Supplemental Online Content

Writing Committee and Steering Committee for the RELAx Collaborative Group. Effect of a lower vs higher positive end-expiratory pressure strategy on ventilator-free days in ICU patients without ARDS: a randomized clinical trial. *JAMA*. Published online December 9, 2020. doi:10.1001/jama.2020.23517

This supplemental material has been provided by the authors to give readers additional information about their work.

eAppendix 1. Lists of committees, investigators and study sites

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The writing committee was composed by Anna Geke Algera (Department of Intensive Care & Laboratory of Experimental Intensive Care and Anesthesiology, Amsterdam UMC location AMC, Amsterdam, the Netherlands), Luigi Pisani (Department of Intensive Care & Laboratory of Experimental Intensive Care and Anesthesiology, Amsterdam UMC location AMC, Amsterdam, the Netherlands), Ary Serpa Neto (Department of Critical Care Medicine, Hospital Israelita Albert Einstein, São Paulo, Brazil & Australian and New Zealand Intensive Care Research Centre (ANZIC-RC), Monash University, Melbourne, Australia & Department of Intensive Care & Laboratory of Experimental Intensive Care and Anesthesiology, Amsterdam UMC location AMC, Amsterdam, the Netherlands), Marcelo Gama de Abreu (Pulmonary Engineering Group, University Hospital Carl Gustav Carus, Dresden, Germany), Paolo Pelosi (Department of Surgical Sciences and Integrated Diagnostics, San Martino Policlinico Hospital, IRCCS for Oncology, University of Genoa, Genoa, Italy), Marcus J. Schultz (Department of Intensive Care & Laboratory of Experimental Intensive Care and Anesthesiology, Amsterdam UMC location AMC, Amsterdam, the Netherlands & Mahidol-Oxford Tropical Medicine Research Unit (MORU), Mahidol University, Bangkok, Thailand), Frederique Paulus (Department of Intensive Care & Laboratory of Experimental Intensive Care and Anesthesiology, Amsterdam UMC location AMC, Amsterdam, the Netherlands & ACHIEVE Centre of Expertise, Faculty of Health, Amsterdam University of Applied Sciences, Amsterdam, The Netherlands). All members of the writing committee contributed equally.

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1.4 Data safety and monitoring committee

Patient data and safety was monitored by a committee, which was composed of a chairperson (Ignacio Martin-Loeches) and three further members (Paolo Severgnini, Frank van Haren and Antonio Artigas). The DSMB was supported by Ary Serpa Neto, who provided the data and safety monitoring committee with reports for review. The committee monitored the safety by monitoring the ventilation specific complications in both ventilation groups, the overall status of the trial (e.g. progress of patient enrollment, general adherence to protocol and completeness of data entry).

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eAppendix 2. Supplementary Methods

Key exclusion criteria

Next to ARDS, other exclusion criteria were age younger than 18 years; pregnancy; ventilation lasting longer than 12 hours before admission to the ICU; COPD GOLD class III/IV; restrictive pulmonary disease; increased and uncontrollable intracranial pressure; delayed cerebral ischemia; ongoing cardiac ischemia; morbid obesity; necrotizing fasciitis; severe untreatable anemia; neurologic diagnosis that could prolong duration of mechanical ventilation; carbon monoxide poisoning; receiving ECMO, participation in another study with similar endpoint, and previously randomized in this trial.

Ventilation protocol

The commonly used ventilator modes (volume controlled ventilation, pressure controlled ventilation and pressure support ventilation) are highly recommended, but all ventilator modes are allowed as long as they do not automatically adjust PEEP and FiO_2. Tidal volume size is between 6 – 8 ml/kg predicted body weight (PBW), which is calculated according to the following formula [58]: 50 + 0.91 x (centimeters of height – 152.4) for males and 45.5 + 0.91 x (centimeters of height – 152.4) for females. The respiratory rate is adjusted to obtain a normal arterial blood pH (7.35 to 7.45). In case of metabolic acidosis or alkalosis, a lower or higher than normal $PaCO_2$ can be accepted, which is left to the discretion of the attending physician. Recruitment maneuvers are allowed when deemed necessary, but the decision to perform a recruitment maneuver is also left to the discretion of the attending physician.

Weaning from the ventilator

Daily assessment of the ability to breathe with pressure support ventilation was conducted when FiO_2 was less than or equal to 0.4, or when FiO_2 was lower than the day before. In addition, the ventilator was switched to pressure support ventilation if the attending nurse or physician considered the patient awake enough to breathe with pressure support ventilation. Assessment of the ability to breathe with pressure support ventilation was also required if patient-ventilator asynchrony was noticed.

A patient was assumed to be ready for extubation if responsive and cooperative, with adequate cough reflex, PaO_2/FiO_2 >200 mmHg at $FiO_2 \leq 0.40$ and a respiratory rate between 8 to 30 breath per minute with no signs of respiratory distress, for at least 30 minutes. Patients assigned to the low PEEP strategy were weaned and extubated at the lowest PEEP used. A patient assigned to the high PEEP strategy was extubated at 8 cm H_2O, or PEEP could be set at 5 cm H_2O for 1 to 2 hours to check for extubation readiness. The attending physician made the final decision for extubation. If a patient needed to be re-intubated within 28 days after randomization, ventilation followed the previous assigned PEEP strategy.

Tracheostomy was preferably not performed within 10 days after the initiation of invasive ventilation. Indications included expected duration of ventilation >14 days, a persistent Glasgow Coma Scale <7 with inadequate swallow or cough reflex or retention of sputum, severe ICU-acquired weakness evaluated by clinical inspection, and repeated respiratory failure after successive tracheal extubations.

Standard Care

Standard care followed local clinical guidelines and was performed by independent board-certified ICU physicians and board-certified ICU nurses not involved in the trial. The nurse-to-patient ratio in the participating centers varied from 1:1 to 1:2, depending on severity of illness. ICU physicians rotated in 24/7 shifts, meaning that there was always an ICU physician present in the ICU. Physician and nursing staffs used restrictive sedation, preferring analgo-sedation over hypno-sedation, and restrictive intravenous fluid resuscitation. ICU nurses performed standard airway care, including endotracheal suctioning, and tracheostomy care if applicable. Endotracheal suction was performed only when clinically indicated and according to current guidelines.[1]

Infection prevention

Infection prevention strategies consisted of frequent oral care (tooth brushing and rinsing of the oral cavity every six hours), head–of–bed elevation, hand washing, and use of selective decontamination of the digestive tract.[2]

eTable 1. Definitions of Secondary Outcomes

Outcomes	Definition
Ventilator–free days at day 28	Start time: day of randomization (the same as the day of intubation due to the strict time for inclusion) Timeframe: 28 days Successful extubation: >24 hours without reintubation in a 28–day survivor Interval reintubation: counted from the day of the last successful extubation if there were repeated intubation episodes in the first 28 days Non–invasive ventilation: not counted Tracheostomy: same as above (>24 hours off positive pressure ventilation) 28–day non–survivors: 0 ventilator–free days even if extubated in the period Death after 28 days: censored and considered the duration of ventilation only
Duration of ventilation in survivors	Duration, in days, between intubation and successfully extubation, defined as a patient breathing without invasive assistance of the mechanical ventilator for at least 24 consecutive hours. All relevant data will be taken into account and collected, including all additional periods of ventilation during the first 28 days. Only patients surviving the first 28 days will be considered
Incidence of new ARDS	According to the Berlin definition[a] Only ARDS occurring after the first 48 hours of randomization will be considered and the degree of severity will be reported
Incidence of early or late suspected VAP	New or progressive radiographic infiltrate plus at least two of the following: • Temperature >38.5ºC; and/or • Leukocytosis (>12,000 cells/mm^3) or leucopenia (<4,000 cells/$mm^{3)}$; and/or • Purulent secretions. Only suspected VAP occurring after the first 48 hours of randomization will be considered
Incidence of early or late confirmed VAP	New or progressive radiographic infiltrate, with microbiological confirmation and plus at least two of the following: • Temperature >38.5ºC; and/or • Leukocytosis (>12,000 cells/mm^3) or leucopenia (<4,000 cells/$mm^{3)}$; and/or • Purulent secretions. Only confirmed VAP occurring after the first 48 hours of randomization will be considered
Incidence of early or late severe atelectasis	At least complete lobar atelectasis of a lung on chest radiograph or other kind of imaging suitable for diagnosis severe atelectasis Any severe atelectasis occurring after the randomization will be considered
Incidence of early or late severe hypoxemia	SpO_2 <88% or PaO_2 <55 mm Hg and needing a rise of the oxygen fraction to more 0.6 and/or a rise of the PEEP level to more than 5 cm H_2O (in low PEEP arm) or more than 8 cm H_2O (in liberal PEEP arm) Any severe hypoxemia occurring after the randomization will be considered

eTable 1. Definitions of Secondary Outcomes (continued)

Outcomes	Definition
Incidence of early or late pneumothorax	Air in the pleural space with no vascular bed surrounding the visceral pleura on chest radiograph or other kind of imaging suitable for diagnosis pneumothorax Any pneumothorax occurring after the randomization will be considered
Need for early or late rescue strategies for severe hypoxemia or severe atelectasis	Need of one of the following: • Recruitment maneuvers; and/or • Prone positioning; and/or • Bronchoscopy for opening atelectasis Any need for rescue occurring after the randomization will be considered and the maneuvers will be reported as a collapsed composite of need for rescue and also individually
Days with hemodynamic support	Number of ICU days with any use of vasopressors/inotropes for more than 1 hour on a day.
Days with sedation	Number of ICU days with any use of sedatives for more than 1 hour on a day.
ICU length of stay	Number of days from ICU admission till ICU discharge
Hospital length of stay	Number of days from hospital admission till hospital discharge
ICU mortality	Any death occurring during ICU stay
Hospital mortality	Any death occurring during hospital stay
28–day mortality	Any death occurring during the first 28 days after randomization
90–day mortality	Any death occurring during the first 90 days after randomization

Abbreviations: ARDS, acute respiratory distress syndrome; VAP, ventilator–associated pneumonia; ICU, intensive care unit

SI conversion factors: to convert PaO_2 to kPa, divide by 7.5

[a] ARDS Definition Task Force, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin Definition. JAMA 2012;307:2526-33.

eTable 2. Daily Ventilatory Variables, Arterial Blood Gases and Vital Signs in the First Three Days after Randomization

	After Randomization			Day 01		
	Lower PEEP (*n* = 476)	Higher PEEP (*n* = 493)	*p* value	Lower PEEP (*n* = 476)	Higher PEEP (*n* = 493)	*p* value
Number of patients, No. %	472 (99.2)	492 (99.8)		413 (92.0)	441 (94.3)	
PEEP, median (IQR), cm H_2O	5.0 (3.0 – 7.0)	8.0 (8.0 – 8.0)	< 0.001	1.8 (0.0 – 5.0)	8.0 (8.0 – 8.0)	< 0.001
Tidal volume, median (IQR), mL/kg PBW	6.7 (5.9 – 7.8)	7.0 (6.2 – 8.1)	0.004	7.0 (6.1 – 8.6)	7.1 (6.3 – 8.5)	0.27
Plateau pressure, median (IQR), cm H_2O	19.0 (15.0 – 23.0)	21.0 (18.0 – 24.9)	< 0.001	15.0 (11.0 – 21.0)	19.0 (16.0 – 22.9)	< 0.001
Total respiratory rate, median (IQR), breaths/min	20.0 (17.0 – 23.0)	20.0 (16.0 – 22.0)	0.07	19.0 (16.0 – 24.0)	19.0 (16.0 – 24.0)	0.75
Driving pressure, median (IQR), cm H_2O	14.0 (11.0 – 17.0)	13.0 (10.0 – 16.0)	0.23	13.0 (10.0 – 16.0)	12.0 (8.0 – 14.0)	0.001
FiO_2, median (IQR)	0.48 (0.40 – 0.60)	0.45 (0.35 – 0.60)	0.02	0.38 (0.30 – 0.50)	0.32 (0.25 – 0.42)	< 0.001
PaO_2 / FiO_2 ratio, median (IQR), mm Hg	204.4 (137.9 – 304.4)	217.0 (142.8 – 330.7)	0.33	225.0 (158.5 – 294.0)	274.4 (186.7 – 356.3)	< 0.001
$PaCO_2$, median (IQR), mm Hg	40.5 (36.0 – 47.3)	40.5 (35.3 – 46.5)	0.79	39.0 (34.5 – 45.0)	39.0 (34.5 – 44.3)	0.90
Arterial pH, median (IQR)	7.33 (7.25 – 7.41)	7.33 (7.25 – 7.40)	0.76	7.39 (7.33 – 7.44)	7.38 (7.31 – 7.43)	0.18
SpO_2, median (IQR), %	97.0 (94.4 – 99.6)	98.0 (95.0 – 100.0)	0.10	96.0 (94.2 – 97.5)	96.5 (94.8 – 98.0)	0.003
SpO_2 / FiO_2 ratio, median (IQR), mm Hg	202.0 (158.3 – 250.0)	222.2 (163.3 – 285.7)	0.02	257.3 (195.5 – 322.9)	305.8 (227.4 – 385.0)	< 0.001
Heart rate, median (IQR), beats/min	88.0 (73.0 – 107.0)	89.0 (70.0 – 106.0)	0.62	85.0 (69.0 – 103.0)	84.0 (69.0 – 103.0)	0.82
Mean arterial pressure, median (IQR), mm Hg	75.0 (66.0 – 87.0)	76.0 (67.0 – 87.0)	0.54	74.5 (67.0 – 83.0)	75.0 (68.0 – 83.0)	0.50

eTable 2. Daily Ventilatory Variables, Arterial Blood Gases and Vital Signs in the First Three Days after Randomization (continued)

	Day 02			Day 03		
	Lower PEEP (*n* = 476)	**Higher PEEP (*n* = 493)**	***p* value**	**Lower PEEP (*n* = 476)**	**Higher PEEP (*n* = 493)**	***p* value**
Number of patients, No. %	270 (73.2)	266 (69.6)		199 (70.7)	200 (70.7)	
PEEP, median (IQR), cm H_2O	1.5 (0.0 – 5.0)	8.0 (8.0 – 8.0)	< 0.001	2.5 (0.0 – 6.0)	8.0 (8.0 – 8.0)	< 0.001
Tidal volume, median (IQR), mL/kg PBW	7.3 (6.1 – 8.7)	7.3 (6.4 – 9.0)	0.18	7.0 (6.0 – 8.8)	7.6 (6.5 – 9.2)	0.02
Plateau pressure, median (IQR), cm H_2O	15.0 (10.0 – 21.0)	18.0 (14.0 – 23.0)	< 0.001	16.0 (12.0 – 21.0)	18.0 (14.0 – 22.0)	0.001
Total respiratory rate, median (IQR), breaths/min	20.0 (16.0 – 24.0)	20.0 (15.0 – 24.0)	0.81	21.0 (16.0 – 26.0)	19.0 (15.0 – 24.0)	0.03
Driving pressure, median (IQR), cm H_2O	12.0 (8.0 – 16.0)	11.0 (7.0 – 15.0)	0.007	13.0 (9.0 – 16.0)	10.4 (7.0 – 15.0)	0.002
FiO_2, median (IQR)	0.40 (0.30 – 0.50)	0.32 (0.25 – 0.42)	< 0.001	0.40 (0.31 – 0.52)	0.32 (0.25 – 0.42)	< 0.001
PaO_2 / FiO_2 ratio, median (IQR), mm Hg	203.1 (146.3 – 275.0)	248.1 (174.5 – 326.8)	< 0.001	188.8 (133.7 – 246.9)	244.5 (174.9 – 326.3)	< 0.001
$PaCO_2$, median (IQR), mm Hg	39.8 (35.3 – 45.0)	39.8 (35.3 – 45.4)	0.94	41.3 (36.8 – 47.3)	40.5 (36.8 – 46.5)	0.53
Arterial pH, median (IQR)	7.41 (7.35 – 7.46)	7.40 (7.35 – 7.45)	0.33	7.43 (7.36 – 7.47)	7.43 (7.36 – 7.47)	0.47
SpO_2, median (IQR), %	95.5 (94.0 – 97.0)	96.4 (94.6 – 97.8)	< 0.001	95.1 (93.8 – 96.8)	96.2 (94.5 – 97.2)	< 0.001
SpO_2 / FiO_2 ratio, median (IQR), mm Hg	249.5 (195.6 – 313.3)	306.1 (229.6 – 384.2)	< 0.001	236.9 (186.7 – 313.3)	310.8 (231.0 – 388.9)	< 0.001
Heart rate, median (IQR), beats/min	91.0 (76.0 – 107.0)	89.0 (74.0 – 103.0)	0.19	92.0 (74.2 – 107.8)	87.0 (75.0 – 100.0)	0.02
Mean arterial pressure, median (IQR), mm Hg	79.0 (69.0 – 89.0)	77.0 (69.0 – 89.0)	0.80	80.0 (70.0 – 91.0)	79.0 (70.0 – 92.0)	0.89

Percentages may not total 100 because of rounding

Abbreviations: FiO_2, denotes fraction of inspired oxygen; PaO_2, partial pressure of arterial oxygen; $PaCO_2$, partial pressure of carbon dioxide; PBW, predicted body weight; PEEP, positive end-expiratory pressure and SpO_2 oxygen saturation as measured by pulse oximetry.

SI conversion factors: to convert $PaCO_2$ and SpO_2 / FiO_2 to kPa, divide by 7.5

eTable 3. Daily Sedation, Fluids, Transfusion and Vasopressors

	After Randomization			Day 01		
	Lower PEEP (n = 476)	Higher PEEP (n = 493)	p value	Lower PEEP (n = 476)	Higher PEEP (n = 493)	p value
Number of patients, No. (%)	476 (100.0)	493 (100.0)		476 (99.6)	493 (100.0)	
Sedation						
Lowest RASS, median (IQR)[a]	-5.0 (-5.0 – -4.0)	-5.0 (-5.0 – -4.0)	0.82	-4.0 (-5.0 – -1.0)	-4.0 (-5.0 – -2.0)	0.19
Light sedation, No. (%)[b]	45 (11.2)	36 (8.6)	0.24	116 (29.5)	110 (26.3)	0.31
Deep sedation, No. (%)[c]	357 (88.6)	382 (91.4)	0.20	274 (69.7)	307 (73.3)	0.27
Continuous infusion of sedatives, No. (%)	431 (90.9)	436 (88.8)	0.29	323 (72.6)	352 (76.0)	0.25
Hours under sedatives, median (IQR)	7.0 (3.0 – 12.0)	7.0 (3.0 – 12.0)	0.91	18.0 (11.0 – 24.0)	16.0 (9.0 – 24.0)	0.08
Cumulative hours since randomization, median (IQR)	7.0 (3.0 – 12.0)	7.0 (3.0 – 12.0)	0.91	22.0 (8.0 – 30.0)	21.0 (8.0 – 29.0)	0.54
Fluids						
Crystalloids, median (IQR), ml[d]	1500.0 (659.0 – 2952.2)	1544.0 (579.0 – 3205.0)	0.71	1647.0 (855.5 – 2775.0)	1851.5 (858.5 – 2873.8)	0.29
Colloids, median (IQR), ml[d]	200.0 (100.0 – 300.0)	200.0 (100.0 – 475.0)	0.99	200.0 (100.0 – 200.0)	220.0 (125.0 – 384.0)	0.16
Fluid balance, median (IQR), ml	1042.0 (127.2 – 2756.5)	1161.0 (138.2 – 3053.0)	0.33	1413.5 (266.5 – 2847.5)	1765.0 (523.6 – 3175.2)	0.03
Cumulative fluid balance since randomization, milliliters, median (IQR)	1042.0 (127.2 – 2756.5)	1161.0 (138.2 – 3053.0)	0.33	2597.0 (676 – 5225.5)	3010.0 (1146.0 – 5753.0)	0.05
Transfusion						
Red blood cell, No. (%)	46 (9.7)	42 (8.5)	0.58	41 (8.6)	31 (6.3)	0.18
Units of red blood cell, median (IQR)[d]	2.0 (1.2 – 5.0)	2.0 (1.0 – 4.0)	0.68	1.0 (1.0 – 2.0)	1.5 (1.0 – 2.0)	0.12
Fresh frozen plasma, No. (%)	23 (4.8)	28 (5.7)	0.57	4 (0.8)	11 (2.2)	0.12
Units of fresh frozen plasma, median (IQR)[d]	2.0 (2.0 – 6.0)	2.0 (2.0 – 4.2)	0.89	1.5 (1.0 – 5.0)	1.0 (1.0 – 3.0)	0.84

eTable 3. Daily Sedation, Fluids, Transfusion and Vasopressors (continued)

	After Randomization			Day 01		
	Lower PEEP (*n* = 476)	Higher PEEP (*n* = 493)	*p* value	Lower PEEP (*n* = 476)	Higher PEEP (*n* = 493)	*p* value
Platelets, No. (%)	22 (4.6)	25 (5.1)	0.77	7 (1.5)	8 (1.6)	0.99
Units of platelets, median (IQR)[d]	1.0 (1.0 – 2.8)	1.0 (1.0 – 2.0)	0.95	1.0 (1.0 – 2.0)	1.0 (1.0 – 1.2)	0.30
Vasopressors						
Continuous infusion of vasopressors, No. (%)	334 (70.6)	375 (76.5)	0.04	311 (69.9)	334 (72.1)	0.47
Hours under vasopressors, median (IQR)	9.0 (4.0 – 15.0)	8.0 (4.0 – 13.0)	0.20	21.0 (11.0 – 24.0)	18.0 (10.0 – 24.0)	0.13
Cumulative hours since randomization, median (IQR)	9.0 (4.0 – 15.0)	8.0 (4.0 – 13.0)	0.18	24.0 (11.2 – 32.0)	23.0 (12.0 – 31.0)	0.13
SOFA, median (IQR) [e]	9.0 (7.0 – 12.0)	10.0 (8.0 – 12.0)	0.43	8.0 (6.0 – 11.0)	8.0 (5.0 – 11.0)	0.22

Percentages may not total 100 because of rounding

Abbreviations: RASS, Richmond Agitation-Sedation Scale; SOFA, Sequential Organ Failure Assessment

[a] RASS scores ranges from -5 to +4, with higher scores indicating a more combative and aggressive patient.

[b] Light sedation defined when +2 ≤ RASS ≤ +2.

[c] Deep sedation defined when RASS ≤ -3.

[d] Calculate only among who received it.

[e] SOFA score ranges from 0 to 24, with higher scores indicating more severe disease and a higher risk of death.

eTable 3. Daily sedation, fluids, transfusion and vasopressors (continued)

	Day 02			Day 03		
	Lower PEEP (*n* = 476)	**Higher PEEP (*n* = 493)**	***p* value**	**Lower PEEP (*n* = 476)**	**Higher PEEP (*n* = 493)**	***p* value**
Number of patients, No. (%)	373 (78.0)	384 (77.9)		295 (62.0)	286 (58.0)	
Sedation						
Lowest RASS, median (IQR) [a]	-3.0 (-5.0 – -1.0)	-3.0 (-5.0 – 0.0)	0.671	-2.0 (-5.0 – 0.0)	-3.0 (-5.0 – 0.0)	0.224
Light sedation, No. (%)[b]	151 (48.4)	157 (48.0)	0.937	124 (50.4)	110 (45.5)	0.279
Deep sedation, No. (%)[c]	159 (51.0)	166 (50.8)	0.999	120 (48.8)	132 (54.5)	0.206
Continuous infusion of sedatives, No. (%)	182 (49.5)	186 (48.8)	0.884	130 (45.1)	125 (44.5)	0.933
Hours under sedatives, median (IQR)	21.0 (11.0 – 24.0)	20.0 (10.2 – 24.0)	0.732	20.0 (11.0 – 24.0)	20.0 (10.0 – 24.0)	0.817
Cumulative hours since randomization, median (IQR)	23.0 (8 – 45)	24.0 (9 – 44)	0.725	23.0 (8 – 53.0)	24.0 (9.0 – 50.0)	0.816
Fluids						
Crystalloids, median (IQR), ml[d]	939.0 (482.0 – 1711.0)	1007.5 (423.2 – 1760.0)	0.569	790.5 (360.0 – 1327.8)	741.0 (360.0 – 1309.5)	0.973
Colloids, median (IQR), ml[d]	200.0 (100.0 – 212.0)	200.0 (100.0 – 300.0)	0.880	200.0 (100.0 – 225.0)	100.0 (90.0 – 200.0)	0.398
Fluid balance, median (IQR), ml	592.0 (-302.0 – 1936.0)	762.0 (-160.8 – 2027.5)	0.340	190.0 (-754.0 – 1338.0)	417.0 (-570.0 – 1347.0)	0.283
Cumulative fluid balance since randomization, median (IQR), ml	3171.0 (777.5 – 6395.0)	3726.0 (1153.0 – 6688.0)	0.081	3299.0 (727.5 – 6915.5)	3868.0 (999.0 – 7621.0)	0.073
Transfusion						
Red blood cell, No. (%)	21 (5.6)	28 (7.3)	0.378	23 (7.8)	11 (3.8)	0.051
Units of red blood cell, median (IQR)[d]	1.0 (1.0 – 2.0)	1.0 (1.0 – 2.0)	0.275	1.0 (1.0 – 1.0)	2.0 (1.0 – 2.0)	0.058
Fresh frozen plasma, No. (%)	1 (0.3)	0 (0.0)	0.493	2 (0.7)	0 (0.0)	0.499

eTable 3. Daily sedation, fluids, transfusion and vasopressors (continued)

	Day 02			Day 03		
	Lower PEEP (*n* = 476)	**Higher PEEP (*n* = 493)**	***p* value**	**Lower PEEP (*n* = 476)**	**Higher PEEP (*n* = 493)**	***p* value**
Units of fresh frozen plasma, median (IQR)[d]	1.0 (1.0 – 1.0)	---	---	2.5 (1.8 – 3.2)	---	---
Platelets, No. (%)	8 (2.1)	4 (1.0)	0.26	7 (2.4)	0 (0.0)	0.02
Units of platelets, median (IQR)[d]	1.0 (1.0 – 1.2)	1.0 (1.0 – 1.0)	0.29	1.0 (1.0 – 1.5)	---	---
Vasopressors						
Continuous infusion of vasopressors, No. (%)	182 (49.6)	189 (49.6)	0.99	121 (42.2)	108 (38.4)	0.39
Hours under vasopressors, median (IQR)	21.5 (11.0 – 24.0)	17.0 (11.0 – 24.0)	0.14	24.0 (11.0 – 24.0)	22.0 (9.8 – 24.0)	0.31
Cumulative hours since randomization, median (IQR)	29.0 (13.0 – 49.0)	25.0 (13.0 – 46.0)	0.15	30.0 (13.0 – 59.7)	26.0 (13.0 – 49.0)	0.13
SOFA, median (IQR)[e]	7.0 (5.0 – 10.0)	7.0 (4.0 – 11.0)	0.330	7.0 (4.0 – 11.0)	7.0 (5.0 – 10.2)	0.50

Percentages may not total 100 because of rounding

Abbreviations: RASS, Richmond Agitation-Sedation Scale; SOFA, Sequential Organ Failure Assessment

[a] RASS scores ranges from -5 to +4, with higher scores indicating a more combative and aggressive patient.

[b] Light sedation defined when +2 ≤ RASS ≤ +2.

[c] Deep sedation defined when RASS ≤ -3.

[d] Calculate only among who received it.

[e] SOFA score ranges from 0 to 24, with higher scores indicating more severe disease and a higher risk of death.

eTable 4. Adherence to the Protocol with Respect to PEEP, FiO_2 and SpO_2 in the First Five Days[a]

	Lower PEEP (*n* = 476)	Higher PEEP (*n* = 493)	Median Difference (95% CI)[b]	*p* value
Measurements PEEP ≤5 cm H_2O per patient				
Ratio per observations[c]	1.0 (0.6 – 1.0)	0.0 (0.0 – 0.0)	0.91 (0.86 to 0.96)	< 0.001
Total number of observations	5.0 (2.0 – 11.0)	0.0 (0.0 – 0.0)	5.00 (3.08 to 6.91)	< 0.001
Measurements PEEP <5 cm H_2O per patient				
Ratio per observations[c]	0.7 (0.2 – 1.0)	0.0 (0.0 – 0.0)	0.66 (0.54 to 0.77)	< 0.001
Total number of observations	3.0 (1.0 – 9.0)	0.0 (0.0 – 0.0)	3.00 (1.94 to 4.06)	< 0.001
Measurements PEEP 0 cm H_2O per patient				
Ratio per observations[c]	0.2 (0.0 – 0.7)	0.0 (0.0 – 0.0)	0.34 (0.25 to 0.44)	< 0.001
Total number of observations	1.0 (0.0 – 4.0)	0.0 (0.0 – 0.0)	1.00 (-0.38 to 2.38)	0.16
Measurements PEEP 8 cm H_2O per patient				
Ratio per observations[c]	0.0 (0.0 – 0.0)	0.9 (0.4 – 1.0)	-0.91 (-1.17 to -0.65)	< 0.001
Total number of observations	0.0 (0.0 – 0.0)	4.0 (1.0 – 11.0)	-4.00 (-6.20 to -1.80)	< 0.001
Measurements PEEP 8 cm H_2O per patient				
Ratio per observations[c]	0.0 (0.0 – 0.1)	0.0 (0.0 – 0.2)	0.07 (-0.01 to 0.14)	0.09
Total number of observations	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.0)	-0.00 (-0.17 to 0.17)	0.99
Measurements FiO_2 >0.60 per patient				
Ratio per observations[c]	0.0 (0.0 – 0.1)	0.0 (0.0 – 0.0)	0.01 (-0.01 to 0.04)	0.20
Total number of observations	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.0)	0.00 (-0.00 to 0.00)	0.002
Measurements FiO_2 1.00 per patient				
Ratio per observations[c]	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.00 (-0.00 to 0.01)	0.16
Total number of observations	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.10 (0.02 to 0.18)	0.02
Measurements FiO_2 0.21 per patient				
Ratio per observations[c]	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.2)	-0.09 (-0.15 to -0.00)	0.03
Total number of observations	0.0 (0.0 – 0.0)	0.0 (0.0 – 1.0)	0.00 (-0.00 to 0.00)	0.99
Measurements SpO_2 <92% per patient				
Ratio per observations[c]	0.0 (0.0 – 0.1)	0.0 (0.0 – 0.0)	0.02 (0.00 to 0.04)	0.03
Total number of observations	0.0 (0.0 – 1.0)	0.0 (0.0 – 1.0)	-0.00 (-0.06 to 0.06)	0.99
Measurements SpO_2 <88% per patient				
Ratio per observations[c]	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	0.00 (-0.01 to 0.02)	0.52
Total number of observations	0.0 (0.0 – 0.0)	0.0 (0.0 – 0.0)	-0.00 (-0.03 to 0.03)	0.99
Measurements SpO_2 >96% per patient				
Ratio per observations[c]	0.4 (0.2 – 0.8)	0.6 (0.3 – 0.8)	-0.14 (-0.22 to -0.06)	< 0.001
Total number of observations	3.0 (1.0 – 6.0)	3.0 (1.0 – 7.0)	-0.50 (-1.27 to 0.27)	0.20

Data are median (quartile 25% - quartile 75%).

Abbreviations: CI, confidence interval; FiO_2, fraction of inspired oxygen; PEEP, positive end-expiratory pressure; and SpO_2, oxygen saturation as measured by pulse oximetry.

[a] PEEP, FiO_2 and SpO_2 obtained from values recorded every six hours until day 5 post-randomization or until extubation.

[b] Median difference estimated using mixed-effect quantile models with random effect for centers. Quantile models considered a $\tau = 0.50$ and an asymmetric Laplace distribution. *p* values and confidence intervals were extracted after 1,000 bootstrap samplings.

[c] Ratio calculated as the number of observations in the proposed range divided by the total number of observations available per patient.

eTable 5. Per-protocol Analysis of the Primary Outcome

	Lower PEEP (*n* = 411)	Higher PEEP (*n* = 441)	Effect Estimate (95% CI)	*p* value
Ventilator-free days at day 28				
Mean (SD)	14.3 (12.4)	13.5 (12.5)	1.08 (0.97 to ∞)	0.003
Median (IQR)	19.7 (0.0 – 26.6)	17.7 (0.0 – 26.4)		

Abbreviations: CI, confidence interval; PEEP, positive end-expiratory pressure.

eTable 6. Adjusted Analyses for the Primary and Secondary Outcomes

	Lower PEEP (*n* = 476)	Higher PEEP (*n* = 493)	Effect Estimate* (95% CI)	*p* value
Primary outcome				
Ventilator-free days at day 28				
Mean (SD)	13.8 (12.4)	13.4 (12.5)	1.04 (0.93 to ∞)[a]	0.02[b]
Median (IQR)	17.7 (0.0 – 26.6)	16.7 (0.0 – 26.5)		
Secondary outcomes				
Duration of ventilation in survivors, days				
Mean (SD)	5.5 (7.4)	4.8 (6.6)	0.88 (0.73 to 1.06)[c]	0.19
Median (IQR)	2.0 (0.8 – 6.8)	2.0 (1.0 – 5.7)		
ARDS, No. (%)	13 (2.7)	5 (1.0)	2.97 (0.93 to 9.48)[d]	0.07
Suspected VAP, No. (%)	10 (2.1)	10 (2.0)	0.93 (0.37 to 2.32)[d]	0.88
Confirmed VAP, No. (%)	6 (1.3)	7 (1.4)	0.73 (0.23 to 2.33)[d]	0.60
Severe atelectasis, No. (%)	20 (4.2)	15 (3.0)	1.63 (0.75 to 3.53)[d]	0.22
Severe hypoxemia, No. (%)	98 (20.6)	87 (17.6)	1.67 (1.11 to 2.51)[d]	0.01
Pneumothorax, No. (%)	19 (4.0)	12 (2.4)	1.76 (0.84 to 3.70)[d]	0.14
Need for rescue strategy, No. (%)	94 (19.7)	72 (14.6)	1.70 (1.14 to 2.54)[d]	0.009
Recruitment maneuvers	62 (13.0)	39 (7.9)	2.06 (1.24 to 3.42)[d]	---**
Prone positioning	25 (5.3)	29 (5.9)	1.24 (0.64 to 2.40)[d]	---**
Bronchoscopy for atelectasis	30 (6.3)	26 (5.3)	1.01 (0.56 to 1.83)[d]	---**
Days with continuous vasopressor				
Mean (SD)	3.1 (3.7)	3.1 (3.5)	0.12 (-0.41 to 0.66)[e]	0.65
Median (IQR)	2.0 (1.0 – 4.0)	2.0 (1.0 – 3.0)		
Days with continuous sedation				
Mean (SD)	3.5 (3.9)	3.3 (3.8)	0.45 (-0.09 to 0.99)[e]	0.10
Median (IQR)	2.0 (1.0 – 4.0)	2.0 (1.0 – 4.0)		
ICU length of stay				
Mean (SD)	8.1 (11.5)	7.2 (10.3)	0.93 (0.78 to 1.11)[c]	0.41
Median (IQR)	4.0 (2.0 – 10.0)	4.0 (2.0 – 8.0)		
Hospital length of stay				
Mean (SD)	19.9 (22.1)	19.0 (21.4)	0.99 (0.82 to 1.20)[c]	0.90
Median (IQR)	12.0 (5.0 – 26.2)	12.0 (4.0 – 24.0)		
Mortality, No. (%)				
ICU	163 / 476 (34.2)	185 / 492 (37.6)	0.86 (0.62 to 1.20)[d]	0.37
Hospital	185 / 472 (39.2)	208 / 489 (42.5)	0.85 (0.61 to 1.18)[d]	0.34
28-day	183 (38.4)	207 (42.0)	0.96 (0.76 to 1.21)[c]	0.72
90-day	196 / 471 (41.6)	218 / 492 (44.3)	1.00 (0.80 to 1.25)[c]	0.99

Percentages may not total 100 because of rounding

Abbreviations: ARDS, acute respiratory distress syndrome; CI, confidence interval; ICU, intensive care unit; IQR, interquartile range; PEEP, positive end-expiratory pressure and VAP, ventilator-associated pneumonia.

* all models were adjusted by age, gender, APACHE IV and considered site as random effect

[a] Effect estimate is mean ratio (one-sided 95% confidence interval) from a generalized additive model for location scale and shape (GAMLSS) considering a zero-inflated beta distribution and using the delta method to estimate the confidence interval.

[b] *p* value for noninferiority.

[c] Effect estimate is hazard ratio (two-sided 95% confidence interval) from a (shared-frailty) Cox proportional hazard model: *p* value for the Schoenfeld residuals is 0.310 for duration of ventilation in survivors, 0.772 for ICU length of stay, 0.772 for hospital length of stay, 0.507 for 28-day mortality and 0.257 for 90-day mortality.

[d] Effect estimate is odds ratio (two-sided 95% confidence interval) from mixed-effect generalized linear model with binomial distribution.

[e] Effect estimate is mean difference (two-sided 95% confidence interval) from a mixed-effect generalized linear model with Gaussian distribution.

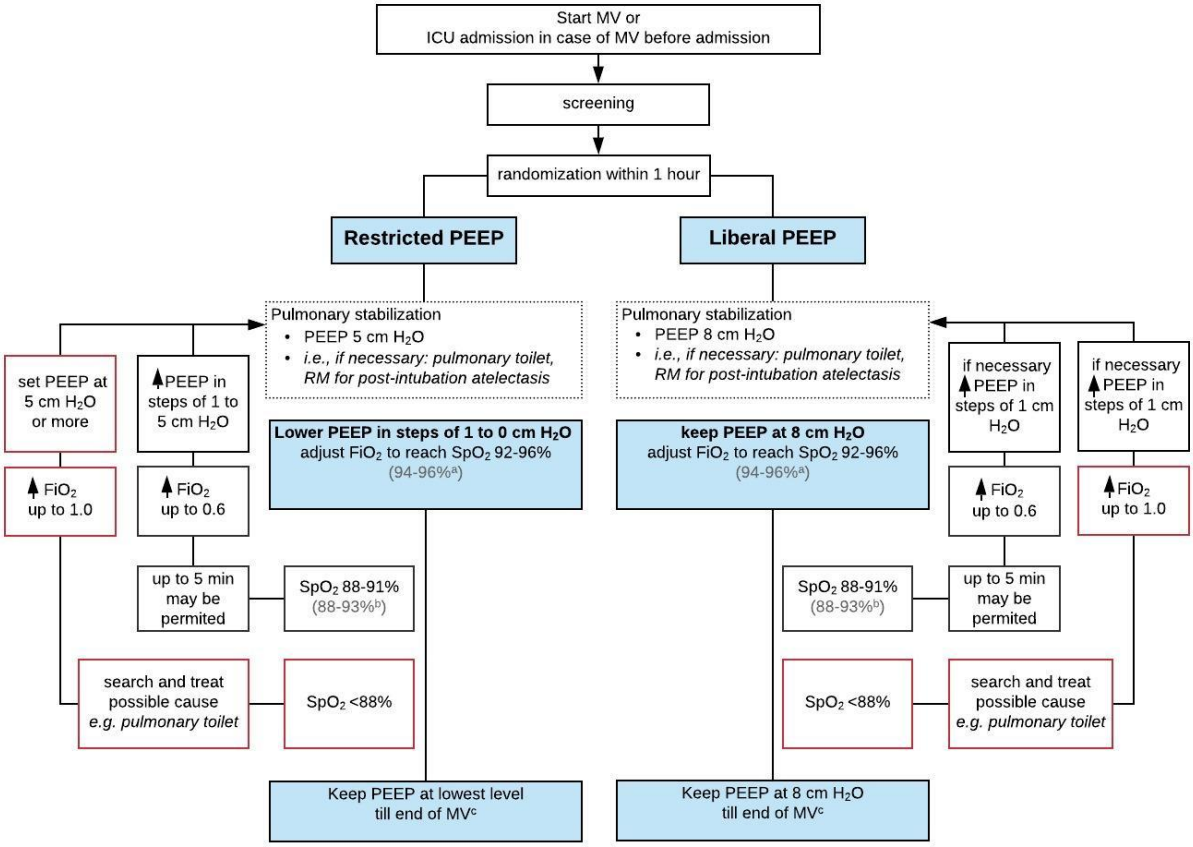
eTable 7. Significance Levels for Secondary Outcomes in Table 2 of Paper after Correction for Multiple Comparisons

	Unadjusted *p* value	Corrected *p* value[a]
Need for rescue strategy	0.03363912	0.5382259
ARDS	0.05739909	0.8609864
Pneumothorax	0.16840820	1.0000000
Severe hypoxemia	0.24419260	1.0000000
28-day mortality	0.26874700	1.0000000
ICU mortality	0.27639520	1.0000000
Hospital mortality	0.29228750	1.0000000
Severe atelectasis	0.33368880	1.0000000
Duration of ventilation in survivors	0.37096350	1.0000000
Days with continuous sedation	0.37380150	1.0000000
90-day mortality	0.38139980	1.0000000
ICU length of stay	0.69219170	1.0000000
Days with continuous vasopressor	0.82849270	1.0000000
Confirmed VAP	0.82931610	1.0000000
Hospital length of stay	0.86010650	1.0000000
Suspected VAP	0.93679940	1.0000000

Abbreviations: ARDS, acute respiratory distress syndrome; ICU, intensive care unit and VAP, ventilator-associated pneumonia

[a] Holm-Bonferroni procedure for multiple statistical tests controlling for the 16 comparisons in the table. The overall table-wise Type I error rate is controlled at 5%.

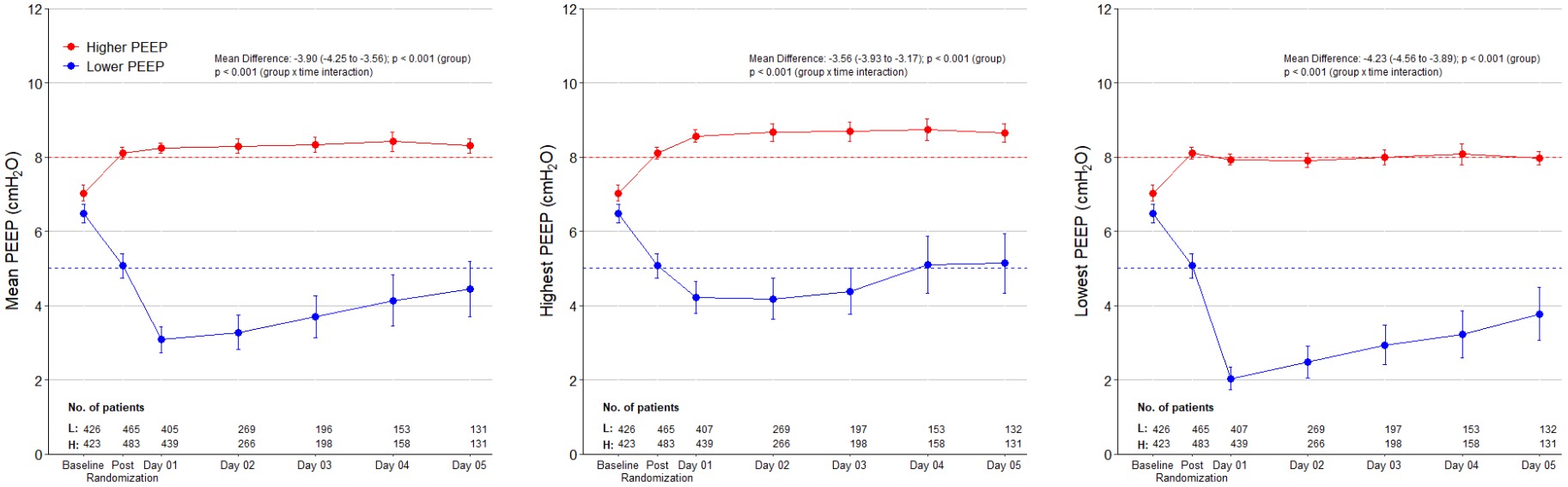
eFigure 1. Flowchart of Ventilator Settings in the Two Ventilation Strategies



[a] = 94-96%, [b] = 88-93%, higher oxygen targets are allowed for patients who develop:
1) ongoing cardiac ischemia due to cardiac infarction and failed revascularisation
2) delayed cerebral ischemia after subarachnoid hemorrhage
3) increased and uncontrollable intracranial pressure (≥ 18 mmHg)
4) necrotizing fasciitis
5) severe untreatable anemie, such as in case of Jehovah's Witnesses
[c], short periods of PEEP at 5 cm H_2O are allowed to evaluate whether the patient can be extubated

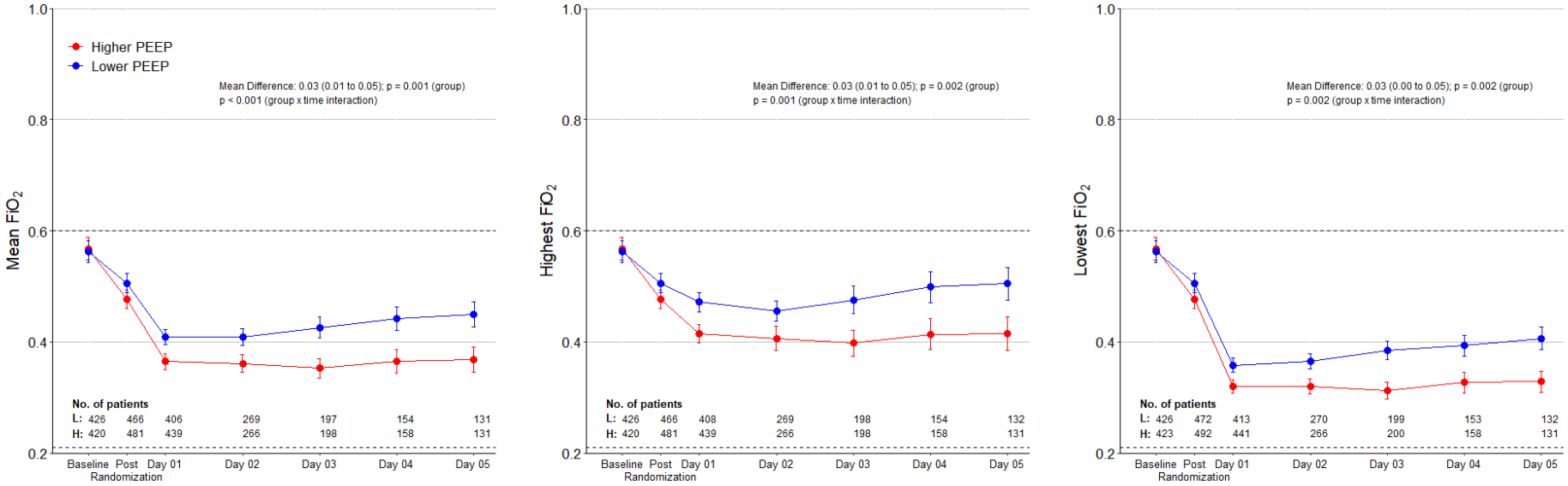
Abbreviations: PEEP, positive end-expiratory pressure; MV, mechanical ventilation; PBW, predicted body weight; RM, recruitment maneuver.

eFigure 2. Mean, Highest and Lowest PEEP in the First Five Days According to the Allocation Group



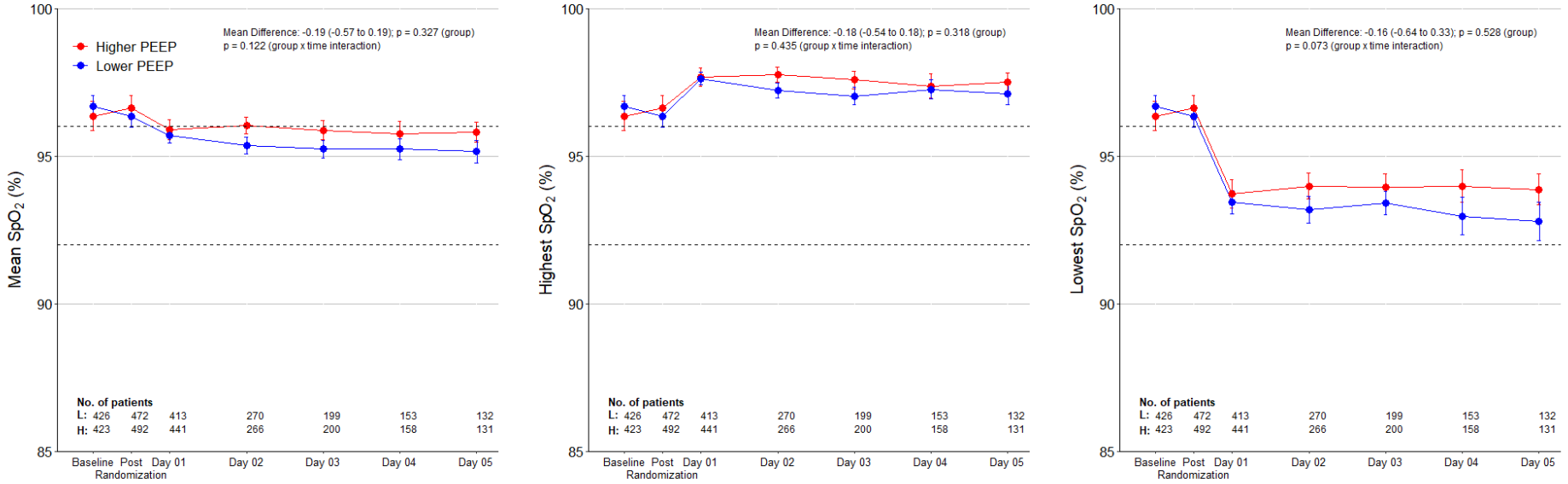
Circles are mean and error bars 95% confidence interval. Mean, highest and lowest PEEP recorded from measurements of PEEP taken every six hours while the patient was invasively ventilated. Mean difference and 95% confidence interval is the overall mean difference for the period calculated from a mixed-effect linear model with an interaction among treatment arm and time (treated as a continuous variable) and with random effect for patients (to account for repeated measurements) and centers. Baseline values were not considered in the mixed-effect model. Blue dashed line represents the upper limit of the target of the lower PEEP group, and the red dashed line represents the target of the higher PEEP group.

eFigure 3. Mean, Highest and Lowest FiO_2 in the First Five Days According to the Allocation Group



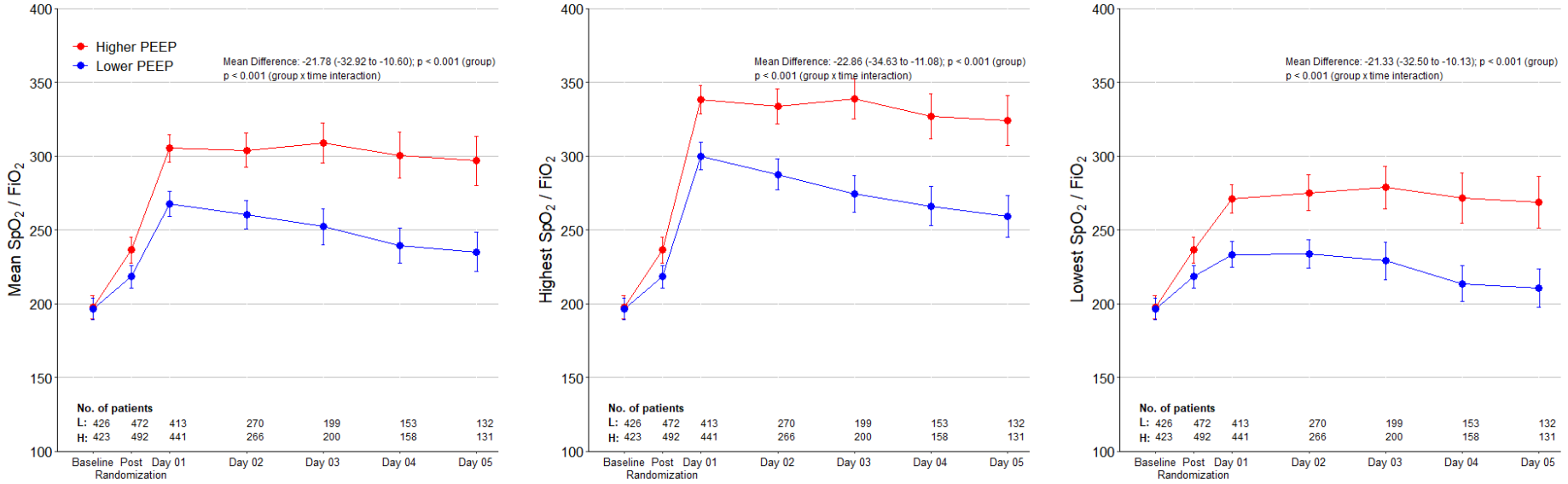
Circles are mean and error bars 95% confidence interval. Mean, highest and lowest FiO_2 recorded from measurements of FiO_2 taken every six hours while the patient was invasively ventilated. Mean difference and 95% confidence interval is the overall mean difference for the period calculated from a mixed-effect linear model with an interaction among treatment arm and time (treated as a continuous variable) and with random effect for patients (to account for repeated measurements) and centers. Baseline values were not considered in the mixed-effect model. Black dashed lines represent the upper and lower targets of the intervention.

eFigure 4. Mean, Highest and Lowest SpO_2 in the First Five Days According to the Allocation Group



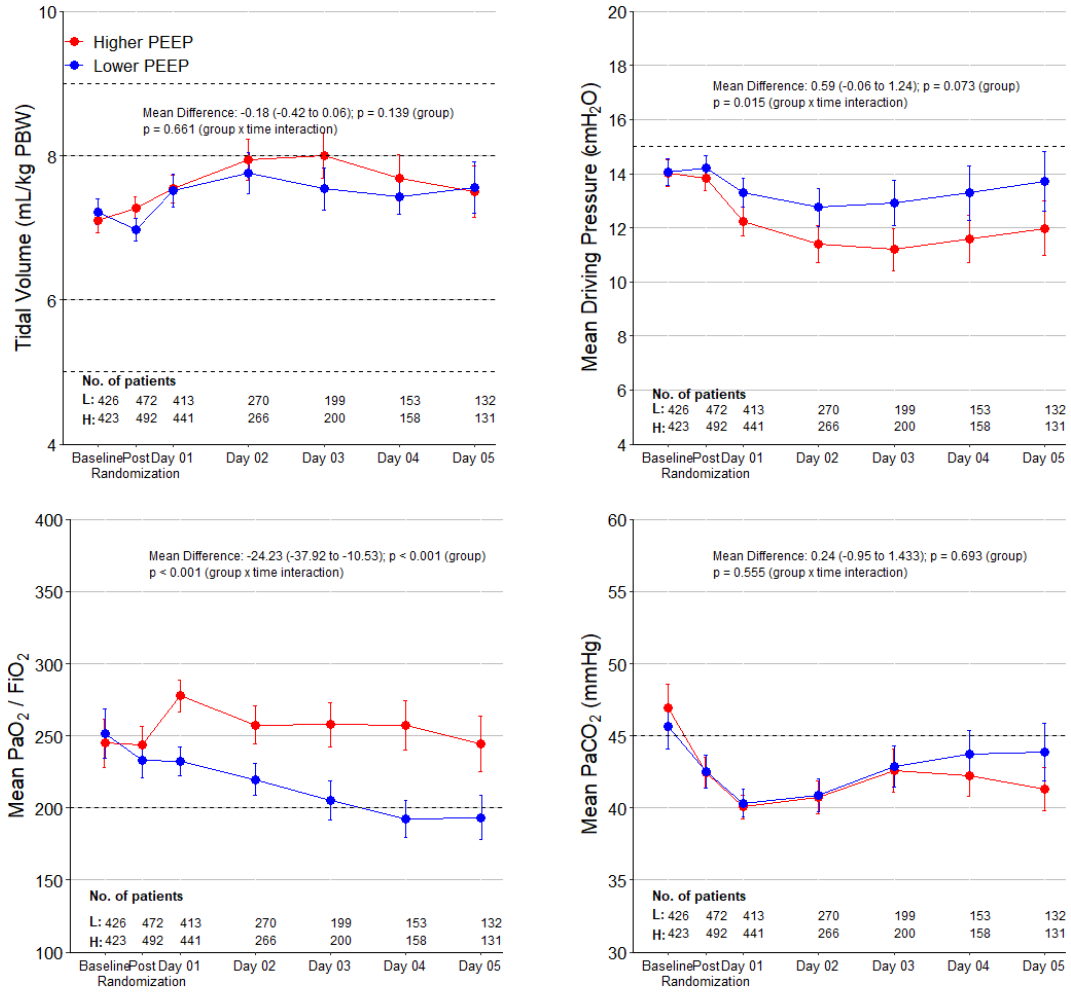
Circles are mean and error bars 95% confidence interval. Mean, highest and lowest SpO_2 recorded from measurements of SpO_2 taken every six hours while the patient was invasively ventilated. Mean difference and 95% confidence interval is the overall mean difference for the period calculated from a mixed-effect linear model with an interaction among treatment arm and time (treated as a continuous variable) and with random effect for patients (to account for repeated measurements) and centers. Baseline values were not considered in the mixed-effect model. Black dashed lines represent the upper and lower targets of the intervention.

eFigure 5. Mean, Highest and Lowest SpO_2 / FiO_2 in the First Five Days According to the Allocation Group



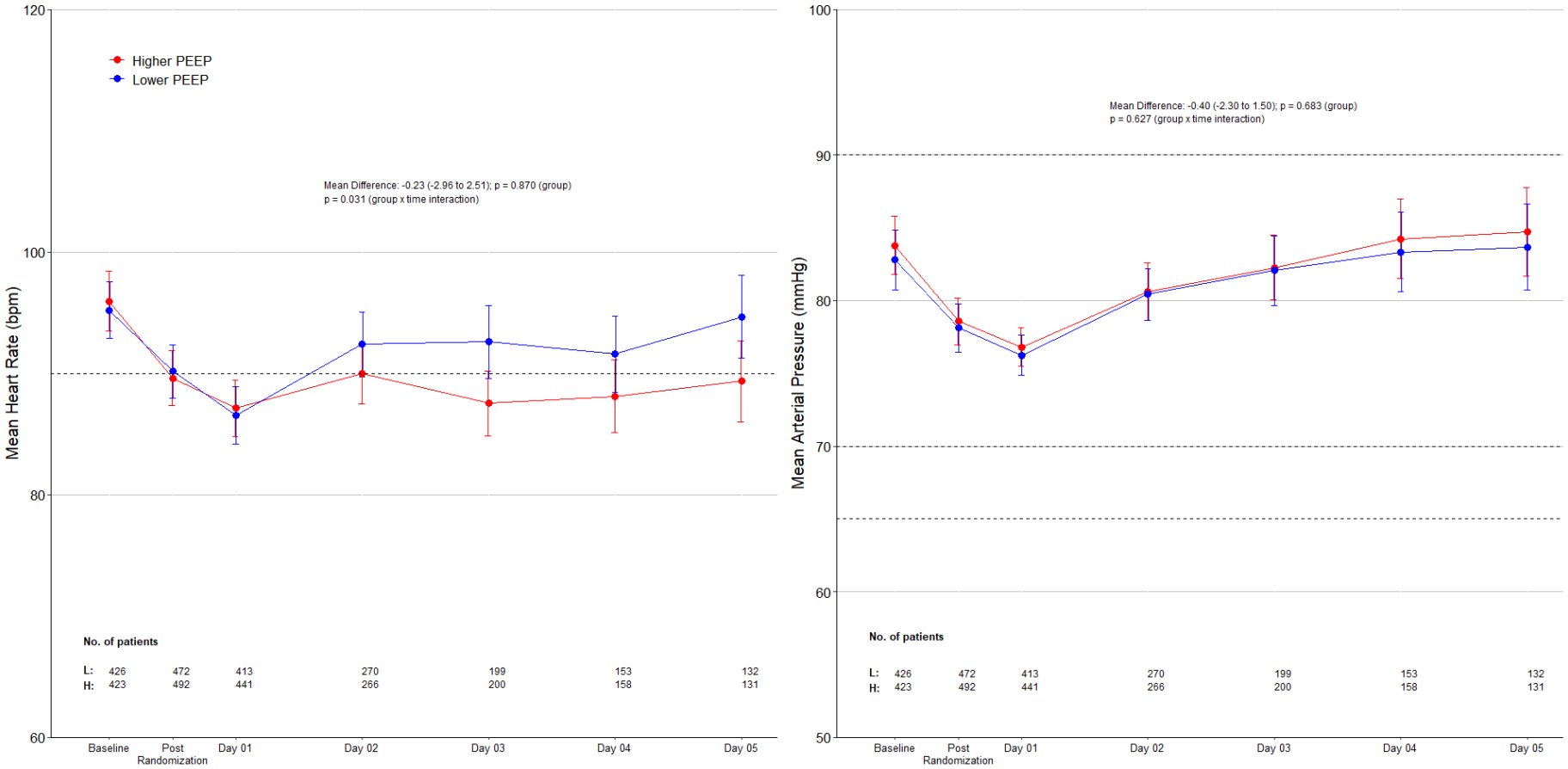
Circles are mean and error bars 95% confidence interval. Mean, highest and lowest SpO_2 / FiO_2 recorded from measurements of SpO_2 / FiO_2 taken every six hours while the patient was invasively ventilated. Mean difference and 95% confidence interval is the overall mean difference for the period calculated from a mixed-effect linear model with an interaction among treatment arm and time (treated as a continuous variable) and with random effect for patients (to account for repeated measurements) and centers. Baseline values were not considered in the mixed-effect model.

eFigure 6. Mean Tidal Volume, Driving Pressure, PaO_2 / FiO_2 and $PaCO_2$ in the First Five Days According to the Allocation Group



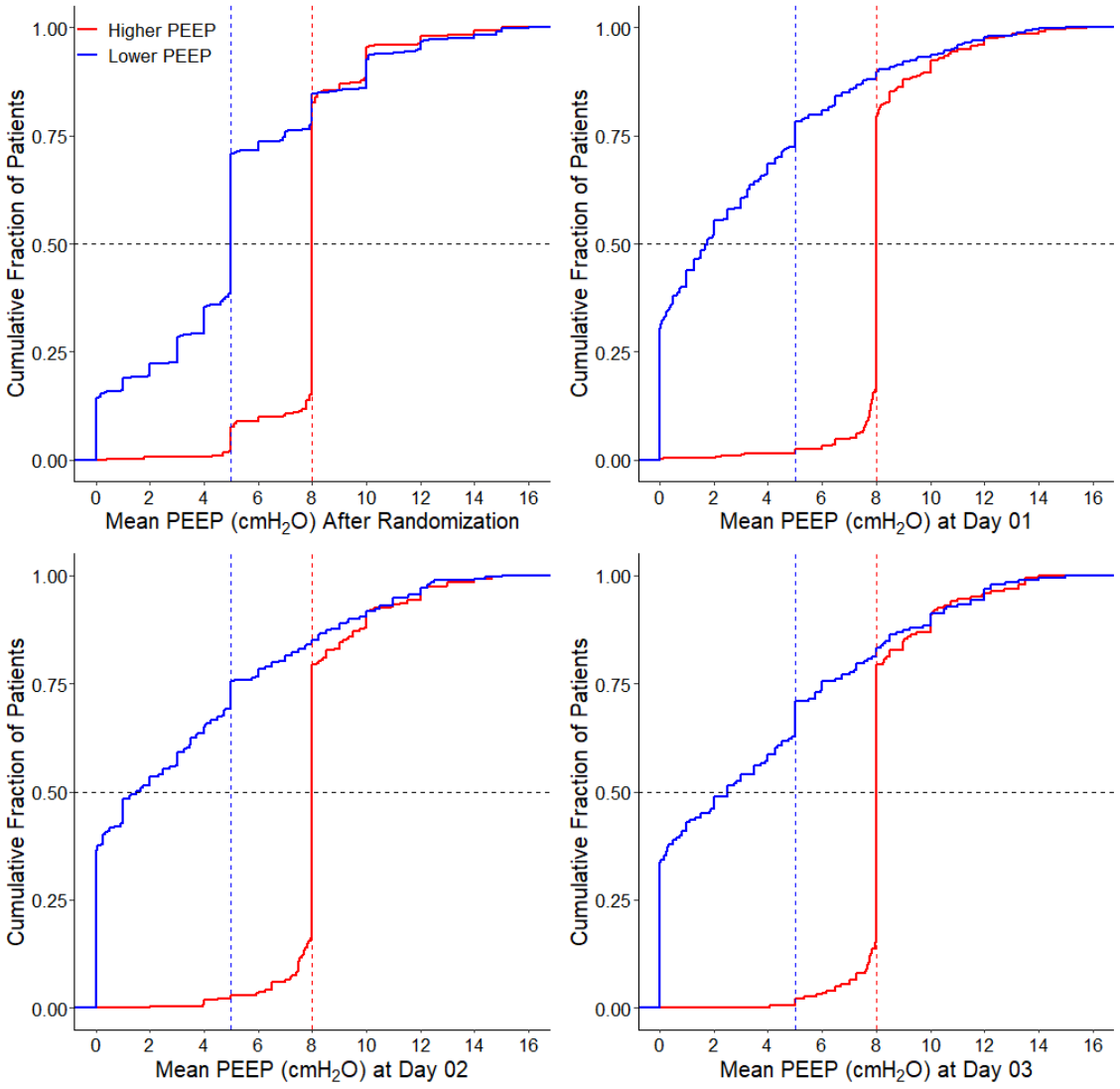
Circles are mean and error bars 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period calculated from a mixed-effect linear model with an interaction among treatment arm and time (treated as a continuous variable) and with random effect for patients (to account for repeated measurements) and centers. Baseline values were not considered in the mixed-effect model.
Black dashed lines represent well accepted safety cut-offs for the variables presented.

eFigure 7. Mean Heart Rate and Mean Arterial Pressure in the First Five Days According to the Allocation Group



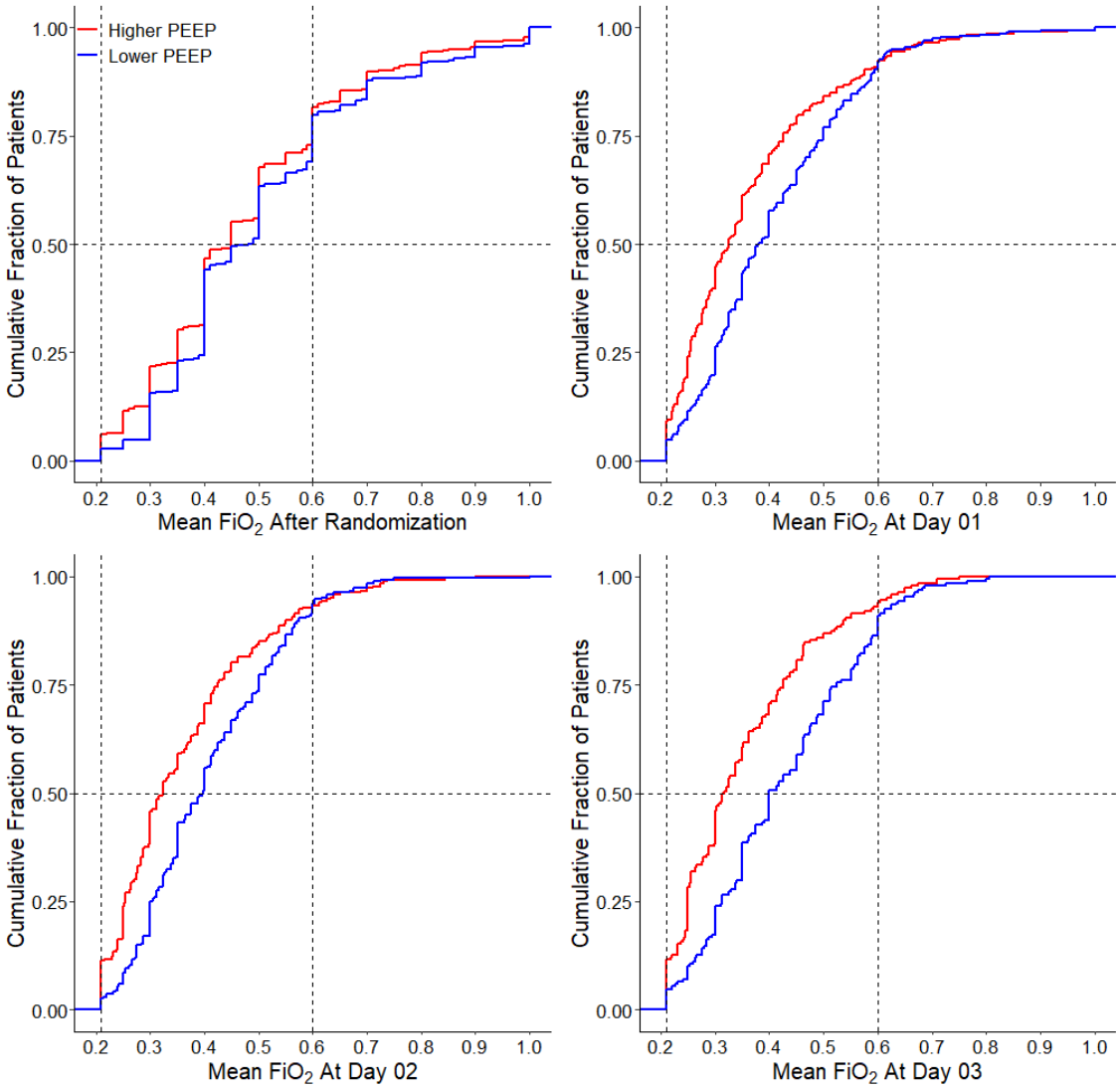
Circles are mean and error bars 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period calculated from a mixed-effect linear model with an interaction among treatment arm and time (treated as a continuous variable) and with random effect for patients (to account for repeated measurements) and centers. Baseline values were not considered in the mixed-effect model.
Black dashed lines represent well accepted safety cut-offs for the variables presented.

eFigure 8. Cumulative Distribution of PEEP in the First Three Days According to the Allocation Group



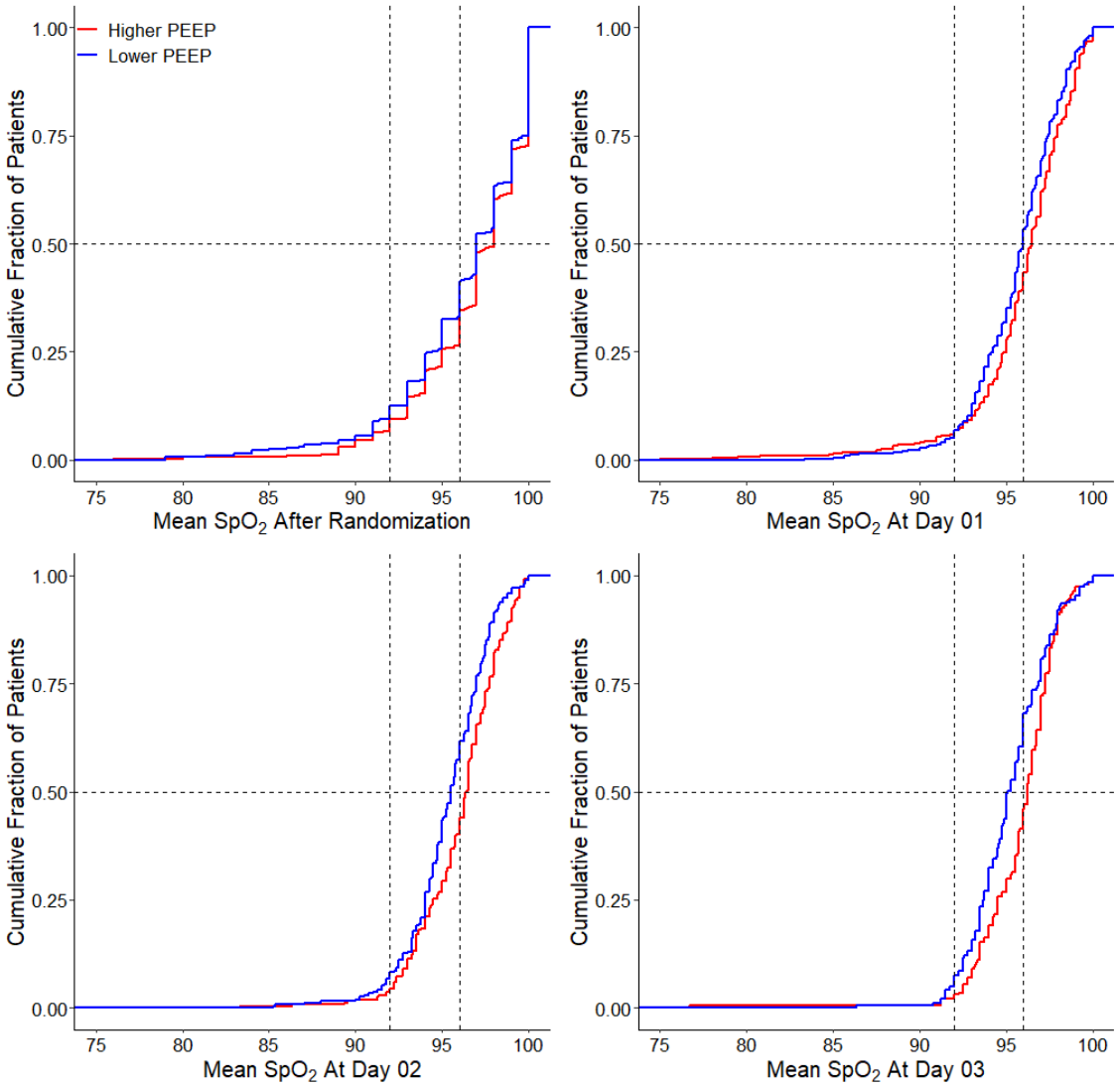
Cumulative distribution plot showing the mean PEEP by treatment group. The mean PEEP was calculated from recordings of PEEP taken every six hours.
Black horizontal dashed line represents 50% of patients, and blue and red vertical dashed lines represent the targets of the intervention in each group.

eFigure 9. Cumulative Distribution of FiO_2 in the First Three Days According to the Allocation Group



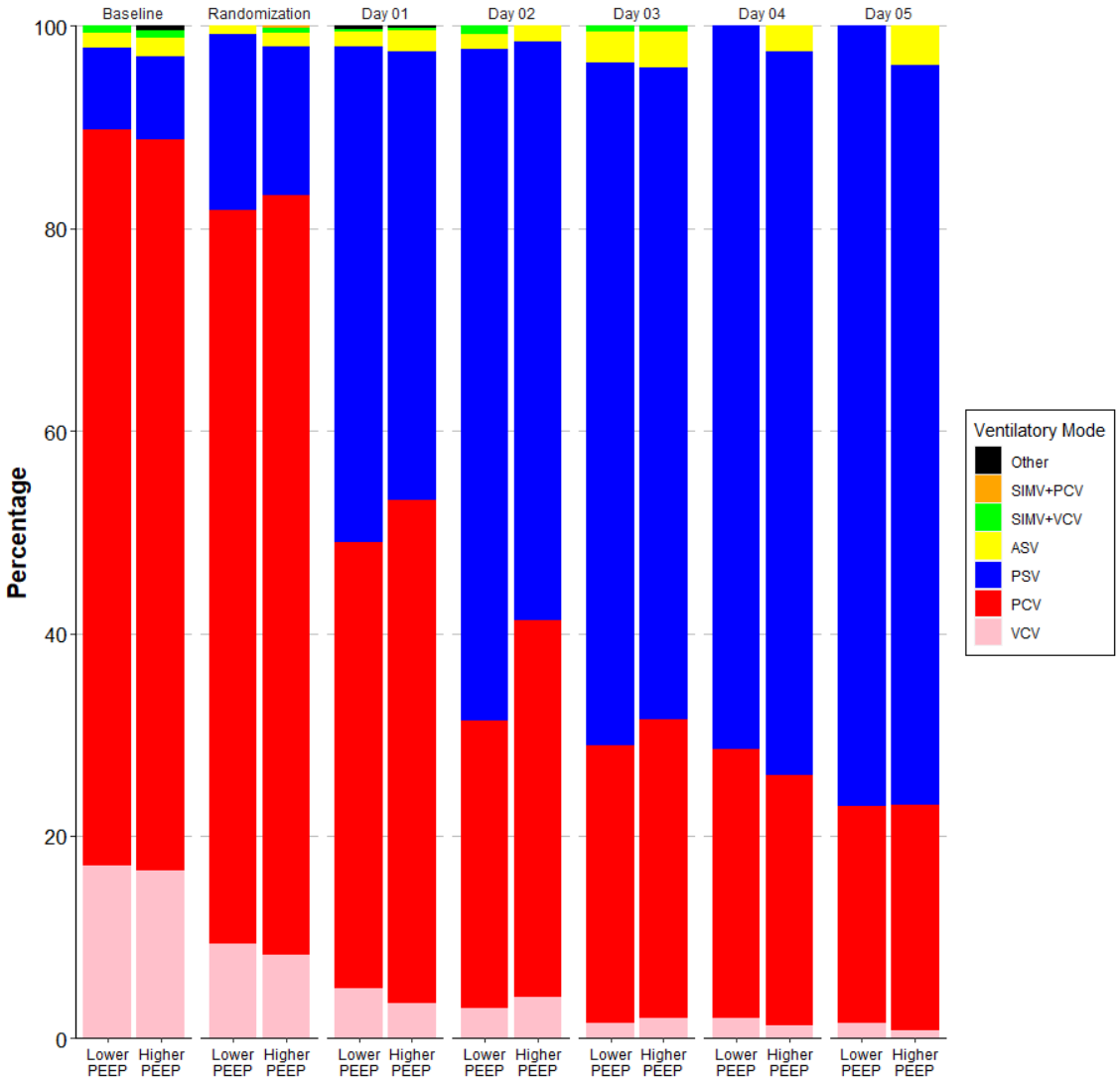
Cumulative distribution plot showing the mean FiO_2 by treatment group. The mean FiO_2 was calculated from recordings of FiO_2 taken every six hours.
Black horizontal dashed line represents 50% of patients, and black vertical dashed lines represent the upper and lower targets of FiO_2.

eFigure 10. Cumulative Distribution of SpO_2 in the First Three Days According to the Allocation Group



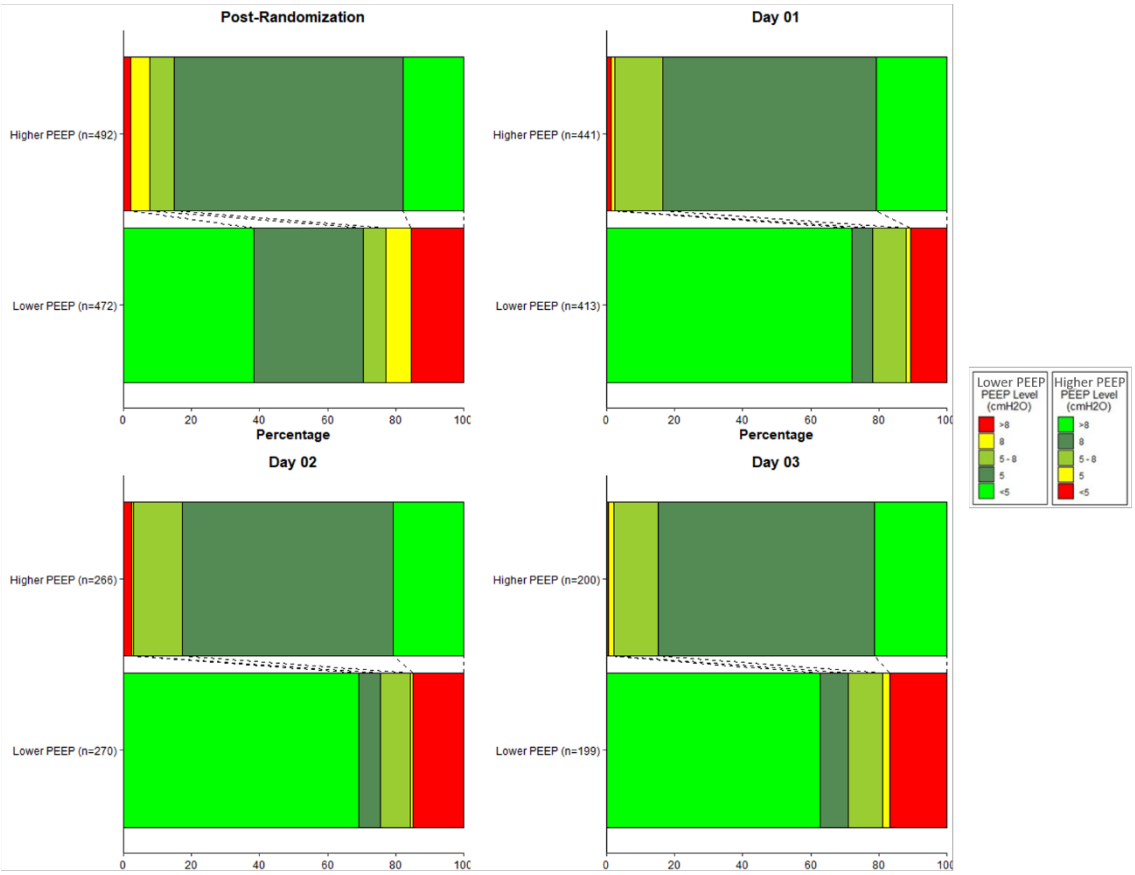
Cumulative distribution plot showing the mean SpO_2 by treatment group. The mean SpO_2 was calculated from recordings of SpO_2 taken every six hours.
Black horizontal dashed line represents 50% of patients, and black vertical dashed lines represent the upper and lower targets of SpO_2.

eFigure 11. Ventilatory Modes in the First Five Days According to the Allocation Group



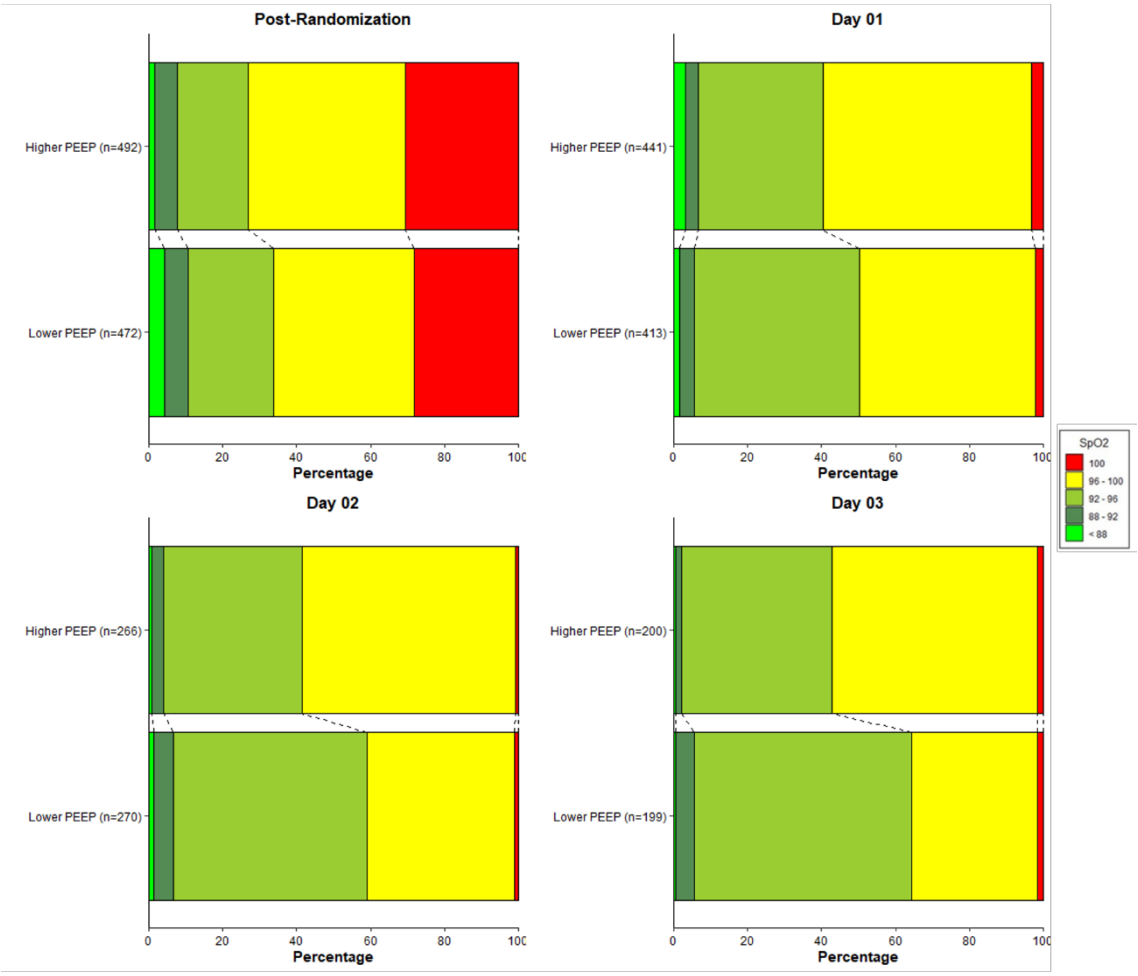
VCV denotes volume-controlled ventilation, PCV pressure-controlled ventilation, PSV pressure support ventilation, ASV adaptive support ventilation, SIMV+VCV synchronized intermittent mandatory volume controlled-ventilation and SIMV+PCV synchronized intermittent mandatory pressure controlled-ventilation.

eFigure 12. Percentage of Patients in Each Group of PEEP in the First Three Days According to the Allocation Group



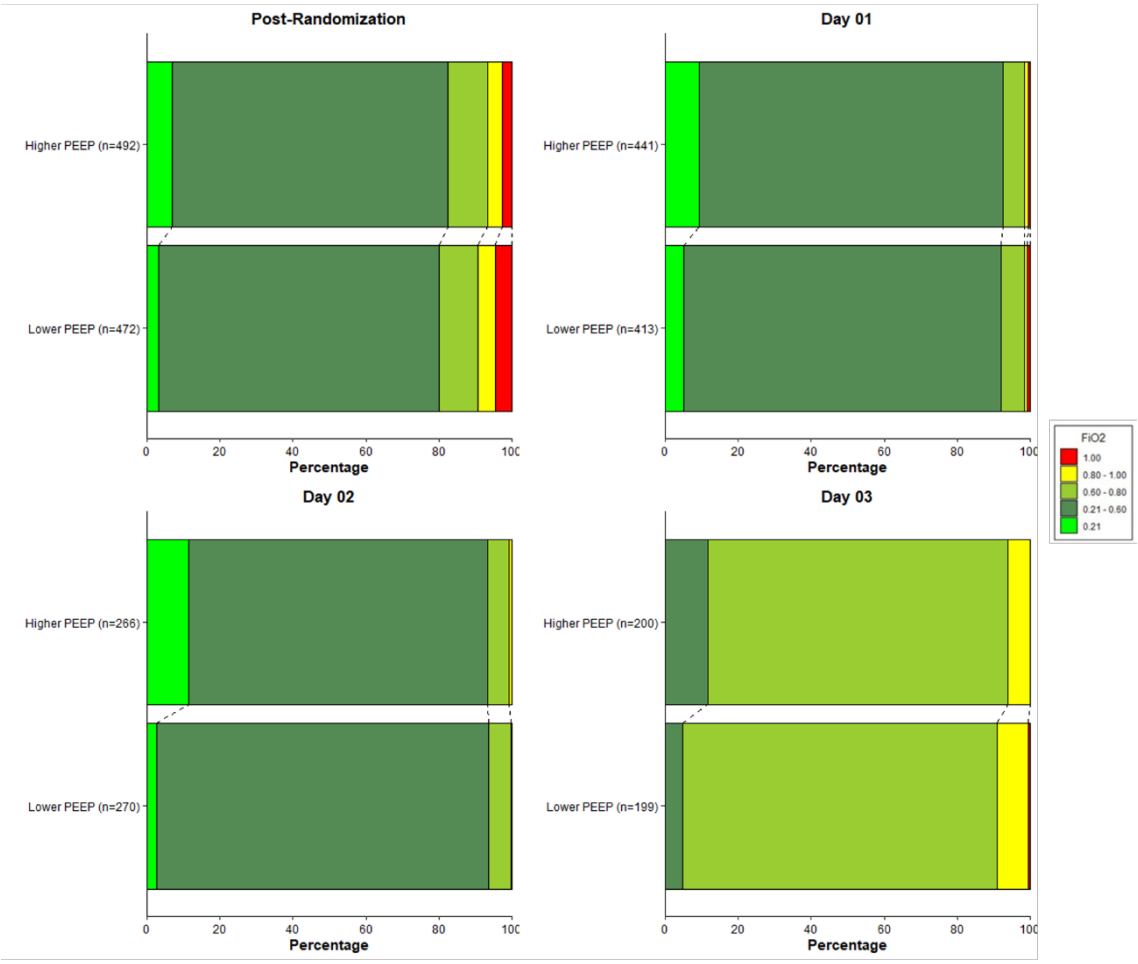
Categories calculated according to the mean of measurements of PEEP took every six hours.

eFigure 13. Percentage of Patients in Each Group of SpO_2 in the First Three Days According to the Allocation Group



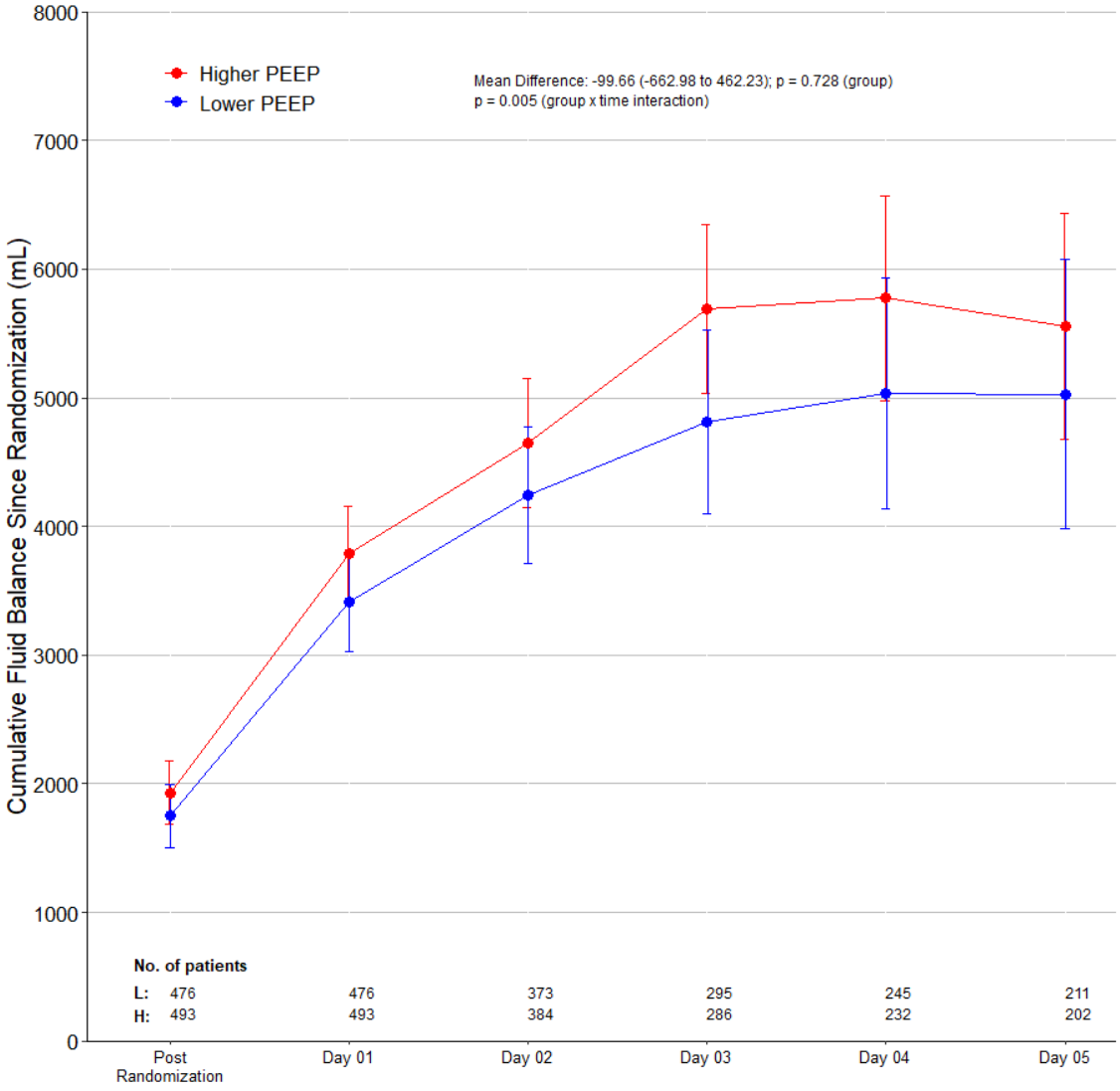
Categories calculated according to the mean of measurements of SpO_2 took every six hours.

eFigure 14. Percentage of Patients in Each Group of FiO_2 in the First Three Days According to the Allocation Group



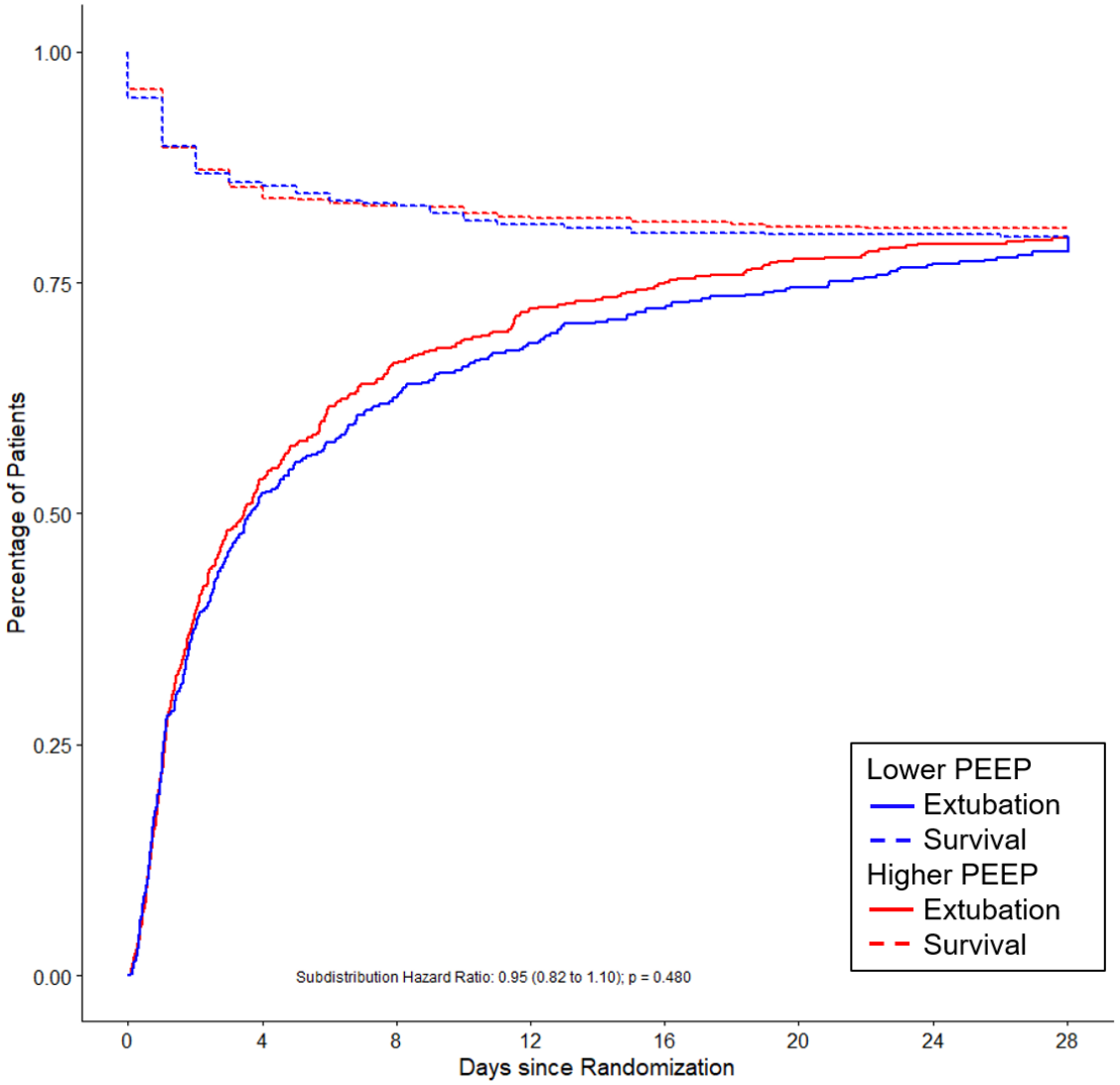
Categories calculated according to the mean of measurements of FiO_2 took every six hours.

eFigure 15. Cumulative Fluid Balance in the First Five Days According to the Allocation Group



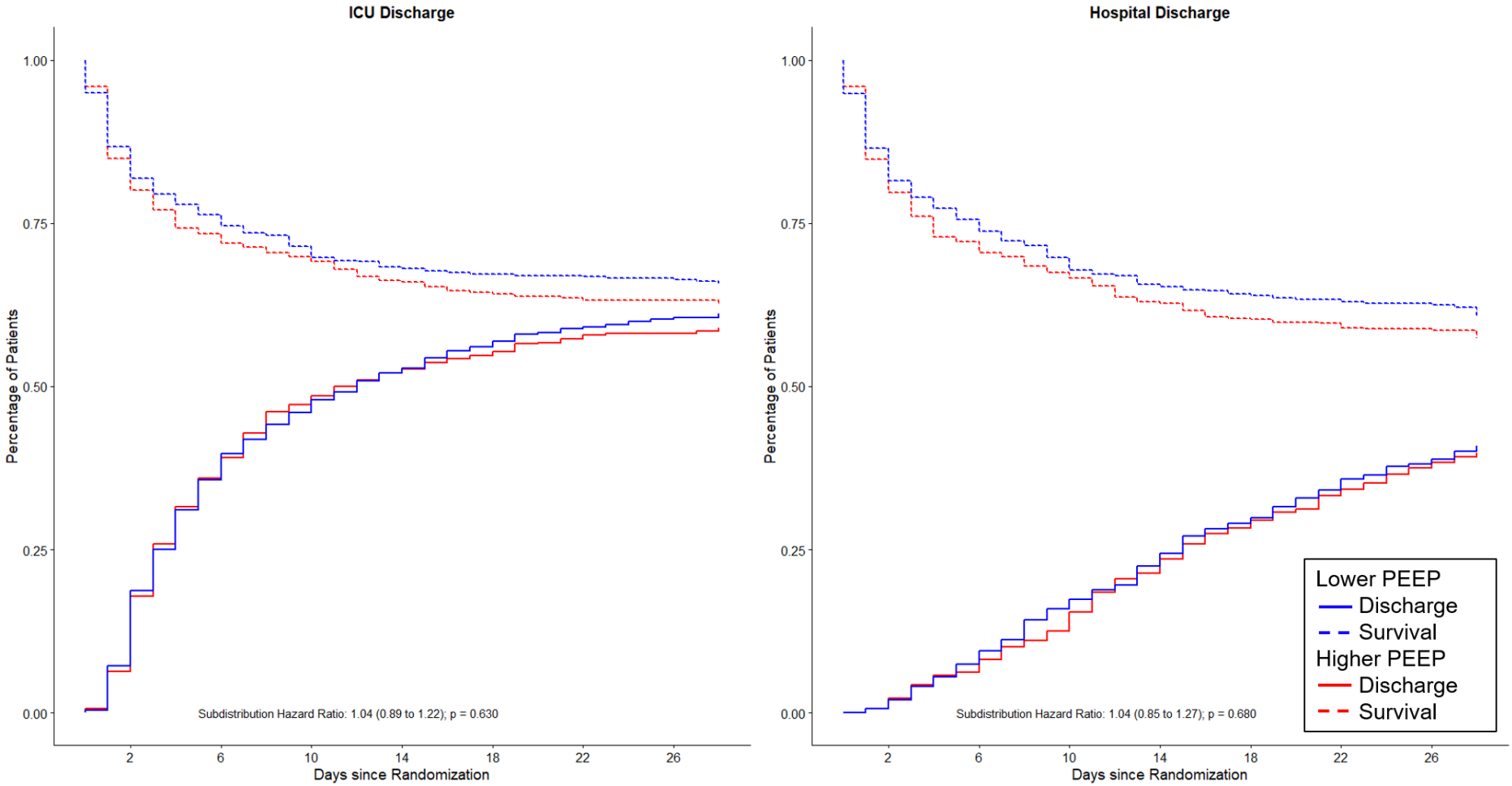
Circles are mean and error bars 95% confidence interval. Mean difference and 95% confidence interval is the overall mean difference for the period calculated from a mixed-effect linear model with an interaction among treatment arm and time (treated as a continuous variable) and with random effect for patients (to account for repeated measurements) and centers.

eFigure 16. Patients Who Survived and Were Extubated during the First 28 Days after Randomization



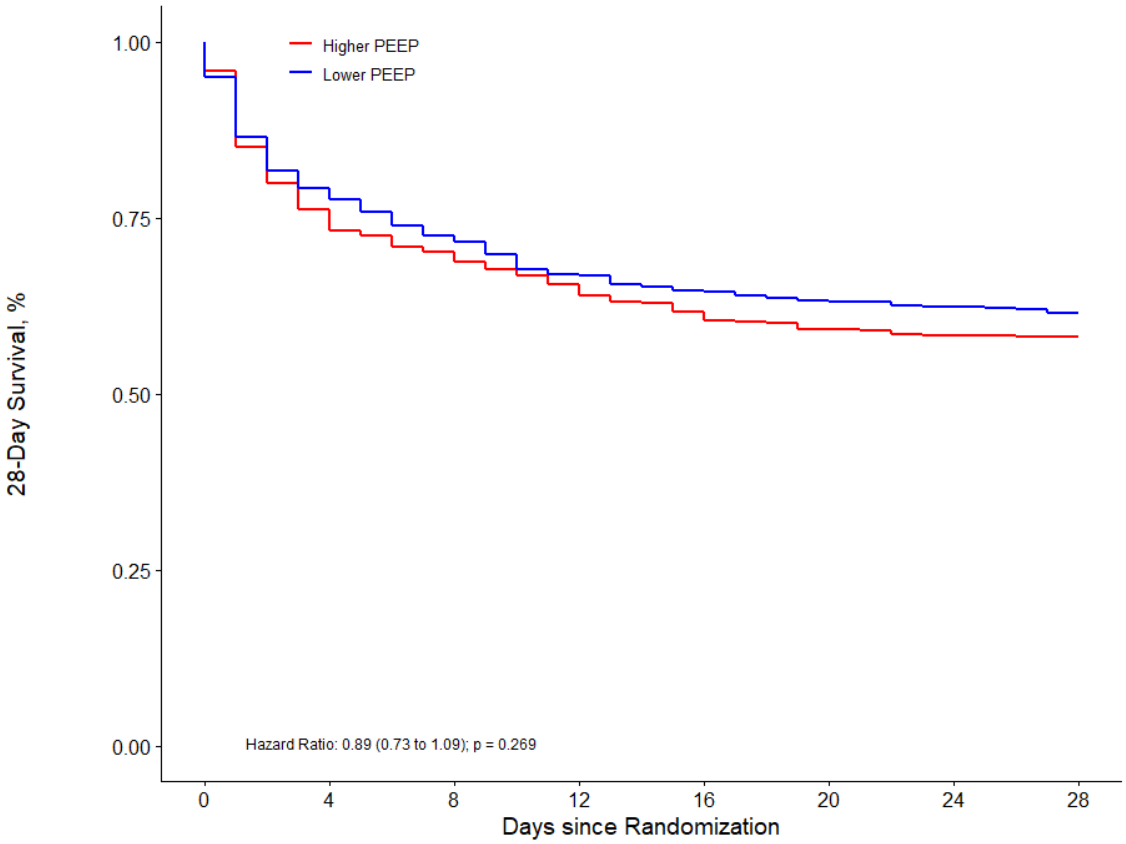
Cumulative Incidence Function for the time until freedom of invasive ventilation in all patients in both groups with death before extubation treated as competing risk and with an unadjusted subdistribution hazard ratio and 95% confidence interval calculated from a Fine–Gray model

eFigure 17. Patients Who Survived and Were Discharged Alive from the ICU and Hospital During the First 28 Days after Randomization



Cumulative Incidence Function for the time until being discharged alive from the ICU or hospital in all patients in both groups with death before discharge treated as competing risk and with an unadjusted subdistribution hazard ratio and 95% confidence interval calculated from a Fine–Gray model

eFigure 18. Kaplan–Meier Estimates for Patients in the Low and High PEEP groups



No. at Risk

Higher PEEP	493	376	346	323	304	292	287	286
Lower PEEP	476	377	345	319	308	301	297	293

Kaplan–Meier curve for the 28–day survival in both groups. An unadjusted hazard ratio and 95% confidence interval calculated from a Cox proportional hazard model is presented.

eReferences

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2. Oostdijk EAN, Kesecioglu J, Schultz MJ, et al. Notice of Retraction and Replacement: Oostdijk et al. Effects of Decontamination of the Oropharynx and Intestinal Tract on Antibiotic Resistance in ICUs: A Randomized Clinical Trial. JAMA . 2014;312(14):1429-1437. JAMA. 2017;317(15):1583. doi: 10.1001/jama.2017.1282.