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Clinical paper

Effects of very early hyperoxemia on neurologic outcome after out-of-hospital cardiac arrest: A secondary analysis of the TTM-2 trial

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ABSTRACT

Purpose: Hyperoxemia is common in patients resuscitated after out-of-hospital cardiac arrest (OHCA) admitted to the intensive care unit (ICU) and may increase the risk of mortality. However, the effect of hyperoxemia on functional outcome, specifically related to the timing of exposure to hyperoxemia, remains unclear.
Methods: The secondary analysis of the Target Temperature Management 2 (TTM-2) randomized trial. The primary aim was to identify the best cut-off of partial arterial pressure of oxygen (PaO_2) to predict poor functional outcome within the first 24 h from admission, with this period further separated into 'very early' (0–4 h), 'early' (8–24 h), and 'late' (28–72 h) periods. Hyperoxemia was defined as the highest PaO_2 recorded during each period. Poor functional outcome was defined as a 6 months modified Rankin Score (mRS) of 4 to 6.
Results: A total of 1,631 patients were analysed for the 'very early' and 'early' periods, and 1,591 in the 'late period'. In a multivariate logistic regression model, a PaO_2 above 245 mmHg during the very early phase was independently associated with a higher probability of poor functional outcome (Odds Ratio, OR = 1.63, 95 % Confidence Interval, CI 1.08–2.44, p = 0.019). No significant associations were found for the later periods.
Conclusions: Very early hyperoxemia after ICU admission is associated with higher risk of poor functional outcome after OHCA. Avoiding hyperoxia in the initial hours after resuscitation should be considered.

Introduction

Over the past decade, several randomized controlled trials (RCTs) have evaluated different oxygenation strategies for patients admitted to the intensive care unit (ICU) [1–6]. Overall, it remains unproven whether restrictive strategies perform better than more liberal strategies in oxygen administration [7].

Hyperoxemia linked to adverse outcomes has been reported across various populations and clinical scenarios, including myocardial infarction, stroke, traumatic brain injury, sepsis, veno-arterial extracorporeal membrane oxygenation, and critically ill children [8–13]. In retrospective studies examining the impact of severe hyperoxemia, this condition is usually defined as a partial arterial pressure of oxygen (PaO_2) above 300 mmHg, though sometimes a 200 mmHg cut-off is also used [13]. However, high-quality prospective data defining the precise level of hyperoxemia that causes patient harm are currently lacking [14].

Notably, certain populations may be more susceptible to hyperoxemia-driven cell damage. Additionally, in some clinical scenarios, the injury related to hyperoxemia may be time-dependent, with variable upper limits of PaO_2 associated with worse outcomes at different time points. Patients resuscitated from cardiac arrest (CA) are an archetypal example of this phenomenon. Indeed, the ischemia–reperfusion insult triggers several processes contributing to neuronal death, including protein synthesis inhibition, release of excitatory amino acids, cellular energetic failure and oxidative stress. Oxidative stress leads to significant production of oxygen radicals, which can be further exacerbated by elevated PaO_2 levels, intensifying oxidative damage in the brain [15,16].

Very limited evidence with a high risk of confounding factors has linked exposure to very high PaO_2 levels (severe hyperoxemia) with worse outcomes in ICU patients [17]. The Target Temperature management 2 (TTM-2) trial was an international, multicentre RCT which compared the effects of normothermia (temperature $\leq$ 37.5 °C), versus hypothermia (target 33 °C until 28 h after randomization, followed by rewarming to 37 °C) [18]. In a previous secondary analysis of TTM-2 trial data, we identified the best cut-offs associated with 6-month mortality during the whole ICU stay: $PaO_2 < 69$ mmHg (Risk Ratio (RR) of 1.009, 95 % Confidence Interval (CI) 0.93–1.09) and $PaO_2 > 195$ mmHg (RR of 1.006, 95 % CI 0.95–1.06)[19].

We conducted a secondary analysis of the TTM-2 trial, aimed to address the current uncertainty about the effect of timing, as prior studies are generally limited in their ability to do this, using a structured neuro-prognostic assessment that occurred in TTM-2 [19]. We separated the first 72 h after ICU admission in very early (0–4 h), early (8–24 h) and late (28–72 h) periods, according to the defined protocol timing of arterial blood gas analysis (ABG) (see TTM-2 study protocol [20] and according to previous literature [17]). We hypothesised that exposure to hyperoxemia is more harmful in the initial hours following CA and that it is independently associated with poor functional outcome.

Materials and Methods

Data management and collection

This secondary analysis was conducted according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (Supplementary Data). Ethical approval was obtained in the coordinating centre and each participating centre, as well as informed consent according to local regulations. This study was conducted in accordance with the principles of the Declaration of Helsinki, and the Medical Research Involving Human Subjects Act (WMO) and was approved by the TTM-2 steering committee. No further ethical approval was necessary for the development of this study.

The details of the study protocol and clinical management of patients have been comprehensively outlined previously [20]. Ventilatory management followed the local practices at each participating centre. Data on patients were systematically collected at several time points: upon hospital admission, throughout their stay in the ICU, at ICU discharge, at hospital discharge, and during a 6-month follow-up period. These data encompassed a range of parameters, including patients' demographics, pre-existing comorbidities (assessed using the Charlson Comorbidity Index), and specifics of the CA (location, timing, type, and management, such as: onsite bystander cardiopulmonary resuscitation (CPR), time of return of spontaneous circulation (ROSC), out-of-hospital location of CA, initial cardiac rhythm, witnessed CA), as well as clinical presentation (the presence of shock at admission, ST-elevation myocardial infarction (STEMI)), detailed ventilatory settings, and clinical outcomes. STEMI was defined as a new ST-segment elevation $\geq$ 1 mm in $\geq$ 2 contiguous ECG leads. Shock on admission was defined as blood pressure (BP) < 90 mmHg for at least 30 min or the need for supportive measures to maintain a systolic $\geq$ 90 mmHg and end-organ hypoperfusion (cool extremities, or urine output of less than 30 ml/hr, and a HR > 60 beats per minute). Additionally, ABG values, such as PaO_2, were obtained every 4 h for the first 32 h, and then, every 8 h until day 3 (72 h). This implies that the observed PaO_2 values were not continuous, with missing information between successive ABG measurements. For purpose of this study, we identified the peak (maximum) PaO_2 value for each period, defined as the highest observed value during each time frame. Specifically, the maximum PaO_2 for the 'very early' period was taken from the values observed at 0 and 4 h. For the 'early' period, the peak PaO_2 was the highest value recorded at 8, 12, 16, 20, or

24 h. Similarly, the maximum PaO_2 for the 'late' period was the highest value noted at 28, 32, 40, 48, 56, 64, or 72 h.

Objectives and definitions

The primary aim of this study was to determine the optimal PaO_2 cut-offs related to 6 months poor functional outcome by analysing distinct periods within the first 72 h post-cardiac arrest: the first day, further separated into the very early (0–4 h) and early (8–24 h), and the subsequent period defined as late (28–72 h). Such separation was chosen according to results from available literature [13,17] and the design of data collection of the TTM-2 trial, which occurred every 4 h from admission [18].

The secondary aim was to evaluate the effect of timing of hyperoxemia according to the presence of pre-CA cardiovascular comorbidities, which were defined as the presence of at least one of the following conditions: hypertension, myocardial infarction, percutaneous coronary intervention, coronary artery bypass graft surgery, or heart failure. We hypothesised that patients with cardiovascular comorbidities could be more vulnerable to the pathological effects of hyperoxemia.

Clinical outcome measures

The primary clinical outcome was the patients' functional outcome at 6-month follow-up evaluated through the Modified Rankin Scale (mRS). The mRS score for neurologic disability is a 7-category scoring system, ranging from no symptoms (score 0) to patient's death (score 6), where poor functional outcome is defined as a mRS score ranging from 4 to 6.

A trained outcome assessor used a structured questionnaire to evaluate the patient's condition. The functional score was determined after face-to-face or telephone interviews with patients, relatives, and health care providers.

Statistical analysis

Data on patients' characteristics are presented as medians [interquartile range (IQR)] for continuous variables, or as percentages for categorical variables. The comparisons of medians and frequencies among the two independent categories were carried out using U Mann-Whitney test (numerical data) or Chi-square test (categorical data), respectively. The relative distribution analysis was used to determine the cut-off point along the continuum of the PaO_2 that separated good and poor functional outcome at the end of the follow-up. The relative distribution is non-parametric approach to visualize and analyse differences or changes in distributions[21,22]. In that approach, the values of one group are expressed as positions in the distribution of the other group, which provides an analysis of the distribution of these "relative ranks". In our analysis, the quantile (proportion) distribution of the marker for patients with good functional outcome (plotted on the x-axis plus the corresponding marker values at the top) was plotted against the proportion ratio of the marker distribution for patients with poor functional outcome. The comparison of clinical characteristics between groups, determined based on the best cut-off of the peak PaO_2 values, was tested using contingency table or Kruskal-Wallis ANOVA test. Univariate logistic regression analysis was performed to evaluate factors associated with functional outcome. The following clinical factors were considered: age, sex, body mass index (BMI), Charlson comorbidity index, state of shock at admission, STEMI, specifics of the CA and the determined cut-offs of the peak PaO_2. From this initial set of covariates, a final model was developed by backward elimination in multivariate logistic regression. The results of logistic regression were reported as odds ratios (OR) with corresponding 95 % confidence intervals (CI). The R statistical language (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. www.R-project.org/version 3.3.3) [23], STATISTICA 13 (Tibco, Palo Alto, USA) and STATA SE v. 18 (STATA Corporation, Texas, USA) and were used to perform the statistical analysis. The level of significance was set as 0.05.

Results

Characteristics of the patients

From the 1,861 patients enrolled in the TTM-2 trial, we conducted separate analyses for different periods according to data availability. Table 1 presents patients' clinical characteristics according to the periods observed.

For the analysis of the first day after ICU admission (covering the very early and the early periods), 1631 patients were included (230 patients were excluded for missing data). The median age was 65 [Q1-Q3: 55–73] years, and 326 (20 %) were female. At 6-month follow-up, 770 (47 %) patients were dead, and a total of 841 (52 %) had poor functional outcome (mRS 4–6). For the late period analysis, 1,591 patients were included (270 patients were excluded for missing data). The median age was 65 [Q1-Q3: 55–73] years, and 308 (19 %) were female. At 6-month follow-up, 712 (45 %) patients were dead, and a total of 787 (49 %) had poor functional outcome.

Table 1
Clinical patients' characteristics, comorbidities, pre-hospital settings/interventions for the early period analysis (covering periods 0–24 h and 28–72 h) and late periods. Data are presented as median (upper quartile-lower quartile) or as number of observations (% of the group).

	0–24 h (very early, early) n = 1631	28–72 h (late) n = 1591
Age, years, *median (Q1-Q3)*	65 (55–73)	65 (55–73)
Gender, female, *n (%)*	326 (20 %)	308 (19 %)
Height, cm, *median (*Q1-Q3*)*	175 (170–180)	175 (170–180)
Weight, kg, *median (*Q1-Q3*)*	80 (73–92)	81 (75–92)
BMI, kg/m^2, *median (*Q1-Q3*)*	26.5 (24.2–30.1)	26.6 (24.2—30.1)
Hypertension, *n (%)*	580 (36 %)	555 (35 %)
Diabetes mellitus, *n (%)*	302 (19 %)	291 (18 %)
Myocardial infarction,*n (%)*	258 (16 %)	256 (16 %)
Percutaneous coronary intervention, *n (%)*	237 (15 %)	237 (15 %)
Coronary artery bypass graft, *n (%)*	135 (8 %)	129 (8 %)
Heart failure, *n (%)*	160 (10 %)	157 (10 %)
Charlson comorbidity index, *median (*Q1-Q3*)*	3.0 (1.0–4.0)	3.0 (1.0–4.0)
Location of cardiac arrest, *n (%)*		
Home	844 (52 %)	819 (51 %)
Public place	589 (36 %)	581 (37 %)
Other	198 (12 %)	191 (12 %)
Witnessed cardiac arrest, *n (%)*	1490 (91 %)	1456 (92 %)
Bystander performed CPR,*n (%)*	1320 (81 %)	1291 (81 %)
Type of rhythm, *n (%)*		
Not shockable	406 (25 %)	383 (24 %)
Shockable	1225 (75 %)	1208 (76 %)
Time to ROSC, minutes, *median (*Q1-Q3*)*	25.0 (16.0–38.0)	25.0 (16.0–38.0)
TTM-2 randomization treatment, *n (%)*		
Normothermia	819 (50 %)	797 (50 %)
Hypothermia	812 (50 %)	794 (50 %)
Functional outcome after 6 months, *n (%)*		
Poor (4–6)	841 (52 %)	787 (49 %)
Good (0–3)	790 (48 %)	804 (51 %)
Mortality after 6 months, *n (%)*		
Non-survivors	770 (47 %)	712 (45 %)
Survivors	861 (53 %)	879 (55 %)

Abbreviations: BMI, body mass index, ROSC, return of spontaneous circulation, CPR, cardio-pulmonary resuscitation, TTM-2, target temperature management.

Very early period (within 4 h from admission)

Distribution of very early peak PaO_2

Median values of very early peak PaO_2 are presented in Fig. 1A. The number of patients with very early peak PaO_2 measured at admission (n = 794; 49 %) was not significantly different from those measured 4 h later (n = 837; 51 %). However, patients experiencing peak PaO_2 at admission had significantly higher PaO_2 (137 ± 120 mmHg) as compared to those with peak at 4 h after ICU admission (113 ± 55 mmHg, $p < 0.001$, Fig. 1D).

Very early peak PaO_2 best thresholds and association with poor functional outcome

Fig. 2A shows the thresholds of very early peak PaO_2 for predicting poor functional outcome. The lower limit was 131 mmHg (RR = 1.00, 95 %CI 0.840–1.151) and the upper limit was 245 mmHg (RR = 0.99, 95 %CI 0.842–1.145). In the cohort, 903 (55 %) had a very early peak $PaO_2 < 131$ mmHg, where 54 % had poor outcome and 51 % dead. 183 (12 %) of the cohort had a very early peak $PaO_2 > 245$ mmHg, where 57 % had poor outcome and 54 % dead. The characteristics of patients based on these cut-offs are presented in Table 2. There was a significant association between very early peak PaO_2 outside the specified lower (<131 mmHg; OR = 1.43; 95 %CI 1.16–1.77; p = 0.001) and upper (>245 mmHg; OR = 1.59; 95 %CI 1.13–2.23; p = 0.007) limits and poor functional outcome, Fig. 3A. Univariate logistic regression analysis, including clinical co-factors, is detailed in Sup. Table S1. The relationship between mRS scores and the defined cut-offs is presented in Supplementary Figure 1. In the contingency table, a significant relationship was found between mRS scores and very early hypoxia/normoxia/ hyperoxia, both when assessed as dichotomised categories (good and poor) ($p < 0.001$) and as separate grades ($p < 0.001$). In the adjusted multivariate logistic regression model for poor functional outcomes ($p < 0.001$), $PaO_2 > 245$ mmHg in the very early phase remained independently associated with poor outcome (OR = 1.63, 95 %CI 1.08–2.44, p = 0.019) (Fig. 3B). Detailed results of the adjusted analysis are presented in Table 3.

Very early peak PaO_2 thresholds vs cardiac comorbidities

We found that of 1557 patients available for the analysis (missing data in 74 cases), 50 % of them had cardiac comorbidities. Detailed results of the analysis of the impact of cardiac comorbidities on the very early peak PaO_2 thresholds are presented in the Supplementary Data (Supplementary Figure 2A and Supplementary Figure S4). The results of the univariate and multivariate logistic regression analysis to predict poor outcome at a very early period in patients with cardiac comorbidities are presented in Sup. Table S2 and Table S3, respectively.

Early period (8–24 h)

Median peak PaO_2 values during the early period are presented in Fig. 1B. Early peak PaO_2 was most commonly observed at 8 h (n = 652, 40 %) and 12 h (n = 342, 21 %), with fewer occurrences at later timepoints: 16 h (n = 250, 15 %), 20 h (n = 180, 11 %), and 24 h (n = 207,

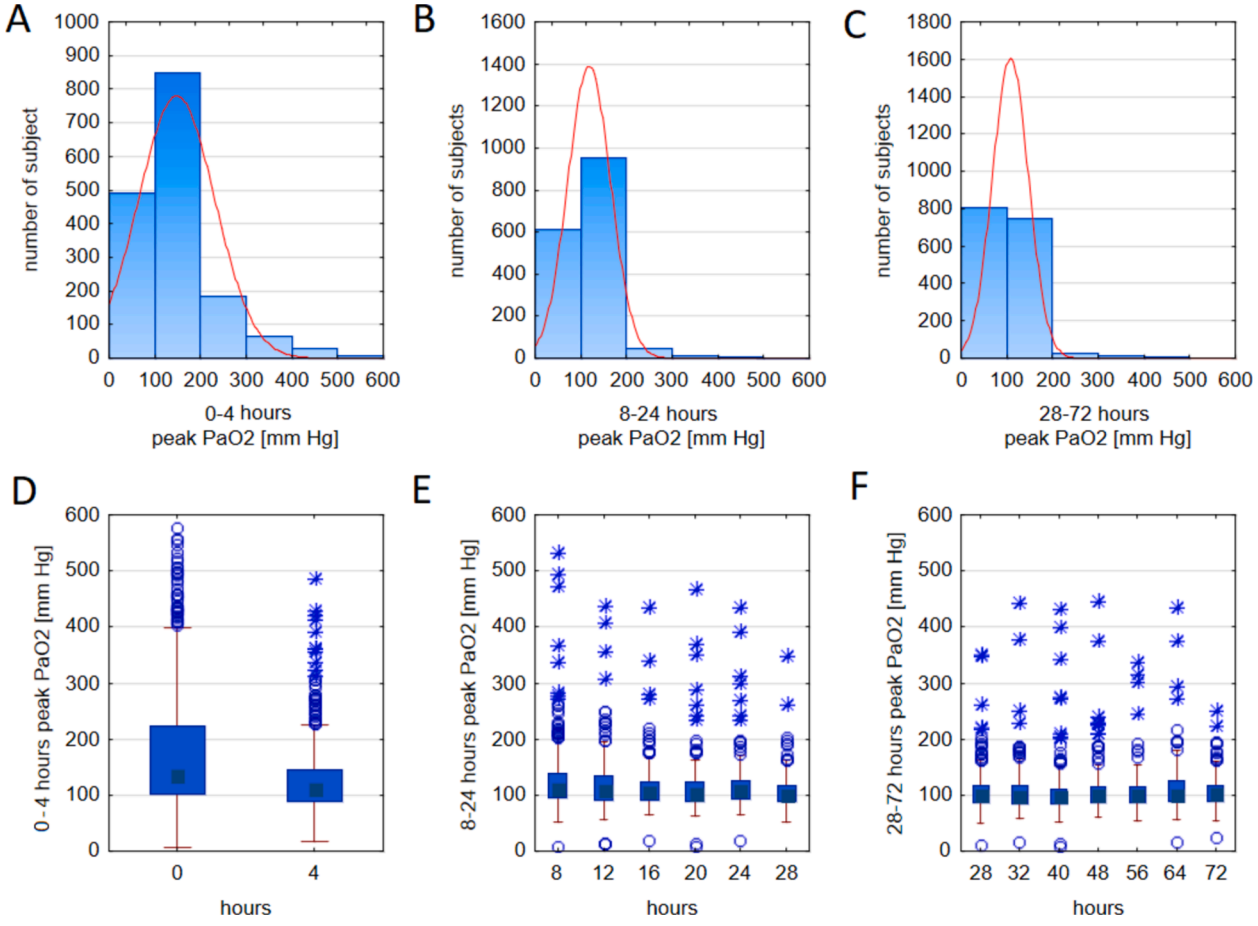

Fig. 1. The distribution of peak PaO_2 values is shown for three time intervals: A) 0–4 h, B) 8–24 h, and C) 28–72 h. Comparisons of peak PaO_2 values within these intervals are presented in D) 0–4 h, E) 8–24 h, and F) 28–72 h, considering the timing of their occurrence. Data are presented as medians with interquartile ranges, with outliers marked as circles and extreme values indicated by asterisks.

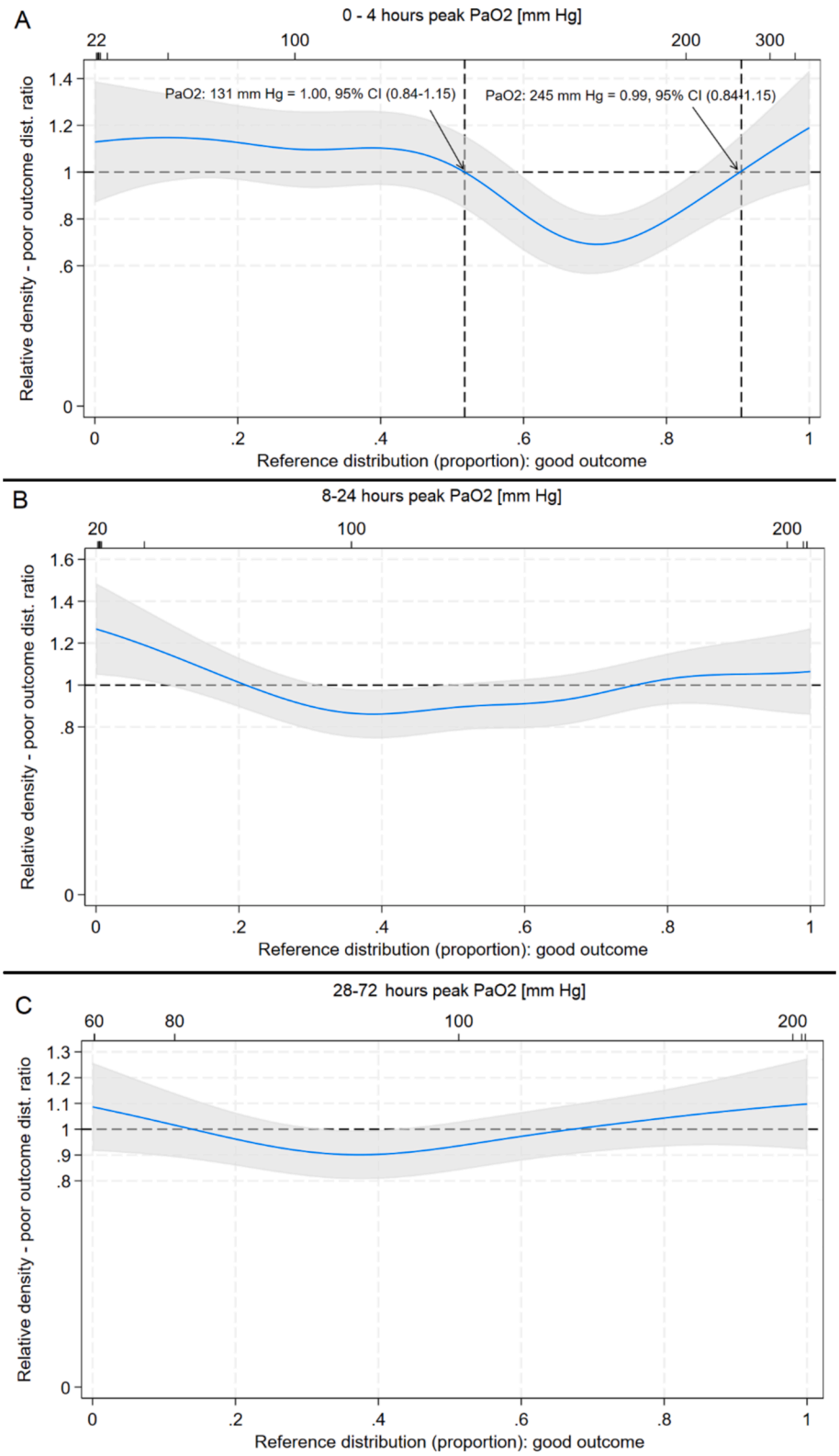

Fig. 2. Relative distribution analysis for the definition of the best cut-off A) 0–4 h B) 8–24 h C) 28–72 h peak of arterial pressure of oxygen (PaO_2) associated with poor functional outcome in modified Rankin scale. In this analysis, the quantile distribution of the peak of PaO_2 patients with good outcome (plotted on the OX axis with reference value in [mm Hg] presented on the top) is plotted against the proportion ratio of the peak of PaO_2 distribution for poor outcome. Therefore, the best cut-off, along a continuum of the peak of PaO_2 that separates good and poor outcome is obtained.

Table 2
Baseline patients' characteristics, comorbidities, pre-hospital settings/interventions in the patients stratified according to the new oxygen cut-offs in the 0–4 h after cardiac arrest for functional outcome prediction. Data are presented as median (upper quartile-lower quartile) or as number of observations (% of the group).

	PaO_2 < 131 mmHg (n = 903,55 %)	PaO_2 131–245 mmHg (n = 545, 33 %)	PaO_2 > 245 mmHg (n = 183,12 %)	p-value
Age, years, *median (Q1-Q3)*	66 (57–73)	63 (54–73)	63 (53–73)	**0.014**
Gender, female, *n (%)*	170 (19 %)	99 (18 %)	57 (32 %)	**<0.001**
Height, cm, *median (Q1-Q3)*	175 (170–180)	175 (170–180)	175 (165–180)	**<0.001**
Weight, kg, *median (Q1-Q3)*	83 (75–95)	80 (73–90)	77 (69–88)	**<0.001**
BMI, kg/m^2, *median (Q1-Q3)*	27.1 (24.7–30.8)	26.1 (23.9–29.4)	25.9 (23.1–28.7)	**<0.001**
Hypertension, *n (%)*	341 (37 %)	183 (34 %)	56 (30 %)	0.186
Diabetes mellitus, *n (%)*	191 (21 %)	77 (14 %)	34 (19 %)	**0.004**
Myocardial infarction, *n (%)*	163 (18 %)	68 (12 %)	27 (15 %)	**0.043**
Percutaneous coronary intervention, *n (%)*	145 (16 %)	66 (12 %)	26 (14 %)	0.186
Coronary artery bypass graft, *n (%)*	80 (9 %)	41 (7 %)	14 (8 %)	0.553
Heart failure, *n (%)*	103 (11 %)	42 (8 %)	15 (8 %)	0.103
Charlson comorbidity index, points, *median (Q1-Q3)*	3.0 (2.0–4.0)	2.0 (1.0–4.0)	3.0 (1.0–4.0)	**<0.001**
Location of cardiac arrest, *n (%)*				
Home	463 (51 %)	279 (51 %)	102 (56 %)	0.824
Public place	327 (36 %)	200 (37 %)	62 (34 %)	
Other	113 (13 %)	66 (12 %)	19 (10 %)	
Witnessed cardiac arrest, *n (%)*	828 (92 %)	493 (90 %)	169 (92 %)	0.633
Bystander performed CPR, *n (%)*	746 (83 %)	430 (79 %)	144 (79 %)	0.156
Type of rhythm, *n (%)*				
Not shockable	235 (26 %)	124 (23 %)	47 (26 %)	0.365
Shockable	668 (74 %)	421 (77 %)	136 (74 %)	
Time to ROSC, minutes, *median (Q1-Q3)*	26.0 (17.0–40.0)	25.0 (16.0–35.0)	25.0 (15.0–35.0)	**0.004**
TTM-2 randomization treatment, *n (%)*				
Normothermia	440 (49 %)	290 (53 %)	89 (49 %)	0.229
Hypothermia	463 (51 %)	255 (47 %)	94 (51 %)	
Functional outcome after 6 months, *n (%)*				
poor (mRS 4–6)	490 (54 %)	247 (45 %)	104 (57 %)	**0.001**
good (mRS 0–3)	413 (46 %)	298 (55 %)	70 (43 %)	
Mortality after 6 months, *n (%)*				
Non-survivors	456 (51 %)	216 (40 %)	98 (54 %)	**<0.001**
Survivors	447 (49 %)	329 (60 %)	85 (46 %)	

Abbreviations: BMI, body mass index, ROSC, return of spontaneous circulation, CPR, cardio-pulmonary resuscitation, TTM-2, target temperature management.

13 %), p < 0.001. A significant difference was noted in early peak PaO_2 across different observation times (p = 0.001), as shown in Fig. 1E.

We did not observe an association between median PaO_2 change during the early period and neurological outcome at six months. Consequently, we were not able to determine optimal cut-off points for predicting functional outcome, as presented in Fig. 2B. Moreover, no differences were observed in the trajectories of early peak PaO_2 values between patients with poor and good functional outcomes, regardless of the presence or absence of cardiac comorbidities, see Supplementary Figure 2B and Supplementary Figure 3B.

Late period (24–72 h)

Median values of late peak PaO_2 are presented in Fig. 1C. Late peak PaO_2 was most frequently observed at 28 h (n = 356, 22 %) and 32 h (n = 265, 17 %). A significant difference was found in late peak PaO_2 concerning the time of its observation (p < 0.001), as shown in Fig. 1F.

No differences were observed in the trajectories of late PaO_2 values between patients experiencing poor or good functional outcome, as shown in Fig. 2C. Data about cardiac comorbidities was not available in 69 cases. We found that of 1522 patients available for the analysis, 50 % of them had cardiac comorbidities. Similarly to the early period, no differences were noted in the trajectories of late peak PaO_2 values according to functional outcome, both in those with and without cardiac comorbidities, as shown in Supplementary Figure 2C and Supplementary Figure 3C.

Discussion

Our main finding is that very early hyperoxemia (0–4 h after ICU admission), but not early (8–24 h) nor late (28–72 h), is independently associated with poor functional outcome in out of hospital CA patients. There is growing evidence of the harm of being exposed to very high PaO_2 levels in critically ill patients, with indications that the harm is correlated with both the time of exposure and severity of exposure [16]. However, these hypotheses are mainly derived from observational data, often including numerous confounding factors that cannot always be fully addressed. Instead, our data are gathered from a high-quality database derived from a multicentric RCT, the TTM-2 trial. However, the TTM-2 did not allocate patients to different oxygenation strategies but rather compared the effects of normothermia versus hypothermia in post-CA patients [18]. Whilst this trial provides granular prospective data obtained from a randomized patients cohort and our analysis is based on data of greater quality, by definition our results cannot yield causation but rather suggest an association between very early hyperoxemia and neurological outcome.

In our previous analysis of this patient population, we examined the prevalence of hypoxemia (PaO_2 < 60 mmHg) and severe hyperoxemia (PaO_2 > 300 mmHg)[19], identifying thresholds associated with increased 6-month mortality: PaO_2 < 69 mmHg (RR = 1.009) and PaO_2 > 195 mmHg (RR = 1.006). Additionally, the time exposure to hyperoxemia (measured by the area under the curve) was significantly linked to mortality (p = 0.003). However, unexpectedly, in that analysis we found no association between hyperoxemia and poor functional outcomes. This led us to speculate that the absence of such an association may be attributed to a time-dependent effect of high PaO_2 values on outcomes.

Although weak evidence suggests that hyperoxemia might be better tolerated in the initial phase after CA, particularly within the first 6 h after ICU admission [17], it is more plausible from a physiological standpoint that hyperoxemia in the first few hours post-ROSC could exacerbate oxidative stress. This hypothesis aligns with our findings, showing an independent association between a very early peak of PaO_2 above 245 mmHg in the first 4 h after ICU admission and poor functional outcome. Patients with very early peak of PaO_2 above this threshold had a 57 % rate of poor functional recovery, marking an over 10 % absolute difference compared to those within the optimal PaO_2 peak range of 131–245 mmHg (Table 2). Despite the timing of occurrence of very early peak PaO_2 being almost equally split between ICU admission (49 %) and at 4 h post-admission (51 %), peaks at admission were approximately 25 mmHg higher than those at 4 h.

To our knowledge, this is the largest prospective study exploring the effect at different time periods of being exposed to hyperoxemia in resuscitated OHCA patients. The secondary analysis design and the multicentre nature of our study allowed us to obtain an important number of measurements over time with a large sample size. However, our results were obtained from a randomized study and their

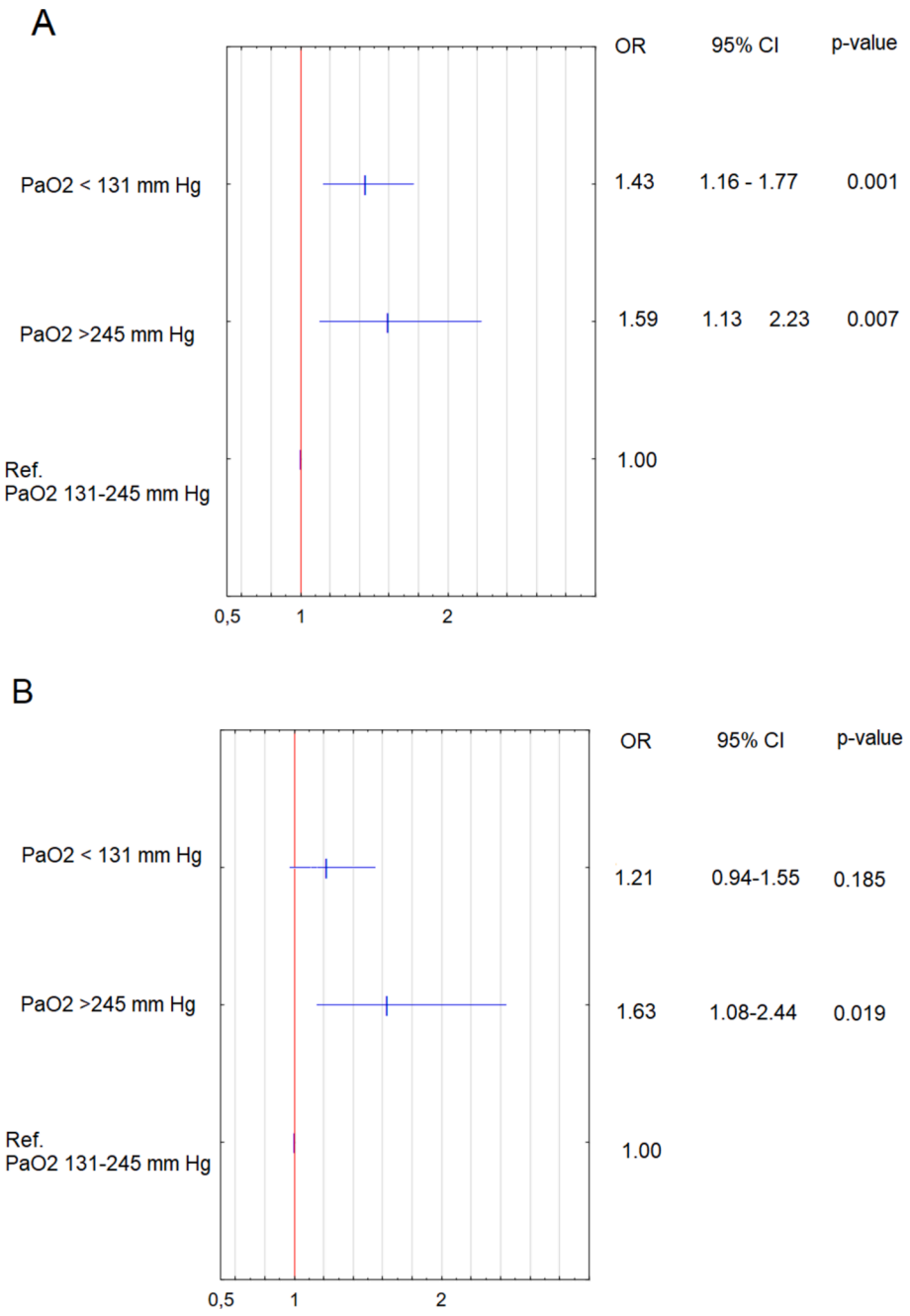

Fig. 3. Relative Confidence interval plot with Odds Ratio (OR) of trajectories of 0–4 h peak of arterial pressure of oxygen (PaO_2) within the optimal range (131–245 mm Hg, reference), below the lower limit (<131 mm Hg) and above the upper limit (>245 mm Hg) concerning 6-month functional outcome (A) derived from univariate logistic regression models, (B) adjusted for clinical co-factors. Horizontal lines represent the 95 % confidence interval (CI).

generalizability to other contexts remains uncertain. We found no evidence that high PaO_2 levels beyond the initial 4 h after ICU admission impacted functional recovery. The very early exposure (0–4 h) to high PaO_2 levels is related to worse functional outcome, with 245 mmHg identified as the critical threshold and this association is robust when accounting for the various variables in the multivariable model.

The European Resuscitation Council (ERC) guidelines recommended high FiO_2 during CPR and for transferring CA patients after ROSC [24]. This approach, especially in patients without severe cardiopulmonary dysfunction, carries the risk of inducing severe hyperoxemia. On the other hand, targeting lower values of oxygen saturation before ICU admission may be harmful, as shown by the EXACT RCT [1]. Once ROSC is achieved and the patient is admitted to the ICU, multiple tasks should be accomplished, meanwhile there is a clear risk of leaving the patient on unnecessary high FiO_2. Indeed, clinical handover, writing notes and ordering exams, inserting central venous catheter and arterial line, are likely to absorb the attention of medical staff, distracting them from adjusting FiO_2 on the ventilator. Indeed, post-CA mechanical ventilation practices vary widely, and the optimal PaO_2 and CO_2 levels remain unclear [6,25]. Nonetheless, we acknowledge that from a clinical standpoint, the avoidance of hyperoxemia can be difficult in the first hours under certain conditions. Indeed, it is certainly fundamental to avoid hypoxemia for the known negative impact on prognosis, and the task of providing optimal FiO_2 on the ventilator can be a challenge when the signal of SaO_2 is suboptimal due to vasoconstriction and inadequate peripheral perfusion. Overall, our findings underscore the need for clinicians to avoid not only hypoxemia but also elevated PaO_2 and SaO_2 levels. In this regard, the EXACT RCT, which compared targeting SaO_2 of

Table 3
Multivariate logistic regression analysis to predict poor functional outcome after 6 months using 0–4 h peak PaO_2 (n = 1631).

Explanatory Variables	Regression coefficient	OR (95 % CI)	p-value
0–4 h peak PaO_2 [mm Hg] (ref. 131–245)			
<131	0.19	1.21 (0.94–1.55)	0.148
>245	0.49	1.63 (1.08–2.44)	**0.019**
Age [years]	0.03	1.03 (1.01–1.05)	**<0.001**
Gender (ref. men)			
women	0.34	1.40 (1.03–1.89)	**0.029**
Hypertension (ref. no)			
yes	0.48	1.62 (0.93–2.81)	0.087
Diabetes mellitus (ref. no)			
yes	−0.10	1.90 (1.46–2.45)	0.578
Myocardial infarction (ref. no)			
yes	−0.35	0.71 (0.46–1.09)	0.112
Percutaneous coronary intervention (ref. no)			
yes	0.09	1.10 (0.73–1.65)	0.661
Heart failure (ref. no)			
yes	0.17	1.19 (0.75–1.65)	0.460
Charlson comorbidity index	0.23	1.25 (1.11–1.41)	**<0.001**
Location of cardiac arrest (Ref. Home)			
Public place	−0.49	0.61 (0.48–0.79)	**<0.001**
Other	−0.53	0.59 (0.41–0.86)	**0.006**
Bystander performed CPR (ref. no)			
yes	−0.42	0.66 (0.48–0.89)	**0.007**
Type of rhythm (ref. Not shockable)			
Shockable	−1.50	0.22 (0.17–0.30)	**<0.001**
Time to ROSC	0.04	1.04 (1.03–1.04)	**<0.001**

Abbreviations: ROSC, return of spontaneous circulation, CPR, cardio-pulmonary resuscitation.

90 %-94 % versus 98 %-100 % in CA patients until ICU admission, was stopped earlier due to the pandemic but the group of patients randomized to lower SaO_2 had a non-significant trend towards lower survival (38.3 % vs 47.9 %) and significantly higher occurrence of hypoxemic episodes [1]. Regarding the impact of hypoxemia, in the univariate analysis we found that a value of PaO_2 below 131 mmHg in the very early period identified patients with poor prognosis. However, this finding was not confirmed by the multivariate analysis. This result suggests that these patients suffer from other conditions acting as confounders and reducing the peak of PaO_2. Among others, pulmonary contusions from prolonged CPR, aspiration, pneumonia, or other underlying cardiac and/or lung diseases may affect the values of PaO_2.

Interestingly, whilst our results should prompt clinicians' attention towards avoidance of very early hyperoxemia, one RCT studied the effect of moderate "hyperoxemia" after CA with a target PaO_2 range of 150–187.5 mmHg, as compared to a normoxemia target [26]. In this trial, neuron-specific enolase (NSE) level, a marker of brain injury, was not different between the two groups. This suggests that targeting supra-normal PaO_2 levels does not confer additional benefits or harms in terms of reducing brain damage. Whether there is an optimal time period for treating CA patients with moderate hyperoxemia remains to be studied.

We also investigated whether the very early peak PaO_2 had a greater impact on patients with cardiac comorbidities. In the univariate analysis, we identified a similar optimal peak PaO_2 range (134–221 mmHg) These findings were not confirmed in the multivariate analysis. As shock reduces the reliability of pulse oximetry, we speculated that a more liberal use of FiO_2 occurs in these patients and that the observed association could have been a surrogate for impaired tissue perfusion, which in turn identify a subset of patients that are more likely to experience a poor outcome [27]. Patients admitted with severe circulatory failure represent an even greater challenge for the clinicians and are likely to be treated with higher FiO_2 settings on ICU admission. Hence, we acknowledge that shock can act as a confounder on the association between hyperoxemia and poor outcome. Further high-quality studies on optimal PaO_2 targets could be useful for this selected group of patients.

Limitations

This study has several limitations that need to be taken into account. Firstly, this is a secondary analysis of a randomized controlled trial, but our analysis relies on observational data; therefore, this makes it not possible to draw any causality relationship in our findings. Secondly, the data available in the TTM-2 dataset included PaO_2 values within the first 72 h, and therefore no information are provided regarding the very late phase of oxygen exposure. Third, the definitions of the periods and the peak of hyperoxemia are based on the available literature and clinical experience, but little evidence are available regarding this point. Finally, many other confounding factors could have been taken in consideration to be included in the analysis (including the mode of ventilation or more granular data on arterial blood gases), but this decision was made in the planning of the data collection for the TTM-2 trial in order to avoid excessive burden to the centres included for data collection.

Conclusions

Our results indicate a significant association between a peak of PaO_2 exceeding 245 mmHg in the first 4 h after ICU admission and poor functional outcomes in patients resuscitated after OHCA. This reflects the importance of closely monitoring and managing PaO_2 levels immediately post-admission to improve the prognoses of CA patients. Whilst further research is required to explore the mechanisms of this association, clinicians should consider avoiding high PaO_2 levels and titrating the FiO_2.

Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

Ethical approval was obtained in the coordinating center and in each participating centers as well as informed consent according to local regulations. This sub-study was approved on the 23rd of February 2017 by the TTM-2 steering committee (https://ttm2trial.org/substudy-proposals). The protocol of the analysis was previously approved by the TTM-2 steering committee and then published. No further ethical approval was necessary for the development of this study.

Consent for publication

Not applicable.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: [Dr. Taccone received lecture fees from BD, Edwards, Integra. CR received fees from Edwards. The other authors declare that they have no conflict of interest].

Appendix A. Supplementary data

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