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High PEEP/low FiO_2 ventilation is associated with lower mortality in COVID–19

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ABSTRACT

Rationale: The positive end–expiratory pressure (PEEP) strategy in patients with coronavirus 2019 (COVID–19) acute respiratory distress syndrome (ARDS) remains debated. Most studies originate from the initial waves of the pandemic. Here we aimed to assess the impact of high PEEP/low FiO_2 ventilation on outcomes during the second wave in the Netherlands.
Methods: Retrospective observational study of invasively ventilated COVID–19 patients during the second wave. Patients were categorized based on whether they received high PEEP or low PEEP ventilation according to the ARDS Network tables. The primary outcome was ICU mortality, and secondary outcomes included hospital and 90–day mortality, duration of ventilation and length of stay, and the occurrence of kidney injury. Propensity matching was performed to correct for factors with a known relationship to ICU mortality.
Results: This analysis included 790 COVID–ARDS patients. At ICU discharge, 32 (22.5%) out of 142 high PEEP patients and 254 (39.2%) out of 848 low PEEP patients had died (HR 0.66 [0.46–0.96]; $P = 0.03$). High PEEP was linked to improved secondary outcomes. Matched analysis did not change findings.
Conclusions: High PEEP ventilation was associated with improved ICU survival in patients with COVID–ARDS.

1. Introduction

Ventilation using high positive end–expiratory pressure (PEEP) can recruit atelectatic lung tissue, improving oxygenation through a reduction in ventilation–perfusion mismatch [1-3]. However, high PEEP ventilation may also lead to ventilator–induced lung injury by

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[1] PRoVAcT–COVID, 'PRactice of Ventilation and Adjunctive Therapies in ICU patients with COVID–19' a complete list of the PRoVAcT–COVID investigators is provided on page 8

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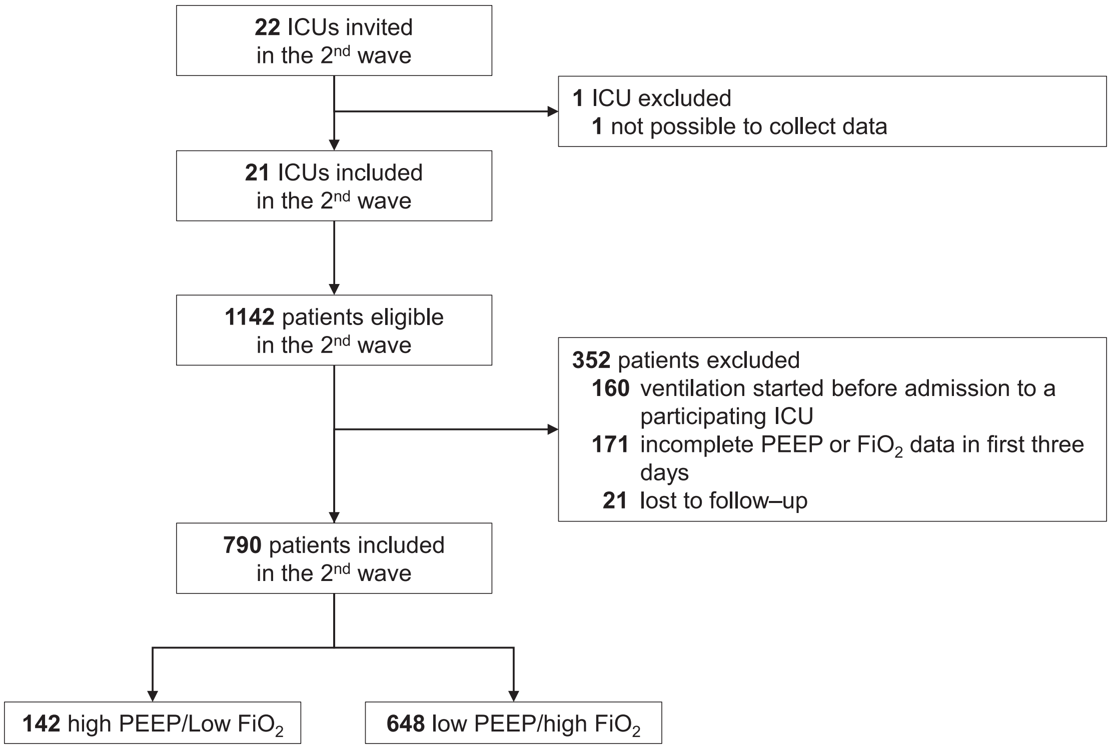

Fig. 1. Patient flow.
Abbreviations: ICU, intensive care unit; PEEP, positive end–expiratory pressure; FiO_2, fraction of inspired oxygen.

overdistending other lung areas [4,5]. The evidence regarding the outcome benefits of high PEEP ventilation in acute respiratory distress syndrome (ARDS) patients is conflicting, with previous studies showing conflicting results [6-9].

Research on patients with coronavirus 2019 (COVID–19) related ARDS demonstrated no outcome benefit of ventilation using high PEEP [10,11]. Three studies even indicated harm, with high PEEP ventilation worsening systemic circulation [10,12] and increasing the incidence of acute kidney failure [10,13]. It is crucial to consider that these studies were conducted during the initial waves of the pandemic, where the immediate response to severe hypoxemia involved prompt intubation and often high PEEP ventilation to improve oxygenation [10,14,15].

We analyzed data from a national database, named 'PRactice of Ventilation and Adjunctive Therapies in COVID–19 patients' (PRoVAcT–COVID)', to assess the impact of high PEEP ventilation on outcomes during the second wave of the national outbreak in the Netherlands. Notably, the care for hypoxemic COVID–19 patients evolved from the first to the second wave, with an emphasis on high–-flow oxygen (HFNO) therapy [16,17] awake prone positioning [18], and less use of high PEEP ventilation in these patients [14]. We hypothesized that low PEEP/high FiO_2 ventilation would be beneficial in patients admitted in the second wave. Propensity score matching was employed to account for factors known to influence outcomes.

2. Methods

2.1. Study design, ethical approval and patient selection

The PRoVAcT–COVID database comprises individual patient data from the second wave of the national COVID–19 outbreak, spanning from October 1 to December 31, 2020. This database integrates data from the PRoVENT–COVID study and PRoAcT–COVID study, registered on clinicaltrials.gov (study identifiers NCT04346342 and NCT04719182, respectively), and has been expanded and enhanced. Previous analyses have been conducted on the individual datasets. Approval for PRoVAcT–COVID was granted by the Institutional Review Board of the Amsterdam University Medical Centers, location 'AMC' (W20_157 #20.171 and W20_526 #20.583, respectively), which waived the requirement for individual patient informed consent. PRoVAcT–COVID is registered on clinicaltrials.gov (study identifier NCT05954351).

Patients eligible for this analysis met the following criteria: (1) receiving invasive ventilation; (2) experiencing acute hypoxemic respiratory failure; (3) attributable to COVID–19; and (4) admitted during the second wave of the national outbreak. Patients admitted under invasive ventilation from a non–participating ICU were excluded, since these patients could not be classified according to PEEP and FiO_2 from start of ventilation. For the same reason, we excluded patients with incomplete datasets regarding PEEP or FiO_2. We also excluded patients that were lost to follow–up for the primary endpoint.

2.2. Collected data

Patient demographics and baseline characteristics were collected at baseline, including age, sex, body height and weight, presence of pregnancy, medical history of diabetes, hypertension, heart failure, chronic kidney disease, chronic obstructive pulmonary disorder (COPD), active malignancy, and immunosuppression, use of angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers at home; and the administration of glucocorticosteroids and monoclonal antibodies (including tocilizumab) in hospital before admission to the ICU. Ventilator settings and ventilation variables and parameters were collected daily from intubation up to day 7, including mode of ventilation, tidal volume (V_T) and set and measured respiratory rate (RR), PEEP and maximum airway pressure (Pmax), and FiO_2, were all collected at a fixed time point per day, i.e., within one hour after intubation on the day of intubation day and closest to 08:00 AM on each calendar day of ventilation. Vital parameters were collected daily from intubation up to day 7, including heart rate, mean arterial pressure (MAP), cumulative fluid balance and plasma creatinine levels, measures of gas exchange

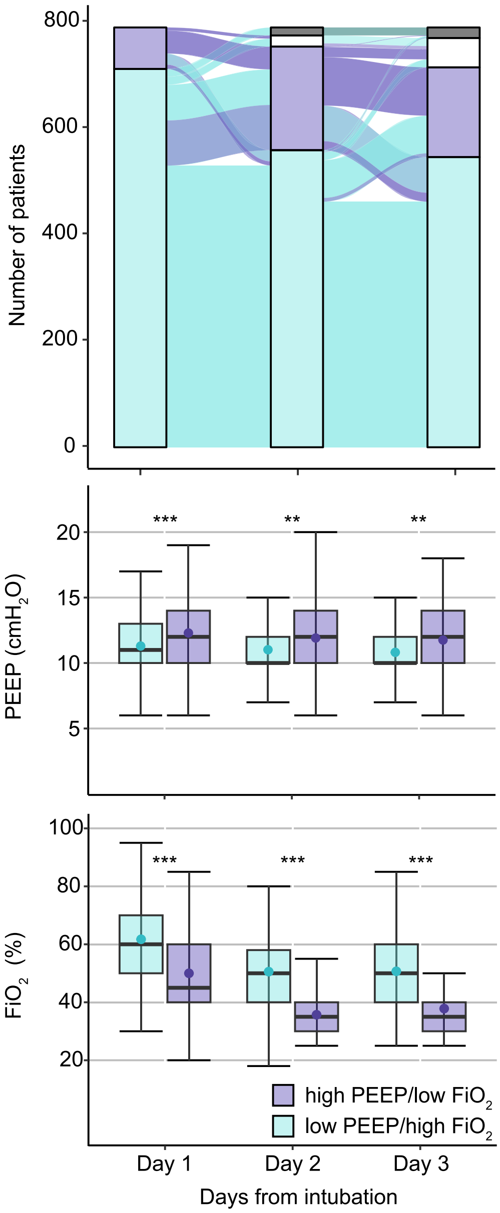

Fig. 2. Group assignment for the initial 3 days of ventilation according to the PEEP/FiO_2 ARDS Network tables.
(Top panel) patient flow of PEEP groups, bars representing daily classification, flow color total classification, extubation shown in white and death in black; (middle panel) lines represent the mean, dots the median, box the interquartile ranges and whiskers the 95% confidence interval for PEEP in the two groups; (lower panel) lines represent the mean, dots the median, box the interquartile ranges and whiskers the 95% confidence interval for FiO_2 in the two groups.
Abbreviations: PEEP, positive end–expiratory pressure; FiO_2, fraction of inspired oxygen. * *P* value ≤0.05; ** *P* value ≤0.01; *** *P* value ≤0.001.

including arterial pH, arterial partial pressure of oxygen (PaO_2), and arterial partial pressure of carbon dioxide ($PaCO_2$), use of continuous or intermittent infusion of neuromuscular blocking agents (NMBA), and use of vasopressors or inotropes. Sequential Organ Failure Assessment (SOFA) score were calculated. During follow–up thromboembolic events, air leaks including pneumothorax, pneumomediastinum or subcutaneous emphysema on chest imaging, tracheostomy, date of liberation from mechanical ventilation, date of last day in the ICU and in hospital, occurrence of acute kidney injury, and life status at ICU and hospital discharge, and at day 28 and 90 were recorded.

Table 1
Baseline characteristics.

	High PEEP/low FiO_2 (N = 142)	**Low PEEP/high FiO_2 (N = 648)**	***P* value**
Age (years)	64.5 [55–71]	67 [60–73]	0.001
Sex(male)	104 (73.2)	461 (71.1)	0.69
Height (cm)	175 [166–180]	174 [168–180]	0.58
Weight (kg)	88 [79–102]	86 [77–99]	0.12
BMI (kg/m^2)	29.5 [26–34]	29 [26–32]	0.08
SOFA score	7 [5–8]	7 [6–9]	0.09
Heart rate	79 [67–98]	82 [67–99]	0.56
Mean arterial pressure	83 [72–93]	81 [71–93]	0.82
Arterial pH	7.37 [7.34–7.44]	7.37 [7.31–7.43]	0.25
PaO_2 (kPa)	10.5 [8.9–13.2]	10.0 [8.5–11.5]	0.01
$PaCO_2$ (kPa)	5.4 [4.8–6.6]	5.6 [4.8–6.4]	0.85
Cumulative fluid balance (+/− mL)	+72 [−290 – +982]	+350 [−226 – +1072]	0.08
Pregnancy	3 (2.11)	0 (0)	1.00
Medical history			
Diabetes	49 (34.5)	193 (29.8)	0.32
Hypertension	50 (35.2)	228 (35.2)	1.00
Heart failure	4 (2.8)	32 (4.9)	0.38
Chronic kidney disease	13 (9.2)	49 (7.6)	0.64
Baseline creatinine (μmol/L)	73 [59–104]	77 [62–106]	0.17
COPD	13 (9.2)	66 (10.2)	0.83
Active hematological malignancy	5 (3.5)	38 (5.9)	0.36
Active solid tumor malignancy	2 (1.4)	13 (2.0)	0.89
Immunosuppression	0 (0.0)	22 (3.4)	0.05
Home medication			
ACE inhibitors	23 (16.2)	111 (17.1)	0.89
Angiotensin receptor blocker	28 (19.7)	90 (13.9)	0.10
Covid–19 therapies			
Systemic glucocorticosteroids	60 (54.1)	309 (56.2)	0.76
Monoclonal antibodies including tociluzimab	5 (4.5)	21 (3.8)	0.94

Data are median [IQR] or number (N (%)). Percentages may not total 100 because of rounding. Abbreviations: PEEP, positive end–expiratory pressure; FiO_2, fraction of inspired oxygen; BMI, body mass index; SOFA, sequential organ failure score; PaO_2, partial pressure of oxygen; $PaCO_2$, partial pressure of carbon dioxide; COPD, chronic obstructive pulmonary disease; ACE, angiotensin–converting enzyme; All baseline variables represent measurements closest to 1 h after intubation.

2.3. Group assignment

Following the methodology employed in a prior study on COVID–ARDS patients undergoing invasive ventilation [10], patients were categorized based on their PEEP and FiO_2 settings during the initial 3 full calendar days of invasive ventilation; a patient was classified according to the high or low PEEP/FiO_2 ARDS Network table for each calendar day; the strategy most frequently employed in these 3 days was used to categorize the patient as ventilated according to the high PEEP/low FiO_2 ARDS Network table (**Supplementary Methods**), subsequently referred to in text as 'high PEEP' patients, or according to the low PEEP/high FiO_2 ARDS Network table, hereafter denoted in text as 'low PEEP' patients.

2.4. Study endpoints

The primary endpoint was ICU mortality. Secondary endpoints included mortality in hospital and at day 28 and 90; duration of ventilation in survivors and non–survivors and the number of days free from the ventilator and alive at day 28 (VFD–28); duration of stay in ICU and hospital; occurrence of acute kidney injury; occurrence of tracheostomy;

Table 2
Baseline ventilatory characteristics.

	High PEEP/low FiO_2 (N = 142)	Low PEEP/high FiO_2 (N = 648)	*P* value
Ventilatory modes			0.08
PCV	76 (53.5)	295 (45.5)	
VCV	16 (11.3)	68 (10.5)	
PSV	35 (24.6)	236 (36.4)	
Automated	10 (7.0)	37 (5.7)	
Other	5 (3.5)	12 (1.9)	
Calculated modes			
Passively ventilated	58 (54.7)	293 (55.2)	1.00
Settings and parameters			
V_T (ml/kg PBW)	6.4 [5.8–7.6]	6.6 [5.9–7.4]	0.45
RR (breaths/min)	22 [19–26]	21 [18–25]	0.42
Pmax (cmH_2O)	26 [22–29]	26 [23−30]	0.33
PEEP (cmH_2O)	12 [10–14]	12 [10–12]	<0.001
FiO_2 (%)	55 [40–70]	70 [55–80]	<0.001
et–CO_2 (mmHg)	32 [28–39]	33 [28–38]	0.84
ΔP (cmH_2O)	14 [12–16]	15 [13–18]	0.03
C_{RS} (ml/cmH_2O)	30.8 [25.3–38.5]	28.6 [23.1–35.5]	0.08
MP (J/min)	19.5 [15.5–22.8]	18.3 [14.9–23.0]	0.31
Dead space[1]	0.24 [0.10–0.32]	0.22 [0.12–0.31]	0.92
VR	1.8 [1.3–2]	1.6 [1.3–2]	0.36
PaO_2/FiO_2 (mmHg)	156 [106–242]	113 [87–154]	<0.001
PaO_2/FiO_2 > 200	52 (36.7)	66 (10.2)	
PaO_2/FiO_2 100–200	60 (42.3)	344 (53.3)	
PaO_2/FiO_2 < 100	30 (21.1)	236 (36.5)	

Data are median [IQR] or number (N (%)). Percentages may not total 100 because of rounding. Abbreviations: PEEP, positive end–expiratory pressure; PCV, pressure controlled ventilation; VCV, volume controlled ventilation; PSV, pressure support ventilation; V_T, tidal volume; PBW, predicted body weight; RR, respiratory rate; Pmax, maximum airway pressure; FiO_2, fraction of inspired oxygen; et–CO_2, end–tidal carbon dioxide; ΔP, driving pressure; $C_{RS,}$ respiratory system compliance; MP, mechanical power; VR, ventilatory ratio; PaO_2, partial pressure of oxygen. All baseline variables represent measurements closest to 1 h after intubation. Compliance, mechanical power and driving pressure are only calculated in patients that received controlled ventilation. [1] Enghoff.

occurrence of air leaks, and occurrence of thromboembolic events.

2.5. Definitions and calculations

For the calculation of ΔP and C_{RS}, we used Pmax and PEEP since inspiratory and expiratory holds were seldom reported and likely seldom performed. This means that we actually calculated the dynamic driving pressure (ΔP) and the dynamic respiratory system compliance (C_{RS}). We also calculated mechanical power of ventilation (MP), fractional dead space, and ventilatory ratio (VR).

The following equations were used:

ΔP (cm H_2O) = Pmax–PEEP [eq. 1].

C_{RS} (ml/cmH_2O) = V_T/ΔP [eq. 2].

MP (J/min) = 0.098 * V_T * RR * (Pmax − 0.5 * ΔP) [eq. 3].

fractional dead space = $PaCO_2$ – end–tidal (et) CO_2/$PaCO_2$ [eq. 4].

VR = minute ventilation * $PaCO_2$/predicted body weight * 100 * 37.5), wherein minute ventilation is V_T * RR [eq. 5].

To compute VFD–28, patients who succumbed before day 28 were assigned 0 VFD–28. Occurrence of acute kidney injury was according to current criteria [19].

2.6. Post–hoc power calculation

We performed a post–hoc power calculation using the available sample, observed effect size and α 0.05 for the primary outcome in the unmatched cohort [20].

2.7. Statistical analysis

The amount of missing data was low, as shown in the **Supplementary Table E1**. Continuous variables are presented as median [IQR], and categorical variables as numbers and percentages.

High PEEP patients and low PEEP patients were compared using Wilcoxon rank–sum test for continuous variables and Fisher exact tests for categorical variables. Daily classification of patients according to the PEEP/FiO_2 combinations are visualized in alluvial plots, together with PEEP and FiO_2 levels for each day.

Key ventilator settings and ventilation variables and parameters are presented in cumulative distribution plots and line graphs. Trends over time are assessed with mixed–effect linear models with center and patients treated as random effect to account for clustering and repeated measurements, and with PEEP group, time as a continuous variable, and an interaction of PEEP group and time as fixed effect. Overall *P* values from this analysis represent the overall difference among groups over time and *P* values from interaction represents whether the trend over time differed among the groups. In addition, to compare variables at each day a pairwise comparison was performed.

High PEEP patients and low PEEP patients were compared for ICU, hospital, 28–day and 90–day mortality by using a (shared–frailty) Cox proportional hazard model and presented as hazard ratio (HR) and 95%–confidence intervals (CIs). Duration of invasive ventilation and ICU and hospital length of stay were compared through a clustered Fine–Gray competing risk model, with death before extubation or discharge, respectively, treated as competing risk, and presented as subdistribution HR and 95%–confidence interval, and graphically presented in cumulative incidence plots. All models will consider the patient as random effect. VFD–28 was compared using the Mann–Whitney *U* test. Binary outcomes were compared using mixed-effect logistic regression models and presented as odds ratio (OR) and 95%–CIs.

For the matched analysis we used a covariate–balancing propensity score (CBPS) for matching, using the nearest neighbor without replacement method, a ratio of 4 (closest to representing ratio in the unmatched cohort) and an initial caliper width of 0.2 [21]. The following baseline variables were considered in the matching progress: age, sex, body mass index (BMI), serum creatinine concentration, history of hypertension, history of diabetes, use of ACE inhibitors, angiotensin receptor blockers, heart rate, mean arterial pressure, arterial pH, and the presence of bilateral opacities on chest imaging. All variables were selected a priori and based on clinical relevance and known association with outcomes in this group. Ventilatory variables such as PaO_2/FiO_2 ratio were not considered due to possible influence of the PEEP level on this value. If for a variable <5% of data is missing at random, data was imputed using predictive mean matching. If for a variable >5% of data was missing, or < 5% not at random, the patient was excluded from this part of the analysis.

We conducted a first sensitivity analysis using two generalized linear mixed–effect models assessing the association between (1) ICU mortality, PEEP group and propensity score and (2) ICU mortality, PEEP group and all variables used for the matching procedure. In a second sensitivity analysis we first excluded patients that were ventilated for the majority of available PEEP/FiO_2 combinations to a strategy in between the low PEEP/high FiO_2 table and high PEEP/low FiO2 table (0 in **Supplementary Fig. E12**). Second, we excluded patients ventilated to multiple strategies for an equal number of days (for example due to extubation or death).

All analyses were conducted in R v.4.2.1 (R Foundation, Vienna, Austria); the significance level was set at 0.05.

3. Results

3.1. Patients

Of a total of 1142 COVID–19 patients who had received invasive

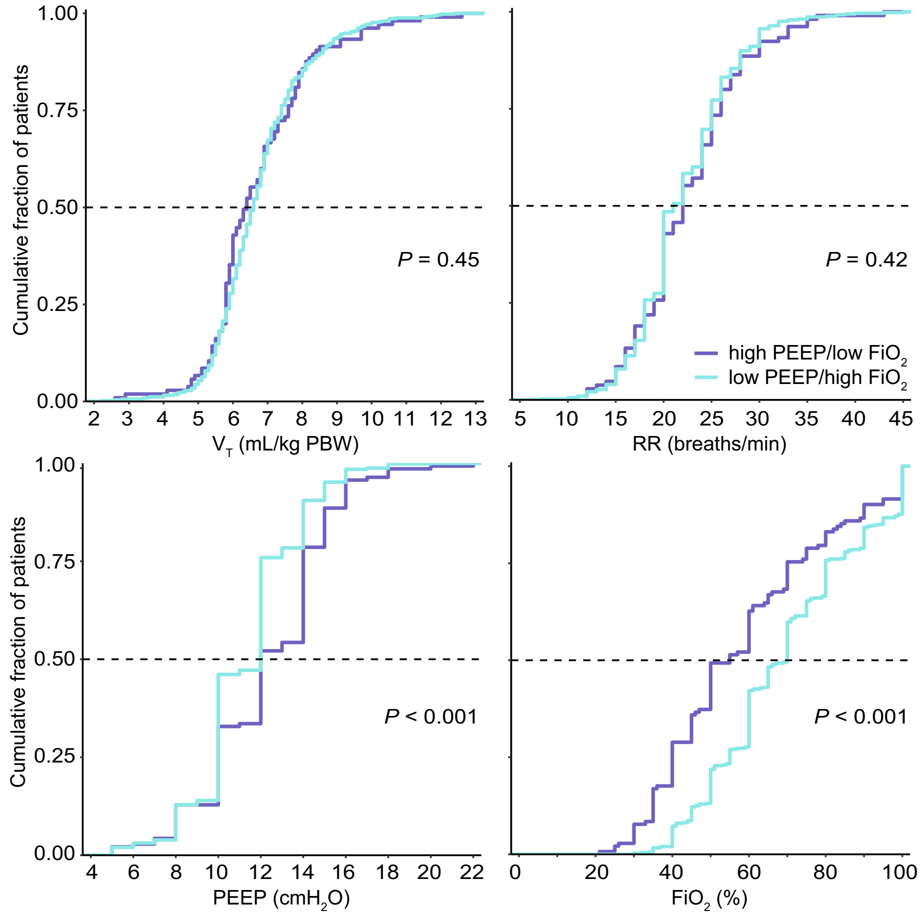

Fig. 3. Baseline ventilation characteristics.
Abbreviations: V_T, tidal volume; PBW, predicted body weight; PEEP, positive end–expiratory pressure; FiO_2, fraction of inspired oxygen.

ventilation in the second wave of the national outbreak, we included 790 patients (Fig. 1). Main reasons for exclusion were start of invasive ventilation in a non–participating ICU, and incomplete data for classification of patients. Of the included patients, 142 were classified as high PEEP patients and 648 as low PEEP patients (Fig. 2). Compared to low PEEP patients, high PEEP patients were younger, and had a higher median PaO_2 at baseline (Table 1). At baseline, high PEEP patients were ventilated with higher median PEEP, a lower median FiO_2, a lower median ΔP, and a higher median PaO_2/FiO_2 (Table 2, Fig. 3 **and Supplementary Fig. E2**).

3.2. Ventilation characteristics

Over the initial 4 days of invasive ventilation, high PEEP patients received ventilation with higher median PEEP and lower median FiO_2 (**Supplementary Table E2** and **Supplementary Fig. E3**). Compared to low PEEP, high PEEP patients had higher median PaO_2/FiO_2 ratios (**Supplementary Fig. E4**).

3.3. ICU mortality

ICU mortality occurred in 32 (22.5%) patients in the high PEEP groups versus in 254 (39.2%) patients in the low PEEP group (HR 0.66 [0.46–0.96]; $P = 0.03$).

3.4. Other outcomes

High PEEP patients had lower hospital, 28– and 90–day mortality rates, a shorter median duration of ventilation and more VFD–28 (Table 3, Fig. 4 **and Supplementary Fig. E6 and E7**). Compared to low PEEP patients, high PEEP patients had a shorter ICU and hospital length of stay. Acute kidney injury occurred less often, occurrence of tracheostomy, air leaks and thromboembolic events was not different.

3.5. Matched analysis

The matched analysis, including 103 high PEEP patients and 368 low PEEP patients, did not change the findings (**Supplementary Table E3–E5** and **Supplementary Fig. E11**).

3.6. Sensitivity analyses

All sensitivity analyses did not change the findings (**Supplementary Table E6–E8**).

4. Discussion

The findings of this analysis of COVID–19 ARDS patients in the second wave of the national outbreak in the Netherlands can be summarized as follows: (1) one in every six patients received a high PEEP/low FiO_2 ventilation strategy; (2) high PEEP/low FiO_2 ventilation was associated with enhanced survival; (3) reduced duration of ventilation and length of stay; and (4) a lower incidence of acute kidney injury. These findings were consistently validated in a propensity score matched analysis.

This study has notable strengths. To our knowledge, it is the first to explore the associations between PEEP strategy and outcomes during the second wave of the pandemic. This is significant, given the substantial

Table 3
Outcomes.

	High PEEP/low FiO_2 (N = 142)	Low PEEP/high FiO_2 (N = 648)	HR or OR	95% CI	*P* value
Primary outcome					
ICU mortality	32 (22.5)	254 (39.2)	0.66	0.46–0.96	0.03
Secondary outcomes					
Hospital mortality	33 (23.7)	263 (41.1)	0.60	0.42–0.86	0.01
28–day mortality	28 (20.1)	227 (35.3)	0.51	0.34–0.75	<0.001
90–day mortality	33 (23.7)	266 (41.6)	0.50	0.35–0.72	<0.001
Duration of ventilation (days)	9 [4–22]	11 [6–23]	1.67	1.36–2.06	<0.001
Ventilator–free days at day 28 (days)	17 [0–24]	0 [0–21]			<0.001
ICU length of stay	12 [7–21]	15 [8–26]	1.67	1.35–2.07	<0.001
Hospital length of stay	24 [14–36]	23 [16–38]	1.69	1.36–2.11	<0.001
Tracheostomy	20 (14.4)	85 (14.0)	1.03	0.07–16.09	0.95
Air leaks	10 (9.0)	47 (8.6)	1.05	0.02–54.32	0.98
Thromboembolic complications	19 (17.6)	123 (30.0)	0.72	0.42–1.22	0.22
Pulmonary embolism	19 (17.6)	109 (20.4)	0.82	0.05–0.12	0.89
Deep vein thrombosis	0 (0.0)	14 (2.6)			1.00
Acute kidney injury	42 (29.6)	251 (38.7)	0.66	0.45–0.98	0.04
Use of NMBAs	106 (74.6)	512 (79.0)	0.78	0.51–1.19	0.26
Days of use	3 [1–6]	3 [1–8]			0.18
Use of vasopressors or inotropes	99 (89.2)	475 (86.2)	1.34	0.04–43.15	0.87

Data are median [IQR] or number (N (%)). Percentages may not total 100 because of rounding. Abbreviations: PEEP, positive end–expiratory pressure; FiO_2, fraction of inspired oxygen; HR, hazard ratio; OR, odds ratio; CI, confidence interval; ICU, intensive care unit; NMBA, neuromuscular blocking agents. For mortality the HR is assessed trough a shared–frailty cox proportional hazard model. For duration of ventilation and ICU and hospital length of stay the HR presented is a subdistribution HR assessed trough a Fine–Gray competing risk model with death as competing risk. Ventilator–free days are compared using the Mann–Whitney U test. Binary outcomes were compared using mixed–effect logistic regression models and presented as OR and 95%–CIs.

changes in the care for critically ill COVID–19 patients observed after the first wave, including a decrease in intubations [16,17,22], an increase in prone positioning [18,22], and a more judicious use of high PEEP [14]. The study encompassed over one–third of all COVID–ARDS patients undergoing invasive ventilation in the second wave of the national outbreak in the Netherlands. The involvement of both academic and non–academic, as well as teaching and non–teaching hospitals, reflects an inclusive approach that enhances the accuracy of the national portrayal of respiratory care and outcomes, contributing to the generalizability of the findings. To ensure data integrity, thorough training and explicit instructions were provided to data collectors before obtaining detailed information. Patient classification followed a previously employed method, utilizing the PEEP/FiO_2 tables of the ARDS Network. The study employed objective endpoints, achieved near–complete follow–up, and strictly adhered to a pre–established analysis plan. Last but not least, to correct for confounders that may explain outcome differences between the two groups, we applied propensity score matching, confirming all the findings of the unmatched analysis.

Our findings do not align, at least in part, with previous studies of PEEP in ARDS patients, which showed no clinical benefit or even harm from high PEEP. Indeed, the 'Assessment of Low Tidal Volume and Elevated End–Expiratory Volume to Obviate Lung Injury' (ALVEOLI) study [7], the 'Lung Open Ventilation Study' (LOVS) study [8], and the 'Expiratory Pressure Study' (EXPRESS) study [6], which compared lower versus higher PEEP in ARDS patients, all showed no benefit of higher PEEP. In contrast, the 'Alveolar Recruitment for ARDS Trial' (ART) [9], a study that compared lower PEEP without recruitment maneuvers to higher PEEP with recruitment maneuvers, found that higher PEEP with recruitment maneuvers was associated with increased mortality. However, a meta–analysis of individual patient data from the ALVEOLI –, LOVS –, and EXPRESS study suggested a potential benefit in severe ARDS cases [23], and a Bayesian analysis of ART indicated that the benefits of high PEEP might be confined to patients with recruitable lung lesions [24]. Furthermore, posthoc analyses of ventilation studies in ARDS patients [25-27] and the 'Lung Imaging for Ventilatory Settings in ARDS' (LIVES) study [28] suggest that specific subphenotypes, particularly those with recruitable lung tissue, may benefit more from high PEEP. Notably, in that latter study patients that were misclassified and consequently received the wrong ventilation strategy—i.e. high PEEP in patients with focal ARDS and low PEEP in patients with non–focal ARDS— experienced very high mortality rates.

Our findings do also not align with previous studies of PEEP in COVID–ARDS patients. In one study, performed in the first wave of the COVID–19 outbreak, we ourselves found that high PEEP/low FiO_2 ventilation did not improve survival but was associated with a higher incidence of acute kidney injury [10]. Speculatively, we suggest that patients in the second wave of the pandemic in the Netherlands might have benefited more from higher PEEP due to a change in patient selection criteria. Unlike the first wave, where all hypoxemic patients were intubated for invasive ventilation, the second wave saw this intervention primarily used in patients who did not respond well to noninvasive measures, such as high—flow nasal oxygen. This likely resulted in a shift from unselected COVID–19 ARDS patients—many of whom may not benefit from higher PEEP—to patients with a different subphenotype, possibly those with more severe ARDS or ARDS with more recruitable lung tissue, who could benefit more from high PEEP.

One notable finding in our analysis was the significantly lower incidence of high PEEP ventilation usage, a finding in stark contrast to prior studies on ventilation in COVID–ARDS conducted during the initial waves of the pandemic [10,29-31]. Notably, our patient group appeared to be more severely affected, with a higher prevalence of moderate–to–severe ARDS compared to earlier studies [30,32,33] and with a higher level of critical illness, evident in a higher SAPS II [14] and SOFA score [32,34].

Given the findings of our study and the uncertainty regarding which patients specifically benefit from and which do not benefit from high PEEP/low FiO_2 ventilation, titrating PEEP in patients with ARDS in general, and patients with COVID–ARDS in particular, remains a challenge. In any case, our study findings seem to contradict the most recent guidelines for ARDS patient ventilation, which generally do not advise using the high PEEP/FiO_2 table from the ARDS network [35,36]. It also highlights the need to explore strategies for early identification of patients who may benefit from high PEEP ventilation.

This study has limitations. Specifically, we could not capture the exact reasons for why healthcare workers choose between the high or low PEEP tables and how PEEP was titrated thereafter, leaving us to speculate. During the initial waves of the pandemic, a diverse range of healthcare workers cared for critically ill invasively ventilated patients, some with less experience in invasive ventilation than typically expected. These healthcare workers likely relied on emerging literature, which sometimes offered conflicting advice on PEEP, as well as early discussions on different COVID–19 phenotypes that might respond differently to high PEEP. Additionally, it is possible that healthcare workers adhered to local guidelines that favored either the low PEEP/high FiO2 or the high PEEP/low FiO2 tables, or a combination of both. Data on the implementation of local protocols for PEEP titration was not

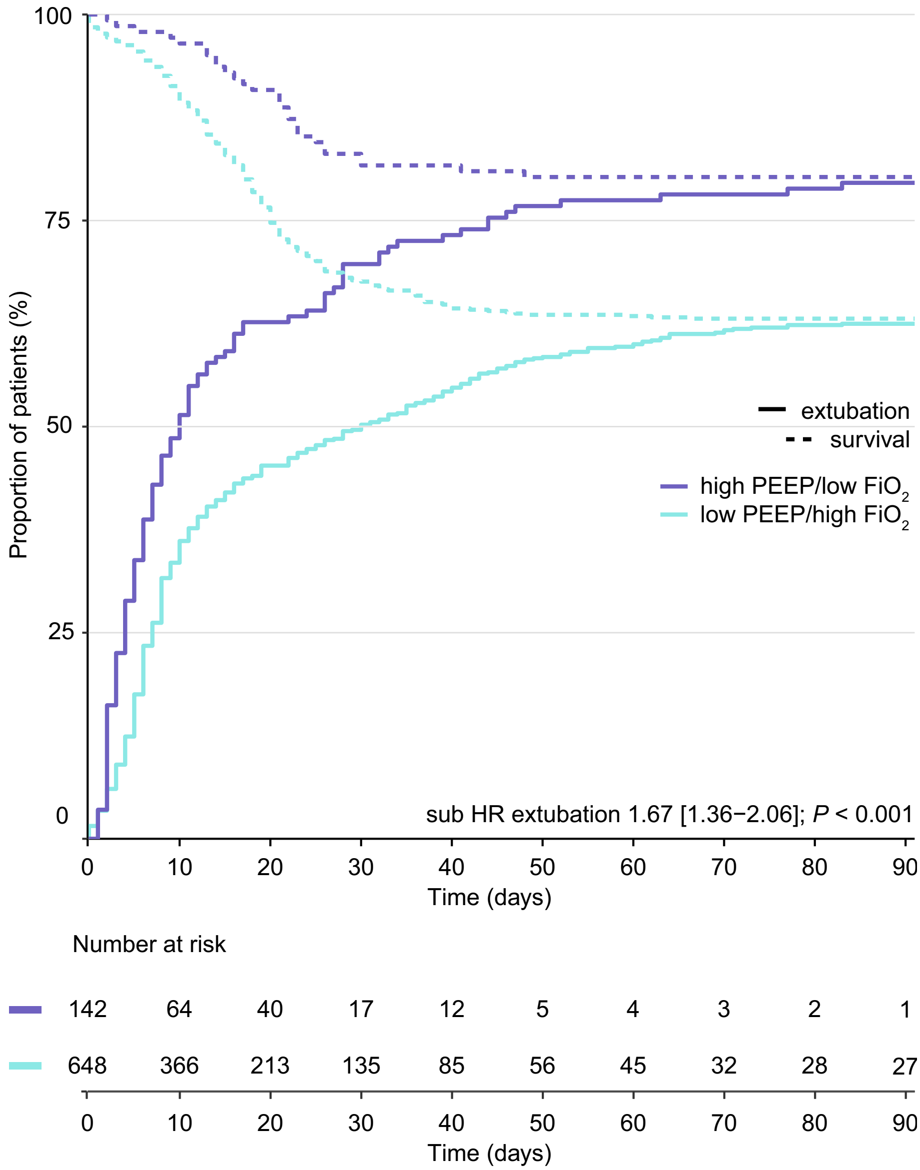

Fig. 4. Mortality and pattern of extubation in the two PEEP groups.
Abbreviations: PEEP, positive end–expiratory pressure; FiO_2, fraction of inspired oxygen; Sub HR, subdistribution HR.

collected, however we therefore designed our analysis to prevent bias from a center effect. Additionally, patient classification relied on data for ventilation variables from only the initial 3 full calendar days of invasive ventilation. We recognize the potential impact of ventilation practices and adjunctive treatments beyond day 3 on outcomes. Lastly, due to the observational nature of the study, establishing a causal relationship is not possible, and the findings should be considered exploratory, providing statistical support and rationale for further investigations.

5. Conclusion

In the second wave of national outbreak of COVID–19 in the Netherlands, ventilation with high PEEP/low FiO_2 was associated with better outcomes, including a lower mortality, shorter duration of ventilation and length of stay, and less acute kidney injury.

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CRediT authorship contribution statement

Robin L. Goossen: Writing – original draft, Project administration, Investigation, Formal analysis. **Relin van Vliet:** Writing – review & editing, Project administration, Investigation. **Lieuwe D.J. Bos:** Writing – review & editing. **Laura A. Buiteman-Kruizinga:** Writing – review & editing, Conceptualization. **Markus W. Hollman:** Writing – review & editing. **Sheila N. Myatra:** Writing – review & editing, Conceptualization. **Ary Serpa Neto:** Writing – review & editing, Conceptualization. **Peter E. Spronk:** Writing – review & editing. **Meta C.E. van der Woude:** Writing – review & editing. **David M.P. van Meenen:** Resources, Project administration, Methodology, Conceptualization. **Frederique Paulus:** Writing – review & editing, Resources, Project administration, Methodology, Conceptualization. **Marcus J. Schultz:** Writing – review & editing, Writing – original draft, Conceptualization.

Declaration of competing interest

None.

Data availability

All of the individual participant data collected in this dataset, after deidentification, will be shared with researchers who provide a methodologically sound proposal. Proposals should be directed to d.m.vanmeenen@amsterdamumc.nl, starting from 1 year after publication of this work.

Appendix A. Supplementary data

Supplementary material to this article can be found online at https://doi.org/10.1016/j.jcrc.2024.154854.

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