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Supplementary appendix

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Ventilation Management and Clinical Outcome in Invasively Ventilated COVID–19 Patients (PRoVENT–COVID) – a national, multicentre, observational cohort study

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*‘PRactice of VENTilation in COVID–19 study’

Supplementary Appendix

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Protocol with updated analysis plan (June 01, 2020)

PRactice of VENTilation in COVID–19 patients (PRoVENT-COVID) – an observational study of invasively ventilated patients in the Netherlands

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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

AKI	Acute Kidney Injury
APACHE	Acute Physiology And Chronic Health Evaluation
ARDS	Acute Respiratory Distress Syndrome
COVID-19	Coronavirus disease 2019
DP	Driving Pressure
$EtCO_2$	End-tidal Carbon Dioxide
FiO_2	Fraction of inspired Oxygen
HCO_3^-	Bicarbonate
IBW	Ideal Body Weight
ICU	Intensive Care Unit
I:E ratio	Inspiratory : Expiratory ratio
NIV	Non-invasive ventilation
P_{max}	Maximum airway pressure
P_{peak}	Peak pressure
$P_{plateau}$	Plateau pressure
PaO_2	Partial Arterial Pressure of Oxygen
$PaCO_2$	Partial Arterial Pressure of Carbon Dioxide
PBW	Predicted Body Weight
PEEP	Positive End–Expiratory Pressure
RR	Respiratory Rate
SaO_2	Saturation of Arterial Oxygen
SAPS	Simplified Acute Physiology Score
SARS–CoV–2	Severe acute respiratory coronavirus–2
SD	Standard Deviation
SOFA	Sequential Organ Failure Assessment Score
SpO_2	Saturation of peripheral Oxygen
V_T	Tidal Volume
VILI	Ventilator induced lung injury
VTE	Expiratory tidal volume

SUMMARY

Rationale

The novel coronavirus disease (COVID–19) pandemic is rapidly expanding across the world, with over 60.000 new cases each day as of late March 2020. Healthcare workers are struggling to provide the best care for patients with proven or suspected COVID–19. Approaches for clinical care vary widely between and within countries and new insights are acquired rapidly. This includes the way invasive ventilation is applied.

Objective

To determine and compare invasive ventilation settings and parameters in COVID–19 patients in the Netherlands, and to determine associations with clinical outcomes.

Hypotheses

Invasive ventilation settings and parameters vary between intensive care units (ICUs) in hospitals in the Netherlands; certain ventilator settings have an independent association with duration of ventilation in COVID–19 patients.

Study design

National, multicenter, service review.

Study population

Invasively ventilated patients with proven or suspected COVID–19.

Methods

In every patient, granular ventilator settings and parameters are collected from start of invasive ventilation for up to 72 hours. Patients will be followed up until ICU and hospital discharge, and until day 90.

Study endpoints

Main ventilator settings (including tidal volume, airway pressures, oxygen fraction and respiratory rate) (primary) and parameters (blood gas results); use of rescue therapies (including prone positioning); use of sedatives, vasopressors and inotropes; daily cumulative fluid balances; development of kidney injury; ventilator–free days and alive at day 28 (VFD–28), duration of ICU and hospital stay, and ICU, hospital and 90–day mortality.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness

Retrospective collection of data regarding ventilation management and major clinical endpoints is without risk for the individual patient.

1. INTRODUCTION AND RATIONALE

1.1 The coronavirus disease 2019

Coronavirus disease 2019 (COVID–19) is a lower respiratory tract infection caused by the severe acute respiratory coronavirus–2 (SARS–CoV–2), of which the first outbreak was reported in Wuhan, China in the beginning of December, 2019. Since then, it has rapidly spread across the globe, with over 60.000 new cases each day as of late March 2020.

Although most people who are infected by SARS–CoV–2 only develop mild symptoms, an estimated 5% of reported cases are admitted to the intensive care unit (ICU) because of severe hypoxemia and dyspnoea [1]. The majority of these patients have shown to require invasive ventilation, and in this group, the mortality is considerable [2].

1.2 Lung protective ventilation

Although invasive ventilation can be a necessary supportive strategy in patients with respiratory failure, it also has the potential to worsen pre-existing lung injury or even initiate it [3]. 'Ventilator-induced lung injury' (VILI) is mainly due to overdistension of the lungs, and is associated with a longer duration of ventilation and a higher mortality [4]. Lung protective ventilation, featuring low tidal volume (V_T), reduced inspiratory plateau pressure ($P_{plateau}$) [5] and low driving pressure (DP) [6] has been suggested to reduce the risk of mortality and is considered the standard of care ([7-10]. The benefit of high positive end–expiratory pressure (PEEP) remains uncertain, as does the use of recruitment maneuvers. There is evidence that high PEEP with recruitment maneuvers harms patients with ARDS [11]. It is highly uncertain whether high PEEP with recruitment maneuvers benefits COVID–19 patients.

1.3 Need for an observational study on ventilator settings

Due to the rapid spread of COVID–19, ICUs worldwide are being overloaded with patients requiring invasive ventilation and healthcare workers are struggling to provide the best care. Approaches in clinical care are already known to vary widely between countries and regions, including the way invasive ventilation is applied [12-15]. It is probable that these variances are amplified by a lack of consensus in treatment due to the novelty of COVID–19. Because invasive ventilation of itself has a strong potential to cause lung damage, these variances could be associated with a difference in patient–centered outcomes, like duration of ventilation and mortality.

Therefore, it is of the utmost importance to observe ventilation strategies that are currently being applied in the treatment of COVID–19 patients. To make haste in this time of crisis, we propose a national, observational, retrospective study that is focused on the inventory of ventilation parameters. This study will form an important first step in creating standard guidelines for invasive ventilation of COVID–19 patients. Implementation of standard guidelines could reduce mortality worldwide.

2. OBJECTIVES AND HYPOTHESIS

2.1 Objectives

2.1.1 Primary objective

To determine and compare invasive ventilation settings and parameters in COVID–19 patients in intensive care units (ICU) of hospitals in the Netherlands.

2.1.2 Secondary objective

To determine whether certain ventilation settings have an independent association with duration of ventilation.

2.2 Hypothesis

2.2.1 Primary hypothesis

There is substantial variation in ventilation practices in COVID–19 patients admitted to the ICU's of hospitals in the Netherlands.

2.2.2 Secondary hypothesis

Certain ventilation settings impact duration of ventilation.

3. STUDY DESIGN

Multicenter, national, retrospective, observational study in COVID–19 patients with respiratory failure, requiring invasive ventilation in intensive care unit (ICU) settings in hospitals in the Netherlands.

4. STUDY POPULATION

4.1 Population (base)

The data of at least 1,000 consecutively invasively ventilated COVID–19 patients admitted to intensive care units (ICUs) of hospitals in the Netherlands. This study will not be restricted to the 'formal' ICUs, as patients may also receive invasive ventilation at other locations within the hospital during the COVID–19 pandemic.

4.2 Inclusion criteria

- COVID–19, confirmed with PCR and/or presence of typical abnormalities on chest computer tomography (CT)
- Suspected COVID–19 infection, with no exclusion of diagnosis
- Having received invasive ventilation

4.3 Exclusion criteria

- Age <18 years
- Already included in the same study in another hospital
- Having had received invasive ventilation > 24 hours in a non–participating hospital

4.4 Sample size calculation

No formal sample size calculation is needed. We expect to capture at least 1,000 patients, but will continue collecting data of new patients for at least 8 weeks.

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameters

- Ventilation mode;
- Tidal volume set (V_T) (mL);
- Expiratory tidal volume (VTE)
- Positive end–expiratory pressure (PEEP) (cm H_2O);
- Maximum airway pressure (P_{max}) (cm H_2O) or plateau pressure ($P_{plateau}$) or peak pressure (P_{peak}) (cm H_2O);
- Level of pressure support above PEEP (cm H_2O);
- Inspired fraction of oxygen (FiO_2) (%);
- Set and measured respiratory rate (RR) (min^{-1}); and
- Inspiration to expiration ratio (I:E) (ratio).

5.1.2 Secondary study parameters

- Number of ventilation–free days and alive at day 28 (VFD–28);
- Duration of ventilation in survivors;
- Use of prone positioning;
- Use of recruitment maneuvers;
- Incidence of acute kidney injury (AKI);
- Duration of ICU stay;
- Duration of hospital stay;
- ICU mortality;
- Hospital mortality;
- 28-day mortality; and
- 90-day mortality.

5.2 Randomisation, blinding and treatment allocation

Not applicable.

5.3 Study procedures

Patients will be included by the attending clinician. Participating centers will be visited by researchers to collect data of included patients.

5.4 Data collection

5.4.1 Demographic data

- Age (age categories);
- Gender (male or female);
- Height (cm);
- Weight (kg);
- Medication (categories); and
- Comorbidities (categories).

5.4.2 Data on day of intubation OR admission to ICU if transferred from another hospital with mechanical ventilation

- Date of hospital admission;
- Date of ICU admission;
- Date and time of intubation (if possible, also in transferred patients);
- Transferred under ventilation (if applicable) (yes or no);
- Duration of ventilation in previous hospital (if applicable) (days);
- Use of non-invasive ventilation (NIV) before intubation (yes or no) and if so, duration (hours);
- Acute Physiology and Chronic Health (APACHE) II score or APACHE IV score, or Simplified Acute Physiology Score (SAPS) II;
- Sequential Organ Failure Scores (SOFA); and
- Plasma creatinine in 24 hours before admission/intubation (mmol/L)

5.4.3 Repeated measures

- Within one hour after initiation of ventilation OR within first hour of arrival when the patient has been intubated in another hospital, AND 3 times a day at fixed time points (8:00 AM, and 4:00 PM and 8:00 PM) for a following 3-day period:
  - Ventilation data
    - Ventilation mode;

- Tidal volume set (V_T) (mL);
- Expiratory tidal volume (VTE);
- Positive end–expiratory pressure (PEEP) (cm H_2O);
- Maximum airway pressure (P_{max}) (cm H_2O) or plateau pressure ($P_{plateau}$) or peak pressure (P_{peak}) (cm H_2O);
- Level of pressure support above PEEP (cm H_2O);
- Inspired fraction of oxygen (FiO_2) (%);
- Set an measured respiratory rate (RR) (min-1);
- Inspiration to expiration ratio (I:E) (ratio);
- Saturation of peripheral oxygen (SpO_2) (%); and
- End-tidal carbondioxide (E_TCO_2) (kPa).

- Arterial blood gas (ABG) analysis
  - pH;
  - Partial pressure of oxygen (PaO_2) (kPa or mmHg);
  - Partial pressure of carbon dioxide ($PaCO_2$) (kPa or mm Hg);
  - Bicarbonate (HCO_3-) (mmol/L);
  - Arterial saturation of oxygen (SaO_2) (%);
  - Arterial lactate levels (mmol/L);
  - FiO_2 (%) at time point of ABG; and
  - Position of patient in which ABG was taken.
- Hemodynamics
  - Mean arterial pressure (mmHg);
  - Heart rate (bpm);

- 3 times a day at fixed time points (8:00 AM, and 4:00 PM and 8:00 PM) for a following 3-day period:
  - Received paralytic drugs within the previous 8 hours (yes or no).
- Every day at 8:00 AM for 72–hour period after admission
  - Life status (alive or deceased);
  - Location (in ICU, hospital or other facility);
  - Intubation status;
  - Sequential Organ Failure Scores (SOFA);
  - Cumulative dose of sedatives (mg);
  - Cumulative dose of vasopressors (mg);
  - Cumulative fluid balance during last 24 hours (ml);
  - Amount of fluid administered during last 24 hours (ml);
  - Urine output (ml/hour); and
  - Plasma creatinine (mmol/L).
  - Prone position (yes or no), and if yes, time and duration (hours);
  - ABG in supine position;
  - Use of recruitment maneuver (yes or no);
  - Undergoing veno–venous, veno–arterial or arterio–venous extracorporeal membrane oxygenation (ECMO) (yes or no);
  - Pneumothorax (yes or no)
- Follow-up
  - Life status at day 7, day 28 and day 90;
  - Alive (yes or no), and if not, the date of passing;
  - Location (ICU, hospital, home);
  - Intubated (yes or no), and if not, extubation date;
  - Acute Kidney Injury (yes or no);
  - Date of discharge from ICU; and
  - Date of discharge from hospital.

5.5 Withdrawal of individual subjects

Not applicable.

5.6 Replacement of individual subjects after withdrawal

Not applicable.

5.7 Follow-up of subjects withdrawn from treatment

Not applicable.

5.8 Premature termination of the study

Not applicable.

6. SAFETY REPORTING

6.1 Temporary halt for reasons of subject safety

Not applicable.

6.2 Serious adverse events (SAEs)

Not applicable.

6.3 Follow-up of adverse events

Not applicable.

6.4 Data Safety Monitoring Board (DSMB)

Not applicable.

7. STATISTICAL ANALYSIS

Descriptive statistics will be used to describe the study population, and data are expressed in number and relative proportions for categorical variables and median (quartile 25% – quartile 75%) for continuous variables.

As the outcome of this study is urgently needed, data analysis will be done in two sequential steps. The first step includes an analysis of all patients admitted for invasive ventilation in one of the participating ICUs in the first four weeks after admission of the first COVID–19 patients, which was in all centers within the first weeks of March 2020. This part of the analysis focusses on ventilation practices in the first weeks of the pandemic in the Netherlands. This analysis may underestimate the effect of ventilation variables and parameters on outcomes, as many patients will not yet be weaned from the ventilator and remain admitted in the ICU. The second step includes an analysis of all COVID–19 patients admitted during the total 10 weeks PRoVENT COVID will enroll patients, with a complete follow up till day 90. This analysis will provide an answer to the question whether certain ventilator settings, variables and parameters are associated with patient–centered and other important outcomes.

All analyses will be performed using multilevel (patients nested in hospitals), mixed modelling with hospitals as random effect. Ventilatory variables and parameters will be compared among the groups, and absolute differences with the respective 95%–confidence interval (CI) will be calculated as the absolute difference from a mixed–effect linear model considering the hospitals as random effect to account for within–center clustering. Categorical variables will be compared as the risk difference from the same model.

Cumulative distribution plots will be used to demonstrate the cumulative distribution frequency of ventilation variables. Vertical dotted lines will represent the cut–off for each variable and the horizontal dotted lines the respective proportion of patients reaching each cut–off. Cut–offs to form matrices may use widely accepted values for each variable, specifically 8 mL/kg PBW for tidal volume, 10 cm H_2O for PEEP, 30 cm H_2O for plateau pressure, and 15 cm H_2O for ΔP.

Mixed–effect multivariable logistic or linear regression model will used to identify factors independently associated with major outcomes, like death and VFD–28. Subanalyses are planned to investigate differences in ventilation practice and outcomes in the following prespecified subgroups: women versus men, and patients categorized by the body mass index.

All analyses will be conducted in R v.3.60 and a p value < 0.05 will be considered statistically significant.

8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

This study will be conducted according to the principles of the Declaration of Helsinki (revision Fortaleza, Brazil, October 2013).

8.2 Recruitment and consent

Since the proposed study concerns a service review, no research related interventions will take place. Therefore, no ethical concerns exist. As pseudo–anonymous data, which can no longer be attributed to a specific data subject will be used, there is no concern for informed consent.

8.3 Benefits and risks assessment, group relatedness

This study does not result in any risk or burdens to patients.

8.4 Compensation for injury

Not applicable.

9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents

Subject data will be stored a pseudo–anonymized, which means that relating the individual data to identifiable patients would require disproportional effort. Used data as written in the case report form will not contain any identifiable or relatable data. All handling of personal data will comply with the General Data Protection Regulation and the 'Reuse of care data for the purpose of research' standard of the AMC.

9.2 Monitoring and Quality Assurance

Not applicable.

9.3 Amendments

Not applicable.

9.4 Annual progress report

Not applicable.

9.5 Temporary halt and (prematurely) end of study report

Not applicable.

9.6 Public disclosure and publication policy

Not applicable.

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Appendix Table 1 - Linearity Assumption Assessed Using the Box-Tidwell Power Transformation for the Full Model of 28-Day Mortality

	28-Day Mortality
	***p* value**
Ventilatory variables at the first day*	
PEEP, cmH_2O	0.49
Tidal volume, mL/kg PBW	0.53
Respiratory system compliance, mL/cmH_2O	0.22
Oxygenation variables at the first day*	
PaO_2 / FiO_2	0.013
Laboratory tests at the first day*	
pH	0.14
Lactate, mmol/L	0.07
Creatinine, µmol/L	0.66
Vital signs at the first day*	
Heart rate, bpm	0.60
Mean arterial pressure, mmHg	0.60
Baseline characteristics	
Age, years	0.72
Body mass index, kg/m^2	0.25

Fluid balance was not assessed because the Box-Tidwell test does not accept negative values. The linearity assumption for fluid balance was confirmed in a scatter plot of the predictor against the logit.

Appendix Table 2 – Amount of missing data

	Overall (*n* = 553)
Age	0 (0.0)
Gender	0 (0.0)
Body mass index	7 (1.3)
Transferred intubated	0 (0.0)
Use of non-invasive ventilation	64 (11.6)
Chest CT scan performed	0 (0.0)
Chest X-ray performed	185 (33.5)
Pneumothorax at baseline	424 (76.7)
SAPS II	355 (64.2)
APACHE II	407 (73.6)
APACHE IV	282 (51.0)
SOFA	300 (54.2)
Severity ARDS	12 (2.2)
Hypertension	0 (0.0)
Heart failure	0 (0.0)
Diabetes	0 (0.0)
Chronic kidney disease	0 (0.0)
Baseline creatinine	14 (2.5)
Liver cirrhosis	0 (0.0)
Chronic obstructive pulmonary disease	0 (0.0)
Active hematological neoplasia	0 (0.0)
Active solid neoplasia	0 (0.0)
Neuromuscular disease	0 (0.0)
Immunosuppression	0 (0.0)
Systemic steroids	0 (0.0)
Inhaled steroids	0 (0.0)
Angiotensin converting enzyme inhibitor	0 (0.0)
Angiotensin II receptor blocker	0 (0.0)
Beta-blockers	0 (0.0)
Insulin	0 (0.0)
Metformin	0 (0.0)
Statins	0 (0.0)
Calcium channel blockers	0 (0.0)
Continuous sedation	2 (0.4)
Vasopressor	2 (0.4)
Fluid balance	6 (1.1)
Urine output	10 (1.8)
Mode of ventilation	2 (0.4)
Tidal volume	22 (4.0)
PEEP	2 (0.4)
Peak pressure	48 (8.7)
Driving pressure	49 (8.8)
Compliance	63 (11.4)
Total respiratory rate	12 (2.2)
FiO_2	3 (0.5)
SpO_2 / FiO_2	3 (0.5)
$etCO_2$	31 (5.6)
Mean arterial pressure	1 (0.2)
Heart rate	0 (0.0)

Appendix Table 2 – Amount of missing data

	Overall (*n* = 553)
pH	2 (0.4)
PaO_2	2 (0.4)
PaO_2 / FiO_2	5 (0.9)
$PaCO_2$, mmHg	2 (0.4)
Lactate, mmol/L	24 (4.3)
Use of neuromuscular blockade	21 (3.8)
Prone positioning	9 (1.6)
Recruitment maneuver	109 (19.7)
ECMO	8 (1.4)
Ventilator-free days at day 28	48 (8.7)
Successful extubation	0 (0.0)
Duration of ventilation	72 (13.0)
Tracheostomy	0 (0.0)
Reintubation	7 (1.3)
Pneumothorax	11 (2.0)
Thromboembolic complications	1 (0.2)
Pulmonary embolism	1 (0.2)
Deep vein thrombosis	1 (0.2)
Ischemic stroke	1 (0.2)
Myocardial infarction	1 (0.2)
Systemic arterial embolism	1 (0.2)
Acute kidney injury	0 (0.0)
Need for renal replacement therapy	1 (0.2)
ICU length of stay	138 (25.0)
Hospital length of stay	107 (19.3)
ICU mortality	51 (9.2)
Hospital mortality	317 (57.3)
7-Day mortality	20 (3.6)
28-Day mortality	23 (4.2)

SAPS: Simplified Acute Physiology Score; APACHE: Acute Physiology And Chronic Health Evaluation; SOFA: Sequential Organ Failure Assessment; ARDS: Acute Respiratory Distress Syndrome; PEEP: positive end-expiratory pressure; FiO_2: inspired fraction of oxygen; ECMO: extracorporeal membrane oxygenation; ICU: Intensive Care Unit

Appendix Table 3 – Characteristics of Advanced Life Support in the First 4 Days of Ventilation

	Day 00	Day 01	Day 02	Day 03
Organ support				
SOFA	8.0 (6.0 – 11.0)	7.0 (6.0 – 10.0)	7.0 (6.0 – 11.0)	7.0 (6.0 – 11.0)
Continuous sedation – no (%)	532 (96.6)	521 (94.2)	481 (87.0)	448 (81.2)
Vasopressor – no (%)	430 (78.0)	465 (84.1)	409 (74.0)	354 (64.1)
Fluid balance, mL	584.0 (32.7 – 1327.5)	1552.0 (798.9 – 2300.5)	1154.7 (398.8 – 1883.5)	673.5 (-80.5 – 1562.5)
Urine output, mL	635.0 (335.0 – 1130.0)	1110.0 (766.2 – 1607.5)	1255.0 (845.0 – 1816.2)	1420.0 (950.0 – 2110.0)
Ventilation support				
Mode of ventilation – no (%)				
Volume-controlled	104 (18.8)	75 (14.1)	59 (11.9)	54 (11.4)
Pressure-controlled	277 (50.2)	241 (45.3)	206 (41.5)	178 (37.6)
Pressure-support	25 (4.5)	81 (15.2)	107 (21.6)	127 (26.8)
SIMV	36 (6.5)	39 (7.3)	35 (7.1)	34 (7.2)
APRV	21 (3.8)	26 (4.9)	17 (3.4)	15 (3.2)
INTELLiVENT-ASV	32 (5.8)	23 (4.3)	28 (5.6)	24 (5.1)
Other	57 (10.3)	47 (8.8)	44 (8.9)	41 (8.7)
Tidal volume, mL/kg PBW	6.5 (5.9 – 7.1)	6.5 (6.0 – 7.3)	6.6 (6.0 – 7.3)	6.6 (6.0 – 7.3)
PEEP, cmH_2O	13.6 (12.0 – 15.0)	14.0 (11.7 – 15.0)	13.7 (11.3 – 15.0)	13.3 (10.9 – 15.3)
Peak pressure, cmH_2O	27.0 (24.0 – 30.0)	26.5 (23.0 – 29.7)	26.3 (23.0 – 29.7)	26.7 (22.7 – 30.3)
Driving pressure, cmH_2O	13.5 (11.5 – 16.0)	12.7 (10.5 – 15.7)	13.0 (10.7 – 16.0)	13.3 (11.0 – 16.0)
Mechanical power, J/min	19.0 (15.4 – 23.0)	19.5 (15.3 – 24.0)	20.2 (15.6 – 24.8)	20.5 (16.3 – 25.3)
Compliance, mL/cmH_2O	33.7 (28.0 – 42.5)	36.5 (29.0 – 46.4)	35.6 (28.5 – 47.3)	35.1 (28.2 – 46.6)
Total respiratory rate, mpm	21.7 (19.5 – 24.0)	22.0 (19.7 – 25.3)	23.3 (20.0 – 26.2)	24.0 (20.7 – 26.7)
FiO_2	0.56 (0.47 – 0.65)	0.43 (0.39 – 0.52)	0.43 (0.38 – 0.50)	0.45 (0.40 – 0.53)
SpO_2 / FiO_2	177.7 (151.3 – 211.2)	222.2 (186.5 – 248.6)	220.0 (185.3 – 250.4)	209.6 (179.7 – 243.8)
$etCO_2$, mmHg	36.8 (32.6 – 42.4)	37.8 (33.2 – 43.0)	38.5 (33.7 – 43.4)	38.8 (33.9 – 44.8)
Vital signs				
Mean arterial pressure, mmHg	79.8 (73.5 – 88.0)	76.0 (71.2 – 81.7)	77.3 (72.3 – 83.3)	78.0 (73.0 – 84.1)
Heart rate, bpm	82.0 (72.0 – 94.7)	80.0 (69.2 – 93.3)	82.7 (70.3 – 96.1)	85.0 (74.2 – 97.3)
Laboratory tests				
pH	7.36 (7.31 – 7.41)	7.37 (7.31 – 7.41)	7.36 (7.31 – 7.41)	7.38 (7.32 – 7.42)
PaO_2 / FiO_2	158.8 (128.6 – 200.5)	182.1 (148.5 – 214.2)	175.6 (143.1 – 206.1)	166.5 (135.5 – 199.5)
$PaCO_2$, mmHg	44.3 (39.0 – 50.6)	45.5 (40.8 – 51.3)	47.7 (42.8 – 54.8)	49.1 (44.0 – 55.6)
Lactate, mmol/L	1.1 (0.9 – 1.4)	1.2 (1.0 – 1.5)	1.3 (1.0 – 1.6)	1.3 (1.0 – 1.6)
Creatinine, µmol/L	74.0 (62.0 – 98.0)	85.0 (66.0 – 125.8)	88.0 (66.0 – 141.5)	86.0 (66.0 – 138.0)
Rescue therapy – no (%)				
Use of neuromuscular blockade	126 (23.7)	182 (35.0)	183 (37.6)	144 (31.9)
Hours of use of neuromuscular blockade[a]	8.0 (8.0 – 16.0)	16.0 (16.0 – 24.0)	24.0 (16.0 – 24.0)	20.0 (8.0 – 24.0)
Prone positioning	135 (24.8)	208 (39.3)	192 (38.4)	184 (38.8)
Duration of prone positioning, hours[a]	8.0 (4.0 – 12.0)	14.0 (10.0 – 19.0)	14.0 (10.0 – 19.1)	14.0 (11.0 – 19.2)
Recruitment manoeuvre	5 (1.1)	13 (3.1)	10 (2.5)	7 (1.8)
ECMO	1 (0.2)	1 (0.2)	2 (0.4)	2 (0.4)

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding

APRV: airway pressure release ventilation; ASV: adaptive support ventilation; ECMO: extracorporeal membrane oxygenation; FiO_2: inspired fraction of oxygen; PEEP: positive end-expiratory pressure; SIMV: synchronized intermittent mandatory ventilation

[a] In patients who received it

Appendix Table 4 - Full Multivariable Model Assessing Predictors of 28-Day Mortality

	Odds Ratio (95% CI)	*p* value
Ventilatory variables at the first day*		
PEEP, cmH_2O	1.08 (0.85 to 1.39)	0.51
Tidal volume, mL/kg PBW	1.28 (1.00 to 1.64)	0.049
Respiratory system compliance, mL/cmH_2O	0.75 (0.57 to 0.98)	0.037
Oxygenation variables at the first day*		
PaO_2 / FiO_2	0.98 (0.95 to 1.01)	0.11
PaO_2 / FiO_2'	1.24 (1.00 to 1.54)	0.053
PaO_2 / FiO_2''	0.38 (0.16 to 0.88)	0.025
PaO_2 / FiO_2'''	3.86 (1.34 to 11.08)	0.012
Laboratory tests at the first day*		
pH	0.71 (0.55 to 0.93)	0.012
Lactate, mmol/L	1.12 (0.88 to 1.43)	0.37
Creatinine, µmol/L	1.04 (0.82 to 1.32)	0.76
Vital signs at the first day*		
Heart rate, bpm	1.02 (1.00 to 1.03)	0.013
Mean arterial pressure, mmHg	0.99 (0.96 to 1.02)	0.46
Organ support at the first day		
Use of vasopressor	2.07 (0.76 to 5.66)	0.16
Fluid balance, mL	1.07 (0.85 to 1.36)	0.55
Baseline characteristics		
Age, years	2.19 (1.65 to 2.90)	< 0.0001
Male gender	2.16 (1.24 to 3.78)	0.007
Body mass index, kg/m^2	0.85 (0.66 to 1.09)	0.19
Hypertension	1.16 (0.72 to 1.88)	0.54
Heart failure	0.73 (0.26 to 2.08)	0.56
Diabetes	1.58 (0.93 to 2.67)	0.09
Chronic kidney disease	0.89 (0.30 to 2.61)	0.83
Chronic obstructive pulmonary disease	1.70 (0.86 to 3.36)	0.13
Use of angiotensin converting enzyme inhibitor	0.85 (0.47 to 1.53)	0.59
Use of angiotensin II receptor blocker	0.60 (0.30 to 1.21)	0.15

* median value from a maximum of six assessments during the first 24 hours

PaO_2 / FiO_2 were modelled non-linearly with restrict cubic splines according to evidence obtained from the data

All models are mixed-effect models with centers as random effect and considering a binomial distribution

All continuous variables were entered after standardization to improve convergence of the model, and odds ratio represent the increase in one standard deviation of the variable.

Appendix Table 5 - Full Multivariable Model Assessing Predictors of VFD-28

	Mean Difference (95% CI)	*p* value
Ventilatory variables at the first day*		
PEEP, cmH_2O	-0.73 (-1.52 to 0.06)	0.07
Tidal volume, mL/kg PBW	-0.35 (-1.15 to 0.45)	0.39
Respiratory system compliance, mL/cmH_2O	7.16 (1.36 to 12.96)	0.016
Respiratory system compliance, mL/cmH_2O'	-43.40 (-106.99 to 20.19)	0.18
Respiratory system compliance, mL/cmH_2O''	67.61 (-59.13 to 194.35)	0.30
Respiratory system compliance, mL/cmH_2O'''	-30.38 (-100.08 to 39.32)	0.39
Oxygenation variables at the first day*		
PaO_2 / FiO_2	1.00 (0.27 to 1.72)	0.007
Laboratory tests at the first day*		
pH	0.81 (-1.14 to 2.76)	0.42
pH'	0.49 (-7.72 to 8.70)	0.91
pH''	0.21 (-13.58 to 13.99)	0.98
pH'''	0.10 (-7.43 to 7.62)	0.98
Lactate, mmol/L	1.01 (-11.33 to 13.35)	0.87
Lactate, mmol/L'	-70.52 (-297.23 to 156.20)	0.54
Lactate, mmol/L''	97.03 (-319.33 to 513.39)	0.65
Lactate, mmol/L'''	-27.70 (-232.71 to 177.31)	0.79
Creatinine, µmol/L	-3.28 (-15.18 to 8.61)	0.59
Creatinine, µmol/L'	25.88 (-267.31 to 319.07)	0.86
Creatinine, µmol/L''	-36.77 (-550.66 to 477.12)	0.89
Creatinine, µmol/L'''	14.25 (-220.85 to 249.35)	0.90
Vital signs at the first day*		
Heart rate, bpm	-0.62 (-1.36 to 0.11)	0.10
Mean arterial pressure, mmHg	0.06 (-3.62 to 3.74)	0.97
Mean arterial pressure, mmHg'	-2.30 (-27.22 to 22.63)	0.86
Mean arterial pressure, mmHg''	10.59 (-34.00 to 55.18)	0.64
Mean arterial pressure, mmHg'''	-8.08 (-31.60 to 15.43)	0.50
Organ support at the first day		
Use of vasopressor	0.80 (-1.80 to 3.40)	0.54
Fluid balance, mL	-0.24 (-1.01 to 0.53)	0.55
Baseline characteristics		
Age, years	-2.13 (-2.90 to -1.35)	< 0.0001
Male gender	-2.38 (-4.24 to -0.52)	0.013
Body mass index, kg/m^2	0.51 (-0.24 to 1.26)	0.18
Hypertension	-0.01 (-1.58 to 1.57)	0.99
Heart failure	1.22 (-2.03 to 4.46)	0.46
Diabetes	-1.12 (-2.88 to 0.64)	0.21
Chronic kidney disease	-0.53 (-4.17 to 3.10)	0.77
Chronic obstructive pulmonary disease	-0.71 (-3.00 to 1.58)	0.54
Use of angiotensin converting enzyme inhibitor	2.75 (0.86 to 4.63)	0.004
Use of angiotensin II receptor blocker	0.24 (-2.05 to 2.53)	0.84

* median value from a maximum of six assessments during the first 24 hours

Respiratory system compliance, pH, lactate, creatinine and mean arterial pressure were modelled non-linearly with restrict cubic splines according to evidence obtained from the data

All models are mixed-effect models with centers as random effect and considering a binomial distribution

All continuous variables were entered after standardization to improve convergence of the model, and the mean difference represents the increase in one standard deviation of the variable.

Appendix Table 6 - Variance-Inflation Factor for Both Models

	28-Day Mortality	VFD at Day 28
	Variance-Inflation Factor	**Variance-Inflation Factor**
Ventilatory variables at the first day*		
PEEP, cmH_2O	1.186	1.190
Tidal volume, mL/kg PBW	1.389	1.405
Respiratory system compliance, mL/cmH_2O	1.518	1.495
Oxygenation variables at the first day*		
PaO_2 / FiO_2	1.119	1.118
Laboratory tests at the first day*		
pH	1.363	1.440
Lactate, mmol/L	1.074	1.089
Creatinine, µmol/L	1.355	1.397
Vital signs at the first day*		
Heart rate, bpm	1.222	1.207
Mean arterial pressure, mmHg	1.156	1.178
Organ support at the first day		
Use of vasopressor	1.060	1.129
Fluid balance, mL	1.175	1.227
Baseline characteristics		
Age, years	1.204	1.345
Male gender	1.292	1.280
Body mass index, kg/m^2	1.309	1.312
Hypertension	1.273	1.310
Heart failure	1.145	1.126
Diabetes	1.149	1.154
Chronic kidney disease	1.201	1.224
Chronic obstructive pulmonary disease	1.053	1.066
Use of angiotensin converting enzyme inhibitor	1.287	1.290
Use of angiotensin II receptor blocker	1.252	1.218

The variance-inflation factor of a variable is a measure for how easily it is predicted from a linear regression using the other predictors. Taking the square root of the VIF tells you how much larger the standard error of the estimated coefficient is respect to the case when that predictor is independent of the other predictors.

A general guideline is that a VIF larger than 5 or 10 is large, indicating that the model has problems estimating the coefficient.

Also, if the VIF is larger than 1 / (1-R^2), then that predictor is more related to the other predictors than it is to the response. This value is 1.403 for the 28-day mortality model and 1.317

Appendix Table 7 - Clinical Outcomes According to the Severity of ARDS at Baseline[a]

	Mild ARDS (*n* = 135)	Moderate ARDS (*n* = 360)	Severe ARDS (*n* = 46)	*p* value
Ventilatory support				
Ventilator-free days at day 28, days	4.0 (0.0 – 16.0)	0.0 (0.0 – 15.0)	0.0 (0.0 – 8.0)	0.019
Mean ± standard deviation	8.2 ± 9.1	6.5 ± 8.4	4.2 ± 6.7	0.019
Successful extubation – no (%)	74 / 135 (54.8)	166 / 360 (46.1)	21 / 46 (45.7)	0.22
Duration of ventilation, days	13.5 (7.5 – 20.5)	13.5 (8.5 – 22.5)	14.5 (8.0 – 22.5)	0.74
In survivors, days	15.5 (8.5 – 22.2)	16.5 (10.5 – 27.5)	20.5 (15.0 – 30.5)	0.09
Tracheostomy – no (%)	25 / 135 (18.5)	40 / 360 (11.1)	6 / 46 (13.0)	0.09
Reintubation – no (%)	19 / 133 (14.3)	43 / 355 (12.1)	6 / 46 (13.0)	0.78
Pneumothorax – no (%)	4 / 131 (3.1)	2 / 353 (0.6)	0 / 46 (0.0)	0.09
Complications				
Thromboembolic complications	35 / 135 (25.9)	70 / 359 (19.5)	10 / 46 (21.7)	0.29
Pulmonary embolism*	20 / 135 (14.8)	48 / 359 (13.4)	6 / 46 (13.0)	0.92
Deep vein thrombosis	7 / 135 (5.2)	13 / 359 (3.6)	3 / 46 (6.5)	0.45
Ischemic stroke	6 / 135 (4.4)	5 / 359 (1.4)	2 / 46 (4.3)	0.07
Myocardial infarction	4 / 135 (3.0)	4 / 359 (1.1)	0 / 46 (0.0)	0.32
Systemic arterial embolism	1 / 135 (0.7)	1 / 359 (0.3)	1 / 46 (2.2)	0.14
Acute kidney injury**	59 / 135 (43.7)	171 / 360 (47.5)	27 / 46 (58.7)	0.22
Need for renal replacement therapy	19 / 134 (14.2)	62 / 360 (17.2)	12 / 46 (26.1)	0.19
Clinical outcomes				
ICU length of stay, days	13.5 (8.0 – 22.0)	15.0 (9.0 – 26.0)	13.0 (7.0 – 23.5)	0.41
In survivors, days	14.0 (8.0 – 22.0)	16.5 (10.0 – 29.8)	21.5 (13.2 – 31.8)	0.02
Hospital length of stay, days	20.0 (11.2 – 30.8)	19.0 (11.0 – 30.0)	20.0 (10.5 – 35.0)	0.99
In survivors, days	23.0 (16.0 – 32.0)	27.0 (19.0 – 39.2)	35.5 (27.5 – 36.2)	0.009
Mortality – no (%)				
Day 7	15 / 131 (11.5)	55 / 345 (15.9)	9 / 46 (19.6)	0.30
Day 28	40 / 131 (30.5)	122 / 343 (35.6)	21 / 45 (46.7)	0.15
ICU	38 / 121 (31.4)	135 / 327 (41.3)	21 / 43 (48.8)	0.07
Hospital	43 / 100 (43.0)	136 / 283 (48.1)	22 / 38 (57.9)	0.29

Data are median (quartile 25% - quartile 75%) or No (%). Percentages may not total 100 because of rounding

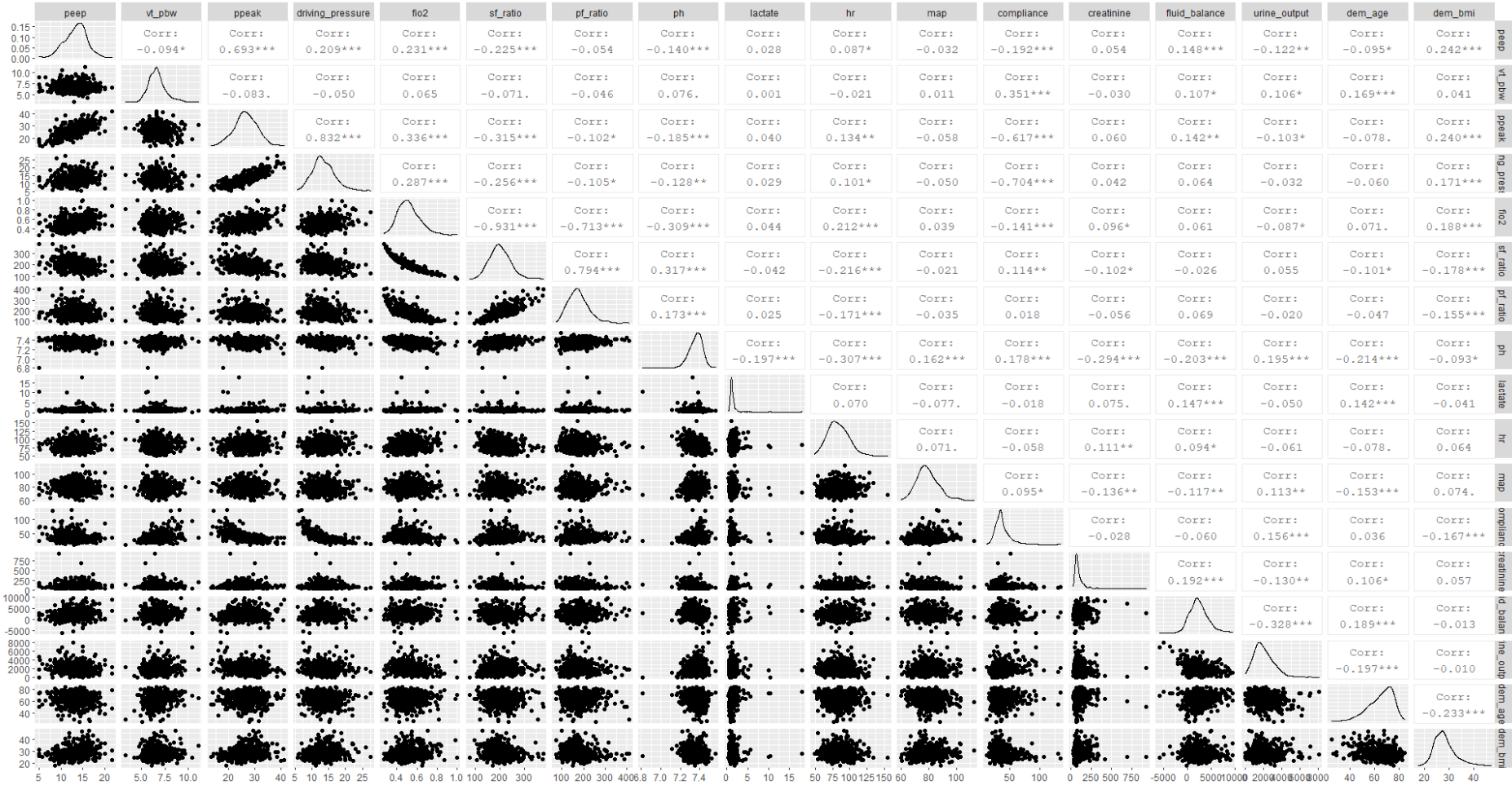
Outcomes assessed until day 28 when not indicated

[a] Baseline PaO_2 / FiO_2 ratio was missing in 12 patients.

* Pulmonary embolism was defined when confirmed by chest CT angiography or when highly suspicious according to clinical assessment and treated accordingly by the attending physician

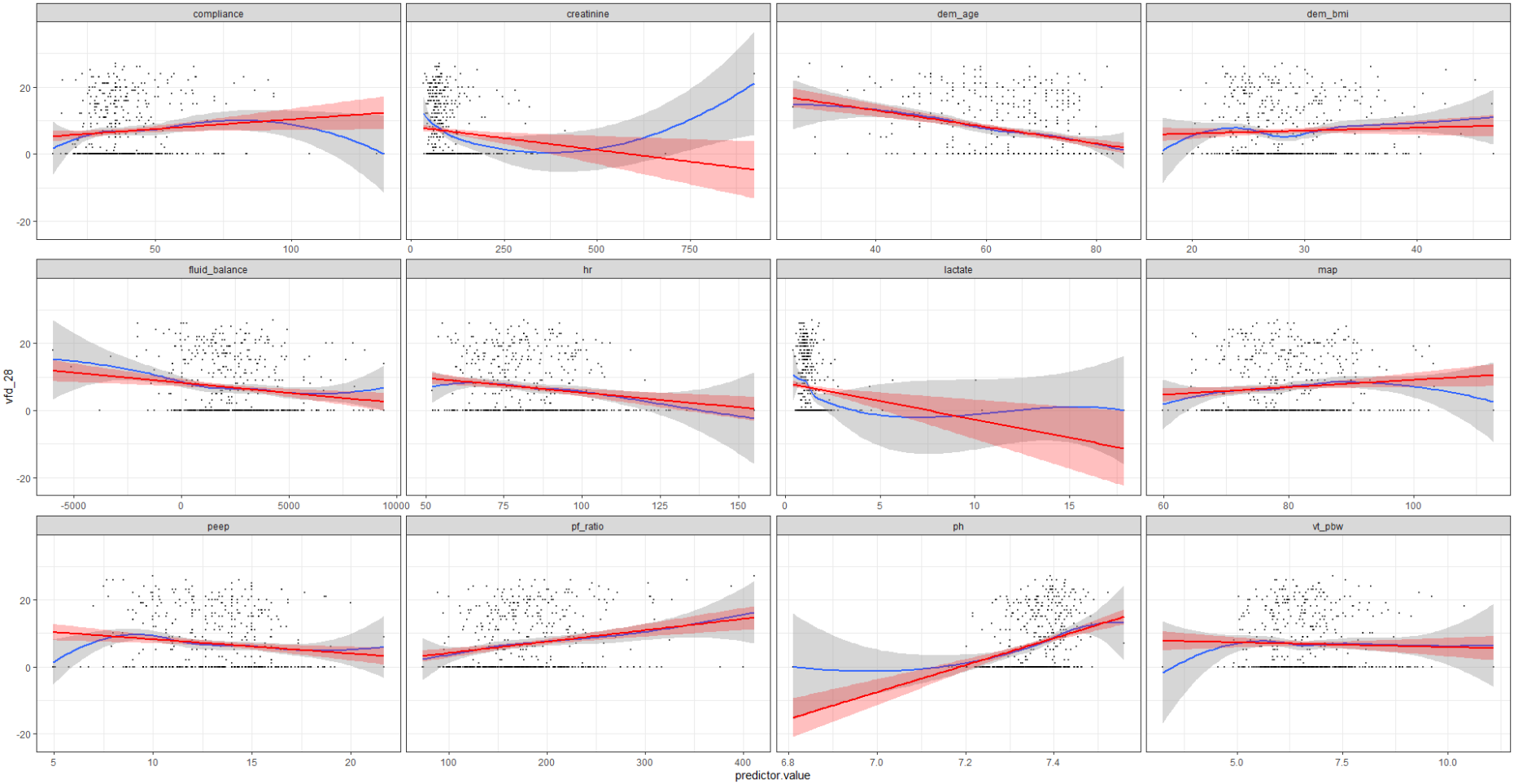
** Acute kidney injury was defined when one of the following criteria was met at any point within 28 days after intubation: 1) a 1.5-fold increase of creatinine compared to baseline; and/or 2) an absolute creatinine increase of 26.5 µmol/L compared to baseline; and/or) a urinary output <0.5 mL/kg per hour for more than 6 hours.

Appendix Figure 1 - Correlation Matrix Assessing the Correlation Between Continuous Predictors Considered for the Multivariable Models



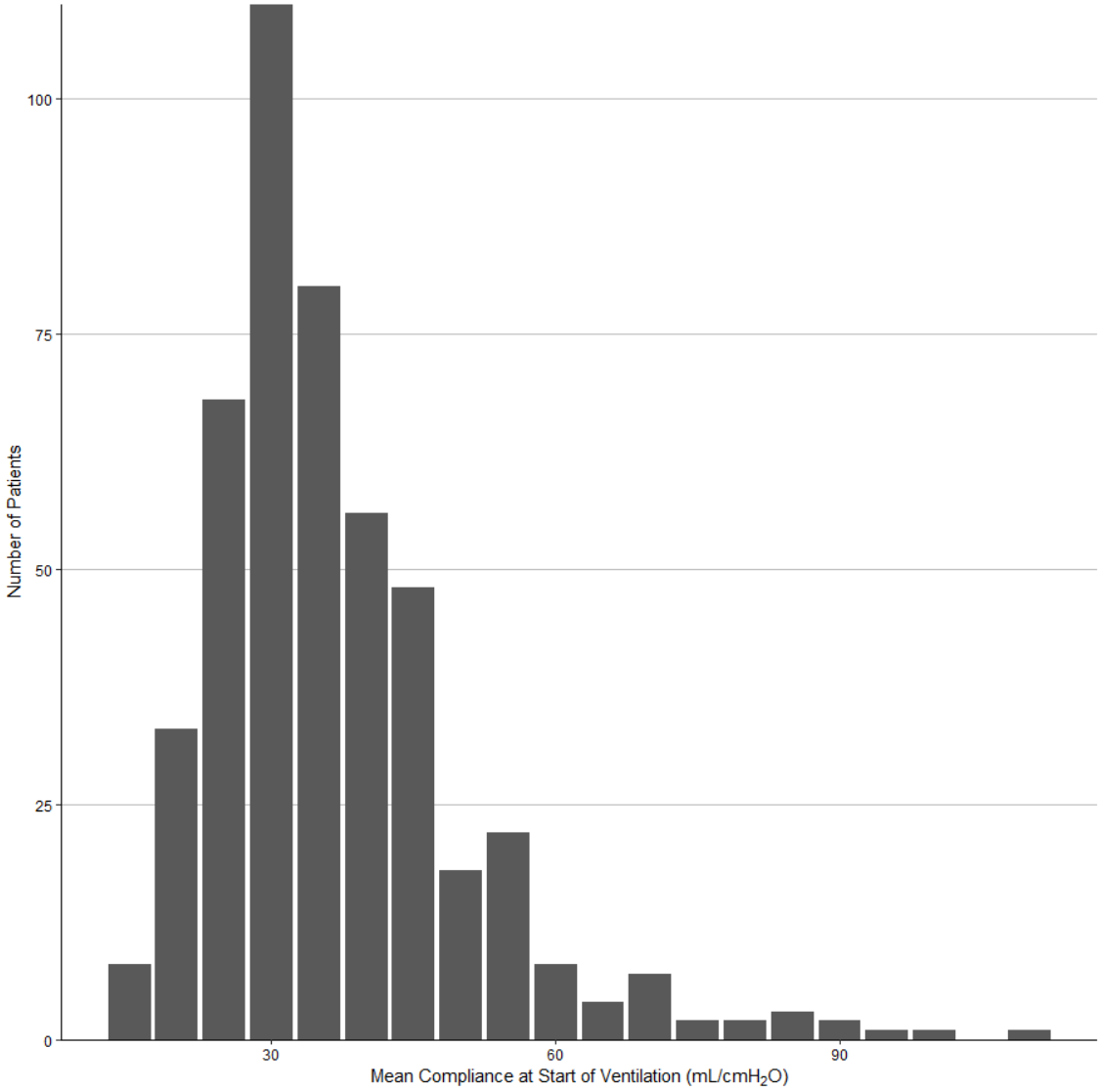
Peak pressure and driving pressure were excluded due to collinearity with respiratory compliance (which was judged to be more important in the model) and FiO_2 was excluded due to collinearity with PaO_2 / FiO_2.

Appendix Figure 2 - Test for Linearity Assumption Among Continuous Predictors and Ventilator-Free Days at Day 28



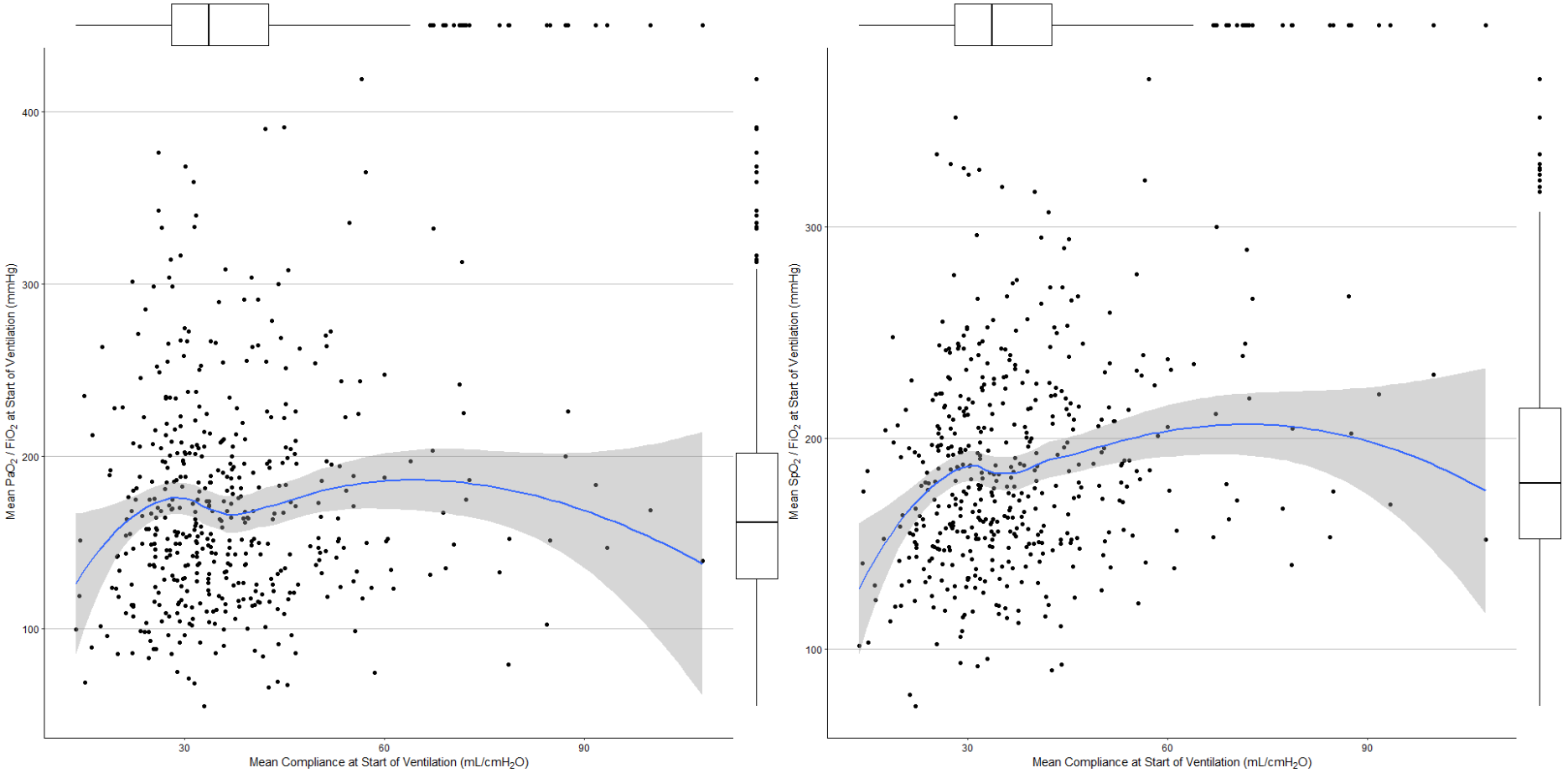
Blue line is a LOESS curve and red line is from a linear regression.

Appendix Figure 3 – Histogram of Respiratory System Compliance at the First Day of Ventilation



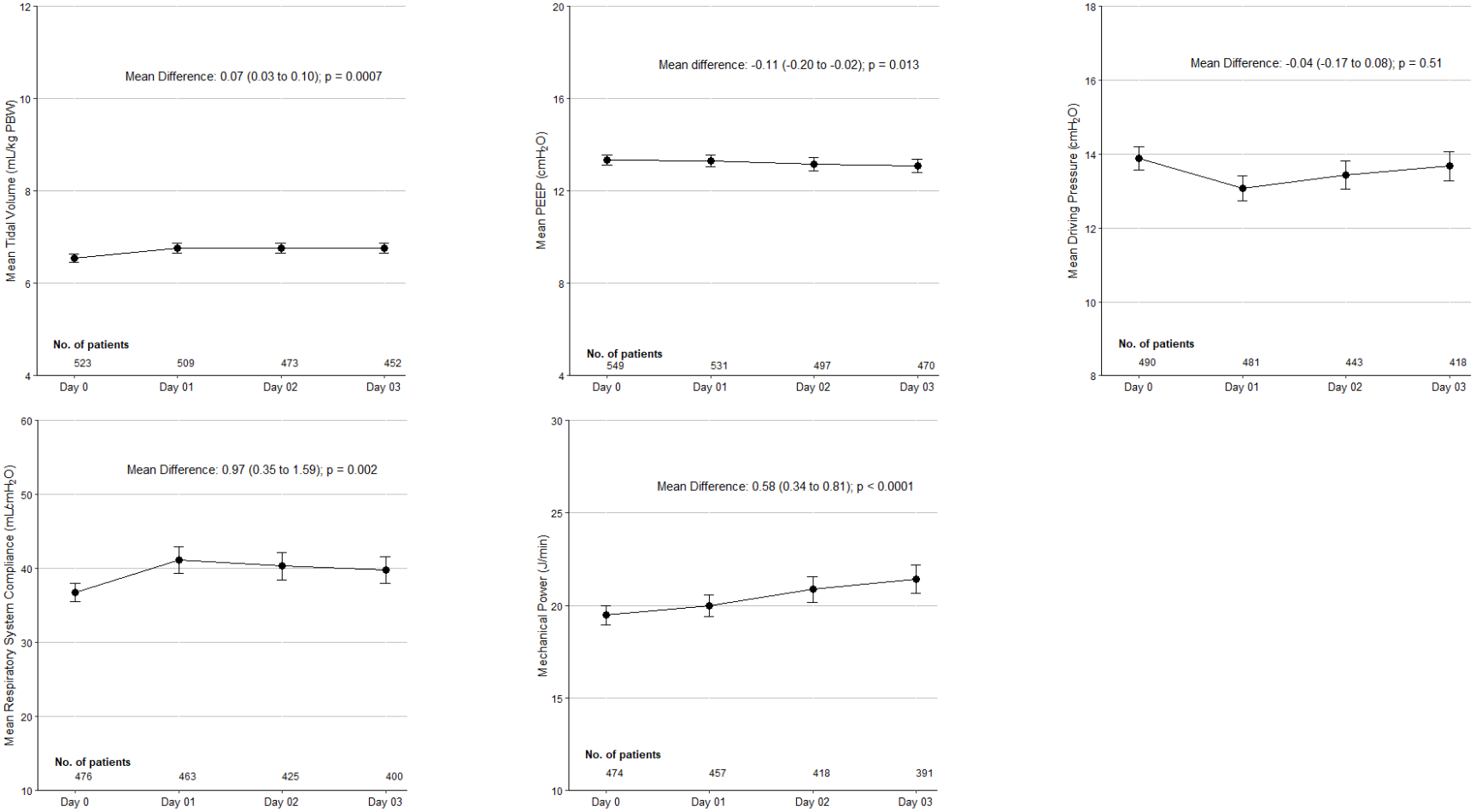
Values were mean from three measurements during the day.

Appendix Figure 4 – Relationship Between Respiratory System Compliance and Oxygenation in the First Day of Ventilation



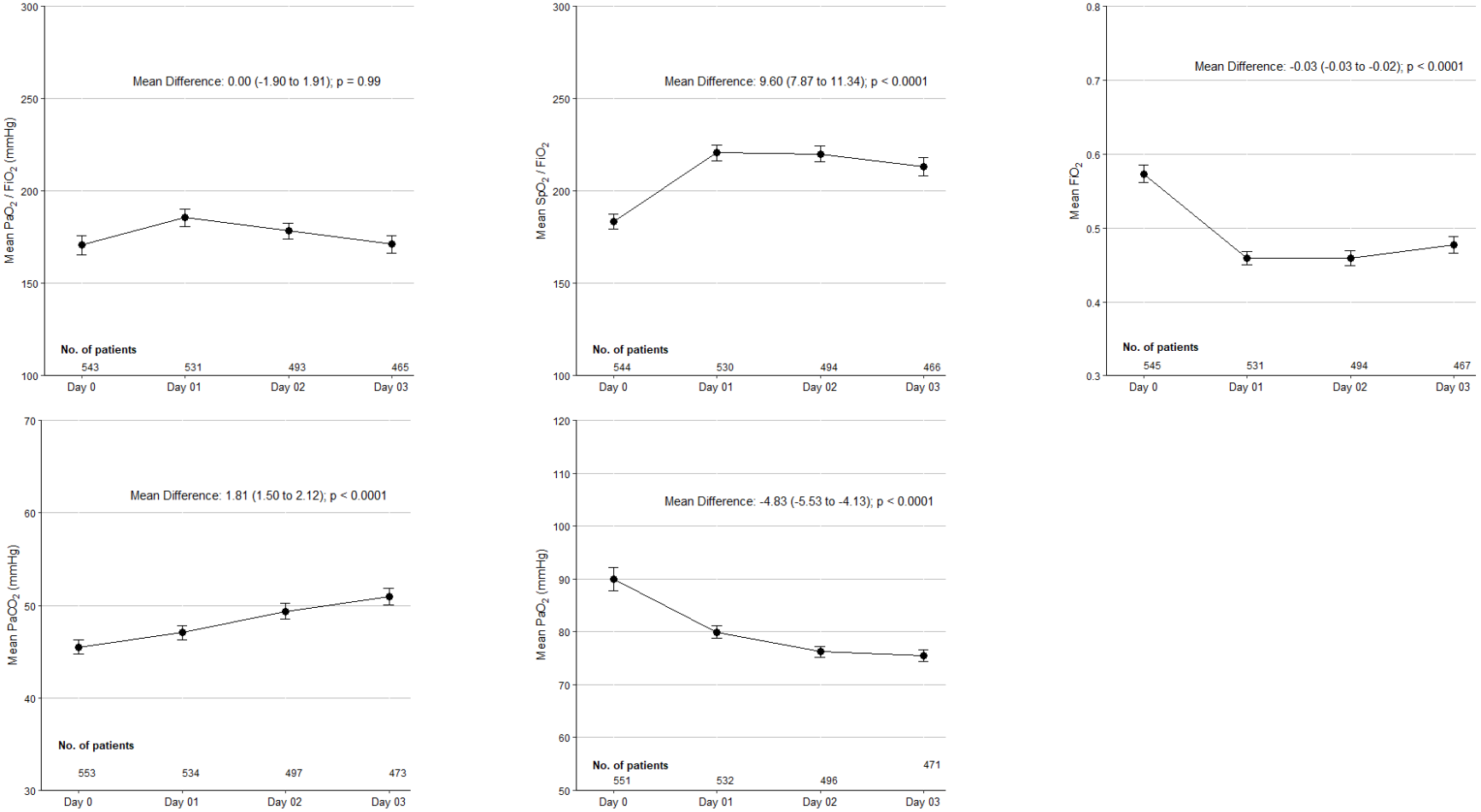
Values were mean from three measurements during the day. A robust locally weighted scatter plot smoothing (LOWESS) method was applied to investigate the relationship between the variables. The smoothing curves used a bandwidth of 0.75, a polynomial regression with 1 degree of freedom, and a tricubic weight function so that observations furthest from the point of interest were assigned the least weight.

Appendix Figure 5 – Trend of Ventilatory Variables of the First Three Days of Ventilation



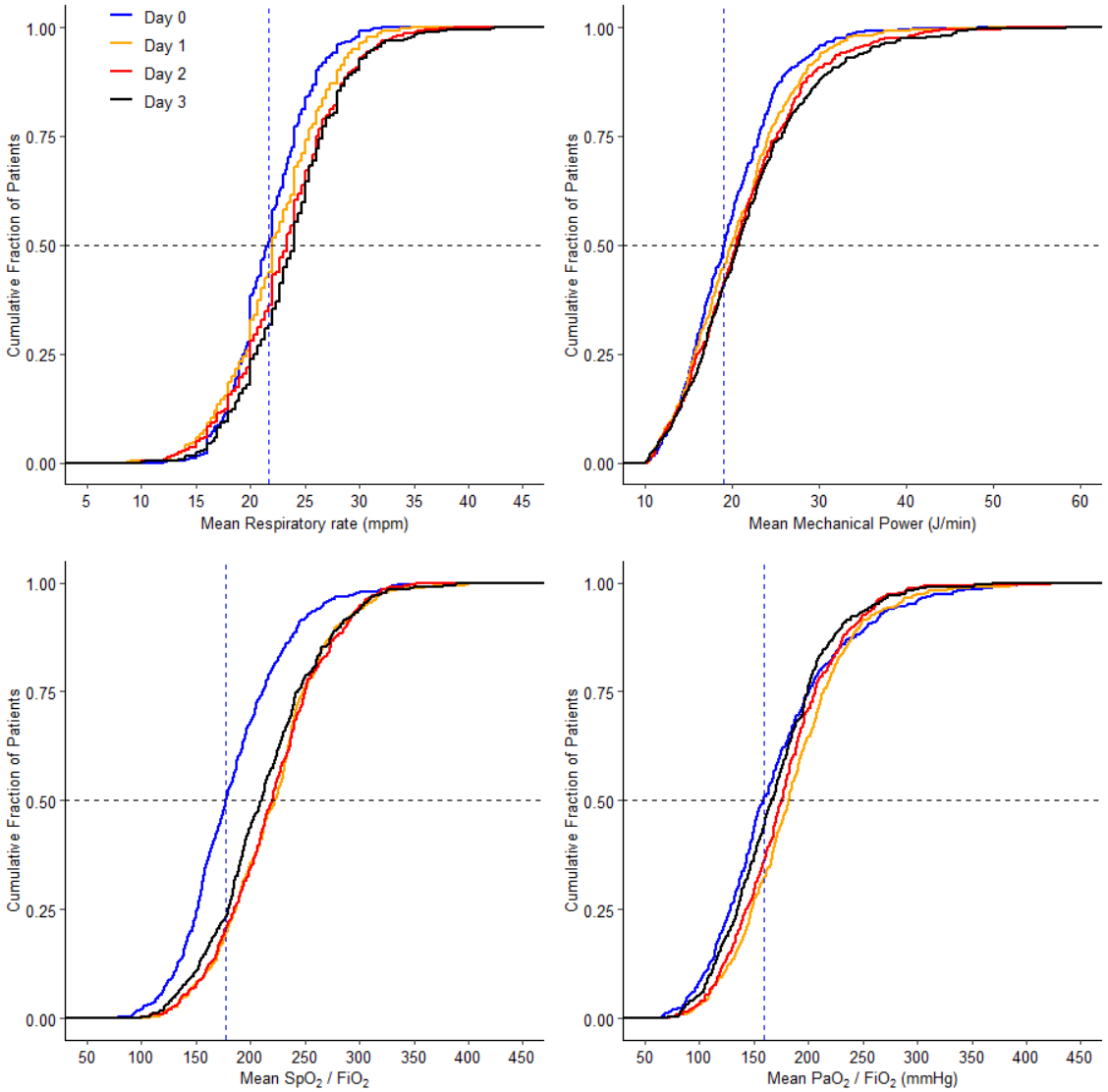
P value was calculated from a mixed-effect linear model with centre as random effect, with random slopes and intercept for patients and with an unstructured covariance matrix. Circles are mean from three measurements each day and error bars are 95% confidence interval.

Appendix Figure 6 – Trend of Oxygenation Variables of the First Three Days of Ventilation



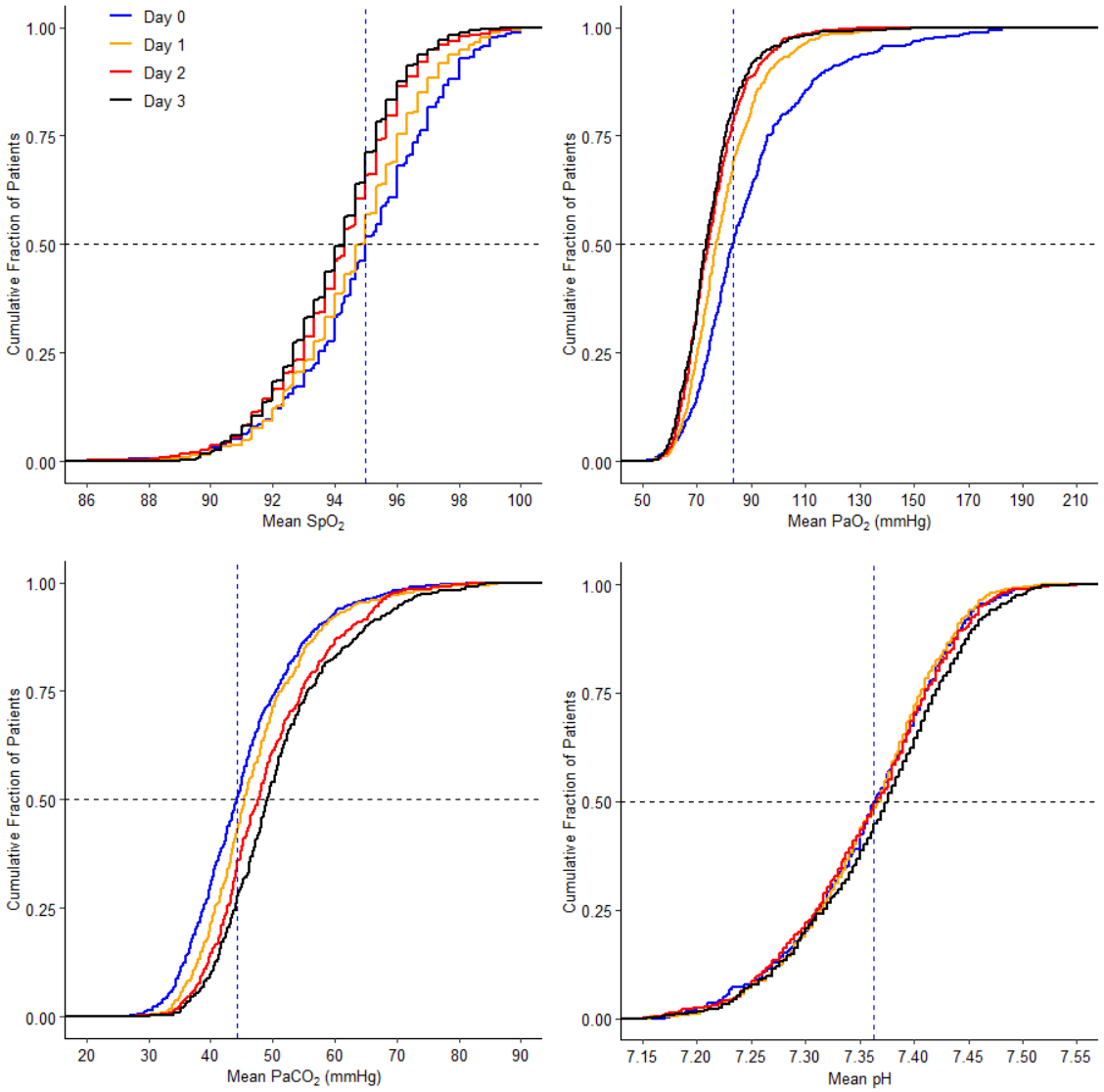
P value was calculated from a mixed-effect linear model with centre as random effect, with random slopes and intercept for patients and with an unstructured covariance matrix. Circles are mean from three measurements each day and error bars are 95% confidence interval.

Appendix Figure 7 – Cumulative Distribution Plots of Ventilatory and Oxygenation Variables



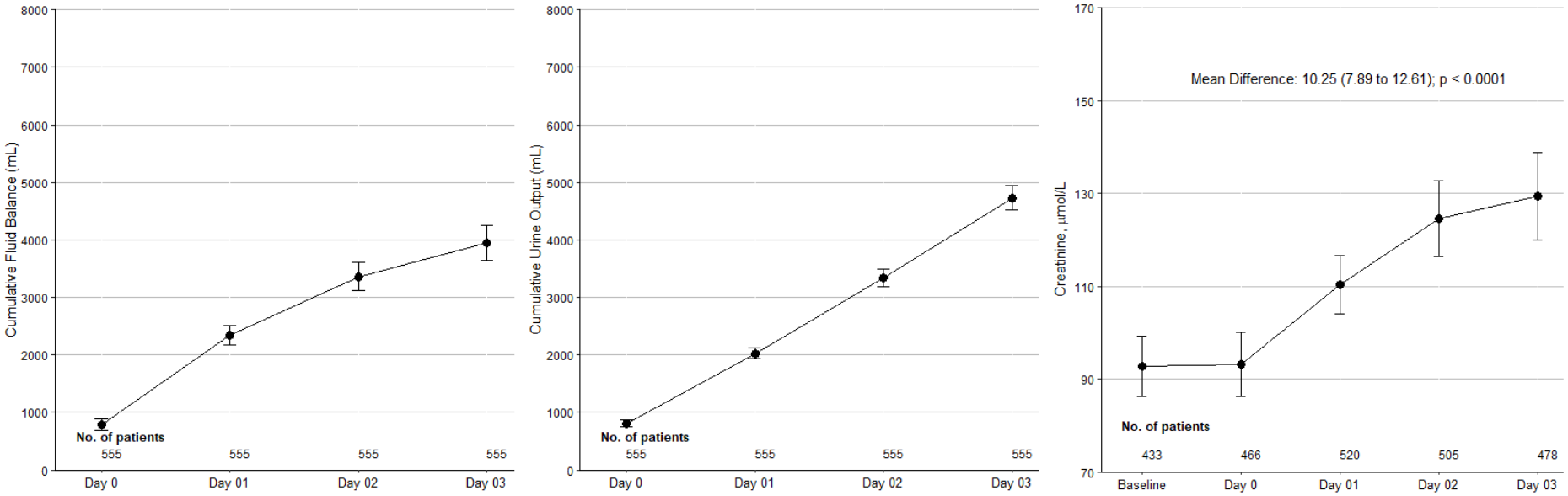
Horizontal dotted lines represent 50% of the patients and vertical dotted lines represent the median of the variable at the start of ventilation. All measurements are mean over three measurements per day.

Appendix Figure 8 – Cumulative Distribution Plots of Ventilatory and Oxygenation Variables



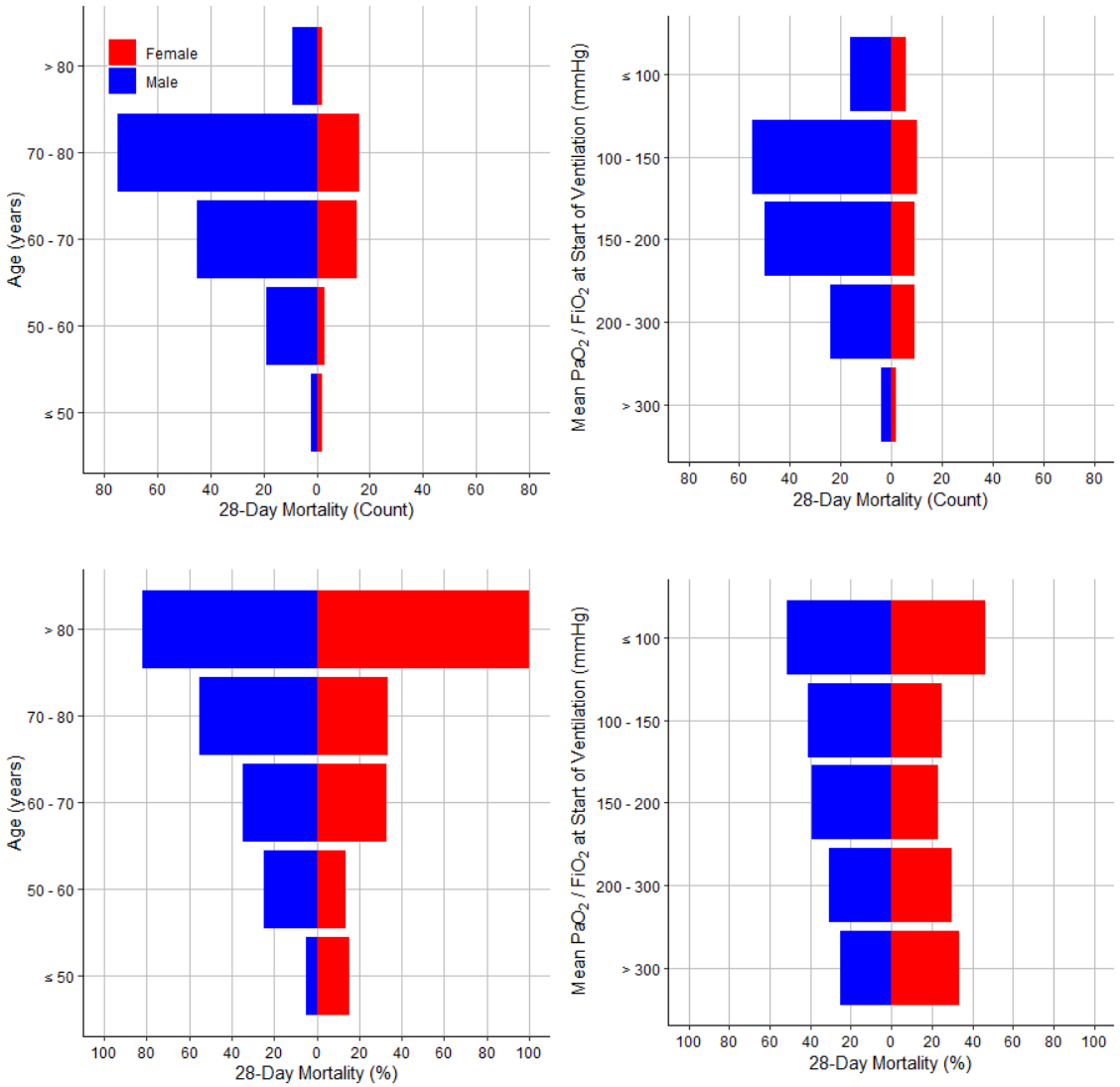
Horizontal dotted lines represent 50% of the patients and vertical dotted lines represent the median of the variable at the start of ventilation. All measurements are mean over three measurements per day.

Appendix Figure 9 – Trend of Urinary Variables of the First Three Days of Ventilation



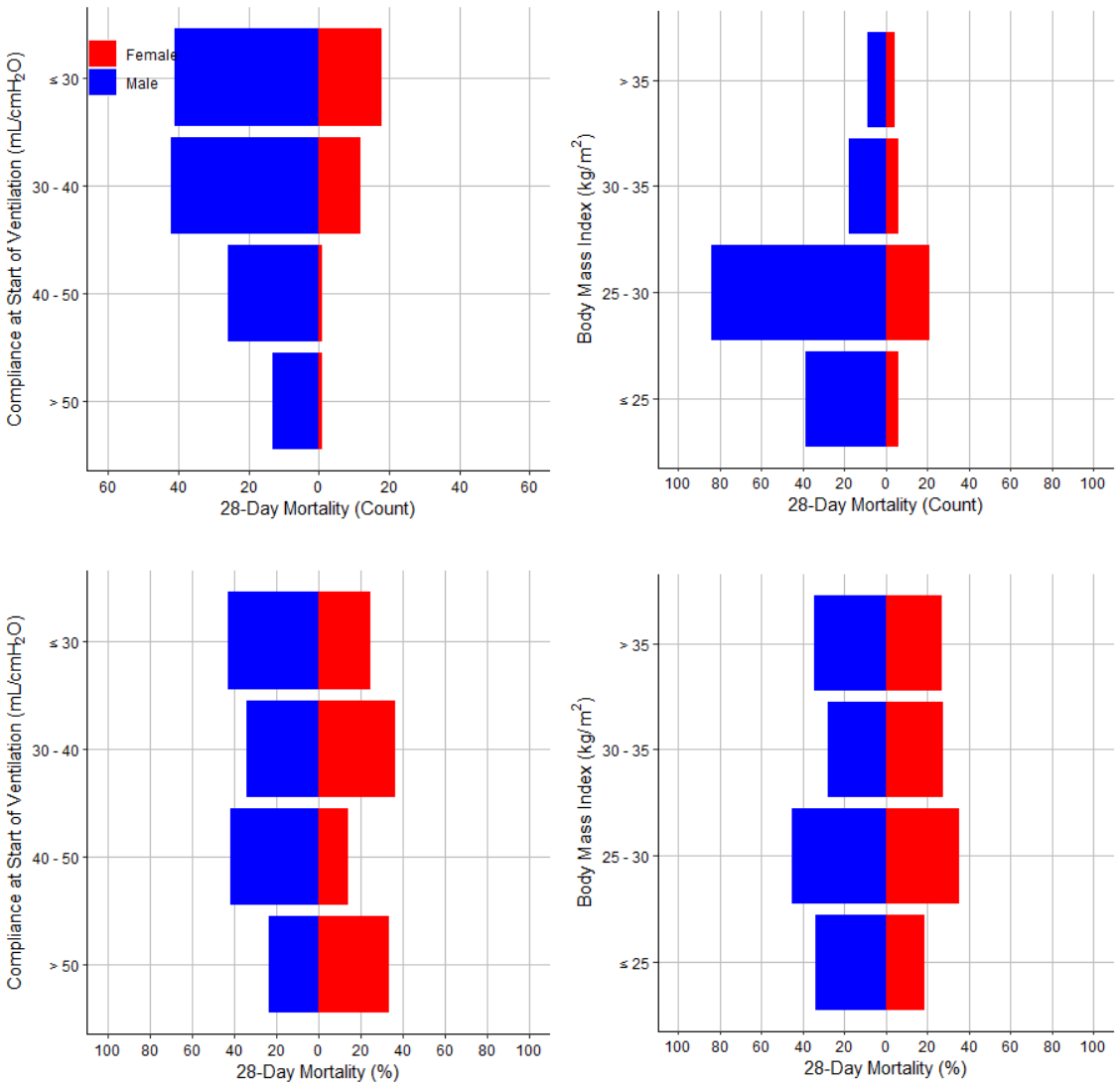
P value was calculated from a mixed-effect linear model with centre as random effect, with random slopes and intercept for patients and with an unstructured covariance matrix. Circles are mean from three measurements each day and error bars are 95% confidence interval. *P* value was not calculated for cumulative fluid balance and urine output because cumulative variables are expected to increase over time.

Appendix Figure 10 – 28–day Mortality According to Age and PaO_2 / FiO_2 at the Start of Ventilation



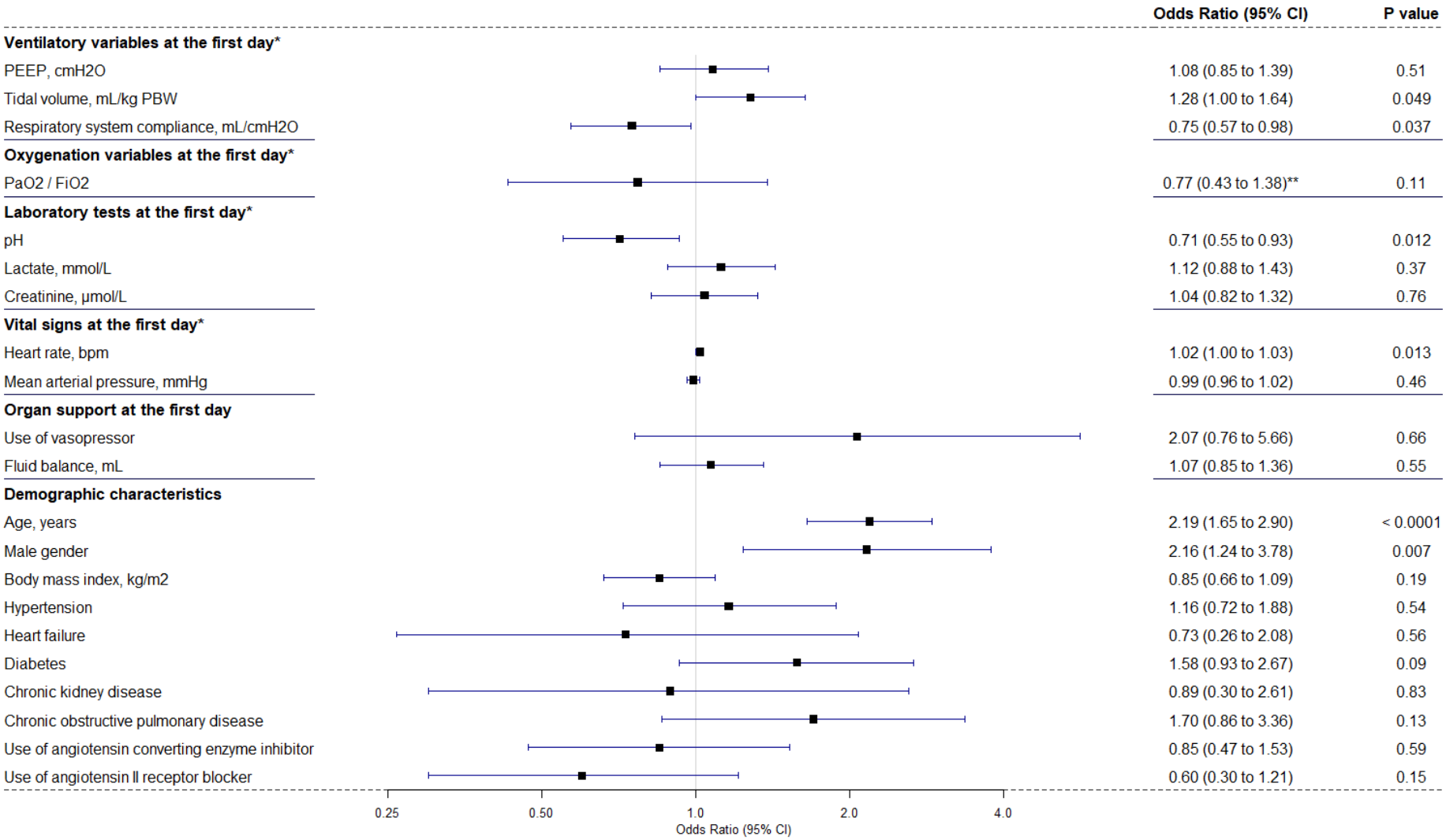
Mortality rates in groups stratified for age and mean PaO2/FiO2

Appendix Figure 11 – 28–day Mortality According to Body Mass Index and Respiratory System Compliance at the Start of Ventilation



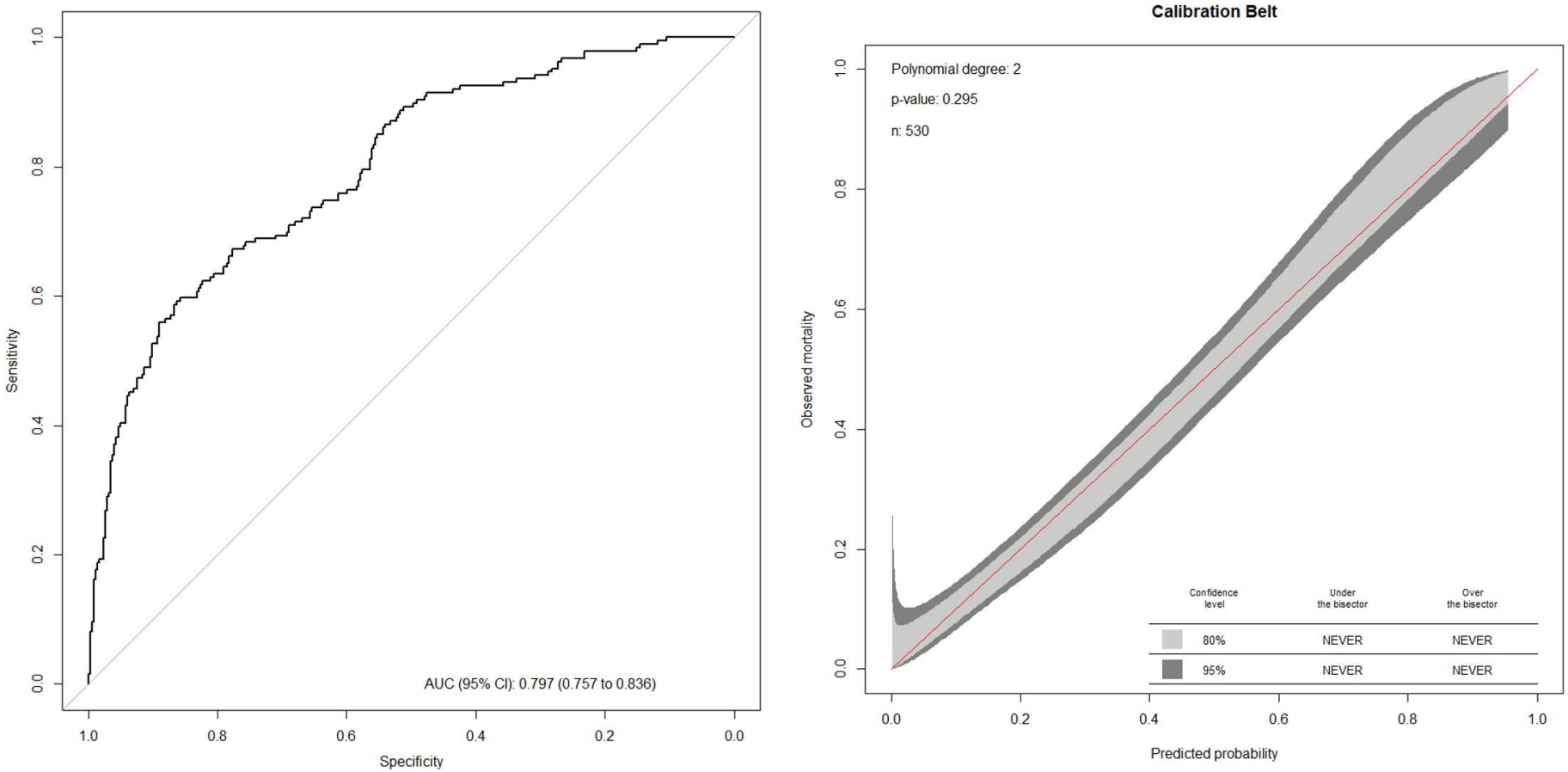
Mortality rates in groups stratified for compliance and Body Mass Index

Appendix Figure 12 - Results of the Final Multivariable Model for 28-Day Mortality



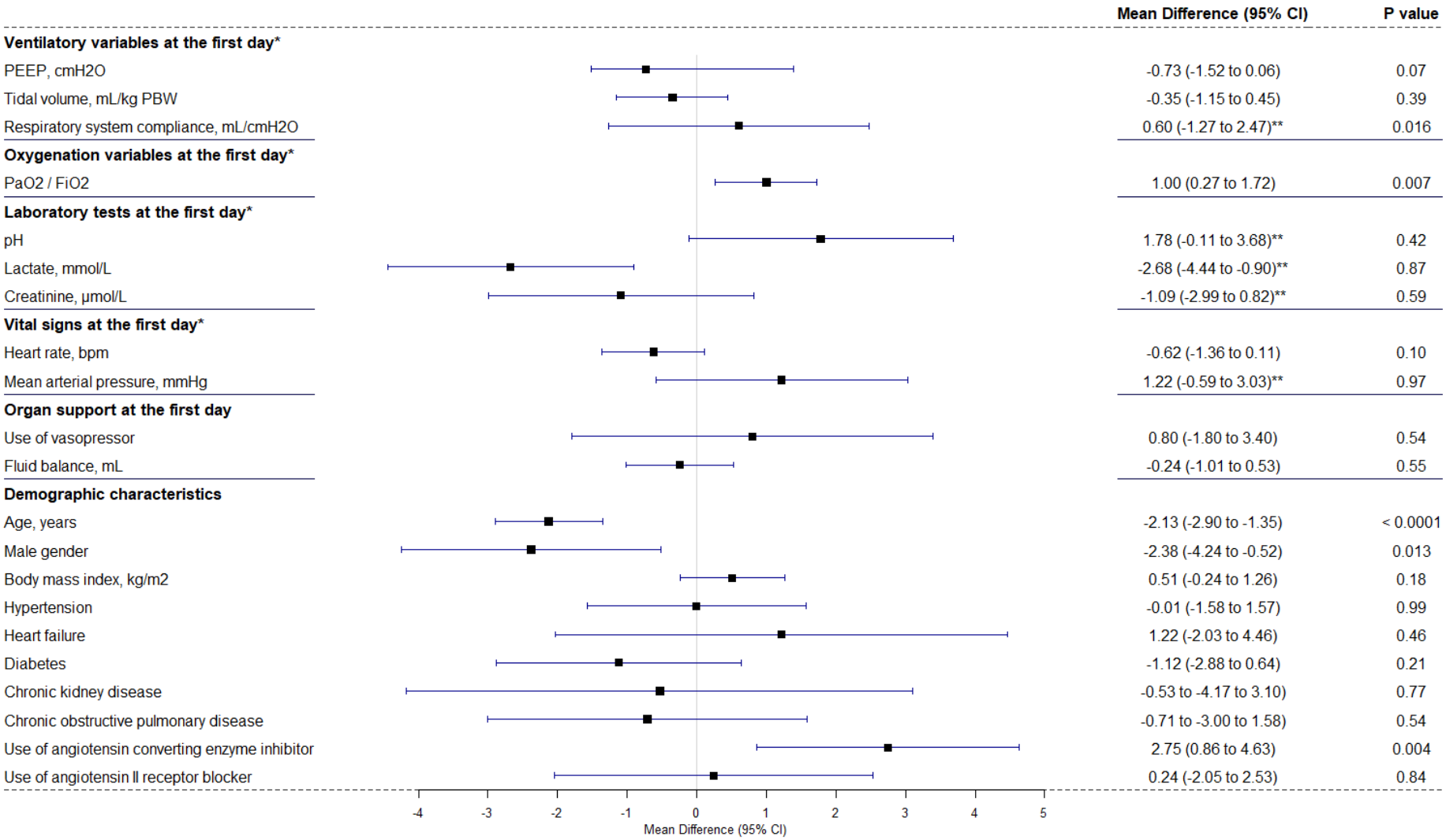
** Variables included as restricted cubic splines and odds ratio is determined over the quartile range observed for the variable (estimated effect of an inter-quartile range increase in the predictor variable) and p value reported is for the first spline.

Appendix Figure 13 - Discrimination and Calibration of the Multivariable Model Assessing 28-Day Mortality



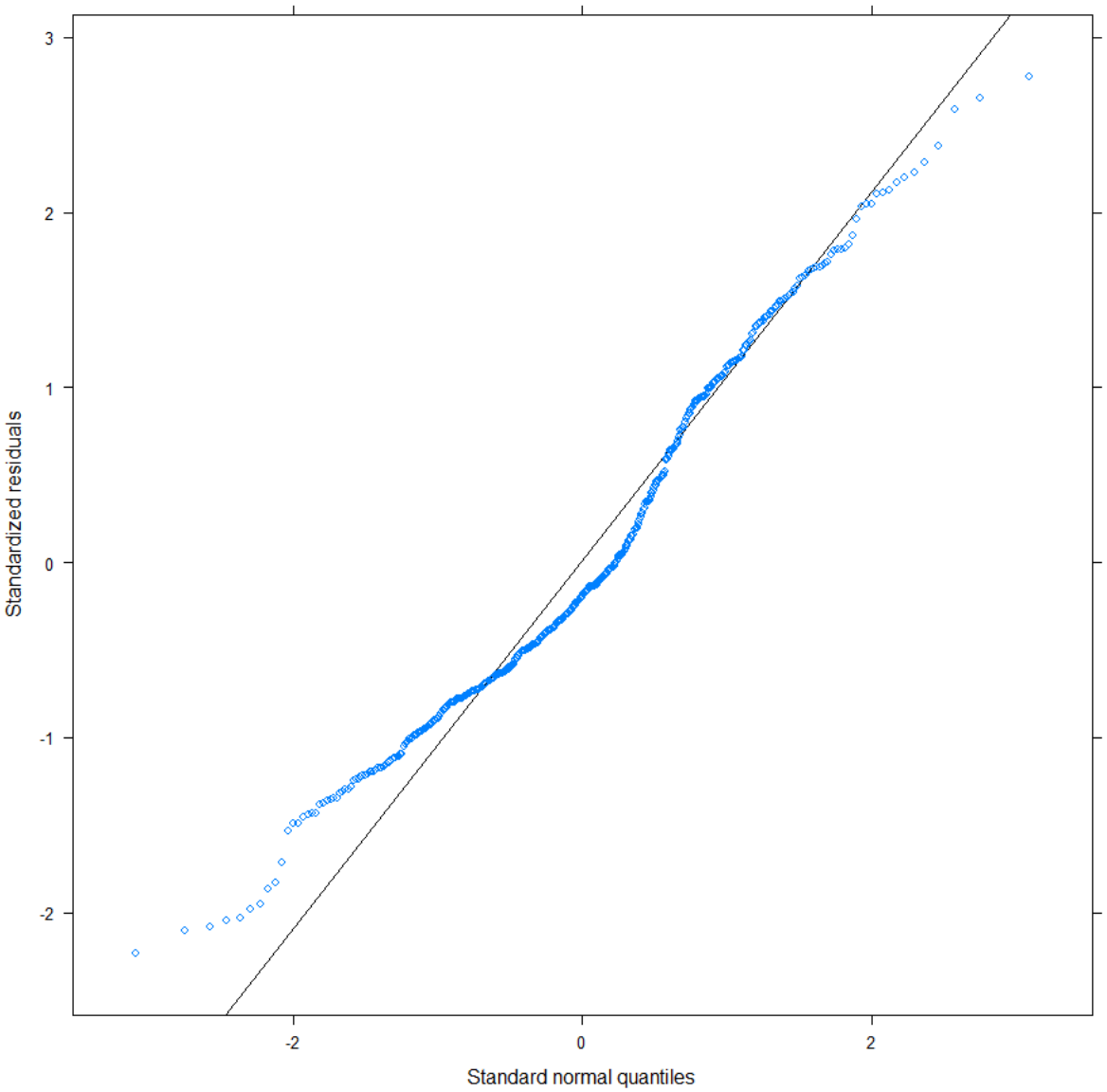
ROC curve and c-statistic is shown in the left plot. Calibration belt is show in the right plot.

Appendix Figure 14 - Results of the Final Multivariable Model for Ventilator-Free Days at Day 28



** Variables included as restricted cubic splines and mean difference is determined over the quartile range observed for the variable (estimated effect of an inter-quartile range increase in the predictor variable) and p value reported is for the first spline.

Appendix Figure 15 - Normality of Residuals in the Ventilator-Free Days at Day 28 Model



QQ plot.

Appendix Figure 16 - Cumulative Incidence of Extubation with Death Before Extubation Treated as a Competing Risk and 28-Day Survival in Overall Cohort