ORIGINAL ARTICLE

Association of early positive end-expiratory pressure settings with ventilator-free days in patients with coronavirus disease 2019 acute respiratory distress syndrome

A secondary analysis of the Practice of VENTilation in COVID-19 study

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BACKGROUND There is uncertainty about how much positive end-expiratory pressure (PEEP) should be used in patients with acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19).

OBJECTIVE To investigate whether a higher PEEP strategy is superior to a lower PEEP strategy regarding the number of ventilator-free days (VFDs).

DESIGN Multicentre observational study conducted from 1 March to 1 June 2020.

SETTING AND PATIENTS Twenty-two ICUs in The Netherlands and 933 invasively ventilated COVID-19 ARDS patients.

INTERVENTIONS Patients were categorised retrospectively as having received invasive ventilation with higher ($n=259$) or lower PEEP ($n=674$), based on the high and low PEEP/FiO_2 tables of the ARDS Network, and using ventilator settings and parameters in the first hour of invasive ventilation, and every 8 h thereafter at fixed time points during the first four calendar days. We also used propensity score matching to control for observed confounding factors that might influence outcomes.

MAIN OUTCOMES AND MEASURES The primary outcome was the number of VFDs. Secondary outcomes included distant organ failures including acute kidney injury (AKI) and use of renal replacement therapy (RRT), and mortality.

RESULTS In the unmatched cohort, the higher PEEP strategy had no association with the median [IQR] number of VFDs (2.0 [0.0 to 15.0] vs. 0.0 [0.0 to 16.0] days). The median (95% confidence interval) difference was 0.21 (-3.34 to 3.78) days, $P=0.905$. In the matched cohort, the higher PEEP group had an association with a lower median number of VFDs (0.0 [0.0 to 14.0] vs. 6.0 [0.0 to 17.0] days) a median difference of -4.65 (-8.92 to -0.39) days, $P=0.032$. The higher PEEP strategy had associations with higher incidence of AKI (in the matched cohort) and more use of RRT (in the unmatched and matched cohorts). The higher PEEP strategy had no association with mortality.

CONCLUSION In COVID-19 ARDS, use of higher PEEP may be associated with a lower number of VFDs, and may increase the incidence of AKI and need for RRT.

TRIAL REGISTRATION Practice of VENTilation in COVID-19 is registered at ClinicalTrials.gov, NCT04346342.

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KEY POINTS

- In an unmatched cohort of COVID-19 ARDS patients, a higher PEEP strategy did not have an association with the number of VFDs; in a matched cohort a higher PEEP strategy had an association with a lower number of VFDs.
- In an unmatched cohort, a higher PEEP strategy had an association with more use of RRT; in a matched cohort, a higher PEEP strategy had an association with a higher incidence of AKI and more use of RRT.
- A randomised clinical trial is highly needed to determine the effects of a higher PEEP strategy versus a lower PEEP strategy on outcomes in patients with COVID-19 ARDS.

Introduction

In patients with acute respiratory distress syndrome (ARDS), higher positive end-expiratory pressure (PEEP) may prevent atelectasis, improve oxygenation and reduce ventilator-induced lung injury.[1] However, mortality benefit was not found in three randomised clinical trials,[2–4] and in one study, higher PEEP with aggressive recruitment manoeuvres worsened outcome.[5] A more recent study suggests benefit from higher PEEP in patients with 'recruitable' lung tissue, but harm in patients who have 'nonrecruitable' lung lesions.[6]

Patients with ARDS due to coronavirus disease 2019 (COVID-19) typically suffer from severe and often refractory hypoxaemia, and have a low respiratory system compliance.[7–9] There is substantial debate as to whether COVID-19 ARDS differs from ARDS from other causes,[10] and also whether COVID-19 patients have 'recruitable' or 'nonrecruitable' lung lesions.[11,12] As COVID-19 patients frequently have microthrombi and pulmonary embolism as one other cause of hypoxaemia,[13] a higher PEEP strategy may not necessarily correct hypoxaemia, while it can increase the risks of barotrauma and haemodynamic deterioration.[14]

It remains uncertain how much PEEP should be used in COVID-19 ARDS patients. In the absence of randomised clinical trial evidence, it has been recommended to use higher PEEP, according to the high PEEP/$F_I O_2$ table of the ARDS Network.[15–17] We undertook the 'Practice of VENTilation in COVID-19' (PRoVENT-COVID) study to investigate ventilation management over the first 4 calendar days of invasive ventilation, and epidemiological characteristics and outcomes in invasively ventilated COVID-19 ARDS patients in the Netherlands.[18,19] The current analysis investigates the association of early PEEP settings with outcomes, including duration of invasive ventilation, distant organ failures and mortality. We hypothesised that a higher PEEP strategy would be superior to a lower PEEP strategy.

Methods

The PRoVENT-COVID study is an investigator-initiated, multicentre, observational cohort study undertaken in 22 ICUs in the Netherlands. The protocol including the statistical analysis plan has been published[18] and the final protocol is available in Supplement 1, http://links.lww.com/EJA/A591. A statistical analysis plan for the current analysis was written before assessing the database, which is available in Supplement 2, http://links.lww.com/EJA/A591. Study sites were recruited through direct contact by members of the steering committee of the PRoVENT-COVID study. Study coordinators contacted the local doctors, trained data collectors to assist the local doctors and monitored the study according to the International Conference on Harmonisation Good Clinical Practice guidelines. Integrity and timely completion of data collection were ensured by the study coordinators.

The study was conducted in accordance with the Declaration of Helsinki and was registered at ClinicalTrials.gov (trial identification number NCT04346342). The Institutional Review Board of the Amsterdam UMC (Location AMC), Amsterdam, The Netherlands (Chairperson Prof Dr J.A. Swinkels) approved the study protocol on 7 April 2020 (W20_157 # 20.171) and need for patient informed consent was waived.

Patients

Consecutive patients aged at least 18 years were eligible for participation in the PRoVENT-COVID study if they were admitted to one of the participating ICUs and had received invasive ventilation for COVID-19 ARDS. The study itself had no exclusion criteria. For the current

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analysis, we excluded patients transferred from or to a nonparticipating centre within the first 2 calendar days of invasive ventilation, as it was impossible to collect ventilation variables, including early PEEP settings and other parameters in the nonparticipating centres.

Patient characteristics and data regarding premorbid conditions and 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 and parameters were collected. Thereafter, patients were categorised retrospectively as having received invasive ventilation according to a higher or lower PEEP strategy, using the high and low PEEP/F_IO_2 tables of the ARDS Network. We used the 8-hourly collected PEEP/F_IO_2 combinations to classify the applied PEEP strategy as 'higher PEEP' if it fitted the high PEEP/F_IO_2 ARDS Network table, or as 'lower PEEP' if it fitted the low PEEP/F_IO_2 ARDS Network table. For combinations that did not fit in either table, we classified them as follows: in case PEEP was higher than in the high PEEP/F_IO_2 table, it was classified as higher PEEP; in case PEEP was lower than in the high PEEP/F_IO_2 table, it was classified as lower PEEP (see Supplemental eFigure 1, http://links.lww.com/EJA/A591). Each patient was then categorised according to the majority of the available PEEP/F_IO_2 combinations as a higher PEEP or lower PEEP patient; the first available PEEP/F_IO_2 combination, that is, directly after intubation and start of invasive ventilation, was not used for patient categorisation.

Outcomes

The primary outcome was the number of days free from invasive ventilation and alive at day 28 [ventilator-free days (VFDs)], calculated from the moment of start of invasive ventilation, even 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 had 0 VFDs, even if extubated before day 28. A day on noninvasive ventilation (NIV) also counted in the number of VFDs.[20]

Secondary outcomes were acute kidney injury (AKI) defined by 'Kidney Disease: Improving Global Outcome'[21]; use of renal replacement therapy (RRT) for AKI; and mortality rates in the ICU, the hospital and at 28 and 90 days. Other endpoints were duration of invasive ventilation in survivors; ICU and hospital length of stay; need for adjunctive treatments for refractory hypoxaemia, including prone positioning, lung recruitment manoeuvres, muscle paralysis and extracorporeal membrane oxygenation in the first 4 calendar days of invasive ventilation; the number of days with continuous sedation, vasopressor or inotrope administration; occurrence of reintubation or tracheostomy; pneumothorax and thromboembolic complications.

Statistical analysis

The amount of missing data was low for most of the variables (Supplementary eTable 1, http://links.lww.com/EJA/A591). Continuous variables are presented as median [IQR], and categorical variables as numbers and percentages. The PEEP groups were compared using Wilcoxon rank-sum test for continuous variables and Fisher exact tests for categorical variables.

Ventilatory variables and parameters over the first 4 calendar days are presented in line plots. The trend over time of ventilatory variables was assessed with mixed-effect linear models with centre and patients treated as random effects to account for clustering and repeated measurements, and with PEEP strategy, time as a continuous variable, and an interaction of PEEP and time as fixed effect. Overall P values from this analysis represent the overall difference among groups over time and P values from interaction represent a statistical assessment of whether the trend over time differed among the groups. All daily measurements of ventilatory variables, collected every 8 h, were aggregated as the mean per day. To further expand the analyses, the highest and lowest values each day were also compared between the groups using the same strategy. In addition, to compare variables at each day, the collection day was entered as a categorical variable in the model described above, and the P value for the daily difference was extracted using pairwise comparisons after Bonferroni correction.

The primary analysis was based on the unmatched cohort. The PEEP groups were compared for the primary outcome using median differences and 95% confidence intervals (CIs) from a mixed-effect quantile model considering $T = 0.50$ and an asymmetrical Laplace distribution. P values were extracted after 1000 bootstrap samplings. Binary outcomes were compared using mixed-effect logistic regression models and presented as odds ratio and 95% CIs. ICU and hospital length of stay, and 28-day and 90-day mortality, were compared using a (shared-frailty) Cox proportional hazard model and presented as hazard ratio and 95% CIs. The comparison was presented graphically through Kaplan–Meier curves. For the ICU and hospital length of stay analyses, all patients who died prior to discharge were assigned the maximum length of stay to account for death as a competing risk in this model. The proportional hazard assumption was assessed through Schoenfeld residuals. Duration of invasive ventilation was compared through a clustered Fine–Gray competing risk model, with death before extubation treated as a competing risk, and presented as subdistribution hazard ratio and 95% CIs in cumulative incidence plots. All models considered the centre as a random effect.

The secondary analysis was based on the matched cohort. A complete description is described in the Supplementary eMethods, http://links.lww.com/EJA/A591. We used

a covariate-balancing propensity score (CBPS) for matching.[22] The CBPS was estimated for each patient with logistic regression using relevant prognostic variables. The following baseline variables (measured at baseline or within 1 h after intubation) were considered in the matching process: age, sex, BMI, PaO_2/FiO_2, plasma creatinine concentration, hypertension, diabetes, use of angiotensin converting enzyme inhibitors, use of angiotensin II receptor blockers, use of a vasopressor or an inotrope, fluid balance, pH, mean arterial pressure, heart rate and respiratory system compliance. All variables were selected a priori and based on clinical relevance and known association with outcomes in this group of patients.

All analyses were conducted in R v.4.0.2 (R Foundation, Vienna, Austria) and significance level was set at 0.05.

Results
Study population
Thirty-one ICUs were invited to participate in the PRoVENT-COVID study, of which 22 met inclusion criteria. From 1 March to 1 June 2020, 1340 patients were screened. Final follow-up was completed on 1 September 2020. A total of 218 patients were not enrolled, of whom 62 (4.6%) had an alternative diagnosis, and 150 (11.1%) never received invasive ventilation (Supplementary eFigure 2, http://links.lww.com/EJA/A591). An additional 189 patients were excluded, mainly because they had received invasive ventilation in a nonparticipating hospital in the first 4 calendar days of ventilation. Of the enrolled 933 patients, 259 (27.8%) were categorised as higher PEEP patients, and 674 (72.2%) as lower PEEP patients. Of all patients, 468 could be matched, 234 (50%) in the higher PEEP group and 234 (50%) in the lower PEEP group. Details on the matching process are shown in Supplementary eResults and eFigures 3 and 4, http://links.lww.com/EJA/A591.

Figure 1, supplementary eFigure 1, eTable 2 and eFigures 5 to 11, http://links.lww.com/EJA/A591 show group assignment of patients in the unmatched and the matched cohorts, and PEEP and FiO_2. Table 1 shows the baseline characteristics of the PEEP groups in the unmatched and matched cohorts. The main difference between the two PEEP groups in the unmatched cohort was ARDS severity. In the matched cohort, the main difference was the proportion of patients on inhaled steroids at baseline. Ventilation management is detailed in Table 2, Supplementary eTables 3 and 4, and eFigures 12 and 13, http://links.lww.com/EJA/A591. Respiratory system compliance was not different between the higher and lower PEEP groups, neither in the unmatched nor in the matched cohorts (eFigure 14). PaO_2/FiO_2 and plasma creatinine concentration were higher in the higher PEEP group; use of vasopressors, prone positioning, daily urine output and fluid balance were not different

(Supplementary eFigures 15 to 17, http://links.lww.com/EJA/A591).

Outcomes in the unmatched cohort and matched cohort
Outcomes in the matched and unmatched cohorts are summarised in Table 3, Fig. 2 and Supplementary eFigure 18, http://links.lww.com/EJA/A591.

In the unmatched cohort, 28 days after the start of invasive ventilation, patients in the higher PEEP group had a median of 2 [IQR 0 to 15] VFDs compared with 0 [0 to 16] VFDs in the lower PEEP group [median difference 0.21 (95% CI −3.34 to 3.78) days, $P = 0.905$]. Patients in the higher PEEP group needed RRT more often than patients in the lower PEEP group. Mortality rates and other endpoints were not different between the higher and lower PEEP groups.

In the matched cohort, 28 days after the start of invasive ventilation, patients in the higher PEEP group had median of 0 [0 to 14] VFDs days compared with 6 [0 to 17] VFDs in the lower PEEP group [median difference −4.65 (95% CI −8.92 to −0.39) days, $P = 0.032$]. Patients in the higher PEEP group developed AKI and received RRT more often than patients in the lower PEEP group. Mortality rates and other endpoints were not different between the higher and lower PEEP groups in the matched cohort.

Discussion
The findings of this study can be summarised as follows: in an unmatched cohort of COVID-19 ARDS patients, a higher PEEP strategy had no association with the number of VFDs but this strategy was associated with a greater use of RRT; in a matched cohort, a higher PEEP strategy was associated with a lower number of VFDs, more AKI and a greater use of RRT; and neither in the unmatched nor in the matched cohort did use of higher PEEP have an association with mortality.

To our knowledge, this is the first study to investigate associations between early PEEP settings and outcome in COVID-19 ARDS patients using the ARDS Network tables for patient classification. A composite endpoint was chosen as the primary endpoint because it reflects duration of invasive ventilation in surviving patients, but also mortality. The study was designed to minimise bias by strictly adhering to a predefined statistical analysis plan, and there was minimal loss to follow-up. The study involved one-third of all COVID-19 ARDS patients receiving invasive ventilation in the first months of the national outbreak in the Netherlands, and patients were enrolled in 22 university hospitals, nonuniversity teaching and nonteaching hospitals, contributing to its generalisability. In addition, patients were enrolled in the trial over a period of 3 months, during which general care for COVID-19 patients did not change, that is, before

Fig. 1 Group assignment, positive end-expiratory pressure and F_iO_2 in the higher (pink) and lower (green) positive end-expiratory pressure groups, before (left panels) and after (right panels) matching. The figure shows the median, lowest and highest positive end-expiratory pressure and F_iO_2 values. Horizontal bars inside boxes represent medians; box tops and bottoms, interquartile ranges. Whiskers extend to 1.5 times the interquartile range beyond the first and third quartiles per the conventional Tukey method. Circles represent means.
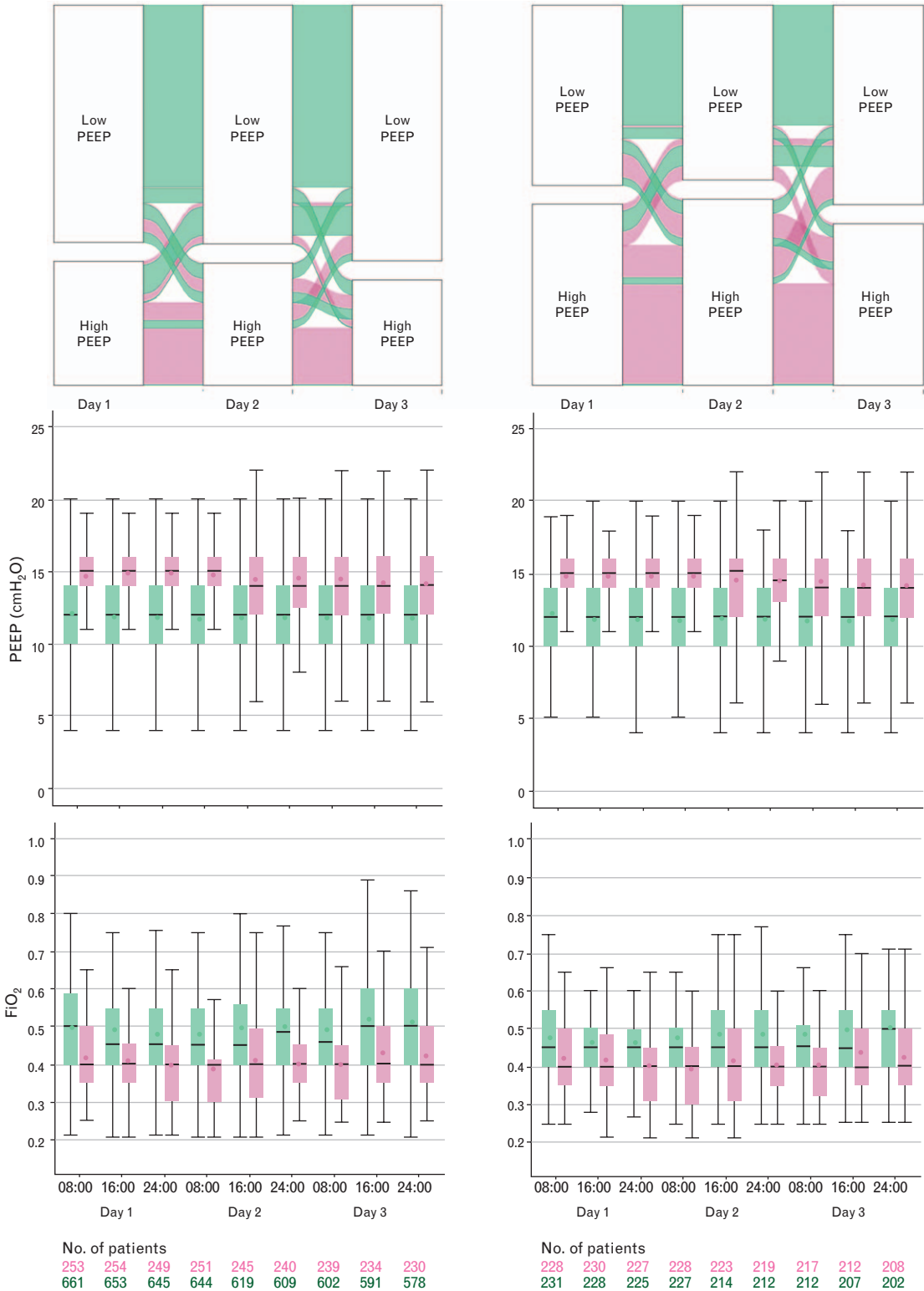
Table 1 Baseline characteristics of the patients before and after matching

	Unmatched cohort (n=933)				Matched cohort (n=468)			
	High PEEP, n=259	Low PEEP, n=674	SMD	P	High PEEP, n=234	Low PEEP, n=234	SMD	P
Age (years)	64.0 [56.0 to 71.0]	66.0 [58.0 to 73.0]	0.201	0.018	65.0 [59.0 to 71.0]	64.0 [55.2 to 71.0]	0.134	0.268
Male sex	192 (74.1)	483 (71.7)	0.056	0.463	175 (74.8)	176 (75.2)	0.010	0.999
BMI (kg m^{-2})	27.8 [25.8 to 31.1]	27.6 [25.2 to 30.7]	0.105	0.327	27.7 [25.4 to 30.4]	28.1 [25.7 to 31.3]	0.105	0.303
Transferred under invasive ventilation	29 (11.2)	59 (8.8)	0.082	0.261	23 (9.8)	22 (9.4)	0.014	0.999
Days between intubation and admission	0 [0 to 0]	0 [0 to 0]	0.047	0.514	0 [0 to 0]	0 [0 to 0]	0.039	0.675
Use of noninvasive ventilation	24/242 (9.9)	52/630 (8.3)	0.058	0.424	23/220 (10.5)	20 (9.3)	0.037	0.749
Duration of noninvasive ventilation (h)	8.0 [5.5 to 14.0]	7.0 [2.0 to 20.0]	0.036	0.976	8.0 [4.4 to 14.0]	5.5 [2.2 to 9.0]	0.135	0.749
Chest CT scan performed	94/253 (37.1)	229/660 (34.7)	0.053	0.486	83/228 (36.4)	82/228 (36.0)	0.009	0.999
Lung parenchyma affected			0.071	0.987			0.266	0.610
0%	3/94 (3.2)	8/229 (3.5)			1/83 (1.2)	5/82 (6.1)		
25%	28/94 (29.8)	75/229 (32.8)			27/83 (32.5)	24/82 (29.3)		
50%	29/94 (30.9)	68/229 (29.7)			24/83 (28.9)	23/82 (28.0)		
75%	28/94 (29.8)	65/229 (28.4)			26/83 (31.3)	25/82 (30.5)		
100%	6/94 (6.4)	13/229 (5.7)			5/83 (6.0)	5/82 (6.1)		
Chest radiograph performed	142/163 (87.1)	384/431 (89.1)	0.054	0.567	132/148 (89.2)	133/149 (89.3)	0.019	0.999
Quadrants affected			0.184	0.306			0.287	0.151
1	13/139 (9.4)	24/384 (6.2)			13/130 (10.0)	5/133 (3.8)		
2	37/139 (26.6)	85/384 (22.1)			35/130 (26.9)	30/133 (22.6)		
3	32/139 (23.0)	110/384 (28.6)			29/130 (22.3)	35/133 (26.3)		
4	57/139 (41.0)	165/384 (43.0)			53/130 (40.8)	63/133 (47.4)		
Severity of ARDS			0.447	<0.001			0.158	0.246
Mild	81/256 (31.6)	103/663 (15.5)			63 (26.9)	52 (22.2)		
Moderate	161/256 (62.9)	469/663 (70.7)			157 (67.1)	160 (68.4)		
Severe	14/256 (5.5)	91/663 (13.7)			14 (6.0)	22 (9.4)		
Co-existing disorders								
Hypertension	86 (33.2)	227 (33.7)	0.010	0.938	77 (32.9)	81 (34.6)	0.036	0.769
Heart failure	8 (3.1)	31 (4.6)	0.079	0.364	8 (3.4)	14 (6.0)	0.121	0.275
Diabetes	56 (21.6)	154 (22.8)	0.030	0.727	54 (23.1)	51 (21.8)	0.031	0.825
Chronic kidney disease	14 (5.4)	28 (4.2)	0.059	0.480	11 (4.7)	10 (4.3)	0.021	0.999
Baseline creatinine^a (μmol l^{-1})	78 [65.0 to 98.8]	77.0 [63.0 to 96.0]	0.025	0.305	80.0 [67.0 to 99.0]	77.0 [66.0 to 94.8]	0.052	0.337
Liver cirrhosis	1 (0.4)	2 (0.3)	0.015	0.999	1 (0.4)	1 (0.4)	<0.001	0.999
Chronic obstructive pulmonary disease	13 (5.0)	63 (9.3)	0.168	0.032	12 (5.1)	23 (9.8)	0.179	0.078
Active haematological neoplasia	5 (1.9)	10 (1.5)	0.034	0.574	5 (2.1)	5 (2.1)	<0.001	0.999
Active solid neoplasia	8 (3.1)	16 (2.4)	0.044	0.498	8 (3.4)	5 (2.1)	0.078	0.576
Neuromuscular disease	4 (1.5)	4 (0.6)	0.093	0.228	4 (1.7)	3 (1.3)	0.035	0.999
Immunosuppression	7 (2.7)	16 (2.4)	0.021	0.814	7 (3.0)	8 (3.4)	0.024	0.999
Previous medication								
Systemic steroids	13 (5.0)	23 (3.4)	0.080	0.258	12 (5.1)	7 (3.0)	0.108	0.349
Inhalation steroids	22 (8.5)	88 (13.1)	0.148	0.054	18 (7.7)	38 (16.2)	0.266	0.006
Angiotensin converting enzyme inhibitor	49 (18.9)	112 (16.6)	0.060	0.439	44 (18.8)	52 (22.2)	0.085	0.423
Angiotensin II receptor blocker	26 (10.0)	78 (11.6)	0.049	0.562	25 (10.7)	19 (8.1)	0.088	0.429
Beta-blockers	34 (13.1)	145 (21.5)	0.223	0.004	30 (12.8)	46 (19.7)	0.186	0.060
Insulin	15 (5.8)	50 (7.4)	0.066	0.473	14 (6.0)	18 (7.7)	0.068	0.583
Metformin	44 (17.0)	105 (15.6)	0.038	0.618	42 (17.9)	35 (15.0)	0.081	0.455
Statins	67 (25.9)	217 (32.2)	0.140	0.068	61 (26.1)	81 (34.6)	0.187	0.056
Calcium channel blockers	50 (19.3)	118 (17.5)	0.046	0.568	47 (20.1)	40 (17.1)	0.077	0.476
Vital signs								
Heart rate (bpm)	82.5 [72.0 to 95.5]	84.5 [75.0 to 98.0]	0.130	0.215	83.0 [72.0 to 96.0]	83.4 [70.5 to 98.6]	0.025	0.820
Mean arterial pressure (mmHg)	79.5 [73.7 to 86.2]	81.0 [73.5 to 88.5]	0.061	0.740	79.9 [74.2 to 86.1]	79.9 [73.0 to 87.5]	0.062	0.317
Organ support								
Continuous sedation	249 (96.1)	646 (96.1)	<0.001	0.457	225 (96.2)	224 (96.1)	0.001	0.544
Inotropic or vasopressor	206 (79.5)	526 (78.3)	0.031	0.488	189 (80.8)	188 (80.7)	0.002	0.872
Vasopressor	206 (79.5)	525 (78.1)	0.035	0.507	189 (80.8)	187 (80.3)	0.013	0.870
Inotropic	6 (2.3)	33 (4.9)	0.139	0.724	6 (2.6)	16 (6.9)	0.204	0.884
Fluid balance (ml)	584.0 [22.0 to 1227.0]	648.0 [41.5 to 1492.0]	0.105	0.623	605.0 [9.6 to 1298.0]	635.0 [30.0 to 1428.5]	0.091	0.320
Urine output (ml)	720.0 [362.5 to 1125.0]	710.0 [383.8 to 1165.0]	0.053	0.836	720.0 [362.5 to 1107.5]	700.0 [400.0 to 1190.0]	0.070	0.997

Data are median [IQR] or number (%). Percentages may not total 100 because of rounding. CT, computed tomography; PEEP, positive end-expiratory pressure; SMD, standardised mean difference. ^{a}Most recent measurement in 24 h before intubation, or at ICU admission under invasive ventilation.

Table 2   Ventilatory variables and rescue therapy at start of ventilation before and after matching

| | Unmatched cohort, *n*=933 | | | | Matched cohort, *n*=468 | | | |
	High PEEP, *n*=259	Low PEEP, *n*=674	SMD	*P**	High PEEP, *n*=234	Low PEEP, *n*=234	SMD	*P**
Ventilation support								
Assisted ventilation	84/257 (32.7)	185/671 (27.6)	0.112	0.092	77/232 (33.2)	61/233 (26.2)	0.154	0.265
Tidal volume (ml kg^{-1} PBW)	6.4 [5.9 to 7.1]	6.5 [5.9 to 7.0]	0.043	0.296	6.4 [5.9 to 7.1]	6.4 [5.9 to 7.0]	0.028	0.642
PEEP (cmH$_2$O)	14.2 [13.0 to 16.0]	12.0 [10.0 to 14.0]	0.911	<0.001	14.3 [13.0 to 16.0]	12.0 [10.1 to 14.0]	0.927	<0.001
Peak pressure (cmH$_2$O)	28.0 [25.5 to 30.5]	26.0 [23.0 to 29.3]	0.391	<0.001	28.0 [25.5 to 30.5]	26.3 [23.0 to 29.5]	0.346	0.007
Driving pressure (cmH$_2$O)	13.8 [12.0 to 15.7]	14.0 [11.9 to 16.2]	0.130	0.180	13.7 [11.8 to 15.5]	14.2 [11.5 to 16.7]	0.158	0.425
Mechanical power (J min^{-1})	19.4 [16.4 to 23.8]	18.0 [14.8 to 21.5]	0.294	0.009	19.4 [16.4 to 23.9]	18.2 [15.0 to 21.4]	0.267	0.061
Compliance (ml cmH$_2$O^{-1})	33.5 [27.5 to 39.5]	33.1 [26.5 to 41.1]	0.037	0.807	33.7 [28.5 to 40.1]	33.8 [26.1 to 42.2]	0.007	0.924
Total respiratory rate (min^{-1})	21.7 [19.7 to 24.0]	21.5 [19.1 to 24.0]	0.027	0.835	21.7 [19.8 to 24.0]	21.5 [19.0 to 24.0]	0.087	0.480
FiO_2	0.52 [0.45 to 0.63]	0.60 [0.50 to 0.70]	0.385	<0.001	0.53 [0.45 to 0.65]	0.57 [0.48 to 0.68]	0.163	0.079
etCO$_2$ (kPa)	4.9 [4.4 to 5.6]	4.9 [4.3 to 5.5]	0.086	0.799	4.9 [4.4 to 5.6]	4.9 [4.3 to 5.5]	0.067	0.662
Fractional dead space, Enghoff	0.14 [0.07 to 0.23]	0.19 [0.10 to 0.29]	0.424	<0.001	0.15 [0.08 to 0.24]	0.18 [0.09 to 0.26]	0.225	0.063
Laboratory tests								
pH	7.37 [7.32 to 7.41]	7.36 [7.30 to 7.40]	0.195	0.046	7.37 [7.32 to 7.40]	7.37 [7.32 to 7.41]	0.084	0.115
PaO_2 (kPa)	11.5 [10.0 to 13.5]	10.7 [9.6 to 12.5]	0.267	<0.001	11.4 [9.9 to 13.1]	11.0 [9.7 to 13.1]	0.035	0.311
PaO_2/FiO_2	19.0 [14.2 to 25.7]	16.9 [12.7 to 22.3]	0.193	<0.001	17.9 [14.0 to 23.9]	18.2 [14.2 to 24.8]	0.083	0.587
$PaCO_2$ (kPa)	5.7 [4.9 to 6.3]	6.0 [5.3 to 6.7]	0.319	0.004	5.8 [5.1 to 6.4]	5.8 [5.2 to 6.4]	0.060	0.730
Lactate (mmol l^{-1})	1.1 [0.9 to 1.4]	1.2 [0.9 to 1.5]	0.151	0.073	1.1 [0.9 to 1.4]	1.2 [1.0 to 1.4]	0.150	0.132
Creatinine (μmol l^{-1})	74.0 [62.8 to 93.5]	74.0 [61.0 to 97.0]	0.013	0.961	76.0 [64.0 to 96.2]	74.0 [63.0 to 95.2]	0.070	0.658
Rescue therapy								
Prone positioning	58 (22.9)	231 (34.8)	0.265	0.048	55 (24.0)	75 (32.8)	0.195	0.175
Duration (h^a)	8.0 [5.0 to 12.0]	8.0 [4.0 to 14.0]	0.169	0.739	8.0 [6.0 to 12.0]	9.0 [4.0 to 14.0]	0.143	0.651
Recruitment manoeuvre	5 (2.6)	15 (2.7)	0.007	0.964	5 (2.9)	5 (2.6)	0.018	0.903
ECMO	0 (0.0)	0 (0.0)	<0.001	0.999	0 (0.0)	0 (0.0)	<0.001	0.999
Use of NMBA	77 (30.0)	175 (26.0)	0.088	0.111	75 (32.2)	59 (25.2)	0.155	0.052
Hours of use^a	0.0 [0.0 to 8.0]	0.0 [0.0 to 8.0]	0.046	0.241	0.0 [0.0 to 8.0]	0.0 [0.0 to 6.0]	0.085	0.101

Data are median [IQR] or number (%). Percentages may not total 100 because of rounding. ECMO, extracorporeal membrane oxygenation; NMBA, neuromuscular blocking agent; PBW, predicted body weight; PEEP, positive end-expiratory pressure; SMD, standardised mean difference. ^{a} In patients who received it. * Calculated using pairwise contrasts in a mixed-effect generalised linear model with day, group and an interaction day group as fixed effect, and with patients and centre as random effect. A binomial distribution was used for binary variables and a Gaussian distribution for continuous.

treatment with dexamethasone became standard practice. As such, the findings of this study extend our understanding of the effects of higher PEEP in ARDS patients in general,[2–5] and in COVID-19 ARDS in particular.

The, at times, extreme hypoxaemia may have triggered the use of higher PEEP in COVID-19 ARDS patients. Early in the global pandemic, it was presumed that there could be two phenotypes of COVID-19 ARDS, with different pulmonary compliances and shunt fractions, and also dissimilarities in recruitability. However, in the current cohort, respiratory system compliance was consistently low,[20] in line with the findings in other studies.[7,23,24] Furthermore, it has been shown that recruitment manoeuvres neither reduced shunt fraction nor increased systemic oxygenation.[25] Of note, PEEP in the lower PEEP group in our study was higher than that in one large observational study in patients with ARDS from another origin,[26] and also higher than in various studies in patients with ARDS related to COVID-19.[7,23,24,27] By now, this preference for higher PEEP may have waned for two reasons; healthcare providers may have realised increasingly that higher PEEP may not improve oxygenation, at least not in all patients, and that other measures such as prone positioning are more effective in achieving this goal. Also, it may be that healthcare

providers increasingly accept lower oxygen levels, realising that any attempt to 'normalise' physiology as much as possible could come at the cost of harm. One recent report even suggests that higher PEEP should be avoided, limiting PEEP strictly to values necessary to maintain sufficient oxygenation.[28] Prospective interventional studies remain needed to determine the best PEEP strategy in COVID-19 ARDS.

Invasive ventilation with higher PEEP was associated with higher incidences of AKI and use of RRT. In critically ill patients, invasive ventilation is associated with an increased risk of AKI, but it is uncertain if the amount of PEEP modifies this risk.[29] Higher PEEP may affect kidney function by reducing renal perfusion or increasing venous congestion through its effects on the heart.[30] The need for RRT for AKI increases workload and costs[31] and is associated with worse outcomes.[32] In addition, in COVID-19 patients, efficient RRT is hampered by the high occurrence of circuit thrombosis,[33–36] leading to long down-times. Last but not least, due to the overwhelming numbers of COVID-19 patients and the frequent need for replacement of clotted circuits, many ICUs could quickly run out of the medical supplies needed for this therapy.

All models considered the centres as a random effect to account for the clustering of the patients within centres.

Table 3 Clinical outcomes according to groups before and after matching

	Unmatched cohort, n=933				Matched cohort, n=468			
	High PEEP, n=259	Low PEEP, n=674	Effect estimate (95% CI)	P	High PEEP, n=234	Low PEEP, n=234	Effect estimate (95% CI)	P
Primary outcome								
Ventilator-free days at day 28 (days)	2.0 [0.0 to 15.0]	0.0 [0.0 to 16.0]	0.21 (−3.34 to 3.78)[a]	0.905	0.0 [0.0 to 14.0]	6.0 [0.0 to 17.0]	−4.65 (−8.92 to −0.39)[a]	0.032
Mean ± SD	7.5 ± 8.7	7.6 ± 8.8			6.9 ± 8.5	8.5 ± 8.8		
Secondary outcomes								
Duration of ventilation (days)	14.5 [7.0 to 24.0]	13.0 [8.0 to 22.3]	1.03 (0.75 to 1.42)[b]	0.850	15.0 [7.0 to 25.0]	13.0 [9.0 to 22.0]	0.79 (0.58 to 1.09)[b]	0.150
In survivors at day 28 (days)	17.0 [9.0 to 27.8]	15.0 [9.0 to 28.0]			18.0 [10.0 to 29.0]	14.0 [9.0 to 24.5]		
Tracheostomy	42/257 (16.3)	105 (15.6)	0.95 (0.61 to 1.48)[c]	0.830	39/233 (16.7)	34 (14.5)	0.80 (0.44 to 1.48)[c]	0.486
Reintubation	29/256 (11.3)	88/671 (13.1)	0.90 (0.56 to 1.45)[c]	0.673	26/232 (11.2)	30/232 (12.9)	0.87 (0.48 to 1.57)[c]	0.646
Pneumothorax	4/252 (1.6)	3/643 (0.5)	3.97 (0.76 to 20.70)[c]	0.102	4/228 (1.8)	1/225 (0.4)	4.02 (0.35 to 46.51)[c]	0.265
Thromboembolic complications	72 (27.8)	202 (30.0)	0.80 (0.57 to 1.15)[c]	0.227	68 (29.1)	72 (30.8)	0.87 (0.56 to 1.36)[c]	0.544
Pulmonary embolism	55 (21.2)	155 (23.0)	0.81 (0.54 to 1.19)[c]	0.281	53 (22.6)	56 (23.9)	0.89 (0.54 to 1.46)[c]	0.643
Deep vein thrombosis	9 (3.5)	41 (6.1)	0.77 (0.32 to 1.84)[c]	0.559	9 (3.8)	19 (8.1)	0.54 (0.21 to 1.39)[c]	0.201
Ischaemic stroke	9 (3.5)	21 (3.1)	1.33 (0.56 to 3.17)[c]	0.519	8 (3.4)	3 (1.3)	2.99 (0.73 to 12.26)[c]	0.128
Myocardial infarction	3 (1.2)	13 (1.9)	0.61 (0.17 to 2.26)[c]	0.460	2 (0.9)	4 (1.7)	0.50 (0.09 to 2.73)[c]	0.420
Systemic arterial embolism	0 (0.0)	4 (0.6)	–	–	0 (0.0)	1 (0.4)	–	–
Acute kidney injury	134/257 (52.1)	303/672 (45.1)	1.36 (0.99 to 1.86)[c]	0.056	129/232 (55.6)	107/233 (45.9)	1.49 (1.02 to 2.18)[c]	0.039
Need for RRT	62 (23.9)	113 (16.8)	1.54 (1.05 to 2.27)[c]	0.027	60 (25.6)	42 (17.9)	1.58 (1.01 to 2.46)[c]	0.045
Need of rescue therapy[d]	188/258 (72.9)	526/670 (78.5)	0.86 (0.59 to 1.26)[c]	0.444	175/233 (75.1)	183/232 (78.9)	0.83 (0.51 to 1.35)[c]	0.450
Prone positioning	129/257 (50.2)	426/670 (63.6)	0.66 (0.46 to 0.94)[c]	0.023	121/232 (52.2)	141/233 (60.5)	0.71 (0.44 to 1.12)[c]	0.142
Recruitment manoeuvre	16/196 (8.2)	40/575 (7.0)	1.22 (0.60 to 2.5)[c]	0.588	15/175 (8.6)	13/202 (6.4)	1.45 (0.59 to 3.61)[c]	0.420
Use of NMBA	125 (48.3)	337 (50.0)	0.98 (0.70 to 1.39)[c]	0.931	116 (49.6)	124 (53.0)	0.95 (0.61 to 1.48)[c]	0.825
ECMO	1/258 (0.4)	7 (1.1)	0.37 (0.04 to 2.99)[c]	0.348	1/233 (0.4)	3/229 (1.3)	0.32 (0.03 to 3.14)[c]	0.332
Use of continuous sedation[d]	259 (100.0)	669 (99.3)	–	–	234 (100.0)	233 (99.6)	–	–
Use of inotrope or vasopressor[d]	250 (96.5)	640 (95.0)	1.40 (0.64 to 3.07)[c]	0.402	227 (97.0)	222 (94.9)	1.78 (0.67 to 4.74)[c]	0.250
Use of vasopressor	250 (96.5)	639 (94.8)	1.46 (0.67 to 3.17)[c]	0.342	227 (97.0)	221 (94.4)	1.91 (0.75 to 4.87)[c]	0.177
Use of inotrope	12 (4.6)	84 (12.5)	0.59 (0.28 to 1.27)[c]	0.177	11 (4.7)	33 (14.1)	0.65 (0.26 to 1.65)[c]	0.369
ICU length of stay (days)	16.0 [9.0 to 27.0]	15.0 [9.0 to 26.0]	1.15 (0.95 to 1.40)[e]	0.140	16.0 [9.0 to 28.0]	15.0 [10.0 to 25.0]	0.86 (0.68 to 1.09)[e]	0.230
In survivors (days)	19.5 [11.8 to 30.3]	18.0 [11.0 to 30.8]			20.0 [12.0 to 31.8]	16.0 [11.0 to 29.0]		
Hospital length of stay (days)	24.0 [13.0 to 39.0]	23.0 [15.0 to 37.0]	1.14 (0.93 to 1.40)[e]	0.190	23.5 [13.0 to 40.0]	24.5 [17.0 to 36.0]	0.88 (0.69 to 1.13)[e]	0.310
In survivors (days)	31.0 [20.0 to 47.0]	30.0 [21.0 to 45.0]			32.0 [20.0 to 48.0]	28.0 [21.0 to 41.3]		
ICU mortality	77/254 (30.3)	239/664 (36.0)	0.75 (0.53 to 1.05)[c]	0.097	77/231 (33.3)	69/232 (29.7)	1.24 (0.80 to 1.91)[c]	0.332
Hospital mortality	79/242 (32.6)	246/647 (38.0)	0.76 (0.54 to 1.08)[c]	0.124	79/223 (35.4)	74/226 (32.7)	1.18 (0.77 to 1.82)[c]	0.451
28-Day mortality	71/255 (27.8)	216/668 (32.3)	0.85 (0.63 to 1.14)[e]	0.270	71/230 (30.9)	63/233 (27.0)	1.30 (0.90 to 1.88)[e]	0.170
90-Day mortality	79/242 (32.6)	259/625 (41.4)	0.77 (0.58 to 1.02)[e]	0.067	79/230 (35.9)	78/214 (36.4)	1.15 (0.81 to 1.64)[e]	0.430

Data are median [IQR], mean ± SD or number (%). Percentages may not total 100 because of rounding. CI, confidence interval; ECMO, extracorporeal membrane oxygenation; NMBA, neuromuscular blocking agent; PEEP, positive end-expiratory pressure; RRT, renal replacement therapy. [a] Median difference from a mixed-effect quantile model considering a $T = 0.50$ and an asymmetric Laplace distribution. P values were extracted after 1000 bootstrap samplings. [b] Subdistribution hazard ratio from a clustered Fine–Gray competing risk model, with death before extubation treated as competing risk. [c] Odds ratio from mixed-effect logistic regression models. [d] Assessed in the first 4 days of ventilation. [e] Hazard ratio from a (shared-frailty) Cox proportional hazard model. For the ICU and hospital length of stay analyses, all patients who died prior to discharge were assigned the maximum length of stay to account for death as a competing risk in this model. P value for Schoenfeld residuals: ICU length of stay ($P = 0.420$ in the unmatched cohort and $P = 0.330$ for the matched cohort); hospital length of stay ($P = 0.830$ in the unmatched cohort and $P = 0.770$ for the matched cohort); 7-day mortality ($P = 0.380$ in the unmatched cohort and $P = 0.780$ in the matched cohort); 28-day mortality ($P = 0.260$ in the unmatched cohort and $P = 0.110$ in the matched cohort); 90-day mortality ($P = 0.100$ in the unmatched cohort and $P = 0.055$ in the matched cohort).

Fig. 2 Mortality and pattern of extubation in the higher (pink) and lower (green) positive end-expiratory pressure groups, before (left panels) and after (right panels) matching. HR, hazard ratio.
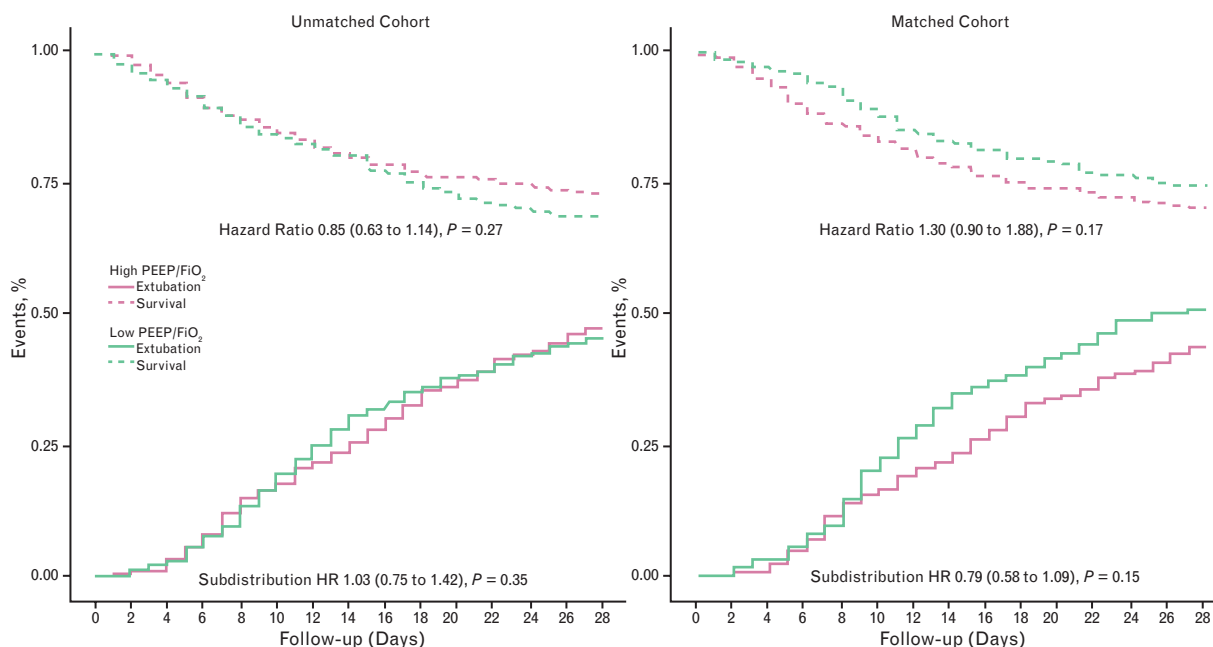
It was not our plan to compare PEEP level across centres or the reason why centres were not included as a fixed effect. While differences in PaO_2/FiO_2 between the groups in the matched cohort may suggest differences in disease severity, matching was also based on Sequential Organ Failure Assessment and Acute Physiology and Chronic Health Evaluation-II or IV scores, making it very unlikely that patients in the higher PEEP group were sicker than patients in the lower PEEP group. Of note, the standardised mean difference was higher than 10% for some variables, but if stricter calipers were used, the groups became too small to provide meaningful analysis. While in the unmatched cohort there was no difference in steroid use at baseline, after matching there was a difference in use of inhalational steroids between the two PEEP groups.

The PROVENT-COVID study had limitations. We did not collect data regarding the degree to which local protocols for prone positioning and lung recruitment were in place, or whether other treatments, such as antiviral or antimalarial treatments, were used. However, none of the randomised clinical trials of these treatments showed an effect on the two components of the primary outcome used in the current study. We also did not collect reasons for changes in PEEP settings, which could have been based on changes of PaO_2 or SpO_2, responses to therapies such as prone positioning, or haemodynamic side effects such as hypotension. Recruitment manoeuvres were used infrequently, but

it is possible that this was reported incompletely in the patient records, and therefore could not be captured in retrospect. Ventilation variables and adjunctive treatments data were collected for the first 4 calendar days of invasive ventilation, to keep the workload of the study acceptable. We cannot exclude, however, that ventilation practices and use of adjunctive treatments beyond day 4 also have an impact on outcome. It is not implausible that concerns about aerosol formation and spreading, for example, with use of NIV, influenced decisions on extubation. If this happened, however, it probably affected duration of invasive ventilation in both groups but it does hamper generalisation to cohorts of ARDS patients in which there is less concern about the risk of infection of personnel. Because it is common practice to extubate at lower PEEP, use of higher PEEP at least in theory could also delay weaning, thus reducing the number of VFDs. Finally, due to the observational nature of the study, no causal relationship can be determined and the findings should be seen only as exploratory and can only provide the statistical underpinning and rationale for further investigations.

In conclusion, in COVID-19 ARDS patients, a higher PEEP strategy may reduce the number of VFDs and increase the incidences of AKI and use of RRT. A randomised clinical trial in patients with COVID-19 ARDS is needed to better define the effects of a higher PEEP strategy versus a lower PEEP strategy on outcomes.

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