Supplemental Online Content

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

eAppendix 1. Data Collection and Study Procedures

Step 1: Identification of eligible patients meeting all the inclusion criteria

- Age ≥18 years
- ≥ 2 positive SIRS-criteria:
  - Temperature > 38°C or hypothermia < 36°C
  - Heart rate > 90 bpm
  - Respiratory rate > 20 /min or pCO2 < 32 mmHg (4.3 kPa)
  - Number of leucocytes > 12 x 10^9/L or < 4 x 10^9/L or >10% bands
- Within 12 hours of admittance to the ICU
- Expected stay of more than 48 hours as estimated by the attending physician

Step 2: Identification of patients meeting any of the exclusion criteria

- Elective surgery
- Carbon monoxide poisoning
- Cyanide intoxication
- Methemoglobinemia
- Sickle cell anemia
- Severe pulmonary arterial hypertension (WHO class III or IV)
- Known severe ARDS (PaO_2/FIO_2 ≤100 mmHg and PEEP ≥ 5 H_2O)
- Known cardiac right to left shunting
- Pregnancy
- Severe COPD (Gold class III or IV) or other severe chronic pulmonary disease

Step 3: Randomization, blinding and treatment allocation

Randomization was performed with the use of a randomization list generated by a web-based computer program. Castor EDC (electronic data capture system) https://www.castoredc.com/electronic-data-capture-system/.

Step 4: Consent procedures

- Deferred consent assumed
- Deferred consent by patient representative
- Obtain routine clinical data (demographic characteristics, reason of admission, comorbidity, APACHE II)

For this study we initially assumed deferred consent and we appeal to the emergency procedure for consent in medical research as stated in article 6, paragraph 4 of the Dutch WMO.

The motivation for assumed deferred consent was as follows: Oxygen suppletion is applied to almost all ICU-patients. To alleviate respiratory distress oxygen therapy is initiated and cannot be postponed. Patients admitted to an Intensive Care Unit (ICU) are mostly incompetent to give informed consent. Obtaining informed consent from a legal representative takes time (on average up to 12 hours), even by an experienced research team. Oxygenation targets according to randomization were applied immediately.

Informed consent from the legal representative was requested as soon as possible thereafter, but never later than 24 hours after randomization. If informed consent was not obtained within those 24 hours, or if a legal representative denies participation within this time frame, the patient was excluded and data was no longer be used. The patient was oxygenated according to the policy of the attending physician.

During hospital admission, we attempted to achieve informed consent from the patients themselves. If this was not possible (*for example* due to incomplete neurological or physical recovery, or due to early transfer to another hospital) we sent a letter to the patients to inform them that we would use the data and blood samples obtained

during the study unless they denied this by telephone or email. To patients who did not recover sufficiently to understand the letter and take a considered decision about the study we did not send such a letter.

Subjects could be withdrawn from the study at any time upon request without any consequences. The investigator could also decide to withdraw a subject from the study for urgent medical reasons.

Step 5: Study procedures

- Titration of FIO_2, based on measured PaO_2
    - group low-normal PaO_2: target PaO_2 at ICU of 75 (60 – 90) mmHg (8-12 kPa)
    - group high-normal PaO_2: target PaO_2 at ICU of 120 (105 – 135) mmHg (14-18 kPa)
- Blood sample collection at baseline and on day 2, and 4 for determination of parameters of oxidative stress and tissue/organ perfusion (in total 40 ml extra for study). Remaining blood material after analysis was stored for additional analyses in the future.

Data collection was also done using Castor EDC.
The following data were collected:

- Inclusion related data:
    - Inclusion criteria
    - Exclusion criteria
    - Stratification data
    - Randomization data
    - Consent data
- Chronic diagnoses at admission
    - Chronic renal failure
    - Chronic dialysis
    - Malignancy (metastatic)
    - Hematologic malignancy
    - AIDS
    - Immunological failure (immune compromised)
    - Diabetes with medication
    - Heart failure (NYHA IV)
    - Chronic obstructive pulmonary disease with medication
    - Cirrhosis of the liver
    - Recent myocardial infarction (< 6 months)
- Acute diagnoses at admission
    - CPR within 24 hours of admission
    - Trauma within 24 hours of admission
    - Stroke within 24 hours of admission
    - Life threatening hemorrhage within 24 hours of admission
    - Suspected pneumonia
    - Suspected peritonitis or abdominal infection
    - Suspected soft tissue infection
    - Suspected systemic infection

- Daily registration from day 1 to 15
    - Day and time of admission
    - Time of start of study
    - Mechanical ventilation
    - Oxygen administration
    - Number of blood gas samples
    - Number of blood gas samples with PaO_2 outside of target range

    - Protocol compliance
    - Lowest PaO_2/FIO_2 ratio
    - Use of NO (Nitric oxide) or extracorporal life support
    - Lowest mean arterial pressure
    - Highest dose of norepinephrine for at least one hour
    - Highest dose of epinephrine for at least one hour
    - Dobutamine use for at least one hour
    - Enoximone use for at least one hour
    - Use of cardiac assist device
    - SOFA laboratory values
    - SOFA clinical observation
    - Use of renal replacement therapy
    - Dismissal from ICU to general ward
    - Deceased?
    - Description of chest X-ray with oxygenation and ventilatory data
- Follow up
    - Consent obtained
    - Remained on ICU > 24 hours
    - Dismissal (alive) within 3 month from ICU
    - Date and time of dismissal to general ward
    - Mechanical ventilation on ICU
    - Date and time of intubation
    - Successfully weaned and extubated within one month of inclusion (no reintubation within 48 hours)
    - CK and maximum CK-MB
    - Antibiotic therapy for suspected infection
    - Date of start antibiotics
    - Fever or hypothermia before start of antibiotics
    - Leucocytosis or leucopenia before start of antibiotics
    - Deceased within 3 months of inclusion
    - Registration of SAE
    - Start renal replacement therapy > 24 hours after admission to ICU
    - Start of cardiac assist device > 24 hours after admission to ICU
    - Prone ventilation
    - New myocardial infarction on ICU
    - New hepatic failure on ICU
    - New stroke on ICU

Step 6: Primary and secondary endpoints

These are all described in the main article.

Step 7: Handling and storage of data and documents

Patient data have been stored anonymously. Data will not be directly traceable to the individual patients, as all patients are coded. The key to the code is separately safeguarded by the primary investigator. Data will be stored for 15 years.

eAppendix 2. Example Calculations of the Primary Outcome $SOFA_{RANK}$

To calculate the primary outcome $SOFA_{RANK}$, the daily total SOFA score minus the baseline SOFA score was summed over the first 14 study days. Discharge was counted (from the day of discharge forward) as a score of 0 minus baseline score and death was counted (from the day of death forward) as a maximum score of 20 minus baseline score. The resulting cumulative daily delta score was used to rank participants from fast organ failure improvement (lowest scores) to worsening organ failure and death (highest scores).
In the example cases below, patient C had the best outcome (fastest organ failure resolution, lowest $SOFA_{RANK}$ score), followed in rank order by patients A, B and D.

	Patient A					Patient B			
	Study day	**SOFA score**	**SOFA score adjusted**	**SOFA score adjusted minus baseline**		**Study day**	**SOFA score**	**SOFA score adjusted**	**SOFA score adjusted minus baseline**
	Baseline	5	5			*Baseline*	5	5	
	1	5	5	0		*1*	6	6	1
	2	3	3	-2		*2*	6	6	1
	3	6	6	1		*3*	9	9	4
	4	3	3	-2		*4*	9	9	4
	5	2	2	-3		*5*	8	8	3
	6	6	6	1		*6*	8	8	3
	7	6	6	1		*7*	5	5	0
	8	5	5	0		*8*	6	6	1
	9	5	5	0		*9*	7	7	2
	10	4	4	-1		*10*	11	11	6
	11	8	8	3		*11*	9	9	4
	12	5	5	0		*12*	7	7	2
	13	7	7	2		*13*	7	7	2
	14	7	7	2		*14*	7	7	2
SOFArank score				***2***					***35***

	Patient C					Patient D			
	Study day	**SOFA score**	**SOFA score adjusted**	**SOFA score adjusted minus baseline**		**Study day**	**SOFA score**	**SOFA score adjusted**	**SOFA score adjusted minus baseline**
	Baseline	6	6			*Baseline*	4	4	
	1	6	6	0		*1*	4	4	0
	2	7	7	1		*2*	4	4	0
	3	8	8	2		*3*	4	4	0
	4	1	1	-5		*4*	3	3	-1
	5	2	2	-4		*5*	6	6	2
	6	1	1	-5		*6*	11	11	7
	7	0	0	-6		*7*	15	15	11
	8	1	1	-5		*8*	Deceased	20	16
	9	0	0	-6		*9*	Deceased	20	16
	10	Discharged	0	-6		*10*	Deceased	20	16
	11	Discharged	0	-6		*11*	Deceased	20	16
	12	Discharged	0	-6		*12*	Deceased	20	16
	13	Discharged	0	-6		*13*	Deceased	20	16

	14	Discharged	0	-6		*14*	Deceased	20	16
SOFArank score				***-58***					***131***

eAppendix 3. Definitions of Predefined Adverse Events

- Death
- Kidney replacement therapy for acute kidney failure
- Severe respiratory failure necessitating prone ventilation (at the discretion of the treating physician)
- New myocardial infarction according to the ESC/AHA Third Universal Definition of Myocardial Infarction
- New liver failure, defined as new hyperbilirubinemia (> 50 mmol/L) or other signs of severe acute liver dysfunction (INR > 1.5, hepatic encephalopathy)
- New ischemic or hemorrhagic stroke

eAppendix 4. Adjustment of the Effect Estimate on the Primary Endpoint by Stratification Variables

As a post-hoc analysis, the primary outcome was adjusted for the effect by site, reason of admittance (medical, surgical, or trauma) , age category (< 50, 50 - 70, and > 70 years) and gender.

The regression output below show the linear regression estimate of $SOFA_{Rank}$ (primary endpoint) as a function of randomized group allocation *without* adjustment for stratification variables.

Linear model of SOFArank as a function of group allocation

```
Residuals:
     Min       1Q   Median       3Q      Max
-210.007 -100.119    1.993   90.421  209.546

Coefficients:
               Estimate Std. Error t value Pr(>|t|)
(Intercept)     211.007      8.048   26.22   <2e-16 ***
groupHigh PaO2  -21.553     11.527   -1.87   0.0622 .
```

The estimates are in rank units. Patients randomized to the high-normal PaO_2 group had SOFA outcomes that were on average 21.5 ranks lower (better) than those randomized to the low-normal PaO_2 group (p=0.062). This analysis is practically equivalent to the Wilcoxon rank-sum test, which yielded p=0.063.

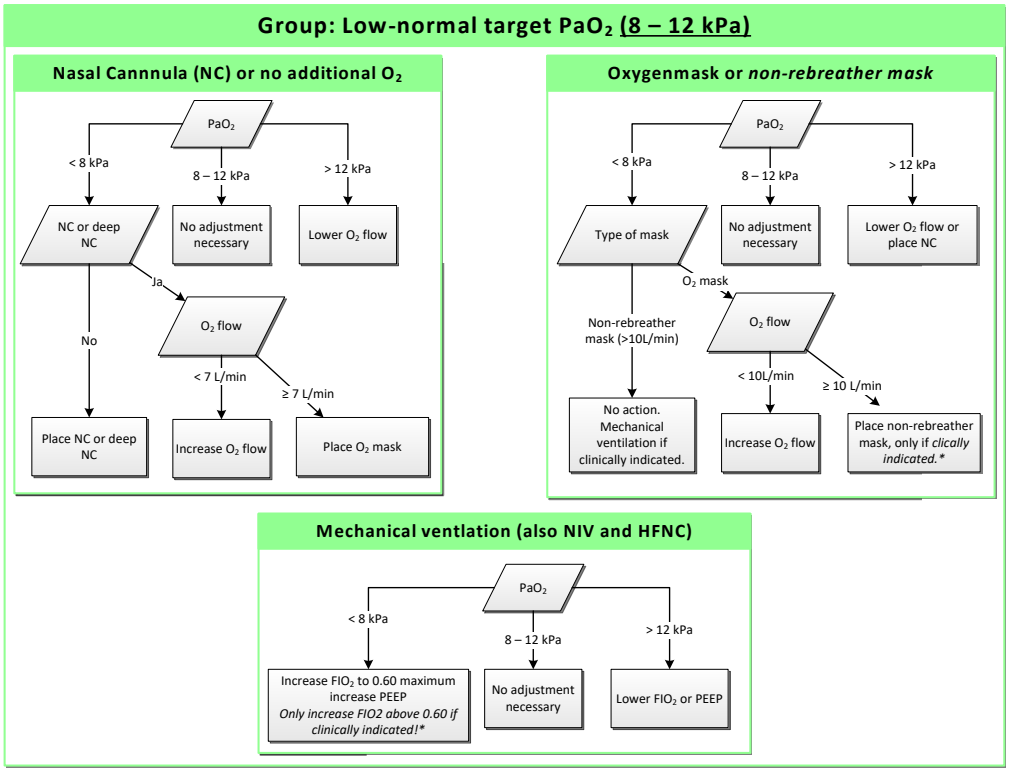
The regression output below show the mixed effects linear regression estimate of $SOFA_{Rank}$ (primary endpoint) as a function of randomized group allocation *with* adjustment for stratification variables (included in the model as random effects).

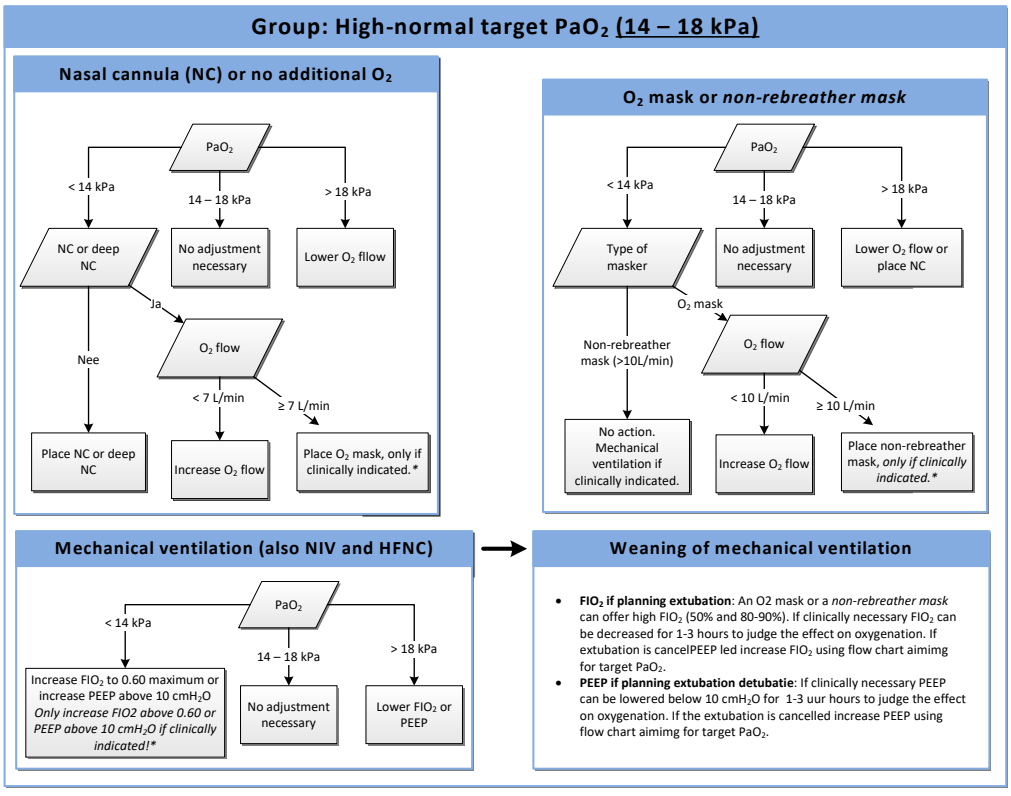
Linear mixed effects model of SOFArank as a function of (fixed effect) group and (random effects) site, reason for admission, age category and gender.

```
REML estimator

Scaled residuals:
     Min       1Q   Median       3Q      Max
-1.82240 -0.86881  0.01729  0.78466  1.81840

Random effects:
 Groups      Name        Variance Std.Dev.
 site        (Intercept)     0      0.0
 incl_rvo    (Intercept)     0      0.0
 incl_agecat (Intercept)     0      0.0
 gender_male (Intercept)     0      0.0
 Residual                13279    115.2
Number of obs: 400, groups:  site, 4; incl_rvo, 3; incl_agecat, 3; gender_male, 2

Fixed effects:
               Estimate Std. Error      df t value Pr(>|t|)
(Intercept)     211.007      8.048 398.000   26.22   <2e-16 ***
groupHigh PaO2  -21.553     11.527 398.000   -1.87   0.0622 .
```

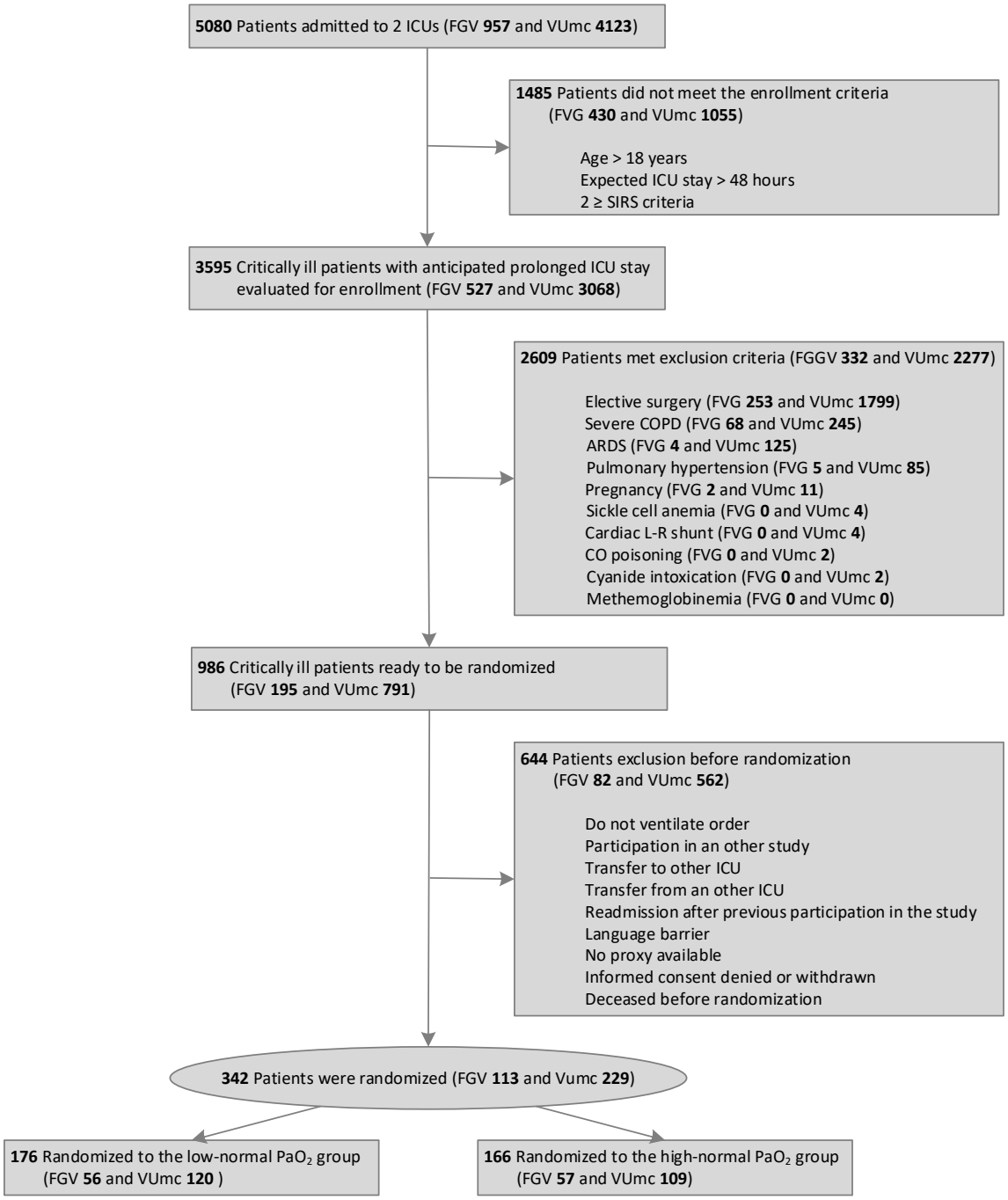
The estimates are in rank units. None of the stratification variables had an effect on SOFArank (the random effects variance estimates were all 0), leaving the effect of group on SOFArank unchanged compared to the unadjusted analysis.

eFigure 1. Flowcharts of Oxygen Administration



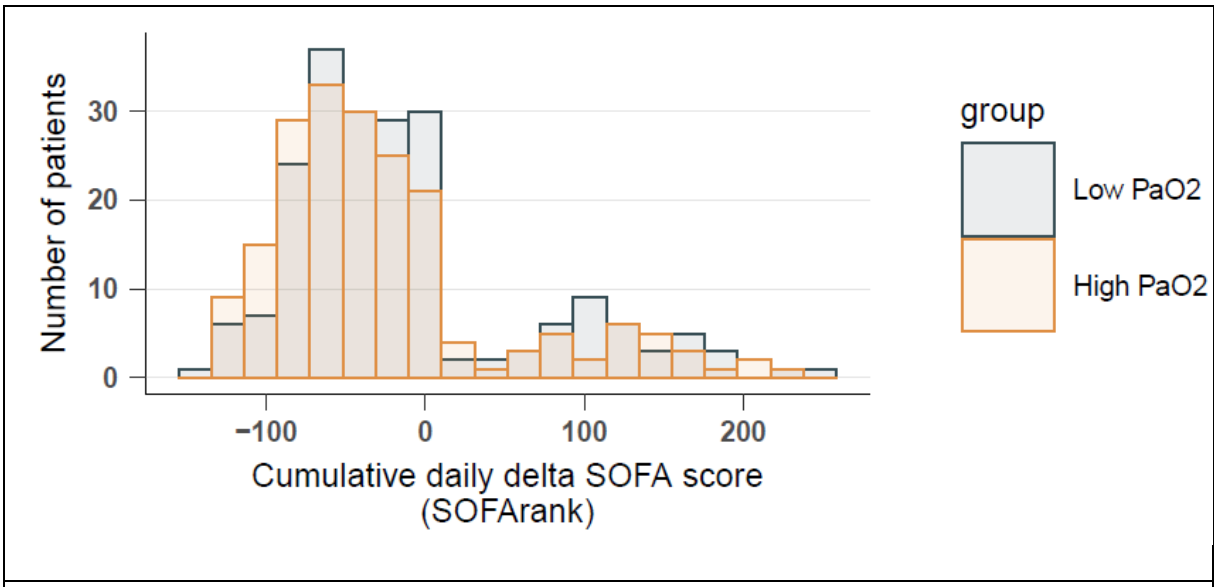


eFigure 2. Detailed Screening Flow Chart Franciscus Gasthuis & Vlietland and Amsterdam UMC-location VUmc



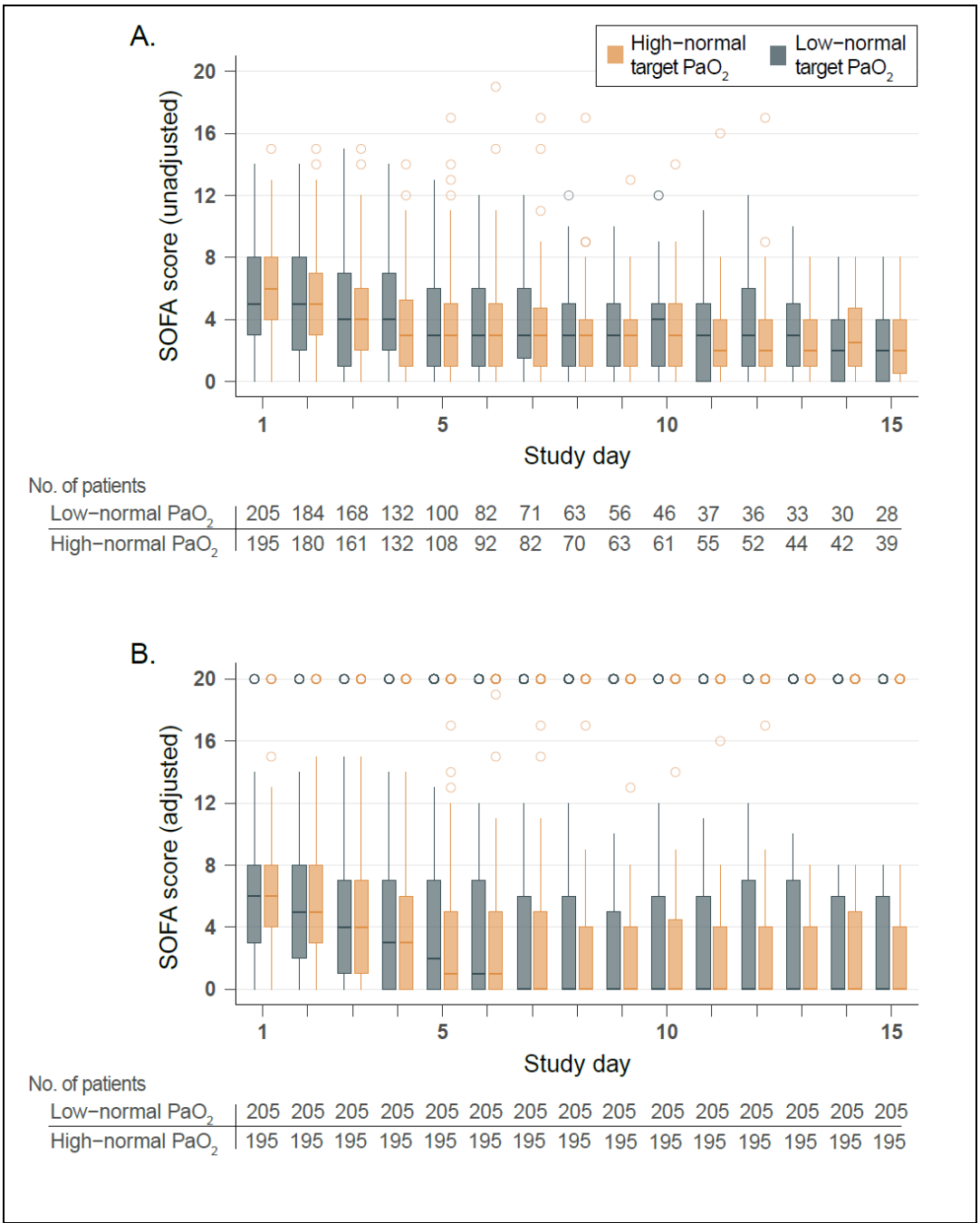
eFigure 2: Inclusion flow chart of two hospitals Franciscus Gasthuis &Vlietland (first data) and Amsterdam UMC – location VUmc (second data) of which elaborate inclusion data were available.

eFigure 3. The Distribution of the Primary Endpoint



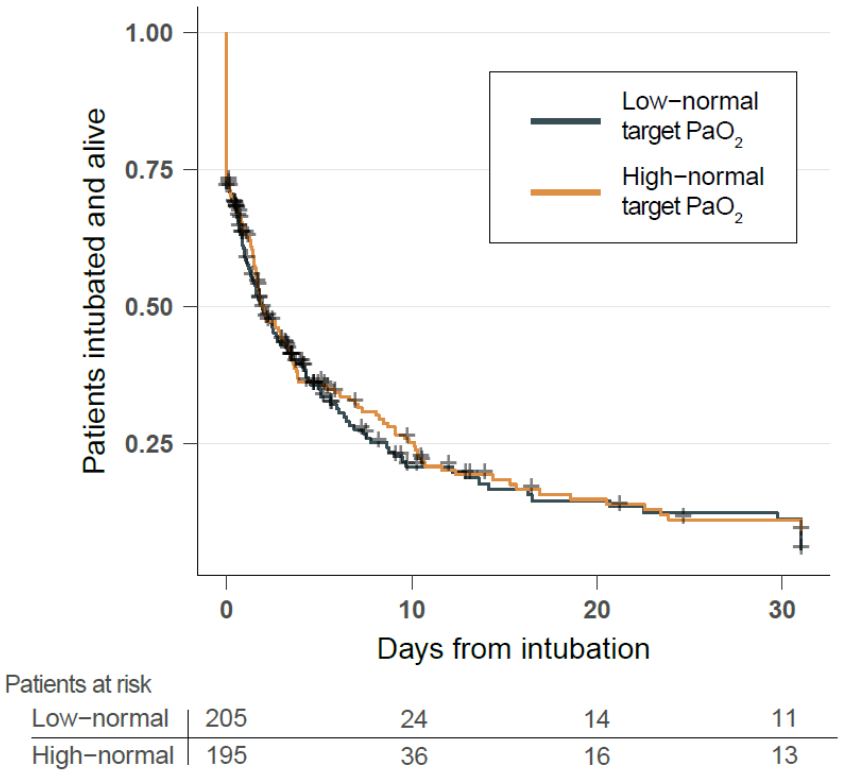
eFigure 3: The distribution of the primary endpoint. The primary endpoint was a ranked outcome of non-respiratory organ failure quantified by the non-respiratory components of the Sequential Organ Failure Assessment (SOFA) score. For each patient, the daily SOFA score minus the baseline SOFA score was summed over the first 14 study days.

eFigure 4. SOFA Scores Over Time



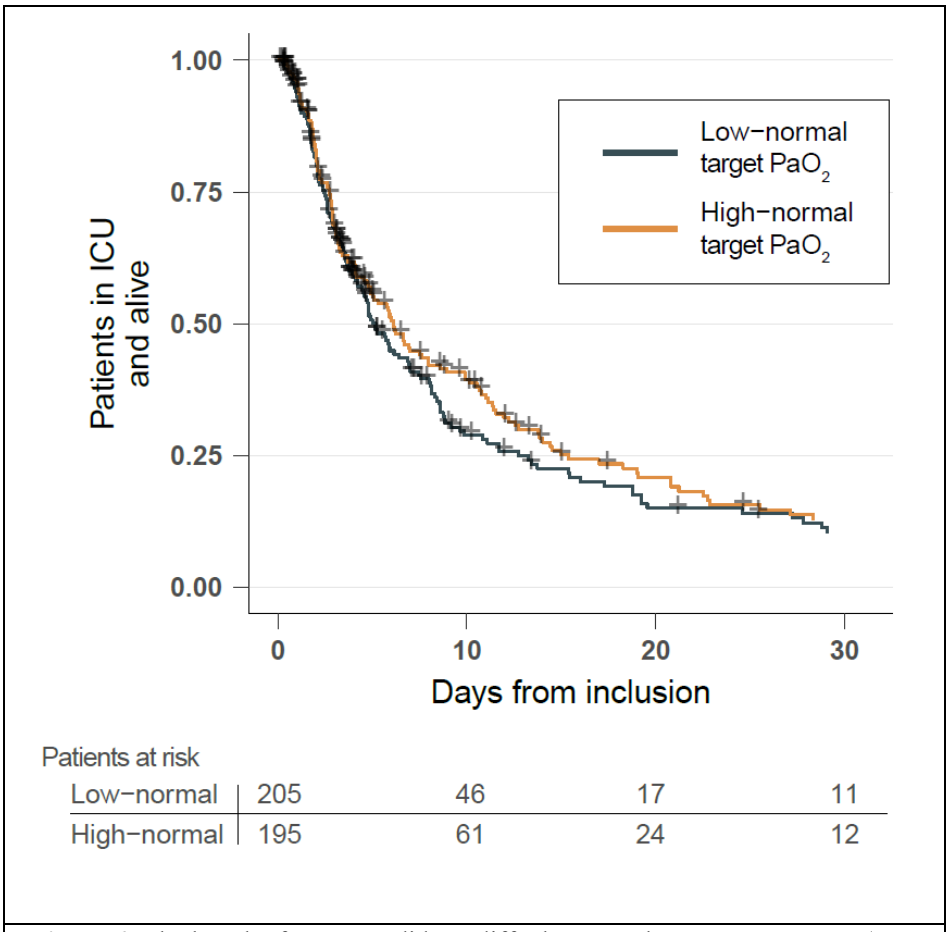
eFigure 4: SOFA scores over time. Boxes represent median and interquartile range, whiskers extend to the lowest and highest observations within 1.5x interquartile range, the circles represent outlier observations. A: Unadjusted SOFA scores, in which patients discharged or deceased are removed from the dataset from the day of discharge or death. B: Adjusted SOFA scores, in which discharge was counted (from the day of discharge forward) as a score of 0 and death was counted (from the day of death forward) as a maximum score of 20. The primary endpoint was based on the adjusted scores.

eFigure 5. Duration of Mechanical Ventilation



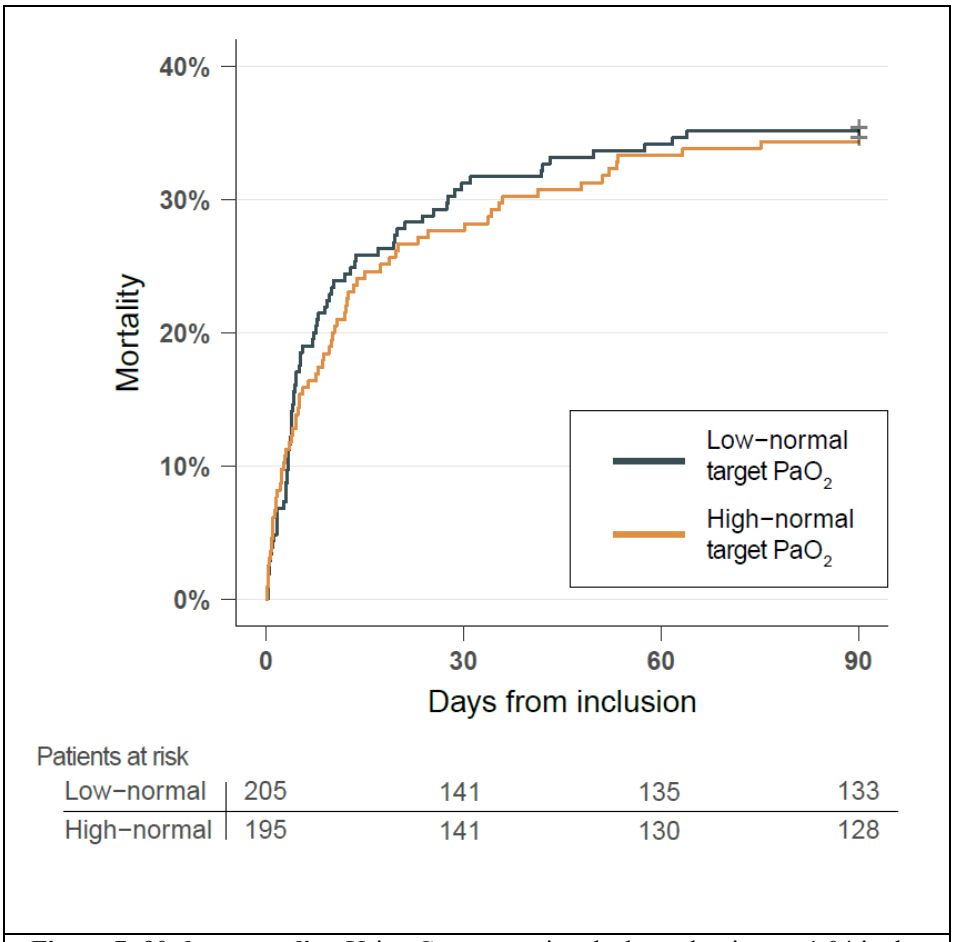
eFigure 5: Duration of mechanical ventilation did not differ between the treatment groups (P = 0.55 using a Cox proportional hazards model).

eFigure 6. Length of ICU Stay



eFigure 6: The length of ICU stay did not differ between the treatment groups (P = 0.20 using a Cox proportional hazards model).

eFigure 7. 90-Day Mortality



eFigure 7: 90-day mortality. Using Cox-regression the hazard ratio was 1.04 in the low-normal group compared to the high-normal group (95% CI 0.74 - 1.45, P=0.83). The duration of follow-up was 90 days for all patients.

eTable 1: Oxygenation (Secondary Endpoint)				
Group	**Low-normal PaO_2** N = 205	**High-normal PaO_2** N=195	**Difference** (95% CI)	**P**
Oxygenation indices				
PaO_2 (kPa) Median (IQR)	10.8 (9.77 - 12.0)	12.8 (10.9 - 14.9)	-1.93 (-2.12 to -1.74)	<0.001
SaO_2 (%) Median (IQR)	96.0 (95.0 - 97.1)	97.4 (96.0 - 98.2)	-1.11 (-1.24 to -1.00)	<0.001
SpO_2 (%) Median (IQR)	95.8 (94.6 - 97.0)	97.2 (95.6 - 98.5)	-1.01 (-1.22 to -0.93)	<0.001
FIO_2 Median (IQR)	0.40 (0.31 - 0.50)	0.51 (0.40 - 0.59)	-0.09 (-0.10 to -0.08)	<0.001
Hypoxemia				
Mild hypoxemic periods PaO_2 5 - 7.3 kPa (number)	132/6777 (1.9 %)	91/7436 (1.2 %)	0.73 (0.30 to 1.20) (%)	<0.001
Severe hypoxemic periods PaO_2 < 5 kPa (number)	16/6777 (0.23 %)	12/7436 (0.16 %)	0.08 (-0.09 to 0.23) (%)	0.42
Hyperoxemia				
Hyperoxemic periods PaO_2 > 13.3 kPa (number)	1056/6777 (15.6%)	3296/7436 (44.3%)	-28.7 (-30.2 to -27.3) (%)	<0.001
Hyperoxemic periods PaO_2 > 16.7 kPa (number)	319/6777 (4.7%)	1216/7436 (16.4%)	-11.6 (-12.6 to -10.6) (%)	<0.001
Hyperoxemic periods PaO_2 > 18 kPa (number)	197/6777 (2.9%)	697/7436 (9.4%)	-6.4 (-7.2 to -5.7) (%)	<0.001

PaO_2 (arterial oxygen partial pressure), SaO_2 (arterial oxyhemoglobin saturation in blood gas samples), SpO_2 (pulse oximeter measured oxyhemoglobin saturation), FIO_2 (inspired oxygen fraction). Oxygenation indices were based on a median of 5 (IQR 3-7) arterial blood gas measurements per patient per day, which were time-weighted and averaged per patient-day before aggregation by study group. Over the entire course of the ICU admission in 205 patients with low-normal target PaO_2 6777 blood gas samples were taken, in the 195 patients with high-normal target PaO_2 7436 blood gas samples were taken. This table shows the unadjusted numbers and percentages of samples with PaO_2 values in the hypoxemic and hyperoxemic range. Conversion factor SI to conventional units : To convert PaO_2 from kPa to mmHg, multiply values by 7.5.

eTable 2: Number of Blood Gas Samples Taken per Patient per Day

Study day	**Median number of samples**	**Lowest number of samples**	**Highest number of samples**
1	4	0	14
2	6	0	16
3	5	0	15
4	5	0	13
5	5	0	17
6	5	0	17
7	5	0	12
8	5	0	11
9	5	0	13
10	5	0	11
11	4.5	0	11
12	5	0	12
13	4	0	11
14	4	0	10
15	4	0	10