

ORIGINAL WORK



# Functional Outcomes in Patients Admitted to the Intensive Care Unit with Traumatic Brain Injury and Exposed to Hyperoxia: A Retrospective Multicentre Cohort Study

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## Abstract

**Background:** Supplemental oxygen administration to critically ill patients is ubiquitous in the intensive care unit (ICU). Uncertainty persists as to whether hyperoxia is benign in patients with traumatic brain injury (TBI), particularly in regard to their long-term functional neurological outcomes.

**Methods:** We conducted a retrospective multicenter cohort study of invasively ventilated patients with TBI admitted to the ICU. A database linkage between the Australian and New Zealand Intensive Care Society Adult Patient Database (ANZICS-APD) and the Victorian State Trauma Registry (VSTR) was utilized. The primary exposure variable was minimum acute physiology and chronic health evaluation (APACHE) III  $P_aO_2$  in the first 24 h of ICU. We defined hypoxia as  $P_aO_2 < 60$  mmHg, normoxia as 60–299 mmHg, and hyperoxia as  $\geq 300$  mmHg. The primary outcome was a Glasgow Outcome Scale-Extended (GOSE)  $< 5$  at 6 months while secondary outcomes included 12 and 24 months GOSE and mortality at each of these timepoints. Additional sensitivity analyses were undertaken in the following subgroups: isolated head injury, patients with operative intervention, head injury severity, and  $P_aO_2$  either subcategorized by increments of 60 mmHg or treated as a continuous variable.

**Results:** A total of 3699 patients met the inclusion criteria. The mean age was 42.8 years, 77.7% were male and the mean acute physiology and chronic health evaluation (APACHE) III score was 60.1 (26.3). 2842 patients experienced normoxia, and 783 hyperoxia. The primary outcome occurred in 1470 (47.1%) of patients overall with 1123 (47.1%) from the normoxia group and 312 (45.9%) from the hyperoxia group—odds ratio 0.99 (0.78–1.25). No significant differences in outcomes between groups at 6, 12, and 24 months were observed. Sensitivity analyses did not identify subgroups that were adversely affected by exposure to hyperoxia.

**Conclusions:** No associations were observed between hyperoxia in ICU during the first 24 h and adverse neurological outcome at 6 months in ventilated TBI patients.

**Keywords:** Hyperoxia, Critical care, Traumatic brain injury, Functional neurological outcome, Glasgow Outcome Score-Extended, Oxygen toxicity

## Introduction

Supplementation of oxygen in critically ill patients is ubiquitous [1–3]. However, increasing recognition that hyperoxia may not be benign, has led to re-examination of liberal oxygen administration in this setting [4, 5]. Indeed, retrospective studies have raised concern about

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greater mortality with hyperoxia [6–8], albeit a recent large, multicenter randomized controlled trial (ICU-ROX) demonstrated no effect of liberal oxygen exposure on ventilator-free days or mortality in a mixed intensive care unit (ICU) population [9].

In traumatic brain injury (TBI) specifically, the impact of hyperoxia on patient-centered outcomes remains confused. A retrospective cohort study of 1547 patients with TBI from North America, found hyperoxia was associated with both increased mortality and a worse Glasgow Coma Scale (GCS) score at hospital discharge [10]. In contrast, others have shown no association between oxygen exposure and mortality [11, 12], including a large retrospective bi-national multicenter study of over 20,000 patients [13].

Clinical concern about the deleterious effects of hyperoxia persist however, because functional outcome may be more sensitive than crude mortality to any potential exposure related injury. Currently, there is a paucity of data exploring the association between hyperoxia and functional outcome in TBI, an endpoint that has critical implications for patients, caregivers, and the community.

In view of this knowledge gap, we designed a retrospective cohort study to explore the association between early hyperoxia (as measured by the partial arterial pressure of oxygen [ $P_aO_2$ ]) and 6, 12, and 24 months functional outcomes in ventilated TBI patients admitted to the ICU. We hypothesized that early hyperoxia would be associated with a higher proportion of adverse functional outcomes.

## Methods

### Design

We undertook a retrospective multicenter observational cohort study of mechanically ventilated TBI patients admitted to ICU in Victoria, Australia. This utilized linked data, from the Australian and New Zealand Intensive Care Society (ANZICS) Centre for Outcome and Resource Evaluation (CORE) Adult Patient Database (APD), and the Victoria State Trauma Registry (VSTR). The APD is a binational voluntary database containing records on over 2 million ICU admissions. De-identified data are entered on a quarterly basis, and are primarily used for quality assurance and benchmarking activities. ICUs at major tertiary trauma centers in Australia and New Zealand contribute data.

The VSTR receives data from 138 health services in the Australian state of Victoria, capturing all major trauma patients from a population of approximately 6.3 million people, and aims to improve the delivery of trauma care by reducing preventable deaths and permanent disability from major trauma. The VSTR includes the follow-up of major trauma patients who survive to hospital discharge and utilizes a dedicated call center, with trained staff to

undertake the 6-month GOSE assessment [14, 15]. Individual patient records in the ANZICS-APD and VSTR were linked for the period January 1, 2005, through to December 31, 2017. This was performed using a probabilistic merge using site, admission date, discharge date, age, gender, mortality status, and ICU length of stay. All data included were de-identified.

### Case Selection and Data Extraction

All patient records in the linked database were adult (age > 17 years) non-transferred index trauma admissions to Victorian hospitals for the study period. From this cohort, we then selected patients who had a primary APACHE III-J code of head injury  $\pm$  multitrauma. We excluded patients who were not mechanically ventilated, and those with missing ICU  $P_aO_2$  data. These criteria match that of our previous study concerning in-hospital mortality [13].

Data from the ANZICS-APD included: age, gender, date of admission, GCS, hospital and ICU admission source, hospital and ICU length of stay, discharge location, level of admitting hospital, APACHE II and III scores (as well as their predicted mortality), and the Australian and New Zealand Risk of Death (ANZROD) (including the related component physiological data required for this model). All physiological data recorded in the ANZICS-APD represent the ‘worst’ values recorded in the first 24-h of ICU admission. In the case of GCS, this is the lowest value recorded at the time of, or just prior to institution of sedation and/or neuromuscular blockade.

Data from the VSTR included: initial ambulance GCS, Injury Severity Scores (ISS), and functional assessment at 6, 12, and 24 months. The latter were undertaken using the Glasgow Outcome Scale-Extended (GOSE) [16]. An adverse neurological outcome was defined as a GOSE < 5 at 6 months, and was used as the study’s primary outcome.

Oxygen exposure in the first 24-h was determined using the ‘worst’  $P_aO_2$  values from the ANZICS-APD [17]. For ABGs where the patient is intubated and the  $FiO_2$  values are  $\geq 0.5$ , the A-a gradient is used to determine the APACHE III-J score. For ABGs where the patient is not intubated, or for intubated patients with  $FiO_2$  values < 0.5, the  $P_aO_2$  value is used to determine the APACHE III-J score. For the purposes of analysis, we defined hypoxia as a  $P_aO_2$  < 60 mmHg, normoxia as 60–299 mmHg, and hyperoxia as  $\geq 300$  mmHg. This is similar to our previous work concerning in-hospital mortality [13] and is based on prior work by Bellomo et al. [18]. To provide greater granularity, we also considered six categories of  $P_aO_2$ , e.g. < 60, 60–120, 120–180, 180–240, 240–300,

and >300 mmHg, and additionally examined  $P_aO_2$  as a continuous variable.

### Statistical Analysis

The primary exposure variable of interest was  $P_aO_2$  as defined above. The primary outcome was GOSE at 6 months, with a value <5 being considered as unfavorable. This dichotomy is consistent with previous large TBI trials conducted in our region [19–21]. Group comparisons between those with and without an adverse outcome, were performed using Chi square tests for equal proportion, analysis of variance for normally distributed data and Kruskal–Wallis tests otherwise, with results presented as counts (%), means (standard deviations) or medians [interquartile range (IQR)], respectively. GOSE at 12 and 24 months were similarly examined as secondary outcomes.

To explore the relationship between oxygen exposure and outcome, hierarchical logistic regression models were used with patients nested within sites and sites treated as a random variable adjusting for patient severity and utilizing three categories of  $P_aO_2$ : hypoxia, normoxia, and hyperoxia. Patient severity was measured by ANZROD [22] with the oxygen component removed to avoid confounding with  $P_aO_2$ . Of note, this methodology includes treatment limitations on ICU admission as a covariate. Results are presented as odds ratios (95% CI) referenced against a normal range (60–299). Additional sensitivity was performed using the six categories of  $P_aO_2$ , as described above.

Subgroup analysis included those coded as having an isolated head injury, non-operative versus postoperative admissions, and on the basis of TBI severity (GCS <9, 9–12, and >12). Based on the observed standard deviation in  $P_aO_2$  of 133, this study has 90% power (2 sided  $p$  value of 0.05) to detect a 15 mmHg difference in  $P_aO_2$  between patients with good and bad outcomes in the primary analysis. No imputation was made for missing data, and all proportions were reported on the basis of available data. SAS version 14.3 (SAS Institute Inc., Cary, NC, USA) and Stata® version 14 (StataCorp LLC, College Station, TX USA) were employed for statistical analysis, with a  $p$  value <0.05 deemed as statistically significant. No adjustment has been made for multiple comparisons.

## Results

### Baseline Characteristics

Linking the ANZICS-APD and VSTR for the period 1 January 2005 to 31 December 2017 yielded 13,596 patients. 4456 of these were identified as having head injury ± multitrauma based on APACHE III-J diagnostic codes. Patients not requiring intubation were excluded from this group, as were 16 patients for whom  $P_aO_2$  data

was missing, leaving 3699 in the final dataset for analysis (Fig. 1).

The mean patient age was 42.8 (19.9) years, 77.7% of patients were male, and the initial median ambulance GCS was 9 [4–14]. The mean APACHE III score was 60.1 (26.3) and the mean ISS was 26.5 (12.7) in keeping with a cohort of patients suffering ‘major trauma’ [23]. The median worst  $P_aO_2$  in the overall cohort was 150 [95–278] mmHg. The median  $P_aO_2$  for the hypoxia, normoxia, and hyperoxia groups was 52 [45–57 mmHg], 126 [90–191] mmHg, and 401 [335–478] mmHg, respectively. Baseline characteristics are presented in Table 1.

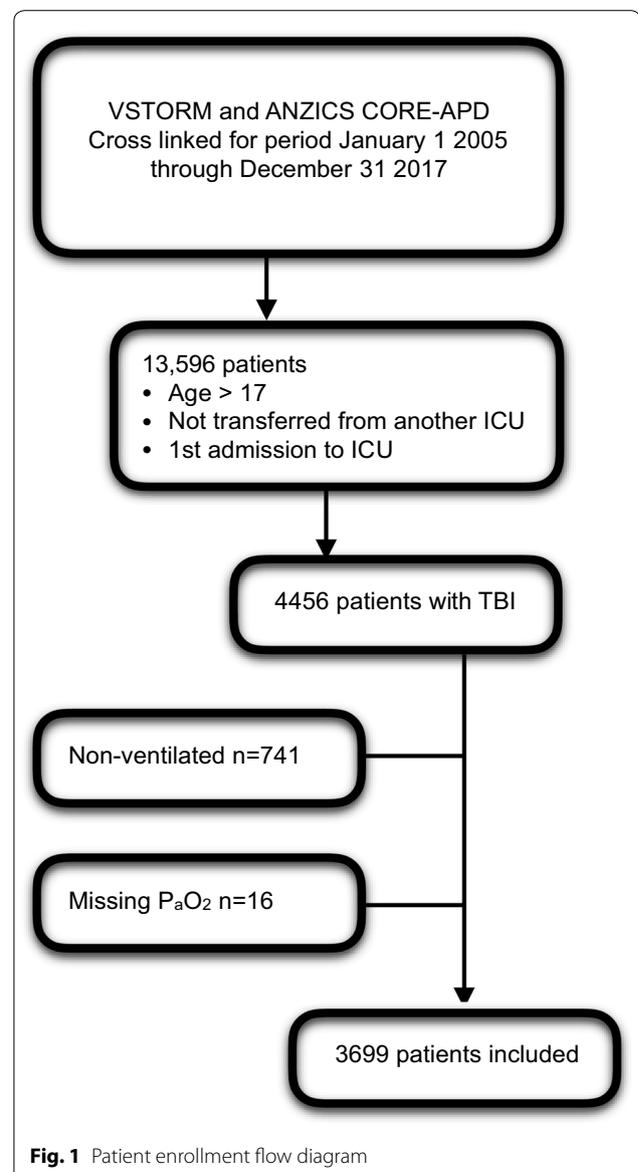
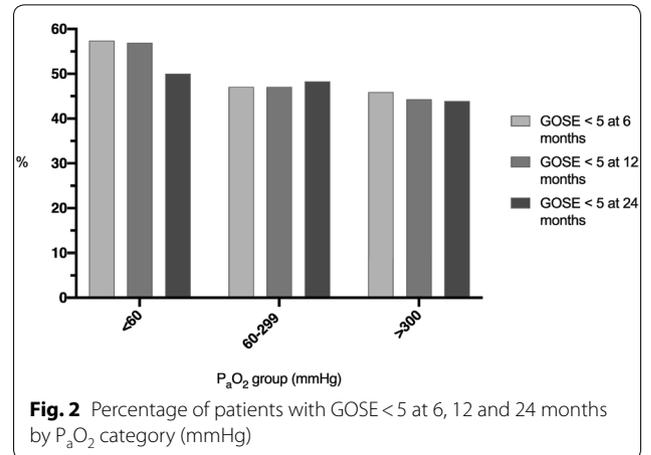


Fig. 1 Patient enrollment flow diagram

### Primary Analysis

A GOSE <5 at 6 months occurred in 47.1% (1470/3123) of patients overall, 47.1% (1123/2384) in the normoxia group and 45.9% (312/680) in the hyperoxia group (Fig. 2). The odd's ratio (OR) with 95% confidence intervals (CI) for the primary outcome in the hyperoxia group was 0.99 (0.78–1.25). Secondary outcomes by  $P_aO_2$  subgroups are presented in Table 2. The ICU mortality was 14.2% (525/3699), while the overall in-hospital mortality for the cohort was 17.7% (656/3699). At 6 months 22.8% (713/3123) had died.



**Fig. 2** Percentage of patients with GOSE <5 at 6, 12 and 24 months by  $P_aO_2$  category (mmHg)

**Table 1** Baseline patient characteristics

	<i>n</i>	All patients	$P_aO_2 < 60$ mmHg	$P_aO_2$ 60–300 mmHg	$P_aO_2 > 300$
Age	3699	42.8 (19.9)	44.5 (22.3)	43.2 (20.1)	41 (19.1)
Male gender	3699	2873 (77.7%)	63 (85.1%)	2215 (78%)	595 (75.8%)
Isolated head injury	3699	682 (18.4%)	16 (21.6%)	491 (17.3%)	175 (22.3%)
Operative care prior to ICU	3699	1402 (37.9%)	32 (43.2%)	1036 (36.5%)	334 (42.5%)
Operative care prior to or during ICU admission	3699	2181 (59%)	39 (52.7%)	1635 (57.6%)	507 (64.6%)
ANZROD probability of death: median [IQR]	3699	6.4 [2.2–21.2]%	18.6 [3.3–43.6]%	6.2 [2.1–20.7]%	6.6 [2.4–21.2]%
Mean (std)	3699	16.8 (22.4)%	27.6 (28.4)%	16.6 (22.3)%	16.4 (22.0)%
ANZROD with $O_2$ component removed: median [IQR]	3699	7.0 [2.3–22.1]%	16.1 [2.9–36.1]%	6.9 [2.3–22.1]%	6.9 [2.4–21.4]%
Mean (std)	3699	17.0 (22.2)%	25.2 (27.5)%	17.0 (22.2)%	16.3 (21.5)%
Proceeded to organ donation	3699	44 (1.2%)	4 (5.4%)	34 (1.2%)	6 (0.8%)
Injury Severity Score (ISS)	3698	26 [17–34]	28 [21–41]	25 [17–34]	26 [18–34]
Ambulance initial GCS	3699	8 [3–13]	8 [4–14]	8 [3–13]	8 [3–13]
GCS in ICU (APACHE II)	3691	8 [4–13]	8 [5–13]	8 [4–13]	8 [5–12]
Worst $P_aO_2$ in first 24 h (APACHE II)	3698	150 [95–278]	52 [45–57]	126 [90–191]	401 [335–478]
Highest $FiO_2$ in first 24 h (APACHE II)	3697	0.5 [0.35–1]	0.85 [0.4–1]	0.5 [0.3–0.6]	1 [0.8–1]
Highest $P_aCO_2$ in first 24 h (APACHE II)	3698	39.8 (7.1)	49.1 (15.9)	39.8 (6.7)	38.9 (6.5)
Highest respiratory rate in first 24 h (APACHE II)	3365	15.9 (6.9)	19.5 (8.6)	16 (7.0)	15.5 (6.2)
APACHE II score	3699	17.6 (7.6)	22.2 (8.8)	17.3 (7.6)	18 (7.3)
APACHE III risk of death	3699	15.4 [6.3–37.7]%	23.5 [13.1–55.2]%	14.8 [6.0–37.2]%	16.0 [7.1–38.6]%
APACHE III 3 score	3699	60.1 (26.3)	75.2 (28.9)	59.3 (26.4)	61.7 (24.9)
Hospital admission source: home	3699	2702 (73%)	52 (70.3%)	2041 (71.9%)	609 (77.6%)
Hospital admission source: other hospital	3699	803 (21.7%)	16 (21.6%)	625 (22%)	162 (20.6%)
Hospital admission source: other hospital ED	3699	43 (1.2%)	3 (4.1%)	34 (1.2%)	6 (0.8%)
Hospital admission source: unknown	3699	108 (2.9%)	3 (4.1%)	103 (3.6%)	2 (0.3%)
ICU admission source: operating theatre	3699	1332 (36%)	30 (40.5%)	985 (34.7%)	317 (40.4%)
ICU admission source: emergency	3699	2232 (60.3%)	40 (54.1%)	1765 (62.1%)	427 (54.4%)
ICU admission source: ward	3699	31 (0.8%)	2 (2.7%)	20 (0.7%)	9 (1.1%)
ICU admission source: other ICU or hosp	3699	104 (2.8%)	2 (2.7%)	70 (2.5%)	32 (4.1%)
Hospital type: rural	3699	17 (0.5%)	1 (1.4%)	14 (0.5%)	2 (0.3%)
Hospital type: metropolitan	3699	20 (0.5%)	1 (1.4%)	11 (0.4%)	8 (1%)
Hospital type: tertiary	3699	3662 (99%)	72 (97.3%)	2815 (99.1%)	775 (98.7%)

With (standard deviation) for means and [interquartile ranges] for medians

APACHE acute physiology and chronic health evaluation, ANZROD Australian and New Zealand Risk of Death, ED emergency department, GCS Glasgow Coma Scale, ICU intensive care unit, IQR interquartile range

**Table 2 Patient outcome characteristics**

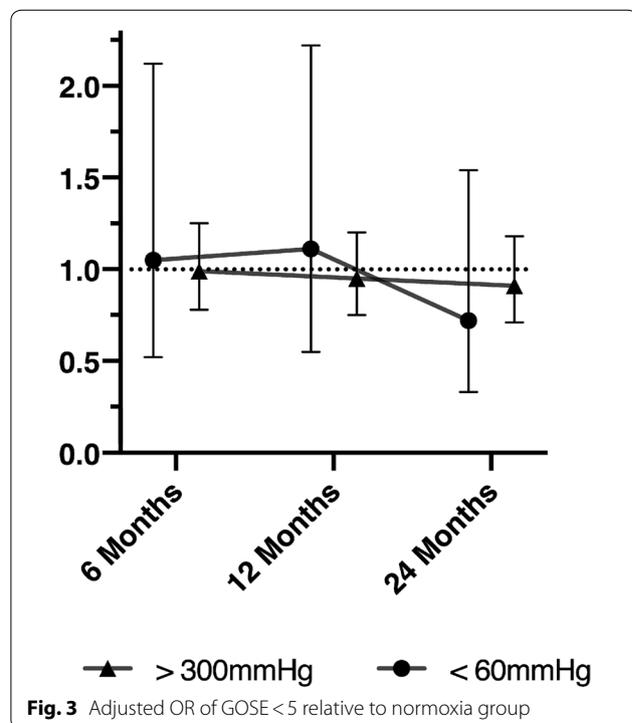
	<i>n</i>	All patients	$P_aO_2 < 60$ mmHg	$P_aO_2$ 60–300 mmHg	$P_aO_2 > 300$	<i>p</i>
Died in ICU	3699	525 (14.2%)	19 (25.7%)	398 (14%)	108 (13.8%)	0.017
ICU LOS (days)	3699	5.7 [2.6–11.7]	7.6 [2.1–14.3]	5.7 [2.6–11.5]	5.9 [2.4–11.7]	0.67
ICU LOS for survivors (days)	3174	6.4 [2.9–12.3]	10.3 [4.0–16.5]	6.2 [2.9–12.2]	6.5 [2.7–12.4]	0.033
ICU LOS for deaths (days)	525	3.2 [1.2–7.2]	1.5 [0.4–6.0]	3.2 [1.3–7.0]	3.9 [1.1–7.5]	0.1
Hospital outcome: death	3699	656 (17.7%)	21 (28.4%)	498 (17.5%)	137 (17.5%)	0.05
Hospital LOS in days	3699	13.2 [6.6–23.9]	13 [5.9–27]	13 [6.6–23.7]	13.8 [6.6–24.1]	0.82
Hospital LOS for survivors (days)	3043	15.8 [9.0–25.9]	19.6 [11.7–28.4]	15.5 [9–25.8]	16.3 [9.3–25.6]	0.14
Hospital LOS for deaths (days)	656	4.3 [1.4–9.4]	1.6 [0.7–8.2]	4.3 [1.5–9.7]	4.5 [1.7–8.9]	0.15
Hospital outcome: home	3699	814 (22%)	15 (20.3%)	643 (22.6%)	156 (19.9%)	0.24
Nursing home/chronic care/palliative	3699	1760 (47.6%)	32 (43.2%)	1324 (46.6%)	404 (51.5%)	0.042
Hospital outcome: other hospital	3699	337 (9.1%)	4 (5.4%)	270 (9.5%)	63 (8%)	0.24
Hospital outcome: rehab	3699	129 (3.5%)	2 (2.7%)	102 (3.6%)	25 (3.2%)	0.8
Tracheostomy indicator	190	39 (20.5%)	1 (25%)	34 (22.2%)	4 (12.1%)	0.42
Death at 6 months	3123	713 (22.8%)	21 (34.4%)	548 (23%)	144 (21.2%)	0.06
Death at 12 months	2815	746 (26.5%)	21 (36.2%)	577 (27.2%)	148 (23.3%)	0.036
Death at 24 months	2577	774 (30%)	21 (38.9%)	597 (31%)	156 (26.1%)	0.027
GOSE at 6 months	3123	5 [3–6]	4 [1–6]	5 [3–6]	5 [3–6]	0.16
GOSE at 12 months	2815	5 [1–6]	3.5 [1–6]	5 [1–6]	5 [3–6]	0.13
GOSE at 24 months	2577	5 [1–6]	4.5 [1–6]	5 [1–6]	5 [1–6]	0.04
GOSE <5 at 6 months	3123	1470 (47.1%)	35 (57.4%)	1123 (47.1%)	312 (45.9%)	0.23
GOSE <5 at 12 months	2815	1313 (46.6%)	33 (56.9%)	999 (47.1%)	281 (44.3%)	0.13
GOSE <5 at 24 months	2577	1220 (47.3%)	27 (50%)	931 (48.3%)	262 (43.9%)	0.15

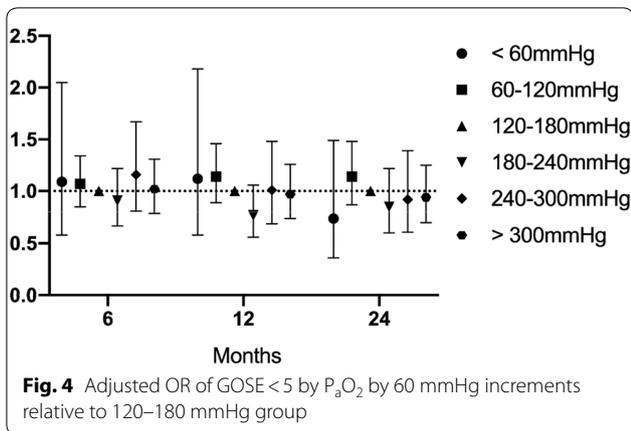
With (standard deviation) for means and [interquartile ranges] for medians

GOSE Glasgow Outcome Scale-Extended, ICU intensive care unit, LOS length of stay

### Adjusted and Sensitivity Analysis

Odds ratios (95% CI) for an adverse functional outcome at 6, 12, and 24 months, based on  $P_aO_2$  category (hypoxia, normoxia, or hyperoxia) are presented in Fig. 3. Sensitivity analyses for patients with an isolated head injury, who required operative care, and according to TBI severity (GCS < 9; GCS 9–12; GCS > 12) are presented in the supplementary material, along with the isolated mortality data for each analysis. Hyperoxia was not associated with a greater likelihood of adverse functional outcomes overall, nor in any of the pre-defined subgroups. Moreover, subgrouping  $P_aO_2$  values by 60 mmHg increments, did not result in identification of subgroups with an increased OR of adverse functional neurological outcome or death. These data are presented in Fig. 4. Finally, as a further sensitivity analysis, we treated  $P_aO_2$  as a continuous variable, and generated a Locally Weighted Scatterplot Smoothing (LOESS) of predicted risk of a GOSE < 5 at 6 months, versus worst  $P_aO_2$  in the first 24 h of ICU admission (see supplementary material). When treated as a continuous variable (including splines), there was no evidence of a significant relationship between  $P_aO_2$  and worse outcomes.





## Discussion

### Key Findings

In a large cohort of mechanically ventilated TBI patients, hyperoxia in the first 24 h of ICU admission was not associated with greater neurological morbidity at 6 months. This finding was consistent regardless of TBI severity, the need for operative care, and whether or not the head injury was isolated, or part of multisystem trauma. These findings were consistent out to 24 months of follow-up and persisted regardless of how  $P_{aO_2}$  was subcategorized.

### Relationship to Previous Studies

Our study is unique in its investigation of long-term functional outcomes in a large cohort of TBI patients. In regard to mortality, the three largest randomized controlled trials of liberal versus conservative oxygen exposure in general ICU patients have shown mixed results. The hyperoxia intervention arm of the French HYPERS2S study received an  $FiO_2$  of 1.0 and was stopped early for safety after recruitment of 442 patients, with strong mortality and morbidity signals for harm [24]. The OXYGEN-ICU trial enrolled 434 patients from a single Italian centre and compared target oxygen saturations of 94–98% with >97% [25]. They observed statistically significant associations between hyperoxia and shock, liver failure, and new bacteraemia. ICU-ROX, the largest of these studies to date, with 1000 patients, found no difference between outcomes with a targeted  $SpO_2$  of <97% versus usual care. This study included only a small number of patients with TBI (17 patients) [9] limiting its comparability to our study's population.

Studies focused on TBI have, to date, had mixed results and varied in quality and setting. A retrospective registry study of 3420 patients in the US found an association between extreme hyperoxia on the initial hospital blood gas and mortality—however, this was only seen with a

$P_{aO_2}$  above 487 mmHg, not lower, limiting generalizability [26]. They observed a similar association using discharge destination as a proxy for functional outcome status at discharge from hospital. These results primarily reflected pre-hospital care, rather than oxygen exposure in the ICU. In contrast, a US prospective single-center cohort study of 653 patients with TBI found no association between hyperoxia in the first 24 h of ICU and excess mortality [12]. A small Iranian randomized controlled trial of 68 patients with severe TBI exposed patients to either 50% or 80% oxygen during the first 6 h of their ICU admission. They measured functional outcomes including the Glasgow Outcome Score at 6 months and reported significant improvements with higher  $FiO_2$  exposure [27]. However, given the small sample and large putative effect size, this result must be viewed cautiously. Finally, a small Finnish pilot randomized controlled trial of 65 severe TBI patients did not show differences in biochemical markers of neurological injury when patients were treated with either an  $FiO_2$  of 0.4 or 0.7, providing mechanistic evidence that hyperoxia is not injurious to this population [28].

### Study Implications

In this study, no relationship was observed between hyperoxia in the first 24-h in ICU, and greater adverse functional outcomes in mechanically ventilated TBI patients. Given the lack of high-quality data to guide practice otherwise, our results imply that rigorous clinical avoidance of hyperoxia in TBI patients may not be necessary, and should reinforce clinical equipoise for future randomized controlled trials in this area. Specifically, given our findings, and those of previous clinical trials [9, 29], it may be that optimization of cerebral oxygenation represents the most logical study intervention, as opposed to simply avoiding hyperoxia.

### Strengths

The key strength of our study and its unique contribution to the TBI literature is our examination of long-term neurological outcomes. Functional neurological outcome after TBI may potentially be differentially and subtly more sensitive to exposure to hyperoxia in the hours following injury. Studies focused on mortality may be insensitive to long-term neurological morbidity and disability, and as such, our work provides critically needed insights.

Linkage between the ANZICS-APD and VSTR has also meant we have captured a large cohort of patients, managed within a standardized comprehensive state-wide trauma system, with relatively homogenous ventilation and/or oxygenation strategies. Data were collected by trained staff for the purposes of audit and quality assurance, and for this reason, are unlikely to be subject to

bias. Moreover, use of centralized VSTR follow-up has ensured consistency in applying the GOSE. Finally, we have used statistically robust techniques, using validated markers of illness severity, to control for known confounders.

### Limitations

As with any registry-based project, data were missing in some cases. Importantly, our secondary analysis suggested no differential effect of hyperoxia according to TBI severity, and given that hyperoxia may arguably be more harmful with more severe brain injury, it is unlikely that excluding these patients has concealed any signal. In a similar fashion, follow-up at 6, 12, and 24 months was not complete in all cases, albeit our cohort still represents one of the largest published to date regarding longer-term functional outcomes following TBI.

As our data demonstrate, TBI patients typically have a lengthy stay in both the ICU and hospital, and our ability to quantify oxygen exposure over this entire period is limited. Although the hyperoxia group manifest very high  $P_aO_2$  values during the first 24 h in ICU—their nominated  $P_aO_2$  represents the *minimum*  $P_aO_2$  in this period—we were unable to quantify this over any other time frame (either before ICU admission or after 24-h). As such, our study does not examine the effect of pre-hospital and Emergency Department hyperoxia, which may be more prevalent.

Finally, we acknowledge that our cohort includes patients with varying degrees of multitrauma, and different subtypes of TBI (e.g., subdural hematoma versus diffuse axonal injury). Albeit such heterogeneity may have weakened the signal overall, we did not observe any significant association between hyperoxia and adverse functional outcomes in isolated head injury, operative versus non-operative diagnosis, nor on the basis of TBI severity.

### Conclusions

In a large cohort study of TBI patients, managed in a comprehensive state-wide trauma system, we found no association between hyperoxia in the first 24-h of ICU admission, and adverse long-term functional outcomes. This finding was consistent, regardless of need for surgery, presence of multitrauma, severity of head injury, or degree of hyperoxia.

#### Electronic supplementary material

The online version of this article (<https://doi.org/10.1007/s12028-020-01033-y>) contains supplementary material, which is available to authorized users.

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#### Author Contributions

MW/AU designed the study. BG/DP/MB had full access to the raw data. Statistical analysis was performed by MB. MW/AU drafted the initial manuscript. All authors critically revised the manuscript for important intellectual content and read and approved the final version.

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#### Conflict of interest

The authors declare that they have no conflict of interest.

#### Ethical approval/Informed consent

Access to the data was granted by the ANZICS CORE management committee and the VSTR data custodians. Ethics approval was obtained from The Alfred Health Human Research Ethics Committee (Ref: 243/19), with a waiver of individual patient informed consent.

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