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...
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 metaanalysis 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 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 Neu- roTrauma 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 (PaO2max) and FiO2 (FiO2max) exposures.
- The mean of the highest daily PaO2 (PaO2mean) and FiO2 (FiO2mean).
- The mean of the swings of PaO2 (ΔPaO2mean) and of FiO2 (ΔFiO2mean). 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 PaO2max, FiO2max, PaO2mean, FiO2mean or ΔPaO2mean, ΔFiO2mean (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
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 PaO2max (OR 1.02, 95% CI 1–1.04) and ΔPaO2mean (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 (PaO2max OR 1.03, 95% CI 1.01–1.05; PaO2mean OR 1.08, 95% CI 1.04–1.13; ΔPaO2mean 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 ΔPaO2mean confirmed its positive
| 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] |
| pH, median [IQR] | Lowest 7.34 [7.29–7.39] | 7.33 [7.29–7.37] |
| NA (n) | 3 | 0 |
| Highest 7.43 [7.39–7.47] | 7.41 [7.38–7.45] |
| 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] |
| Mean ICP, median [IQR] | 11 [6–15] | 11 [8–15] |
| Brain injury severity | | | |
| Marshall CT Classification, median [IQR] | 3 [2–6] | 2 [2–6] |
| NFAP, median [IQR] | ng/mL | 20.5 [7–50.8] / |
| NA (n) | 198 | 159 |
| Oxygenation | | | |
| Day 1 PaO2 overall, mean (SD) | mmHg | 207.17 (99.91) | 328.18 (144.46) |
| PaO2mean, mean (SD) | mmHg | 155.79 (46.93) | 197.79 (73.79) |
| PaO2max, mean (SD) | mmHg | 230.92 (102.95) | 356.01 (134.47) |
| ΔPaO2mean, mean (SD) | mmHg | 57 (36.7) | 98.20 (59.95) |
| Day 1 — PaO2/FiO2, mean (SD) | mmHg | 412.48 (197.08) | 453.59 (207.1) |
| Day 1 FiO2 overall, mean (SD) | 0.54 (0.21) | 0.76 (0.26) |
| FiO2mean, mean (SD) | 0.45 (0.15) | 0.48 (0.15) |
| FiO2max, mean (SD) | 0.59 (0.22) | 0.82 (0.23) |
| ΔFiO2mean, mean (SD) | 0.05 (0.08) | 0.15 (0.11) |
| Functional neurologic outcome | | | |
| GOSE < 4 | 528 (48.7) | 53 (33.3) |
| GOSE > 4 | 439 (40.5) | 95 (59.7) |
| NA | 117 (10.8) | 11 (7) |
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\textsubscript{2max} 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 PaO\textsubscript{2max} and for both PaO\textsubscript{2mean} and ΔPaO\textsubscript{2mean} 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, FiO\textsubscript{2max}, FiO\textsubscript{2mean} and ΔFiO\textsubscript{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). 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

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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\textsubscript{2}) < 8 kPa (60 mmHg), oxygen saturation (SaO\textsubscript{2}) < 90%, or both |
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| 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 |
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 FiO2max—and for both FiO2mean and ΔFiO2mean 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 PaO2 and FiO2 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 PaO2 levels beyond 450 mmHg and PaCO2 > 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 PaO2 were available (825 lowest and 826 highest daily values) for an overall median value of PaO2 and FiO2 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 PaO2 (median 6, IQR 3–7). The median of the highest PaO2 level during the first 7 days since ICU admission was 133 (IQR 109–212) (Supplemental Fig. 2). The highest median FiO2 levels during the first 7 days since ICU admission was 0.35 (IQR 0.25–0.5) (Supplemental Fig. 2). Mean PaO2max, PaO2mean and ΔPaO2mean were 356, 197 and 98 mmHg, respectively. Mean FiO2max, FiO2mean and ΔFiO2mean were 0.82, 0.48 and 0.15 mmHg, respectively. Center variability in PaO2 (panel A) and FiO2 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 14). After adjustment for the same confounders, we observed that \( \Delta PaO_2_{mean} \) (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.

### 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* 95% CI \( p \) value        | OR* 95% CI \( p \) value        |
| \( PaO_{2\text{max}} \) (for 10 mmHg increase) | 1.01 0.98–1.04 0.433 | 1 0.97–1.04 0.898 |
| \( PaO_{2\text{mean}} \) (for 10 mmHg increase) | 1.01 0.96–1.07 0.656 | 1.05 0.99–1.11 0.118 |
| \( \Delta PaO_{2\text{mean}} \) (for 10 mmHg increase) | 1.03 0.96–1.12 0.376 | 1.08 1–1.18 0.054 |

| Model 2     | 6-month GOSE \( N = 141 \) patients, 92 GOSE \( \leq 4 \) | 6-month mortality \( N = 141 \) patients, 39 died |
|-------------|---------------------------------|---------------------------------|
| \( FiO_{2\text{max}} \) (for 0.1 increase) | 1.06 0.89–1.26 0.492 | 1 0.83–1.23 0.963 |
| \( FiO_{2\text{mean}} \) (for 0.1 increase) | 1.02 0.77–1.34 0.911 | 1.32 0.98–1.8 0.069 |
| \( \Delta FiO_{2\text{mean}} \) (for 0.1 increase) | 1.15 0.79–1.69 0.483 | 1 0.68–1.48 0.981 |

* OR is for 10 mmHg increase in \( PaO_2 \) covariate

* OR regards 0.1 increments in \( FiO_2 \) covariate

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**Fig. 3** Tensor cubic spline for the interaction between \( PaO_{2\text{max}} \) and \( FiO_{2\text{max}} \) 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 \( PaO_{2\text{max}} \) 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 \( FiO_{2\text{max}} \) 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.

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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, \( PaO_{2\text{max}}, PaO_{2\text{mean}} \) and \( \Delta PaO_{2\text{mean}} \) 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, \( FiO_{2\text{max}}, FiO_{2\text{mean}} \) and \( \Delta FiO_{2\text{mean}} \) for OzENTER-TBI with a dummy variable for center. Full models with all covariates estimates are reported in the Supplemental material.
Supplemental oxygen administration and outcome
After adjustment for confounders, FiO2_{max}, FiO2_{mean} and \Delta FiO2_{mean} confirmed the data of CENTER-TBI with no significant association with neurological outcome. However, increases in FiO2_{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 PaO2 during the first week of ICU admission.
2. Exposure to high PaO2 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 a higher serum concentration of GFAP.
3. A higher average daily variability in PaO2 (ΔPaO2_{mean}) predicts an unfavorable GOSE at 6 months in CENTER-TBI. These findings were not validated in the OzENTER-TBI cohort, where only ΔPaO2_{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 FiO2_{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 PaO2 levels above 120 mmHg [20, 21], during the first week after ICU admission. Despite hyperoxemia being quite often defined as the presence of a PaO2 > 120 [20, 22, 23], there is no agreement in the literature about a confounder estimate for both outcomes was described in Supplemental Tables 16 and 17.

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 PaO2 levels (interpreted for each 10-mmHg increase) or the daily highest PaO2 variability. This may suggest that clinicians should pay attention not just to the absolute values of PaO2 but also to the daily swings of blood oxygenation. We logically hypothesized that PaO2 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., FiO2), similarly to the association reported between blood oxygenation and mortality, we showed that the highest the levels of FiO2 or the most elevated average daily swings of FiO2 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 FiO2 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 FiO2 levels to target a physiological range of blood oxygenation.

Furthermore, avoiding major changes in daily FiO2—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 PaO2 should be considered safe in TBI patients [20]. The pathophysiological mechanisms behind the role of oxygen toxicity induced by hyperoxia (i.e., high FiO2) [31, 32] and hyperoxemia (i.e., high PaO2) [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 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 FiO2. Hyperoxia marginally reduced lactate levels in brain tissue after TBI. However, the estimated redox status of the cells did not change and cerebral O2 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 PaO2 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 PaO2 increased mortality [51].

In contrast, so far, 4 big RCTs (LOCO2 trial [52], ICU-ROX trial [53], HOT-ICU trial [54] and O2-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., PaO2, SpO2 and SaO2), 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 (ACTRN1262000391976)—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., PaO2 and FiO2) 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.
Conclusion

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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Publishers Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 21 June 2022 Accepted: 17 August 2022
Published: 20 October 2022

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