Oxygen desaturation and adverse outcomes in acute stroke: secondary analysis of the HeadPoST study

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Abstract

Objective: Uncertainty exists over the prognostic significance of low arterial oxygen saturation (SaO_2) in acute stroke. We aimed to determine the strength of association of SaO_2 and adverse outcomes among participants of the international Head Positioning in acute Stroke Trial (HeadPoST).

Methods: Post-hoc analyzes of HeadPoST, a pragmatic cluster-crossover randomized trial of lying flat versus sitting up head positioning in 11,093 patients (age ≥18 years) with acute stroke at 114 hospitals in 9 countries during 2015-2016. Associations of the lowest recorded SaO_2 level, as a continuous measure and as a cut-point for desaturation (SaO_2 <93%), in the first 24 hours and clinical outcomes of death or dependency (modified Rankin scale [mRS] scores 3-6) and any serious adverse event (SAE) at 90 days, were assessed in generalized linear mixed models adjusted for baseline and in-hospital management confounders.

Results: There was an inverse J-shaped association between SaO_2 and death or dependency, with a nadir for optimal outcome at 96-97%. Patients with SaO_2 desaturation were older, and had greater neurological impairment, premorbid disability and cardiorespiratory disease. Desaturation was not clearly associated with death or dependency (adjusted odds ratio [aOR] 1.19, 95% confidence interval [CI] 0.95-1.48) but was with SAEs (aOR 1.34, 95% CI 1.07-1.68), without heterogeneity by head position, cardiac-respiratory comorbidity, or other pre-specified subgroups.

Conclusions: Any change in SaO_2 outside of 96-97% is associated with poorer outcome after acute stroke.

Clinical trial registration: HeadPoST is registered at ClinicalTrials.gov (NCT02162017).

Introduction

Hypoxia is common in patients who have suffered an acute stroke, the result of many factors including the severity of the neurological deficit, dysphagia, sleep apnea, and cardiac or respiratory disease.[1] Given that it can cause harms, such as worsening of the cerebral lesion, guidelines are consistent in recommending that patients with an acute stroke, as well as anyone with a critical illnesses, be carefully monitored and for supplementary oxygen to be used when the levels of arterial oxygen saturation (SaO_2) fall below 93% or 94%.[2-4] Although randomized trials have not shown a benefit from the routine use of supplementary oxygen in acute stroke,[5-8] prompt correction of SaO_2 desaturation is likely to improve outcomes, although supporting evidence is limited.[1] The few studies that have evaluated the influence of different head positions in bed suggest that SaO_2 improves with head elevation or sitting up,[9, 10] but these data are derived from small samples where high-risk patients have been excluded.[11] Herein, we present post-hoc analyzes of the large international, Head Positioning in Acute Stroke Trial (HeadPoST) dataset,[12] to determine any associations between the lowest SaO_2 recorded during patient monitoring in the first 24 hours after hospital admission for acute stroke and 90-day clinical outcomes; and whether this was modified by head position or comorbid cardiorespiratory illness.

Methods

Study population

HeadPoST was a multicenter, cluster crossover, clinical trial in 11,093 adults (age ≥18 years) with presumed acute stroke (both ischemic and hemorrhagic) randomly allocated to the lying flat or sitting up head position soon after presentation at 114 hospitals in 9 countries between March 2015 and November 2016.[8] A guardian

consent process was used to implement the randomized intervention as a policy of usual service delivery to a pre-defined patient cluster; patients provided consent for the use of their medical record data and centralized telephone follow-up. HeadPoST is registered at ClinicalTrials.gov (NCT02162017).

Procedures

Demographic, medical history and clinical information, including the severity of neurological impairment on the National Institutes of Health Stroke Scale (NIHSS), were recorded at baseline. Data were collected on the lowest SaO_2 within the first 24 hours as part of a protocol for standard monitoring of vital signs and adherence to the allocated head position. Trained staff, blind to treatment allocation, contacted patients not known to have died, by telephone to assess their functional status on the modified Rankin scale (mRS) at 90 days. The primary outcome for these analyzes was death or dependency (mRS scores 3-6). Secondary outcomes were all-cause and cause-specific, serious adverse events (SAEs), reported by site investigators during the hospital stay to the end of follow-up at 90 days (see appendix for list of SAEs).[8]

Statistical analysis

Continuous relationships of lowest SaO_2 level and clinical outcomes were visualized using restricted cubic splines fitted with 3-5 knots for placement, as recommended by Harrell,[13] with optimal knots selected according to the likelihood ratio test and Aikaike information classification (AIC). Associations were also assessed according to SaO_2 desaturation as a binary variable, defined as <93% by the 1st decile of distribution and according to clinical guideline recommended threshold for use of supplementary oxygen.[14] These levels were assessed by generalized linear mixed (GLM) models

that were built with adjustment for the fixed effects of head position (lying-flat versus sitting-up) and cross-over period, random effects of cluster, random interaction effects between cluster and crossover period, and potential confounding baseline (Model 1) and relevant hospital management variables (Model 2) (with P <0.20 from Table 1). A sensitivity analysis used a SaO_2 <92%, another popular definition of desaturation.[15] Due to the high proportion of missing data in SaO_2 and baseline blood glucose level, multiple imputation was also used as another form of sensitivity analysis (Model 3), where all covariates and outcomes[16] were used with a fully conditional specification of 20 imputed sets through PROC MI according to fully conditional method (FCS) methods. A propensity score matching approach was also conducted as a sensitivity analysis to address variable imbalance between the two groups in exploring associations of desaturation and clinical outcomes (described in supplemental materials). Pre-specified subgroup analysis considered participating region, age, stroke subtype, baseline neurological severity, pre-morbid function, presence of dysphagia, allocated head position, comorbid cardiorespiratory disorder (i.e. heart failure or chronic obstructive pulmonary disease [COPD] / emphysema), and time from the onset of symptoms to hospital arrival. Estimates are presented as adjusted odds ratios (aOR) and 95% confidence intervals (CI), and a two-sided P <0.05 was considered statistically significant. All analyses were performed with SAS version 9.3 (SAS Institute, Cary, NC).

Data sharing

Individual participant data used in these analyses can be shared by formal request, with the protocol from any qualified investigator, to the Research Office of The George Institute for Global Health, Australia.

Results

There were 8067 (73%) patients (mean age 69 years; 58.6% male) from the total study population with data on their lowest SaO_2 level recorded in the 24 hours after hospital admission (Supplemental Figure S1): the median lowest SaO_2 was 95% (IQR 94%-97%) and the 1st decile was 93% (Supplemental Figure S2). Participants who lacked data on SaO_2 were significantly more often from China, had greater prior strokes and comorbid conditions of COPD/emphysema and ischemic stroke, with adjustment of study design (Supplemental Table S1). Among the 8,067 patients with SaO_2 recorded, 784 (9.7%) met the definition of SaO_2 desaturation (<93%), and they were older, more often female, arrived earlier to hospital, had greater neurological severity, higher baseline blood glucose, more premorbid disability, cardiac and respiratory co-morbidities and dysphagia, than other patients (Table 1).

Figure 1A shows a reverse J-shape relationship between the lowest SaO_2 in first 24 hours post-stroke and death or dependency, with a nadir at 96-97%. When analyzed as a binary variable, patients with SaO_2 desaturation (<93%) had a higher odds, albeit non-significant, association of death or dependency (55.6% vs. 40.0%; aOR 1.19, 95% CI 0.95-1.48; Table 2). The relationship of SaO_2 and SAEs was inverse linear, with a decrease in SAEs as SaO_2 increased (Figure 1B), which translated into a significant association between SaO_2 desaturation (<93%) and any SAE (aOR 1.34, 95% CI 1.07-1.68; Table 2). These results were consistent after multiple imputation (Table 2), when using a lower cut-point of <92% for SaO_2 desaturation (Supplemental Table S2), and after propensity score matching to adjust unbalanced covariates (Supplemental Tables S3 and S4). Although desaturation was associated with stroke-specific SAEs in Model 1 (aOR 1.54, 95% ci 1.12-2.12), the significance

was lost after adjustment of hospital management variables (aOR 1.38, 95% CI 0.98-1.93; Table 2).

There was no evidence of heterogeneity in the association between SaO_2 desaturation across subgroups for death or dependency (Supplemental Figure S3), and for SAEs (Supplementary Figure S4). In particular, there was no clear modification of these associations by different head position, comorbid cardiorespiratory disease, and dysphagia, nor was there any heterogeneity across regions. However, significant higher odds of poor outcome were found in males and without dysphagia (Figures S3). Moreover, minor stroke, ICH, lying flat, and presence of cardiac-respiratory comorbidity, were all related to a higher odds of SAEs in subgroup analysis (Figure S4). The level of the lowest SaO_2 at which the spline for death and disability had its nadir was consistent across stroke subtypes (Supplementary Figures S5), but varied across regions: ranging between 95% to 98% (Supplementary Figures S6). Post-hoc power calculations underlying these analyzes based on the observed outcomes are outlined in the Appendix (Supplementary Table S5).

Discussion

In these secondary analyzes of a large clinical cohort, patients with the lowest SaO_2 of around 96-97% early after the onset of stroke had a better clinical outcome compared to others with either lower or higher levels of SaO_2. Patients with SaO_2 desaturation were more often older, frailer, and had greater neurological impairment, than other patients, which placed them at higher odds of adverse outcomes.

Our results are consistent with the conclusions drawn from a recent review of hypoxia in stroke, where there is no clear association of SaO_2 desaturation, as a binary cut-

point variable, and adverse functional outcome.[1] Although another study showed that hypoxic (SaO_2 <93%) patients treated with supplemental oxygen had improved neurological function by one week, this might have been a chance finding due to the small sample and/or an imbalance in baseline neurological severity between the groups.[17] As some studies have shown an increased odds of adverse outcomes at much lower cut points to define hypoxia (SaO_2 <90%),[18] our finding of a poor outcome in patients with higher levels of SaO_2 might be due to reverse causality, where supplementary oxygen had been used in high-risk patients. This is supported the significant relationship between desaturation and stroke-specific SAEs being eliminated after adjustment of aspects of hospital management. As the normal range of SaO_2 in healthy adults is 95-98%,[19] the finding of poor outcome associated with SaO_2 at full concentration (100%) supports the potential for mechanisms such as oxidative stress to be exacerbated by over-aggressive use of oxygen treatment.[20, 21] Other studies have shown that inappropriately high oxygen therapy is associated with greater mortality without any improvement in patient-centred outcomes.[22] As such, guidelines recommend that supplementary oxygen should not be used routinely, but instead restricted to those with evidence of desaturation, with a SaO_2 of 94-96% being a reasonable treatment target.[3, 14]

Compared to other studies[23-25] suggesting that females have greater respiratory effort and are less prone to ischemic injury than males, we could not find any heterogeneity by sex, nor according to the presence of dysphagia or neurological severity; but this might be due to incomplete adjustment for confounding, such as the use of supplementary oxygen in sicker patients. Similarly, although there was no clear influence of head position on the association of SaO_2 desaturation and poor outcome, the higher odds of SAEs in those who were lying flat could have been due to reduced

lung expansion and gas exchange,[10] and risk of aspiration, especially in the presence of dysphagia.[26] Moreover, the smaller sample size of subgroup analyzes and different national standards of care, could have influenced the varying nadir of SaO_2 for optimal outcome across regions.

A strength of our study was the inclusion of a large sample of patients with a broad range of characteristics who were managed across a variety of health systems. However, there are several limitations, one which being the high proportion of missing data, which may have introduced further bias on top of selection bias pertaining to the data being derived from a clinical trial population. Despite consistency of the results after multiple imputation, the assumption that missingness occurred at random for these analyzes may not have applied, and thus the observed data may not have been sufficient to explain the association. Another major limitation is the availability of only a single exposure measure, that of the lowest recorded SaO_2 in the first 24 hours after hospital admission, being recorded as a measure of safety to the allocated head position. A full appreciation of the role of desaturation would require data on the timing of SaO_2 desaturation, its change, purpose of measurement, and its management. As SaO_2 is physiologically dynamic, a single measure will not adequately capture the frequency and duration of episodes of SaO_2 desaturation,[18] and chance and bias further complicate post-hoc analyzes with variable cut-off points for SaO_2. Taken together with issues of indication bias and reduced power in subgroup analysis and of disease-specific SAEs, any associations may not be causal, and caution should be applied when interpreting these results.

In summary, a SaO_2 of 96-97% is associated with optimal functional recovery from acute stroke, with poor outcomes evident at both lower and higher values without any

clear influence of head position or cardiorespiratory disease this association. Further research is required to determine the potential impact of avoiding SaO_2 desaturation and/or over-correction to full SaO_2 concentration in acute stroke.

Author Contributions

CSA and MO contributed to the concept and rationale for the study. MO undertook statistical analyzes with assistance from LB. MO wrote the first draft of manuscript with input from CSA. All authors commented upon and approved the final version of the manuscript for publication.

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Statement of ethics

The appropriate ethics committee at each participating centre approved the study protocol. A senior executive officer at each centre acted as a 'guardian' and provided institutional consent for this low-risk intervention to be implemented as part of routine nursing care in each cluster. Written informed consent was sought from all patients or approved surrogates for ongoing assessments and data collection.

Disclosures

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conduct of the study; and research grants from CONICYT, outside the submitted work. CR has received funding from the UK National Institute for Health Research (NIHR) for a trial of routine oxygen supplementation in acute stroke as well as other stroke studies; and she is a member of the Data Safety Monitoring committee for the EU FP7 funded PROOF study assessing the effects of high flow oxygen treatment during mechanical thrombectomy. SM was a member of the NHMRC Research Committee during 2015-2018. OMPN received grants for the Brazilian Stroke Research Network by DECIT/MS and CNPQ (402388/2013-5) for conduct this study. TGR is an NIHR Senior Investigator. CSA is an NHMRC Senior Investigator and grants, honoraria and travel reimbursement from Takeda outside of this study. The other authors have no disclosures to report.

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Table 1. Baseline characteristics and hospital management by lowest level of arterial oxygen saturation (SaO_2) in the first 24 hours after acute stroke

	Lowest SaO_2		
Variables	<93% (n=784 [9.7%])	93-100% (n=7283 [90.3%])	P value
Age	72.7 (13.00)	68.6 (14.00)	<0.001
Female	354 (45.2)	2987 (41.0)	0.025
Region			<0.001
Australia/UK	418 (53.3)	3958 (54.5)	
China/Taiwan	176 (22.5)	2194 (30.1)	
India/Sri Lanka	44 (5.6)	457 (6.3)	
South America	146 (18.6)	674 (9.3)	
Premorbid mRS scores 2-5	196 (25.1)	1401 (19.3)	<0.001
NIHSS score	6 (3-13)	4 (2-9)	<0.001
⩾15	169 (21.8)	842 (11.8)	<0.001
Systolic blood pressure, mmHg	152 (135-176)	152 (135-172)	0.749
Blood glucose level, mmol/L	6.5 (5.6-8.5)	6.1 (5.3-7.7)	<0.001
Time from symptom onset to hospital arrival, hrs	4.1 (1.8-14.1)	6.2 (2.1-23.5)	<0.001
Medical history and medications			
Heart failure	49 (6.3)	279 (3.9)	0.001
COPD/emphysema	72 (9.3)	262 (3.6)	<0.001
Hypertension	541 (69.2)	4621 (63.6)	<0.001
Atrial fibrillation	117 (15.0)	875 (12.1)	0.017
Coronary heart disease	114 (14.7)	1027 (14.2)	0.719
Diabetes mellitus	202 (25.8)	1705 (23.5)	0.143
Hyperlipidemia	245 (31.5)	2051 (28.3)	0.060
Previous stroke	178 (22.8)	1598 (22.0)	0.619
Other major health conditions	184 (23.8)	1318 (18.3)	<0.001
Current smoker	127 (16.4)	1275 (17.7)	0.352
Antiplatelet use in AIS	318 (48.1)	3092 (50.4)	0.270

Anticoagulant use in AIS	82 (12.4)	529 (8.7)	0.002
Dysphagia	264 (34.2)	1370 (19.0)	<0.001
Final diagnosis			0.431
Acute ischemic stroke	664 (84.7)	6143 (84.4)	
AIS subtype			<0.001
Large vessel occlusion	168 (25.3)	1896 (30.9)	
Cardioembolic	146 (22.0)	922 (15.0)	
Lacunar	158 (23.5)	1600 (26.1)	
Other	194 (29.2)	1725 (28.1)	
Intracerebral haemorrhage	74 (9.4)	629 (8.6)	
Presence of intraventricular blood	16 (22.2)	188 (30.1)	0.165
Haematoma volume	10 (3-15)	10 (3-15)	0.446
Not AIS/ICH*	46 (5.9)	504 (6.9)	
Hospitalisation management			
Reperfusion therapy† for AIS	151 (22.8)	1030 (16.8)	<0.001
Surgical procedures‡ for ICH	3 (4.1)	4 (0.6)	0.005
Withdraw active care	26 (3.4)	66 (0.9)	<0.001
Endotracheal intubation	21 (2.7)	60 (0.8)	<0.001

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, COPD chronic obstructive pulmonary disease, ICH intracerebral haemorrhage, 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, tumour or other sources
†Reperfusion therapy includes recombinant tissue-type plasminogen activator (rt-PA) treatment (intravenous or intra-arterial) or endovascular clot retrieval
‡ICH surgical procedures include decompressive hemicarnectormy, open craniotomy surgical evacuation, minimally invasive surgery or intraventricular drainage

Table 2. Association of arterial oxygen saturation (SaO_2) and clinical outcomes at 90 days after acute stroke

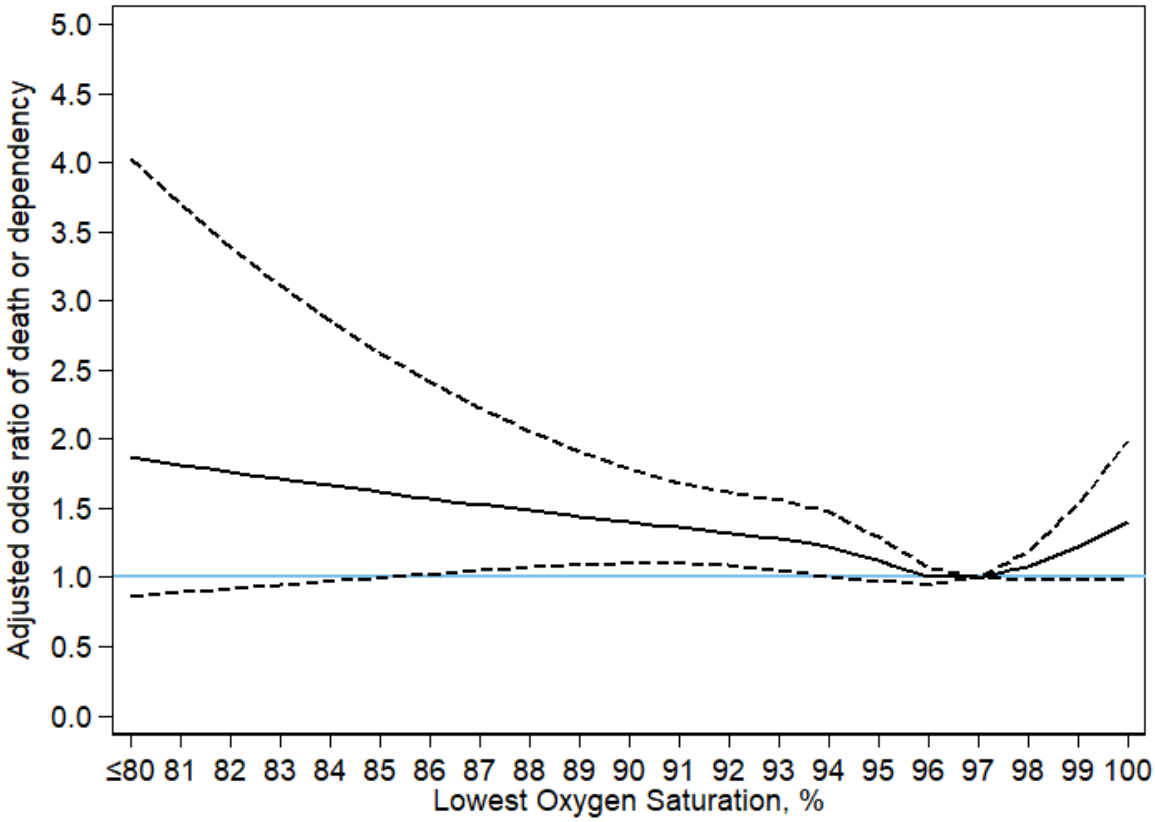
	SaO_2		Model 1		Model 2		Model 3	
Outcome	<93%	93-100%	aOR (95% CI)	P value	aOR (95% CI)	P value	aOR (95% CI)	P value
Death or dependency	380/683* (55.6)	2503/6266* (40.0)	1.20 (0.96-1.50)	0.102	1.19 (0.95-1.48)	0.133	1.16 (0.97-1.39)	0.106
Any SAEs	197/784† (25.1)	1085/7283† (14.9)	1.41 (1.13-1.76)	0.002	1.34 (1.07-1.68)	0.012	1.26 (1.03-1.52)	0.023
Acute stroke	70/784 (8.9)	364/7283 (5.0)	1.54 (1.12-2.12)	0.008	1.38 (0.98-1.93)	0.063		
Cardiac/other vascular disease	27/784 (3.4)	168/7283 (2.3)	1.12 (0.70-1.79)	0.631	1.12 (0.70-1.80)	0.624		
Pneumonia	49/784 (5.1)	212/7283 (2.9)	1.18 (0.79-1.76)	0.433	1.12 (0.74-1.68)	0.597		
Other infection	12/784 (1.5)	86/7283 (1.2)	0.97 (0.49-1.92)	0.923	0.95 (0.47-1.89)	0.875		
Other SAEs	38/784 (4.5)	252/7283 (3.4)	1.29 (0.88-1.90)	0.200	1.28 (0.87-1.89)	0.208		

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

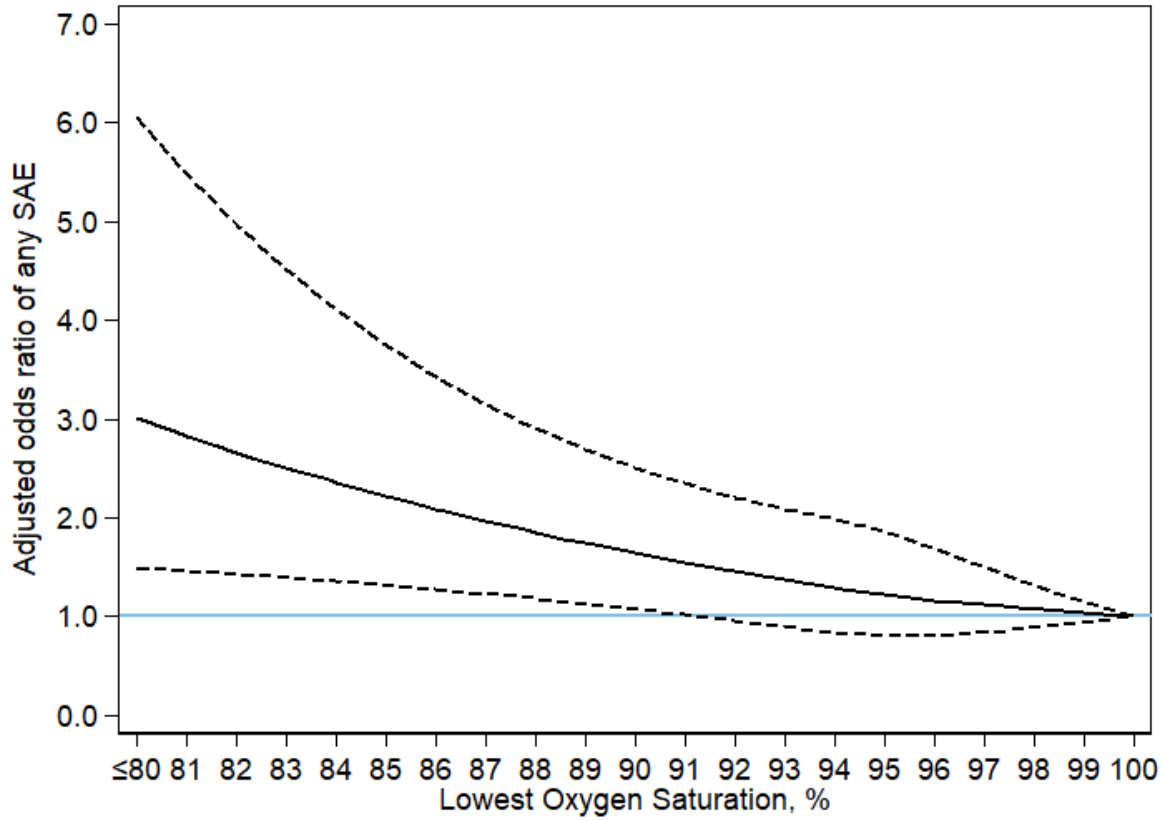
Model 1: aOR obtained from generalized linear mixed models with adjustment for study design (fixed effects of head position and cross-over period, random effects of cluster, and random interaction effects between cluster and crossover period) and baseline variables of age, sex, region, history of diabetes 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

Figure 1. Relationship of lowest arterial oxygen saturation (SaO_2) in first 24 hours of acute stroke and clinical outcomes

A. Death or dependency at 90 days



B. Serious adverse events (SAE) within 90 days



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

A. Spline fitted with 4 knots (percentiles 5^{th}, 35^{th}, 65^{th}, 95^{th}) for SaO_2, with 97% as reference. Solid line indicates adjusted odds ratio; dotted lines indicates 95% confidence intervals.

B. Spline fitted with 3 knots (percentiles 25^{th}, 50^{th}, 75^{th}) for SaO_2 with 100% as reference. Solid line indicates adjusted odds ratio; dotted lines indicates 95% confidence intervals.