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Mortality associated with early changes in ARDS severity in COVID–19 patients – Insights from the PRoVENT–COVID study

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ABSTRACT

Purpose: We investigated changes in ARDS severity and associations with outcome in COVID–19 ARDS patients.
Methods: We compared outcomes in patients with ARDS classified as 'mild', 'moderate' or 'severe' at calendar day 1, and after reclassification at calendar day 2. The primary endpoint was 28–day mortality. We also identified which ventilatory parameters had an association with presence of severe ARDS at day 2. We repeated the analysis for reclassification at calendar day 4.
Results: Of 895 patients, 8.5%, 60.1% and 31.4% had mild, moderate and severe ARDS at day 1. These proportions were 13.5%, 72.6% and 13.9% at day 2. 28–day mortality was 25.3%, 31.3% and 32.0% in patients with mild, moderate and severe ARDS at day 1 ($p = 0.537$), compared to 28.6%, 29.2% and 44.3% in patients reclassified at day 2 ($p = 0.005$). No ventilatory parameter had an independent association with presence of severe ARDS at day 2. Findings were not different reclassifying at day 4.
Conclusions: In this cohort of COVID–19 patients, ARDS severity and mortality between severity classes changed substantially over the first 4 days of ventilation. These findings are important, as reclassification could help identify target patients that may benefit from alternative approaches.

1. Introduction

Mortality is substantial in coronavirus disease 2019 (COVID–19) patients who need invasive ventilation for acute respiratory distress syndrome (ARDS) [1-3]. The Berlin definition for ARDS can be used for risk classification based on the partial pressure of arterial oxygen/fraction of inspired oxygen (PaO_2/FiO_2) ratio [4]. In patients with ARDS due to a cause other than COVID–19, ARDS severity has been shown to change over the first days of ventilation, associated with alterations in outcomes [5-7]. Whether this also applies to COVID–19 patients with ARDS can be expected, but is uncertain.

COVID–19 patients with ARDS could embody a heterogeneous group with diverse evolutions, which could be due to different ARDS phenotypes, but also disparate responses to typical aspects of care, including invasive ventilation strategies [8]. We hypothesized that ARDS severity in COVID–19 patients may change over the first 2 calendar days of invasive ventilation, and that these changes could be associated with different outcomes.

To test these hypotheses, we performed a secondary analysis of the 'PRactice of VENTilation in COVID–19' (PRoVENT–COVID) study, to determine and compare outcomes in patients classified as having mild, moderate and severe ARDS at calendar day 1 of invasive ventilation, and after reclassification at calendar day 2 and at calendar day 4. We also wished to identify which ventilatory parameters have an independent association with presence of severe ARDS at day 2 and 4.

2. Methods

2.1. Design, settings and participants

The PRoVENT–COVID study is an investigator–initiated, multicenter, observational cohort study undertaken at 22 intensive care units (ICU) in the first 3 months of the pandemic in the Netherlands [9]. The study protocol was approved by the institutional review boards of all centers, need for individual patient informed consent was waived.

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Study details can be found in the Supplementary Data 1 [10]. The study was registered at www.clinicaltrials.gov (study identifier NCT04346342). A finalized statistical analysis plan for the current analysis was published online [11].

Consecutive patients ≥18 years of age were eligible for participation if admitted to one of the participating ICUs and had received invasive ventilation for COVID–19. A COVID–19 diagnosis had to be definite by a positive reverse transcriptase–polymerase chain reaction for severe acute respiratory syndrome coronavirus 2, and the diagnosis and severity of ARDS was confirmed by using the Berlin definition [4]. The PRoVENT–COVID study had no exclusion criteria. For the current analysis we excluded patients if transferred after the first 2 days of ventilation from a non–participating center, or within the first 2 days of ventilation to a non–participating center, as it was impossible to collect complete sets of ventilation variables and parameters in the non–participating centers. We also excluded patients with incomplete datasets (missing data in PaO_2/FiO_2 ratio), patients receiving extracorporeal membrane oxygenation (ECMO) in the first 2 calendar days of ventilation, and patients that died in the first 2 calendar days of ventilation.

2.2. Data collection and analyses

Demographics and data regarding premorbid diseases and home medication were collected at baseline. In the first hour of invasive ventilation and every 8 h thereafter, at fixed time points, during the first 4 calendar days, ventilator settings, ventilation variables and parameters were collected.

For severity classification at calendar day 1, and for reclassification at calendar day 2, we used the cutoffs used in the Berlin definition [4]. Accordingly, we classified ARDS as (1) 'mild' ($300 > PaO_2/FiO_2 \geq 200$ mmHg); (2) 'moderate' ($200 > PaO_2/FiO_2 \geq 100$ mmHg); or (3) 'severe' ($PaO_2/FiO_2 < 100$ mmHg) in each patient at the first two consecutive days. Patients were always classified using the worst PaO_2/FiO_2 of the applicable calendar day.

The dynamic driving pressure (ΔP) and mechanical power of ventilation (MP) were calculated using standard formulas [12,13], i.e., ΔP (in cm H_2O) = peak pressure (P_{peak}) – positive end–expiratory pressure (PEEP); and MP (in J/min) = 0.098 * tidal volume (V_T) * respiratory rate (RR) * (Ppeak – 0.5 * ΔP).

The primary outcome was 28–day mortality. Secondary outcomes were death in ICU, in hospital and at day 90; the number of ventilator–free days and alive at day 28 (VFD–28), and duration of ventilation in survivors. VFD–28 was defined as the number of days that a patient was alive and free from invasive ventilation, calculated from the moment of start of invasive ventilation, if the period of unassisted breathing lasted longer than 24 consecutive hours and considering the last date of successful extubation––patients who died within 28 days were classified as having '0' VFD–28 s, even if extubated in the period.

2.3. Statistical analysis

The sample size was based on the number of available patients. Continuous variables are presented as medians (quartile 25% – quartile 75%) and categorical variables as numbers and percentages. The groups were compared using Kruskal–Wallis test for continuous variables, and Fisher exact tests for categorical variables. The primary outcome was shown in Kaplan–Meier curves and groups were compared through a Log–Rank test. Cumulative incidence plots were used to report time until extubation or ICU discharge, with death before the event treated as competing risk, and with the comparison of the groups done with a Gray test.

Factors associated with presence of severe ARDS at calendar day 2 were assessed in a multivariable model considering the following variables based on clinical relevance: 1) ventilator variables and parameters at calendar day 1, aggregated as the median from a maximum of four assessment, and including tidal volume adjusted by predicted body weight (PBW), RR, PEEP, P_{peak}, dynamic ΔP, MP, and respiratory system compliance (C_{RS}); 2) laboratory tests and vital signs at calendar day 1, aggregated as the median from a maximum of four assessments, and including arterial pH, plasma lactate, plasma creatinine, heart rate and mean arterial pressure; 3) organ support at calendar day 1, including use of vasopressor and cumulative fluid balance; 4) rescue therapies at calendar day 1, including prone positioning and use of neuromuscular blocking agents (NMBA); and 5) demographic characteristics, including age, gender, body mass index, and a history of hypertension, heart failure, diabetes, chronic kidney disease, chronic obstructive pulmonary disease, use of angiotensin converting enzyme inhibitors or use of angiotensin II receptor blockers. FiO_2 was excluded due to association with PaO_2/FiO_2, used to define the outcome. Variables with a $p < 0.10$ in the univariable model were selected and included in the multivariable model.

In all models, the participating center was included as random effect to account for clustering. When predictors considered in the models were missing in less than 5% of the patients, these values were imputed by the median. In addition, multicollinearity in the final models was assessed using variance–inflation factors. The linearity assumption of continuous variables was assessed through the Box–Tidwell transformation considering the full model, testing the log–odds and the predictor variable. Variables not satisfying this criterion were entered as restricted cubic splines in the final model. All continuous variables were entered after standardization to improve convergence of the model, and all effect estimates represent the increase in one standard deviation of the variable.

To account for the prolonged ventilation in COVID–19 patients, one pre–planned sensitivity analysis considered reclassification of ARDS severity as described above but at calendar day 4 instead of calendar day 2.

All models were repeated after multiple imputation of missing data. All analyses were conducted in R v.4.0.2 (R Foundation, Vienna, Austria) and significance level was set at 0.05.

3. Results

Of 1111 patients included in the PRoVENT–COVID study, 895 were included in the current analysis (eFigure 1 in Supplementary Data 2). Main reasons for exclusion were that patients did not have ARDS, did not receive invasive ventilation, or had an alternative diagnosis. Having had received ventilation for longer than 2 calendar days in a non–participating center before arrival in a participating center was another important reason for exclusion.

3.1. Early course of ARDS severity

At calendar day 1, 76 (8.5%) patients had ARDS classified as mild, and 538 (60.1%) and 281 (31.4%) as moderate or severe. Body mass index and the incidence of chronic obstructive pulmonary disease increased with ARDS severity (Table 1). ΔP and P_{peak} increased, and C_{RS} decreased with ARDS severity. Heart rate, mean arterial pressure, partial pressure of arterial carbon dioxide ($PaCO_2$) and lactate increased with ARDS severity. Prone positioning, recruitment maneuvers and NMBA were most often used in patients with ARDS classified as severe at calendar day 1.

Substantial changes in ARDS severity were seen from calendar day 1 to 2 (Fig. 1). At calendar day 2, 8 (0.9%) patients no longer had ARDS according to the Berlin definition. Of patients who had ARDS classified as mild at calendar day 2, 22.5%, 64.2%, and 13.3% of patients had ARDS classified as mild, moderate or severe at calendar day 1. These proportions were 7.0%, 63.4%, and 29.7%, and 0.8%, 39.0%, and 60.2% for patients with ARDS classified as moderate and severe, respectively, at calendar day 2. PEEP decreased with ARDS severity, and heart rate, $PaCO_2$, RR and FiO_2 increased with ARDS severity at calendar day 2 (Table 2).

Table 1
Baseline characteristics of the included patients according to ARDS severity at calendar day 1.

	Mild ($n = 76$)	Moderate ($n = 538$)	Severe ($n = 281$)	p value
Age, years	65.5 (56.8–73.0)	66.0 (57.2–72.0)	65.0 (59.0–72.0)	0.889
Male gender – no (%)	54 (71.1)	395 (73.4)	199 (70.8)	0.695
Body mass index, kg/m^2	27.4 (25.2–31.0)	27.3 (25.1–30.1)	28.4 (25.9–31.3)	0.007
Transferred under invasive ventilation	15 (19.7)	62 (11.5)	8 (2.8)	< 0.001
Days between intubation and admission	0.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	0.753
Use of non-invasive ventilation – no (%)	4/68 (5.9)	43/499 (8.6)	26/270 (9.6)	0.683
Duration of non-invasive ventilation, hours	14.0 (10.0–43.0)	8.0 (2.0–24.0)	8.0 (2.0–9.5)	0.430
Chest CT scan performed – no (%)	35/74 (47.3)	165/523 (31.5)	109/279 (39.1)	0.009
Lung parenchyma affected – no (%)				0.004
0%	2/36 (5.6)	6/168 (3.6)	2/109 (1.8)	
25%	13/36 (36.1)	58/168 (34.5)	29/109 (26.6)	
50%	15/36 (41.7)	36/168 (21.4)	43/109 (39.4)	
75%	4/36 (11.1)	60/168 (35.7)	26/109 (23.9)	
100%	2/36 (5.6)	8/168 (4.8)	9/109 (8.3)	
Chest X-ray performed – no (%)	32/39 (82.1)	321/359 (89.4)	146/169 (86.4)	0.262
Quadrants affected – no (%)				0.534
1	4/30 (13.3)	20/321 (6.2)	12/146 (8.2)	
2	5/30 (16.7)	75/321 (23.4)	32/146 (21.9)	
3	7/30 (23.3)	82/321 (25.5)	45/146 (30.8)	
4	14/30 (46.7)	144/321 (44.9)	57/146 (39.0)	
Co-existing disorders – no (%)				
Hypertension	20 (26.3)	186 (34.6)	95 (33.8)	0.371
Heart failure	1 (1.3)	25 (4.6)	12 (4.3)	0.471
Diabetes	18 (23.7)	119 (22.1)	66 (23.5)	0.880
Chronic kidney disease	4 (5.3)	26 (4.8)	11 (3.9)	0.752
Baseline creatinine, μmol/L[a]	75.0 (64.2–108.2)	78.0 (64.0–97.0)	77.5 (60.0–96.0)	0.537
Liver cirrhosis	0 (0.0)	3 (0.6)	0 (0.0)	0.659
Chronic obstructive pulmonary disease	3 (3.9)	38 (7.1)	33 (11.7)	0.030
Active hematological neoplasia	3 (3.9)	8 (1.5)	3 (1.1)	0.168
Active solid neoplasia	2 (2.6)	15 (2.8)	7 (2.5)	0.999
Neuromuscular disease	0 (0.0)	8 (1.5)	0 (0.0)	0.093
Immunosuppression	0 (0.0)	19 (3.5)	4 (1.4)	0.081
Previous medication – no (%)				
Systemic steroids	3 (3.9)	24 (4.5)	9 (3.2)	0.696
Inhalation steroids	10 (13.2)	60 (11.2)	33 (11.7)	0.803
Angiotensin converting enzyme inhibitor	11 (14.5)	108 (20.1)	38 (13.5)	0.050
Angiotensin II receptor blocker	6 (7.9)	61 (11.3)	31 (11.0)	0.730
Beta-blockers	12 (15.8)	109 (20.3)	52 (18.5)	0.638
Insulin	13 (17.1)	33 (6.1)	16 (5.7)	0.004
Metformin	15 (19.7)	86 (16.0)	45 (16.0)	0.677
Statins	24 (31.6)	175 (32.5)	77 (27.4)	0.310
Calcium channel blockers	13 (17.1)	95 (17.7)	55 (19.6)	0.791
Vital signs at day 01				
Heart rate, bpm[b]	82.0 (70.9–91.1)	83.0 (72.8–96.0)	86.5 (76.5–99.7)	0.001
Mean arterial pressure, mmHg[b]	78.3 (74.5–84.6)	79.5 (73.1–86.2)	82.0 (75.7–90.7)	0.001
Laboratory tests at day 01				
pH[b]	7.38 (7.32–7.40)	7.36 (7.32–7.41)	7.35 (7.29–7.40)	0.009
Worst PaO_2/FiO_2, mmHg[c]	228.6 (213.9–247.4)	135.0 (115.5–160.7)	84.0 (71.5–91.8)	< 0.001
$PaCO_2$, mmHg[b]	40.9 (36.8–46.8)	43.5 (39.0–48.5)	46.0 (40.5–52.3)	< 0.001
Lactate mmol/L[b]	1.1 (0.9–1.5)	1.1 (0.9–1.4)	1.2 (1.0–1.5)	0.026
Organ support at day 01 – no (%)				
Continuous sedation	73/75 (97.3)	522/537 (97.2)	267 (95.0)	0.279
Inotropic or vasopressor	59/75 (78.7)	428/537 (79.7)	222 (79.0)	0.958
Vasopressor	59/75 (78.7)	428/537 (79.7)	221 (78.6)	0.918
Inotropic	2/75 (2.7)	24/537 (4.5)	11 (3.9)	0.870
Fluid balance, mL	460.0 (−164.0–1251.0)	611.0 (101.5–1375.0)	751.0 (0.0–1575.3)	0.183
Urine output, mL	755.0 (350.0–1220.0)	715.0 (395.0–1164.0)	712.0 (370.0–1144.5)	0.869
Ventilation support at day 01				
Assisted ventilation – no (%)	17 (22.4)	165 (30.8)	76 (27.2)	0.243
Tidal volume, mL/kg PBW[b]	6.5 (5.7–7.2)	6.4 (5.9–7.0)	6.5 (5.9–7.1)	0.965
PEEP, cmH_2O[b]	13.2 (11.6–15.0)	12.7 (11.0–14.7)	13.0 (11.0–14.5)	0.556
Peak pressure, cmH_2O[b]	27.0 (24.0–28.4)	26.2 (23.3–29.3)	27.2 (24.5–30.5)	0.004
Driving pressure, cmH_2O[b]	13.0 (11.5–15.6)	13.3 (11.5–15.9)	14.3 (12.8–16.7)	< 0.001
Mechanical power, J/min[b]	18.9 (14.6–21.9)	18.1 (14.9–21.8)	18.6 (15.8–23.1)	0.073
Compliance, mL/cmH_2O[b]	32.0 (28.1–39.4)	33.8 (27.3–41.7)	31.9 (25.7–38.6)	0.012
Total respiratory rate, mpm[b]	21.0 (18.8–23.7)	21.3 (19.3–23.8)	22.0 (19.5–24.7)	0.050
FiO_2[b]	0.45 (0.38–0.53)	0.54 (0.47–0.60)	0.70 (0.62–0.80)	< 0.001
$etCO_2$, mmHg[b]	37.5 (33.6–40.6)	36.7 (32.5–41.6)	35.8 (32.3–41.8)	0.734

(continued on next page)

Table 1 (*continued*)

	Mild ($n = 76$)	Moderate ($n = 538$)	Severe ($n = 281$)	p value
Rescue therapy at day 01 – no (%)				
Prone positioning	9/75 (12.0)	135/529 (25.5)	133/274 (48.5)	< 0.001
Duration, hours[a]	3.0 (1.5–8.0)	8.0 (4.0–13.8)	9.5 (5.2–14.0)	0.061
Recruitment manoeuvre	1/66 (1.5)	5/451 (1.1)	13/214 (6.1)	0.001
ECMO	0 (0.0)	0 (0.0)	0 (0.0)	–
Use of NMBA	10/75 (13.3)	139 (25.8)	94/280 (33.6)	0.001
Hours of use	0.0 (0.0–0.0)	0.0 (0.0–8.0)	0.0 (0.0–8.0)	< 0.001

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding
CT: computed tomography; PaO2: arterial partial pressure of oxygen; FiO2: Fraction of inspired oxygen; PaCO2: arterial partial pressure of carbon dioxide; PBW: predicted body weight; PEEP positive end expiratory pressure; ECMO: extracorporeal membrane oxygenation; FiO_2: inspired fraction of oxygen; etCO2: End tidal carbon dioxide; NMBA: neuromuscular blocking agent.
[a] Most recent measurement in 24 h before intubation, or at ICU admission under invasive ventilation.
[b] Aggregate as the mean of four values.
[c] Worst value of four available.

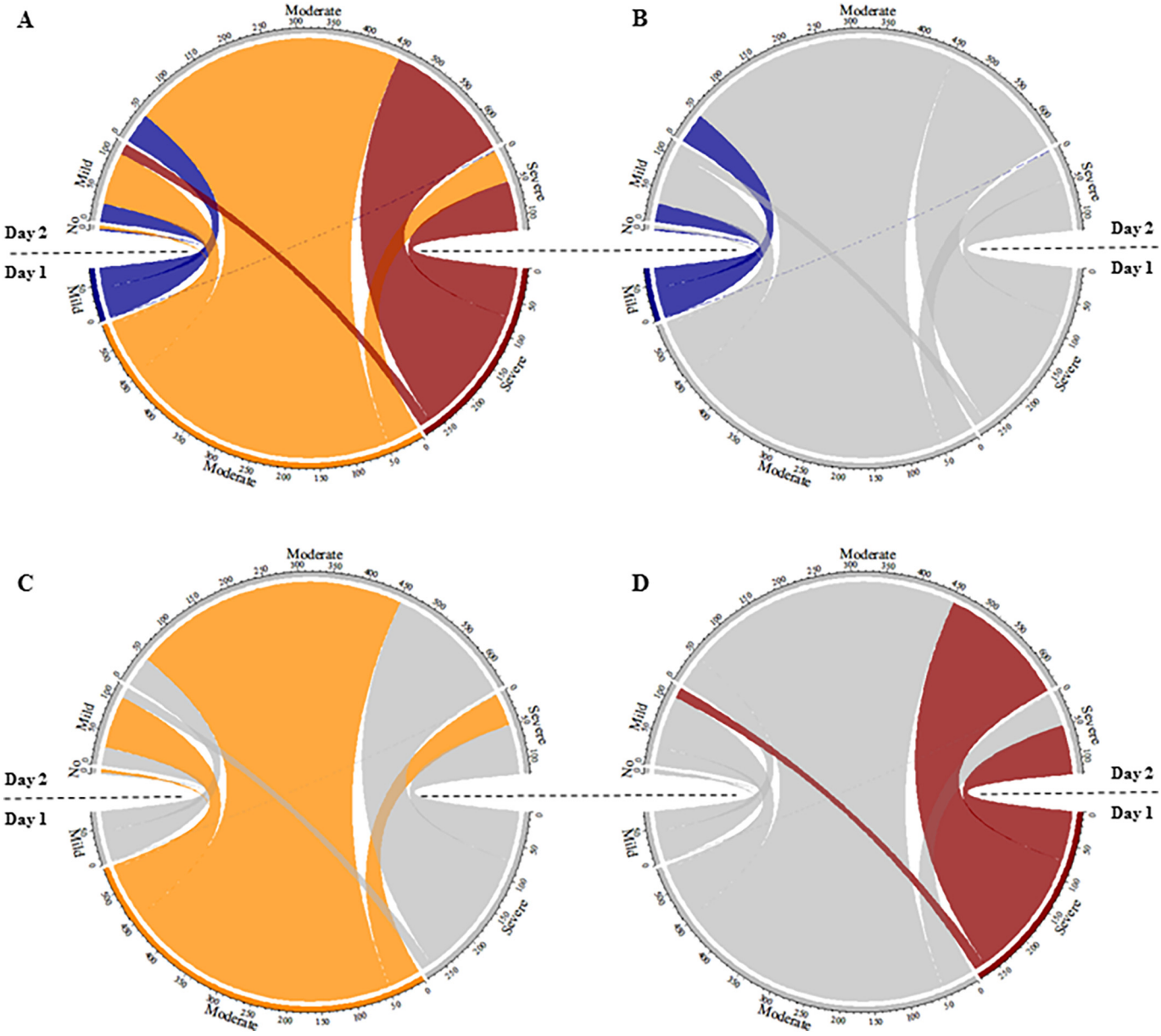

Fig. 1. Evolution of ARDS severity over the first 2 calendar days of invasive ventilation.
Chord diagram depicting the evolution of ARDS severity at day 1 and subsequent ARDS severity at day 2. The bottom part of the diagram represents patients ranked by ARDS severity at day 1, the top part represents the same patients ranked according to presence and evolution of ARDS severity at day 2. Ribbons show the evolution of ARDS from day 1 to day 2.
The first diagram (a) presents all patients combined. The other diagrams (b–d) highlight ARDS severity classes separately. Of 76 patients with mild ARDS at day 1, 3 (3.9%), 27 (35.5%), 45 (59.2%) and 1 (1.3%) patients had respectively no, mild, moderate and severe ARDS at day 2. Of 538 patients with moderate ARDS at day 1, 5 (0.9%), 77 (14.3%), 408 (75.8%) and 48 (8.9%) patients had respectively no, mild, moderate and severe ARDS at day 2. Of 281 patients with severe ARDS at day 1, 16 (5.7%), 191 (68.0%) and 74 (26.3%) patients had respectively mild, moderate and severe ARDS at day 2.

Table 2
Baseline characteristics of the included patients according to ARDS severity at calendar day 2.

	Mild ($n = 120$)	Moderate ($n = 644$)	Severe ($n = 123$)	p value
Age, years	66.0 (56.8–70.2)	65.0 (58.8–72.0)	66.0 (57.0–72.0)	0.670
Male gender – no (%)	83 (69.2)	477 (74.1)	84 (68.3)	0.259
Body mass index, kg/m^2	26.9 (24.8–30.4)	27.7 (25.6–30.8)	27.7 (25.4–31.7)	0.265
Transferred under invasive ventilation	19 (15.8)	56 (8.7)	8 (6.5)	0.034
Days between intubation and admission	0.0 (0.0–1.0)	1.0 (0.0–1.0)	1.0 (0.0–1.0)	0.675
Use of non-invasive ventilation – no (%)	7 (6.5)	55 (9.2)	11 (9.2)	0.722
Duration of non-invasive ventilation, hours	10.0 (6.0–21.5)	7.5 (2.0–12.8)	12.0 (6.5–21.0)	0.422
Chest CT scan performed – no (%)	38 (32.8)	219 (34.7)	47 (39.2)	0.544
Lung parenchyma affected – no (%)				0.217
0%	2 (5.3)	6 (2.7)	1 (2.1)	
25%	11 (28.9)	78 (35.0)	10 (21.3)	
50%	10 (26.3)	67 (30.0)	15 (31.9)	
75%	11 (28.9)	63 (28.3)	15 (31.9)	
100%	4 (10.5)	9 (4.0)	6 (12.8)	
Chest X-ray performed – no (%)	64 (80.0)	369 (90.0)	64 (87.7)	0.045
Quadrants affected – no (%)				0.544
1	3 (4.8)	30 (8.1)	3 (4.7)	
2	15 (23.8)	85 (23.0)	12 (18.8)	
3	21 (33.3)	90 (24.4)	23 (35.9)	
4	24 (38.1)	164 (44.4)	26 (40.6)	
Co-existing disorders – no (%)				
Hypertension	38 (31.7)	210 (32.6)	48 (39.0)	0.365
Heart failure	6 (5.0)	29 (4.5)	3 (2.4)	0.552
Diabetes	22 (18.3)	150 (23.3)	28 (22.8)	0.518
Chronic kidney disease	6 (5.0)	27 (4.2)	4 (3.3)	0.765
Baseline creatinine, μmol/L[a]	77.0 (62.0–92.0)	77.0 (63.0–98.0)	79.0 (64.0–98.0)	0.722
Liver cirrhosis	0 (0.0)	3 (0.5)	0 (0.0)	0.999
Chronic obstructive pulmonary disease	7 (5.8)	51 (7.9)	16 (13.0)	0.114
Active hematological neoplasia	5 (4.2)	6 (0.9)	2 (1.6)	0.024
Active solid neoplasia	4 (3.3)	18 (2.8)	2 (1.6)	0.707
Neuromuscular disease	0 (0.0)	7 (1.1)	1 (0.8)	0.845
Immunosuppression	6 (5.0)	13 (2.0)	2 (1.6)	0.171
Previous medication – no (%)				
Systemic steroids	8 (6.7)	22 (3.4)	5 (4.1)	0.209
Inhalation steroids	10 (8.3)	80 (12.4)	12 (9.8)	0.375
Angiotensin converting enzyme inhibitor	22 (18.3)	109 (16.9)	23 (18.7)	0.817
Angiotensin II receptor blocker	14 (11.7)	70 (10.9)	13 (10.6)	0.939
Beta-blockers	24 (20.0)	116 (18.0)	32 (26.0)	0.121
Insulin	6 (5.0)	48 (7.5)	7 (5.7)	0.620
Metformin	17 (14.2)	112 (17.4)	15 (12.2)	0.305
Statins	41 (34.2)	193 (30.0)	39 (31.7)	0.627
Calcium channel blockers	21 (17.5)	111 (17.2)	30 (24.4)	0.175
Vital signs at day 01				
Heart rate, bpm[b]	81.0 (70.0–95.8)	84.0 (73.5–96.0)	86.7 (78.5–101.8)	0.004
Mean arterial pressure, mmHg[b]	79.0 (73.6–86.2)	80.5 (73.5–87.5)	80.3 (75.5–90.9)	0.157
Laboratory tests at day 01				
pH*b*	7.4 (7.3–7.4)	7.4 (7.3–7.4)	7.3 (7.3–7.4)	0.290
Worst PaO_2/FiO_2, mmHg[c]	161.3 (119.0–190.9)	121.3 (96.1–153.6)	93.3 (77.0–113.4)	< 0.001
$PaCO_2$, mmHg[b]	41.9 (36.8–47.0)	44.3 (39.5–49.6)	46.9 (40.3–51.9)	< 0.001
Lactate mmol/L[b]	1.1 (0.9–1.5)	1.1 (0.9–1.4)	1.2 (0.9–1.4)	0.808
Organ support at day 01 – no (%)				
Continuous sedation	115 (95.8)	623 (97.0)	117 (95.1)	0.407
Inotropic or vasopressor	96 (80.0)	518 (80.7)	90 (73.2)	0.164
Vasopressor	96 (80.0)	517 (80.5)	90 (73.2)	0.180
Inotropic	6 (5.0)	28 (4.4)	3 (2.4)	0.589
Fluid balance, mL	743.0 (10.5–1603.0)	614.0 (38.9–1384.2)	640.0 (126.6–1400.7)	0.647
Urine output, mL	725.0 (402.5–1095.0)	712.5 (372.5–1165.0)	720.0 (405.0–1195.0)	0.985
Ventilation support at day 01				
Assisted ventilation – no (%)	35 (29.2)	191 (29.8)	30 (24.6)	0.530
Tidal volume, mL/kg PBW[b]	6.5 (5.9–7.1)	6.4 (5.9–7.0)	6.3 (5.9–7.2)	0.828
PEEP, cmH_2O[b]	13.1 (11.5–15.0)	13.0 (11.0–14.8)	12.0 (10.0–14.0)	0.012
Peak pressure, cmH_2O[b]	26.5 (23.8–29.6)	26.7 (23.8–29.7)	27.0 (23.5–30.8)	0.794
Driving pressure, cmH_2O[b]	13.5 (12.0–15.3)	13.8 (11.7–16.0)	14.0 (12.2–17.8)	0.086
Mechanical power, J/min[b]	17.9 (15.4–20.5)	18.3 (15.2–22.1)	18.5 (14.8–23.6)	0.514
Compliance, mL/cmH_2O[b]	33.6 (27.0–41.0)	33.3 (27.5–40.4)	32.3 (24.2–39.1)	0.320
Total respiratory rate, mpm[b]	20.7 (19.5–23.4)	21.5 (19.2–24.0)	22.3 (19.8–25.6)	0.024
FiO_2[b]	0.50 (0.43–0.60)	0.57 (0.50–0.67)	0.68 (0.60–0.78)	< 0.001
$etCO_2$, mmHg[b]	35.9 (31.5–41.1)	36.8 (32.6–42.0)	35.9 (32.4–40.5)	0.408

(continued on next page)

Table 2 (*continued*)

	Mild ($n = 120$)	Moderate ($n = 644$)	Severe ($n = 123$)	p value
Rescue therapy at day 01 – no (%)				
Prone positioning	23 (19.7)	193 (30.5)	59 (49.2)	< 0.001
Duration, hours[a]	8.5 (5.2–12.0)	8.0 (4.0–14.0)	9.0 (6.0–15.0)	0.281
Recruitment manoeuvre	2 (2.0)	6 (1.2)	10 (9.5)	< 0.001
ECMO	0 (0.0)	0 (0.0)	0 (0.0)	–
Use of NMBA	26 (21.7)	181 (28.1)	35 (28.5)	0.326
Hours of use	0.0 (0.0–0.0)	0.0 (0.0–8.0)	0.0 (0.0–8.0)	0.228

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding
CT: computed tomography; PaO2: arterial partial pressure of oxygen; FiO2: Fraction of inspired oxygen; PaCO2: arterial partial pressure of carbon dioxide; PBW: predicted body weight; PEEP positive end expiratory pressure; ECMO: extracorporeal membrane oxygenation; FiO_2: inspired fraction of oxygen; etCO2: End tidal carbon dioxide; NMBA: neuromuscular blocking agent.
[a] Most recent measurement in 24 h before intubation, or at ICU admission under invasive ventilation.
[b] Aggregate as the mean of four values.
[c] Worst value of four available.

3.2. Outcomes

28–day mortality was 25.3% in patients with ARDS classified at calendar day 1 as mild, and 31.3% and 32.0% in patients with ARDS classified at that day as moderate and severe (Fig. 2 and eTable 1 in Supplementary Data 2). 28–day mortality was 28.6% and 29.2% in patients with ARDS classified at calendar day 2 as mild and moderate, and increased to 44.3% in patients with ARDS classified as severe (eTable 2 in Supplementary Data 2). Likewise, mortality in ICU, hospital, and at day 90 changed after reclassification (eTable 1, eTable 2 and eFigure 2 in Supplementary Data 2), but the number of VFD–28 and duration of ventilation in survivors was not affected by reclassification at calendar day 2.

3.3. Factors associated with presence of severe ARDS at calendar day 2

In univariable analysis, ARDS severity at calendar day 1, heart rate, RR, ΔP and use of prone positioning were associated with presence of severe ARDS at calendar day 2 (Table 3). In multivariable analysis, no single ventilator setting had an independent association with presence of severe ARDS at calendar day 2. Only presence of severe ARDS at calendar day 1 was independently associated with presence of severe ARDS at calendar day 2.

3.4. Reclassification at calendar day 4

The sensitivity analysis for reclassification of ARDS severity did not change the findings (eTable 3, eTable 4, eFigure 3 and eFigure 4 in Supplementary Data 2), though chronic obstructive pulmonary disease as co–existing disorder, fluid balance and C_{RS} at calendar day 1 had an independent association with presence of severe ARDS at calendar day 4 (eTable 5 in Supplementary Data 2).

4. Discussion

The finding of this analysis of a large cohort of COVID–19 patients receiving invasive ventilation for ARDS can be summarized as follows: (1) ARDS severity changes over the first 2 calendar days of ventilation; and (2) reclassification of severity at calendar day 2 results in groups with more contrast in outcome than classification of severity at calendar day 1. Indeed, (3) patients with severe ARDS at calendar day 2, which could have been caused by persistence or worsening of the oxygenation

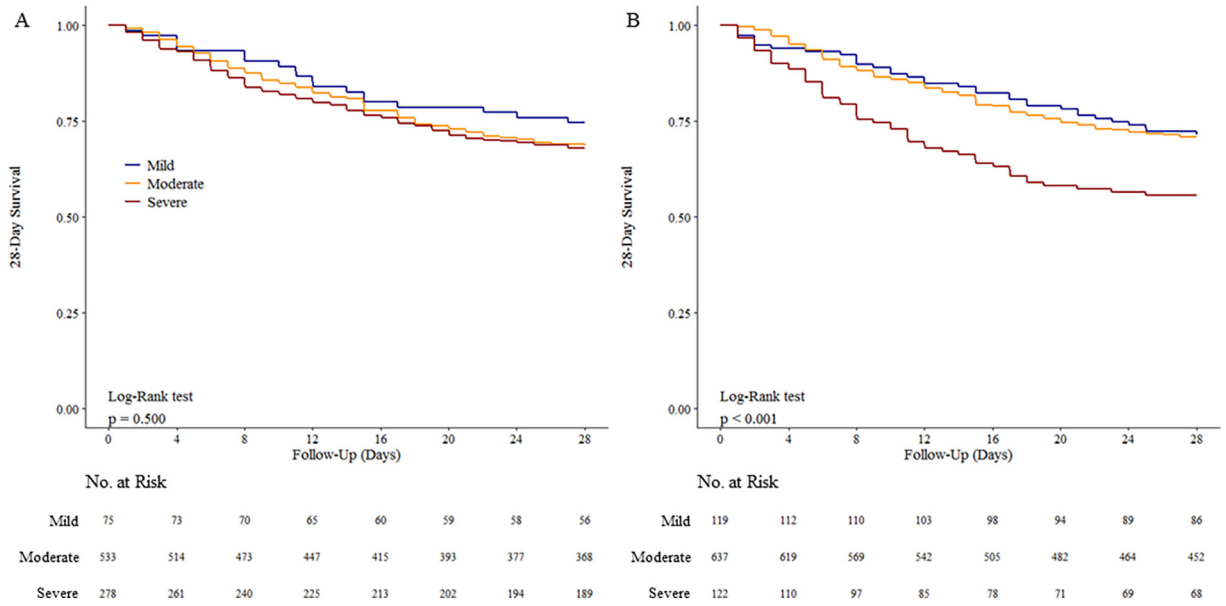

Fig. 2. Kaplan–Meier curves for 28–day mortality for ARDS severity at calendar day 1 and 2.
The left diagram (a) shows the probability of 28–day mortality by ARDS severity class at calendar day 1. The right diagram (b) shows the probability of 28–day mortality by ARDS severity class at calendar day 2. Kaplan–Meier curves comparing the probability of survival in mild (blue), moderate (orange), and severe ARDS (red) groups. Log-rank tests show an overall difference between groups and a lower probability of 28–day mortality survival in the severe ARDS group as compared to the mild and moderate ARDS group at calendar day 2.

Table 3
Factors associated with presence of severe ARDS at calendar day 2.

	Univariable Analysis		Multivariable Analysis	
	Odds Ratio (95% CI)	*p* value	Odds Ratio (95% CI)	*p* value
Demographic characteristics				
Age	1.01 (0.82 to 1.24)	0.920	–	–
Male gender	0.83 (0.54 to 1.28)	0.395	–	–
Body mass index	1.11 (0.93 to 1.32)	0.232	–	–
Co-existing disorders				
Hypertension	1.17 (0.77 to 1.77)	0.458	–	–
Heart failure	0.43 (0.13 to 1.46)	0.176	–	–
Diabetes	0.97 (0.60 to 1.56)	0.901	–	–
Chronic kidney disease	0.54 (0.18 to 1.60)	0.266	–	–
Chronic obstructive pulmonary disease	1.86 (0.99 to 3.48)	0.054	1.61 (0.84 to 3.08)	0.154
Active hematological neoplasia	1.32 (0.27 to 6.49)	0.734	–	–
Active solid neoplasia	0.61 (0.14 to 2.66)	0.509	–	–
Category of ARDS at day 01				
Mild	1 (Reference)		1 (Reference)	
Moderate	6.93 (0.95 to 50.30)	0.055	6.45 (0.88 to 47.06)	0.066
Severe	23.83 (3.28 to 173.07)	0.001	18.19 (2.48 to 133.55)	0.004
Previous medication				
Angiotensin converting enzyme inhibitor	1.10 (0.66 to 1.82)	0.722	–	–
Angiotensin II receptor blocker	0.98 (0.51 to 1.86)	0.943	–	–
Vital signs at day 01				
Heart rate	1.34 (1.10 to 1.62)	0.003	1.22 (0.99 to 1.52)	0.063
Mean arterial pressure	1.17 (0.96 to 1.42)	0.118	–	–
Laboratory tests at day 01				
Creatinine	0.92 (0.69 to 1.23)	0.585	–	–
pH	0.87 (0.72 to 1.05)	0.157	–	–
Ventilation support at day 01				
Tidal volume per PBW	1.06 (0.87 to 1.29)	0.543	–	–
PEEP	0.93 (0.75 to 1.15)	0.501	–	–
Peak pressure	1.11 (0.92 to 1.35)	0.287	–	–
Total respiratory rate	1.29 (1.07 to 1.57)	0.009	1.17 (0.94 to 1.45)	0.152
Driving pressure	1.24 (1.03 to 1.50)	0.025	1.03 (0.83 to 1.28)	0.799
Mechanical power	1.14 (0.94 to 1.38)	0.186	–	–
Compliance	0.86 (0.68 to 1.07)	0.174	–	–
Organ support at day 01				
Fluid balance	1.16 (0.95 to 1.41)	0.142	–	–
Use of vasopressor	0.73 (0.46 to 1.16)	0.181	–	–
Rescue therapy at day 01				
Prone positioning	1.99 (1.29 to 3.06)	0.002	1.30 (0.82 to 2.05)	0.262
Use of NMBA	1.31 (0.83 to 2.07)	0.247	–	–

Continuous variables were included after standardization and the hazard ratio represents the increase in one standard deviation of the variable.
c-statistic for the multivariable model is 0.790 (0.746 to 0.835). Brier score for the multivariable model is 0.098.
PBW: predicted body weight; PEEP positive end expiratory pressure; NMBA: neuromuscular blocking agent.

problems, have much higher mortality rates than patients with mild or moderate ARDS. (4) There was no single ventilator setting that had an independent association with presence of severe ARDS at calendar day 2.

ARDS severity in our study was similar to that in two other studies originating from France [14] and the United Kingdom [15]. In one study conducted in France, Belgium and Switzerland, named the COVID–ICU study, changes in ARDS severity from day 1 through day 7 and their association with mortality were reported, but that analysis was restricted to patients with worsening severity [14]. That study found 12% of patients with ARDS classified as mild, and 16% of patients with ARDS classified as moderate to progress to severe ARDS, which is in line with the finding of our study. Our results are also in line with those from one study in Spain that showed an increase in the proportion of patients with moderate ARDS within the first 2 days of ventilation [16].

The findings of our study in patients with COVID–19 ARDS iterate the prognostic value of reclassification of ARDS severity as found in patients with ARDS due to a cause other than COVID–19 [5-7]. Increased contrast in 90–day mortality between ARDS severity groups was seen with reclassification of ARDS severity in the LUNG SAFE study [6]. In that study, severe ARDS at the second day of ventilation was associated with a 90–day mortality of 57%, similar to the current findings. Comparable findings came from another analysis of LUNG SAFE, that focused on improving, persisting and worsening severity in patients with ARDS classified as mild at the first day of ventilation [5], and a study that assessed the prognostic value of PaO_2/FiO_2 the day after ARDS was diagnosed [7]. In contrast to our study, the latter study included only patients presenting with moderate and severe ARDS, and PaO_2/FiO_2 were collected at standard ventilator settings.

In our study, we did not observe any difference in outcomes in ARDS classes at baseline, whereas one study did show a difference in 90–day mortality in ARDS classes at baseline [14]. It could be that our cohort was too small to show a difference. One noticeable finding in our study was that the proportion of patients that no longer had ARDS at calendar day 2 was low, less than 1%, and quite different from one study in patients with ARDS due to another cause than COVID–19 that showed almost 25% to have resolved ARDS after 24 h [6]. This might be explained by a difference in the pathophysiology, as ARDS caused by COVID–19 shows more pulmonary thrombosis and angiogenesis than ARDS caused by an equally severe influenza virus infection [17,18].

In our study, there were no ventilatory variables that had an independent association with presence of severe ARDS at calendar day 2. This is, at least in part in contrast with findings of a secondary analysis of the LUNG SAFE study, that showed tidal volume size to have an association with persistence of ARDS after 24 h [6]. It should be noticed, though, that in our cohort tidal volumes were low, median 6.4 (5.9–7.0) ml/kg PBW [9] and even lower than that reported in the LUNG SAFE study, mean 7.6 ± 1.9 ml/kg PBW [6]. Probably, tidal volume size was already sufficiently low to protect against additional lung injury caused by the

ventilator. Furthermore, the use of prone positioning has shown to improve patient outcomes when used in the early phase of ARDS [19]. Our study did not show an association between the use of prone positioning and presence of severe ARDS at calendar day 2. As prone positioning decreases ventilator-induced lung injury by balancing the pulmonary stress and strain of invasive ventilation, the effect of prone positioning on ARDS severity could be delayed and therefore unnoticed in our study. Besides, our study did not find an association between the use of NMBA and presence of severe ARDS at calendar day 2. The value of the use of NMBA is not undisputed, as two studies have shown varying results of the use NMBA on mortality in ARDS patients [20,21].

For daily practice, we would advise healthcare providers to reclassify ARDS severity after calendar day 1 in order to raise awareness for a patient's mortality risk. This could help consider alternative approaches for these high–risk patients, such as ECMO, which could improve outcomes. Besides, our study has implications for clinical trial design and patient enrolment. The use of baseline classification for enrolment may cause bias, as a treatment might benefit a more defined subgroup of patients with according risk of mortality. Furthermore, improving stratification of enrolled patients can reduce the necessary sample size, since it makes treatment effects easier to detect, which is an acknowledged problem in ventilator studies conducted in the critically ill. If a specific intervention allows, we recommend randomizing patients with ARDS after the first calendar day.

Our study has several strengths. First, it is one of the largest multicenter studies that collected granular data regarding ventilator settings, and ventilation variables and parameters. We used strict inclusion and exclusion criteria, to prevent bias that could have been caused by patients who received invasive ventilation in non–participating centers; we also strictly followed the statistical analysis plan, updated and finalized before assessing the database. Follow–up was up to day 90, allowing us to report several important endpoints in COVID–19 ARDS patients. The cohort included patients admitted in academic and non–academic centers, increasing the generalizability of the findings. Collection of data took place within a relative short timeframe, preventing against changes in care over time.

Our study also has limitations. Our patient cohort may not be representative of actual clinical practice in ICUs worldwide, due to its national character. Furthermore, patient management was based on the insights at the time of the early months of the pandemic––there was for instance no standard use of dexamethasone and clinician's awareness for thromboembolic complications was less refined, which could influence the course of ARDS, and patients' outcomes. Also, D–dimer levels were not measured routinely and could thus not be used in the models, while it has been recently reported as strongly associated with mortality [22]. Given the size of our database, small differences between groups may achieve statistical significance but be of uncertain clinical significance. Finally, by design, observational studies cannot adjust for unmeasured confounders and rely on the data collected by the investigators.

5. Conclusion

In this national multicenter observational study, ARDS severity changes substantially over the first calendar days of ventilation and reclassification of ARDS severity at calendar day 2 results in more contrast in mortality rates between ARDS severity classes. We found no single ventilation parameter that had an independent association with presence of severe ARDS at day 2. Reclassification at successive days of invasive ventilation could help identify target patients that may benefit from alternative approaches.

Availability of data and materials

A dataset will be made available upon request to the corresponding authors one year after the publication of this study. The request must include a statistical analysis plan.

Consent for publication

Not applicable.

Ethics approval and consent to participate

The institutional review boards of the participating centers approved the study protocol and need for patient informed consent was waived.

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Declaration of Competing Interest

ASN reports personal fees from Dräger, outside of the submitted work. The other authors declare no competing interests.

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Appendix A. Supplementary data

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