Non-linear association between arterial oxygen tension and survival after out-of-hospital cardiac arrest: a multicentre observational study

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Abstract

Background: Studies to identify safe oxygenation targets after out-of-hospital cardiac arrest (OHCA) have often assumed a linear relationship between arterial oxygen tension (PaO_2) and survival, or have dichotomised PaO_2 at a supra-physiological level. We hypothesised that abnormalities in mean PaO_2 (both high and low) would be associated with decreased survival after OHCA.

Methods: We conducted a retrospective multicentre cohort study of adult OHCA patients who received mechanical ventilation on admission to the intensive care unit (ICU). The potential non-linear relationship between the mean PaO_2 within the first 24-hours of ICU admission and survival to hospital discharge (STHD) was assessed by a four-knot restricted cubic spline function with adjustment for potential confounders.

Results: 3764 arterial blood gas results were available for 491 patients in the first 24-hours of ICU admission. The relationship between mean PaO_2 over the first 24-hours and STHD was an inverted U-shape, with highest survival for those with a mean PaO_2 between 100 and 180 mmHg (reference category) compared to a mean PaO_2 of <100 mmHg (adjusted odds ratio [aOR] 0.50 95% confidence interval [CI] 0.30, 0.84), or >180 mmHg (aOR 0.41, 95% CI 0.18, 0.92). Mean PaO_2 within 24-hours was the third most important predictor and explained 9.1% of the variability in STHD.

Conclusion: The mean PaO_2 within the first 24-hours after admission for OHCA has a non-linear association with the highest STHD seen between 100 and 180 mmHg. Randomised

controlled trials are now needed to validate the optimal oxygenation targets in mechanically ventilated OHCA patients

Key Words

Arterial blood gas analysis, arterial oxygen tension, emergency medical services, out-of-hospital cardiac arrest, post-resuscitation care, survival, neurological outcome

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Introduction

Hypoxic-ischaemic encephalopathy (HIE) after return of spontaneous circulation (ROSC) in out-of-hospital cardiac arrest (OHCA) is a major determinant of in-hospital mortality and neurological dysfunction.[1,2] The pathophysiology of HIE is complex, but well described in both animal[3] and human studies.[2,4] The nature and extent of the subsequent brain injury depends on the underlying cause of the arrest, the time to ROSC and post-resuscitation management.[5,6]

As both hypoxaemia and hyperoxaemia worsen outcomes in critically ill patients without OHCA,[7] such a relationship may also exist after OHCA. Research suggests survival from HIE depends upon minimising secondary insults to the brain,[1,6] primarily by optimising the balance between adequate cerebral oxygen delivery and use,[8] and possibly also reducing oxygen's potential harm through reactive oxygen free radicals.[8] Clinicians can theoretically optimise oxygen delivery and consumption through temperature control and maintaining arterial oxygen tension (PaO_2) at or near a target range in patients requiring mechanical ventilation (MV) after OHCA.[1] The scientific basis for avoiding excessive oxygen in the presence of HIE is strong, particularly during the first 24-hours after cardiac arrest when reperfusion injury (including neuronal death) due to oxidative stress and mitochondrial production of reactive oxygen species is expected.[8] However, there are limited randomised controlled clinical trials (RCT's) comparing different PaO_2 targets during the early post-resuscitation period, and results from observational studies are conflicting.[9]

Studies investigating the association between PaO_2 and outcome after OHCA have typically used linear models in their analyses or arbitrarily selected PaO_2 cut points.[9] However, the linearity assumption conflicts with the expectation that both hypoxaemia and hyperoxaemia may be harmful, and that an optimal range of oxygenation may exist after cardiac arrest. We hypothesised that a non-linear relationship exists between PaO_2 and outcome after OHCA, with improved survival and neurological outcome with an intermediate level of oxygen tension compared to either low to normal or extremely high oxygen tensions. Our aim was therefore to assess the association of exposure to different PaO_2 levels over the first 24-hours of ICU admission with survival to hospital discharge (STHD) in adult patients with OHCA of medical aetiology. Secondary outcomes were 12-month survival and good neurological outcome at hospital discharge.

Methods

Study Type and Setting

We conducted a retrospective cohort study of OHCA patients attended by emergency medical services (EMS) and admitted to the four adult tertiary hospitals[10] (see Supplementary Text 1) in Perth, Western Australia (WA) between 1st January 2012 and 31st December 2017.

In the Perth metropolitan area (population 2.05 million),[11] EMS are provided by St John Western Australia (SJWA) using a single tier of road-based paramedics. Advanced life support is provided according to SJWA Clinical Practice Guidelines (CPGs),[12] based on those of the Australian and New Zealand Committee on Resuscitation (ANZCOR).[13]

In accordance with SJWA CPGs at the time, OHCA patients who were not declared dead at scene were transported to the nearest emergency department (ED) for stabilisation.[12] Patients transferred to a tertiary hospital from the ED of a non-tertiary hospital were defined as 'indirect' transport patients, as distinct from a 'direct transport' patient.

Participants

We included adult patients (≥18 years) with OHCA of presumed medical aetiology.[14] We excluded patients who did not receive MV on admission to ICU and those who did not have an arterial blood gas (ABG) result recorded in the first six hours of ICU admission.

Post-Resuscitation Care

Consistent with the ANZCOR[15] guidelines at the time, routine post-resuscitation care in ICU included (1) targeted temperature management (TTM) and treatment of hyperpyrexia; (2) protective ventilation to maintain normoxia and normocapnia; (3) haemodynamic management; (4) percutaneous coronary intervention following ROSC with ST-elevation; and (5) multimodal neurological prognostication >72-hours after OHCA.

Data Sources

We identified patients from the SJWA OHCA Registry.[16] A structured medical chart review was conducted by a single data extractor (NM) to collect in-hospital clinical interventions, neurological outcomes and ABG results for the study cohort.

Data Collected

The following demographic and clinical data were extracted from the SJWA OHCA Registry: age (continuous variable), sex (female/male), arrest location (home/public location), witness status (paramedic witnessed/bystander witnessed/ unwitnessed), bystander cardiopulmonary resuscitation (CPR) (yes/no), shockable first arrest rhythm (yes/no), EMS response time (from emergency call until arrival at the scene), time between EMS attendance and tertiary ICU admission and transport group (direct/indirect).

Data extracted from medical chart review included: pre-arrest neurological function (as described below), primary diagnosis in ED and at hospital discharge, in-hospital clinical interventions including angiography/ PCI and TTM in ICU (defined as any attempt to control body temperature within the first 24-hours of ICU admission).[1] All ABG results were collected for the first 72-hours of ICU admission, and ABG results within the first 24-hours and first 72-hours were used for the primary and sensitivity analyses, respectively.

Outcome Measures

The primary outcome was STHD. Secondary outcomes were good neurological outcome at hospital discharge and 12-month survival from the date of OHCA. Good neurological outcome was defined as a Cerebral Performance Category (CPC) score[17] at hospital discharge of 1 (good cerebral performance) or 2 (moderate cerebral disability).[18] Twelve month survival was operationally defined as no death record in the WA State Death Registry from the date of arrest until 12-months later.

Statistical Analyses

Continuous variables are reported as means with standard deviation (SD) or medians with interquartile range (IQR) and categorical variables as percentages. Differences between groups were assessed using the student's t-test, Mann-Whitney U and Kruskal-Wallis test for continuous variables, and Fishers Exact Test and Pearson chi-squared test for categorical variables.

As many physiological variables are related to clinical outcomes in a non-linear and non-monotonic fashion,[19,20] the relationship between mean PaO_2 during the first 24-hours in ICU after OHCA and survival was analysed using a four-knot restricted-cubic-spline function.[21] We assessed the importance of mean PaO_2 relative to plausible physiological predictors in explaining the variability in observed hospital mortality by each predictor's chi square contribution in a multivariable logistic regression.[22] (See Supplementary Text 2)

We also conducted two sensitivity analyses examining whether the mean PaO_2 during the first 48 and 72-hours in ICU after OHCA remained important in determining survival. All statistical tests were two-tailed and analysed using SPSS for Windows (version 24.0, IBM, USA) and S-PLUS (version 8.2, 2010; TIBCP Software Inc., USA); an alpha probability <5% was taken as significant.

Ethics approval

The study was approved (with waiver of consent) by the Curtin University Human Research Ethics Committee (HREC) (HR 199/2014) and each study hospital's HREC: Royal Perth Hospital (13-044), Sir Charles Gairdner Hospital (2012-184), Fremantle Hospital (AR-13-96) and Fiona Stanley Hospital (2015-091); and the SJWA Research Governance Committee,

Results

Selection of the study population and its characteristics

As shown in Fig. 1, 491 patients met the inclusion criteria and were included in the final analysis. Of these, 231 (47.0%) STHD; 209/231 (90.5%) with a good neurological outcome. Of the hospital survivors, 224/231 (97%) survived to 12-months.

Table 1 shows the study population characteristics, stratified by those who did and did not STHD. Prehospital factors associated with STHD were: male (51.9% vs 35% p=0.001), younger (median 56 vs 63 years, p=0.001), initial shockable arrest rhythm (84.0% vs 43.8%, p=<0.001), and bystander CPR (77.9% vs 63.1%, p=<0.001),

In-hospital factors associated with STHD were: ROSC on arrival to the first ED (93.1% vs 76.5%, p=<0.001), ED diagnosis of acute coronary syndrome (39.8% vs 24.2%, p=<0.001), ED diagnosis of STEMI (27.3% vs 16.9%, p=0.01), PCI within 24-hours of EMS call (35.9% vs 22.7%, p=0.001) and TTM in ICU (88.3% vs 75.0%, p=<0.001).

The association between oxygen tension after OHCA and survival

In the first 24-hours of ICU admission 3764 ABG samples were collected, a median of 7 ABG per patient (IQR 5-10). Supplemental Fig. 1 shows the individual PaO_2 data for all ABG's in the first 24-hours of ICU admission, stratified by STHD.

Using a linear model, the mean PaO_2 during the first 24-hours of ICU admission had no significant association with STHD after adjusting for known predictors of survival after OHCA (p=0.97) (Supplementary Fig. 2). Using a four-knot analysis while adjusting for plausible physiological predictors of survival after OHCA, the mean PaO_2 had a non-linear, inverted U-shaped relationship with both STHD and 12-month survival (Fig. 2 and 3). The calibration of the multivariable model allowing for non-linear effect of PaO_2 on STHD is described in Supplementary Fig. 3.

Based on the shape of the non-linear relationship between 24-hour mean PaO_2 and survival outcomes (Fig. 2 and 3), we defined three categories of oxygenation: low to normal (<100 mmHg; n=115), intermediately elevated (100-180 mmHg; n=336) and highly elevated (>180 mmHg; n=40) referring to them respectively as normoxaemic, mildly to moderately hyperoxaemic, and severely hyperoxaemic. We found hypoxaemia (PaO_2 <60 mmHg) was uncommon in our cohort. The normoxaemic group had a slightly higher incidence of at least one episode of hypoxaemia compared to those with mild to moderate hyperoxaemia and severe hyperoxaemia (4.3% vs 0.6% vs 0.0%, respectively; chi squared p value 0.011) (Supplementary Fig. 4).

In univariate analyses, the three groups had similar age and sex distributions but patients in the mild to moderate hyperoxaemia group, compared to those in the normoxemia and severe hypoxaemia group, were more likely to have an initial shockable arrest rhythm (67.9% vs 53.9% vs 45.0%) (p=<0.001) (Supplementary Table 1). They were also more likely to have ROSC on arrival to the first ED (87.8% vs 74.8% vs 82.5%) (p=0.004), a diagnosis of STEMI in ED (25.6% vs 17.4% vs 2.5%) (p=0.002), PCI within 24-hours of OHCA (32.1% vs 24.3% vs 15.0%) (p=0.04) and received TTM in ICU (86.0% vs 73.9% vs 62.5%) (p=<0.001).

The association between mean PaO_2 within the first 24-hours of ICU admission (categorised using the cut points defined above) and STHD or 12-month survival remained unchanged throughout the stepwise forward logistic regression (Table 2). When compared to the reference group of those with PaO_2 100-180 mmHg, normoxemia (adjusted odds ratio [aOR] 0.50; 95% confidence interval [CI] 0.30-0.84) and severe hyperoxaemia (aOR 0.41; 95% CI 0.18-0.92) were both associated with reduced odds of STHD. Results for 12-month survival and good CPC at hospital discharge were similar (Supplementary Fig. 5).

Relative importance of PaO_2 on survival compared to other known predictors

In the restricted-cubic-spline multivariable model, initial shockable rhythm was the most important, explaining 55.2 % of the variability in STHD, followed by witnessed arrest (12.0%). Mean PaO_2 within 24-hours was the third most important, explaining 9.1% of the variability in STHD (Fig. 4). PCI within the first 24-hours after OHCA and ED diagnosis of STEMI had little prognostic value, each explaining 0.1% of the variability in STHD (Fig. 4).

Sensitivity analyses

The associations between mean PaO_2 and survival (STHD and 12-month survival remained similar to the 24-hour results when the period of oxygen exposure was extended to 48-hours or 72-hours after OHCA (Supplementary Tables 2 and 3).

Discussion

In this multicentre retrospective cohort study of 491 OHCA patients mechanically ventilated in ICU, we found mild to moderate hyperoxaemia within the first 24-hours after OHCA was associated with significantly higher odds of STHD and 12-month survival compared to normoxaemia (<100 mmHg) or severe hyperoxaemia (>180 mmHg). The non-linear inverted U-shaped association between PaO_2 and survival highlights a potential simple intervention to improve patient outcomes after OHCA.

The American Heart Association guidelines recommend monitoring oxyhemoglobin saturation and titrating the fraction of inspired oxygen (FiO_2) , and avoiding excessively high inspiratory oxygen concentrations after ROSC.[23] These recommendations were based on observational studies suggesting that hyperoxaemia may increase mortality after cardiac arrest, with a physiologically plausible mechanism of harm from reactive oxygen species with exposure to excessive oxygen. However, many of the existing observational studies[24-33] are limited by methodological issues that this study has attempted to address.

Previous studies have assessed the effect of PaO_2 on survival after OHCA using a single value (or time point) of PaO_2 as the measure of the degree of oxygen exposure, for example the first recorded PaO_2,[24,30] or highest PaO_2,[26,27] or worst PaO_2[25,31] within the first 24-hours of ICU admission, primarily because that data was the only information recorded in their databases. The use of a single PaO_2 measurement at a point in time does not reflect the true extent of oxygen exposure during the vulnerable period of reperfusion injury to the brain which may last for 24-hours or longer. Using a single highest or lowest value of PaO_2 recorded within the first 24-hours after OHCA as a measure of oxygen exposure is also more likely to induce misclassification of the true exposure. Palmer et al.[34] found a high PaO_2 in the first ABG results was likely to trigger action to decrease the FiO_2, attempting to normalize the arterial oxygen tension. More recent studies have sought to overcome any effect from variation in sampling times by expanding their analyses beyond a single point. For example, Roberts et al. measured PaO_2 at both one and six hours after ROSC.[32] Even so, this study was limited by only studying oxygen exposure within the first six hours. Measuring oxygen exposure at multiple time points over a 24-hour period (and beyond) are physiologically more robust.

With only two small RCT's[35,36] assessing different levels of PaO_2 after cardiac arrest, using previously published thresholds to define an arterial oxygen tension that is considered safe or most appropriate for patients after OHCA has no strong scientific basis. Arbitrarily categorising PaO_2 without considering its potential non-linear effect on patient outcome will not only reduce statistical power but it can also result in incorrect inferences and conclusions, as we have demonstrated (in Supplementary Fig. 2 compared to Fig. 2 and 3). Our results suggest that the effect of PaO_2 on survival is "dose dependent" with harm occurring at a PaO_2 less than the 300 mmHg as suggested by others[9] and also when PaO_2 is less than 100 mmHg. Results from the EXACT study[37], a multicentre, single-blind, randomised, parallel-group, controlled trial to determine whether early oxygen titration improves STHD in adult OHCA patients should provide higher quality evidence on the effect of hyperoxaemia on outcomes.

Study strengths and limitations

A strength of our study is inclusion of only OHCA patients (other studies have included in-hospital arrests) who were admitted to the ICUs of all four adult tertiary hospitals in Perth over a six-year period. We were able to adjust for a number of prehospital and in-hospital prognostic variables. Using the mean PaO_2 values derived from multiple ABG results over the first 24-hours is more representative of the real oxygen exposure during the crucial reperfusion injury period after OHCA. More importantly, we have allowed the association between this more accurate measure of oxygen exposure and survival to be modelled non-linearly, instead of forcing the data to fit into a linear relationship which may be non-physiological.[26] Many physiological derangements and pharmacological activities exhibit a non-linear or sometimes non-monotonic relationship with clinical outcomes.[19,20] Based on previous evidence indicating that both hypoxaemia and hyperoxaemia can worsen outcomes in critically ill patients without OHCA[7], our hypothesis, study design and results are both relevant to, and consistent with the results of these studies.

We acknowledge the limitations of this study. First, our results can only imply association and suggest a need to conduct an adequately powered RCT to validate the optimal oxygenation targets in mechanically ventilated OHCA patients. Second, the interhospital transfer of OHCA patients was at the discretion of ED physicians, and this may have resulted in selection bias in our cohort; although the majority of patients (75.0%) were directly transported to a tertiary hospital Third, due to the observational nature of the study, there were variations in the timing and frequency of ABG analyses and other interventions between different study centres. An important therapy after OHCA is TTM which was used in the majority of patients during the study period, although the precise targets did vary (33-37° C).[38] Fourth, it is unclear whether clinicians corrected the ABG values to the patient's actual body temperature (pH-stat) or not (alpha-stat), which may potentially induce a small degree of variability in the reported PaO_2 data.[39] Fifth, in highlighting a PaO_2 of 100-180 mmHg as an optimal target for patients who require MV after OHCA, we acknowledge that this is a target averaged over the first 24-hours, and that real-time (minute-by-minute) targets could potentially be broader without causing significant harm. Sixth, it is possible that cofounding by severity has influenced our study results where patients with more severe illness receive a higher level of FiO_2, resulting in poorer outcomes because of their illness severity instead of oxygen exposure.[40] Seventh, it is possible that variables not included in our analyses contributed to outcomes from HIE. Finally, we have no information on PaO_2 levels before ICU admission where patients may have received a higher FiO_2 in the immediate post-resuscitation period. The SJWA CPG during the study period was to administer 100% FiO_2 in the prehospital setting.

Conclusion

When compared to an arterial oxygen tension that is considered low or normal (<100 mmHg) and severely hyperoxaemia (>180 mmHg), an exposure to mild to moderate hyperoxaemia within the first 24-hours of ICU admission after OHCA was associated with a significantly higher chance of STHD and to 12-months. This generates the hypothesis that mild to moderate hyperoxaemia (100-180 mmHg) in the first 24-hours of ICU admission after OHCA, improves outcomes, but this needs to be tested in a RCT.

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Disclosures

None

Authors' contributions

Study design: NM, JF

Data retrieval: NM, GD

Data interpretation: KM, JF, SB, GD, JB

Statistical data analysis: KM, NM (non-cubic spline analysis)

Drafting of article: NM

Critical revision: all authors

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Figure Legend

Fig. 1: Flow chart of included and excluded adult OHCA patients (≥18 years) with OHCA of medical aetiology attended by EMS paramedics and transported to a tertiary hospital in Perth, WA between the 1st of January 2012 and 31st of December 2017.

Abbreviations indicate as follows: ABG, arterial blood gas; CPC, cerebral performance category; ED, emergency department; EMS, emergency medical services; HITH, hospital in the home; ICU, intensive care unit; MV, mechanical ventilation; OHCA, out-of-hospital cardiac arrest; PaO_2, arterial oxygen tension; ROSC, return of spontaneous circulation; STHD, survival to hospital discharge.

Fig. 2: Mean PaO_2 within the first 24-hours of ICU admission with log odds of STHD using RCS function. Dotted lines indicate 95 % CI.

Abbreviations indicate as follows: CI, confidence interval; ICU, intensive care unit; PaO_2, arterial oxygen tension; RCS, restricted cubic spline function; STHD, survival to hospital discharge.

Fig. 3: Mean PaO_2 within the first 24-hours of ICU admission with log odds of survival to 12-months using RCS function. Dotted lines indicate 95 % CI.

Abbreviations indicate as follows: CI, confidence interval; ICU, intensive care unit; PaO_2, arterial oxygen tension; RCS, restricted cubic spline function.

Fig. 4: Predictors of in-hospital mortality using mean PaO_2 within the first 24-hours of ICU admission.

Abbreviations indicate as follows: CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ICU, intensive care unit; PaO_2, arterial oxygen tension; PCI, percutaneous coronary intervention within the first 24-hours; STEMI, ST-elevation myocardial infarction; STHD, survival to hospital discharge.

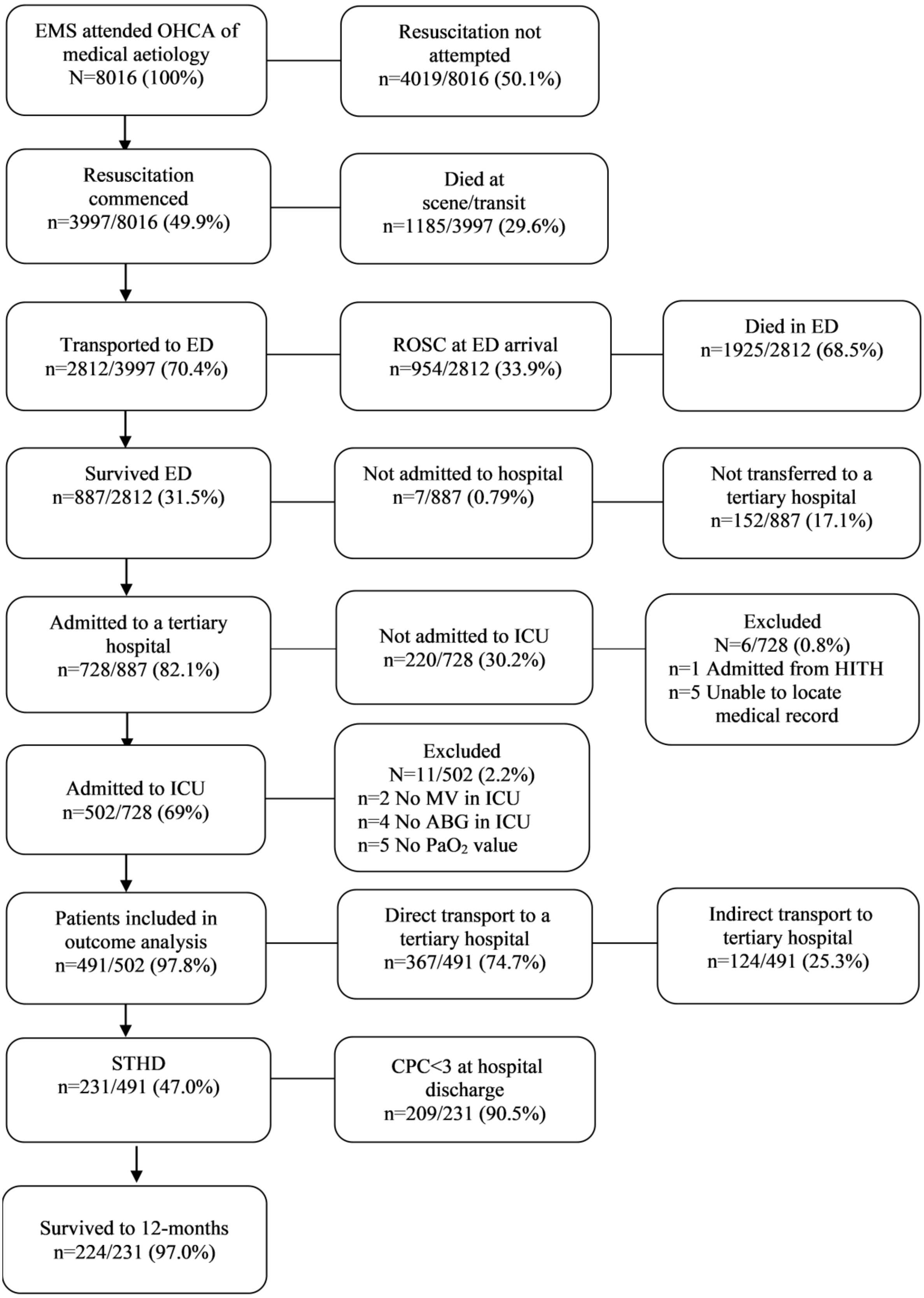

EMS attended OHCA of medical aetiology N=8016 (100%)
Resuscitation not attempted n=4019/8016 (50.1%)
Resuscitation commenced n=3997/8016 (49.9%)
Died at scene/transit n=1185/3997 (29.6%)
Transported to ED n=2812/3997 (70.4%)
ROSC at ED arrival n=954/2812 (33.9%)
Died in ED n=1925/2812 (68.5%)
Survived ED n=887/2812 (31.5%)
Not admitted to hospital n=7/887 (0.79%)
Not transferred to a tertiary hospital n=152/887 (17.1%)
Admitted to a tertiary hospital n=728/887 (82.1%)
Not admitted to ICU n=220/728 (30.2%)
Excluded N=6/728 (0.8%) n=1 Admitted from HITH n=5 Unable to locate medical record
Admitted to ICU n=502/728 (69%)
Excluded N=11/502 (2.2%) n=2 No MV in ICU n=4 No ABG in ICU n=5 No PaO_2 value
Patients included in outcome analysis n=491/502 (97.8%)
Direct transport to a tertiary hospital n=367/491 (74.7%)
Indirect transport to tertiary hospital n=124/491 (25.3%)
STHD n=231/491 (47.0%)
CPC<3 at hospital discharge n=209/231 (90.5%)
Survived to 12-months n=224/231 (97.0%)

Fig. 1: Flow chart of included and excluded adult OHCA patients (≥18 years) with OHCA of medical aetiology attended by EMS paramedics and transported to a tertiary hospital in Perth, WA between the 1st of January 2012 and 31st of December 2017.

Abbreviations indicate as follows: ABG, arterial blood gas; CPC, cerebral performance category; ED, emergency department; EMS, emergency medical services; HITH, hospital in the home; ICU, intensive care unit; MV, mechanical ventilation; OHCA, out-of-hospital cardiac arrest; PaO_2, arterial oxygen tension; ROSC, return of spontaneous circulation; STHD, survival to hospital discharge.

Table 1: Demographic and OHCA characteristics of patients with OHCA of medical aetiology admitted to a tertiary hospital ICU stratified by STHD.

	Total	**Survivors (% survivors)**	**Non-Survivors (% non-survivors)**	**p-values**
No. (%) of patients	**491**	**231 (47.0)**	**260 (53.0)**	
Median (IQR) Age, years	59 (48-70)	56 (46-67)	63 (50-72)	**0.001**
Sex				
Male	351 (71.5)	182 (78.8)	169 (65.0)	**0.001**
Female	140 (28.5)	49 (21.2)	91 (35.0)	
Pre-arrest CPC score				
CPC 1 or 2	485 (98.8)	230 (99.6)	255 (98.1)	0.22
CPC 3	6 (1.2)	1 (0.4)	5 (1.9)	
Witnessed arrest				
Paramedic	43 (8.8)	21 (9.1)	22 (8.5)	0.65
Bystander	233 (47.5)	114 (49.4)	119 (45.8)	
Unwitnessed	215 (43.8)	96 (41.6)	119 (45.8)	
Bystander CPR	344 (70.1)	180 (77.9)	164 (63.1)	**<0.001**
Initial arrest rhythm				
VF/VT	308 (62.7)	194 (84.0)	114 (43.8)	**<0.001**
PEA/Asystole[*]	183 (37.3)	37 (16.0)	146 (56.2)	
Median (IQR) EMS response time, minutes[†]	8 (6-10)	7 (6-10)	8 (6-10)	**0.01**
Median (IQR) time to first ED, minutes[‡]	46 (38-54)	43 (36-51)	48 (41-57)	**<0.001**
Median (IQR) time to tertiary ICU, minutes[§]	228 (178-284)	216 (167-275)	236 (192-292)	0.06

Direct transport patients (n=367)	211 (165-262)	201 (160-261)	217 (174-266)	0.05
Indirect transport patients (n=124)	291(243-342)	282 (242-351)	292 (248-337)	0.44
ROSC on arrival to first ED	414 (84.3)	215 (93.1)	199 (76.5)	**<0.001**
Place of intubation[#]				
Pre-hospital	202 (41.1)	53 (22.9)	149 (57.3)	**<0.001**
ED	285 (58.0)	176 (76.2)	109 (41.9)	
Diagnosis of ACS at ED discharge	155 (31.6)	92 (39.8)	63 (24.2)	**<0.001**
Diagnosis of STEMI at ED discharge	107 (21.8)	63 (27.3)	44 (16.9)	**0.01**
PCI (≤24-hours)[‖]	142 (28.9)	83 (35.9)	59 (22.7)	**0.001**
Median (IQR) duration of ICU stay (days)	2 (1-5)	3 (2-5)	2 (1-5)	**0.002**
TTM in ICU	399 (81.3)	204 (88.3)	195 (75.0)	**<0.001**
Inotropes in ICU	427 (87.0)	194 (84.0)	233 (89.6)	0.06

Data are presented as count (percentage) unless indicated otherwise

* Includes 8 patients where 'Initial arrest rhythm' is unknown

† Time interval from EMS call to arrival on scene

‡ Time interval from EMS call to arrival at first ED

§ Time interval from EMS call to arrival at a tertiary hospital ICU

‖ Time interval from EMS call to arrival in CCL

Excludes 3 patients intubated in CCL and one patient intubated in OR

Abbreviations indicate as follows: ACS, acute coronary syndrome; CCL, cardiac catheterization laboratory; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; ED, emergency department; EMS, emergency medical services; ICU, intensive care unit; OR, operating room; PCI, percutaneous coronary intervention within the first 24-hours; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; STEMI, ST-elevation myocardial infarction; STHD, survival to hospital discharge; TTM, targeted temperature management; VF, ventricular fibrillation; VT, ventricular tachycardia.

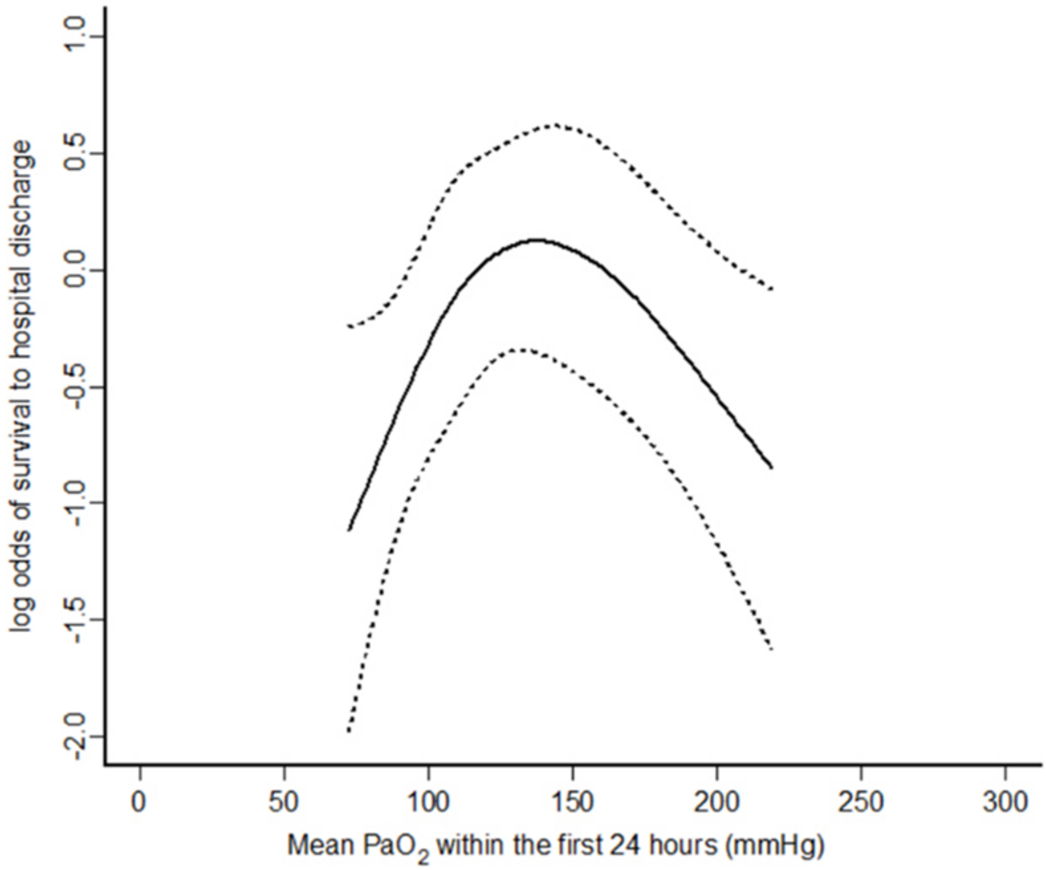


Fig. 2: Mean PaO_2 within the first 24-hours of ICU admission with log odds of STHD using RCS function. Dotted lines indicate 95 % CI.

Abbreviations indicate as follows: CI, confidence interval; ICU, intensive care unit; PaO_2, arterial oxygen tension; RCS, restricted cubic spline function; STHD, survival to hospital discharge.

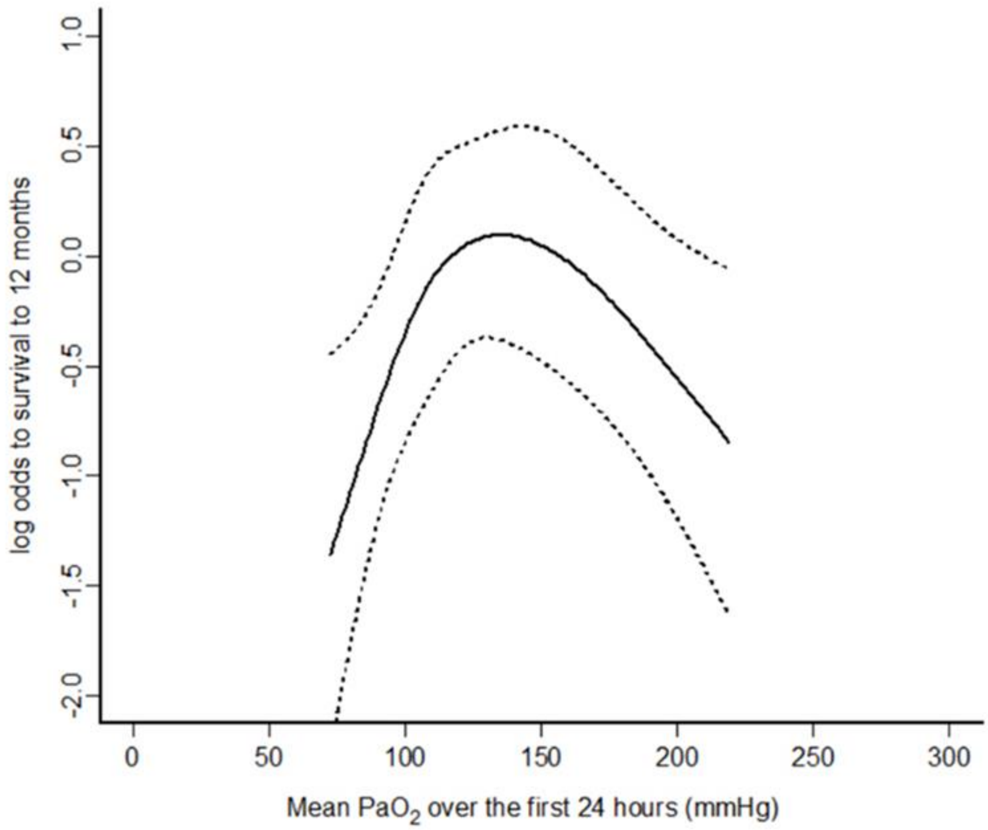


Fig. 3: Mean PaO_2 within the first 24-hours of ICU admission with log odds of survival to 12-months using RCS function. Dotted lines indicate 95 % CI.

Abbreviations indicate as follows: CI, confidence interval; ICU, intensive care unit; PaO_2, arterial oxygen tension; RCS, restricted cubic spline function.

Table 2. Logistic regression assessing the associations between the mean arterial oxygen tension (PaO2) within the *first 24-hours* of admission to the intensive care unit (ICU) – grouped as (a) normoxaemic (<100 mmHg), (b) mild to moderate hyperoxaemic (100-180 mmHg) and (c) severe hyperoxaemic (>180 mmHg) after out of hospital cardiac arrest and survival to hospital discharge or 12-months with stepwise adjustments for potential confounders (N=491). Mild to moderate hyperoxaemic (100-180 mmHg) was used as the reference group.

Confounders used for adjustment	Mean arterial oxygen tension within the first 24-hours after cardiac arrest in relation to survival	OR (95%CI) for survival to hospital discharge (n=231, 47.0%)	OR (95%CI) for survival to 12-months (n=224, 45.6%)
None	(a) mild to moderate hyperoxaemic	1 (reference)	1 (reference)
	(b) normoxaemic	0.43 (0.28-0.68)	0.40 (0.26-0.63)
	(c) severe hyperoxaemic	0.42 (0.21-0.84)	0.44 (0.22-0.88)
Age	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.47 (0.30-0.73)	0.43 (0.27-0.68)
	(c) severe hyperoxaemic	0.38 (0.19-0.77)	0.40 (0.20-0.81)

Age & sex	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.44 (0.28-0.70) 0.39 (0.19-0.79)	1 0.41 (0.25-0.64) 0.41 (0.20-0.84)
Age, sex, & witnessed arrest	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.43 (0.27-0.68) 0.39 (0.19-0.80)	1 0.40 (0.25-0.64) 0.41 (0.20-0.85)
Age, sex, witnessed arrest, & bystander CPR	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.42 (0.26-0.67) 0.37 (0.18-0.76)	1 0.39 (0.24-0.62) 0.39 (0.19-0.80)
Age, sex, witnessed arrest, bystander CPR & shockable first rhythm	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.47 (0.29-0.78) 0.44 (0.20-0.98)	1 0.43 (0.26-0.72) 0.47 (0.21-1.05)

Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, & EMS response time	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.48 (0.29-0.80) 0.43 (0.19-0.95)	1 0.44 (0.26-0.73) 0.45 (0.20-1.02)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, & time between EMS attendance and tertiary ICU admission	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.50 (0.30-0.83) 0.41 (0.18-0.91)	1 0.46 (0.27-0.77) 0.43 (0.19-0.98)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, & pre-cardiac arrest CPC score	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.50 (0.30-0.84) 0.41 (0.18-0.92)	1 0.46 (0.28-0.78) 0.43 (0.19-0.98)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score & STEMI	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.51 (0.30-0.84) 0.41 (0.18-0.93)	1 0.46 (0.28-0.78) 0.44 (0.19-1.00)

*Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score, STEMI & PCI	(a) mild to moderate	1[#]	1[##]
	hyperoxaemic	0.50 (0.30-0.84)	0.46 (0.27-0.77)
	(b) normoxaemic	0.41 (0.18-0.92)	0.43 (0.19-0.99)
	(c) severe hyperoxaemic		
	- age	0.98 (0.96-0.99)	0.98 (0.96-0.99)
	- sex (female)	0.62 (0.38-1.02)	0.59 (0.35-0.97)
	- witness arrest (paramedic	5.19 (2.05-13.14)	5.19 (2.01-13.41)
	witnessed vs unwitnessed)		
	- bystander CPR	1.99 (1.14-3.48)	2.30 (1.30-4.09)
	- shockable first rhythm	7.01 (4.15-11.83)	7.61 (4.44-13.04)
	- EMS response time (per min	0.92 (0.86-0.98)	0.91 (0.85-0.97)
	increment)	1.00 (1.00-1.00)	1.00 (1.00-1.00)
	- time between EMS		
	attendance and tertiary ICU	4.47 (0.37-53.62)	4.36 (0.34-55.28)
	admission		
	- category 1 pre-cardiac arrest	1.18 (0.63-2.20)	1.38 (0.73-2.59)
	CPC score	0.84 (0.47-1.49)	0.75 (0.42-1.34)

	(no disability vs with disability) - STEMI - PCI		

**The Hosmer-Lemeshow Chi-Square and Nagelkerke R2 for the final fully adjusted model for survival to hospital discharge were 5.816 (p=0.67~~68~~) and 0.35~~46~~, respectively. The Hosmer-Lemeshow Chi-Square and Nagelkerke R2 for the final fully adjusted model for survival to 12-months were 7.867 (p=0.45~~47~~) and 0.370, respectively. #The p-value for PaO2 modelled as a continuous variable, allowing non-linearity with a 4-knot restricted cubic spline function to predict hospital survival, was 0.006~~3~~; the p-value for shockable rhythm, witnessed arrest, age, sex, bystander CPR, EMS response time, EMS to ICU admission, pre-arrest CPC score, STEMI and PCI were <0.001~~01~~, <0.001~~08~~, 0.002~~16~~, 0.04~~30~~, 0.01~~46~~, 0.01~~13~~, 0.10~~06~~, 0.10~~00~~, 0.37~~01~~, 0.58~~35~~ and 0.61~~066~~. ##The p-value for PaO2 modelled as a continuous variable, allowing non-linearity with a 4-knot restricted cubic spline function to predict survival to 12-months, was 0.004~~37~~; the p-value for shockable rhythm, witnessed arrest, age, sex, bystander CPR, EMS response time, EMS to ICU admission, pre-arrest CPC score, STEMI and PCI were <0.001~~01~~, 0.001~~4~~, 0.003~~1~~, 0.027~~66~~, 0.004~~0~~, 0.008~~76~~, 0.06~~06~~, 0.46~~23~~, 0..30~~30~~ and 0.38~~770~~*

Abbreviations indicate as follows: CI, confidence interval; CPC, Cerebral Performance Category; CPR, Cardiopulmonary Resuscitation; EMS, Emergency Medical Services; ICU, intensive care unit; OR, odds ratio; PCI, percutaneous coronary intervention within the first 24-hours; STEMI, ST-segment elevation myocardial infarction.

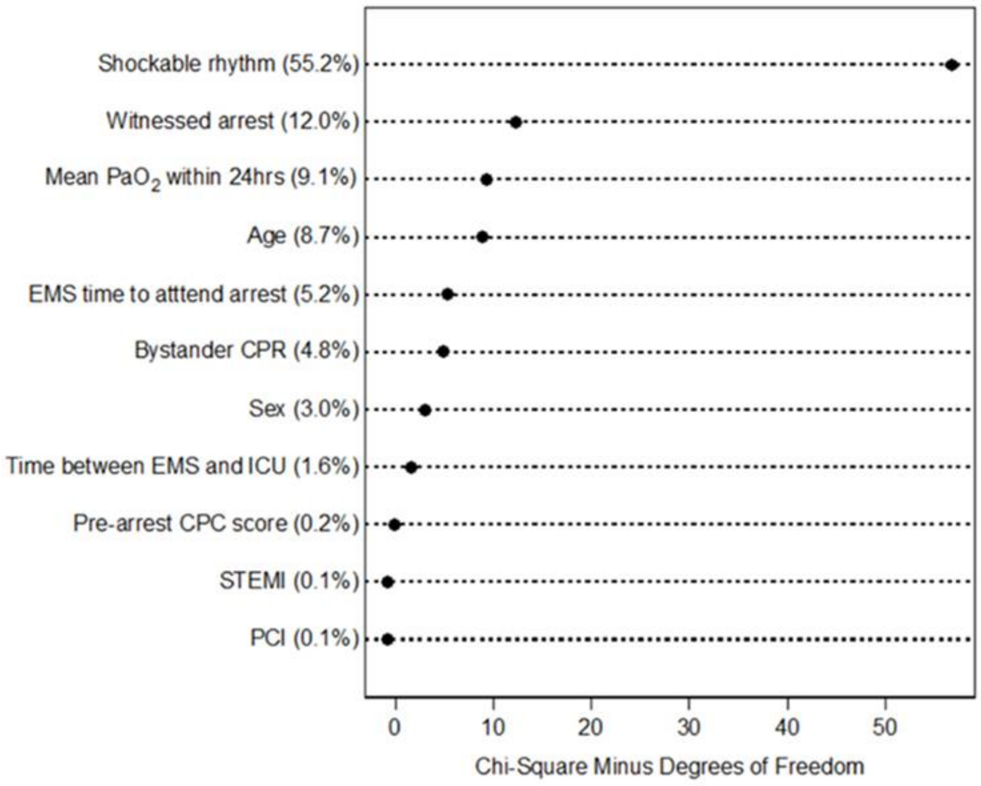


Fig. 4: Predictors of in-hospital mortality using mean PaO_2 within the first 24-hours of ICU admission.

Abbreviations indicate as follows: CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; EMS, emergency medical services; ICU, intensive care unit; PaO_2, arterial oxygen tension; PCI, percutaneous coronary intervention within the first 24-hours; STEMI, ST-elevation myocardial infarction; STHD, survival to hospital discharge.

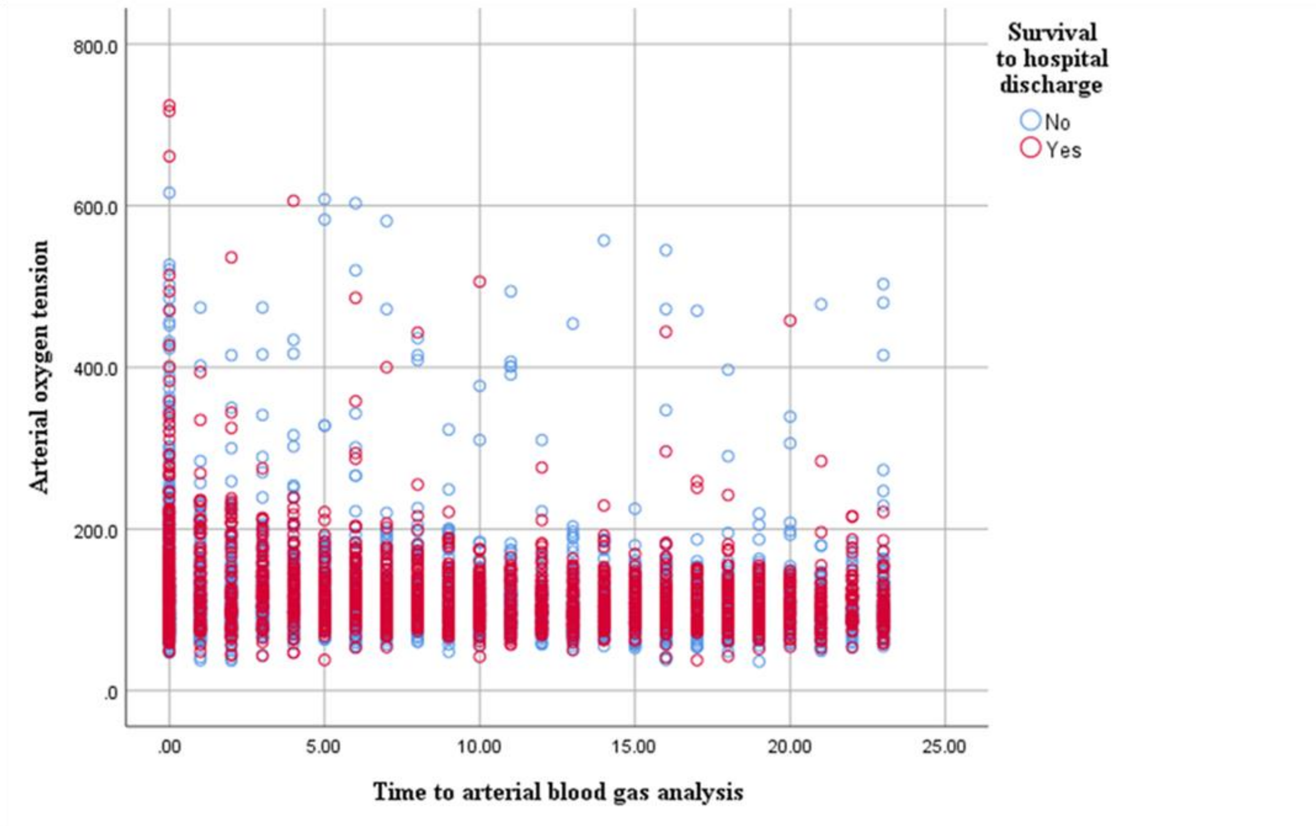
Supplementary Materials

Supplementary Text 1: Further information about adult tertiary hospitals in Perth, Western Australia (WA).

During the study period four adult tertiary hospitals (Royal Perth Hospital, Sir Charles Gairdner Hospital, Fremantle Hospital and Fiona Stanley Hospital) were operating in Perth, WA. Of these, two hospital ICUs had restricted operating periods. Fremantle Hospital ICU operated until February 2015 and Fiona Stanley Hospital ICU operated from February 2015 onwards.

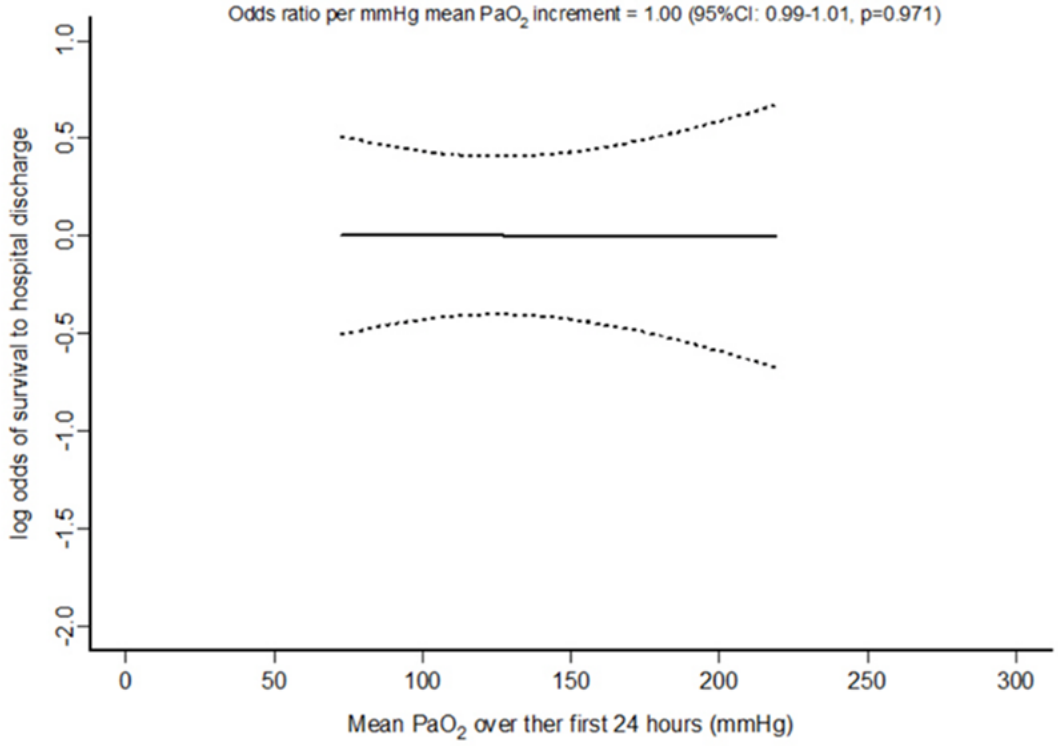
Supplementary Text 2: Further information about the statistical analysis.

As stated, we assessed the importance of mean PaO_2 relative to plausible physiological predictors in explaining the variability in the observed hospital mortality by each predictor's Chi Square contribution in a multivariable logistic regression. This is similar to the incremental contribution of each predictor to the area under the receiver operating characteristics curve, or c-index, of the final model. After confirming a non-linear inverted U-shaped relationship between the mean PaO_2 and survival, cut points were then identified visually, based on the shape of the spline curve, and used to generate corresponding odds ratios to facilitate clinical interpretation of this inverted U-shaped relationship. We then performed a stepwise forward logistic regression to confirm the robustness and consistency of the non-linear relationship between the mean PaO_2 and survival, after adjusting for plausible physiological predictors of survival after OHCA. In conducting the multivariable analyses, we also added two *a priori* defined predictors to other known predictors of survival after OHCA, whether the patients had a diagnosis of STEMI on arrival to the ED and received PCI within 24-hours of the EMS call.

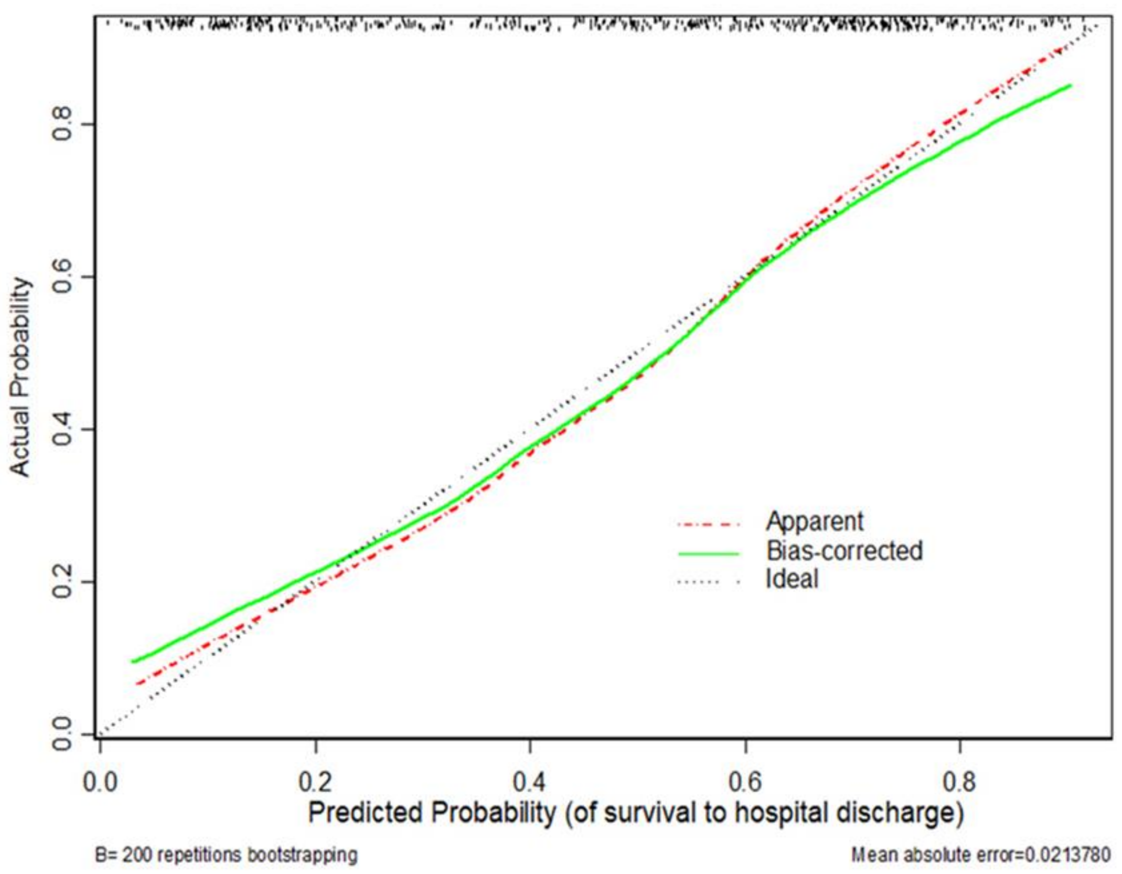


Supplementary Fig. 1: All individual PaO_2 values (mmHg) over the first 24-hours of ICU admission. Data are shown according to STHD.

Abbreviations indicate as follows: ICU, intensive care unit; PaO_2, arterial oxygen tension; STHD, survival to hospital discharge.

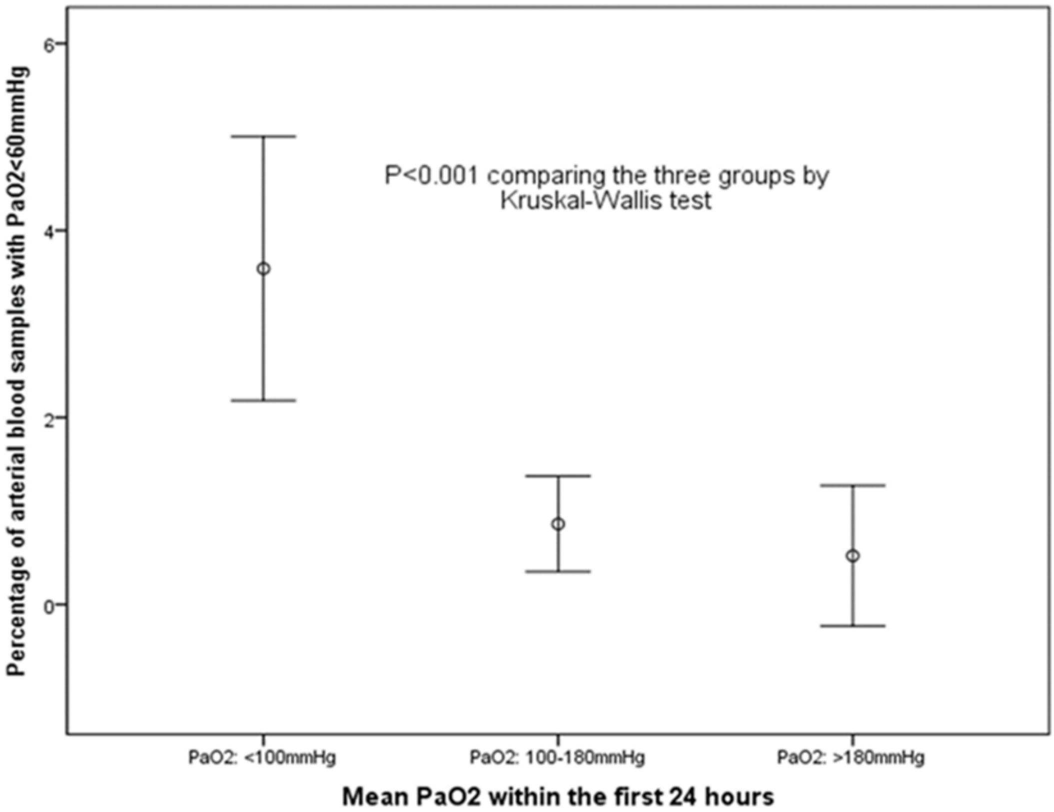


Supplementary Fig. 2: Mean PaO_2 within the first 24-hours of ICU admission with log odds of STHD adjusting for plausible physiological predictors of survival (listed in Table 2) without allowing non-linearity with a restricted cubic spline function for the mean PaO_2. Dotted lines indicate 95 % confidence intervals.



Supplementary Fig. 3: Calibration of the final multivariable model allowing non-linearity for the mean PaO_2 within the first 24-hours of admission after OHCA after adjusting for the plausible predictors of survival (listed in Table 2). The ideal calibration line is defined by the black dotted line, the apparent calibration line of the model is defined by the red dotted line and the bias-corrected (using bootstrapping sampling with 200 repetitions) is defined by the green continuous line. The distribution of the predicted chance of survival to hospital discharge of all patients is defined by the density of data points on the top of the graph.

Abbreviations indicate as follows: OHCA, out-of-hospital cardiac arrest; PaO_2, arterial oxygen tension.



Supplementary Fig. 4: Percentage of ABG samples and 95% CI with PaO_2 <60mmHg in the first 24-hours of ICU admission.

Abbreviations indicate as follows: ABG, arterial blood gas; CI, confidence interval; ICU, intensive care unit; PaO_2, arterial oxygen tension.

Supplementary Table 1: Demographic and OHCA characteristics of patients with OHCA of medical aetiology admitted to a tertiary hospital stratified by mean PaO_2 in the first 24-hours of ICU admission.

	Normoxaemic group (<100 mmHg)	**Mild to moderate hyperoxaemic group (100-180 mmHg)**	**Severe hyperoxaemic group (>180 mmHg)**	**p-values**
No. (%) of patients	**115 (23.4)**	**336 (68.4)**	**40 (8.1)**	
Mean PaO_2, mmHg	81.2 (11.95)	125.2 (19.6)	280.2 (110.2)	**<0.001**
Median (IQR) Age, years	64 (52-73)	59 (47-69)	53 (44-68)	**0.01**
Sex				
Male	87 (75.7)	238 (70.8)	26 (65.0)	0.39
Female	28 (24.3)	98 (29.2)	14 (35.0)	
Pre-arrest CPC score				
CPC 1 or 2	113 (98.3)	333 (99.1)	39 (97.5)	0.38
CPC 3	2 (1.7)	3 (0.9)	1 (2.5)	
Witnessed arrest				
Paramedic	16 (13.9)	24 (7.1)	3 (7.5)	0.25
Bystander	53 (46.1)	164 (48.8)	17 (42.5)	
Unwitnessed	46 (40.0)	148 (44.0)	20 (50.0)	
Bystander CPR	77 (67.0)	237 (70.5)	29 (72.5)	0.72
Initial arrest rhythm				
VF/VT	62 (53.9)	228 (67.9)	18 (45.0)	**0.001**
PEA/Asystole[*]	53 (46.1)	108 (32.1)	22 (55.0)	
Median (IQR) EMS response time, minutes[†]	8 (6-11)	8 (6-10)	8 (5-11)	0.23
Median (IQR) time to first ED, minutes[‡]	48 (38-56)	46 (38-53)	47 (37-56)	0.42

Median (IQR) time to tertiary ICU, minutes§	250 (196-321)	224 (172-281)	196 (163-253)	**0.01**
Direct transport patients (n=367)	224 (186-267)	211 (160-265)	179 (155-222)	0.20
Indirect transport patients (n=124)	327 (284-366)	274 (242-339)	251 (233-295)	0.21
ROSC on arrival to first ED	86 (74.8)	295 (87.8)	33 (82.5)	**0.004**
Place of intubation#				
Pre-hospital	50 (43.5)	137 (40.8)	15 (37.5)	**0.76**
ED	64 (55.7)	196 (58.3)	25 (62.5)	
Diagnosis of ACS at ED discharge	30 (26.1)	115 (34.2)	10 (25.0)	0.18
Diagnosis of STEMI at ED discharge	20 (17.4)	86 (25.6)	1 (2.5)	**0.002**
PCI (≤24-hours)‖	28 (24.3)	108 (32.1)	6 (15.0)	**0.04**
Duration of ICU stay (days)	2 (1-5)	3 (1-5)	2 (0-5)	0.67
TTM in ICU	85 (73.9)	289 (86.0)	25 (62.5)	**<0.001**
Inotropes in ICU	102 (88.7)	291 (86.6)	34 (85.0)	0.78

Data are presented as mean (standard deviation), median (interquartile range) or count (percentage)

* Includes 8 patients where 'Initial arrest rhythm' is unknown

† Time interval from EMS call to arrival on scene

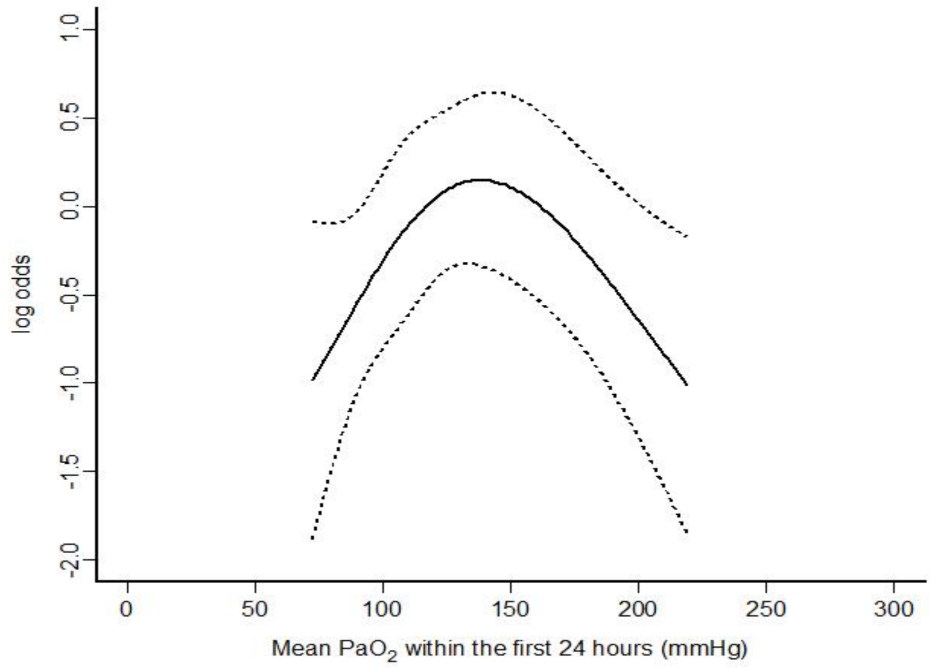
‡ Time interval from EMS call to arrival at first ED

§ Time interval from EMS call to arrival at a tertiary hospital ICU

‖ Time interval from EMS call to arrival in CCL

\# Excludes 3 patients intubated in CCL and one patient intubated in OR

Abbreviations indicate as follows: ACS, acute coronary syndrome; CCL, cardiac catheterization laboratory; CPC, cerebral performance category; CPR, cardiopulmonary resuscitation; ED, emergency department; EMS, emergency medical services; ICU, intensive care unit; PCI, percutaneous coronary intervention; PEA, pulseless electrical activity; ROSC, return of spontaneous circulation; STEMI, ST-elevation myocardial infarction; STHD, survival to hospital discharge; TTM, targeted temperature management; VF, ventricular fibrillation; VT, ventricular tachycardia.



Supplementary Fig. 5: The association between the mean PaO_2 within the first 24-hours after OHCA and odd of having a good CPC score - independent in activities of daily living - at hospital discharge. Contribution of each predictor including the non-linear component of the PaO_2 in the multivariable model is listed below the graph.

	Wald Statistics		
Factors	**Chi-Square**	**d.f.**	**P value**
Mean PaO_2 within 24hrs	12.03	3	0.007
Nonlinear	11.99	2	0.003
Age	6.07	1	0.014
Sex	0.88	1	0.35
Bystander CPR	6.71	1	0.01
Witnessed arrest	13.68	2	0.001
CPC score pre-arrest	1.95	2	0.38
Shockable	55.56	2	<0.001
EMS time	5.02	1	0.03
EMS to ICU time	4.01	1	0.05
STEMI	0.01	1	0.94
PCI	0.36	1	0.55
TOTAL	**97.78**	**16**	**<0.001**

Abbreviations indicate as follows: CPC, cerebral performance category, CPR, cardiopulmonary resuscitation. EMS, emergency medical services. ICU, intensive care unit. STEMI, ST-segment elevation myocardial infarction. PaO_2, arterial oxygen tension, PCI, percutaneous coronary intervention within the first 24-hours.

Supplementary Table 2. Logistic regression assessing the associations between the mean PaO_2 within the *first 48-hours* of admission to the ICU – grouped as (a) normoxaemic (<100 mmHg), (b) mild to moderate hyperoxaemic (100-180 mmHg) and (c) severe hyperoxaemic (>180 mmHg) after out of hospital cardiac arrest and survival to hospital discharge or 12-months with stepwise adjustments for potential confounders (N=491). Mild to moderate hyperoxaemic (100-180 mmHg) was used as the reference group.

Confounders used for adjustment	Mean arterial oxygen tension within the first 48-hours after cardiac arrest in relation to survival	OR (95%CI) for survival to hospital discharge (n=231, 47.0%)	OR (95%CI) for survival to 12-months (n=224, 45.6%)
None	(d) mild to moderate hyperoxaemic	1 (reference)	1 (reference)
	(e) normoxaemic	0.52 (0.35-0.78)	0.50 (0.34-0.75)
	(f) severe hyperoxaemic	0.28 (0.11-0.66)	0.29 (0.12-0.70)
Age	(d) mild to moderate hyperoxaemic	1	1
	(e) normoxaemic	0.56 (0.37-0.83)	0.53 (0.36-0.80)
	(f) severe hyperoxaemic	0.24 (0.10-0.60)	0.26 (0.11-0.63)
Age & sex	(d) mild to moderate hyperoxaemic	1	1

	(e) normoxaemic (f) severe hyperoxaemic	0.52 (0.35-0.60) 0.24 (0.10-0.60)	0.50 (0.33-0.76) 0.26 (0.11-0.64)
Age, sex, & witnessed arrest	(d) mild to moderate hyperoxaemic (e) normoxaemic (f) severe hyperoxaemic	1 0.51 (0.33-0.77) 0.24 (0.10-0.59)	1 0.49 (0.32-0.75) 0.26 (0.10-0.64)
Age, sex, witnessed arrest, & bystander CPR	(d) mild to moderate hyperoxaemic (e) normoxaemic (f) severe hyperoxaemic	1 0.50 (0.33-0.77) 0.25 (0.10-0.61)	1 0.49 (0.32-0.75) 0.27 (0.11-0.67)
Age, sex, witnessed arrest, bystander CPR & shockable first rhythm	(d) mild to moderate hyperoxaemic (e) normoxaemic (f) severe hyperoxaemic	1 0.52 (0.33-0.82) 0.27 (0.10-0.77)	1 0.50 (0.31-0.79) 0.30 (0.11-0.85)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, & EMS response time	(d) mild to moderate hyperoxaemic (e) normoxaemic (f) severe hyperoxaemic	1 0.55 (0.35-0.87) 0.29 (0.11-0.82)	1 0.53 (0.33-0.85) 0.33 (0.12-0.93)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, & time between EMS attendance and tertiary ICU admission	(d) mild to moderate hyperoxaemic (e) normoxaemic (f) severe hyperoxaemic	1 0.56 (0.35-0.88) 0.28 (0.10-0.77)	1 0.54 (0.34-0.87) 0.31 (0.11-0.87)

Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, & pre-cardiac arrest CPC score	(d) mild to moderate hyperoxaemic (e) normoxaemic (f) severe hyperoxaemic	1 0.56 (0.35-0.89) 0.28 (0.10-0.78)	1 0.55 (0.34-0.88) 0.31 (0.11-0.88)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score & STEMI	(d) mild to moderate hyperoxaemic (e) normoxaemic (f) severe hyperoxaemic	1 0.56 (0.35-0.89) 0.28 (0.10-0.79)	1 0.55 (0.34-0.87) 0.31 (0.11-0.88)
*Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score, STEMI & PCI	(d) mild to moderate hyperoxaemic (e) normoxaemic (f) severe hyperoxaemic	1 0.56 (0.35-0.89) 0.28 (0.10-0.79)	1 0.55 (0.34-0.88) 0.31 (0.11-0.89)

	- age	0.98 (0.96-0.99)	0.98 (0.96-0.99)
	- sex (female)	0.62 (0.38-1.01)	0.59 (0.35-0.97)
	- witness arrest (paramedic	5.27 (2.08-13.33)	5.22 (2.02-13.44)
	witnessed vs unwitnessed)		
	- bystander CPR	1.87 (1.07-3.27)	2.16 (1.22-3.83)
	- shockable first rhythm	7.05 (4.18-11.91)	7.67 (4.48-13.15)
	- EMS response time (per min	0.93 (0.87-0.99)	0.92 (0.86-0.98)
	increment)	1.00 (0.99-1.00)	0.99 (0.99-1.00)
	- time between EMS attendance		
	and tertiary ICU admission	4.67 (0.38-58.02)	4.61 (0.35-60.64)
	- category 1 pre-cardiac arrest		
	CPC score	1.20 (0.63-2.24)	1.39 (0.74-2.62)
	(no disability vs with	0.93 (0.52-1.65)	0.83 (0.46-1.49)
	disability)		
	- STEMI		
	- PCI		

**The Hosmer-Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to hospital discharge were 6.644 (p=0.58~~75~~) and 0.348, respectively.*

The Hosmer-Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to 12-months were 7.135 (p=0.52~~2~~) and 0.369, respectively.

Abbreviations indicate as follows: CI, confidence interval; CPC, Cerebral Performance Category; CPR, Cardiopulmonary Resuscitation; EMS, Emergency Medical Services; OR, odds ratio; PCI, percutaneous coronary intervention within the first 24-hours; STEMI, ST-segment elevation myocardial infarction.

Supplementary Table 3. Logistic regression assessing the associations between the mean PaO_2 within the *first 72- hours* of admission to the ICU – grouped as (a) normoxaemic (<100 mmHg), (b) mild to moderate hyperoxaemic (100-180 mmHg) and (c) severe hyperoxaemic (>180 mmHg) after OHCA and STHD or 12-months with stepwise adjustments for potential confounders (N=491). Mild to moderate hyperoxaemic (100-180 mmHg) was used as the reference group.

Confounders used for adjustment	**Mean arterial oxygen tension within the first 72-hours after cardiac arrest in relation to survival**	**OR (95%CI) for survival to hospital discharge (n=231, 47.0%)**	**OR (95%CI) for survival to 12-months (n=224, 45.6%)**
None	(a) mild to moderate hyperoxaemic	1 (reference)	1 (reference)
	(b) normoxaemic	0.61 (0.41-0.90)	0.59 (0.40-0.88)
	(c) severe hyperoxaemic	0.19 (0.10-0.52)	0.20 (0.10-0.55)
Age	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.66 (0.44-0.98)	0.64 (0.43-0.95)
	(c) severe hyperoxaemic	0.17 (0.10-0.47)	0.18 (0.10-0.50)
Age & sex	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.62 (0.42-0.93)	0.60 (0.40-0.90)

	(c) severe hyperoxaemic	0.17 (0.10-0.48)	0.18 (0.10-0.51)
Age, sex, & witnessed arrest	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.58 (0.39-0.88)	0.58 (0.38-0.87)
	(c) severe hyperoxaemic	0.17 (0.10-0.46)	0.18 (0.10-0.50)
Age, sex, witnessed arrest, & bystander CPR	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.57 (0.38-0.87)	0.57 (0.37-0.86)
	(c) severe hyperoxaemic	0.17 (0.10-0.48)	0.19 (0.10-0.53)
Age, sex, witnessed arrest, bystander CPR & shockable first rhythm	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.61 (0.39-0.95)	0.60 (0.38-0.94)
	(c) severe hyperoxaemic	0.20 (0.10-0.65)	0.22 (0.10-0.72)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, & EMS response time	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.63 (0.40-0.99)	0.63 (0.40-0.99)
	(c) severe hyperoxaemic	0.21 (0.10-0.99)	0.24 (0.10-0.77)
Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, & time between EMS attendance and tertiary ICU admission	(a) mild to moderate hyperoxaemic	1	1
	(b) normoxaemic	0.65 (0.41-1.03)	0.65 (0.41-1.03)
	(c) severe hyperoxaemic	0.19 (0.10-0.63)	0.21 (0.10-0.70)

Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, & pre-cardiac arrest CPC score	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.65 (0.41-1.04) 0.19 (0.10-0.63)	1 0.65 (0.41-1.04) 0.21 (0.10-0.70)

Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score & STEMI	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1 0.66 (0.41-1.04) 0.19 (0.10-0.63)	1 0.65 (0.41-1.04) 0.21 (0.10-0.71)
*Age, sex, witnessed arrest, bystander CPR, shockable first rhythm, EMS response time, time between EMS attendance and tertiary ICU admission, pre-cardiac arrest CPC score, STEMI & PCI	(a) mild to moderate hyperoxaemic (b) normoxaemic (c) severe hyperoxaemic	1[#] 0.66 (0.42-1.04) 0.19 (0.10-0.64)	1[##] 0.66 (0.41-1.05) 0.22 (0.10-0.71)
	- age - sex (female) - witness arrest (paramedic witnessed vs unwitnessed) - bystander CPR - shockable first rhythm - EMS response time (per min increment)	0.98 (0.96-0.99) 0.63 (0.38-1.03) 5.79 (2.28-14.69) 1.89 (1.01-3.32) 7.04 (4.17-11.88) 0.92 (0.87-0.98) 0.99 (0.99-1.00)	0.98 (0.96-0.99) 0.60 (0.36-0.99) 5.74 (2.23-14.82) 2.18 (1.23-3.88) 7.69 (4.49-13.15) 0.91 (0.86-0.97) 0.99 (0.99-1.00)

	- time between EMS attendance and tertiary ICU admission	5.02 (0.40-63.40)	4.93 (0.37-66.73)
	- category 1 pre-cardiac arrest CPC	1.18 (0.63-2.21)	1.38 (0.73-2.60)
	score	0.92 (0.52-1.64)	0.83 (0.46-1.48)
	(no disability vs with disability)		
	- STEMI		
	- PCI		

**The Hosmer-Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to hospital discharge were 13.208 (p=0.1105) and 0.349, respectively. The Hosmer-Lemeshow Chi-Square and Nagelkerke R^2 for the final fully adjusted model for survival to 12-months were 10.408 (p=0.2438) and 0.369, respectively.*

Abbreviations indicate as follows: CI, confidence interval; CPC, Cerebral Performance Category; CPR, Cardiopulmonary Resuscitation; EMS, Emergency Medical Services; OR, odds ratio; PCI, percutaneous coronary intervention within the first 24-hours; STEMI, ST-segment elevation myocardial infarction.