

Statistical Analysis Plan: Mega-ROX Skin Tone Substudy

OBJECTIVE

The primary objective of this substudy is to determine whether the effect of conservative oxygen therapy compared with liberal oxygen therapy on clinical outcomes varies according to participant skin tone.

The primary hypothesis is that the treatment effect of conservative oxygen therapy on in-hospital mortality and other secondary outcomes differs across categories of baseline skin tone, reflecting potential heterogeneity of treatment effect according to Fitzpatrick skin type.

STUDY POPULATION

The analysis population will include all participants enrolled in the Mega-ROX trial who:

1. were randomised to conservative or liberal oxygen therapy;
2. were enrolled at participating sites where baseline skin tone data were collected; and
3. have a recorded Fitzpatrick skin tone assessment.

Participants will be analysed according to their randomised treatment allocation (intention-to-treat principle), irrespective of adherence to the assigned oxygen strategy.

EXPOSURE VARIABLE: SKIN TONE

Skin tone will be classified according to the baseline Fitzpatrick Skin Type Scale (I–VI).

The primary analysis will model skin tone as an ordinal categorical variable with the following categories:

- I–II (lighter skin tone)
- III–IV (intermediate skin tone)
- V–VI (darker skin tone)

This categorisation is prespecified to simplify interpretation, improve statistical power, and avoid sparse data in individual categories.

Sensitivity analyses will assess skin tone as a six-level categorical variable (I–VI);

PRIMARY ANALYSIS

The primary outcome for this substudy is in-hospital mortality during the index hospitalisation within 90-days.

The primary analysis will assess whether skin tone modifies the effect of conservative versus liberal oxygen therapy using log-binomial regression models including terms for:

- Randomised oxygen strategy;
- Skin tone category;
- The interaction between randomised oxygen strategy and skin tone category.

The model will adjust for the same baseline variables as the primary Mega-ROX analysis, including the presence of ischemic encephalopathy, other brain injuries and conditions, and sepsis at baseline. Adjustment for site as a random effect will also be incorporated.

The global null hypothesis of an equal treatment effect across all skin tone groups will be tested and the p-value for this hypothesis test reported. Relative risks and absolute risk differences within each skin tone group with corresponding 95% confidence intervals will be reported. The risk difference will be obtained from a model with an identity link function; the relative risk obtained from a model with a log link function.

If models fail to converge, the following steps will be taken:

1. Fit a log-binomial with the same link function, adjusting for site with cluster-robust standard errors instead of random effects for site.
2. Combine sites with fewer than 10 patients together and fit the original model.
3. Combine sites with fewer than 20 patients together and fit the original model.
4. Fit the log-binomial model with adjustment for site as a random effect, excluding the term for ischemic encephalopathy
5. Fit the log-binomial model with adjustment for site as a random effect, excluding the term for presence of other brain injuries and conditions.
6. Fit the log-binomial model with adjustment for site as a random effect, excluding the term for sepsis.
7. Fit the log-binomial model with adjustment for site as a random effect, including only the term for ischemic encephalopathy
8. Fit the log-binomial model with adjustment for site as a random effect, including only the term for presence of other brain injuries and conditions.
9. Fit the log-binomial model with adjustment for site as a random effect, including only the term for sepsis.

10. Fit the log-binomial model with adjustment for site as a random effect without including any additional covariates.

SECONDARY ANALYSES

The association between skin tone and treatment effect will be assessed for secondary Mega-ROX outcomes:

- duration of survival up until the last follow-up,
- ICU length of stay,
- hospital length of stay,
- duration of invasive mechanical ventilation, and
- discharged home.

Analyses of the discharged home outcome will use log-binomial models adjusted as described for the primary analysis.

Duration of survival will be by fitting a Cox proportional hazards model, including terms as described for the primary analysis, with robust standard errors to account for clustering by site. If estimation fails, sites with fewer than 10 patients and then, if necessary, sites with fewer than 20 patients will be combined and the model re-fit. A Kaplan-Meier survival plot will be presented, and hazard ratios and 95% confidence intervals for each skin tone group reported.

To account for the competing risk of death, duration of mechanical ventilation, ICU length of stay, and hospital length of stay will be analysed using subdistribution hazard regression models and presented using cumulative incidence functions. Terms as described in the analysis of the primary outcome will be included, with robust standard errors to account for clustering by site. Subdistribution hazard ratios and 95% confidence intervals will be reported for each skin tone group.

MISSING DATA

The proportion of participants with missing Fitzpatrick skin tone data will be reported overall and according to randomised treatment allocation. The primary analysis will be restricted to participants with available skin tone data.

For missing outcome data due to loss to follow-up or withdrawal of consent, multiple imputation will be performed using the approach specified in the primary Mega-ROX statistical analysis plan.

SENSITIVITY ANALYSES AND OTHER ANALYSES

The robustness of findings will be assessed in prespecified sensitivity analyses:

1. Alternative skin tone categorisation
 - Fitzpatrick skin tone as six-level categorical variable (I–VI);
 - Fitzpatrick skin tone analysed as a continuous ordinal variable assuming a linear trend across categories (1–6). For these analyses, the treatment effect for a one-unit increase in skin tone category will be reported.
2. Adjustment for additional baseline characteristics: age, sex, and ethnicity where available.
3. Assessment of potential mechanisms

Exploratory analyses will assess whether oxygen exposure differs according to skin tone among patients assigned to the conservative and liberal oxygen strategies. Measures of oxygen exposure will include:

 - achieved oxygen saturation;
 - time spent within the assigned oxygen saturation range;
 - exposure to oxygen concentrations outside assigned treatment targets.

Analyses will be performed separately within each randomised treatment group to assess whether these measures of oxygen exposure differ according to skin tone category. An additional exploratory analysis will assess whether the difference in oxygen exposure between the conservative and liberal oxygen groups varies according to skin tone. For the primary mechanistic analyses, regression models will be fitted separately within the conservative and liberal oxygen groups, with each oxygen exposure measure as the outcome and skin tone category as the primary explanatory variable, adjusting for the covariates specified for the primary analysis. An additional model including treatment group, skin tone, and their interaction will assess whether the between-group difference in oxygen exposure varies according to skin tone.

MULTIPLICITY

This substudy is designed to evaluate heterogeneity of treatment effect and will be interpreted as exploratory. No adjustment will be made for multiple comparisons. The primary inference will be based on the magnitude and precision of the treatment-by-skin tone interaction effects rather than statistical significance alone.

PROPOSED TABLES AND FIGURES

Table 1. Baseline characteristics of participants included in the skin tone substudy according to Fitzpatrick skin tone category. The purpose of this table is to describe the population and assess whether skin tone categories differ systematically in baseline characteristics.

Table 2. Distribution of Fitzpatrick skin tone categories according to randomised treatment allocation. The purpose of this table is to demonstrate balance between treatment groups and describe the exposure variable.

Table 3. Oxygen exposure metrics by treatment group according to Fitzpatrick skin tone category. The purpose of this table is to evaluate whether skin tone modifies oxygen exposure in patients allocated to conservative or liberal oxygen therapy.

Table 4. Primary and Secondary Outcomes by Treatment Group According to Fitzpatrick Skin Tone Category. This is the main inferential table described treatment effect modification by skin tone.

Table S1. Characteristics of participants from Mega-ROX sites contributing skin tone data compared with sites not contributing skin tone data. The purpose of this table is to provide data on whether sites that contributed to the skin tone study are representative. Data presented will align with data in Table 1 and will include all patients irrespective of whether skin tone data were collected for individual participants

Table S2. Missingness of Fitzpatrick skin tone data. The purpose of this table is to compare the characteristics of patients included in the skin tone study vs. those not included in the skin tone study, limited to sites that contributed data to the skin tone study. The purpose of this table is to provide data on whether participants included in the skin tone study are representative of patients enrolled in Mega-ROX in the sites participating in the skin tone substudy. Data presented will align with data in Table 1.

Table S3. Characteristics of Mega-ROX participants included in the skin tone study vs. those not included in the skin tone study. The purpose of this table is to provide data on whether patients included in the skin tone study are representative. The purpose of this table is to provide data on whether the characteristics of Mega-ROX participants included in the skin tone study differ from those not included in the skin tone study. Data presented will align with data in Table 1.

Table S4. Primary and Secondary Outcomes by Treatment Group According to Fitzpatrick Skin Tone, treated as a 6-level categorical variable.

Table S5. Primary and Secondary Outcome effect estimates by Fitzpatrick Skin Tone Category, adjusting for additional baseline variables.

Table S6. Oxygen exposure metrics by treatment group according to Fitzpatrick skin tone category. The purpose of this table is to evaluate whether skin tone modifies oxygen exposure in patients allocated to conservative or liberal oxygen therapy.

Figure 1. Flow diagram for skin tone substudy: Mega-ROX population -> sites collecting skin tone data -> skin tone data collected -> included in analysis (by treatment allocation at each step)

Figure 2. Primary effect estimates by all six skin tone categories on a Forest plot. Subgroup categories should include all patients included in the skin tone analysis and then the breakdown by skin category with the mortality by treatment group (n/N) the relative risk and 95% CI. The interaction p value should be shown in a footnote. The purpose of this presentation is to explore whether there is a monotonic gradient of mortality treatment effects by skin tone.

Figure S1. Exposure to arterial hypoxaemia by skin tone. This figure will show the effect of conservative vs. liberal oxygen on the relative risk of exposure to a PaO₂ of less than 60mmHg. Effect estimates by all six skin tone categories on a Forest plot. Subgroup categories should include all patients included in the skin tone analysis and then a breakdown by skin tone category (I to VI) with the proportion exposed to hypoxaemia by treatment group (n/N), the associated relative risk and 95% CIs. The interaction p value should be shown in a footnote. The purpose of this presentation is to explore whether there is monotonic gradient of exposure to hypoxaemia by skin tone.

Figure S2. Exposure to arterial hyperoxaemia by skin tone. This figure will show the effect of conservative vs. liberal oxygen on the relative risk of exposure to a PaO₂ of greater than 100mmHg. Effect estimates by all six skin tone categories on a Forest plot. Subgroup categories should include all patients included in the skin tone analysis and then a breakdown by skin tone category (I to VI) with the proportion exposed to hyperoxaemia by treatment group (n/N), the associated relative risk and 95% CIs. The interaction p value should be shown in a footnote. The purpose of this presentation is to explore whether there is monotonic gradient of exposure to hyperoxaemia by skin tone.

MOCK TABLES

Table 1: Baseline characteristics of participants included in the skin tone substudy according to Fitzpatrick skin tone category*			
Characteristic	Fitzpatrick I–II (n=XXX)	Fitzpatrick I–II (n=XXX)	Fitzpatrick I–II (n=XXX)
Age – yr	xx.x ± xx	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Body-mass index†	xx.x ± xx	xx.x ± xx	xx.x ± xx
Clinical Frailty Score‡	x (x to x)	x (x to x)	x (x to x)
Source of admission to ICU – no. (%)			
Emergency department	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Hospital ward	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Transfer from another ICU	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Transfer from another hospital (except from another ICU)	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
From OT following surgery	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Median time from hospital admission to randomization (IQR) – hours	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median time from ICU admission to randomization (IQR) – hours	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
APACHE-II score§	xx.x ± xx	xx.x ± xx	xx.x ± xx
SAPS-III score¶	xx.x ± xx	xx.x ± xx	xx.x ± xx
Subgroup diagnoses – no. (%)			
Ischemic encephalopathy	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Sepsis	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Acute brain injuries and conditions other than ischemic encephalopathy	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
COVID-19 disease	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Enrolled in a low or middle income country	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
ICU admission to randomization less than 2 hours	xxx (xx.x)	xxx (xx.x)	xxx (xx.x)
Baseline oxygen data			
FIO ₂	x.xx ± xx	x.xx ± xx	x.xx ± xx
Median PaO ₂ (IQR) – mmHg	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median PaO ₂ /FIO ₂ ratio (IQR) – mmHg	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)

* Plus-minus values are expressed as mean ± SD.

† Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Scores on the Clinical Frailty Scale include 1 (very fit), 2 (well), 3 (managing well), 4 (vulnerable), 5 (mildly frail), 6 (moderately frail), 7 (severely frail), 8 (very severely frail), and 9 (terminally ill). Patients were evaluated according to their condition before the current admission.

§ Scores on the APACHE II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.

¶ Scores on the SAPS-III range from 0 to 217, with higher scores indicating more severe disease. The SAPS-III score was collected from trial participants from Brazil.

A witnessed arrest was defined as one that was seen or heard by another person or was monitored.

Abbreviations: Acute Physiology And Chronic Health Evaluation; COVID-19: coronavirus disease 2019; FIO₂: fraction of inspired oxygen; ICU: Intensive Care Unit; IQR: interquartile range; PaO₂: arterial partial pressure of oxygen; SAPS 3: Simplified Acute Physiology Score 3; SD: standard deviation.

Table 2: Distribution of Fitzpatrick skin tone categories according to randomised treatment allocation.

Fitzpatrick category	Liberal oxygen (n=XXX)	Conservative oxygen (n=XXX)
I	xxx (xx.x)	xxx (xx.x)
II	xxx (xx.x)	xxx (xx.x)
III	xxx (xx.x)	xxx (xx.x)
IV	xxx (xx.x)	xxx (xx.x)
V	xxx (xx.x)	xxx (xx.x)
VI	xxx (xx.x)	xxx (xx.x)
I-II	xxx (xx.x)	xxx (xx.x)
III-IV	xxx (xx.x)	xxx (xx.x)
V-VI	xxx (xx.x)	xxx (xx.x)

Table 3: Differences in oxygen exposure metrics by treatment group according to Fitzpatrick skin tone category

Characteristic	Skin tone category	Conservative oxygen	Difference between skin tone category and average (95% CI)	Liberal oxygen	Difference between skin tone category and average (95% CI)
Measures of exposure to high arterial oxygen					
Median percentage of hours per patient SpO ₂ ≥97% (IQR)	I	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	II	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	III	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	IV	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	V	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	VI	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
At least one PaO ₂ recording >100 mmHg, n (%)	I	xxx (xx.x)	x.xx (x.xx to x.xx)	xxx (xx.x)	x.xx (x.xx to x.xx)
	II	xxx (xx.x)	x.xx (x.xx to x.xx)	xxx (xx.x)	x.xx (x.xx to x.xx)
	III	xxx (xx.x)	x.xx (x.xx to x.xx)	xxx (xx.x)	x.xx (x.xx to x.xx)
	IV	xxx (xx.x)	x.xx (x.xx to x.xx)	xxx (xx.x)	x.xx (x.xx to x.xx)
	V	xxx (xx.x)	x.xx (x.xx to x.xx)	xxx (xx.x)	x.xx (x.xx to x.xx)
	VI	xxx (xx.x)	x.xx (x.xx to x.xx)	xxx (xx.x)	x.xx (x.xx to x.xx)
Measures of exposure to low arterial oxygen					
Median percentage of hours per patient SpO ₂ <88% (IQR)	I	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	II	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	III	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	IV	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	V	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	VI	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
At least one PaO ₂ recording <60 mmHg, n (%)	I	xxx (xx.x)	x.xx (x.xx to x.xx)	xxx (xx.x)	x.xx (x.xx to x.xx)
	II	xxx (xx.x)	x.xx (x.xx to x.xx)	xxx (xx.x)	x.xx (x.xx to x.xx)
	III	xxx (xx.x)	x.xx (x.xx to x.xx)	xxx (xx.x)	x.xx (x.xx to x.xx)
	IV	xxx (xx.x)	x.xx (x.xx to x.xx)	xxx (xx.x)	x.xx (x.xx to x.xx)
	V	xxx (xx.x)	x.xx (x.xx to x.xx)	xxx (xx.x)	x.xx (x.xx to x.xx)
	VI	xxx (xx.x)	x.xx (x.xx to x.xx)	xxx (xx.x)	x.xx (x.xx to x.xx)
Measures of time spent breathing room air (FIO ₂ = 0.21)					
Median percentage of hours per patient FIO ₂ = 0.21 (IQR)	I	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	II	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	III	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	IV	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	V	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	VI	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)

Table 4: Primary and Secondary Outcomes by Treatment Group According to Fitzpatrick Skin Tone Category*						
Outcome	Skin Tone category	Conservative oxygen	Liberal oxygen	Effect estimate (95% CI)		P value for interaction
Mortality in the index hospitalization within 90 days, n /N (%)	I-II	xx/xxx (x.x)	xx/xxx (x.x)	Relative risk† x.xx (x.xx to x.xx)	Absolute difference x.xx (x.xx to x.xx)	x.xx
	II-IV	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
	V-VI	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
Hours until removed alive from invasive mechanical ventilation; median (IQR)	I-II	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	Subhazard ratio of time to extubation‡ x.xx (x.xx to x.xx)		x.xx
	II-IV	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	Subhazard ratio of time to extubation‡ x.xx (x.xx to x.xx)		
	V-VI	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	Subhazard ratio of time to extubation‡ x.xx (x.xx to x.xx)		
Days until discharged alive from ICU; median (IQR)	I-II	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	Subhazard ratio of time to ICU discharge‡ x.xx (x.xx to x.xx)		x.xx
	II-IV	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	Subhazard ratio of time to ICU discharge‡ x.xx (x.xx to x.xx)		
	V-VI	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	Subhazard ratio of time to ICU discharge‡ x.xx (x.xx to x.xx)		
Days until discharged alive from hospital; median (IQR)	I-II	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	Subhazard ratio of time to hospital discharge‡ x.xx (x.xx to x.xx)		x.xx
	II-IV	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	Subhazard ratio of time to hospital discharge‡ x.xx (x.xx to x.xx)		
	V-VI	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	Subhazard ratio of time to hospital discharge‡ x.xx (x.xx to x.xx)		
Discharged directly home from hospital, n/N (%)	I-II	xx/xxx (x.x)	xx/xxx (x.x)	Relative risk§ x.xx (x.xx to x.xx)	Absolute difference x.xx (x.xx to x.xx)	x.xx
	II-IV	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
	V-VI	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	

* The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive differences between groups.

† Relative risk was calculated using a log-binomial model adjusting for the presence of hypoxic ischemic encephalopathy and other brain injuries and conditions and sepsis at baseline incorporating site as a random effect.

‡ Competing risks regression used to obtain subhazard ratios. Adjustment accounted for the same variables as for the primary outcome analysis.

§ The comparison of the proportions of patients discharged home from hospital used the same method as the primary analysis.

Abbreviations: ICU: intensive care unit; IQR: interquartile range

Table S1: Characteristics of participants from Mega-ROX sites contributing skin tone data compared with participants from sites not contributing skin tone data.

Characteristic	Enrolled in a site participating in the skin tone study	Enrolled in a site not participating in the skin tone study
Age – yr	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)
Body-mass index†	xx.x ± xx	xx.x ± xx
Clinical Frailty Score‡	x (x to x)	x (x to x)
Source of admission to ICU – no. (%)		
Emergency department	xxx (xx.x)	xxx (xx.x)
Hospital ward	xxx (xx.x)	xxx (xx.x)
Transfer from another ICU	xxx (xx.x)	xxx (xx.x)
Transfer from another hospital (except from another ICU)	xxx (xx.x)	xxx (xx.x)
From OT following surgery	xxx (xx.x)	xxx (xx.x)
Median time from hospital admission to randomization (IQR) – hours	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median time from ICU admission to randomization (IQR) – hours	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
APACHE-II score§	xx.x ± xx	xx.x ± xx
SAPS-III score¶	xx.x ± xx	xx.x ± xx
Subgroup diagnoses – no. (%)		
Ischemic encephalopathy	xxx (xx.x)	xxx (xx.x)
Sepsis	xxx (xx.x)	xxx (xx.x)
Acute brain injuries and conditions other than ischemic encephalopathy	xxx (xx.x)	xxx (xx.x)
COVID-19 disease	xxx (xx.x)	xxx (xx.x)
Enrolled in a low or middle income country	xxx (xx.x)	xxx (xx.x)
ICU admission to randomization less than 2 hours	xxx (xx.x)	xxx (xx.x)
Baseline oxygen data		
FIO ₂	x.xx ± xx	x.xx ± xx
Median PaO ₂ (IQR) – mmHg	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median PaO ₂ /FIO ₂ ratio (IQR) – mmHg	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)

* Plus-minus values are expressed as mean ± SD.

† Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Scores on the Clinical Frailty Scale include 1 (very fit), 2 (well), 3 (managing well), 4 (vulnerable), 5 (mildly frail), 6 (moderately frail), 7 (severely frail), 8 (very severely frail), and 9 (terminally ill). Patients were evaluated according to their condition before the current admission.

§ Scores on the APACHE II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.

¶ Scores on the SAPS-III range from 0 to 217, with higher scores indicating more severe disease. The SAPS-III score was collected from trial participants from Brazil.

A witnessed arrest was defined as one that was seen or heard by another person or was monitored.

Abbreviations: Acute Physiology And Chronic Health Evaluation; COVID-19: coronavirus disease 2019; FIO₂: fraction of inspired oxygen; ICU: Intensive Care Unit; IQR: interquartile range; PaO₂: arterial partial pressure of oxygen; SAPS 3: Simplified Acute Physiology Score 3; SD: standard deviation.

Table S2: Characteristics of participants included in the skin tone study vs. those not included in the skin tone study (limited to only those Mega-ROX sites contributing skin tone data)

Characteristic	Included in the skin tone study	Not included in the skin tone study
Age – yr	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)
Body-mass index†	xx.x ± xx	xx.x ± xx
Clinical Frailty Score‡	x (x to x)	x (x to x)
Source of admission to ICU – no. (%)		
Emergency department	xxx (xx.x)	xxx (xx.x)
Hospital ward	xxx (xx.x)	xxx (xx.x)
Transfer from another ICU	xxx (xx.x)	xxx (xx.x)
Transfer from another hospital (except from another ICU)	xxx (xx.x)	xxx (xx.x)
From OT following surgery	xxx (xx.x)	xxx (xx.x)
Median time from hospital admission to randomization (IQR) – hours	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median time from ICU admission to randomization (IQR) – hours	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
APACHE-II score§	xx.x ± xx	xx.x ± xx
SAPS-III score¶	xx.x ± xx	xx.x ± xx
Subgroup diagnoses – no. (%)		
Ischemic encephalopathy	xxx (xx.x)	xxx (xx.x)
Sepsis	xxx (xx.x)	xxx (xx.x)
Acute brain injuries and conditions other than ischemic encephalopathy	xxx (xx.x)	xxx (xx.x)
COVID-19 disease	xxx (xx.x)	xxx (xx.x)
Enrolled in a low or middle income country	xxx (xx.x)	xxx (xx.x)
ICU admission to randomization less than 2 hours	xxx (xx.x)	xxx (xx.x)
Baseline oxygen data		
FIO ₂	x.xx ± xx	x.xx ± xx
Median PaO ₂ (IQR) – mmHg	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median PaO ₂ /FIO ₂ ratio (IQR) – mmHg	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)

* Plus-minus values are expressed as mean ± SD.

† Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Scores on the Clinical Frailty Scale include 1 (very fit), 2 (well), 3 (managing well), 4 (vulnerable), 5 (mildly frail), 6 (moderately frail), 7 (severely frail), 8 (very severely frail), and 9 (terminally ill). Patients were evaluated according to their condition before the current admission.

§ Scores on the APACHE II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.

¶ Scores on the SAPS-III range from 0 to 217, with higher scores indicating more severe disease. The SAPS-III score was collected from trial participants from Brazil.

A witnessed arrest was defined as one that was seen or heard by another person or was monitored.

Abbreviations: Acute Physiology And Chronic Health Evaluation; COVID-19: coronavirus disease 2019; FIO₂: fraction of inspired oxygen; ICU: Intensive Care Unit; IQR: interquartile range; PaO₂: arterial partial pressure of oxygen; SAPS 3: Simplified Acute Physiology Score 3; SD: standard deviation.

Table S3: Characteristics of Mega-ROX participants included in the skin tone study vs. those not included in the skin tone study

Characteristic	Included in the skin tone study	Not included in the skin tone study
Age – yr	xx.x ± xx	xx.x ± xx
Male sex – no. (%)	xxx (xx.x)	xxx (xx.x)
Body-mass index†	xx.x ± xx	xx.x ± xx
Clinical Frailty Score‡	x (x to x)	x (x to x)
Source of admission to ICU – no. (%)		
Emergency department	xxx (xx.x)	xxx (xx.x)
Hospital ward	xxx (xx.x)	xxx (xx.x)
Transfer from another ICU	xxx (xx.x)	xxx (xx.x)
Transfer from another hospital (except from another ICU)	xxx (xx.x)	xxx (xx.x)
From OT following surgery	xxx (xx.x)	xxx (xx.x)
Median time from hospital admission to randomization (IQR) – hours	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median time from ICU admission to randomization (IQR) – hours	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
APACHE-II score§	xx.x ± xx	xx.x ± xx
SAPS-III score¶	xx.x ± xx	xx.x ± xx
Subgroup diagnoses – no. (%)		
Ischemic encephalopathy	xxx (xx.x)	xxx (xx.x)
Sepsis	xxx (xx.x)	xxx (xx.x)
Acute brain injuries and conditions other than ischemic encephalopathy	xxx (xx.x)	xxx (xx.x)
COVID-19 disease	xxx (xx.x)	xxx (xx.x)
Enrolled in a low or middle income country	xxx (xx.x)	xxx (xx.x)
ICU admission to randomization less than 2 hours	xxx (xx.x)	xxx (xx.x)
Baseline oxygen data		
FIO ₂	x.xx ± xx	x.xx ± xx
Median PaO ₂ (IQR) – mmHg	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
Median PaO ₂ /FIO ₂ ratio (IQR) – mmHg	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)

* Plus-minus values are expressed as mean ± SD.

† Body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ Scores on the Clinical Frailty Scale include 1 (very fit), 2 (well), 3 (managing well), 4 (vulnerable), 5 (mildly frail), 6 (moderately frail), 7 (severely frail), 8 (very severely frail), and 9 (terminally ill). Patients were evaluated according to their condition before the current admission.

§ Scores on the APACHE II range from 0 to 71, with higher scores indicating more severe disease and a higher risk of death.

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A witnessed arrest was defined as one that was seen or heard by another person or was monitored.

Abbreviations: Acute Physiology And Chronic Health Evaluation; COVID-19: coronavirus disease 2019; FIO₂: fraction of inspired oxygen; ICU: Intensive Care Unit; IQR: interquartile range; PaO₂: arterial partial pressure of oxygen; SAPS 3: Simplified Acute Physiology Score 3; SD: standard deviation.

Table S4: Primary and Secondary Outcomes by Treatment Group According to Fitzpatrick Skin Tone Category*					
Outcome	Skin Tone category	Conservative oxygen	Liberal oxygen	Effect estimate (95% CI)	
				Relative risk†	Absolute difference
Mortality in the index hospitalization within 90 days, n /N (%)	I	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	II	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	III	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	IV	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	V	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	VI	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
				Subhazard ratio of time to extubation‡	
Hours until removed alive from invasive mechanical ventilation; median (IQR)	I	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	II	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	III	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	IV	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	V	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	VI	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
				Subhazard ratio of time to ICU discharge‡	
Days until discharged alive from ICU; median (IQR)	I	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	II	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	III	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	IV	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	V	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	VI	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
				Subhazard ratio of time to hospital discharge‡	
Days until discharged alive from hospital; median (IQR)	I	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	II	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	III	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	IV	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	V	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
	VI	xx.x (xx.x to xx.x)	xx.x (xx.x to xx.x)	x.xx (x.xx to x.xx)	
				Relative risk†	Absolute difference
Discharged directly home from hospital, n/N (%)	I	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	II	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	III	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	IV	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	V	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	VI	xx/xxx (x.x)	xx/xxx (x.x)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)

* The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive differences between groups.

† Relative risk was calculated using a log-binomial model adjusting for the presence of hypoxic ischemic encephalopathy and other brain injuries and conditions and sepsis at baseline incorporating site as a random effect.

‡ Competing risks regression used to obtain subhazard ratios. Adjustment accounted for the same variables as for the primary outcome analysis.

§ The comparison of the proportions of patients discharged home from hospital used the same method as the primary analysis.

Abbreviations: ICU: intensive care unit; IQR: interquartile range

Table S5: Primary and Secondary Effect Estimates According to Fitzpatrick Skin Tone Category Adjusted for Additional Baseline Variables*

Outcome	Skin Tone category	Adjusted effect estimate (95% CI)	
Mortality in the index hospitalization within 90 days, n /N (%)		Relative risk†	
	I	x.xx	(x.xx to x.xx)
	II	x.xx	(x.xx to x.xx)
	III	x.xx	(x.xx to x.xx)
	IV	x.xx	(x.xx to x.xx)
	V	x.xx	(x.xx to x.xx)
Hours until removed alive from invasive mechanical ventilation; median (IQR)	VI	x.xx	(x.xx to x.xx)
		Subhazard ratio of time to extubation‡	
	I	x.xx	(x.xx to x.xx)
	II	x.xx	(x.xx to x.xx)
	III	x.xx	(x.xx to x.xx)
	IV	x.xx	(x.xx to x.xx)
Days until discharged alive from ICU; median (IQR)	V	x.xx	(x.xx to x.xx)
	VI	x.xx	(x.xx to x.xx)
		Subhazard ratio of time to ICU discharge‡	
	I	x.xx	(x.xx to x.xx)
	II	x.xx	(x.xx to x.xx)
	III	x.xx	(x.xx to x.xx)
Days until discharged alive from hospital; median (IQR)	IV	x.xx	(x.xx to x.xx)
	V	x.xx	(x.xx to x.xx)
	VI	x.xx	(x.xx to x.xx)
		Subhazard ratio of time to hospital discharge‡	
	I	x.xx	(x.xx to x.xx)
	II	x.xx	(x.xx to x.xx)
Discharged directly home from hospital, n/N (%)	III	x.xx	(x.xx to x.xx)
	IV	x.xx	(x.xx to x.xx)
	V	x.xx	(x.xx to x.xx)
	VI	x.xx	(x.xx to x.xx)
		Relative risk†	Absolute difference
	I	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	II	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	III	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	IV	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	V	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)
	VI	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)

* The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive differences between groups.

† Relative risk was calculated using a log-binomial model adjusting for age, sex, ethnicity, the presence of hypoxic ischemic encephalopathy and other brain injuries and conditions and sepsis at baseline incorporating site as a random effect

‡ Competing risks regression used to obtain subhazard ratios adjusted for age, sex, ethnicity, the presence of hypoxic ischemic encephalopathy and other brain injuries and conditions and sepsis at baseline incorporating site as a random effect.

§ The comparison of the proportions of patients discharged home from hospital used the same method as other analyses.

Abbreviations: ICU: intensive care unit; IQR: interquartile range.

Table S6: Oxygen exposure metrics by treatment group according to Fitzpatrick skin tone category					
Characteristic	Skin tone category	Conservative oxygen	Liberal oxygen	Effect estimate (95% CI)*	P value for interaction
Measures of exposure to high arterial oxygen					
Median percentage of hours per patient SpO ₂ ≥97% (IQR)	I-II	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx
	III-IV	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
	V-VI	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
At least one PaO ₂ recording >100 mmHg, n (%)	I-II	xxx (xx.x)	xxx (xx.x)	x.xx (x.xx to x.xx)	x.xx
	III-IV	xxx (xx.x)	xxx (xx.x)	x.xx (x.xx to x.xx)	
	V-VI	xxx (xx.x)	xxx (xx.x)	x.xx (x.xx to x.xx)	
Measures of exposure to low arterial oxygen					
Median percentage of hours per patient SpO ₂ <88% (IQR)	I-II	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx
	III-IV	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
	V-VI	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
At least one PaO ₂ recording <60 mmHg, n (%)	I-II	xxx (xx.x)	xxx (xx.x)	x.xx (x.xx to x.xx)	x.xx
	III-IV	xxx (xx.x)	xxx (xx.x)	x.xx (x.xx to x.xx)	
	V-VI	xxx (xx.x)	xxx (xx.x)	x.xx (x.xx to x.xx)	
Measures of time spent breathing room air (FIO ₂ = 0.21)					
Median percentage of hours per patient FIO ₂ = 0.21 (IQR)	I-II	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx
	III-IV	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	
	V-VI	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	x.xx (x.xx to x.xx)	

* Differences in median values were calculated with the use of quantile regression after adjustment for trial site. For proportions, effect estimates are relative risks calculated using log-binomial models adjusting for trial site. The widths of the confidence intervals have not been adjusted for multiple comparisons, so the intervals should not be used to infer definitive differences between groups.

CI denotes confidence interval, IQR interquartile range, FiO₂ fraction of inspired oxygen, and SpO₂ arterial oxygen saturation as measured by pulse oximetry.

