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ORIGINAL WORK

Individualized Thresholds of Hypoxemia and Hyperoxemia and their Effect on Outcome in Acute Brain Injured Patients: A Secondary Analysis of the ENIO Study

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Abstract

Background: In acute brain injury (ABI), the effects of hypoxemia as a potential cause of secondary brain damage and poor outcome are well documented, whereas the impact of hyperoxemia is unclear. The primary aim of this study was to assess the episodes of hypoxemia and hyperoxemia in patients with ABI during the intensive care unit (ICU) stay and to determine their association with in-hospital mortality. The secondary aim was to identify the optimal thresholds of arterial partial pressure of oxygen (PaO_2) predicting in-hospital mortality.

Methods: We conducted a secondary analysis of a prospective multicenter observational cohort study. Adult patients with ABI (traumatic brain injury, subarachnoid aneurysmal hemorrhage, intracranial hemorrhage, ischemic stroke) with available data on PaO_2 during the ICU stay were included. Hypoxemia was defined as $PaO_2 < 80$ mm Hg, normoxemia was defined as PaO_2 between 80 and 120 mm Hg, mild/moderate hyperoxemia was defined as PaO_2 between 121 and 299 mm Hg, and severe hyperoxemia was defined as PaO_2 levels ≥ 300 mm Hg.

Results: A total of 1,407 patients were included in this study. The mean age was 52 (±18) years, and 929 (66%) were male. Over the ICU stay, the fractions of patients in the study cohort who had at least one episode of hypoxemia, mild/moderate hyperoxemia, and severe hyperoxemia were 31.3%, 53.0%, and 1.7%, respectively. PaO_2 values below 92 mm Hg and above 156 mm Hg were associated with an increased probability of in-hospital mortality. Differences were observed among subgroups of patients with ABI, with consistent effects only seen in patients without traumatic brain injury.

Conclusions: In patients with ABI, hypoxemia and mild/moderate hyperoxemia were relatively frequent. Hypoxemia and hyperoxemia during ICU stay may influence in-hospital mortality. However, the small number of oxygen values collected represents a major limitation of the study.

Keywords: Hyperoxia, Brain injury, Critically ill, Outcome, Hyperoxemia, Oxygen

Introduction

Patients admitted to the intensive care unit (ICU) often require mechanical ventilation and supplemental oxygen [1]. Additional oxygen can increase oxygen delivery in hypoxemic patients, support cell function and metabolism, and limit organ dysfunction [9–15]. However, it

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has been shown that hyperoxemia [16], by enhancing the production of reactive oxygen species, can induce damage to the cells and is associated with worse outcome in critically ill patients [16–21]. Available evidence is not clear regarding the impact of hyperoxemia on the brain oxygenation threshold, which would increase the risk of poor outcome, and its effects in the different acute brain injured populations [1, 7, 22–32].

In a post hoc analysis of patients with traumatic brain injury (TBI), a range of arterial partial pressure of oxygen (PaO_2) of 150–200 mm Hg was independently associated with improved functional and cognitive outcome at 6 months, whereas lower or higher values were not [33]. In patients with ischemic stroke (IS) and intracranial hemorrhage (ICH), severe hyperoxemia ($PaO_2 > 300$ mm Hg) was associated with increased in-hospital mortality [34], although lower thresholds ($PaO_2 > 120$ mm Hg) have also been documented [35]. In patients with subarachnoid hemorrhage (SAH), early hyperoxemia ($PaO_2 > 186$ or > 176 mm Hg) was associated with delayed cerebral ischemia, cerebral vasospasm, and poor outcome [36, 37].

Overall, while a U-shaped relationship between outcome after acute brain injury (ABI) and systemic oxygenation has been suggested, there is uncertainty on specific oxygen thresholds that could be used to guide clinical management [38]. We therefore conducted a secondary analysis of a recent large-scale multicenter observational study of a large population of patients with ABI. The primary aim was to assess the occurrence of hypoxemia and hyperoxemia during the ICU stay and the association with in-hospital mortality. The secondary aim was to identify the best thresholds of PaO_2 associated with in-hospital mortality in the overall population and in different subtypes of ABI.

Methods

Study Design and Ethical Standards

This is a subanalysis of the Extubation Strategies in Neuro-Intensive Care Unit Patients and Associations With Outcomes (ENIO) multicentric observational cohort (NCT03400904), which was approved by the steering committee [39]. The ENIO study was conducted in accordance with the principles of the Declaration of Helsinki, and the Medical Research Involving Human Subjects Act [40]. This study was performed according to the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for observational studies [41] (Table S1). Data management, monitoring, and reporting of the study were performed in accordance with the International Conference on Harmonization Good Clinical Practice Guidelines [42, 43]. Approval to enroll patients in the ENIO main study was obtained from the institutional review board of the promoter center (Groupe Nantais d'Éthique dans le Domaine de la Santé, IRB No. 7/11/2017) and of each participating site. Informed consent was collected in accordance with the local regulations of each involved institutional review board. For this specific subanalysis, no further ethical approval was necessary.

Patients and Inclusion Criteria

The participating centers of the ENIO study were recruited through the Protective Ventilation Network, the European Society of Intensive Care Medicine (ESICM), the French Society of Anesthesiology and Critical Care, and Colegio Mexicano de Medicina Critica, which endorsed the study. The primary objective of the ENIO study was to validate a predictive score for extubation success. Secondary objectives were to describe the reasons for extubation failure and describe the association between different liberation strategies (such as extubation attempt, extubation failure, tracheostomy when extubation strategy was not applied) and outcomes [44].

Patients were recruited over a time frame from the 26th of June 2018 to the 15th of November 2020. The ENIO study enrolled brain injured patients with TBI, SAH, ICH, IS, and other central nervous system pathologies (i.e., brain abscess, empyema, meningitis, encephalitis, or brain tumor) who at the time of inclusion were ≥ 18 years old, were admitted to the ICU with a Glasgow Coma Score (GCS) ≤ 12, required invasive mechanical ventilation (IMV) ≥ 24 h, and underwent an attempt to discontinue IMV (defined as an extubation trial and/or tracheostomy). . Patients were excluded if they were pregnant, had a spinal cord injury above T4, were resuscitated post cardiac arrest, had Guillain–Barré syndrome, underwent withdrawal of life-sustaining treatment in the first 24 h of ICU admission, received a tracheostomy prior to ICU admission, had major respiratory comorbidities (e.g., chronic oxygen therapy at home, chronic obstructive pulmonary disease grade III or IV of the Gold classification), or had major chest trauma [39].

For this subanalysis, patients without available data on arterial oxygenation were also excluded.

Data Collection

For this substudy, the following data from the ENIO data set were selected: demographic and baseline data (age, sex, height, weight, body mass index, previous comorbidities [chronic obstructive pulmonary disease, cardiovascular comorbidities defined as New York Health Association class ≥ 2, arterial hypertension, active smoking, diabetes mellitus, history of malignancy]), type of brain injury, severity of brain injury (e.g., lowest baseline GCS), neurosurgical and neurocritical care management

(e.g., barbiturate coma, therapeutic hypothermia, external ventricular drainage, decompressive craniectomy), airway and ventilatory management (e.g., tracheostomy, gag reflex, cough, spontaneous breathing trial, extubation, reintubation), in-ICU events, and in-hospital and in-ICU outcomes (need for and duration of IMV, ICU length of stay, in-hospital mortality, need for non-IMV and duration). Arterial blood gases data, including PaO_2, and ventilatory settings were collected on days 1, 3, and 7 from ICU admission.

Study Objectives and Definitions

According to the recent recommendations from the panel consensus of the ESICM, the normal range of oxygenation in brain injured patients was defined as PaO_2 levels within 80 and 120 mm Hg [45]. For the primary analysis, patients were divided in four PaO_2 groups, according to the PaO_2 values on day 1 at ICU admission, as follows: (1) hypoxemia, with PaO_2 levels < 80 mm Hg; (2) normoxemia, with PaO_2 levels between 80 and 120 mm Hg [45]; (3) mild/moderate hyperoxemia, with PaO_2 levels between 121 and 299 mm Hg [34, 46]; and (4) severe hyperoxemia, with PaO_2 levels ≥ 300 mm Hg [34, 46]. Despite not being completely confirmed by randomized controlled trials in the literature, we chose the threshold of 300 mm Hg for this specific population of patients because this is the most consistent value investigated and it was found to be associated with outcome [17, 18, 29, 47, 48].

The primary objective was to assess the occurrence of hypoxemia and hyperoxemia during the ICU stay in the study cohort. The secondary aims were (1) to assess the association of oxygen values with hospital mortality, (2) to estimate the best PaO_2 thresholds associated with in-hospital mortality in the entire population, and (3) to assess the best PaO_2 threshold associated with in-hospital mortality in different brain injury groups (TBI, SAH, ICH, IS).

Statistical Analysis

Data on patient characteristics, clinical presentation, ventilator settings, arterial blood gases (ABG), ICU management, and outcomes were presented as means ± SD or medians (interquartile range) for continuous variables or as percentages for the categorical ones. The comparisons of means, medians, and frequencies among patients in the four PaO_2 bins were conducted using one-way analysis of variance, the Kruskal–Wallis test, and the χ^2 test, respectively.

The evaluation of the number of hypoxemia and hyperoxemia episodes over the follow-up was conducted using three different approaches: (1) showing the number of patients with no episodes, one episode, two episodes, and three (or more) episodes as a graph; (2) showing the fraction of patients with at least one episode; and (3) showing the incidence rates as the average number of events per 1 person-day. The latter estimates were obtained by means of a population-averaged Poisson model, a regression method suited for a repeated-measures data, with an exchangeable correlation structure.

Multivariable logistic regressionwas used to determine the strength and direction of the association between PaO_2 (either as continuous or categorical) and in-hospital mortality. The model included age (years); sex; body mass index; prior history of hypertension, diabetes, pulmonary disease, and heart failure; lowest Glasgow score at inclusion; TBI; indication for oxygen administration; positive end-expiratory pressure; respiratory rate (bpm); and indicators for withdrawal of life-sustaining treatment. Variable selection was conducted by a backward elimination using a multivariable fractional polynomial (FP) procedure [49]. In this procedure, the linearity assumption of continuous variables was tested, and the variable transformed with the appropriate FP when the assumption was not met. Risk estimates from the logistic regression were expressed as odds ratios (ORs) with 95% confidence intervals (95% CIs). However, because the association between PaO_2 (modeled as continuous) and hospital mortality included an FP (0.5–1) to capture a U-shape trajectory, the result was instead depicted through a graph in which the OR on the *y*-scale is plotted against the continuum of the marker. To account for interdependence among centers, the models included a cluster-based adjustment of the standard error estimation.

Using relative distribution analysis [50], we searched for the best threshold along the continuum of the PaO_2 that separated hospital survivors vs. nonsurvivors in the entire sample and for each subset of patients with TBI, IS, ICH, and SAH. Results from these analyses were presented as figures, with the thresholds representing the intersection of the proportion ratio trajectory with the *y*-axis line of 1. The 95% CI indicates at which point the associated threshold becomes significant in our sample. These analyses were also adjusted by the same set of covariates used in the logistic regression model in a cluster-based adjustment by clinical center.

After rearrangement of the data set for longitudinal analysis, the evolution of PaO_2 among days 1, 3, and 7 was evaluated with a mixed-effect regression model with random intercept on centers and random coefficient (unstructured covariance) on patient identification. The model was adjusted by the same set of covariates as before. Within the same longitudinal framework, the prognostic effects of PaO_2 on days 1, 3, and 7 were compared with multilevel logistic regression with random

intercept on centers and patient identification. As before, the model was adjusted by the same set of covariates.

In addition, we performed a sensitivity analysis using the longitudinal structure of the data (as repeated measures), and the two main analyses (thresholds calculation and logistic regression) were reproduced.

A two-sided p value of < 0.05 was the threshold used for significance in all analyses. Stata 17.0 [51] was used for data clean-up, preparation, and statistical analysis; CR and RB had full access to all the data in the study and take responsibility for its integrity and the data analysis.

Results

Study Population

A total of 1,407 out of 1,512 patients enrolled in the ENIO study met the inclusion criteria and were included in this study. Table 1 and Table S2 present the characteristics of the overall population at ICU admission, ICU management, and outcomes. The mean age was 52 (± 18) years, and 929 (66%) patients were male; 673 (47.8%) were admitted for TBI, 259 (18.4%) were admitted for SAH, 487 (34.6%) were admitted for ICH, and 132 (9.4%) for IS. An intraparenchymal probe for intracranial pressure (ICP) monitoring was used in 610 (43.4%) patients, and an intraventricular catheter was used in 419 (29.8%) patients. In 1,046 (74.4%) patients, the GCS was below 9 on admission. In-hospital mortality was 11.9%.

Episodes of Hypoxemia and Hyperoxemia

On ICU admission, 186 (13.2%) patients had hypoxemia, 596 (42.4%) had mild/moderate hyperoxemia, and 18 (1.3%) had severe hyperoxemia. The median PaO_2 value was 114 (90–151) mm Hg in the overall population. The characteristics of the patients and their ICU management according to the different PaO_2 groups are presented in Table 1 and Table S2. The numbers of patients who experienced hypoxemia ($PaO_2 < 80$ mm Hg), mild/moderate ($PaO_2 = 121$ to 299 mm Hg), and severe hyperoxemia ($PaO_2 \geq 300$ mm Hg) episodes during the ICU stay are depicted in Fig. 1. Figure S1 includes similar estimates for hypoxemia ($PaO_2 < 80$ mm Hg) and hyperoxemia ($PaO_2 > 120$ mm Hg).

The proportions of patients in the study cohort who had at least one episode of hypoxemia, mild/moderate hyperoxemia, and severe hyperoxemia during their ICU stay were 31.3% ($n = 441$), 53.0% ($n = 746$), and 1.7% ($n = 24$), respectively. The incidence rates for hypoxemia, mild/moderate, and severe hyperoxemia, presented as the average number of episodes per 1 person-day, were 0.034 (95% CI 0.031–0.037), 0.071 (95% CI 0.67–0.76), and 0.002 (95% CI 0.001–0.002).

Median values of PaO_2 significantly decreased over time (Fig. S2). Evolution of PaO_2, evaluated by categories, over the 3 days during the ICU stay is presented in Fig. 2. Overall, the number of patients with normoxemia increased over time (especially from day 3 to day 7), whereas the number of patients with mild/moderate hyperoxemia was reduced. The number of patients with severe hyperoxemia decreased over day 3 and day 7. The number of patients with hypoxemia increased over day 3 and day 7.

Effect of Oxygen on Hospital Mortality in the Overall Cohort

When modeled as continuous variable, PaO_2 had a U-shaped relationship with in-hospital mortality. Values of PaO_2 above 200 mm Hg were independently associated with higher risk of death (omnibus $p = 0.0055$; Fig. 3). The prognostic effect of hyperoxemia diminished over time (Fig. S3), as it was significantly associated with hospital mortality on days 1 and 3 but not on day 7.

Figure 4a shows the relative distribution analyses for the entire cohort assessing the best PaO_2 cutoff point associated with hospital mortality. The best lower and higher thresholds for PaO_2 to predict in-hospital mortality were 84 and 195 mm Hg, respectively. By contrasting the PaO_2 categories derived from these new thresholds against hospital mortality, both hypoxemia (< 92 mm Hg) (OR: 1.84, 95% CI 1.23–2.75, $p = 0.003$) and hyperoxemia (> 156 mm Hg) (OR: 2.11, 95% CI 1.34–3.33, $p = 0.001$) were significant predictors (Fig. 4b) (omnibus value, $p = 0.0003$). Considering the new thresholds, the percentages of patients with at least one episode of hypoxemia were 54.2% ($n = 762$) and 26.5% ($n = 373$) (Fig. S4). The incidence rate (per 1 person-day) for hypoxemia was 0.068 (95% CI 0.064–0.073), and the incidence rate for hyperoxemia was 0.028 (95% CI 0.026–0.031).

We performed a sensitivity analysis with the aim to test how different our results would have been if we included longitudinal PaO_2 measurements (at days 1, 3, and 7); to that extent, all analysis were performed using statistical methods suited for a repeated-measures design. Overall, the U-shaped association with hospital mortality was reproduced, although we could not achieve the same level of significance, mainly because of a reduced sample size (analyses are presented in Figs. S5–S8).

Effect of Oxygen on Hospital Mortality in Different Subgroups Population

In patients with TBI, there was no statistically significant association with in-hospital mortality and PaO_2 (Fig. S9, p values for the interaction between TBI status and PaO_2 as continuous and categorical were $p = 0.1441$ and $p = 0.2803$, respectively). In patients without TBI, mortality had a U-shaped relationship with in-hospital mortality. We found that for the subgroup of patients

Table 1 Characteristics of the patients included in the cohort at admission and outcomes, considering the whole population and according to different subgroups of oxygen ranges

Categories of PaO_2 (ICU day 1)	Hypoxemia *n* = 186 (13.2%)	Normoxemia *n* = 607 (43.1%)	Mild/moderate hyperoxemia *n* = 596 (42.4%)	Severe hyperoxemia *n* = 18 (1.3%)	Total *N* = 1,407 (100.0%)	*p* value
Countries, *n* (%)						
Netherlands	15 (8.1)	20 (3.3)	11 (1.8)	1 (5.6)	47 (3.3)	0.000
France	85 (45.7)	262 (43.2)	279 (46.8)	4 (22.2)	630 (44.8)	
Other	6 (3.2)	18 (3)	10 (1.7)	0 (0)	34 (2.4)	
United Kingdom	6 (3.2)	24 (4)	19 (3.2)	0 (0)	49 (3.5)	
India	9 (4.8)	24 (4)	36 (6)	2 (11.1)	71 (5.0)	
Mexico	30 (16.1)	93 (15.3)	60 (10.1)	3 (16.7)	186 (13.2)	
Argentina	0 (0)	27 (4.4)	18 (3)	0 (0)	45 (3.2)	
Belgium	4 (2.2)	6 (1)	9 (1.5)	0 (0)	19 (1.4)	
Italy	13 (7)	48 (7.9)	66 (11.1)	2 (11.1)	129 (9.2)	
Uruguay	1 (0.5)	1 (0.2)	11 (1.8)	6 (33.3)	19 (1.4)	
Canada	1 (0.5)	6 (1)	3 (0.5)	0 (0)	10 (0.7)	
Spain	1 (0.5)	18 (3)	8 (1.3)	0 (0)	27 (1.9)	
Switzerland	8 (4.3)	35 (5.8)	29 (4.9)	0 (0)	72 (5.1)	
Greece	2 (1.1)	12 (2)	19 (3.2)	0 (0)	33 (2.3)	
Japan	5 (2.7)	11 (1.8)	13 (2.2)	0 (0)	29 (2.1)	
Unitedstates	0 (0)	2 (0.3)	5 (0.8)	0 (0)	7 (0.5)	
Demographic characteristics at ICU admission						
Age, years, mean (SD)	55 (15)	53 (18)	50 (19)	48 (20)	52 (18)	0.000
Sex (male), *n* (%)	125 (67.2)	407 (67.1)	383 (64.3)	14 (77.8)	929 (66)	0.506
Height, cm, mean (SD)	171 (10)	170 (9)	170 (9)	174 (9)	170 (9)	0.153
Weight, kg, mean (SD)	82 (17)	77 (16)	74 (15)	81 (18)	76 (16)	0.000
BMI, mean (SD)	27.9 (6)	26.6 (5)	25.5 (4.8)	26.8 (4.8)	26.3 (5.1)	0.000
Past medical history, *n* (%)						
Chronic pulmonary disease	6 (3.2)	24 (4)	18 (3)	0 (0)	48 (3.4)	0.690
Chronic heart failure	7 (3.8)	22 (3.6)	12 (2)	0 (0)	41 (2.9)	0.285
Hypertension	61 (32.8)	214 (35.3)	146 (24.5)	3 (16.7)	424 (30.2)	0.000
Active smoking	45 (24.7)	147 (24.3)	113 (19.1)	4 (23.5)	309 (22.1)	0.134
Diabetes mellitus	33 (17.7)	77 (12.7)	58 (9.7)	3 (16.7)	171 (12.2)	0.027
Malignancy	7 (3.8)	28 (4.6)	26 (4.4)	0 (0)	61 (4.3)	0.783
Neurological status at ICU admission						
Lowest GCS eyes, median (IQR)	1 (1–2)	1 (1–2)	1(1–2)	2 (1–3)	1 (1–2)	0.102
Lowest GCS verbal, median (IQR)	1(1–2)	1 (1–2)	1 (1–2)	2(1.0–3.3)	1 (1–2)	0.115
Lowest GCS motor, median (IQR)	4 (2–5)	4 (2–5)	4 (2–5)	4 (3.5–5)	4 (2–5)	0.686
Lowest GCS, median (IQR)	7 (5–9)	7 (5–9)	7 (5–8)	8 (6–10.5)	7 (5–9)	0.237
GCS classification of severity of TBI, *n* (%)						
Severe, GCS 3–8	138 (74.2)	450 (74.4)	448 (75.2)	10 (55.6)	1,046 (74.4)	
Moderate, GCS 9–12	48 (25.8)	155 (25.6)	148 (24.8)	8 (44.4)	359 (25.6)	0.315
Episode of anisocoria, *n* (%)	44 (23.7)	152 (25.1)	188 (31.6)	3 (17.6)	387 (27.6)	0.030
Origin of brain injury, *n* (%)						
TBI	83 (44.6)	269 (44.3)	307 (51.5)	14 (77.8)	673 (47.8)	0.004
SAH	40 (21.5)	128 (21.1)	90 (15.1)	1 (5.6)	259 (18.4)	0.015
ICH	71 (38.2)	230 (37.9)	183 (30.7)	3 (16.7)	487 (34.6)	0.015
IS	15 (8.1)	60 (9.9)	55 (9.2)	2 (11.1)	132 (9.4)	0.887
CNS infection	11 (5.9)	35 (5.8)	23 (3.9)	1 (5.6)	70 (5)	0.435
Brain tumor	6 (3.2)	28 (4.6)	30 (5)	0 (0)	64 (4.5)	0.586

Table 1 (continued)

Categories of PaO_2 (ICU day 1)	Hypoxemia *n* = 186 (13.2%)	Normoxemia *n* = 607 (43.1%)	Mild/moderate hyperoxemia *n* = 596 (42.4%)	Severe hyperoxemia *n* = 18 (1.3%)	Total *N* = 1,407 (100.0%)	*p* value
Other	2 (1.1)	11 (1.8)	12 (2)	1 (5.6)	26 (1.9)	0.558
Neurosurgical management during ICU stay, *n* (%)						
Intracranial probe	78 (42.4)	254 (41.8)	273 (45.8)	5 (27.8)	610 (43.4)	0.276
Ventricular drainage	67 (36.2)	188 (31)	161 (27)	3 (16.7)	419 (29.8)	0.052
Posterior fossa injury	7 (3.8)	37 (6.1)	37 (6.2)	0 (0)	81 (5.8)	0.438
Therapeutic hypothermia	7 (3.8)	23 (3.8)	26 (4.4)	1 (5.6)	57 (4.1)	0.941
Barbiturate coma	5 (2.7)	30 (4.9)	45 (7.6)	0 (0)	80 (5.7)	0.035
Neurosurgery	80 (43.2)	243 (40)	234 (39.3)	8 (44.4)	565 (40.2)	0.791
Decompressive craniectomy	29 (15.7)	123 (20.3)	112 (18.8)	2 (11.1)	266 (18.9)	0.439
ICU events and outcomes						
Nosocomial VAP, *n*(%)	89 (48.6)	235 (39)	223 (37.9)	13 (72.2)	560 (40.2)	0.002
Nosocomial VAP SBT, *n* (%)	19 (10.6)	75 (12.6)	73 (12.5)	5 (27.8)	172 (12.5)	0.219
Tracheobronchitis SBT, *n* (%)	12 (6.7)	65 (11)	44 (7.6)	5 (27.8)	126 (9.2)	0.005
ARDS, *n* (%)	27 (14.8)	51 (8.5)	53 (9)	1 (5.6)	132 (9.5)	0.070
Invasive MV, *n* (%)	175 (96.2)	568 (95.1)	576 (98.5)	18 (100)	1,337 (96.7)	0.011
Noninvasive MV, *n* (%)	22 (12)	81 (13.7)	60 (10.3)	3 (16.7)	166 (12)	0.319
High-flow oxygen, *n* (%)	41 (22.3)	98 (16.6)	93 (16)	3 (16.7)	235 (17.1)	0.250
WLST, *n* (%)	8 (4.4)	41 (6.9)	35 (6)	0 (0)	84 (6.1)	0.426
ICU mortality, *n* (%)	13 (7)	43 (7.1)	35 (5.9)	1 (5.6)	92 (6.5)	0.845
Hospital mortality, *n* (%)	26 (14.4)	62 (10.5)	71 (12.5)	2 (11.1)	161 (11.9)	0.509
LOS in ICU, median (IQR)	13 (7–27)	13 (7–25)	13 (7–22)	17.5 (12–32.3)	13 (7–24)	0.162
Tracheostomy cannula, *n* (%)	59 (32.2)	155 (25.8)	167 (28.2)	10 (55.6)	391 (28)	0.020

ARDS acute respiratory distress syndrome, *BMI* body mass index, *CNS* central nervous system, *GCS* Glasgow Coma Scale, *ICH* intracranial hemorrhage, *ICU* intensive care unit, *IQR* interquartile range, *IS* ischemic stroke, *LOS* length of stay, *MV* mechanical ventilation, PaO_2 arterial partial pressure of oxygen, *SAH* subarachnoid hemorrhage, *SBT* spontaneous breathing trial, *TBI* traumatic brain injury, *VAP* ventilator associated pneumonia, *WLST* withdrawal of life-sustaining treatment

with TBI (Fig. 5), the best thresholds for hypoxemia and hyperoxemia were 97 mm Hg (relative risk: 1.002, 95% CI 0.39–1.61) and 156 mm Hg (relative risk: 1.004, 95% CI 037–1.63), without reaching statistical significance. Figure 5 and, more specifically, Fig. S10 show the relative distribution analyses for all subsets of neurocritical pathologies.

Mortality had a U-shaped relationship with PaO_2 in all patients divided according to specific ABI diagnosis; however, only patients with IS showed a strong statistical significance for both hypoxemia and hyperoxemia (Fig. S10). The best thresholds estimated for hypoxemia and hyperoxemia were the following: for IS, 86 and 144 mm Hg; for intracerebral hemorrhage, 80 and 119 mm Hg; and for SAH, 75 and 137 mm Hg, respectively (Fig. S10).

Discussion

In this large cohort of 1,407 patients with ABI, we found that mild/moderate hyperoxemia is very common, that oxygen values are independently associated with higher mortality rates, that the best PaO_2 values below 92 mm Hg and above 156 mm Hg were associated with higher in-hospital mortality in the whole population, and that PaO_2 thresholds associated with in-hospital mortality differed according to the type of injury, with a stronger effect in patients without TBI.

To the best of our knowledge, this is the largest cohort study of heterogenous types of ABI patients investigating the association of PaO_2 values with outcome, with an individualized calculation of the best thresholds for each type of injury. Maintaining appropriate levels of systemic oxygenation for healthy brain physiology may improve outcome [2–8, 16–21].

Acute brain injury includes various heterogeneous diseases with different pathophysiological mechanisms that can lead to various degrees of neuronal damage. Although there is considerable evidence that hypoxemia is a well-known cause of secondary brain damage, more recent research has focused on hyperoxemia, which may induce adverse effects on the cardiovascular, pulmonary, central nervous, and immune systems. These systemic harmful effects are likely due to reactive oxygen species and hyperoxia-induced vasoconstriction, leading to tissue injury and poor clinical outcome [2–8, 16–21].

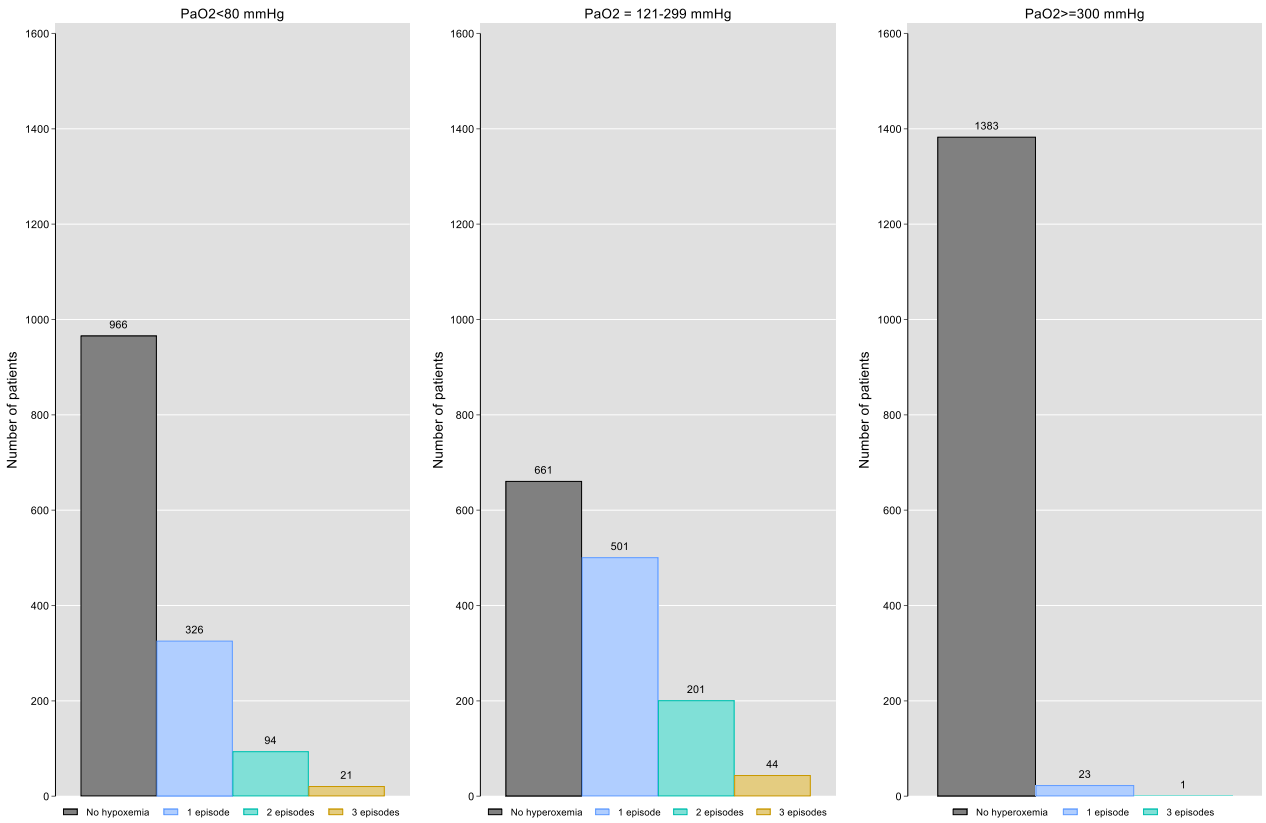

Fig. 1 Frequency distribution of arterial partial pressure of oxygen (PaO_2) classes (standard thresholds). Number of hypoxemia ($PaO_2 < 80$ mmHg), mild/ moderate (PaO_2 between 121 and 299 mmHg) or severe hyperoxemia ($PaO_2 \geq 300$ mmHg) episodes per patient during the first week after intensive care unit admission

The occurrence of hypoxemia and hyperoxemia is variable in the literature [1, 7, 22–32], with overall incidence between 19% and 24.9% for at least one episode of hypoxemia and between 3 and 60% for at least one episode of severe hyperoxemia in patients after cardiac arrest and in general ICU patients [17, 47, 48, 52]. In the present study, we found that the occurrence of mild/moderate hyperoxemia was quite high in comparison with previous literature, whereas severe hyperoxemia was uncommon [17, 47, 48, 52]. This is likely due to increased awareness about the possible detrimental effects of hypoxemia and severe hyperoxemia [47, 53].

We identified lower and higher thresholds for PaO_2 associated with outcome that resulted in an increase in the number of episodes of hypoxemia. Recent recommendations from the ESICM on ventilatory targets in brain injured patients suggest adopting a range of oxygen thresholds between 80 and 120 mm Hg [45]. In our cohort, the thresholds below 84 mm Hg and above 195 mm Hg for hypoxemia and hyperoxemia in the whole population were associated with increased in-hospital mortality, demonstrating that the current thresholds could underestimate the risk of hypoxemia in patients with brain damage and be associated with increased mortality. Considering the higher threshold related to hyperoxemia, our results suggest that there is a wider range compared to current guidelines before hyperoxic neuronal damage occurs. Hyperoxemia seems to be more deleterious in the early phases of ABI, when cerebral hemodynamics are more importantly impaired, and the risk of secondary damage is higher.

These values and thresholds are different from those reported in the general ICU population. In a large meta-analysis of patients with sepsis, critical illness, stroke, trauma, myocardial infarction, or cardiac arrest, a "liberal" oxygen strategy, defined as a target oxygen saturation (SpO_2) of 94–99% [22], which would typically correlate with a PaO_2 range of 60–100 mm Hg, resulted in increased mortality [54]. However, the ABI population might benefit from higher values of oxygen than the general ICU population, as the brain is extremely vulnerable to hypoxic injury as a cause of secondary brain damage. Different types of brain injured patients may have different thresholds. Some authors showed that in patients

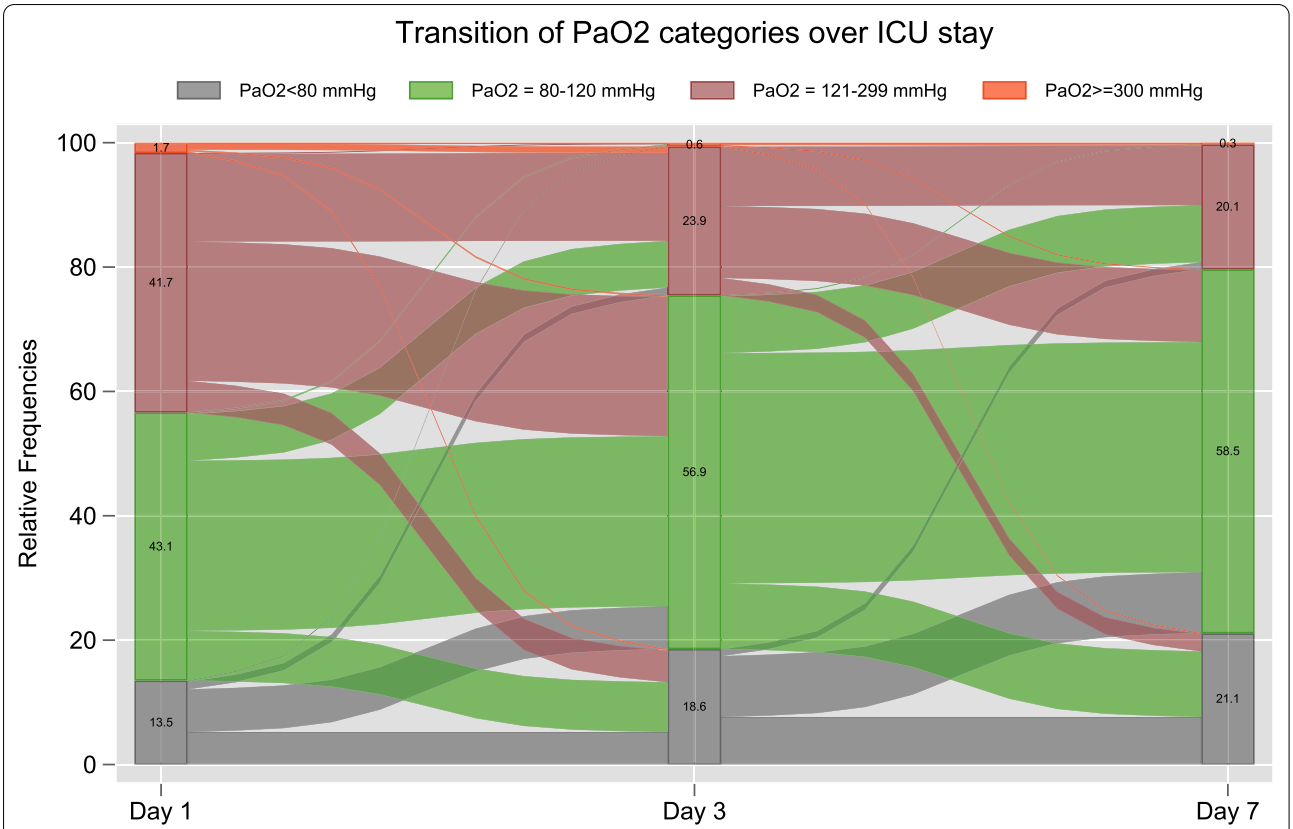

Fig. 2 Evolution of partial pressure of oxygen, PaO_2—evaluated by categories—over the three days during ICU stay. These transitions are shown as percentages on the y-axis

with TBI, values of 150–200 mm Hg were independently associated with improved functional and cognitive outcome at 6 months, but lower and higher values were not [33]. A recent observational study [55] found that the median value of oxygen used on the TBI population was quite high (134 mm Hg), and the ESICM consensus recommends a target of oxygen that is higher compared with that for the general ICU population [45].

Looking at each specific neurological condition, a different association of oxygen levels with outcome was observed according to the subtype considered. In patients with TBI, the guidelines recommend not falling below an oxygenation of 60 mm Hg [56, 57]. Other findings suggested a cutoff for hypoxemia of < 100–110 mm Hg to be associated with mortality without accounting for the "dose" [58]. In our study, the best threshold for hypoxemia was 97 mm Hg, which is considerably higher than current recommendations [56, 57]. This suggests that secondary brain damage after TBI can manifest at PaO_2 levels higher than the recommended 60 mm Hg. In our study, no association with hyperoxemia and in-hospital mortality was observed in the specific population of patients with TBI, which is in contrast with a recent large study from the Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury group [55]. Other authors suggested that adjunctive oxygen can lead to beneficial effects in management of brain edema, control of intracranial pressure, and maintenance of cerebral perfusion pressure, shifting from anaerobic to aerobic metabolism [8]. A recent meta-analysis suggested that hyperoxemia leads to a reduction in lactate and the lactate/pyruvate ratio [59, 60]. In patients with TBI, the main pathophysiological issue is increased intracranial pressure with perivascular edema at the brain–blood barrier level, thus making altered diffusion the main issue to oxygen delivery to the brain. Increased levels of PaO_2 can help in providing appropriate tissue oxygen delivery, improving aerobic metabolism and without causing oxidative stress. In the non-TBI population, the association of hypoxemia and hyperoxemia was more strongly significative, especially for IS, with narrower ranges than in TBI.

In patients with SAH, thresholds of 97 and 150 mm Hg failed to find association with mortality [3], whereas higher thresholds (173 to 186 mm Hg) were independently associated with delayed cerebral ischemia and

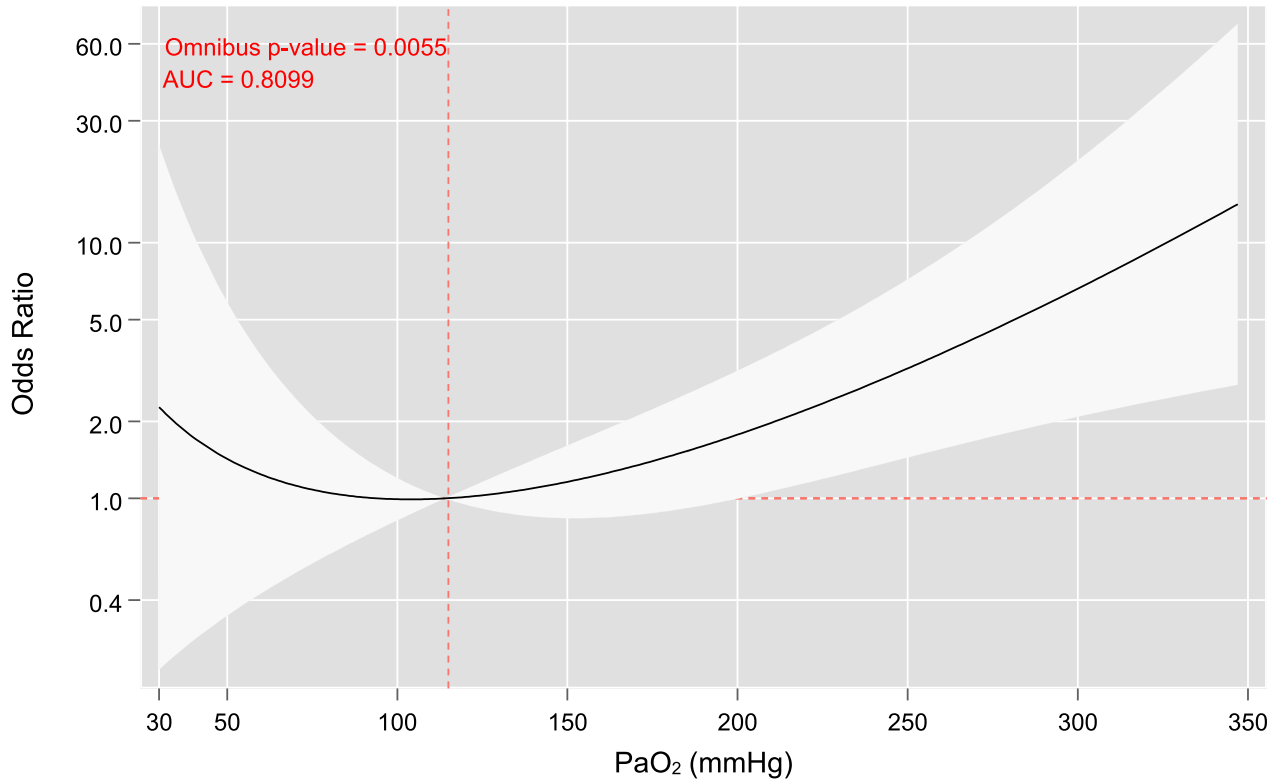

Fig. 3 Arterial partial pressure of oxygen (PaO_2) hospital mortality risk profile. Mortality risk trajectory along PaO_2 continuum. PaO_2 was modeled with a FP of second-degree FP [0.5–1] in a logistic regression model adjusted by age (years), gender, body mass index categories, lowest Glasgow score at inclusion, prior history of hypertension, diabetes, pulmonary disease, and heart failure, traumatic brain injury, indication for oxygen administration, positive end-expiratory pressure at day 1, respiratory rate (b/min) at day 1, and withdrawal of life-sustaining treatment. Also included an adjustment by center as a cluster variable. Just for the figure, PaO_2 was trimmed at 30–350 mm Hg range

poor outcome [36, 61] as well as cerebral vasospasm when patients were exposed to the high PaO_2 values within 72 h after aneurysmal rupture [37].

In patients with ICH, previous studies using thresholds below 97.5 mm Hg for hypoxemia and above 150 mm Hg for hyperoxemia failed to find association with increased 6-month mortality [62].

In acute IS, hyperoxemia thresholds above 300 and 120 mm Hg were associated with in-hospital mortality and 90-day mortality, respectively [34, 35]. These differences might have several pathophysiological reasons. In SAH, brain areas at risk of vasospasm [63, 64], or in stroke, the tissue surrounding a brain hemorrhage or the ischemic areas, may present a reduced oxidative metabolism, using very low oxygen rates, with impaired mitochondrial function and increased sensibility to changes of oxygen levels [65]. The response of the blood–brain barrier to IS includes a reduced oxidative metabolism with cytotoxic brain edema formation and cell swelling, alteration of tight junctions and the extracellular matrix leading to breakdown of the blood–brain barrier, concomitant vasogenic brain edema formation, and ischemia-induced neuroinflammation, which can be particularly vulnerable to hypoxemia but also to hyperoxemia-related oxidative stress.

This study has several limitations. First, this is an observational study; thus, any causality statements cannot be extrapolated from our findings. However, a very robust statistical analysis accounting for confounding factors was performed. Second, blood gas analysis values were collected only at days 1, 3, and 7. Thus, our data do not allow us to explore the effect of the "dose" of oxygen administered to the patient. Further studies with more granular data are necessary in this context. Third, some values were missing in the database. Fourth, more information about long-term mortality and neurological status of this cohort would have been desirable to assess the effect of oxygen derangement on outcome. Fifth, the data set did not include neurological outcome at ICU discharge/follow-up. Sixth, there were no data on cerebral oxygen tension, thus limiting the interpretation of our findings.

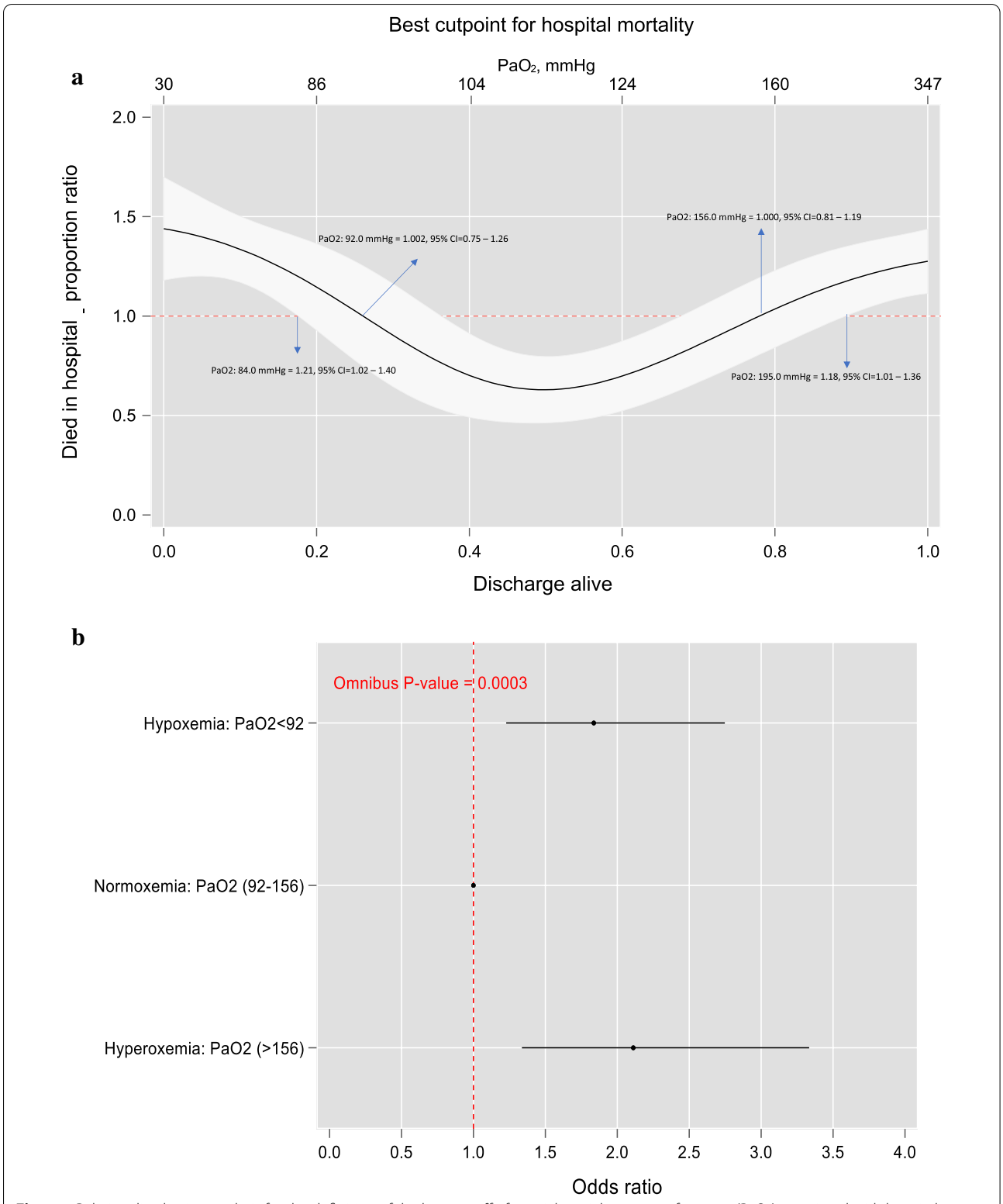

Fig. 4 **a** Relative distribution analysis for the definition of the best cutoff of arterial partial pressure of oxygen (PaO_2) associated with hospital mortality. This figure depicts the proportion ratio of patients who died vs. those who were discharged alive according to their quantile distribution in reference to PaO_2 values. **b** Association between PaO_2 categories and hospital mortality in the overall cohort taking in consideration the new thresholds. This figure depicts the odds ratios of PaO_2 categories on hospital mortality for the entire cohort

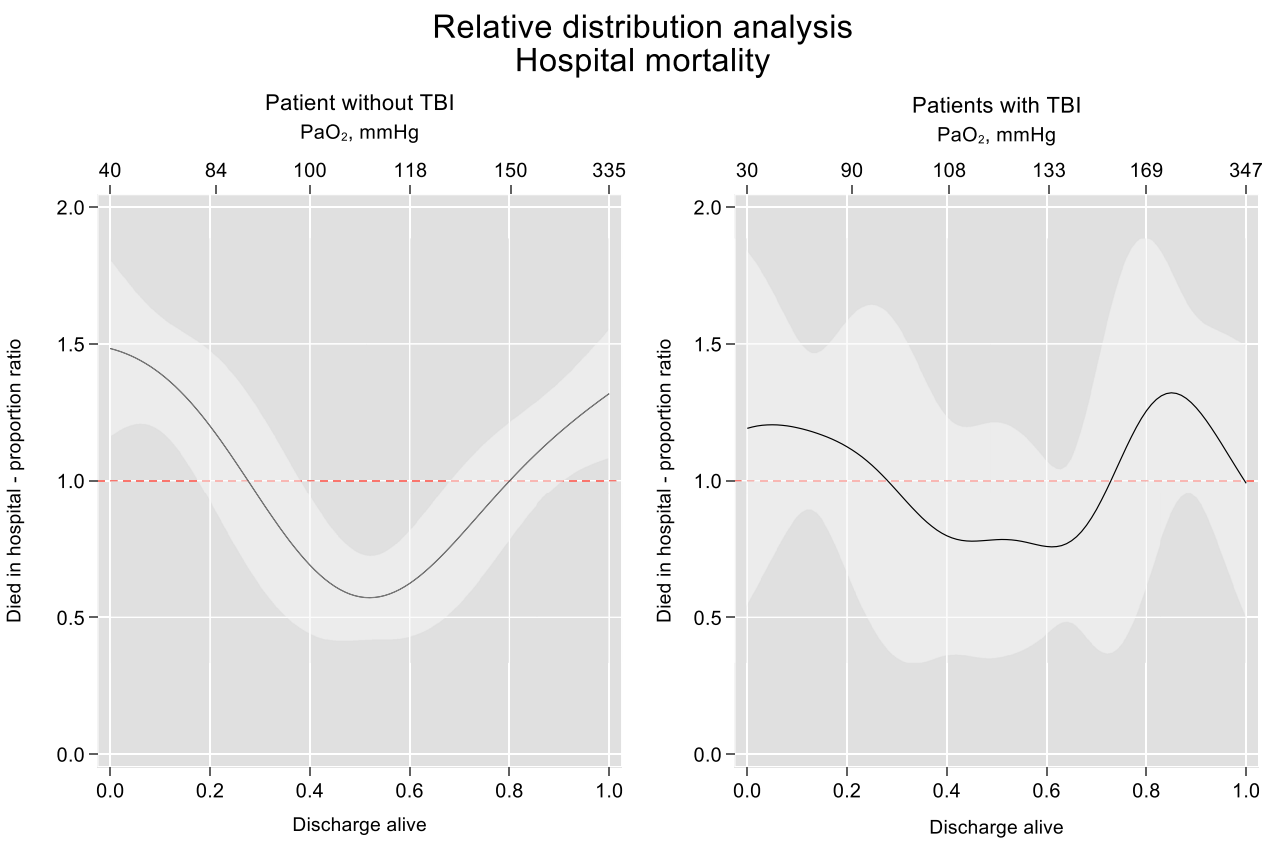

Fig. 5 Relative distribution analysis stratified by TBI. Stratified by presence or not of TBI, this figure depicts the proportion ratio of patients who died vs. those who were discharged alive according to their quantile distribution in reference to their PaO_2 values

Conclusions

In a large cohort of mechanically ventilated patients with ABI, hypoxemia and mild/moderate hyperoxemia were relatively frequent. Oxygen values during ICU stay can influence in-hospital mortality. However, the small number of oxygen values collected represents a major limitation of the study. These results can serve as hypothesis generating to create further randomized controlled trials with this population with specific oxygen thresholds.

Supplementary Information

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Author Contributions

CR and PP: conception of the work, design. CR, DB, RB, and PP: data interpretation, drafting the manuscript, critical revision of the manuscript, final approval. RB and PP: supervision of the work. All authors: critical revision of the manuscript, final approval.

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Data Availability

The data sets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Ethical Approval/Informed Consent

Approval to conduct this subanalysis was not necessary. Approval to enroll patients in the ENIO main study was obtained from the institutional review board of the promoter center (Groupe Nantais d'Éthique dans le Domaine de la Santé, IRB No. 7/11/2017) and of each participating center. Informed consent was generally waived in accordance with the observational nature of the ENIO study but if necessary was collected in accordance with the local regulations of each involved institutional review board. Informed consent was obtained from the patient or from the patient's next of kin in case the patient was unable to give the consent at the time of enrollment.

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