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High arterial oxygen levels and supplemental oxygen administration in traumatic brain injury: insights from CENTER-TBI and OzENTER-TBI

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Abstract

Purpose: The effect of high arterial oxygen levels and supplemental oxygen administration on outcomes in traumatic brain injury (TBI) is debated, and data from large cohorts of TBI patients are limited. We investigated whether exposure to high blood oxygen levels and high oxygen supplementation is independently associated with outcomes in TBI patients admitted to the intensive care unit (ICU) and undergoing mechanical ventilation.

Methods: This is a secondary analysis of two multicenter, prospective, observational, cohort studies performed in Europe and Australia. In TBI patients admitted to ICU, we describe the arterial partial pressure of oxygen (PaO_2) and the oxygen inspired fraction (FiO_2). We explored the association between high PaO_2 and FiO_2 levels within the first week with clinical outcomes. Furthermore, in the CENTER-TBI cohort, we investigate whether PaO_2 and FiO_2 levels may have differential relationships with outcome in the presence of varying levels of brain injury severity (as quantified by levels of glial fibrillary acidic protein (GFAP) in blood samples obtained within 24 h of injury).

Results: The analysis included 1084 patients (11,577 measurements) in the CENTER-TBI cohort, of whom 55% had an unfavorable outcome, and 26% died at a 6-month follow-up. Median PaO_2 ranged from 93 to 166 mmHg. Exposure to higher PaO_2 and FiO_2 in the first seven days after ICU admission was independently associated with a higher mortality rate. A trend of a higher mortality rate was partially confirmed in the OzENTER-TBI cohort ($n = 159$). GFAP was independently associated with mortality and functional neurologic outcome at follow-up, but it did not modulate the outcome impact of high PaO_2 levels, which remained independently associated with 6-month mortality.

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Conclusions: In two large prospective multicenter cohorts of critically ill patients with TBI, levels of PaO_2 and FiO_2 varied widely across centers during the first seven days after ICU admission. Exposure to high arterial blood oxygen or high supplemental oxygen was independently associated with 6-month mortality in the CENTER-TBI cohort, and the severity of brain injury did not modulate this relationship. Due to the limited sample size, the findings were not wholly validated in the external OzENTER-TBI cohort. We cannot exclude the possibility that the worse outcomes associated with higher PaO_2 were due to use of higher FiO_2 in patients with more severe injury or physiological compromise. Further, these findings may not apply to patients in whom FiO_2 and PaO_2 are titrated to brain tissue oxygen monitoring ($PbtO_2$) levels. However, at minimum, these findings support the need for caution with oxygen therapy in TBI, particularly since titration of supplemental oxygen is immediately applicable at the bedside.

Keywords: PaO_2, FiO_2, Traumatic brain injury, GOSE, Mortality, GFAP

Introduction

In patients with traumatic brain injury (TBI), hypoxemia is a major predictor of hospital and 6-month mortality [1]. Oxygen supplementation aims to reverse tissue hypoxia and, thus, improve cell viability, organ function, and survival in critically ill patients [2]. However, this may lead to administering more oxygen than needed to patients admitted to the intensive care unit (ICU) [3].

While hyperbaric oxygen is known to be neurotoxic [4], it is not clear whether high normobaric oxygen levels may play a detrimental role in the brain [5]. Hyperoxia, i.e., high inspiratory oxygen fraction, may be associated with excitotoxicity in severe TBI [6]. Furthermore, hyperoxemia, i.e., high blood oxygen partial pressure levels, may potentially worsen organ injury and impact the case fatality rate of critically ill patients with TBI [7, 8]. Therefore, not only too low but even extreme hyperoxemia might cause injury in TBI patients, as David et al. showed [9]. Data on more than 36,000 mixed ICU patients mechanically ventilated with early arterial partial pressure of oxygen (PaO_2) suggested an independent U-shape association with hospital mortality [10]. A recent metanalysis of 32 studies in acute brain-damaged patients highlighted that hyperoxemia, differently defined across studies, was associated with an increased risk of poor neurological outcomes [11]. Patients with a poor neurological outcome also had a significantly higher maximum PaO_2 and mean PaO_2. These associations were present, especially in patients with subarachnoid hemorrhage and ischemic stroke, but not in traumatic brain injured.

Currently, there is no evidence to support the role of hyperoxemia or hyperoxia in a large real-world dataset of critically ill patients admitted to ICU with severe TBI [12–14].

Therefore, we described variability across centers in the blood oxygen levels (i.e., PaO_2) and oxygen supplementation distributions (i.e., inspiratory oxygen fraction, FiO_2) and investigated whether high PaO_2 and FiO_2 levels are associated with worse 6-month outcomes. We validated our findings in the multicenter Australian OzENTER-TBI database [15]. Finally, we explored whether PaO_2 and FiO_2 levels may contribute differently to outcomes in the presence of increasing levels of glial fibrillary acidic protein (GFAP), a biomarker of brain injury severity.

Take-home message

In two large prospective multicenter cohorts of traumatic brain injured patients, arterial and supplemental oxygen levels varied widely across centers during the first seven days after admission to the intensive care unit.

Exposure to high arterial blood oxygen or high supplemental oxygen—a therapeutic gas immediately titratable at the bedside—was independently associated with 6-month mortality, regardless of brain injury severity.

The aims of this study are to:

1. Describe the values and the differences in PaO_2 and FiO_2 in the first week from ICU admission in mechanically ventilated TBI patients across centers in CENTER-TBI;
2. assess whether high levels of PaO_2 or FiO_2 are independently associated with 6-month mortality and unfavorable neurologic outcome in CENTER-TBI;
3. evaluate whether the impact of high levels of oxygen exposure or high levels of supplemental oxygen on 6-month outcome could be worsened by increasing brain injury severity, as assessed by acute (first 24 h) serum levels of GFAP in the CENTER-TBI cohort.

All these objectives (except the last one) were subsequently validated in an external cohort of patients with traumatic brain injury from OzENTER-TBI. Hypotheses of the current analyses were that exposure to high oxygen and FiO_2 levels in TBI patients mechanically ventilated and admitted to ICU may promote brain injury and have

a negative impact on both functional neurological disability and survival.

Methods

Study design and patients

The Collaborative European NeuroTrauma Effectiveness in Research in Traumatic Brain Injury (CENTER-TBI study, registered at clinicaltrials.gov NCT02210221) is a longitudinal, prospective data collection from TBI patients across 65 centers in Europe between December 2014 and December 2017. The design and the results of the screening and enrollment process have been previously described [12, 13]. The Australia–Europe NeuroTrauma Effectiveness Research in Traumatic Brain Injury OzENTER-TBI Study was conducted in two designated adult major trauma centers in Victoria, Australia, between February 2015 and March 2017 [15]. The Medical Ethics Committees approved both studies in all participating centers, and informed consent was obtained according to local regulations (https://www.center-tbi.eu/project/ethical-approval). Therefore, the studies have been performed per the ethical standards of the Declaration of Helsinki and its later amendments.

In the OzENTER-TBI Study, patients or families were allowed to opt out of data collection. OzENTER-TBI was used as an external validation cohort.

Before starting the analysis, this project on PaO_2 management was preregistered on the CENTER-TBI proposal platform and approved by the CENTER-TBI proposal review committee.

We included all patients in the CENTER-TBI Core study who had:

- a TBI necessitating ICU admission,
- tracheal intubation and mechanical ventilation,
- at least two PaO_2 measurements in the first seven days.

These inclusion criteria were also applied to select patients from the OzENTER-TBI study for the validation cohort.

This report complies with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Data collection and definitions

Detailed information on data collection is available on the study website (https://www.center-tbi.eu/data/dictionary). The daily lowest and highest PaO_2 and FiO_2 values from arterial blood gases—that were collected as per the case report form—were evaluated in this study. Specifically, we investigated the role of variables representing different aspects of arterial oxygen levels and supplemental oxygen administration during the first week of ICU admission, including:

- The highest PaO_2 (PaO_{2max}) and FiO_2 (FiO_{2max}) exposures.
- The mean of the highest daily PaO_2 (PaO_{2mean}) and FiO_2 (FiO_{2mean}).
- The mean of the swings of PaO_2 (ΔPaO_{2mean}) and of FiO_2 (ΔFiO_{2mean}). The swings were calculated daily as the difference between the highest and the lowest PaO_2 and FiO_2. They represent the average day-to-day variability of PaO_2 and FiO_2.

Mortality and functional neurological outcome measured as the 8-point Extended Glasgow Outcome Score (GOSE) were assessed six months post-injury. An unfavorable outcome was defined as GOSE ≤ 4 (i.e., low and upper severe disability, vegetative state, or dead), including both poor functional outcome and mortality. All responses were obtained by trained study personnel—blinded to the PaO_2 and FiO_2 data—from patients or from a proxy (where impaired cognitive capacity prevented patient interview), during a face-to-face visit, by telephone interview, or by postal questionnaire around six months after injury [16].

In CENTER-TBI, the severity of brain injury, traditionally evaluated with clinical and neuroradiologic elements, was also gauged by serum brain injury biomarkers. For this study, a decision was made to use GFAP, a glial cytoskeletal protein, as a proxy measure of brain injury severity. GFAP was the brain injury biomarker with the highest discriminative performance on computed tomography (CT) brain injury [17], and it is strongly associated with mortality and long-term outcomes after injury [18, 19]. GFAP within 24 h after trauma was quantified by an ultrasensitive immunoassay using digital array technology (Single Molecule Arrays, SiMoA)-based assay (Quanterix Corp., Lexington, MA).

Statistical methods

Patient characteristics were described by medians (interquartile range, IQR) or means (standard deviations, SD) as appropriate and counts or proportions. The role of PaO_{2max}, FiO_{2max}, PaO_{2mean}, FiO_{2mean} or ΔPaO_{2mean}, ΔFiO_{2mean} (one at a time) on 6-month mortality and unfavorable neurological outcome was evaluated through mixed-effect logistic regression models, adjusting for the IMPACT core covariates (age, Glasgow Coma Scale (GCS) motor score and pupillary reactivity) and injury severity score (ISS), with the center as a random effect. The assumption of linearity of the effect for continuous variables was evaluated using

splines, and the results of the models were reported as odds ratios (OR) along with the corresponding 95% confidence intervals (CI). To simplify the clinical interpretation of the OR of the exposure variables, PaO_2 and FiO_2 increases were referred to 10 mmHg and 0.1 each, respectively. Then, we enriched the models, including GFAP, which was log-transformed to satisfy the linearity assumption. We also investigated a potential interaction between GFAP and the six variables representing the oxygen status (one at a time) through a flexible approach based on restricted cubic splines and tensor-product splines. The final models were selected using standard statistical performance measures such as Akaike Information Criteria (AIC) and likelihood ratio tests for non-nested and nested models. Finally, we used data from the OzENTER-TBI cohort to validate our findings through the same modeling approach used for CENTER-TBI. However, here we omitted the random term for centers, while including the only two centers in the study as a dummy variable. Analyses were done on complete cases and using the MICE algorithm for multiple imputations of missing data (ten imputed datasets). Tests were performed two-sided with a significance alpha level of 5%. To protect from the risk of alpha inflation in testing the effect of arterial oxygen levels and supplemental oxygen administration on outcomes, we also adjusted the *p* values in the models according to the approach of Benjamini–Hochberg. All analyses were conducted using R statistical software (version 4.03).

Results

Of the 4509 patients included in the CENTER-TBI dataset, 2138 subjects were admitted to ICU and, among these, 1084 (median age was 49 [29–65], and 75% male) from 51 centers fulfilled the inclusion criteria (Supplemental Fig. 1). Half of the population experienced thoracic trauma, which in 41.5% of the cases was major.

All 198 patients included in the OzENTER-TBI dataset were admitted to ICU and, among these, 159 fulfilled the inclusion criteria (Supplemental Figure 1). In OzENTER-TBI, the median age was 39 [24–65], and 77% of the population was male. Almost 55% of the population experienced thoracic trauma, which in 46.5% of the cases was severe or critical. A comprehensive description of the population of the CENTER-TBI and OzENTER-TBI study is reported in Table 1. Patient characteristics stratified by 6-month mortality are described in Supplemental Table 1 (CENTER-TBI) and Supplemental Table 2 (OzENTER-TBI). We focused on the highest PaO_2 and FiO_2 daily levels in the current analysis in both cohorts.

CENTER-TBI

Arterial oxygen levels and supplemental oxygen administration

During the first week of ICU admission, a total of 11,577 measurements of PaO_2 were available (5747 lowest and 5830 highest daily values), for an overall median of PaO_2 and FiO_2 of 112 mmHg (IQR 86–144) and 0.4 (IQR 0.3–0.5), respectively. A total of 526 (48.5%) patients had complete daily measurements of high PaO_2 during the first week (median of 6 measures, IQR 4–7). The remaining patients had, respectively, 6 (136, 12.5%), 5 (72, 6.6%), 4 (89, 8.2%), 3 (94, 8.7%) and 2 (167, 15.4%) daily measurements of PaO_2. The median highest PaO_2 level during the first seven days since ICU admission was 134 mmHg (IQR 113–167). The median of highest FiO_2 levels during the first seven days since ICU admission was 0.45 (IQR 0.40–0.5) (Supplemental Fig. 2). Mean PaO_{2max}, PaO_{2mean} and ΔPaO_{2mean} were 231, 156 and 57 mmHg, respectively. PaO_{2max} showed a strong correlation with ΔPaO_{2mean} ($T_{Kendall} = 0.51$, 95% CI [0.48–0.53]) and with PaO_{2mean} ($T_{Kendall} = 0.66$, 95% CI [0.64–0.68]). Mean FiO_{2max}, FiO_{2mean} and ΔFiO_{2mean} were 0.59, 0.45 and 0.05 mmHg, respectively (Table 1). The highest PaO_2 levels varied widely across centers, with the center-specific median ranging from 88 to 170 mmHg and the highest PaO_2 levels within center ranging from 162 to 612 mmHg. Similarly, the highest median FiO_2 levels during the first seven days since ICU admission varied widely across centers ranging from 0.21 to 0.96. Center variability in PaO_2 (panel A) and FiO_2 levels (panel B) across centers is represented in Fig. 1. Of note, overall median PaO_2 levels in patients with brain tissue oxygen monitoring ($PbtO_2$) were similar compared to the patient population with no $PbtO_2$ monitoring (133 versus 137 mmHg, data not shown) (Supplemental Fig. 3).

Arterial oxygen levels and outcomes in TBI patients

Data on mortality and neurological functional score GOSE at 6 months were available in 967 (89.2%) TBI patients. Five hundred and twenty-eight patients (54.6%) had an unfavorable GOSE at a 6-month follow-up, and 252 died within that period (26.1%). After adjusting, we estimated the OR for a 10 mmHg increase in PaO_2. We found that both PaO_{2max} (OR 1.02, 95% CI 1–1.04) and ΔPaO_{2mean} (OR 1.07, 95% CI 1.03–1.12) were independently associated with an unfavorable functional neurologic outcome as expressed by a GOSE score ≤ 4 at 6-month follow-up (Model 1, Table 2 and Supplemental Table 3 for the estimates in the complete regression model). Furthermore, we observed that all the exposure variables to high PaO_2 were positively associated with an increased risk of mortality (PaO_{2max}, OR 1.03, 95% CI 1.01–1.05; PaO_{2mean}, OR 1.08, 95% CI 1.04–1.13;

Table 1 Characteristics of the study cohorts from CENTER-TBI and OzENTER-TBI

Variable	Level	CENTER-TBI (*N* = 1084)	OzENTER-TBI (*N* = 159)
Demographic characteristics			
Age, median [IQR]		49 [29–65]	39 [24–65]
Sex, *n* (%)	Female	270 (25)	37 (23)
	Male	814 (75)	122 (77)
Clinical presentation			
Hypotension, *n* (%)	No	843 (77.9)	116 (73)
	Yes	239 (22.1)	43 (27)
	NA (*n*)	2	0
Hypoxia, *n* (%)	No	1030 (95)	157 (98.7)
	Yes	54 (5)	2 (1.3)
Injury Severity Score, median [IQR]		34 [25–45]	29 [25–38]
	NA (*n*)	3	0
pH, median [IQR]	Lowest	7.34 [7.29–7.39]	7.33 [7.29–7.37]
	NA (*n*)	20	0
	Highest	7.43 [7.39–7.47]	7.41 [7.38–7.45]
	NA (*n*)	6	0
Neurological presentation			
Pupillary reactivity, *n* (%)	Both reactive	790 (72.9)	119 (74.8)
	One reactive	87 (8)	11 (7)
	Both unreactive	157 (14.5)	25 (15.7)
	NA	50 (4.6)	4 (2.5)
GCS Motor Score, *n* (%)	Localizes/obeys	419 (38.7)	33 (20.7)
	None/extension	493 (45.5)	117 (73.6)
	Any flexion	151 (13.9)	8 (5)
	NA	21 (1.9)	1 (0.7)
GCS score, *n* (%)	GCS > 8	370 (34.1)	58 (36.5)
	GCS ≤ 8	657 (60.6)	97 (61)
	NA	57 (5.3)	4 (2.5)
ICP at ICU admission, median [IQR]		8 [4–14]	11 [7–15]
	NA (*n*)	521	108
Mean ICP, median [IQR]		11 [6–15]	11 [8–15]
	NA (*n*)	521	108
Brain injury severity			
Marshall CT Classification, median [IQR]		3 [2–6]	2 [2–6]
	NA (*n*)	105	21
GFAP, median [IQR]	ng/mL	20.5 [7–50.8]	/
	NA (*n*)	198	159
Oxygenation			
Day 1 $PaO_{2overall}$, mean (SD)	mmHg	207.17 (99.91)	328.18 (144.46)
PaO_{2mean}, mean (SD)	mmHg	155.79 (46.93)	197.79 (73.79)
PaO_{2max}, mean (SD)	mmHg	230.92 (102.95)	356.01 (134.47)
ΔPaO_{2mean}, mean (SD)	mmHg	57 (36.7)	98.20 (59.95)
Day 1—PaO_2/FiO_2, mean (SD)	mmHg	412.48 (197.08)	453.59 (207.1)
Day 1 $FiO_{2overall}$, mean (SD)		0.54 (0.21)	0.76 (0.26)
FiO_{2mean}, mean (SD)		0.45 (0.15)	0.48 (0.15)
FiO_{2max}, mean (SD)		0.59 (0.22)	0.82 (0.23)
ΔFiO_{2mean}, mean (SD)		0.05 (0.08)	0.15 (0.11)
Functional neurologic outcome			
GOSE 6-month follow-up, *n* (%)			
GOSE < = 4		528 (48.7)	53 (33.3)
GOSE > 4		439 (40.5)	95 (59.7)
NA		117 (10.8)	11 (7)

Table 1 (continued)

Hypotension was defined as a documented systolic blood pressure < 90 mmHg; hypoxia was defined as a documented partial pressure of oxygen (PaO_2) < 8 kPa (60 mmHg), oxygen saturation (SaO_2) < 90%, or both

CT computed tomography, *GCS* Glasgow Coma Scale, *GFAP* gliofibrillar acid protein, *GOSE* Glasgow Outcome Scale Extended, *ICP* intracranial pressure, *ICU* intensive care unit, *IQR* interquartile range, *NA* not available, *SD* standard deviation

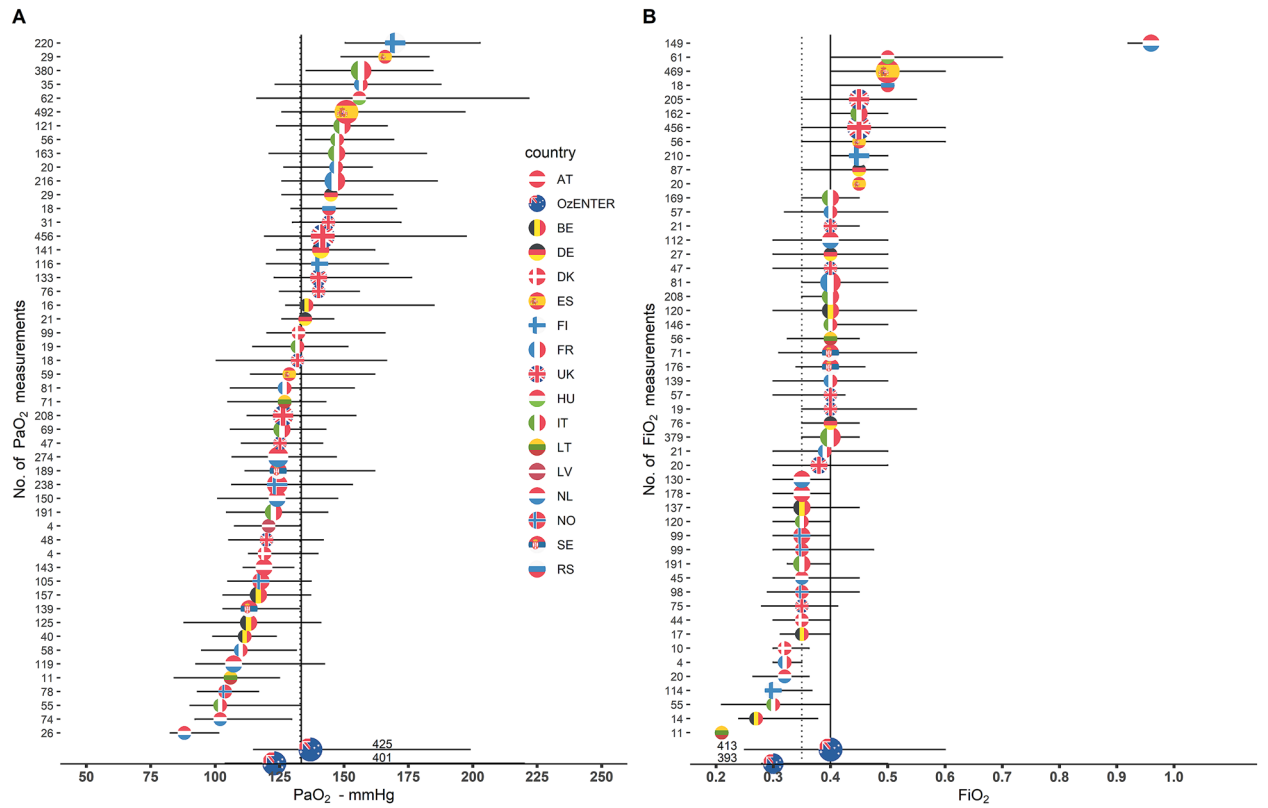

Fig. 1 Center-specific median values of daily highest PaO_2 and FiO_2. **A** Center-specific median values (colored by country flag) of daily highest PaO_2 with the corresponding interquartile range. The solid vertical line represents the overall CENTER-TBI median of daily highest PaO_2 values, while the dashed one refers to OzENTER-TBI, and the size of the dots is proportional to the number of PaO_2 measurements in the center. **B** Center-specific median values (colored by country flag) of daily highest FiO_2 with the corresponding interquartile range. The solid vertical line represents the overall CENTER-TBI median of daily highest FiO_2 values, while the dashed one refers to OzENTER-TBI, and the size of the dots is proportional to the number of FiO_2 measurements in the center

ΔPaO_{2mean}, OR 1.14, 95% CI 1.08–1.2; all estimates for 10 mmHg) (Model 1, Table 2 and Supplemental Table 4). A detailed description of all confounders estimates for both outcomes is described in Supplemental Tables 3 and 4. The estimated probability of mortality from the regression model by arterial oxygen levels is depicted in Fig. 2 (Panel A, B, C).

We also explored the role of exposure to high blood oxygen levels on the neurologic outcome by further adjusting the model for GFAP levels. GFAP was positively associated with a lower GOSE score and a higher mortality rate. Among the variables representing higher blood oxygenation, the ΔPaO_{2mean} confirmed its positive association with a lower GOSE, while all the three high oxygenation variables remained positively associated with a higher mortality rate (Model 2, Table 2). A detailed description of all confounders estimates is reported in Supplemental Tables 5 and 6. We explored the interaction between exposure to high PaO_{2max} and GFAP levels on GOSE and mortality. We did not find any interaction between the studied variables, as shown in Fig. 3 (panels A and B), where the surfaces that represent the smoothed interactions (on log scale) are mainly flattened on zero.

Table 2 Multivariable models on GOSE and mortality at 6-month follow-up in CENTER-TBI (Models 1, 2 and 3)

CENTER-TBI	6-month GOSE *N* = 912 patients, 489 GOSE ≤ 4			6-month mortality *N* = 912 patients, 225 died		
Model 1	**OR[a]**	**95% CI**	***p* value**	**OR[a]**	**95% CI**	***p* value**
PaO_{2max} (for 10 mmHg increase)	1.02	1–1.04	0.014	1.03	1.01–1.05	0.002
PaO_{2mean} (for 10 mmHg increase)	1.03	1–1.07	0.059	1.08	1.04–1.13	< 0.001
ΔPaO_{2mean} (for 10 mmHg increase)[b]	1.07	1.03–1.12	0.001	1.14	1.08–1.20	< 0.001
	6-month GOSE *N* = 764 patients, 407 GOSE ≤ 4			**6-month mortality** *N* = 764 patients, 175 died		
Model 2	**OR[a]**	**95% CI**	***p* value**	**OR[a]**	**95% CI**	***p* value**
Logarithm GFAP	1.51	1.33–1.71	< 0.001	1.51	1.29–1.77	< 0.001
PaO_{2max} (for 10 mmHg increase)	1.02	1–1.03	0.064	1.03	1.01–1.05	0.008
Logarithm GFAP	1.52	1.34–1.72	< 0.001	1.52	1.3–1.78	< 0.001
PaO_{2mean} (for 10 mmHg increase)	1.03	0.99–1.07	0.092	1.09	1.04–1.14	0.001
Logarithm GFAP	1.52	1.34–1.72	< 0.001	1.53	1.3–1.81	< 0.001
ΔPaO_{2mean} (for 10 mmHg increase)	1.05	1–1.11	0.031	1.14	1.08–1.21	< 0.001
	6-month GOSE *N* = 877 patients, 470 GOSE ≤ 4			**6-month mortality** *N* = 877 patients, 212 died		
Model 3	**OR[c]**	**95% CI**	***p* value**	**OR[c]**	**95% CI**	***p* value**
FiO_{2max} (for 0.1 increase)	1.03	0.96–1.1	0.453	1.18	1.08–1.29	< 0.001
FiO_{2mean}, (for 0.1 increase)	1.02	0.92–1.14	0.694	1.31	1.13–1.51	< 0.001
ΔFiO_{2mean}, (for 0.1 increase)	1.03	0.84–1.27	0.761	1.46	1.13–1.88	0.004

Model 1. Adjusted odds ratio with 95% confidence intervals of exposure to high blood oxygen levels within 7 days of ICU admission on GOSE and mortality at 6-month follow-up in CENTER-TBI. Mixed-effect logistic regression models adjusted for age, pupillary reactivity (both reactive, one reactive, both unreactive), GCS motor (any flexion, none/extension, localizes/obey), Injury Severity Score, and, once at a time, PaO_{2max}, PaO_{2mean} and ΔPaO_{2mean} for CENTER-TBI with center as a random effect. *Model 2*. *Model 1* plus the degree of brain injury quantified as GFAP levels. *Model 3*. Adjusted odds ratio with 95% CI of GOSE and mortality at 6-month follow-up in TBI patients exposed to high supplemental oxygen administration within 7 days of ICU admission in CENTER-TBI. Mixed-effect logistic regression models adjusted for age, pupillary reactivity (reactive, one reactive, both unreactive), GCS motor (any flexion, none/extension, localizes/obey) and, once at a time, FiO_{2max}, FiO_{2mean} and ΔFiO_{2mean} for CENTER-TBI with center as a random effect. Full models with all covariates estimates are reported in the Supplemental material

[a] OR is for 10 mmHg increase in PaO_2 covariate

[b] 1 patient did not have low PaO_2

[c] OR regards 0.1 increments in FiO_2 covariate

Supplemental oxygen administration and outcome

After adjustment for confounders, FiO_{2max}, FiO_{2mean} and ΔFiO_{2mean} had no significant association with neurological outcomes. However, they showed a positive independent association with mortality at 6 months (Model 3, Table 2, and Supplemental Tables 7 and 8). The estimated mortality probability by administering supplemental oxygen is depicted in Fig. 2 (Panels D, E, and F).

Results concerning PaO_2 and FiO_2 were confirmed when the Benjamini–Hochberg method was applied to control the false discovery rate (results not shown). The sensitivity analyses accounting for missing data also corroborated the findings from the models on complete cases for both PaO_2 and FiO_2 data (Supplemental Table 9). From the descriptive analysis reported in Supplemental Table 10, patients with and without missing data have similar characteristics. As 5 patients died within 48 h with PaO_2 levels beyond 450 mmHg and $PaCO_2 > 60$ mmHg and may have undergone an apnea breath test, we performed a sensitivity analysis excluding these patients for all the explored outcomes in the original analysis. No differences were observed as reported in Supplemental Table 11.

OzENTER-TBI

Arterial oxygen levels and supplemental oxygen administration

During the first week of ICU admission, a total of 1651 measurements of PaO_2 were available (825 lowest and 826 highest daily values) for an overall median value of PaO_2 and FiO_2 of 133 (IQR 109–212) and 0.3 (IQR 0.25–0.4), respectively. During the first week, 43.4% had complete daily measurements of PaO_2 (median 6, IQR 3–7). The median of the highest PaO_2 level during the first 7 days since ICU admission was 133 (IQR 109–212) (Supplemental Fig. 2). The highest median FiO_2 levels during the first 7 days since ICU admission was 0.35 (IQR

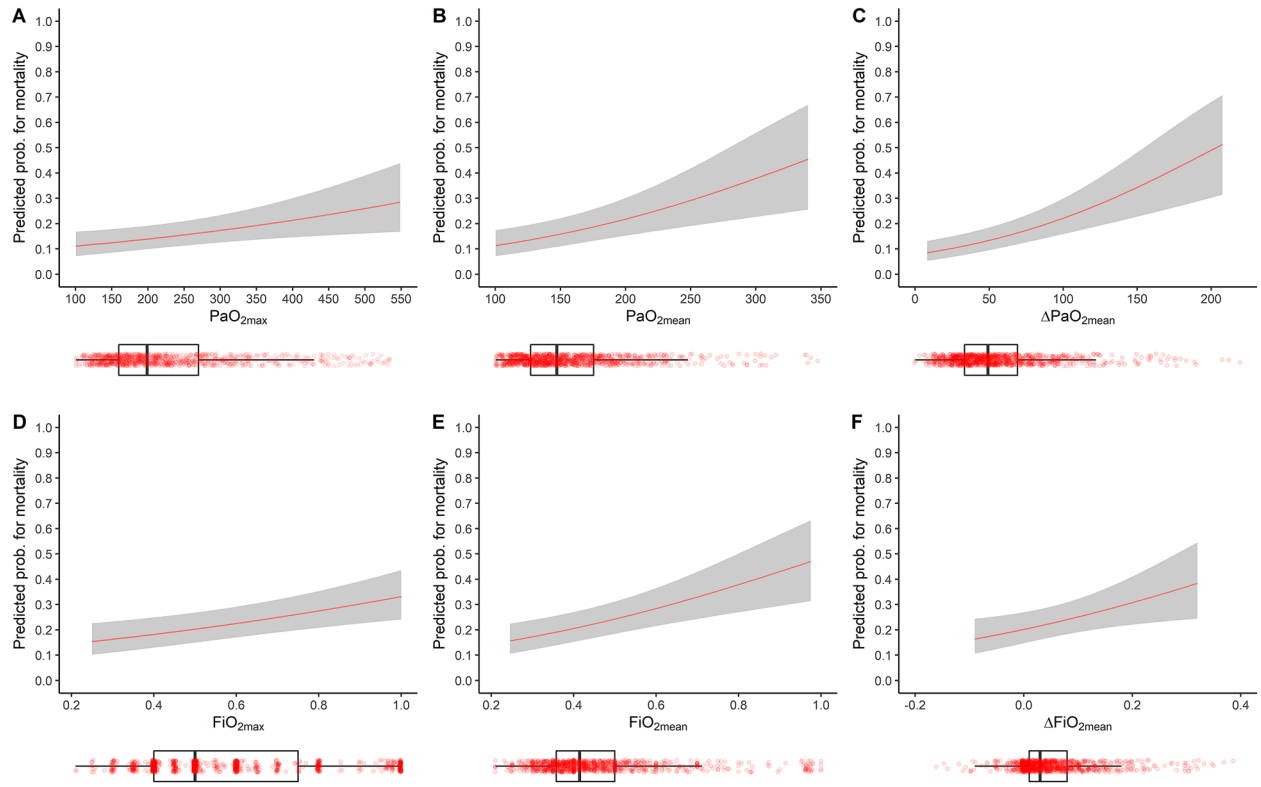

Fig. 2 The model-based probability for mortality. **A**–**C** The probability for mortality estimated by *Model 2* (i.e., Table 2) for PaO_{2max}, PaO_{2mean} and ΔPaO_{2mean} vary through the corresponding spanned range of values, respectively, while continuous variables were set to median value and categorical variables to middle category. **D**–**F** The probability for mortality estimated by *Model 3* (i.e., Table 2) for FiO_{2max}, FiO_{2mean} and ΔFiO_{2mean} vary through the corresponding spanned range of values, respectively. At the same time, continuous variables were set to median value and categorical variables to middle category. Below each panel there are boxplots of the corresponding PaO_2 and FiO_2 variables, with scattered points of all measurements

0.25–0.5) (Supplemental Fig. 2). Mean PaO_{2max}, PaO_{2mean} and ΔPaO_{2mean} were 356, 197 and 98 mmHg, respectively (Table 1). PaO_{2max} showed a strong correlation with ΔPaO_{2mean} ($T_{Kendall} = 0.63$, $p = < 0.001$) and with PaO_{2mean} ($T_{Kendall} = 0.71$, $p < 0.001$). Mean FiO_{2max}, FiO_{2mean} and ΔFiO_{2mean} were 0.82, 0.48 and 0.15 mmHg, respectively. Center variability in PaO_2 (panel A) and FiO_2 levels (panel B) across the 2 centers was represented in Fig. 1.

Arterial oxygen levels and outcomes in TBI patients

Data on mortality and neurological functional score GOSE at 6 months were available for 148 (93.1%) TBI patients. Ninety-five patients (64.2%) had an unfavorable GOSE at 6-month follow-up, and 40 died within that period (27%). After adjusting for multiple confounders, including IMPACT core baseline covariates, ISS and the 2 different centers (i.e., site code), we observed that none of the oxygen exposure variables was independently associated with GOSE (Model 1, Table 3 and Supplemental Table 12). After adjustment for the same confounders, we observed that ΔPaO_{2mean}, (OR 1.08, 95% CI 1–1.18) trended toward a higher mortality rate (Model 1, Table 3 and Supplemental Table 13). A detailed description of all confounders estimates for both outcomes was described in Supplemental Tables 12 and 13.

Supplemental oxygen administration and outcome

After adjustment for confounders, FiO_{2max}, FiO_{2mean} and ΔFiO_{2mean} confirmed the data of CENTER-TBI with no significant association with neurological outcome. However, increases in FiO_{2mean} trended toward a higher mortality rate (Model 2, Table 3). A detailed description of all confounders estimates for both outcomes was described in Supplemental Tables 14 and 15.

Discussion

In this study, we investigated whether exposure to high blood oxygen levels and high oxygen supplementation is

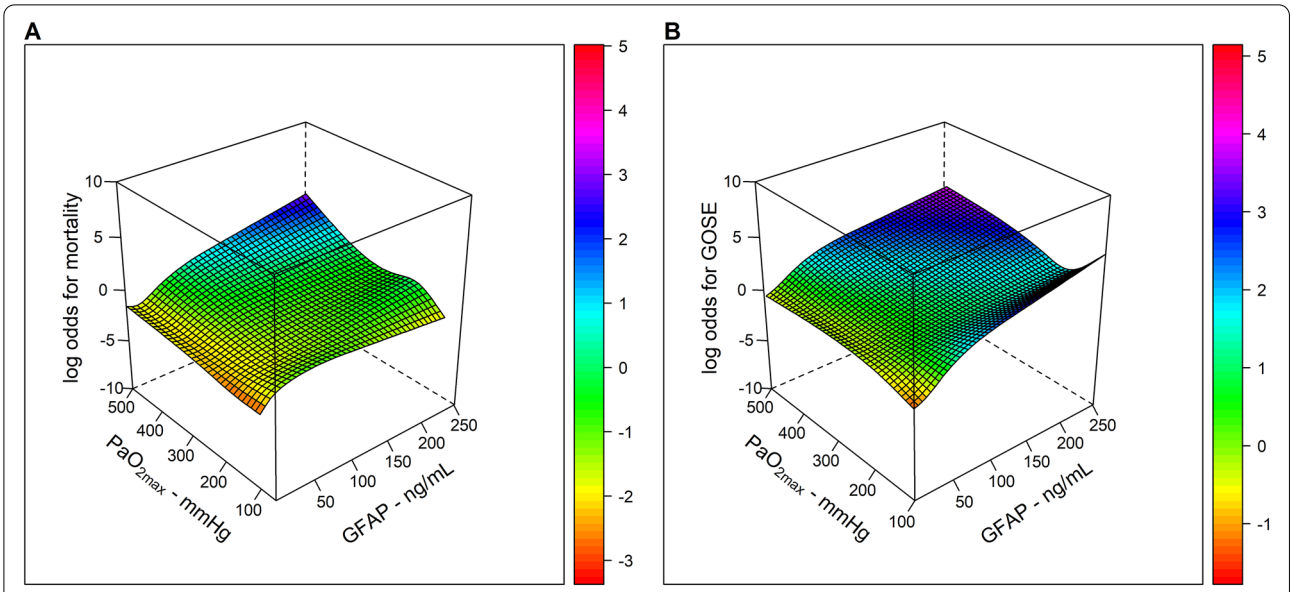

Fig. 3 Tensor cubic spline for the interaction between PaO_{2max} and GFAP. In **A** on the left, we represented the tensor cubic spline with 4 degrees of freedom each, used for the interaction between PaO_{2max} and GFAP in the logistic model with 6-month GOSE as outcome. In **B** on the right, we represented the tensor cubic spline with 4 degrees of freedom each, used for the interaction between PaO_{2max} and GFAP in the logistic model with 6-month mortality as outcome. All other continuous covariates were set to median values and mid-category for categorical ones

Table 3 Multivariable models on GOSE and mortality at 6-month follow-up in OzENTER-TBI (Model 1 and 2)

OzENTER-TBI	6-month GOSE *N* = 141 patients, 92 GOSE ≤ 4			6-month mortality *N* = 141 patients, 39 died		
Model 1	**OR[a]**	**95% CI**	***p* value**	**OR[a]**	**95% CI**	***p* value**
PaO_{2max} (for 10 mmHg increase)	1.01	0.98–1.04	0.433	1	0.97–1.04	0.898
PaO_{2mean} (for 10 mmHg increase)	1.01	0.96–1.07	0.656	1.05	0.99–1.11	0.118
ΔPaO_{2mean} (for 10 mmHg increase)	1.03	0.96–1.12	0.376	1.08	1–1.18	0.054
	6-month GOSE *N* = 141 patients, 92 GOSE ≤ 4			**6-month mortality** *N* = 141 patients, 39 died		
Model 2	**OR[b]**	**95% CI**	***p* value**	**OR***	**95% CI**	***p* value**
FiO_{2max} (for 0.1 increase)	1.06	0.89–1.26	0.492	1	0.83–1.23	0.963
FiO_{2mean} (for 0.1 increase)	1.02	0.77–1.34	0.911	1.32	0.98–1.8	0.069
ΔFiO_{2mean} (for 0.1 increase)	1.15	0.79–1.69	0.483	1	0.68–1.48	0.981

Model 1. Adjusted odds ratio with 95% confidence intervals effect of exposure to high blood oxygen levels within 7 days of ICU admission on GOSE and mortality at 6-month follow-up. Validation on OzENTER-TBI. Standard logistic regression models adjusted for age, pupillary reactivity (both reactive, one reactive, both unreactive), GCS Motor (any flexion, none/extension, localizes/obey), Injury Severity Score, and, once at a time, PaO_{2max}, PaO_{2mean} and ΔPaO_{2mean} for OzENTER-TBI with a dummy variable for center. *Model 2*. Adjusted odds ratio with 95% CI of GOSE and mortality at 6-month follow-up in TBI patients exposed to high supplemental oxygen administration within 7 days of ICU admission in OzENTER-TBI. Standard logistic regression models adjusted for age, pupillary reactivity (both reactive, one reactive, both unreactive), GCS Motor (any flexion, none/extension, localizes/obey) and, once at a time, FiO_{2max}, FiO_{2mean} and ΔFiO_{2mean} for OzENTER-TBI with a dummy variable for center. Full models with all covariates estimates are reported in the Supplemental material

[a] OR is for 10 mmHg increase in PaO_2 covariate

[b] OR regards 0.1 increments in FiO_2 covariate

independently associated with outcomes in TBI patients admitted to ICU and undergoing mechanical ventilation.

The main findings can be summarized as follows:

1. TBI patients were largely exposed, with wide variability between centers, to high levels of PaO_2 during the first week of ICU admission.
2. Exposure to high PaO_2 within seven days after ICU admission was an independent predictor of 6-month

mortality in the CENTER-TBI cohort, even regardless of the severity of brain injury as defined by higher serum concentration of GFAP.
3. A higher average daily variability in PaO_2 (ΔPaO_{2mean}) predicts an unfavorable GOSE at 6 months in CENTER-TBI. These findings were not validated in the OzENTER-TBI cohort, where only ΔPaO_{2mean} trended to a higher mortality rate.
4. Exposure to high levels of supplemental oxygen has an independent positive association with mortality in the CENTER-TBI cohort. In contrast, the association between higher FiO_{2mean} and worse mortality in the OzENTER-TBI cohort showed similar directional trends but did not achieve statistical significance.

The first insight of this study is that more than 50% of TBI patients are exposed to hyperoxemia, defined as PaO_2 levels above 120 mmHg [20, 21], during the first week after ICU admission. Despite hyperoxemia being quite often defined as the presence of a $PaO_2 > 120$ [20, 22, 23], there is no agreement in the literature about a univocal threshold to define it [7, 8, 24–27]. Understanding if there is a maximum dose of oxygen that may be harmful for the brain tissue and whether a prolonged time of exposure to high oxygen levels may impair brain function and have an impact on mortality is debated. The lack of a clear definition of hyperoxemia and a limited time of oxygen exposure may lead to underestimate an association with outcome in TBI patients [27–30], despite some reports of a higher mortality in TBI patients exposed to higher levels of oxygen [7–9, 24].

This clinical investigation highlights a relevant finding that might have a direct potential clinical implication.

We reported that increasing exposure to high blood oxygen levels within the first 7 days after ICU admission independently correlates with long-term mortality in patients with TBI. This association was observed by exploring either the highest PaO_2 levels (interpreted for each 10-mmHg increase) or the daily highest PaO_2 variability. This may suggest that clinicians should pay attention not just to the absolute values of PaO_2 but also to the daily swings of blood oxygenation. We logically hypothesized that PaO_2 levels are driven by inappropriately high inspiratory levels of oxygen administered to TBI patients. When we explored the role of supplemental oxygen use (i.e., FiO_2), similarly to the association reported between blood oxygenation and mortality, we showed that the highest the levels of FiO_2 or the most elevated average daily swings of FiO_2 within the first 7 days, the higher the mortality rate. These findings highlight a direct potential clinical implication for the management of oxygen administration in critically ill patients mechanically ventilated and admitted to the ICU with TBI. The amount of oxygen delivered to TBI patients can be easily titrated by ICU physicians by setting FiO_2 levels on the ventilator. In the presence of an isolated TBI, therefore not involving the lung parenchyma that may lead to impaired oxygenation, high oxygen supplementation may be easily avoided on the ventilator by setting FiO_2 levels to target a physiological range of blood oxygenation.

Furthermore, avoiding major changes in daily FiO_2—if not needed to avoid hypoxemia—should prevent a major blood oxygenation variability and limit exposure to high oxygen levels and its detrimental effects. Our findings are in line with the recent guidelines of the European Society of Intensive Care Medicine (ESICM) on the management of mechanical ventilation in patients with an acute brain injury which, with a low level of evidence, recommend targeting normoxia (80–120 mmHg) regardless of the presence of intracranial pressure (ICP) elevation while it remains unknown whether a certain threshold of high PaO_2 should be considered safe in TBI patients [20]. The pathophysiological mechanisms behind the role of oxygen toxicity induced by hyperoxia (i.e., high FiO_2) [31, 32] and hyperoxemia (i.e., high PaO_2) [33, 34] in humans are widely recognized [5, 35]. On the one hand, hyperoxia has been shown to induce direct pulmonary toxicity by alveolar-capillary leak and fibrogenesis in healthy volunteers [36] and to have cytotoxic properties [37–39]. On the other hand, hyperoxemia increases peripheral vascular resistances [40–43], and determines the production of reactive oxygen species [44, 45] with the release of proinflammatory mediators [46]. In a cohort of severe TBI patients studied with advanced multimodality monitoring, hyperoxia had variable effects on lactate and lactate/pyruvate ratio. Microdialysis did not demonstrate a constant increase in the cerebral metabolic rate of oxygen in at-risk tissue [47]. Similar results have been shown in TBI patients exposed to high FiO_2. Hyperoxia marginally reduced lactate levels in brain tissue after TBI. However, the estimated redox status of the cells did not change and cerebral O_2 extraction seemed to be reduced. These data indicate that glucose oxidation was not improved by hyperoxia in cerebral and adipose tissue and might even be impaired [48].

In recent years, the role of oxygen on outcome has been explored in ICU patients to evaluate whether oxygen's inflammatory and cytotoxic effects on organ viability might translate into a worse survival. Two randomized controlled trials (RCTs) in critically ill (Oxygen-ICU) [49] and in septic patients (HYPERS-2S) [50] showed that targeting higher levels of PaO_2 or hyperoxia could cause a higher mortality rate. A large meta-analysis including critically ill patients confirmed that a

strategy targeting more elevated levels of PaO_2 increased mortality [51].

In contrast, so far, 4 big RCTs ($LOCO_2$ trial [52], ICU-ROX trial [53], HOT-ICU trial [54] and O_2-ICU trial [55]) suggested no significant differences in terms of primary study outcome (i.e., mortality [52, 54]; ventilator-free days [53]; and non-respiratory Sequential Organ Failure Assessment (SOFA) score [55]) between patients managed with lower versus higher oxygen targets. However, these trials showed differences in their study design in terms of targeted physiologic variables of oxygenation (i.e., PaO_2, SpO_2 and SaO_2), targets of oxygenation, safety threshold for oxygen conservative therapy [52] and study outcomes. These trials were in broad populations of critically ill patients, and do not specifically address patients with TBI. Indeed, the one trial that specifically reported on patients with brain injury provided data suggesting that patients with neurological disease not due to hypoxic–ischemic encephalopathy may have had worse outcomes with conservative oxygen therapy [53]. In the meantime, the UK-ROX trial (ISRCTN13384956) and the Mega-ROX trial (ACTRN12620000391976)—two large RCTs aimed at exploring the role of oxygen targets on mortality in critically ill patients—are currently ongoing and will shed further light on the role of oxygen targets on outcome in ICU.

We also investigated whether these negative associations of hyperoxia with outcome were modulated by injury severity, as measured by GFAP levels [17, 56]. GFAP is a biomarker representing glial injury [56] and correlates well with the severity of brain injury evaluated by brain computed tomography [17]. Furthermore, GFAP is associated with outcomes in TBI patients [57]. However, we could not demonstrate an interaction between injury severity (as measured by GFAP levels) and the association between oxygen exposure variables and outcome. This corroborates the idea that oxygen exposure may somehow influence the outcome in TBI patients regardless of the severity of brain injury. Therefore, preventing exposure to high oxygen levels in TBI patients might be suggested even in milder TBI.

However, another potential explanation for the lack of interaction between oxygen levels and GFAP may be the temporal misalignment of GFAP and oxygen levels assessment. TBI is not an acute event but an evolving process. Hence, acute GFAP and sub-acute oxygen level measures may capture distinct complementary aspects providing independent prognostic information which can enable a more effective risk-stratification of patients with TBI. Moreover, it is conceivable that high blood oxygen levels could have a differential effect based on the injury pattern/type rather than the severity of structural brain damage after TBI owing to distinct pathogenetic and pathobiological pathways. In support of such a possibility, robust experimental evidence has indicated specific therapeutic responses according to different injury models as also tracked by circulating GFAP [58, 59].

Strengths

Strengths of this work include the prospective nature of the two multicenter cohorts of patients, with the OzENTER-TBI validation cohort confirming a trend similar to the findings reported in the sizeable CENTER-TBI cohort. Data comes from a large real-world dataset of patients with TBI representing a global population of TBI patients. Evaluating the effect of exposure to oxygen on the outcome is not episodic but integrated over the first week after ICU admission increases the association's credibility. Furthermore, the exposure variables (i.e., PaO_2 and FiO_2) are not evaluated using a pre-set cut-off. Still, their association with the outcome is explored by including them as continuous data, strengthening the findings in the multivariable models. The use of GFAP, which allowed to investigate whether oxygen exposure could play a different contribution to the outcome because of a different degree of brain injury severity, make the results generalizable to most of the spectrum of TBI. Moreover, although we acknowledge that various models were performed, the strong associations we found on mortality were supported even when we accounted for multiple comparisons.

Limitations

Several limitations deserve mention. First, considering the observational nature of the data, it is speculative to draw a direct causal relationship between high arterial oxygen levels and supplemental oxygen administration and their relationship with outcome. Therefore, our results should be taken with caution. Further randomized controlled studies are necessary to assess the effect of high arterial oxygen levels and supplemental oxygen administration on the TBI patients' outcomes. Second, 6-month GOSE and mortality are influenced by several other factors, such as systemic and ICU complications and post-ICU events. To overcome this limitation, we used an analytic model considering the effect of other available confounding factors, particularly patient clinical condition and neuroimaging features.

Besides, in these two cohorts, only a minority of patients had a brain tissue oxygen monitor. As documented by a phase-2 RCT, monitoring brain tissue ($PbtO_2$) oxygenation could reduce brain tissue hypoxia with a trend toward more favorable outcomes compared to treatment driven by intracranial pressure monitoring only [60]. A recent consensus suggested the possibility, in

the presence of low $PbtO_2$ values, of elevating the PaO_2 up to 150 mmHg or higher in more severe cases, fine-tuned to the patient's $PbtO_2$ values [61]. Some phase III randomized trials are ongoing to demonstrate the benefit of exposing hypoxic brain patients to higher oxygen levels. Therefore, our findings are not focused on a population with brain tissue hypoxia but to the overall TBI population, with/without brain hypoxia. However, we did not observe a difference in the distribution of PaO_2 levels between TBI with or without $PbtO_2$ monitoring. We cannot exclude the possibility that the worse outcomes associated with higher PaO_2 were due to use of higher FiO_2 in patients with more severe injury or physiological compromise. Further, these findings may not apply to patients in whom FiO_2 and PaO_2 are titrated to $PbtO_2$ levels.

Moreover, the two cohorts were prospectively collected with the primary aim of assessing the epidemiology and clinical practice in the management of TBI patients. As respiratory targets are not included in the primary outcome, more frequent daily data on gas exchange and more specific data on the ventilator management of these patients are missing and would have strengthened our analysis. Further, we do not have detailed data about the presence of hyperoxemia in patients undergoing an apnea breath test. However, only five patients who died within 48 h had PaO_2 levels beyond 450 mmHg with a $PaCO_2 > 60$ mmHg in the CENTER-TBI dataset, which may suggest an apnea breath test. Sensitivity analyses excluding these patients confirmed the independent association with outcome of both PaO_2 and FiO_2 variables. Finally, our dataset is limited to the first week after TBI. However, our analysis includes data that provides a longitudinal view of PaO_2 management over time.

Conclusions

In two large prospective multicenter cohorts of critically ill patients with TBI arterial oxygen levels and supplemental oxygen, administration varied widely across centers during the first 7 days after ICU admission. Exposure to high arterial blood oxygen and high supplemental oxygen were independently associated with 6-month mortality in the CENTER-TBI cohort. This was not driven by the severity of brain injury quantified by serum levels of GFAP within 24 h. The findings were not externally validated in the OzENTER-TBI cohort likely due to the limited sample size, although the effects were in the same direction of the ones from CENTER-TBI. Titration of supplemental oxygen in the presence of TBI is a practice immediately applicable at bedside. Randomized controlled trials and high-level evidence guidelines are warranted to help clinicians optimize oxygen exposure management in this cohort of patients.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s00134-022-06884-x.

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GC ideated and supervised the project, participated in the data analysis, drafted the manuscript and the supplementary tables, discussed the findings with all the authors and collected the COIs. ER ideated the project, participated in the data analysis and drafted the manuscript and supplementary tables. MP, PR and SG analyzed the data and drafted the manuscript and the supplementary tables. DKM, SM, DJC, AM and EJAW were actively involved the manuscript drafting and revision. All co-authors gave substantial feedback on the manuscript and approved the final version.

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Declarations

Conflicts of interest

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