Electronic supplementary material (ESM)

Oxygen and 6 months outcome after out of hospital cardiac arrest: a preplanned sub-analysis of the Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial

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Further details on statistical analysis methods

Using ordinal logistic regression, we estimated the probability that specific value of PaO_2 (or PaO_2_class) was associated with poor neurological outcome. Using relative distribution analysis, we searched for the best cut-point along the continuum of the PaO_2 that separated 6-months survivors from non-survivors. To account for interdependence among repeated measures, the models included a cluster-based adjustment of the standard error estimation. Linear mixed regression was used to compare the longitudinal trajectories of hourly measured PaO_2 among survival status. For this longitudinal analysis, a repeated measure dataset (included hourly ventilatory markers collected every 4 hours during the first 72 hours after ICU admission) was used and included 18716 observations, after excluding missing values on survival status and PaO_2. A similar set of covariates as in the Cox model, were used for building the adjusted model. To account for the longitudinal nature of the data (interdependence among repeated measures), the model included a random effect (intercept) on patient ID and a random coefficient on the time elicited between PaO_2 measures. CR and RB had full access to all the data in the study and takes responsibility for its integrity and the data analysis.

Table S1. "Strengthening the Reporting of Observational Studies in Epidemiology (STROBE)" statement guidelines.

	Item No.	Recommendation	Page No.	Relevant text from manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1	
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	4	
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	8	
Objectives	3	State specific objectives, including any prespecified hypotheses	9-10	
Methods				
Study design	4	Present key elements of study design early in the paper	10-12	
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	10-12	
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	10-12	

Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	9-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	9-12
Bias	9	Describe any efforts to address potential sources of bias	9-12
Study size	10	Explain how the study size was arrived at	9-12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	12-13
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	12-13
		(*b*) Describe any methods used to examine subgroups and interactions	
		(*c*) Explain how missing data were addressed	
		(d) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analyzed	9-12
		(b) Give reasons for non-participation at each stage	
		(c) Consider use of a flow diagram	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9-12
		(b) Indicate number of participants with missing data for each variable of interest	
		(c) *Cohort study*—Summaries follow-up time (eg, average and total amount)	
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time	9-12
		Case-control study—Report numbers in each exposure category, or summary measures of exposure	
		Cross-sectional study—Report numbers of outcome events or summary measures	
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	14-18
		(*b*) Report category boundaries when continuous variables were categorized	

		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	ESM
Discussion			
Key results	18	Summaries key results with reference to study objectives	18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	18-21
Generalizability	21	Discuss the generalizability (external validity) of the study results	18-21
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based.	23

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org

Table S2. Patients' clinical outcomes in the overall population and stratified according to oxygen values according to conventional thresholds. Data are expressed as median (interquartile range, IQR). ICU, intensive care unit; STEMI, ST elevation myocardial infarction; LOS, length of stay; mRS, modified Rankin Scale. mRS binary defined as poor outcome if points 4-6, good outcome if points 1-3.

	Overall (n=1418, 100.0%)	PaO_2 <60 mmHg (n=79, 5.6%)	PaO_2 60-300 mmHg (n=1239, 87.4%)	PaO_2 >300 mmHg (n=100, 7.1%)	p-value
Neurologic aloutcome					
mRS at 6 months, points, median (IQR)	6.0 (1.0; 6.0)	6.0 (2.0; 6.0)	6.0 (1.0; 6.0)	6.0 (2.0; 6.0)	0.180
Poor neurological outcome, n (%)	756 (54.3)	46 (59.7)	650 (53.4)	60 (60.6)	0.235
Hospital / ICU admission					
Shock diagnosis on admission, yes, n (%)	424 (29.9)	34 (43.0)	364 (29.4)	26 (26.0)	0.025
STEMI diagnosis on admission, yes, n (%)	553 (39.0)	32 (40.5)	488 (39.4)	33 (33.0)	0.003
ICU LOS, days, median (IQR)	5.1 (3.0; 8.7)	5.0 (2.7; 8.9)	5.1 (3.0; 8.7)	5.0 (3.1; 7.6)	0.881
Hospital LOS, days, median (IQR)	9.5 (5.0; 17.0)	9.6 (3.0; 19.0)	9.6 (5.0; 17.4)	8.0 (4.0; 14.9)	0.197
Time to extubation, days, median (IQR)	3.6 (1.9; 6.0)	3.3 (1.9; 6.0)	3.6 (1.9; 6.1)	3.7 (2.0; 5.5)	0.905
Ventilator free days at 30 days, days, median (IQR)	26.4 (23.8; 28.1)	26.7 (23.6; 28.1)	26.4 (23.8; 28.1)	26.5 (24.4; 28.1)	0.847
Ventilator free days before ICU discharge, days, median (IQR)	1.0 (0.0; 2.0)	0.0 (0.0; 1.5)	1.0 (0.0; 2.0)	0.0 (0.0; 1.3)	0.530
Discharged alive from ICU, n (%)	893 (63.0)	48 (60.8)	789 (63.7)	56 (56.0)	0.284

Table S3. Ventilatory settings, respiratory mechanics and gas exchange at admission stratified according to oxygen values according to conventional thresholds. Data are expressed as median (interquartile range, IQR). Table legend: PBW, predicted body weight; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; FiO_2, fraction of inspired oxygen. Ventilatory ratio was calculated as = (minute ventilation × $PaCO_2$) / (PBW × 100 × 37.5).

	Overall (n=1418, 100.0%)	PaO_2 <60 mmHg (n=79, 5.6%)	PaO_2 60-300 mmHg (n=1239, 87.4%)	PaO_2 >300 mmHg (n=100, 7.1%)	p-value
Ventilatory setting and pulmonary mechanics at admission					
Respiratory rate, breaths/min, median (IQR)	16.0 (14.0; 20.0)	16.0 (14.0; 18.5)	16.0 (15.0; 20.0)	16.0 (14.0; 18.0)	0.227
Positive end-expiratory pressure, cmH_2O, median (IQR)	6.0 (5.0; 8.0)	7.0 (5.0; 10.0)	6.0 (5.0; 8.0)	6.0 (5.0; 8.0)	0.101
Plateau pressure, cmH_2O, median (IQR)	20.0 (17.0; 24.0)	21.0 (19.0; 26.3)	20.0 (17.0; 23.0)	20.0 (15.0; 25.0)	0.075
Tidal volume, mL, median (IQR)	500 (445; 560)	508 (462; 600)	500 (440; 560)	500 (450; 600)	0.245
Tidal volume, mL/kg PBW, median (IQR)	7.2 (6.4; 8.2)	7.4 (6.4; 9.3)	7.1 (6.4; 8.2)	7.5 (6.7; 8.5)	0.071
Driving pressure, cmH_2O, median (IQR)	13.0 (10.0; 16.0)	14.5 (12.3; 16.0)	13.0 (10.0; 16.0)	12.0 (10.0; 17.0)	0.265
Compliance of the respiratory system, mL/cmH_2O, median (IQR)	40 (31; 50)	36 (30; 47)	40 (31; 50)	41 (29; 59)	0.368
Mechanical Power, j/min, median (IQR)	16.2 (12.5; 21.6)	17.0 (15.0; 23.5)	16.2 (12.5; 21.5)	15.3 (12.1; 24.4)	0.201
Ventilatory ratio, median (IQR)	1.5 (1.2; 1.8)	1.6 (0.9; 2.1)	1.5 (1.2; 1.8)	1.4 (1.1; 1.9)	0.854
Gas exchange					
Fraction of inspired oxygen (FiO_2), %, median (IQR)	60 (50; 88)	70 (50; 100)	60 (50; 80)	100 (50; 100)	0.000
PaO_2, mmHg, median (IQR)	108.7 (83.2; 163.0)	51.0 (39.7; 56.2)	108.0 (85.5; 148.5)	363.3 (330.5; 433.6)	0.000
PaO_2/ FiO_2 ratio, mmHg, median (IQR)	195.0 (122.8; 307.3)	56.2 (45.7; 83.6)	192.8 (130.1; 284.9)	474.7 (373.4; 670.8)	0.000
$PaCO_2$, mmHg, median (IQR)	45.7 (39.7; 53.2)	48.8 (37.7; 58.1)	45.7 (39.8; 53.0)	42.7 (37.0; 51.7)	0.020
pHa, median (IQR)	7.3 (7.2; 7.3)	7.2 (7.1; 7.3)	7.3 (7.2; 7.3)	7.2 (7.2; 7.3)	0.003
Base excess, mEq/L, median (IQR)	-6.5 (-10.0; -3.7)	-8.0 (-10.5; -4.9)	-6.2 (-9.8; -3.5)	-7.4 (-12.4; -4.3)	0.005

Table S4. Characteristics of the patients, in the overall population and stratified according to the best threshold of oxygen values for mortality. Table legend: data are reported as median (interquartile range, IQR), and number (percentage, %). n=number of patients; BMI, body mass index; IBW, ideal body weight; ROSC, return of spontaneous circulation; CPR, cardio-pulmonary resuscitation; TTM, target temperature management.

	Overall (n=1418, 100.0%)	PaO_2<69 mmHg (n=165, 11.6%)	PaO_2 69-195 mmHg (n=990, 69.8%)	PaO_2 >195 mmHg (n=263, 18.5%)	p-value
Baseline patient characteristics					
Age, years, median (IQR)	65 (55; 74)	66 (58; 75)	65 (55; 74)	65 (55; 74)	0.291
Gender, female, n (%)	292 (20.6)	29 (17.6)	190 (19.2)	73 (27.8)	0.006
Height, cm, median (IQR)	175 (170; 180)	175 (170; 180)	175 (170; 180)	174 (167; 180)	0.001
Weight, kg, median (IQR)	80 (73; 90)	84 (75; 92)	81 (75; 93)	78 (69; 88)	0.000
BMI, kg/m^2, median (IQR)	26.3 (24.1; 29.7)	27.0 (24.7; 30.0)	26.6 (24.2; 30.1)	25.2 (22.9; 28.1)	0.000
Chronic comorbidities					
Hypertension, yes, n (%)	504 (44.8)	63 (47.7)	365 (46.9)	76 (35.5)	0.009
Diabetes mellitus, yes, n (%)	266 (18.8)	35 (21.2)	1818 (18.3)	50 (19.0)	0.667
Myocardial infarction, yes, n (%)	230 (27.3)	31 (31.0)	163 (28.5)	36 (20.9)	0.099
Percutaneous coronary intervention, yes, n (%)	210 (25.3)	28 (28.9)	146 (26.1)	36 (20.7)	0.246
Coronary artery bypass graft, yes, n (%)	112 (15.3)	16 (18.8)	79 (16.1)	17 (11.0)	0.194
Heart failure, yes, n (%)	145 (19.0)	20 (22.5)	104 (20.2)	21 (13.2)	0.098
Charlson comorbidity index, points, median (IQR)	4.0 (2.0; 5.0)	4.0 (3; 6.0)	4.0 (2.0; 5.0)	4.0 (2.0; 5.0)	0.160
Pre-hospital setting / interventions					
Location of cardiac arrest, n (%)					
Home	741 (52.3)	86 (52.1)	505 (51.0)	150 (57.0)	
Public place	509 (35.9)	58 (35.2)	372 (37.6)	79 (30.0)	
Other	168 (11.8)	21 (12.7)	113 (11.4)	34 (12.9)	0.259
Witnessed cardiac arrest, yes, n (%)	1295 (91.3)	155 (93.9)	899 (90.8)	241 (91.6)	0.409
Bystander performed CPR, yes, n (%)	1148 (81.0)	132 (80.0)	810 (81.8)	206 (78.3)	0.416
Type of rhythm, n (%)					

Not shockable	390 (27.5)	55 (33.3)	266 (26.9)	69 (26.2)	0.199
Shockable	1028 (72.5)	110 (66.7)	724 (73.1)	194 (73.8)	
Time to ROSC, minutes, median (IQR)	25.0 (17.0; 39.0)	26.0 (18.5; 40.0)	25.0 (17.0; 40.0)	25.0 (15.0; 34.0)	0.024
TTM randomization treatment, n (%)					
Normothermia	712 (50.2)	88 (53.3)	496 (50.1)	128 (48.7)	0.638
Hypothermia	706 (49.8)	77 (46.7)	494 (49.9)	135 (51.3)	

Table S5. Patients' clinical outcomes in the overall population and stratified according to the new oxygen thresholds. Data are expressed as median (interquartile range, IQR). ICU, intensive care unit; STEMI, ST elevation myocardial infarction; LOS, length of stay; mRS, modified Rankin Scale; mRS binary defined as poor outcome if points 4-6, good outcome if points 1-3.

	Overall (n=1418, 100.0%)	PaO_2 <69 mmHg (n=165, 11.6%)	PaO_2 69-195 mmHg (n=990, 69.8%)	PaO_2 >195 mmHg (n=263, 18.5%)	p-value
Neurologic outcome					
mRS at 6 months, points, median (IQR)	6.0 (1.0; 6.0)	6.0 (2.0; 6.0)	6.0 (1.0; 6.0)	6.0 (2.0; 6.0)	0.192
mRS poor outcome (4-6), n (%)	740 (55.9)	95 (62.1)	508 (54.9)	137 (55.9)	0.254
Hospital / ICU admission					
Shock diagnosis on admission, yes, n (%)	424 (29.9)	65 (39.4)	294 (29.7)	65 (24.7)	0.005
STEMI diagnosis on admission, yes, n (%)	553 (39.4)	62 (39.0)	396 (40.2)	95 (36.7)	0.583
ICU LOS, days, median (IQR)	5.1 (3.0; 8.7)	5.0 (2.9; 8.8)	5.1 (3.0; 8.9)	4.8 (3.0; 7.4)	0.166
Hospital LOS, days, median (IQR)	9.5 (5.0; 17.0)	8.0 (3.0; 16.8)	10.0 (5.0; 18.0)	9.0 (5.0; 14.0)	0.036
Time to extubation, days, median (IQR)	3.6 (1.9; 6.0)	3.7 (2.0; 5.9)	3.8 (1.9; 6.5)	3.3 (1.9; 5.1)	0.288
Ventilator free days at 30 days, days, median (IQR)	26.4 (23.8; 28.1)	26.3 (24.1; 28.0)	26.3 (23.5; 28.1)	26.7 (24.8; 28.1)	0.396
Ventilator free days before ICU discharge, days, median (IQR)	1.0 (0.0; 2.0)	0.0 (0.0; 2.0)	1.0 (0.0; 2.0)	1.0 (0.0; 2.0)	0.511
Discharged alive from ICU, yes, n (%)	893 (63.0)	92 (55.8)	637 (634.3)	164 (62.4)	0.104
Discharged alive from Hospital, n (%)	766 (54.0)	77 (46.7)	550 (55.6)	139 /52.9)	0.097

Table S6. Ventilatory setting, respiratory mechanics and gas exchange at ICU admission stratified according to the new oxygen thresholds. Table legend: Data are expressed as median (interquartile range, IQR). PBW, predicted body weight; PaO_2, arterial partial pressure of oxygen; $PaCO_2$, arterial partial pressure of carbon dioxide; FiO_2, fraction of inspired oxygen. Ventilatory ratio was calculated as = (minute ventilation × $PaCO_2$) / (PBW × 100 × 37.5).

	Overall (n=1418, 100.0%)	PaO_2 <69 mmHg (n=165, 11.6%)	PaO_2 69-195 mmHg (n=990, 69.8%)	PaO_2 >195 mmHg (n=263, 18.5%)	p-value
Ventilatory setting and pulmonary mechanics at ICU admission					
Respiratory rate, breaths/min, median (IQR)	16.0 (14.0; 20.0)	16.0 (15.0; 20.0)	16.0 (15.0; 20.0)	16.0 (14.0; 18.0)	0.010
Positive end-expiratory pressure, cmH_2O, median (IQR)	6.0 (5.0; 8.0)	7.0 (5.0; 10.0)	6.0 (5.0; 8.0)	6.0 (5.0; 8.0)	0.010
Plateau pressure, cmH_2O, median (IQR)	20.0 (17.0; 24.0)	22.0 (19.0; 25.0)	20.0 (17.0; 23.0)	20.0 (16.0; 22.5)	0.004
Tidal volume, mL, median (IQR)	500 (445; 560)	500 (437; 582)	500 (444; 559)	500 (450; 560)	0.919
Tidal volume, mL/kg PBW, median (IQR)	7.2 (6.4; 8.2)	7.3 (6.4; 8.6)	7.1 (6.3; 8.1)	7.6 (6.6; 8.5)	0.022
Driving pressure, cmH_2O, median (IQR)	13.0 (10.0; 16.0)	14.0 (12.0; 16.0)	13.0 (10.0; 16.0)	12.0 (10.0; 16.0)	0.142
Compliance of the respiratory system, mL/cmH_2O, median (IQR)	40.0 (31.0; 50.0)	36.0 (30.0; 46.0)	40.0 (31.0; 50.0)	42.0 (32.0; 53.0)	0.071
Mechanical Power, j/min, median (IQR)	16.2 (12.7; 21.6)	18.3 (14.4; 22.9)	16.0 (12.5; 21.5)	15.2 (11.5; 20.6)	0.006
Ventilatory ratio, median (IQR)	1.45 (1.16; 1.83)	1.60 (1.24; 2.18)	1.46 (1.18; 1.81)	1.32 (1.03; 1.75)	0.001
Gas exchange					
Fraction of inspired oxygen (FiO_2), %, median (IQR)	60 (50; 88)	70 (50; 100)	60 (46; 80)	70 (50; 100)	0.000
PaO_2, mmHg, median (IQR)	108.7 (83.2; 163.0)	60.0 (51.7; 65.2)	105.0 (87.0; 133.0)	273.0 (231.7; 342.7)	0.000
PaO_2/ FiO_2 ratio, mmHg, median (IQR)	195.0 (122.8; 307.3)	75.0 (57.6; 113.6)	180.0 (130.0; 256.9)	410.0 (318.4; 521.9)	0.000
$PaCO_2$, mmHg, median (IQR)	45.7 (39.7; 53.2)	49.5 (41.2; 59.2)	46.0 (40.5; 53.2)	42.0 (36.7; 49.2)	0.000
pHa, median (IQR)	7.3 (7.2; 7.3)	7.2 (7.1; 7.3)	7.3 (7.2; 7.3)	7.3 (7.2; 7.3)	0.001
Base excess, mEq/L, median (IQR)	-6.5 (-10.0; -3.7)	-7.3 (-10.1; -4.5)	-6.2 (-9.7; -3.5)	-6.6 (-10.5; -4.0)	0.204

Figure S1. Hourly oxygen trajectories in the overall population, and by survival status (survivors and non survivors). Partial pressure of oxygen (PaO_2) trajectories over the first 72-h after ICU admission are summarized as medians. PaO_2 values decreased significantly during the first 40 hours and then leveled-off afterwards with median values ranging from 80 to 85 mmHg. shows the frequency distribution of the episodes of PaO_2 <60 mmHg and > 300 mmHg in the whole population during the first 72 hours of mechanical ventilation.

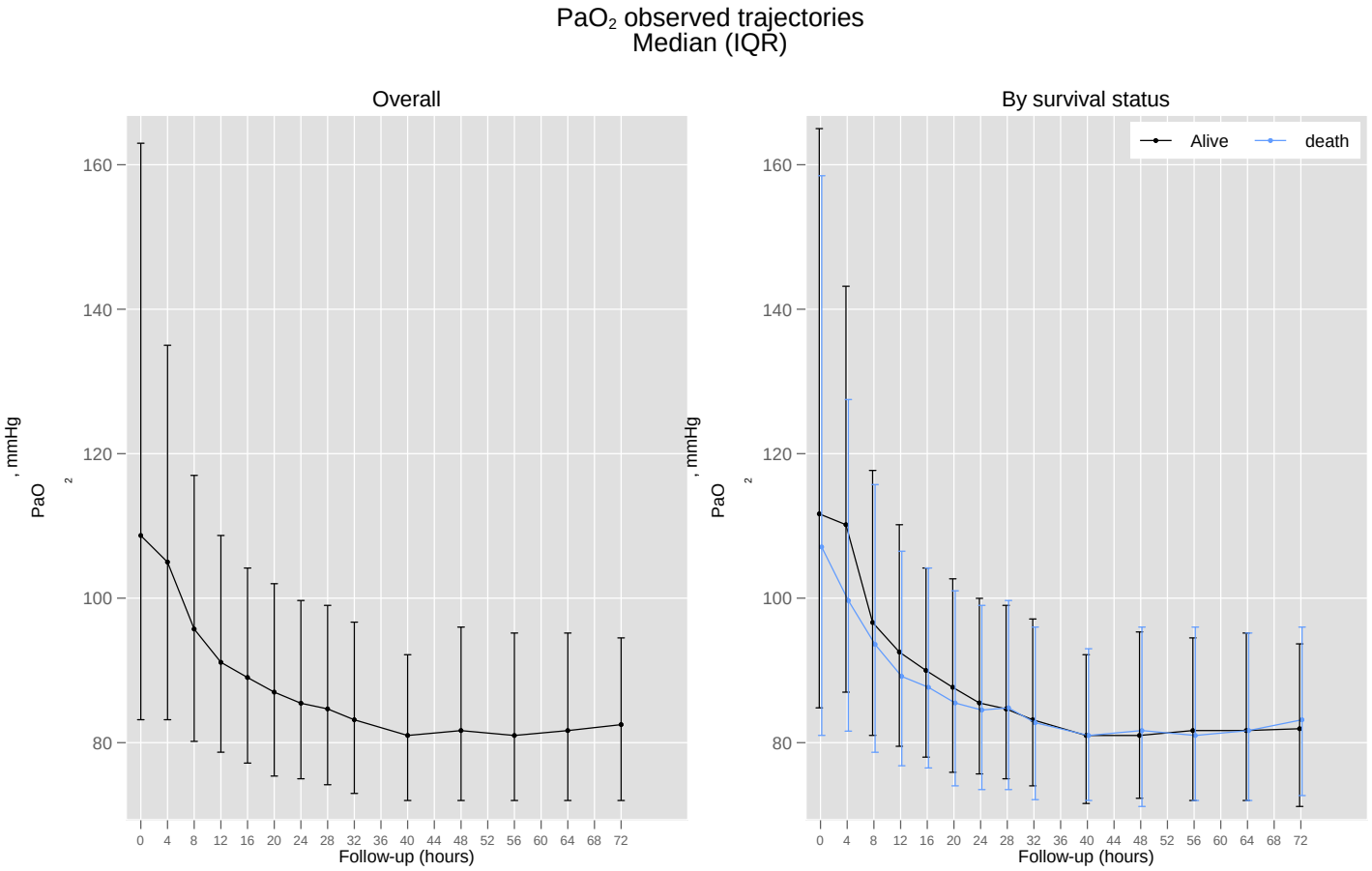
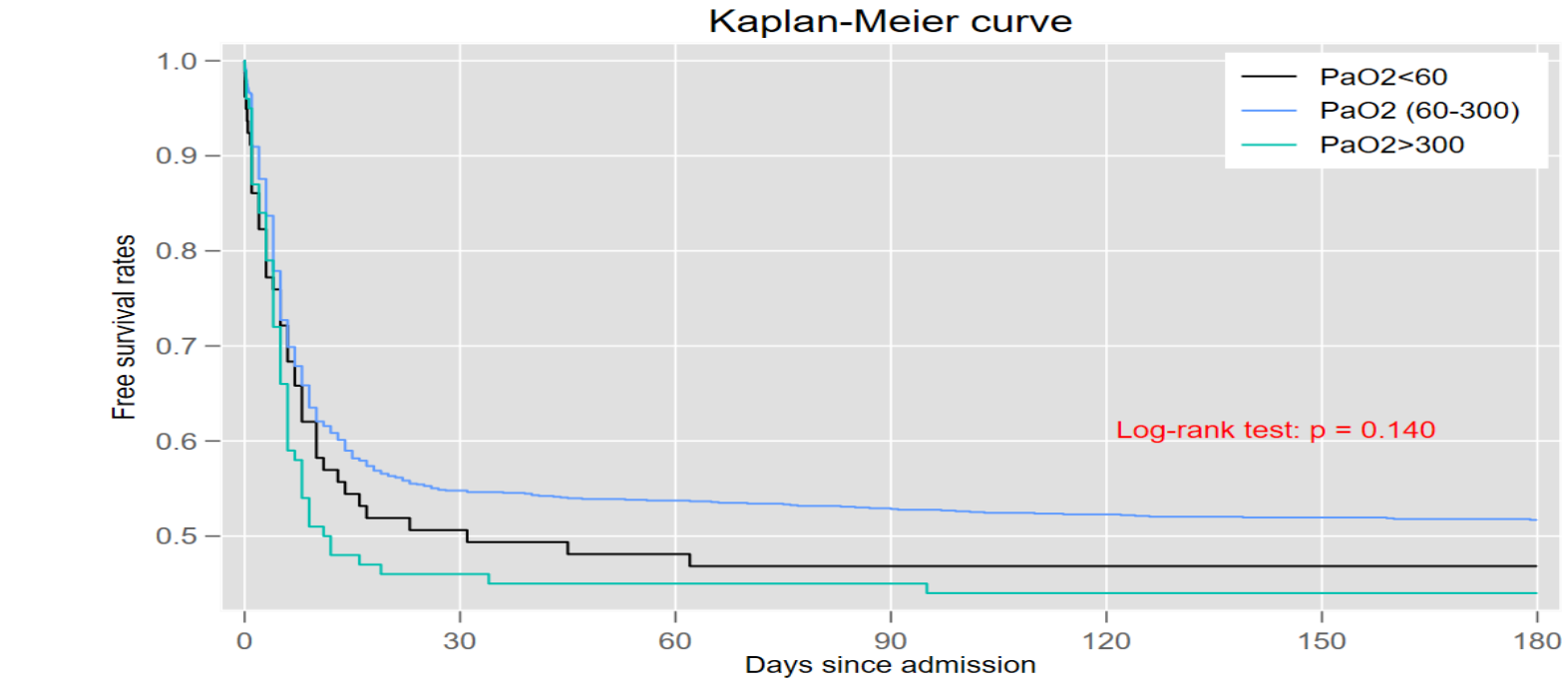


Figure S2 a. Kaplan-Meier curve considering conventional and new thresholds (mmHg). Most deaths occurred during the first 30 days of the follow-up. The log-rank test p-value did not achieve significance (p = 0.140).



Number at risk (events)

PaO2<60	79	(39)	40	(2)	38	(1)	37	(0)	37	(0)	37	(0)	30
PaO2 (60-300)	1239	(560)	678	(13)	665	(10)	655	(8)	647	(4)	643	(3)	482
PaO2>300	100	(54)	46	(1)	45	(0)	45	(1)	44	(0)	44	(0)	36

Figure S3. Hypoxemia and hyperoxemia mortality risk difference considering the dose of oxygen (exposure over time, area under the curve, PaO_2-AUC). Repeated measures of PaO_2 were considered as a single time point reflecting the cumulative effect over time of PaO_2. PaO_2-AUC represents the numerical integration of PaO_2 values and the time between measurements, and as such, provides the cumulative effect over time of PaO_2. The higher/lower the value of PaO_2, indeed influence the AUC in that direction; however, it also includes the time interval between measurements as a function. The narrower is the interval, the higher is the AUC, independently of PaO_2 raw values, or vice versa. We tested the interaction between PaO_2 categorical levels using traditional cut-points (hypo/normo/hyperoxemia) with the PaO_2-AUC and determining the risk difference among hypo vs normoxemia and hyperoxemia vs normoxemia along the PaO_2 -AUC continuum. Left and right panel depicts the differences in mortality risk (expressed as Hazard ratios, HRs) between PaO_2-AUC in the hypoxemia and hyperoxemia groups, respectively with normoxemia as a reference category. In this Cox regression, PaO_2-AUC was modelled with a fractional polynomial of second-degree FP [1 1], and included the following covariates: TTM2 randomization group, age (years), cardiac arrest witnessed, ROSC (min), bystander performed CPR, shockable rhythm, cardiac arrest location (home, public place, other), shock diagnosis on admission, and STEMI diagnosis on admission.

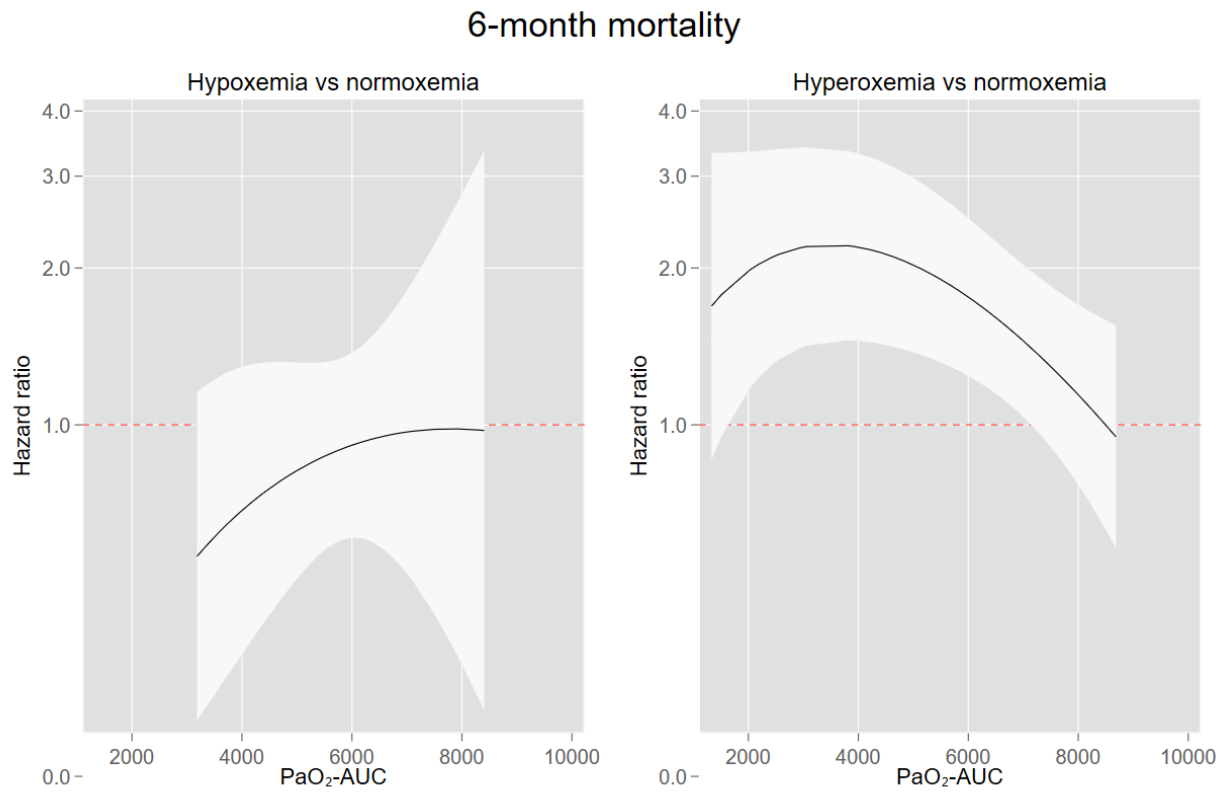

6-month mortality
Hypoxemia vs normoxemia
Hyperoxemia vs normoxemia
Hazard ratio
4.0
3.0
2.0
1.0
0.0
2000
4000
6000
8000
10000
PaO₂-AUC

Figure S4. Interaction between PaO_2 (continuous) and TTM2-arms. Difference in mortality risk (expressed as HRs - interaction p-value = 0.9974) for hypothermia (with normothermia as a reference category) with estimates listed for each value of PaO_2. We tested the interaction between PaO2 categorical levels using Hypo/normothermia as the interacting factor. In this Cox regression, PaO_2 was modelled with a fractional polynomial of second-degree FP [1 1], and included the following covariates: TTM2 randomization group, age (years), cardiac arrest witnessed, time to return to spontaneous circulation, ROSC (min), bystander performed cardiopulmonary resuscitation, CPR, shockable rhythm, cardiac arrest location (home, public place, other), shock diagnosis on admission, and ST-elevated myocardial infarction, STEMI diagnosis on admission.

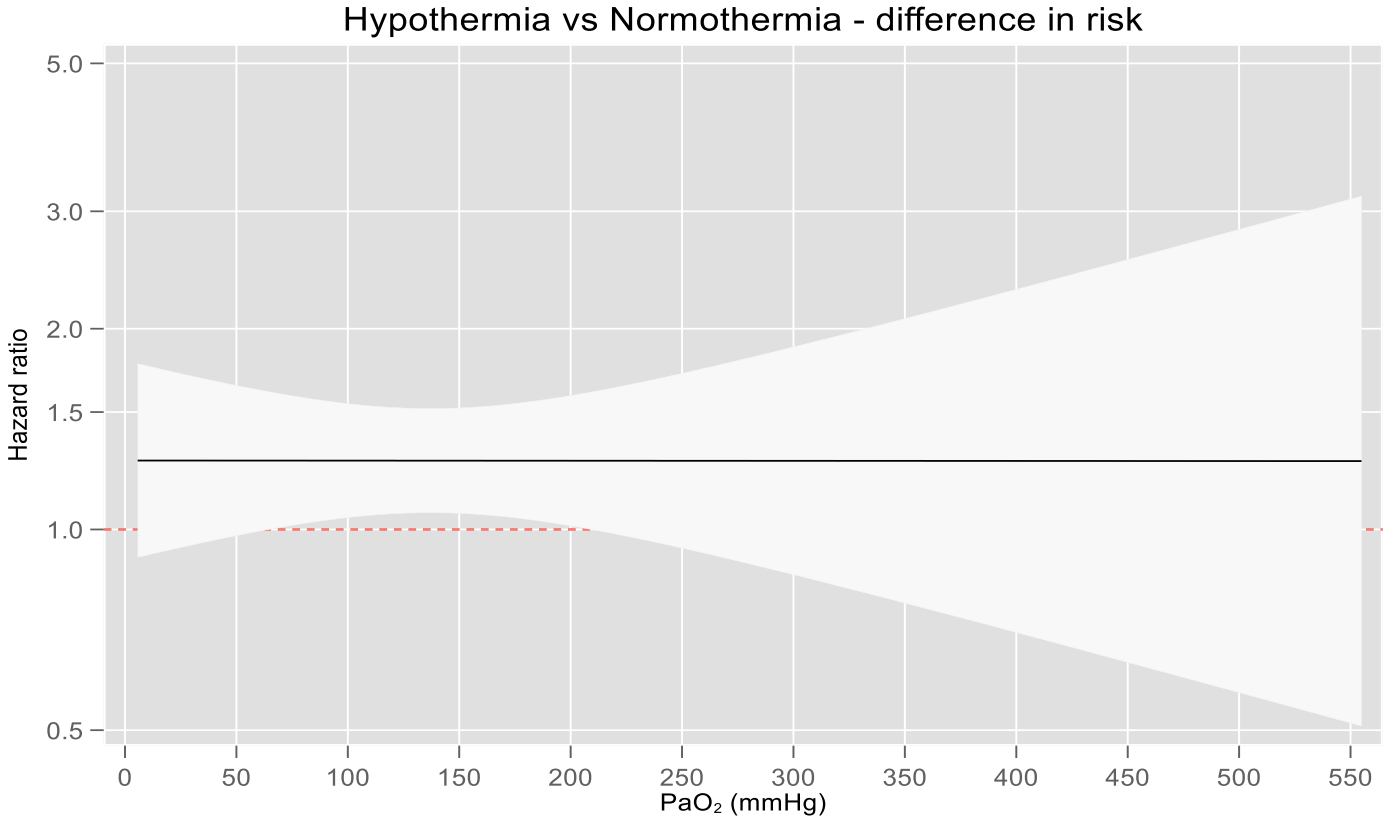


Figure S5. Frequency distribution of modified Rankin Score (mRS) among partial pressure of oxygen, PaO_2 classes.

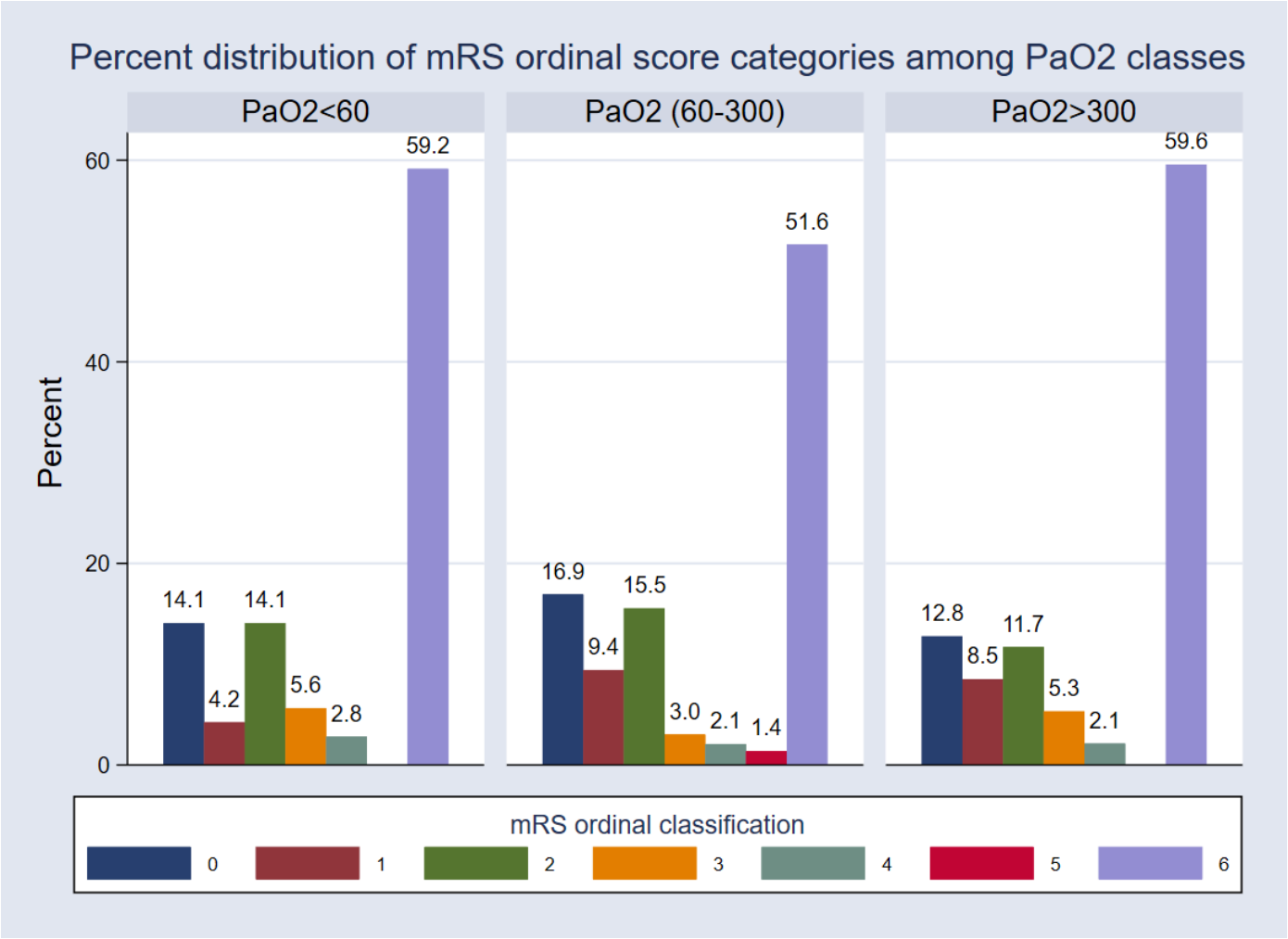


Figure S6. Predicted probability of achieving a modified Rankin Score (mRS) 4 or 5 according to PaO_2 values. Left and right panel of this figure depicts the predicted probability of achieving a mRS score 4 and 5, respectively, according to PaO_2 values. Considering only mRS score 4 and 5, no significant differences among PaO_2 classes were observed (the estimates for score 4 were: hypoxemia vs normoxemia, probability = +0.0005; p=0.59 and hyperoxemia vs normoxemia, probability = –0.0003; p=0.79. The estimates for mRS score 5 were: hypoxemia vs normoxemia, probability = +0.0002; p=0.62 and hyperoxemia vs normoxemia, probability = –0.00017; p=0.79). Similarly, modeling PaO_2 as continuous we found no association between PaO_2 and mRS score 4 (left panel) and score 5 (right panel of ESM figure S6).

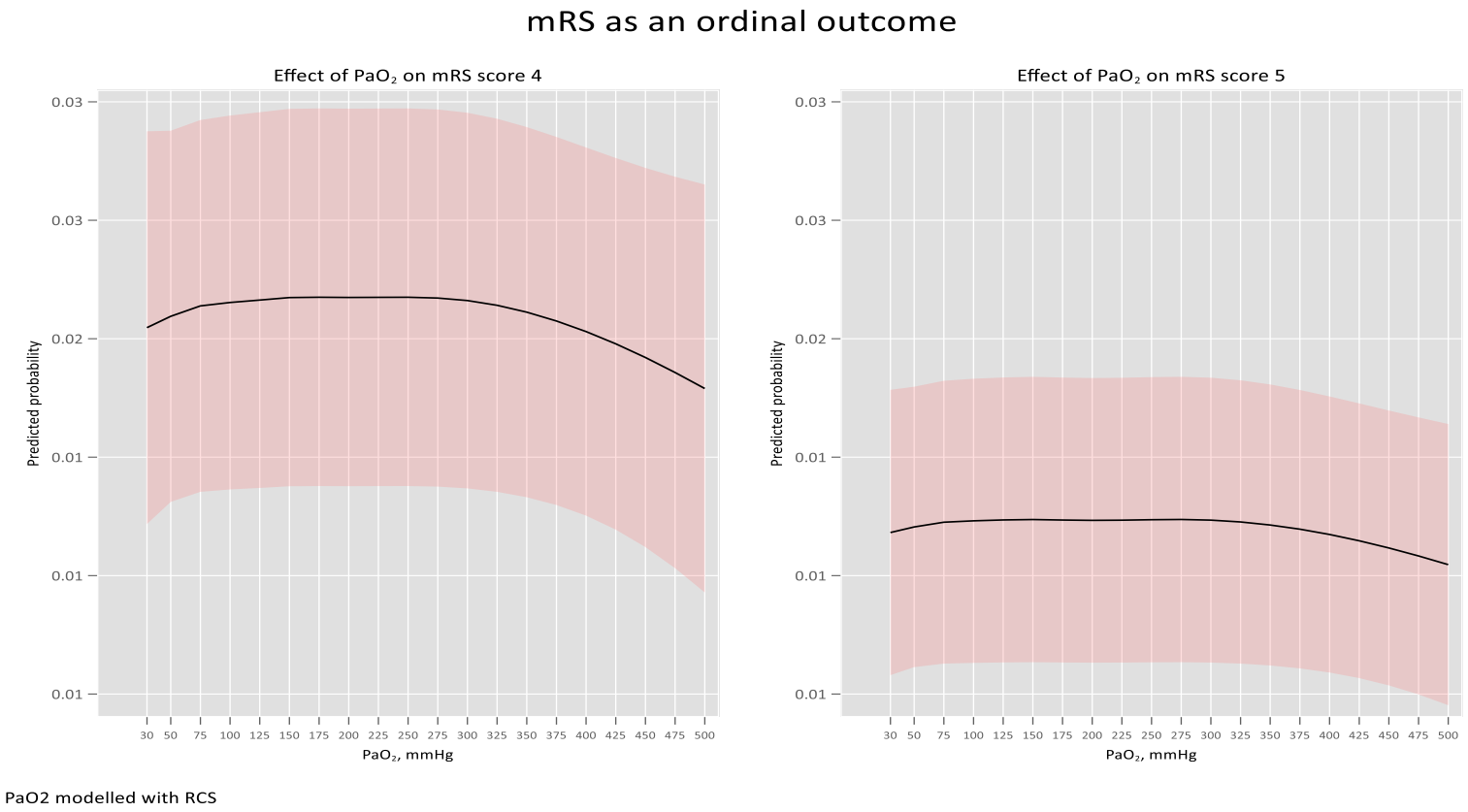
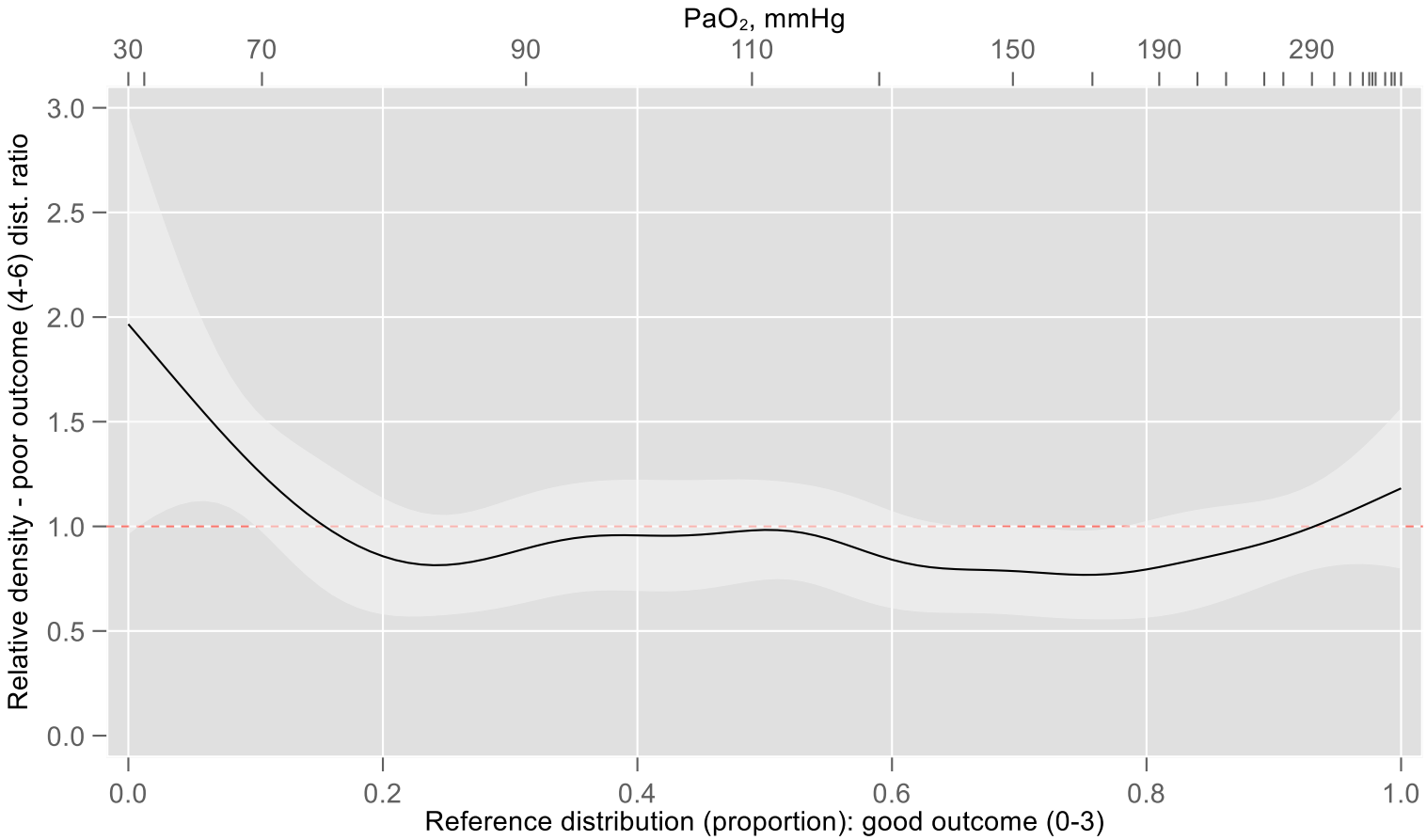
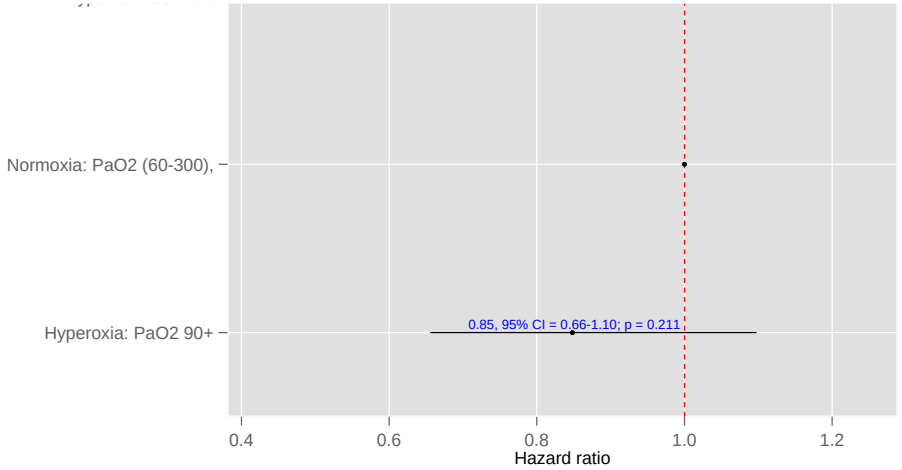


Figure S7. Analysis for the definition of the best cut off point of oxygen values for the prediction of poor neurological outcome.



ESM Appendix. Sensitivity analysis modelling PaO_2 categorical using a90 mmHg as cut-point of hyperoxemia, in a Cox regression for 6-m mortality and using the same set of covariates as the main model. Hyperoxemia did not achieve statistical significance as compare with normoxemia group.



Comparison of baseline characteristics/ventilatory markers/outcomes among those with and without missing values in PaO_2, as an indirect approach to uncover a potential selection bias. No significative difference in outcomes and characteristics was found. Data are reported as mean (standard deviation, SD) and number (percentage, %). Legend: n=number of patients, BMI, body mass index, IBW, ideal body weight, ROSC, return of spontaneous circulation, CPR, cardio-pulmonary resuscitation, PaO2,partial pressure of oxygen, Hx, history, TTM, target temperature management.

Indicator for PaO2 missingness	**PaO2 complete**	**PaO2 missing**	**P-value**
n (%)	1418 (76.2)	443 (23.8)	
Baseline patient characteristics **********	**********	**********	**********
Age, years, mean (SD)	64 (14)	64 (13)	0.943
Categories of PaO2, n (%)			
<30	30 (2.1)	10 (2.3)	
30-49	185 (13.0)	49 (11.1)	
50-69	656 (46.3)	223 (50.3)	
>= 70	547 (38.6)	161 (36.3)	0.437
Gender, n (%)			
Male	1126 (79.4)	351 (79.2)	
Female	292 (20.6)	92 (20.8)	0.937
Height, cm, mean (SD)	175 (9)	174 (10)	0.204
Weight, Kg, mean (SD)	83 (17)	83 (18)	0.995

BMI - original variable, mean (SD)	27.4 (5.8)	27.6 (5.7)	0.477
Categories of BMI, n (%)			
1. Severe thinness	8 (0.6)	1 (0.2)	
2. Moderate thinness	8 (0.6)	1 (0.2)	
3. Mild thinness	8 (0.6)	5 (1.2)	
4. Normal range	491 (35.5)	137 (32.4)	
5. Pre-obese	535 (38.7)	175 (41.4)	
6. Obese class I	224 (16.2)	66 (15.6)	
7. Obese class II	71 (5.1)	25 (5.9)	
8. Obese class III	39 (2.8)	13 (3.1)	0.639
Ideal body weight, mean (SD)	69 (9)	69 (10)	0.254
Prior Hx. of hypertension, n (%)			
No	620 (55.2)	203 (59.4)	
Yes	504 (44.8)	139 (40.6)	0.171
Prior Hx. of diabetes, n (%)			
No	1152 (81.2)	369 (83.3)	
Yes	266 (18.8)	74 (16.7)	0.329
Prior Hx. of MI, n (%)			
No	614 (72.7)	201 (76.1)	
Yes	230 (27.3)	63 (23.9)	0.276
Prior Hx. of PCI, n (%)			
No	620 (74.7)	203 (77.2)	
Yes	210 (25.3)	60 (22.8)	0.415
Prior Hx. of CABG, n (%)			

No	620 (84.7)	203 (84.6)	
Yes	112 (15.3)	37 (15.4)	0.965
Hx. of heart failure, n (%)			
No	618 (81.0)	198 (83.9)	
Yes	145 (19.0)	38 (16.1)	0.314
Charlson comorbidity index, median (IQR)	4.00 (2.00; 5.00)	4.00 (2.00; 5.00)	0.176
Pre-hospital settings/interventions **********	**********	**********	**********
Location of cardiac arrest, n (%)			
1. Home	741 (52.3)	237 (53.5)	
2. Other	168 (11.8)	57 (12.9)	
3. Public place	509 (35.9)	149 (33.6)	0.645
Was cardiac arrest witnessed?, n (%)			
No	123 (8.7)	36 (8.1)	
Yes	1295 (91.3)	407 (91.9)	0.719
Bystander performed CPR, n (%)			
No	270 (19.0)	104 (23.5)	
Yes	1148 (81.0)	339 (76.5)	0.052
Type of rhytm, n (%)			
not shockable	390 (27.5)	100 (22.6)	
shockable	1028 (72.5)	343 (77.4)	0.040
Time to return of spontaneous circulation (ROSC), min, median (IQR)	25.0 (17.0; 39.0)	27.0 (16.0; 42.3)	0.281

Previous RCT **********	**********	**********	**********
TTM2: randomization treatment, n (%)			
Normothermia	712 (50.2)	219 (49.4)	
Hypothermia	706 (49.8)	224 (50.6)	0.776
tympanic temperature at admission, centigrades, mean (SD)	35.4 (1.1)	35.3 (1.1)	0.265
Modified Rankin Scale (mRS) at 6 months **********	**********	**********	**********
Modified Rankin Scale (mRS): scale defining the neurological outcome at 6 months, median (IQR)	6.00 (1.00; 6.00)	6.00 (1.00; 6.00)	0.570
Modified Rankin Scale (mRS): scale defining the neurological outcome at 6 months, n (%)			
0	218 (16.5)	70 (16.5)	
1	120 (9.1)	47 (11.1)	
2	201 (15.2)	58 (13.7)	
3	44 (3.3)	22 (5.2)	
4	28 (2.1)	8 (1.9)	
5	16 (1.2)	4 (0.9)	
6	696 (52.6)	215 (50.7)	0.504
mRS binary: poor outcome (4-6) and good outcome (1-3), n (%)			
Good	583 (44.1)	197 (46.5)	
Poor	740 (55.9)	227 (53.5)	0.388
Hospital/ICU admission **********	**********	**********	**********
Shock diagnosis on admission, n (%)			
FALSE	994 (70.1)	331 (74.7)	
TRUE	424 (29.9)	112 (25.3)	0.061

STEMI diagnosis on admission, n (%)			
No	850 (60.6)	240 (55.0)	
Yes	553 (39.4)	196 (45.0)	0.040
Hospital LOS, days, median (IQR)	9.5 (5.0; 17.0)	10.0 (4.0; 17.5)	0.495
Was the patient mechanically ventilated?, n (%)			
No	7 (0.5)	5 (1.1)	
Yes	1411 (99.5)	438 (98.9)	0.145
Ventilator free days before ICU discharge, median (IQR)	1.00 (0.00; 2.00)	1.00 (0.00; 2.00)	0.904
Was the patient discharged alive from the ICU?, n (%)			
No	525 (37.0)	177 (40.0)	
Yes	893 (63.0)	266 (60.0)	0.267
Was the patient discharged alive from the hospital?, n (%)			
No	652 (46.0)	207 (46.7)	
Yes	766 (54.0)	236 (53.3)	0.783
Survival status since hosp/ICU admission, n (%)			
Alive	722 (50.9)	228 (53.0)	
Died	696 (49.1)	202 (47.0)	0.444
Days to death/censored up to 180 days (end of study), median (IQR)	168 (5; 187)	167 (4; 187)	0.233

Indicator for PaO2 missingness	**PaO2 complete**	**PaO2 missing**	**P-value**
n (%)	1418 (76.2)	443 (23.8)	

Ventilatory markers at ICU admission **********	**********	**********	**********
Positive end-expiratory pressure, cmH{subscript:2}O, median (IQR)	6.00 (5.00; 8.00)	6.00 (5.00; 8.00)	0.451
Tidal Volume, (ml*kg−1 per PBW), mean (sd)	7.59 (5.76)	7.02 (1.72)	0.249
Driving pressure, cmH{subscript:2}O, median (IQR)	13.0 (10.0; 16.0)	12.0 (10.0; 16.0)	0.288
Compliance of respiratory system, median (IQR)	40 (31; 50)	39 (26; 51)	0.521
Mechanical power, j/min, median (IQR)	16.2 (12.7; 21.6)	16.6 (12.1; 22.3)	0.950
Ventilator ratio at baseline, median (IQR)	1.45 (1.16; 1.83)	2.19 (1.53; 3.11)	0.051
fraction of inspired O2, %, median (IQR)	60 (50; 88)	60 (45; 90)	0.505
Partial pressure of carbon dioxide (PaCO{subscript:2}), mmHg, median (IQR)	45.7 (39.7; 53.2)	48.8 (39.5; 51.9)	0.665
pH, mean (SD)	7.24 (0.12)	7.22 (0.11)	0.446
Base excess, mEq/L, median (IQR)	-6.5 (-10.0; -3.7)	-7.2 (-9.2; -5.1)	0.549