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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 (PaO₂) and the oxygen inspired fraction (FiO₂). We explored the association between high PaO₂ and FiO₂ levels within the first week with clinical outcomes. Furthermore, in the CENTER-TBI cohort, we investigate whether PaO₂ and FiO₂ 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 PaO₂ ranged from 93 to 166 mmHg. Exposure to higher PaO₂ and FiO₂ 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 PaO₂ and FiO₂ levels, which remained independently associated with 6-month mortality.

Conclusions: In two large prospective multicenter cohorts of critically ill patients with TBI, levels of PaO₂ and FiO₂ 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

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CENTER-TBI ICU and OzENTER-TBI Participants and Investigators are listed in the Acknowledgements section.

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 PaO₂ were due to use of higher FiO₂ in patients with more severe injury or physiological compromise. Further, these findings may not apply to patients in whom FiO₂ and PaO₂ are titrated to brain tissue oxygen monitoring (PbtO₂) 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: PaO₂, FiO₂, 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 (PaO₂) 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 PaO₂ and mean PaO₂. 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., PaO₂) and oxygen supplementation distributions (i.e., inspiratory oxygen fraction, FiO₂) and investigated whether high PaO₂ and FiO₂ levels are associated with worse 6-month outcomes. We validated our findings in the multicenter Australian OzENTER-TBI database [15]. Finally, we explored whether PaO₂ and FiO₂ levels may contribute differently to outcomes in the

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.

presence of increasing levels of glial fibrillary acidic protein (GFAP), a biomarker of brain injury severity.

The aims of this study are to:

1. Describe the values and the differences in PaO₂ and FiO₂ in the first week from ICU admission in mechanically ventilated TBI patients across centers in CENTER-TBI;
2. assess whether high levels of PaO₂ or FiO₂ 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 (PaO₂) or high levels of supplemental oxygen (FiO₂) 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 FiO₂ 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 PaO₂ 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 PaO₂ 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 PaO₂ and FiO₂ 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 PaO₂ (PaO_{2max}) and FiO₂ (FiO_{2max}) exposures.
- The mean of the highest daily PaO₂ (PaO_{2mean}) and FiO₂ (FiO_{2mean}).
- The mean of the swings of PaO₂ (Δ PaO_{2mean}) and of FiO₂ (Δ FiO_{2mean}). The swings were calculated daily as

the difference between the highest and the lowest PaO₂ and FiO₂. They represent the average day-to-day variability of PaO₂ and FiO₂.

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 PaO₂ and FiO₂ 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 Δ PaO_{2mean}, Δ FiO_{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, PaO₂ and FiO₂ 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 PaO₂ and FiO₂ 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 PaO₂ were available (5747 lowest and 5830 highest daily values), for an overall median of PaO₂ and FiO₂ 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 PaO₂ 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 PaO₂. The median highest PaO₂ level during

the first seven days since ICU admission was 134 mmHg (IQR 113–167). The median of highest FiO₂ 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} ($T_{\text{Kendall}}=0.51$, 95% CI [0.48–0.53]) and with PaO_{2mean} ($T_{\text{Kendall}}=0.66$, 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 PaO₂ levels varied widely across centers, with the center-specific median ranging from 88 to 170 mmHg and the highest PaO₂ levels within center ranging from 162 to 612 mmHg. Similarly, the highest median FiO₂ levels during the first seven days since ICU admission varied widely across centers ranging from 0.21 to 0.96. Center variability in PaO₂ (panel A) and FiO₂ levels (panel B) across centers is represented in Fig. 1. Of note, overall median PaO₂ levels in patients with brain tissue oxygen monitoring (PbtO₂) were similar compared to the patient population with no PbtO₂ 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 PaO₂. 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 PaO₂ 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; 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

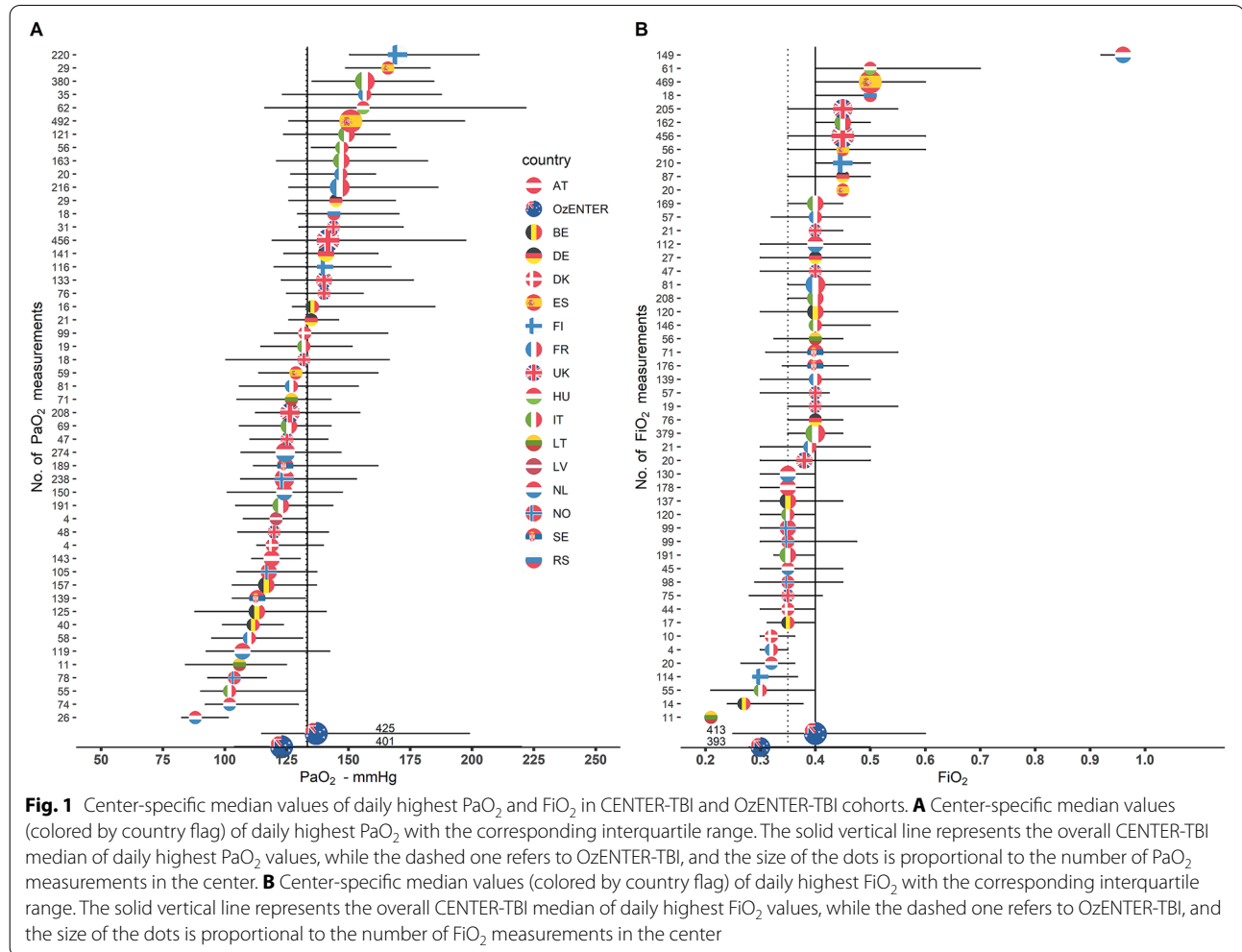
Table 1 Characteristics of the study cohorts from CENTER-TBI and OzENTER-TBI

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)
		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



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 $\text{PaO}_{2\text{max}}$ and GFAP levels on GOSE and mortality. We did not find any interaction between the studied variables, as shown in Supplemental Figure 4 (panel A) and in Fig. 3 (panel A), respectively, for $\text{PaO}_{2\text{max}}$ —and for both $\text{PaO}_{2\text{mean}}$ and $\Delta\text{PaO}_{2\text{mean}}$ as well (data not shown), where the surfaces that represent the smoothed interactions (on log scale) are mainly flattened on zero.

Supplemental oxygen administration and outcome

After adjustment for confounders, $\text{FiO}_{2\text{max}}$, $\text{FiO}_{2\text{mean}}$ and $\Delta\text{FiO}_{2\text{mean}}$ 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). We also explored the role of exposure to high supplemental 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

Table 2 Multivariable models on GOSE and mortality at 6-month follow-up in CENTER-TBI (Models 1, 2, 3 and 4)

CENTER-TBI	6-month GOSE N = 912 patients, 489 GOSE $\leq$ 4			6-month mortality N = 912 patients, 225 died		
Model 1	OR*	95% CI	p	OR*	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
Δ PaO _{2mean} (for 10 mmHg increase) ^b	1.07	1.03–1.12	0.001	1.14	1.08–1.20	<0.001
CENTER-TBI	6-month GOSE N = 764 patients, 407 GOSE $\leq$ 4			6-month mortality N = 764 patients, 175 died		
Model 2	OR*	95% CI	p	OR*	95% CI	p
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
Δ PaO _{2mean} (for 10 mmHg increase)	1.05	1–1.11	0.031	1.14	1.08–1.21	<0.001
CENTER-TBI	6-month GOSE N = 877 patients, 470 GOSE $\leq$ 4			6-month mortality N = 877 patients, 212 died		
Model 3	OR***	95% CI	p	OR***	95% CI	p
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
Δ FiO _{2mean} (for 0.1 increase)	1.03	0.84–1.27	0.761	1.46	1.13–1.88	0.004
CENTER-TBI	6-month GOSE N = 741 patients, 397 GOSE $\leq$ 4			6-month mortality N = 741 patients, 168 died		
Model 4	OR*	95% CI	p	OR*	95% CI	p
Logarithm GFAP	1.52	1.34–1.72	<0.001	1.55	1.31–1.83	<0.001
FiO _{2max} (for 0.1 increase)	1.03	0.96–1.12	0.389	1.20	1.08–1.33	0.001
Logarithm GFAP	1.52	1.34–1.72	<0.001	1.55	1.32–1.84	<0.001
FiO _{2mean} (for 0.1 increase)	1.04	0.93–1.17	0.498	1.33	1.13–1.55	<0.001
Logarithm GFAP	1.51	1.33–1.72	<0.001	1.55	1.31–1.83	<0.001
Δ FiO _{2mean} (for 0.1 increase)	0.98	0.78–1.23	0.846	1.40	1.05–1.87	0.023

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 Δ PaO_{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 Δ FiO_{2mean} for CENTER-TBI with center as a random effect. Full models with all covariates estimates are reported in the Supplemental material. *Model 4.* *Model 3* plus the degree of brain injury quantified as GFAP levels

^a OR is for 10 mmHg increase in PaO₂ covariate

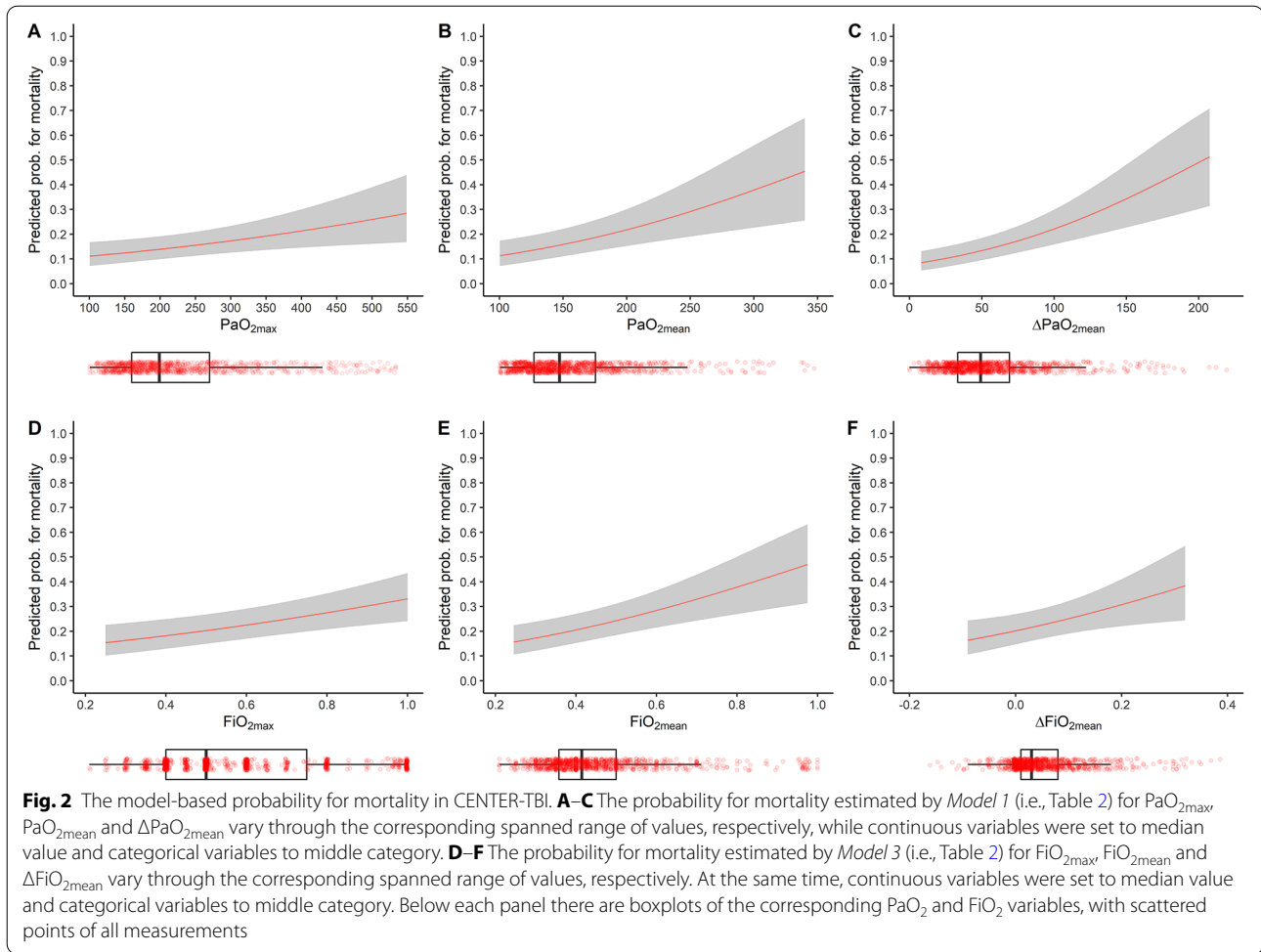
^b 1 patient did not have low PaO₂

^c OR regards 0.1 increments in FiO₂ covariate

supplemental oxygen, no association was observed with GOSE. However, all the three high supplemental oxygen variables remained positively associated with a higher mortality rate (Model 4, Table 2). A detailed description of all confounders estimates is reported in Supplemental Tables 9 and 10. We explored the presence of interaction on GOSE and mortality between exposure to high FiO₂ levels and GFAP levels. We did not find any interaction

among the studied variables, as shown in Supplemental Figure 4 (panel B) and in Fig. 3 (panel B), respectively, for FiO_{2max}—and for both FiO_{2mean} and Δ FiO_{2mean} as well (data not shown)—where the surfaces that represent the smoothed interactions (on log scale) are mainly flattened on zero.

Results concerning PaO₂ and FiO₂ 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 11). From the descriptive analysis reported in Supplemental Table 12, patients with and without missing data have similar characteristics. As 5 patients died within 48 h with PaO_2 levels beyond 450 mmHg and $\text{PaCO}_2 > 60$ 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 13.

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 0.25–0.5) (Supplemental Fig. 2). Mean $\text{PaO}_{2\text{max}}$, $\text{PaO}_{2\text{mean}}$ and $\Delta\text{PaO}_{2\text{mean}}$ were 356, 197 and 98 mmHg, respectively (Table 1). $\text{PaO}_{2\text{max}}$ showed a strong correlation with $\Delta\text{PaO}_{2\text{mean}}$ ($T_{\text{Kendall}} = 0.63$, $p < 0.001$) and with $\text{PaO}_{2\text{mean}}$ ($T_{\text{Kendall}} = 0.71$, $p < 0.001$). Mean $\text{FiO}_{2\text{max}}$, $\text{FiO}_{2\text{mean}}$ and $\Delta\text{FiO}_{2\text{mean}}$ 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,

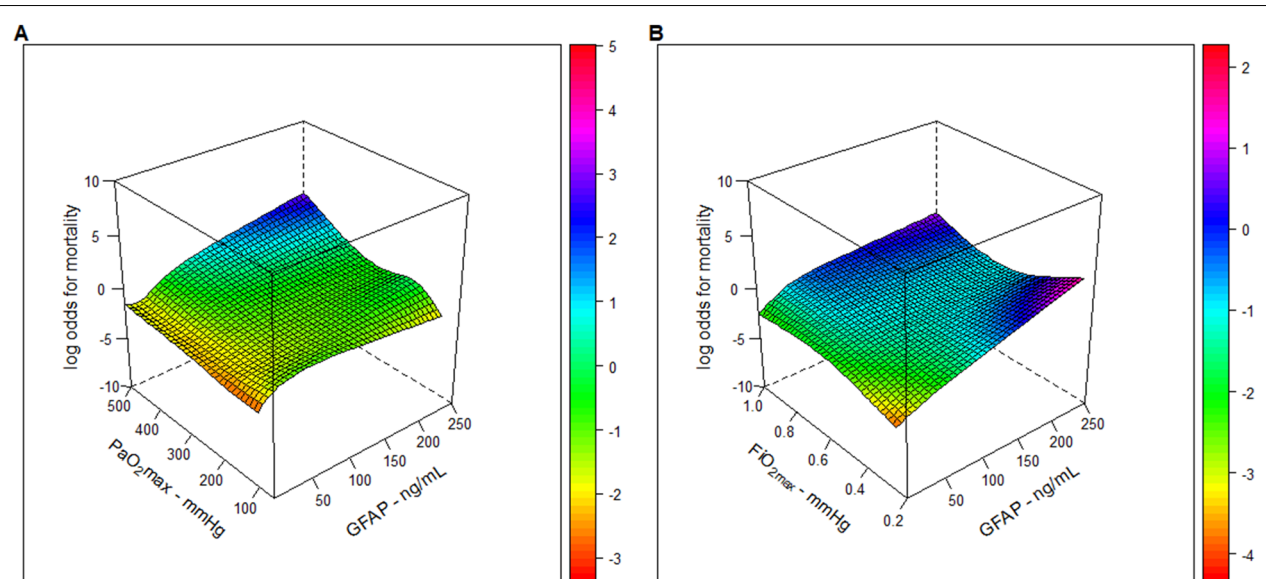


Fig. 3 Tensor cubic spline for the interaction between $\text{PaO}_{2\text{max}}$ and $\text{FiO}_{2\text{max}}$ with GFAP in CENTER-TBI. In **A** on the left, we represented the tensor cubic spline with 4 degrees of freedom each, used for the interaction between $\text{PaO}_{2\text{max}}$ and GFAP in the logistic model with 6-month mortality as outcome. In **B** on the right, we represented the tensor cubic spline with 4 degrees of freedom each, used for the interaction between $\text{FiO}_{2\text{max}}$ 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 $\leq$ 4			6-month mortality N = 141 patients, 39 died		
Model 1	OR ^a	95% CI	p value	OR ^a	95% CI	p value
$\text{PaO}_{2\text{max}}$ (for 10 mmHg increase)	1.01	0.98–1.04	0.433	1	0.97–1.04	0.898
$\text{PaO}_{2\text{mean}}$ (for 10 mmHg increase)	1.01	0.96–1.07	0.656	1.05	0.99–1.11	0.118
$\Delta\text{PaO}_{2\text{mean}}$ (for 10 mmHg increase)	1.03	0.96–1.12	0.376	1.08	1–1.18	0.054
Model 2	OR ^b	95% CI	p value	OR [*]	95% CI	p value
$\text{FiO}_{2\text{max}}$ (for 0.1 increase)	1.06	0.89–1.26	0.492	1	0.83–1.23	0.963
$\text{FiO}_{2\text{mean}}$ (for 0.1 increase)	1.02	0.77–1.34	0.911	1.32	0.98–1.8	0.069
$\Delta\text{FiO}_{2\text{mean}}$ (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, $\text{PaO}_{2\text{max}}$, $\text{PaO}_{2\text{mean}}$ and $\Delta\text{PaO}_{2\text{mean}}$ 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, $\text{FiO}_{2\text{max}}$, $\text{FiO}_{2\text{mean}}$ and $\Delta\text{FiO}_{2\text{mean}}$ 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

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 14). After adjustment for the same confounders,

we observed that $\Delta\text{PaO}_{2\text{mean}}$ (OR 1.08, 95% CI 1–1.18) trended toward a higher mortality rate (Model 1, Table 3 and Supplemental Table 15). A detailed description of all confounders estimates for both outcomes was described in Supplemental Tables 14 and 15.

Supplemental oxygen administration and outcome

After adjustment for confounders, $\text{FiO}_{2\text{max}}$, $\text{FiO}_{2\text{mean}}$ and $\Delta\text{FiO}_{2\text{mean}}$ confirmed the data of CENTER-TBI with no significant association with neurological outcome. However, increases in $\text{FiO}_{2\text{mean}}$ 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 16 and 17.

Discussion

In this study, we investigated whether exposure to high blood oxygen levels and high oxygen supplementation is 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 ($\Delta\text{PaO}_{2\text{mean}}$) predicts an unfavorable GOSE at 6 months in CENTER-TBI. These findings were not validated in the OzENTER-TBI cohort, where only $\Delta\text{PaO}_{2\text{mean}}$ 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 $\text{FiO}_{2\text{mean}}$ 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 $\text{PaO}_2 > 120$ [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 (HYPER-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 (LOCO₂ 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 (PbtO₂) 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 PbtO₂ values, of elevating the PaO₂ up to 150 mmHg or higher in more severe cases, fine-tuned to the patient's PbtO₂ 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 PaO₂ levels between TBI with or without PbtO₂ monitoring. We cannot exclude the possibility that the worse outcomes associated with higher PaO₂ were due to use of higher FiO₂ in patients with more severe injury or physiological compromise. Further, these findings may not apply to patients in whom FiO₂ and PaO₂ are titrated to PbtO₂ 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 PaO₂ levels beyond 450 mmHg with a PaCO₂ > 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 PaO₂ and FiO₂ variables. Finally, our dataset is limited to the first week after TBI. However, our analysis includes data that provides a longitudinal view of PaO₂ 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 in 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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References

- McHugh GS, Engel DC, Butcher I, Steyerberg EW, Lu J, Mushkudiani N, Hernández AV, Marmarou A, Maas AI, Murray GD (2007) The IMPACT study results from the prognostic value of secondary insults in traumatic brain injury. *J Neurotrauma* 24(2):287–293. <https://doi.org/10.1089/neu.2006.0031>
- MacIntyre NR (2014) Tissue hypoxia: implications for the respiratory clinician. *Respir Care* 59(10):1590–1596. <https://doi.org/10.4187/respcare.03357>
- Itagaki T, Nakano Y, Okuda N, Izawa M, Onodera M, Imanaka H, Nishimura M (2015) Hyperoxemia in mechanically ventilated, critically ill subjects: incidence and related factors. *Respir Care* 60(3):335–340. <https://doi.org/10.4187/respcare.03451>
- Behnke AR, Johnson FS, Poppen JR, Motley EP (1934) The effect of oxygen on man at pressures from 1 to 4 atmospheres. *Am J Physiol* 110:565–572
- Singer M, Young PJ, Laffey JG, Asfar P, Taccone FS, Skrifvars MB, Meyhoff CS, Radermacher P (2021) Dangers of hyperoxia. *Crit Care* 25(1):440. <https://doi.org/10.1186/s13054-021-03815-y>
- Quintard H, Patet C, Suys T, Marques-Vidal P, Oddo M (2015) Normobaric hyperoxia is associated with increased cerebral excitotoxicity after severe traumatic brain injury. *Neurocrit Care* 22(2):243–250. <https://doi.org/10.1007/s12028-014-0062-0>
- Brenner M, Stein D, Peter Hu, Kufera J, Woolford M, Scalea T (2012) Association between early hyperoxia and worse outcomes after traumatic brain injury. *Arch Surg* 147(11):1042–1046. <https://doi.org/10.1001/archsurg.2012.1560>
- Rincon F, Kang J, Vibbert M, Urtecho J, Athar MK, Jallo J (2014) Significance of arterial hyperoxia and relationship with case fatality in traumatic brain injury: a multicentre cohort study. *J Neurol Neurosurg Psychiatry* 85(7):799–805. <https://doi.org/10.1136/jnnp-2013-305505>
- Davis DP, Meade W, Sise MJ, Kennedy F, Simon F, Tominaga G, Steele J, Coimbra R (2009) Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. *J Neurotrauma* 26(12):2217–2223. <https://doi.org/10.1089/neu.2009.0940>
- de Jonge E, Peelen L, Keijzers PJ, Joore H, de Lange D, van der Voort PHJ, Bosman RJ, de Waal RA, Wesselink R, de Keizer NF (2008) Association between administered oxygen, arterial partial oxygen pressure and mortality in mechanically ventilated intensive care unit patients. *Crit Care* 12(6):R156. <https://doi.org/10.1186/cc7150>
- Hirunpattarasilp C, Shiina H, Na-Ek N, Attwell D (2022) The effect of hyperoxemia on neurological outcomes of adult patients: a systematic review and meta-analysis. *Neurocrit Care*. <https://doi.org/10.1007/s12028-021-01423-w>
- Maas AIR, Menon DK, Steyerberg EW, Citerio G, Lecky F, Manley GT, Hill S, Legrand V, Sorgner A, CENTER-TBI Participants and Investigators (2015) Collaborative European NeuroTrauma Effectiveness Research in Traumatic Brain Injury (CENTER-TBI): a prospective longitudinal observational study. *Neurosurgery* 76(1):67–80. <https://doi.org/10.1227/NEU.0000000000000575>
- Steyerberg EW, Wieggers E, Sewalt C, Buki A, Citerio G, De Keyser V, Ercole A, Kunzmann K, Lanyon L, Lecky F, Lingsma H, Manley G, Nelson D, Peul W, Stocchetti N, von Steinbüchel N, Vande Vyvere T, Verheyden J, Wilson L, Maas AIR, Menon DK, CENTER-TBI Participants and Investigators (2019) Case-mix, care pathways, and outcomes in patients with traumatic brain injury in CENTER-TBI: a European prospective, multicentre, longitudinal, cohort study. *Lancet Neurol* 18(10):923–934. [https://doi.org/10.1016/S1474-4422\(19\)30232-7](https://doi.org/10.1016/S1474-4422(19)30232-7)
- Young PJ, Mackle D, Hodgson C, Bellomo R, Bailey M, Beasley R, Deane AM, Eastwood G, Finfer S, Freebairn R, King V, Linke N, Litton E, McArthur C, McGuinness S, Panwar R, ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group (2022) Conservative or liberal oxygen therapy for mechanically ventilated adults with acute brain pathologies: A post-hoc subgroup analysis. *J Crit Care* 71:154079. <https://doi.org/10.1016/j.jccr.2022.154079>
- https://www.monash.edu/_data/assets/pdf_file/0003/1049772/OzENT_ER_V2_ANZIC-RC_Web.pdf
- Huijben JA, Dixit A, Stocchetti N, Maas AIR, Lingsma HF, van der Jagt M, Nelson D, Citerio G, Wilson L, Menon DK, Ercole A, CENTER-TBI Investigators and Participants (2021) Use and impact of high intensity treatments in patients with traumatic brain injury across Europe: a CENTER-TBI analysis. *Crit Care* 25(1):78. <https://doi.org/10.1186/s13054-020-03370-y>
- Czeiter E, Amrein K, Gravesteyn BY, Lecky F, Menon DK, Mondello S, Newcombe VFJ, Richter S, Steyerberg EW, Vyvere TV, Verheyden J, Xu H, Yang Z, Maas AIR, Wang KKW, Buki A, CENTER-TBI Participants and Investigators (2020) Blood biomarkers on admission in acute traumatic brain injury: relations to severity, CT findings and care path in the CENTER-TBI study. *EBioMedicine* 56:102785. <https://doi.org/10.1016/j.ebiom.2020.102785>
- Vos PE, Jacobs B, Andriessen TMJC, Lamers KJB, Borm GF, Beems T, Edwards M, Rosmalen CF, Vissers JLM (2010) GFAP and S100B are biomarkers of traumatic brain injury: an observational cohort study. *Neurology* 75:1786–1793. <https://doi.org/10.1212/WNL.0b013e3181fd6d2d>
- Mondello S, Papa L, Buki A, Bullock MR, Czeiter E, Tortella FC, Wang KK, Hayes RL (2011) Neuronal and glial markers are differently associated with computed tomography findings and outcome in patients with severe traumatic brain injury: a case control study. *Crit Care* 15(3):R156. <https://doi.org/10.1186/cc10286>
- Robba C, Poole D, McNett M, Asehnoune K, Bösel J, Bruder N, Chieriegato A, Cinotti R, Duranteau J, Einav S, Ercole A, Ferguson N, Guerin C, Siempos II, Kurtz P, Juffermans NP, Mancebo J, Mascia L, McCredie V, Nin N, Oddo M, Pelosi P, Rabinstein AA, Neto AS, Seder DB, Skrifvars MB, Suarez JJ, Taccone FS, van der Jagt M, Citerio G, Stevens RD (2020) Mechanical ventilation in patients with acute brain injury: recommendations of the European Society of Intensive Care Medicine consensus. *Intensive Care Med* 46(12):2397–2410. <https://doi.org/10.1007/s00134-020-06283-0>
- Aggarwal NR, Brower RG (2014) Targeting normoxemia in acute respiratory distress syndrome may cause worse short-term outcomes because of oxygen toxicity. *Ann Am Thorac Soc* 11(9):1449–1453. <https://doi.org/10.1513/AnnalsATS.201407-297PS>

22. De Graaff AE, Dongelmans DA, Binnekade JM, de Jonge E (2011) Clinicians' response to hyperoxia in ventilated patients in a Dutch ICU depends on the level of FiO_2 . *Intensive Care Med* 37(1):46–51
23. Helmerhorst HJF, Arts DL, Schultz MJ, van der Voort PHJ, Abu-Hanna A, de Jonge E, van Westerloo DJ (2017) Metrics of arterial hyperoxia and associated outcomes in critical care. *Crit Care Med* 45(2):187–195. <https://doi.org/10.1097/CCM.0000000000002084>
24. Hafner S, Beloncle F, Koch A, Radermacher P, Asfar P (2015) Hyperoxia in intensive care, emergency, and peri-operative medicine: Dr. Jekyll or Mr. Hyde? A 2015 update. *Ann Intensive Care* 5:42. <https://doi.org/10.1186/s13613-015-0084-6>
25. Madotto F, Rezoagli E, Pham T, Schmidt M, McNicholas B, Protti A, Panwar R, Bellani G, Fan E, van Haren F, Brochard L, Laffey JG, LUNG SAFE Investigators and the ESICM Trials Group (2020) Hyperoxemia and excess oxygen use in early acute respiratory distress syndrome: insights from the LUNG SAFE study. *Crit Care* 24(1):125. <https://doi.org/10.1186/s13054-020-2826-6>
26. Aggarwal NR, Brower RG, Hager DN, Thompson BT, Netzer G, Shanholtz C, Lagakos A, Checkley W, National Institutes of Health Acute Respiratory Distress Syndrome Network Investigators (2018) Oxygen exposure resulting in arterial oxygen tensions above the protocol goal was associated with worse clinical outcomes in acute respiratory distress syndrome. *Crit Care Med* 46(4):517–524. <https://doi.org/10.1097/CCM.00000000000002886>
27. Alali AS, Temkin N, Vavilala MS, Lele AV, Barber J, Dikmen S, Chesnut RM (2019) Matching early arterial oxygenation to long-term outcome in severe traumatic brain injury: target values. *J Neurosurg* 132(2):537–544
28. Weeden M, Bailey M, Gabbe B, Pilcher D, Bellomo R, Udy A (2021) Functional outcomes in patients admitted to the intensive care unit with traumatic brain injury and exposed to hyperoxia: a retrospective multicentre cohort study. *Neurocrit Care* 34(2):441–448. <https://doi.org/10.1007/s12028-020-01033-y>
29. Rockswold SB, Rockswold GL, Zaun DA, Liu J (2013) A prospective, randomized Phase II clinical trial to evaluate the effect of combined hyperbaric and normobaric hyperoxia on cerebral metabolism, intracranial pressure, oxygen toxicity, and clinical outcome in severe traumatic brain injury. *J Neurosurg* 118(6):1317–1328. <https://doi.org/10.3171/JNS.2013.2>
30. Baekgaard JS, Abback PS, Boubaya M, Moyer JD, Garrigue D, Raux M, Champigneulle B, Dubreuil G, Pottecher J, Laitelart P, Laloum F, Bloch-Queyrat C, Adnet F, Paugam-Burtz C, Traumabase® Study Group (2020) Early hyperoxemia is associated with lower adjusted mortality after severe trauma: results from a French registry. *Crit Care* 24(1):604. <https://doi.org/10.1186/s13054-020-03274-x>
31. Smith JL (1899) The pathological effects due to increase of oxygen tension in the air breathed. *J Physiol* 24(1):19–35. <https://doi.org/10.1113/jphysiol.1899.sp000746>
32. Hedley-Whyte J, Winter PM (1967) Oxygen therapy. *Clin Pharmacol Ther* 8(5):696–737. <https://doi.org/10.1002/cpt196785696>
33. Urner M, Calfee CS, Fan E (2021) Titrating oxygen therapy in critically ill patients. *JAMA* 326(10):911–913. <https://doi.org/10.1001/jama.2021.9843>
34. Angus DC (2020) Oxygen therapy for the critically ill. *N Engl J Med* 382(11):1054–1056. <https://doi.org/10.1056/NEJMe2000800>
35. Frank L, Bucher JR, Roberts RJ (1978) Oxygen toxicity in neonatal and adult animals of various species. *J Appl Physiol* 45:699–704
36. Davis WB, Rennard SI, Bitterman PB, Crystal RG (1983) Pulmonary oxygen toxicity. Early reversible changes in human alveolar structures induced by hyperoxia. *N Engl J Med* 309(15):878–883. <https://doi.org/10.1056/NEJM198310133091502>
37. Mantell LL, Lee PJ (2000) Signal transduction pathways in hyperoxia-induced lung cell death. *Mol Genet Metab* 71(1–2):359–370. <https://doi.org/10.1006/mgme.2000.3046>
38. Wu J, Hafner C, Schramel JP, Kaun C, Krychtiuk KA, Wojta J, Boehme S, Ullrich R, Tretter EV, Markstaller K, Klein KU (2016) Cyclic and constant hyperoxia cause inflammation, apoptosis and cell death in human umbilical vein endothelial cells. *Acta Anaesthesiol Scand* 60(4):492–501. <https://doi.org/10.1111/aas.12646>
39. Wang X, Wang Y, Kim HP, Nakahira K, Ryter SW, Choi AMK (2007) Carbon monoxide protects against hyperoxia-induced endothelial cell apoptosis by inhibiting reactive oxygen species formation. *J Biol Chem* 282(3):1718–1726. <https://doi.org/10.1074/jbc.M607610200>
40. Bak Z, Sjöberg F, Rousseau A, Steinvall I, Janerot-Sjöberg B (2007) Human cardiovascular dose-response to supplemental oxygen. *Acta Physiol (Oxf)* 191(1):15–24. <https://doi.org/10.1111/j.1748-1716.2007.01710.x>
41. Casey DP, Joyner MJ, Claus PL, Curry TB (2013) Vasoconstrictor responsiveness during hyperbaric hyperoxia in contracting human muscle. *J Appl Physiol* (1985) 114(2):217–224. <https://doi.org/10.1152/japplphysiol.01197.2012>
42. Mak S, Egri Z, Tanna G, Colman R, Newton GE (2002) Vitamin C prevents hyperoxia-mediated vasoconstriction and impairment of endothelium-dependent vasodilation. *Am J Physiol Heart Circ Physiol* 282(6):H2414–H2421. <https://doi.org/10.1152/ajpheart.00947.2001>
43. McNulty PH, Robertson BJ, Tulli MA, Hess J, Harach LA, Scott S, Sinoway LI (2007) Effect of hyperoxia and vitamin C on coronary blood flow in patients with ischemic heart disease. *J Appl Physiol* (1985) 102(5):2040–2045. <https://doi.org/10.1152/japplphysiol.00595.2006>
44. Yusa T, Beckman JS, Crapo JD, Freeman BA (1987) Hyperoxia increases H_2O_2 production by brain in vivo. *J Appl Physiol* (1985) 63(1):353–358. <https://doi.org/10.1152/jappl.1987.63.1.353>
45. Brueckl C, Kaestle S, Kerem A, Habazettl H, Krombach F, Kuppe H, Kuebler WM (2006) Hyperoxia-induced reactive oxygen species formation in pulmonary capillary endothelial cells in situ. *Am J Respir Cell Mol Biol* 34(4):453–463. <https://doi.org/10.1165/rcmb.2005-0223OC>
46. Hafner C, Wu J, Tiboldi A, Hess M, Mitulovic G, Kaun C, Krychtiuk KA, Wojta J, Ullrich R, Tretter EV, Markstaller K, Klein KU (2017) Hyperoxia induces inflammation and cytotoxicity in human adult cardiac myocytes. *Shock* 47(4):436–444. <https://doi.org/10.1097/SHK.0000000000000740>
47. Nortje J, Coles JP, Timofeev I, Fryer TD, Aigbirihio FI, Smielewski P, Outtrim JG, Chatfield DA, Pickard JD, Hutchinson PJ, Gupta AK, Menon DK (2008) Effect of hyperoxia on regional oxygenation and metabolism after severe traumatic brain injury: preliminary findings. *Crit Care Med* 36(1):273–281. <https://doi.org/10.1097/01.CCM.00000292014.60835.15>
48. Magnoni S, Ghisoni L, Locatelli M, Caimi M, Colombo A, Valeriani V, Stocchetti N (2003) Lack of improvement in cerebral metabolism after hyperoxia in severe head injury: a microdialysis study. *J Neurosurg* 98(5):952–958. <https://doi.org/10.3171/JNS.2003.98.5.0952>
49. Girardi M, Busani S, Damiani E, Donati A, Rinaldi L, Marudi A, Morelli A, Antonelli M, Singer M (2016) Effect of conservative vs conventional oxygen therapy on mortality among patients in an intensive care unit: the oxygen-ICU randomized clinical trial. *JAMA* 316(15):1583–1589. <https://doi.org/10.1001/jama.2016.11993>
50. Asfar P, Schortgen F, Boissramé-Helms J, Charpentier J, Guérot E, Megarbane B, Grimaldi D, Grelon F, Anguel N, Lasocki S, Henry-Lagarrigue M, Gonzalez F, Legay F, Guitton C, Schenck M, Doise JM, Devaquet J, Van Der Linden T, Chatellier D, Rigaud JP, Dellamonica J, Tamion F, Meziari F, Mercat A, Dreyfuss D, Seegers V, Radermacher P, HYPER25 Investigators; REVA Research Network (2017) Hyperoxia and hypertonic saline in patients with septic shock (HYPER25): a two-by-two factorial, multicentre, randomised, clinical trial. *Lancet Respir Med* 5(3):180–190. [https://doi.org/10.1016/S2213-2600\(17\)30046-2](https://doi.org/10.1016/S2213-2600(17)30046-2)
51. Chu DK, Kim LH, Young PJ, Zamiri N, Almenawer SA, Jaeschke R, Szczeklik W, Schünemann HJ, Neary JD, Alhazzani W (2018) Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet* 391(10131):1693–1705. [https://doi.org/10.1016/S0140-6736\(18\)30479-3](https://doi.org/10.1016/S0140-6736(18)30479-3)
52. Barrot L, Asfar P, Mauny F, Winiszewski H, Montini F, Badie J, Quenot JP, Pili-Floury S, Bouhemad B, Louis G, Souweine B, Collange O, Pottecher J, Levy B, Puyraveau M, Vettoretti L, Constantin JM, Capellier G, LOCO2 Investigators and REVA Research Network (2020) Liberal or conservative oxygen therapy for acute respiratory distress syndrome. *N Engl J Med* 382(11):999–1008. <https://doi.org/10.1056/NEJMoa1916431>
53. Mackle D, Bellomo R, Bailey M, Beasley R, Deane A, Eastwood G, Finfer S, Freebairn R, King V, Linke N, Litton E, McArthur C, McGuinness S, Panwar R, Young P, ICU-ROX Investigators the Australian and New Zealand Intensive Care Society Clinical Trials Group (2020) Conservative oxygen therapy during mechanical ventilation in the ICU. *N Engl J Med* 382(11):989–998. <https://doi.org/10.1056/NEJMoa1903297>
54. Schjørring OL, Klitgaard TL, Perner A, Wetterslev J, Lange T, Siegemund M, Bäcklund M, Keus F, Laake JH, Morgan M, Thormar KM, Rosborg SA, Bisgaard J, Erntgaard AES, Lynnerup AH, Pedersen RL, Crescioli E, Gielstrup TC, Behzadi MT, Poulsen LM, Estrup S, Laigaard JP, Andersen C, Mortensen CB, Brand BA, White J, Jarnvig IL, Møller MH, Quist L, Bestle MH,

-
- Schönemann-Lund M, Kamper MK, Hindborg M, Hollinger A, Gebhard CE, Zellweger N, Meyhoff CS, Hjort M, Bech LK, Grøfte T, Bundgaard H, Østergaard LHM, Thyø MA, Hildebrandt T, Uslu B, Sølling CG, Møller-Nielsen N, Brøchner AC, Borup M, Okkonen M, Dieperink W, Pedersen UG, Andreassen AS, Buus L, Aslam TN, Winding RR, Schefold JC, Thorup SB, Iversen SA, Engstrøm J, Kjær MN, Rasmussen BS, HOT-ICU Investigators (2021) Lower or higher oxygenation targets for acute hypoxemic respiratory failure. *N Engl J Med* 384(14):1301–1311. <https://doi.org/10.1056/NEJMoa2032510>
55. Gelissen H, de Grooth HJ, Smulders Y, Wils EJ, de Ruijter W, Vink R, Smit B, Röttgering J, Atmowihardjo L, Girbes A, Elbers P, Tuinman PR, Oudemans-van Straaten H, de Man A (2021) Effect of low-normal vs high-normal oxygenation targets on organ dysfunction in critically ill patients: a randomized clinical trial. *JAMA* 326(10):940–948. <https://doi.org/10.1001/jama.2021.13011>
56. Abdelhak A, Foschi M, Abu-Rumeileh S, Yue JK, D'Anna L, Huss A, Oeckl P, Ludolph AC, Kuhle J, Petzold A, Manley GT, Green AJ, Otto M, Tuman H (2022) Blood GFAP as an emerging biomarker in brain and spinal cord disorders. *Nat Rev Neurol*. <https://doi.org/10.1038/s41582-021-00616-3>
57. Frankel M, Fan L, Yeatts SD, Jeromin A, Vos PE, Wagner AK, Wolf BJ, Pauls Q, Lunney M, Merck LH, Hall CL, Palesch YY, Silbergleit R, Wright DW (2019) Association of very early serum levels of S100B, glial fibrillary acidic protein, ubiquitin C-terminal hydrolase-L1, and spectrin breakdown product with outcome in ProTECT III. *J Neurotrauma* 36(20):2863–2871. <https://doi.org/10.1089/neu.2018.5809>
58. Kochanek PM, Bramlett HM, Shear DA, Dixon CE, Mondello S, Dietrich WD, Hayes RL, Wang KK, Poloyac SM, Empey PE, Povlishock JT, Mountney A, Browning M, Deng-Bryant Y, Yan HQ, Jackson TC, Catania M, Glushakova O, Richieri SP, Tortella FC (2016) Synthesis of findings, current investigations, and future directions: operation brain trauma therapy. *J Neurotrauma* 33(6):606–614. <https://doi.org/10.1089/neu.2015.4133>
59. Browning M, Shear DA, Bramlett HM, Dixon CE, Mondello S, Schmid KE, Poloyac SM, Dietrich WD, Hayes RL, Wang KK, Povlishock JT, Tortella FC, Kochanek PM (2016) Levetiracetam treatment in traumatic brain injury: operation brain trauma therapy. *J Neurotrauma* 33(6):581–594. <https://doi.org/10.1089/neu.2015.4131>
60. Okonkwo DO, Shutter LA, Moore C, Temkin NR, Puccio AM, Madden CJ, Andaluz N, Chesnut RM, Bullock MR, Grant GA, McGregor J, Weaver M, Jallo J, LeRoux PD, Moberg D, Barber J, Lazaridis C, Diaz-Arrastia RR (2017) Brain oxygen optimization in severe traumatic brain injury phase-II: a phase II randomized trial. *Crit Care Med* 45(11):1907–1914. <https://doi.org/10.1097/CCM.0000000000002619>
61. Chesnut R, Aguilera S, Buki A, Bulger E, Citerio G, Cooper DJ, Arrastia RD, Diringier M, Figaji A, Gao G, Geocadin R, Ghajar J, Harris O, Hoffer A, Hutchinson P, Joseph M, Kitagawa R, Manley G, Mayer S, Menon DK, Meyfroidt G, Michael DB, Oddo M, Okonkwo D, Patel M, Robertson C, Rosenfeld JV, Rubiano AM, Sahuquillo J, Servadei F, Shutter L, Stein D, Stocchetti N, Taccone FS, Timmons S, Tsai E, Ullman JS, Vespa P, Videtta W, Wright DW, Zammit C, Hawryluk GWJ (2020) A management algorithm for adult patients with both brain oxygen and intracranial pressure monitoring: the Seattle International Severe Traumatic Brain Injury Consensus Conference (SIBICC). *Intensive Care Med* 46(5):919–929. <https://doi.org/10.1007/s00134-019-05900-x>