Supplemental Material

Oxygen desaturation and adverse outcome in acute stroke: secondary analyses of the HeadPoST study

Menglu Ouyang MPH,[1,2] Christine Roffe,[3] Laurent Billot MRes,[1] Lili Song MD PhD,[1,2] Xia Wang PhD,[1] Paula Muñoz Venturelli MD PhD,[1,4,5] Pablo M. Lavados MD MPH,[4] Thompson Robinson MD,[6] Sandy Middleton PhD,[7] Verónica V. Olavarría MD MSc.,[4] Caroline L. Watkins PhD,[8] Tsong-Hai Lee MD PhD,[9] Alejandro M Brunser MD, [4] Octavio M. Pontes-Neto MD PhD,[10] Maree L. Hackett PhD,[1,8] Craig S. Anderson MD PhD[1,2,6,11,12]

Appendix 1. Summary of definitions of serious adverse events (SAEs)

Item	Definition
Acute stroke	Cerebral ischemia, cerebral haemorrhage, cerebral edema, brain herniation, raised intracranial pressure
Cardiac/ other vascular disease	Myocardial infarction, heart failure, arrhythmia, sudden death (cardiac, cardiogenic shock), pulmonary embolism, death of unknown cardiac origin, acute pulmonary edema, epilepsy or seizures, carotid endarterectomy (CEA), hypertension, collapse, carotid angioplasty stenting (CAS) or other cardiac origin SAEs
Pneumonia	Pneumonia
Other infection	Urinary tract, septicemia, other type of infection in body, septic shock
Other SAE	Fall, renal failure, death (non-cardiovascular), ulcers, tumor or cancer, depression, anxiety, uncertain death, deep vein thrombosis (DVT), confusion, limb ischemia, meningitis and other undefined

Appendix 2. Propensity score matching approach

The propensity score was generated from all the baseline characteristics listed in Table 1. The propensity matching cohort for the two groups of oxygen desaturation (SaO_2 <93%) and normal group (SaO_2 93-100%) was generated by balanced, parallel (1:1) nearest available neighbour matching with a maximum permitted difference of 0.1 (caliper: 0.1) approach. Absolute standardized difference (ASD) was calculated between the two groups and unbalanced covariates (ASD more than 0.10) were identified. All unbalanced covariates were then adjusted into the multivariable analysis using the generalised linear mixed (GLM) models to obtain the associations of oxygen desaturation and clinical outcomes of (i) death or dependency and (ii) any serious adverse events (SAEs).

Table S1. Baseline characteristics of stroke patients by missing data on arterial oxygen saturation (SaO_2)

Variable	Available (n=8067, 73%)	Missing (n=3026, 27%)	P value*
Age	69.0 (13.96)	65.1 (12.81)	0.496
Male	4726 (58.6)	1983 (64.4)	0.357
Region			
Australia/UK	4376 (54.3)	385 (12.7)	<0.001
China/Taiwan	2370 (29.4)	2282 (75.4)	
India/Sri Lanka	501 (6.2)	269 (8.9)	
South America	820 (10.2)	90 (3.0)	
Premorbid mRS scores 2-5	1597 (19.8)	739 (24.5)	<0.001
NIHSS score at baseline	4.0 (2.0-9.0)	4.0 (2.0-7.0)	0.134
≥15	1011 (12.8)	196 (6.5)	0.596
Systolic BP	152 (135-173)	150 (138-170)	0.438
Blood glucose level	6.1 (5.3-7.7)	6.0 (5.1-7.7)	0.677
Heart rate	76 (68-86)	76 (68-81)	0.009
Time from symptom onset to hospital arrival	6.0 (2.1-22.6)	17.6 (4.5-51.4)	0.444
Heart failure	328 (4.1)	85 (2.8)	0.054
COPD/emphysema	334 (4.2)	72 (2.4)	0.047
Hypertension	5162 (64.2)	1989 (65.9)	0.649
Atrial fibrillation	992 (12.4)	197 (6.6)	0.309
Coronary heart disease	1141 (14.2)	399 (13.3)	0.291
Diabetes mellitus	1907 (23.7)	745 (24.7)	0.870
Hyperlipidemia	2296 (28.6)	436 (14.5)	0.308
Previous stroke	1776 (23.7)	831 (27.5)	0.113
Other major health conditions	1502 (18.9)	267 (9.0)	0.166
Current smoker	1402 (17.6)	723 (24.1)	0.809
Antiplatelet use in AIS	3410 (50.2)	1773 (66.3)	0.631
Anticoagulant use in AIS	611 (9.0)	112 (4.2)	0.328
Dysphagia	1634 (20.4)	411 (13.7)	0.375
Final diagnosis			
Acute ischemic stroke	6807 (84.5)	2678 (88.6)	0.006
Large vessel occlusion	2064 (30.3)	884 (33.0)	0.145
Cardioembolic	1068 (15.7)	167 (6.2)	
Lacunar	1756 (25.8)	1107 (41.3)	
Other	1919 (28.1)	520 (19.4)	
Intracerebral hemorrhage	703 (8.7)	228 (7.5)	
Presence of intraventricular blood	204 (29.3)	66 (29.0)	0.339
Haematoma volume	10 (3-15)	9 (4-15)	0.275
Not AIS/ICH	550 (6.8)	116 (3.8)	
Hospitalisation management			
Reperfusion therapy† for AIS	1181 (17.4)	160 (6.0)	<0.001
Surgical procedures‡ for ICH	7 (1.0)	5 (2.2)	0.623
Withdraw active care	92 (1.2)	21 (0.7)	0.657
Endotracheal intubation	81 (1.0)	20 (0.7)	0.198

Data are mean (SD), median (IQR), and n (%)

AIS denotes acute ischemic stroke, COPD chronic obstructive pulmonary disease, ICH intracerebral haemorrhage, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, UK United Kingdom

*P value from univariate analyses using generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period)
†Reperfusion therapy includes recombinant tissue-type plasminogen activator (rt-PA) treatment (intravenous or intra-arterial) or endovascular clot retrieval
‡ICH surgical procedures include decompressive hemicranectormy, open craniotomy surgical evacuation, minimally invasive surgery or intraventricular drainage

Table S2. Desaturation (<92%) and clinical outcomes at 90 days

	SaO_2		Model 1		Model 2		Model 3	
Outcome	<92%	92-100%	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
Death or dependency	214/365* (58.6)	2669/6584* (40.5)	1.31 (0.98-1.76)	0.069	1.28 (0.95-1.73)	0.105	1.21 (0.94-1.56)	0.136
Any SAEs	122/414† (29.5)	1160/7653† (15.2)	1.76 (1.33-2.32)	<0.001	1.62 (1.21-2.17)	0.001	1.46 (1.14-1.88)	0.004
Acute stroke	42/414 (10.1)	392/7653 (5.1)	1.73 (1.16-2.57)	0.007	1.42 (0.92-2.19)	0.110		
Cardiac/other vascular disease	16/414 (3.9)	179/7653 (2.3)	1.14 (0.63-2.08)	0.660	1.17 (0.64-2.14)	0.602		
Pneumonia	34/414 (8.2)	227/7653 (3.0)	1.58 (0.98-2.54)	0.059	1.51 (0.93-2.46)	0.093		
Other infection	7/414 (1.7)	91/7653 (1.2)	1.13 (0.49-2.26)	0.773	1.11 (0.47-2.59)	0.815		
Other SAE	22/414 (5.3)	268/7653 (3.5)	1.40 (0.86-2.29)	0.178	1.42 (0.87-2.32)	0.164		

Data are n/N (%).
CI denotes confidence interval, SAEs serious adverse events, aOR adjusted odds ratio
*Denominators represent the total number of patients with follow-up to 90-days
†Denominators represent the total number of randomized patients

Model 1: aOR obtained from generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and baseline variables of age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, National Institutes of Health Stroke Scale score, pre-morbid score 0-1 on the modified Rankin scale, dysphagia, hyperlipidemia, other major health conditions, chronic obstructive pulmonary disease, stroke type, antithrombotic treatment, and time from symptom onset to hospital arrival

Model 2: further adjusted management variables include withdraw active care, endotracheal intubation and reperfusion therapy for ischemic stroke during hospitalisation and surgical procedures for intracerebral haemorrhage during hospitalisation

Model 3: imputation dataset analysis based on the variables adjusted in Model 2 with additional adjustment of imputed blood glucose level

Table S3. Propensity score matching of baseline characteristics by lowest level of arterial oxygen saturation (SaO_2)

Variables	Lowest SaO_2 <93% (n=784)	Lowest SaO_2 93-100% (n=7283)	ASD	Lowest SaO_2 <93% (n=784)	Lowest SaO_2 93-100% (n=784)	ASD
Age	72.7 (13.00)	68.6 (14.00)	0.30	72.7 (13.00)	71.0 (13.39)	0.13
Female	354 (45.2)	2987 (41.0)	0.08	354 (45.2)	345 (44.0)	0.02
Region			0.29			0.44
Australia/UK	418 (53.3)	3958 (54.5)		418 (53.3)	455 (58.0)	
China/Taiwan	176 (22.5)	2194 (30.1)		176 (22.5)	247 (31.5)	
India/Sri Lanka	44 (5.6)	457 (6.3)		44 (5.6)	30 (3.8)	
South America	146 (18.6)	674 (9.3)		146 (18.6)	52 (6.6)	
Premorbid mRS scores 2-5	196 (25.1)	1401 (19.3)	0.14	196 (25.1)	177 (22.6)	0.06
NIHSS score	6 (3-13)	4 (2-9)	0.32	6 (3-13)	5 (2-10)	0.20
Systolic blood pressure, mmHg	152 (135-176)	152 (135-172)	<0.01	152 (135-176)	151 (137-170)	<0.01
Blood glucose level, mmol/L	6.5 (5.6-8.5)	6.1 (5.3-7.7)	0.16	6.5 (5.6-8.5)	6.3 (5.4-8.3)	0.07
Time from symptom onset to hospital arrival, hrs	4.1 (1.8-14.1)	6.2 (2.1-23.5)	0.20	4.1 (1.8-14.1)	5.1 (2.0-19.6)	0.14
Medical history and medications						
Heart failure	49 (6.3)	279 (3.9)	0.11	49 (6.3)	41 (5.3)	0.05
COPD/emphysema	72 (9.3)	262 (3.6)	0.23	72 (9.3)	54 (6.9)	0.09
Hypertension	541 (69.2)	4621 (63.6)	0.12	541 (69.2)	502 (64.3)	0.10
Atrial fibrillation	117 (15.0)	875 (12.1)	0.09	117 (15.0)	108 (13.9)	0.04
Coronary heart disease	114 (14.7)	1027 (14.2)	0.01	114 (14.7)	119 (15.2)	0.02
Diabetes mellitus	202 (25.8)	1705 (23.5)	0.05	202 (25.8)	181 (23.2)	0.06
Hyperlipidemia	245 (31.5)	2051 (28.3)	0.07	245 (31.5)	248 (31.7)	<0.01
Previous stroke	178 (22.8)	1598 (22.0)	0.02	178 (22.8)	186 (23.8)	0.02
Other major health conditions	184 (23.8)	1318 (18.3)	0.13	184 (23.8)	159 (20.4)	0.08
Current smoker	127 (16.4)	1275 (17.7)	0.04	127 (16.4)	139 (17.9)	0.04
Antiplatelet use in AIS	318 (48.1)	3092 (50.4)	0.04	318 (48.1)	368 (47.1)	0.04
Anticoagulant use in AIS	82 (12.4)	529 (8.7)	0.01	82 (12.4)	80 (10.2)	<0.01
Dysphagia	264 (34.2)	1370 (19.0)	0.35	264 (34.2)	206 (26.4)	0.17
Final diagnosis			0.04			0.08
AIS	664 (84.7)	6143 (84.4)		664 (84.7)	671 (85.8)	

ICH	74 (9.4)	629 (8.6)	74 (9.4)	58 (7.4)
Not AIS/ICH*	46 (5.9)	504 (6.9)	46 (5.9)	53 (6.8)

Data are mean (SD), median (IQR), and n (%)

Analyses were T-test for normally distributed variables, Wilcoxon rank sum test for skewed continuous variables, and Chi-squared test for categorical variables.

AIS denotes acute ischemic stroke, ASD absolute standardized difference, COPD chronic obstructive pulmonary disease, ICH intracerebral hemorrhage, mRS modified Rankin scale, NIHSS National Institutes of Health Stroke Scale, UK United Kingdom

*includes transient ischemic attack, migraine, seizure, functional weakness, syncope, transient global amnesia, metabolic disorder, tumor or other sources

Table S4. Association of arterial oxygen saturation (SaO_2) and clinical outcomes at 90 days after acute stroke using propensity matching dataset

	SaO_2		Model 1		Model 2	
Outcome	<93%	93-100%	aOR (95% CI)	P value	aOR (95% CI)	P value
Death or dependency	380/683* (55.6)	298/692* (43.1)	1.27 (0.97-1.68)	0.088	Didn't converge	-
Any SAEs	197/784† (25.1)	1355/784† (17.2)	1.38 (1.03-1.85)	0.030	1.40 (1.02-1.90)	0.035

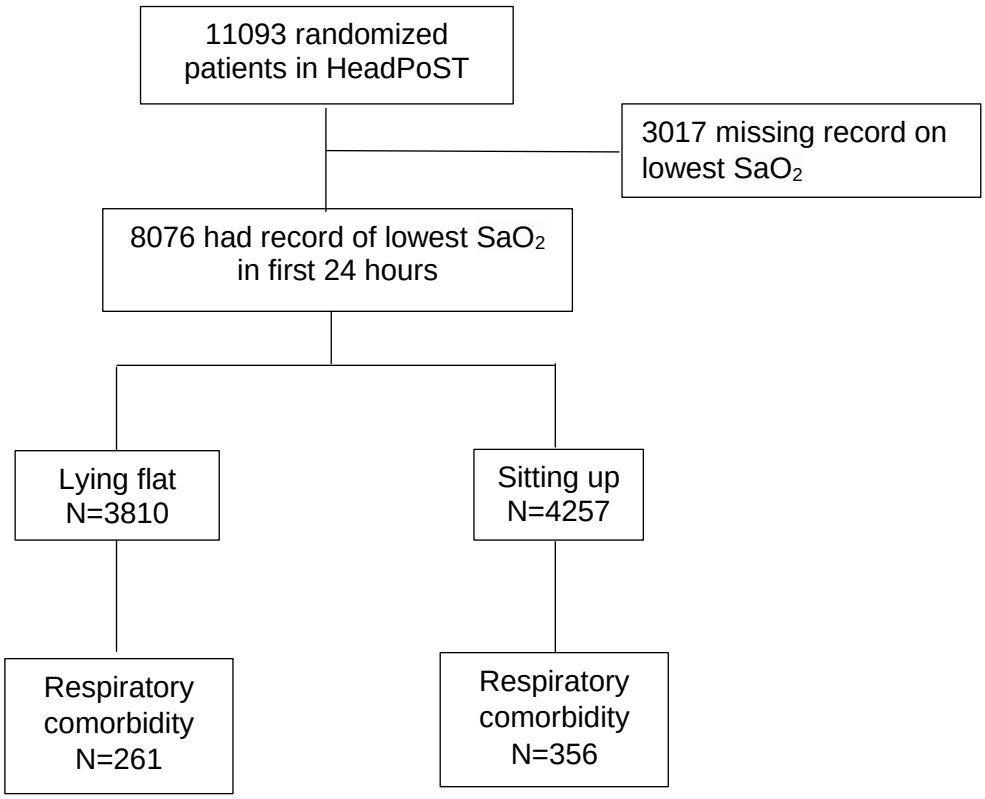
Data are n/N (%)
aOR adjusted odds ratio, CI denotes confidence interval, SAEs serious adverse event
*Denominators represent total number of patients with follow-up to 90-days
†Denominators represent total number of randomized patients

Model 1: aOR obtained from generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and baseline variables of age, region, hypertension, National Institutes of Health Stroke Scale score, dysphagia, and time from symptom onset to hospital arrival
Model 2: further adjusted management variables include withdraw active care, endotracheal intubation and reperfusion therapy for ischemic stroke and surgical procedural intervention for intracerebral hemorrhage during hospitalization

Table S5 Post-hoc power calculations

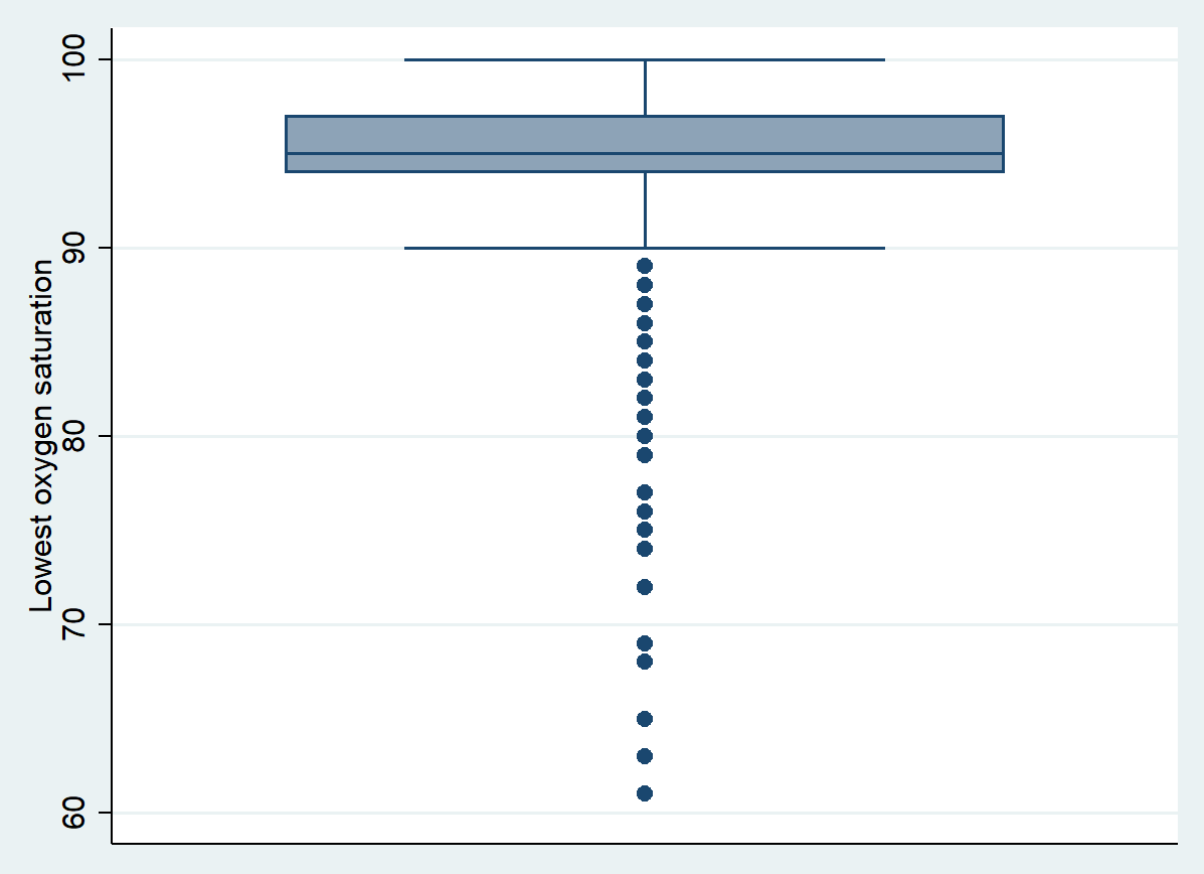
Outcome	Lowest Oxygen Saturation		Power
	<93%	93-100%	
Death or dependency	380/683* (55.6)	2503/6266* (40.0)	>99.9%
Any SAEs	197/784† (25.1)	1085/7283† (14.9)	>99.9%
Acute stroke	70/784 (8.9)	364/7283 (5.0)	99.2%
Cardiac/other vascular disease	27/784 (3.4)	168/7283 (2.3)	50.6%
Pneumonia	49/784 (5.1)	212/7283 (2.9)	90.0%
Other infection	12/784 (1.5)	86/7283 (1.2)	13.3%
Other SAEs	38/784 (4.5)	252/7283 (3.4)	40.9%

Figure S1. Flow chart



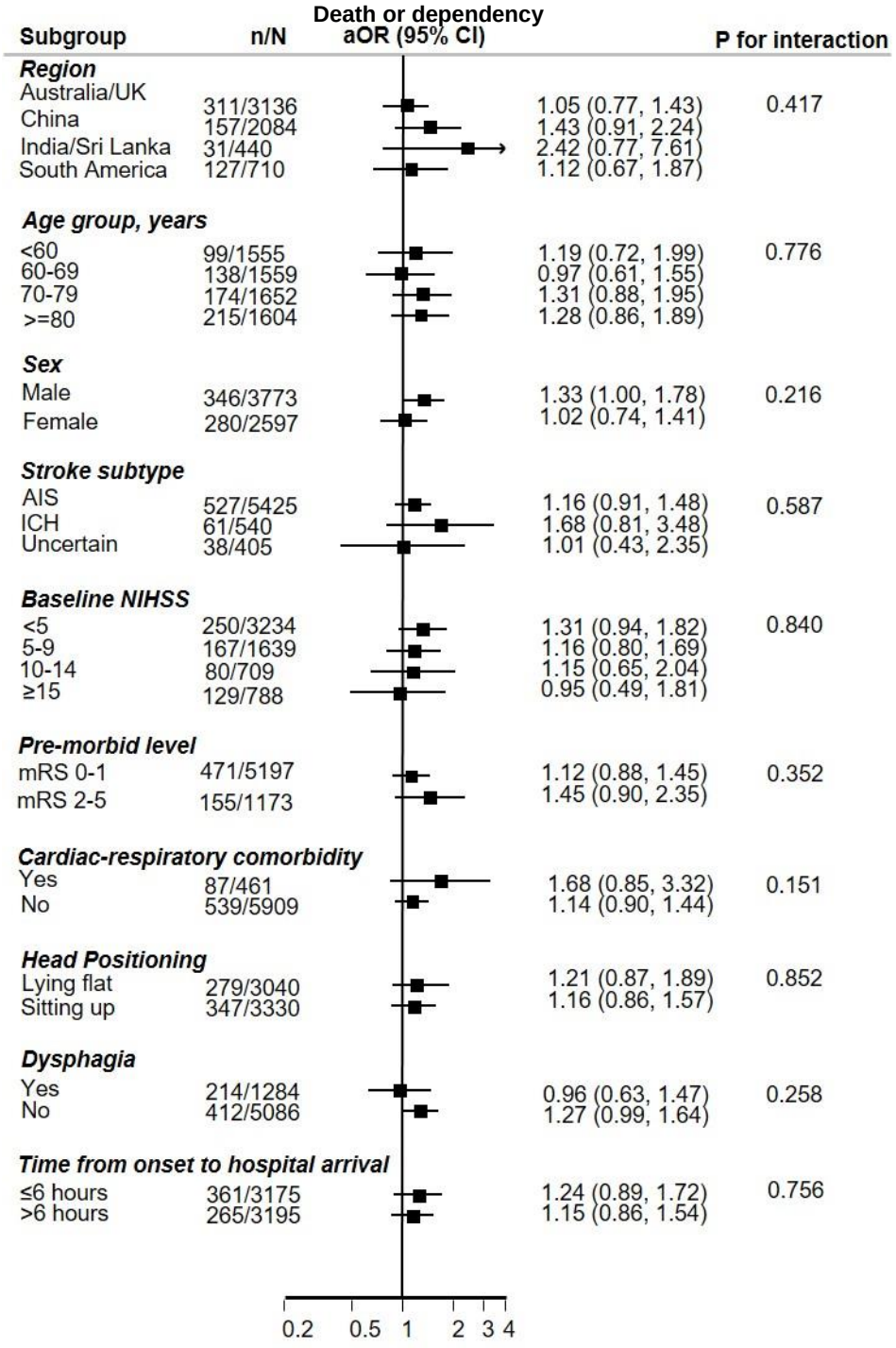
*SaO_2 denotes arterial oxygen saturation

Figure S2. Distribution of the arterial oxygen saturation



Boxes indicate first quartile (Q1) to third quartile (Q3); inner line indicates median; dots indicate outliers.

Figure S3. Subgroup analysis of association of arterial oxygen saturation and death or dependency at 90 days

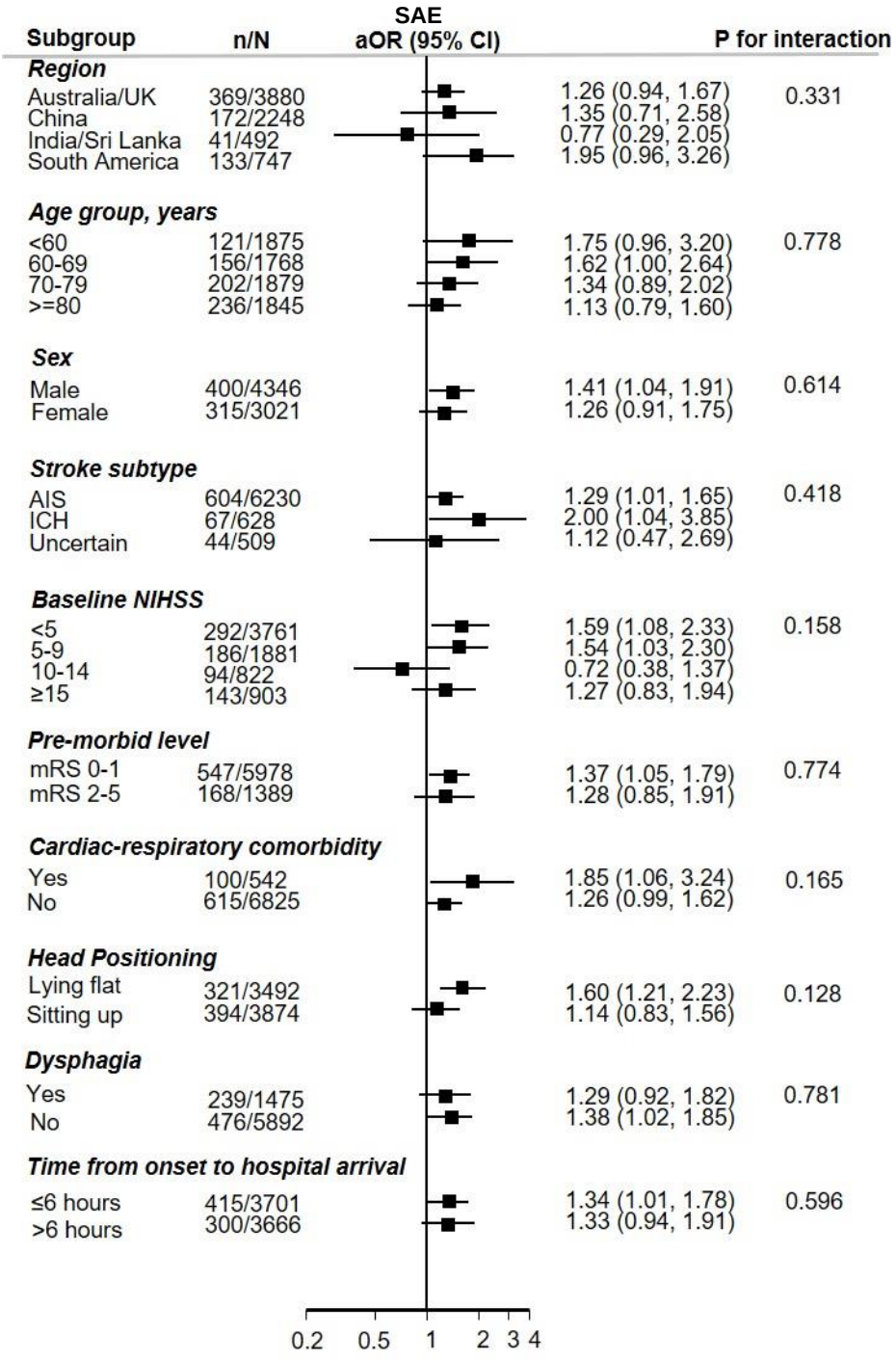


Footnote: AIS denotes acute ischemic stroke, aOR adjusted odds ratio, CI confidence interval, ICH intracerebral haemorrhage, NIHSS National Institutes of Health Stroke Scale

aOR obtained from generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and baseline variables of age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, National Institutes of Health Stroke Scale score, pre-morbid score 0-1 on the modified Rankin scale, dysphagia, hyperlipidemia, other major health conditions, chronic obstructive pulmonary

disease, stroke type, antithrombotic treatment, and time from symptom onset to hospital arrival, withdraw active care, endotracheal intubation and reperfusion therapy for ischemic stroke and surgical procedures for intracerebral haemorrhage during hospitalisation

Figure S4. Subgroup analysis of the association between arterial oxygen saturation and serious adverse events at 90 days



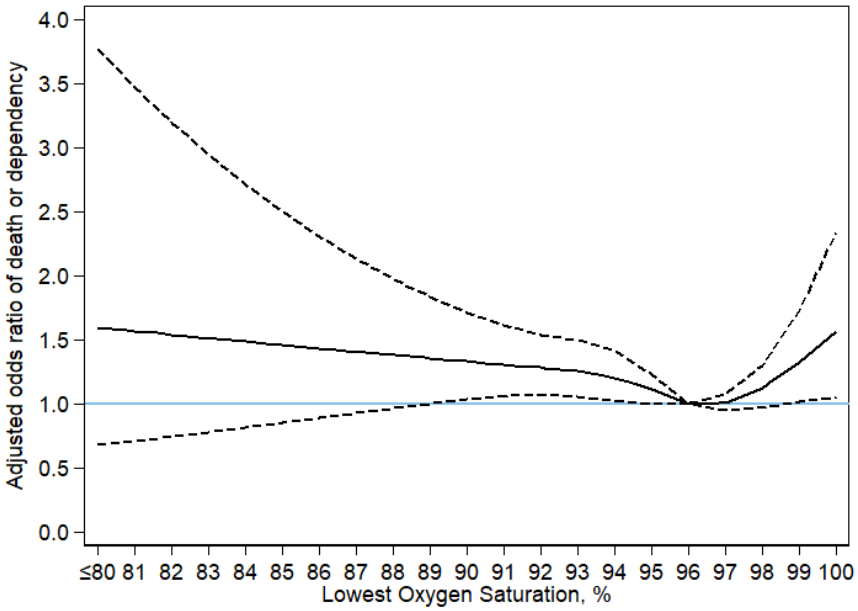
Footnote: AIS denotes acute ischemic stroke, aOR adjusted odds ratio, CI confidence interval, ICH intracerebral haemorrhage, NIHSS National Institutes of Health Stroke Scale

aOR obtained from generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and baseline variables of age, sex, region, history of diabetes mellitus, hypertension, heart failure, atrial fibrillation, National Institutes of Health Stroke Scale score, pre-morbid score 0-1 on the modified Rankin scale, dysphagia, hyperlipidemia, other major health conditions, chronic obstructive pulmonary

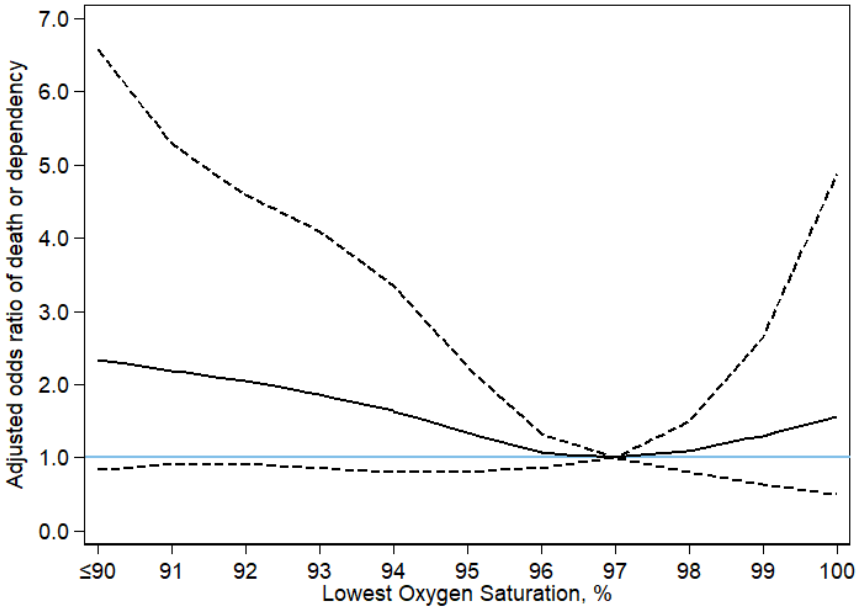
disease, stroke type, antithrombotic treatment, and time from symptom onset to hospital arrival, withdraw active care, endotracheal intubation and reperfusion therapy for ischemic stroke and surgical procedures for intracerebral haemorrhage during hospitalisation

Figure S5. Spline of lowest oxygen saturation and death or dependency at 90 days by stroke subtype

A. Ischemic stroke



B. Haemorrhagic stroke



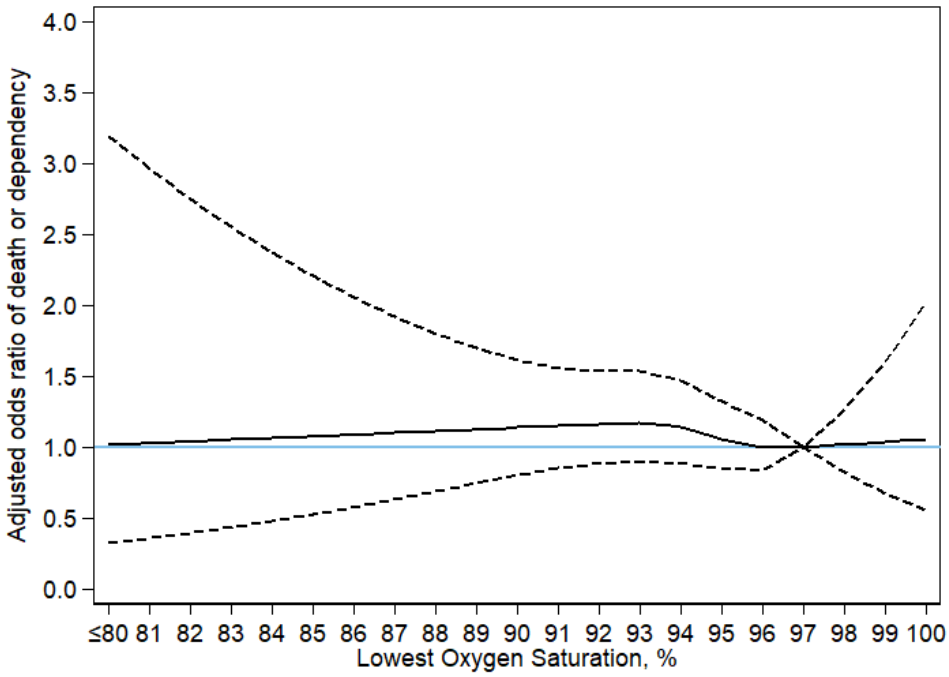
Footnote: Generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and baseline variables of age, sex, region groups, history of coronary heart disease, diabetes mellitus, hypertension, heart failure, atrial fibrillation, National Institutes of Health Stroke Scale score, pre-morbid score 0-1 on the modified Rankin scale, dysphagia, hyperlipidemia, other major health conditions, chronic obstructive pulmonary disease, antithrombotic treatment, and time from symptom onset to hospital arrival, withdraw active care, endotracheal intubation with A. further adjusted

reperfusion therapy and stroke subtype for ischemic stroke and B. further adjusted surgical procedures for haemorrhagic stroke

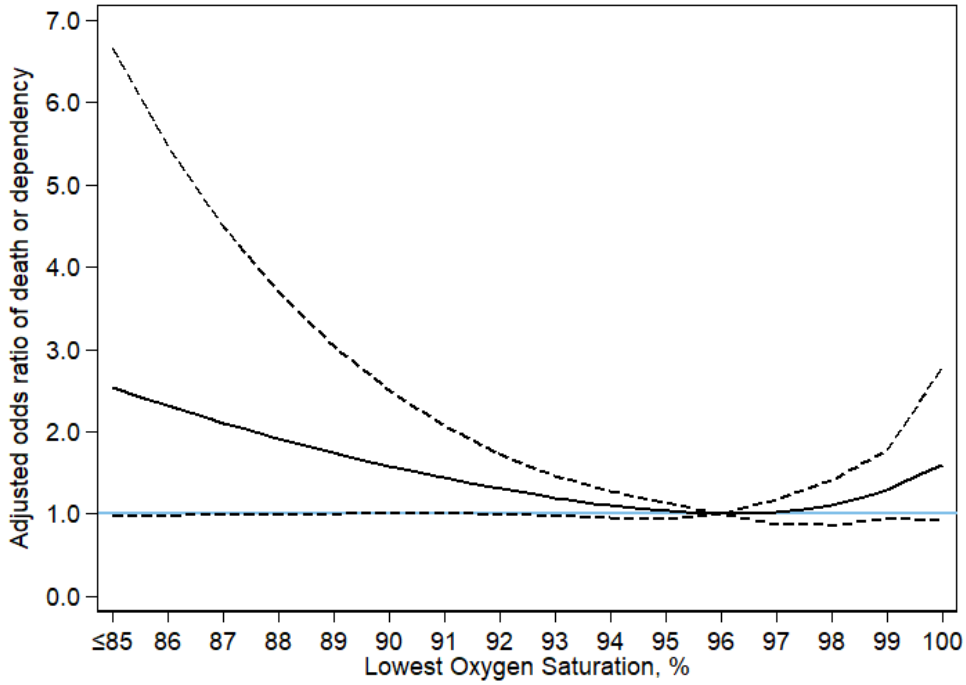
Spline fitted with 4 knots (percentiles 5^{th}, 35^{th}, 65^{th}, 95^{th}) for oxygen saturation, with lowest point as reference; solid line indicates adjusted odds ratio; dotted lines indicates 95% confidence intervals.

Figure S6. Spline of lowest oxygen saturation and death or dependency at 90 days by region

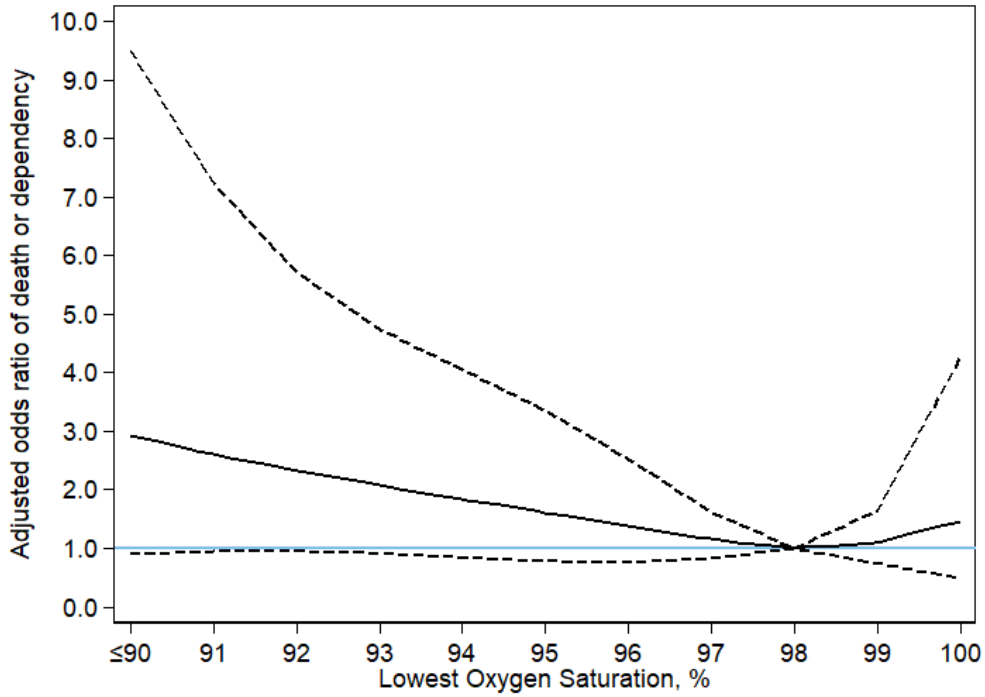
A. Australia and UK



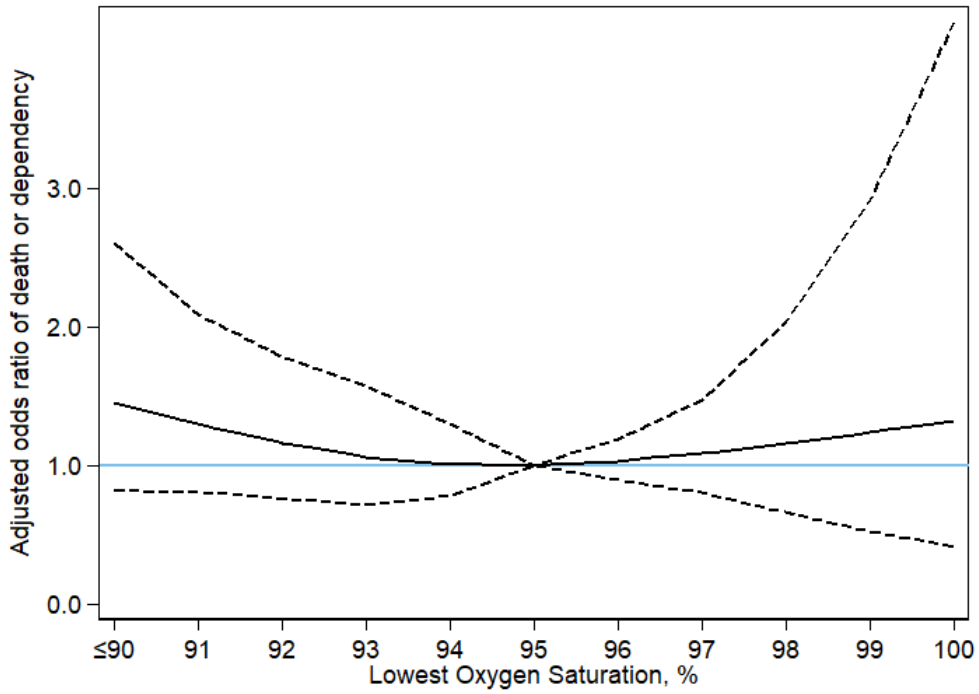
B. China



C. India and Sri Lanka



D. South America



Footnote: Generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and baseline variables of age, sex, history of coronary heart disease, diabetes mellitus, hypertension, heart failure, atrial fibrillation, National Institutes of Health Stroke Scale score, pre-morbid score 0-1 on the modified Rankin scale, dysphagia, hyperlipidemia, other major health conditions, chronic obstructive

pulmonary disease, stroke subtype, antithrombotic treatment, and time from symptom onset to hospital arrival, withdraw active care, endotracheal intubation, reperfusion therapy for ischemic stroke and surgical procedures for haemorrhagic stroke

Spline fitted with 4 knots (percentiles 5^{th}, 35^{th}, 65^{th}, 95^{th}) for oxygen saturation, with lowest point as reference; solid line indicates adjusted odds ratio; dotted lines indicates 95% confidence intervals.