [918–2771] (216)	1726 [852–3095] (259)	1519 [780–3097] (103)	0.910
D-Dimer, ng/mL (*n*)	1200 [720–2620] (498)	1200 [780–2550] (185)	1186 [720–2487] (224)	1219 [600–3030] (89)	0.679
D-Dimer maximum, ng/mL (*n*)	5455 [2975–8005] (700)	5879 [3444–7986] (264)	5413 [2882–8085] (312)	4750 [2439–7486] (124)	0.129
CRP, mg/dL (*n*)	29 [13–140] (637)	45 [15–186] (239)	25 [11–114] (287)	27 [10–88] (111)	< 0.001*
CRP maximum, mg/dL (*n*)	45 [22–252] (721)	139 [26–276] (269)	39 [20–227] (325)	31 [17–203] (127)	< 0.001*
Lymphocytes, 10e3/µL (*n*)	0.6 [0.4–0.9] (694)	0.6 [0.43–1] (262)	0.6 [0.4–0.9] (313)	0.6 [0.33–0.81] (119)	0.109
Lymphocytes min, 10e3/µL (*n*)	0.37 [0.2–0.51] (725)	0.38 [0.22–0.53] (273)	0.36 [0.2–0.5] (325)	0.32 [0.2–0.51] (127)	0.746
IL-6, pg/mL (*n*)	98 [29–270] (157)	97 [36–198] (70)	97 [28–448] (59)	148 [45–414] (28)	0.334
IL-6 max, pg/mL (*n*)	224 [49–986] (310)	313 [63–1000] (129)	180 [49–1000] (131)	154 [40–651] (50)	0.406
Leukocytes, 10^3/µL (*n*)	9.4 [6.5–13] (643)	9.2 [6.1–13.3] (256)	9.7 [6.8–13.8] (284)	8.7 [6.4–11.8] (103)	0.160
Leukocytes max, 10^3/µL (*n*)	14.2 [9.7–20.9] (725)	15.3 [10.6–23] (275)	14 [8.7–20.4] (324)	13.5 [9.2–17.7] (126)	0.015
Procalcitonin, ng/mL (*n*)	0.24 [0.11–0.61] (442)	0.24 [0.13–0.75] (166)	0.23 [0.11–0.5] (202)	0.26 [0.13–0.96] (74)	0.254
Procalcitonin max, ng/mL (*n*)	0.71 [0.27–3.59] (645)	0.85 [0.3–3.84] (238)	0.66 [0.28–3.61] (290)	0.70 [0.23–2.9] (117)	0.169
Platelets, 1000/mm^3 (*n*)	234 [178–314] (712)	237 [179–310] (270)	235 [182–316] (320)	220 [165–301] (122)	0.453
Platelets max, 1000/mm^3 (*n*)	381 [284–476] (727)	386 [288–481] (275)	376 [290–482] (325)	385 [273–463] (127)	0.610
Bilirubin, mg/dL (*n*)	0.67 [0.44–1] (629)	0.62 [0.47–0.9] (229)	0.64 [0.42–1] (292)	0.71 [0.41–1.03] (108)	0.274
Bilirubin max, mg/dL (*n*)	1.36 [0.8–2.9] (698)	1.35 [0.8–2.7] (261)	1.3 [0.8–2.8] (315)	1.47 [0.8–3.5] (122)	0.685
Troponin, ng/mL (*n*)	13 [4.1–39.4] (335)	13 [0.9–39.4] (114)	12.8 [4.1–28.5] (164)	18 [7–65] (57)	0.097
Troponin max, ng/mL (*n*)	26.3 [5.9–117] (568)	29.6 [0.9–111] (202)	24 [6–139.9] (261)	27 [11.9–103] (105)	0.246

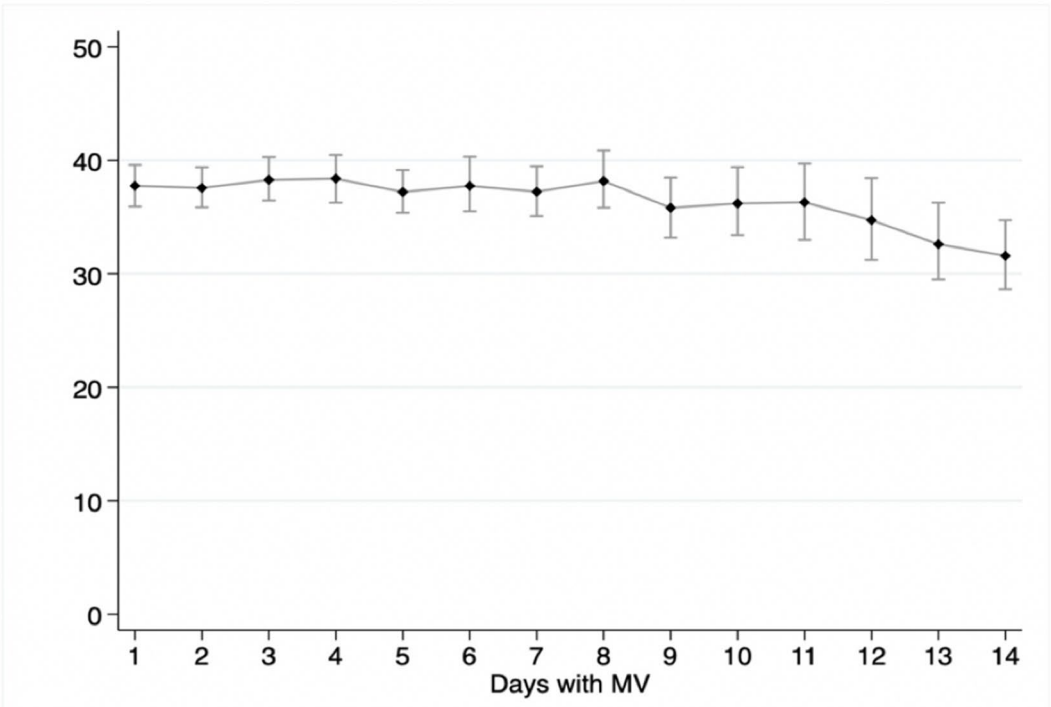
Parameters are shown at baseline (the first day on MV) and during the period of invasive respiratory support (maximum or minimum, depending on the parameter). Categorical variables are expressed as numbers (%), and continuous variables as median (IQR)

ARDS acute respiratory distress syndrome, *COPD* chronic obstructive pulmonary disease, *SOFA* sequential organ failure assessment, *RCP* C-reactive protein, *IL* interleukin, *min* minimum, *max* maximum

*< 0.05 after Benjamini–Hochberg penalization



Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N	742	613	629	593	576	537	514	484	445	419	393	360	355	308
Day	15	16	17	18	19	20	21	22	23	24	25	26	27	28
N	281	257	244	215	208	191	170	142	152	132	126	110	105	105



Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14
N	296	275	267	229	209	188	171	145	114	103	95	77	73	61

Fig. 2 Top panel: daily distribution of patients under invasive mechanical ventilation by ARDS severity (mild, moderate, and severe) from day 1 to 28. Mild: $PaO_2/FiO_2 < 100$ mmHg, moderate: PaO_2/FiO_2 100–200 mmHg, severe: $PaO_2/FiO_2 > 201$ and < 300 mmHg. Bottom panel: Daily mean (95% confidence interval) of respiratory system compliance in cmH_2O. Only patients under controlled mechanical ventilation are included. *ARDS* acute respiratory distress syndrome, *PaO_2/FiO_2* partial pressure of arterial oxygen to inspiratory oxygen fraction ration, *MV* mechanical ventilation

Table 2 Ventilation and outcomes according to ARDS severity

	All ($n=742$)	Severe ARDS ($n=283$)	Moderate ARDS ($n=331$)	Mild ARDS ($n=128$)	*p* value
Modes of ventilation					
Mechanical ventilation on ICU admission (n)	479 (64.6%) (742)	188 (66.4%)	213 (64.4%)	78 (60.9%)	0.56
Days from symptoms onset to mechanical ventilation (n)	12 [9–16] (734)	12 [9–16]	12 [9–17]	11 [8–14]	0.26
Days from hospital admission to mechanical ventilation (n)	5 [2–8] (742)	5 [2–9]	4 [2– 8]	4.5 [2–7]	0.51
Ventilatory parameters					
Tidal volume, ml (n)	6.9 [6.3–7.8] (723)	6.9 [6.3–7.8]	7 [6.3–7.7]	6.9 [6.3–7.9]	0.919
Tidal volume max, ml (n)	8.4 [7.3–9.5] (723)	8.4 [7.3–9.4]	8.4 [7.5–9.7]	8.3 [7.2–9.3]	0.481
Tidal volume $\leq$ 6 ml/kg, PBW (n)	173 (23%) (742)	67 (23%)	76 (23%)	30 (23%)	0.973
PEEP, cmH_2O (n)	12 [11–14] (716)	12 [10–14]	12 [11–14]	12 [12–14]	0.579
PEEP max, cmH_2O (n)	14 [12–15] (716)	14 [12–15]	14 [12–15]	13 [12–15]	0.034
PEEP > 12 cmH_2O (n)	46 (6.4%) (716)	14 (5%)	25 (7.9%)	7 (5.7%)	0.348
Inspiratory oxygen fraction, % (n)	80 [60–100] (728)	100 [80–100]	75 [60–100]	60 [50–80]	< 0.001*
Mean FiO_2, %[#(n)]	61 [53–70] (741)	65 [57–75]	60 [53–69]	53 [47–61]	< 0.001*
Respiratory rate, bpm (n)	24 [20–30] (715)	25 [20–33]	24 [20–28]	23 [18–26]	< 0.001*
Respiratory rate max, bpm (n)	30 [25–35] (734)	30 [27–36]	30 [25–35]	30 [25–35]	< 0.001*
Plateau pressure, cmH_2O (n)	25 [22–29] (215)	25 [20–29]	26 [22–29]	24 [22–26]	0.022
Plateau pressure max, cmH_2O (n)	28 [23–31] (410)	28 [24–30]	28 [23–32]	26 [22–29]	0.011
Driving pressure, cmH_2O (n)	12 [10–16] (260)	13 [9–16]	12 [10–16]	12 [11–14]	0.473
Driving pressure max, cmH_2O (n)	15 [12–19] (386)	15 [12–20]	15 [12–20]	14 [11–17]	0.064
Respiratory system compliance, ml/cmH_2O (n)	35 [27–45] (296)	32 [25–48]	35 [27–45]	35 [30–49]	0.461
Respiratory system compliance min, ml/cmH_2O (n)	29 [22–37] (501)	27 [20–35]	30 [22–37]	32 [23–40]	0.052
Ventilatory ratio (n)	2 [1.49–2.63] (610)	2.09 [1.53–2.71]	2 [1.52–2.59]	1.84 [1.42–2.59]	0.136
Ventilatory ratio max (n)	2.83 [2.23–3.69] (665)	2.92 [2.3–3.7]	2.79 [2.19–3.73]	2.59 [2.03–3.38]	0.015
Arterial blood gases					
$PaO_2/FiO_{2\,(n)}$	120 [83–177] (742)	74 [62–88]	142 [118–166]	260 [222–293]	< 0.001*
PaO_2/FiO_2 min (n)	84 [65–114] (742)	66 [57–80]	104 [76–125]	118 [85–160]	< 0.001*
$PaCO_2$, mmHg (n)	45 [37–55] / (737)	43 [36–52] / 281	46 [38–56] / 329	45 [37–53] / 127	0.026
$PaCO_2$ max, mmHg (n)	62 [53–75] (742)	64 [53–76]	62 [53–75]	58 [48–72]	0.007
Adjunctive therapies					
Recruitment maneuvers	479/602 (79%)	190/237 (80%)	210/264 (79%)	79/101 (78%)	0.910
Prone	564/735 (76%)	238/282 (84.4%)	246/327 (75%)	80/126 (63%)	< 0.001*
Neuromuscular blockers	536/742 (72%)	220/283 (77.7%)	234/331 (70%)	82/128 (64%)	0.011
ECMO	21/738 (2.8%)	11/283 (3.9%)	9/329 (2.7%)	1/126 (0.8%)	0.232
Outcomes					
Ventilation-free days	4 [0–18]	0 [0–16]	6 [0–18]	8 [0–21]	0.069
Discharged from ICU	401/742 (54%)	136/283 (48%)	185/331 (55%)	80/128 (62%)	0.017
Length of time on the ventilator	14 [7–24]	14 [8–24]	14 [7–24]	13 [7–24]	0.582
Still in ICU	100 (13%)	36 (12%)	47 (14%)	17 (13%)	0.880
Still under invasive MV	72 (9.7%)	26 (9.1%)	34 (10%)	12 (9.3%)	1.000
28-day mortality	241 (32%)	111 (39%)	99 (29%)	31 (24%)	0.005
ICU length of stay	19 [11–37]	19 [12–35]	19 [11–39]	19 [11–36]	0.894
ICU length of stay of discharge patients	17 [11–28]	17 [12–28.5]	17 [11–30]	17.5 [10–27]	0.940
ICU length of stay of deceased patients	17 [10–25]	17 [11–27]	17 [9–26]	17 [10–21]	0.803

Parameters are shown at baseline (the first day on MV) and during the period of invasive respiratory support (maximum or minimum, depending on the parameter). Categorical variables are expressed as numbers (%), and continuous variables as median (IQR). Ventilatory ratio is defined as [minute ventilation (ml/min) × $PaCO_2$ (mmHg)/ (predicted body weight × 100 × 37.5)]

ARDS acute respiratory distress syndrome, *PEEP* positive end-expiratory pressure, PaO_2/FiO_2 partial pressure of arterial oxygen to inspiratory oxygen fraction ratio, $PaCO_2$ partial pressure of carbon dioxide, *ECMO* extracorporeal membrane oxygenation, *ICU* intensive care unit

*< 0.05 after Benjamini–Hochberg correction

[#] Mean FiO_2 was calculated with the values reported during the overall period under invasive mechanical ventilation

$p = 0.026$] and moderate ARDS [hazard ratio (RR) 0.69 (95% CI 0.47–0.97), $p = 0.035$] compared to severe ARDS (Fig. 3). Sensitivity analysis for outcomes are shown in Figure S8. The ICU discharge and risk of 28-day mortality was not affected by Crs (Table S3 and Figure S9). The association of driving pressure and Pplat on outcomes is shown in Figure S10. Patients classified as moderate ARDS who, after 24 h of MV moved to mild ARDS, had a strong trend towards a lower 28 day mortality, than those who remained classified as moderate ARDS on day 2, but this association was not statistically significant [HR: 0.55 (95% CI 0.26–1.15), p value = 0.113]. In general, being treated in specific hospitals had no impact on outcomes (Figure S11).

Discussion

In this multicenter, observational study in 742 mechanically ventilated patients with COVID-19 ARDS, predominantly older, male patients with comorbid conditions, with a median ICU length of stay of 21 days, the majority had moderate ARDS, and greater than 80% had low Crs. The values of Crs, Pplat and driving pressure were very similar to previously published cohorts of ARDS patients. On average, patients were managed with low VT and moderate PEEP levels within the standard paradigm of lung-protective VT. Adjunctive therapies, such as RMs or prone position, were used frequently. Mortality at 28-days was similar to patients with non-COVID ARDS.

As previously reported for patients with COVID-19, the most common comorbidities were arterial hypertension and obesity [4, 18]. The main reason for ICU admission in our study was acute respiratory failure, although the SOFA scores indicated more than one organ dysfunction. Hemodynamic impairment requiring vasopressors was the most common associated organ dysfunction, in agreement with the findings of Goyal et al. [18], where 95% of their invasively ventilated patients required vasopressors. Of note, the median time from symptom onset to hospital admission was similar to that reported previously [19]. On average, hypoxia was severe within the range of previous reports on COVID-19 and non-COVID-19 ARDS patients [4, 13, 20]. The proportions of severe COVID-19 ARDS patients were greater than those reported in epidemiological studies of non-COVID-19 ARDS [14] (Table S6). However, we found, as previously reported, a marked redistribution of ARDS severity 24 h after ARDS diagnosis [21]. This reduction in the percentage of patients with severe ARDS criteria may be related to positive pressure ventilation by itself, to the effectiveness of adjunctive measures, or (unlikely) the natural history of the disease process (Fig. 2). Although it was not the aim of this analysis, it is important to highlight that some investigators argue that the degree of ARDS severity is best evaluated 24 h after assessing PaO_2/FiO_2 under certain ventilatory settings [22].

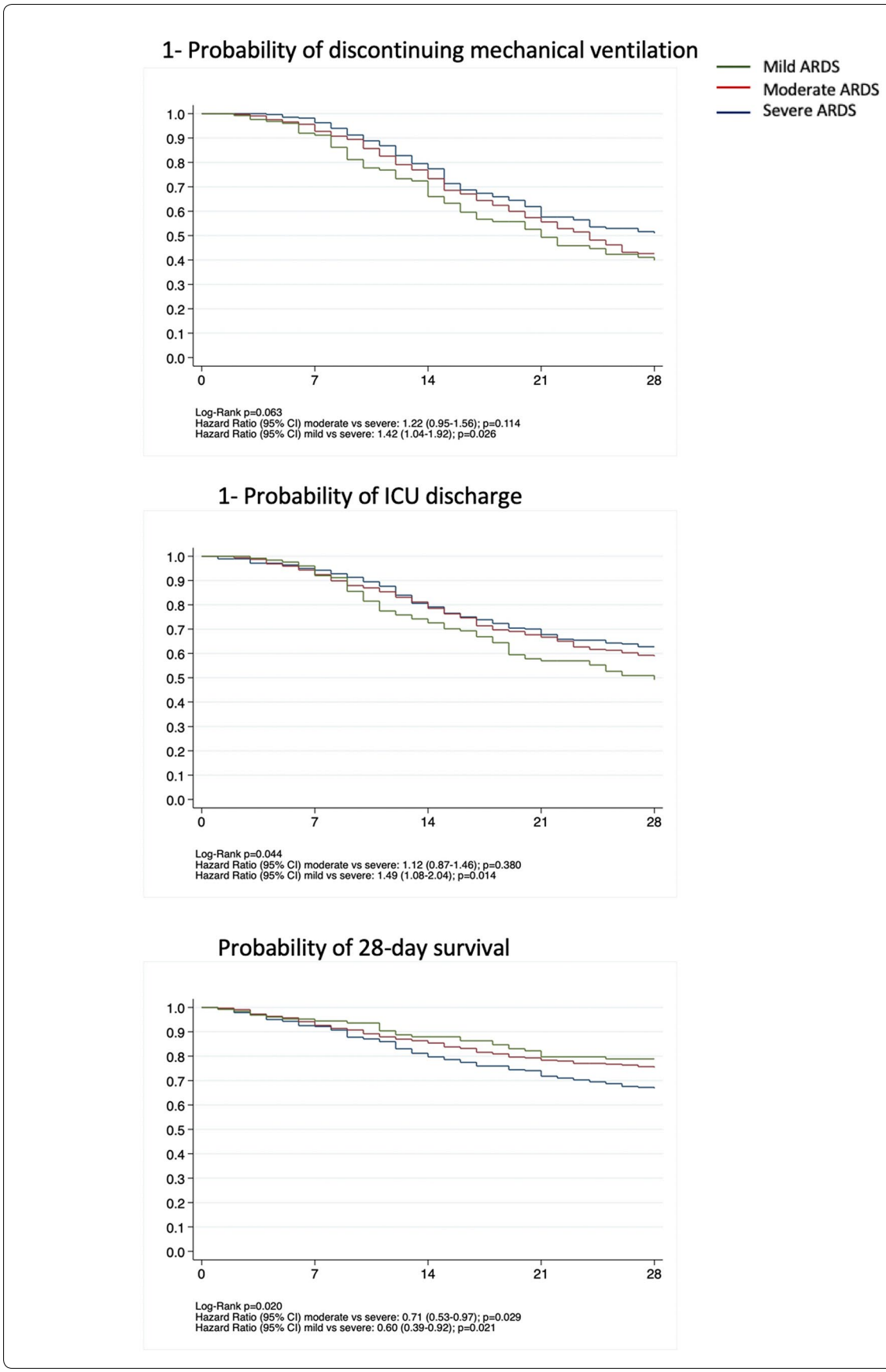
Our findings in a cohort of over 700 patients are in line with preliminary studies of COVID-19 ARDS patients [23, 24]. We found no significant differences when baseline Crs, Pplat and driving pressure were compared to non-COVID-19 ARDS observational and randomized ARDS studies (Table S6). These comparisons were not based on a formal meta-analysis, and thus, these comparisons serve to demonstrate that there are no major differences in these baseline values for COVID-19 ARDS compared to non-COVID-19 ARDS.

In general, compliance with lung-protective ventilation was high, independent of the degree of severity of the disease process and somewhat higher on average than in previous observational studies of non-COVID-19 ARDS patients [13, 20]. This finding was likely due to a greater awareness that these patients had ARDS. As reported in the LUNG SAFE study, one of the main problems in not complying with lung protection strategies was the underdiagnosis of ARDS [25]. In our cohort, invasive MV was maintained within the limits of lung-protective ventilation, as defined using a VT ≤ 8 ml/kg PBW, Pplat < 30 cmH_2O, and a driving pressure ≤ 15 cmH_2O [26]. In our cohort, RMs were the most frequent adjunctive therapies used, followed by prone position, and NMBA. These findings are in contrast to reported practice in non-COVID-19 severe ARDS patients [4, 13, 20]. Surprisingly, the use of RMs was not influenced by ARDS severity or by Crs. Both RMs and prone ventilation are usually performed to improve arterial oxygenation, and reduce ventilator-induced lung injury [27, 28]. The impact of these maneuvers depends on the recruitability of the lung, which has been shown to be variable in COVID-19 ARDS [29].

In our experience, respiratory drive in COVID-19 ARDS patients appeared to be high, despite adequate sedation, making it difficult to maintain low transpulmonary pressures, which could lead to self-inflicted lung

(See figure on next page.)

Fig. 3 Time to event curves using Kaplan–Meier with univariable Cox regression. The probability of discontinuation from mechanical ventilation and the probability of ICU discharge increase with decreasing ARDS. The 28-day probability of death was higher in severe ARDS. *ICU* intensive care unit, *ARDS* acute respiratory distress syndrome


1- Probability of discontinuing mechanical ventilation
Mild ARDS
Moderate ARDS
Severe ARDS
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
7
14
21
28
Log-Rank p=0.063
Hazard Ratio (95% CI) moderate vs severe: 1.22 (0.95-1.56); p=0.114
Hazard Ratio (95% CI) mild vs severe: 1.42 (1.04-1.92); p=0.026
1- Probability of ICU discharge
Log-Rank p=0.044
Hazard Ratio (95% CI) moderate vs severe: 1.12 (0.87-1.46); p=0.380
Hazard Ratio (95% CI) mild vs severe: 1.49 (1.08-2.04); p=0.014
Probability of 28-day survival
Log-Rank p=0.020
Hazard Ratio (95% CI) moderate vs severe: 0.71 (0.53-0.97); p=0.029
Hazard Ratio (95% CI) mild vs severe: 0.60 (0.39-0.92); p=0.021

injury [30]. This bedside observation may explain the large number of patients in whom NMBA were used. Another reason for the high use of NMBA could be the large number of patients treated in the prone position; although NMBA are not required, they are often used in these patients, as reported in previous studies [17]. Nonetheless, the protective effects of NMBA have been seriously questioned in ARDS [16, 31]. The probability of being discharged from the ICU was influenced by ARDS severity but not by Crs, as reported in studies of non-COVID-19 ARDS patients [13]. All-cause 28-day mortality was similar or lower than previously published for non-COVID (Table S6) and COVID-19 ARDS [4, 32, 33] patients.

This study has several strengths. The study was very large with over 700 patients from 36 ICUs. As well, this is the first study to provide very detailed physiological data and ventilation strategies during the entire ventilatory period in COVID-19 ARDS patients. However, we acknowledge a number of limitations. First, our study design did not allow us to analyze potential associations of ventilatory strategies with outcomes. Second, we were unable to determine why certain therapeutic approaches were used; for example, how PEEP was adjusted (pragmatic or individualized approach), or why adjunctive therapies (RM, prone position) were applied (usual practice, refractory hypoxemia, etc.), or the indications and timings of ECMO, or corticosteroids. Third, Cox regression analysis was not adjusted for confounders. The main reasons were the low grade of imbalances in the groups in the relevant baseline variables. Fourth, due to the critical moment of the pandemic, and that most participating centers had rapidly reached ICU saturation and intensivists were forced to make difficult decisions, we did not collect the total number of patients admitted to participant ICUs during the study period. Finally, it is plausible that due to the burden of care experienced by participating clinicians during the study period, the ventilatory strategy and specifically, the use of adjunctive therapies may not be representative of clinical practice in non-pandemic circumstances.

In conclusion, in this large series, COVID-19 ARDS patients appear to have similar physiological features (including respiratory system compliance, plateau pressure and driving pressure) to other causes of ARDS. Compliance with lung-protective ventilation was high, and the risk of 28-day mortality increased with the severity of ARDS, but was not greater than other studies in non-COVID-19 ARDS patients.

Electronic supplementary material

The online version of this article (https://doi.org/10.1007/s00134-020-06192-2) contains supplementary material, which is available to authorized users.

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Data availability

By request to the corresponding author.

Code availability

Not applicable.

Compliance with ethical standards

Conflicts of interest
The authors declare no conflicts of interest in relation to this manuscript.

Ethics approval
The study was approved by the referral Ethics Committee of Hospital Clínic, Barcelona, Spain (code number HBC/2020/0399).

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