Critical Care

RESEARCH

Open Access

Neurological outcomes and mortality following hyperoxemia in adult patients with acute brain injury: an updated meta-analysis and meta-regression

Nekane Romero-Garcia[1,2,3*†], Chiara Robba[4,5†], Berta Monleón[1,2], Ana Ruiz-Zarco[1,2], Maria Pascual-González[1,2], Alberto Ruiz-Pacheco[1,2,3], Felipe Perdomo[1,2], Maria Luisa García-Pérez[1,2,3], Ana Mugarra[1,2], Laura García[1,2], Jose Carbonell[1,2,3], Lavienraj Premraj[6], Fabio Silvio Taccone[7†] and Rafael Badenes[1,2,3†]

Abstract

Background The aim of this study was to evaluate the association of arterial hyperoxemia with neurological outcomes and mortality in adults with acute brain injury (ABI).

Methods Six electronic databases, including MEDLINE, Embase and online registers of clinical trials, were systematically searched from inception to June 1 st, 2024. Studies comparing the effects of hyperoxemia *versus* no hyperoxemia on outcomes of hospitalized adult patients with ABI-related conditions (e.g. traumatic brain injury, post-cardiac arrest, subarachnoid hemorrhage, intracerebral hemorrhage, and ischemic stroke) were included according to PRISMA guidelines. Data were pooled using a random-effects model for unadjusted and covariate-adjusted odds ratios. The primary outcome was poor neurological outcome as defined by each individual study, and the secondary outcome was all-cause mortality. Subgroup analyses were conducted based on principal diagnosis, timing of outcome measures, oxygenation thresholds, among other factors. Meta-regression was applied to identify sources of heterogeneity.

Results After 7,849 nonduplicated records were screened, 66 studies fulfilled eligibility criteria for systematic review. The meta-analysis including 24 studies (16,635 patients) revealed that patients with hyperoxemia are 1.29 times more likely to develop poor neurological outcomes (unadjusted OR, 1.295; 95% Confidence Interval, CI 1.040–1.616) compared with those with no hyperoxemia, particularly in subarachnoid hemorrhage and ischemic stroke subgroups. The meta-analysis including 35 studies (98,207 patients) revealed that all-cause mortality is 1.13 times more likely (OR 1.13; 95% CI 1.002–1.282) in patients with hyperoxemia compared with no hyperoxemia.

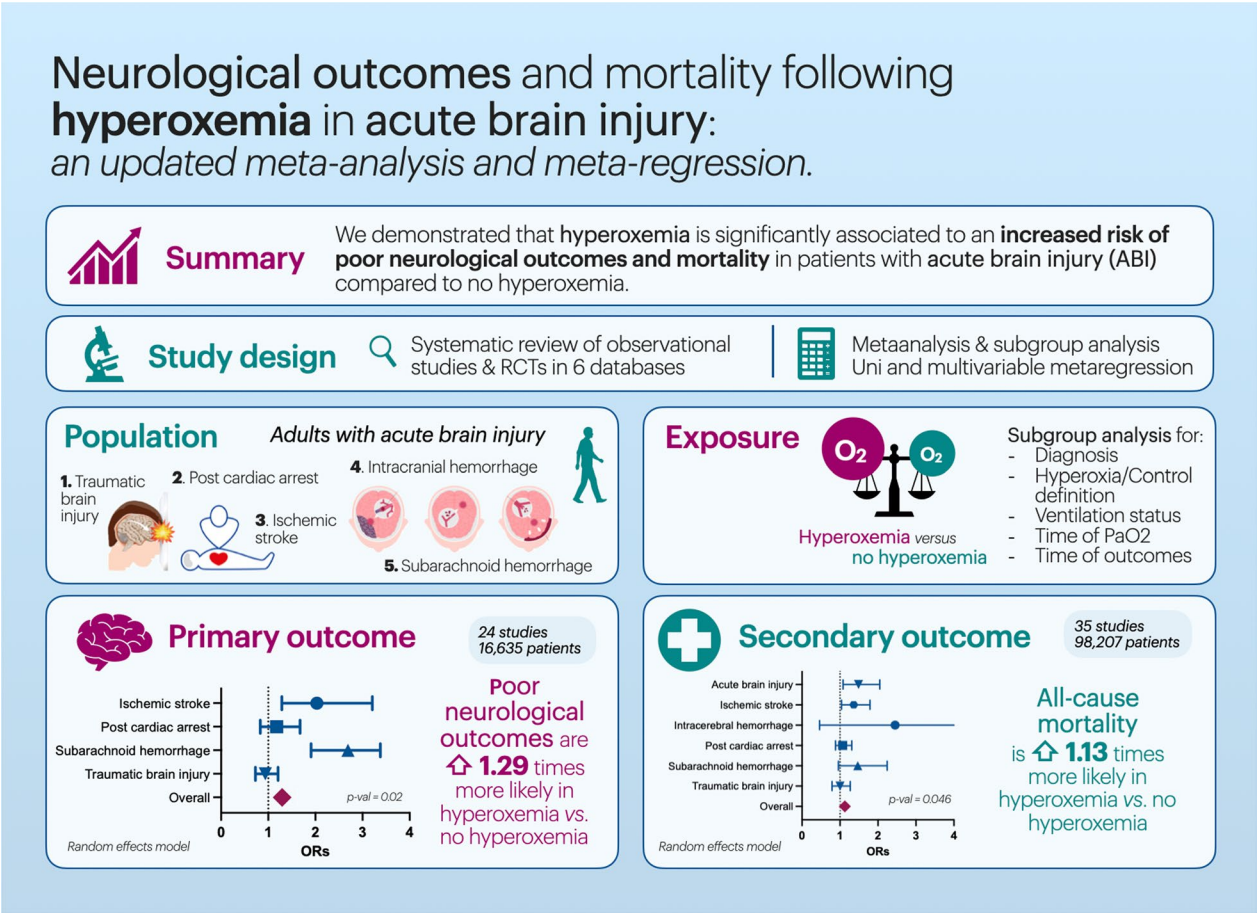
Conclusions In our study we found that hyperoxemia is significantly associated with an increased risk of poor neurological outcomes and mortality in patients with acute brain injury compared to those with no hyperoxemia. Our results suggest the importance of carefully adjusting oxygenation strategies in neurocritical ICUs.

Keywords Hyperoxemia, Acute brain injury, Neurological outcomes, Mortality, Meta-analysis

†Nekane Romero-García and Chiara Robba are first co-authors. Fabio Silvio Taccone and Rafael Badenes are last co-authors.

*Correspondence:
Nekane Romero-Garcia
nekaneromerog@gmail.com; nerogar@alumni.uv.es
Full list of author information is available at the end of the article

Graphical Abstract



Introduction

Acute brain injury (ABI) is an umbrella term encompassing several conditions that lead to sudden, acquired neuronal damage, such as traumatic brain injury (TBI), post-cardiac arrest (PCA) brain injury, subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH), and ischemic stroke (IS) [1, 2]. Ensuring adequate brain oxygenation is a key target in neurocritical care guidelines [3, 4), and supplemental oxygen is commonly administered in intensive care units (ICUs) [5, 6]. Hypoxemia, defined as an arterial partial pressure of oxygen (PaO_2) lower than 80 mmHg (in some cases, < 60 mmHg), has been linked to higher mortality and worse outcomes in patients with ABI [7–9].

Since oxygen therapy is not without adverse effects, over the last decade some authors have emphasized the need to balance the risks of hypoxemia against the risks of hyperoxemia [10]. These include vasoconstriction due to interference with prostaglandin release, which can lead to reduced cerebral perfusion, as well as increased generation of free radicals, contributing to oxidative stress and potential tissue damage [10]. Although there is no universally accepted PaO_2 threshold to define hyperoxemia, most studies use a PaO_2 higher than 120 mmHg as mild, 200 mmHg as moderate, and > 300 mmHg as severe hyperoxemia [5, 11]. In general ICU patients, previous reviews suggest that liberal oxygenation strategies may negatively impact outcomes when compared to more conservative strategies [12–14]. Recent observational studies have hypothesized a U-shaped association between arterial oxygenation and poor outcomes [1, 15], but further studies are needed specifically in ABI populations to establish optimal oxygenation thresholds.

Evidence from randomized clinical trials has been insufficient to resolve this controversy [16–20]. As a result, current TBI ventilation guidelines recommend

maintaining a PaO_2 between 80 and 120 mmHg, though this recommendation is based on a very low level of evidence [21]. Although previous reviews on this topic have been published, there is a compelling rationale to update these works using a more robust methodological approach. First, most meta-analyses focus on general ICU patients rather than specifically on ABI, often including patients with varying diagnoses, such as sepsis or those undergoing cardiac surgery [13, 14, 22, 23]. Second, some meta-analyses combine different outcome measures, such as inspired oxygen fraction (FiO_2), peripheral oxygen saturation (SpO_2) and/or PaO_2, which reduces the comparability of results [24, 25]. Another source of heterogeneity arises from the varying thresholds for hyperoxemia, and control groups used across studies. To improve methodology, researchers should consider excluding non-peer-reviewed sources, publishing a protocol, and using covariate-adjusted odds ratios to better account for confounders and reduce heterogeneity. Moreover, new findings from high-impact study databases, such as those more the recent "Targeted Hypothermia versus Targeted Normothermia after Out-of-Hospital Cardiac Arrest" (TTM- 2) and "Extubation in Neurocritical Care" (ENIO) studies, should be incorporated into updated reviews [1, 15].

Given the high global prevalence of ABI and its growing socioeconomic burden [26–28], preventing oxygen-related iatrogenesis is a critical challenge. Therefore, the goal of this systematic review and meta-analysis was to assess the effect of arterial hyperoxemia on neurological outcomes and mortality in adult hospitalized patients with ABI. The review included subgroup analyses based on the type of ABI, timing of outcome assessments, oxygenation thresholds, and other relevant factors. Meta-regression analyses were applied to identify sources of heterogeneity.

Methods

The protocol for this review was registered with PROSPERO (CRD42023433502) and published in an open-access peer-reviewed journal [29] according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (Table S1 in Supplement) [30].

Search strategy and selection criteria

Two authors independently searched electronic databases for retrospective and prospective cohort studies, as well as randomized clinical trials (RCTs), examining the effect of arterial hyperoxemia on functional outcomes and mortality in patients with ABI. The following databases were searched from inception through June 1, 2024: MEDLINE, Embase, Scopus, Web of Science, The Cochrane Library (Cochrane Central Register of Controlled Trials and Cochrane Database of Systematic Reviews), Cumulative Index to Nursing and Allied Health Literature (CINAHL), and ClinicalTrials.gov. To minimize publication bias, previous reviews, reference lists of included articles, and expert opinions were screened for relevant works.

Authors were contacted via institutional email for clarification when relevant data were missing. The search strategy was not restricted by publication type or language, provided an abstract in English was available (Table S2 in the Supplement). Two authors independently screened abstracts, followed by full texts to determine eligibility for inclusion; discrepancies were resolved by a third independent author. In cases of duplicate publications from the same study, the version with the lowest risk of bias was selected.

We included RCTs and observational studies (both prospective and retrospective cohort studies, and case–control studies). Conference abstracts were included in the systematic review if sufficient data were available for quality assessment but were excluded from the meta-analysis. Grey literature was excluded to minimize risk of bias. Eligible studies included populations of: (1) adult patients (≥ 18 years of age), (2) hospitalized, (3) with a diagnosis of ABI, specifically TBI, PCA (excluding cardiac surgery with cardiopulmonary bypass), SAH, ICH, or IS. Studies involving (1) pediatric patients or (2) patients with neurological comorbidities prior to injury (e.g., dementia, cerebral palsy, previous stroke) were excluded.

The studied exposure was arterial hyperoxemia, defined as elevated PaO_2 values under normobaric conditions; a commonly accepted threshold for hyperoxemia is $PaO_2 > 120$ mmHg [40]. For this analysis, we adopted each study's individual cutoff value, consistent with previous reviews [25, 26]. When multiple cutoff values were provided, we selected the one with: (i) reported covariate-adjusted odds ratios (OR), (ii) designation as the primary objective, or (iii) the most extreme value. For studies presenting ORs for quartiles of PaO_2 distribution, effect estimates for the highest quartile were pooled. The variability in hyperoxemia definitions was addressed through subgroup analysis and meta-regression. Studies were excluded if the exposure was (1) non-arterial hyperoxemia, (2) hyperoxemia not defined by PaO_2 (e.g., using SpO_2 or FiO_2), or (3) hyperbaric oxygenation. Studies based on SpO_2 were excluded due to the inability of SpO_2 to reflect the degree of hyperoxemia.

The comparator or control group was "no hyperoxemia," which could include normoxemia, hypoxemia, or both, depending on the study's definition. When possible, normoxemia was defined as $PaO_2 > 60$ mmHg. If

quartiles of PaO_2 distribution were presented, Q2 was selected as the normoxemia comparator, with Q1 representing the hypoxemia group.

The primary outcome was the incidence of poor neurological outcomes in ABI patients exposed to hyperoxemia. The definition of poor neurological outcomes was based on each study's criteria, including Glasgow Coma Scale (GCS) < 9, Glasgow Outcome Scale (GOS) < 4, Glasgow Outcome Scale Extended (GOSE) < 4, Cerebral Performance Category (CPC) < 2, and modified Rankin Score (mRS) > 3 at a specified time defined by each study as primary outcome. If neurological outcomes were measured at multiple time points and none of them was defined as primary outcome, we will use the longest follow-up period. The secondary outcome was all-cause mortality at the time point defined by each study, or, if mortality was measured at multiple time points, at the longest follow-up period.

Data extraction and statistical analysis

Two investigators independently extracted data using a pre-defined data collection form. Any discrepancies in judgment were resolved by a third investigator and by referencing the original study report. For the meta-analysis, both unadjusted odds ratios (ORs) and covariate-adjusted ORs extracted from each study were considered separately. When studies reported risk ratios (RRs), these were assumed to approximate ORs only when the outcome prevalence was approximately ≤ 10% [31]. Unadjusted ORs were computed from available 2× 2 contingency tables. Studies reporting hazard ratios (HRs) were excluded from quantitative synthesis, consistent with our published protocol. Heterogeneity was quantified using the I^2 statistic and Cochran's Q test, with I^2 values interpreted as follows: 0–30% (not important), 30–60% (moderate), 60–90% (substantial), and > 90% (considerable) [32]. Given the expected clinical and methodological heterogeneity, a random-effects model was employed to pool effect sizes. Our primary analysis used the DerSimonian–Laird estimators.

Subgroup analyses were conducted based on principal diagnosis, ventilation type ("invasive" *versus* "invasive and non-invasive"), PaO_2 type ("first", "lowest", "highest", "specific time" or "average"), PaO_2 threshold used to define hyperoxemia (" ≥ 200/300 mmHg" *versus* "any"), comparator group definition ("normoxemia" as PaO_2 > 60 mmHg *versus* "no hyperoxemia" as any PaO_2 below hyperoxemia threshold), time of outcome measurement (less than 3/6 months *versus* equal to or more than 3/6 months), neurological evaluation score and risk of bias ("good" *versus* "not good"). We used random-effects meta-regression models to explore potential sources of heterogeneity. Candidate moderators included the same variables used in subgroup analyses. Each moderator was first analyzed in a univariate regression mode and then together in multivariate regression. Moderators were selected based on clinical relevance and methodological considerations, and model selection was guided by the Akaike Information Criterion (AIC). We also acknowledge the potential for multiple testing and have interpreted the meta-regression findings with caution, especially considering limited power due to small number of studies. Residual heterogeneity (τ^2) and I^2 were reported before and after adjustment for each moderator.

Study quality assessment and risk of bias

For risk of bias assessment, each study was evaluated by two independent reviewers using the Newcastle–Ottawa Scale (NOS) for observational studies of exposures [33, 34], Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) for observational studies of interventions, or the Cochrane risk-of-bias tool for randomized trials (RoB2) for RCTs. Studies were classified as "good" quality if NOS was higher than 6/9 and all domains were higher than 0, or if Rob2 score was "low" or "some concerns" for RCTs. The overall quality of evidence was subsequently appraised using the GRADE framework [35].

Publication bias was evaluated by visual inspection of funnel plots and quantitatively using Egger's regression test. When significant asymmetry was detected ($p < 0.05$), Duval and Tweedie's trim-and-fill method was applied to estimate the potential impact of unpublished studies on the pooled effect sizes. All analyses were performed with Stata statistical software version 18 (Stata Corp, College Station, Texas, USA) and group subanalysis figures were elaborated in Graphpad Prism version 10.3.1 (464).

Role of the funding source

There was no funding source for this study. NRG and RB had full access to the data and had final responsibility for the decision to submit for publication.

Results

Systematic review

Our search identified 7,849 records after removing duplicates, where 238 were fully assessed for eligibility (Fig. 1). We identified 66 articles which met the inclusion criteria for the systematic review (Table 1); from them, 19 studies were excluded from the quantitative review (Table S3 in the Supplement). 47 studies met inclusion criteria for the meta-analysis, with a total of 26,252 adult patients with ABI analyzed for neurological outcomes (16,635 for the unadjusted and 16,692 for the covariate-adjusted analyses, respectively) and 105,589 for mortality (98,207

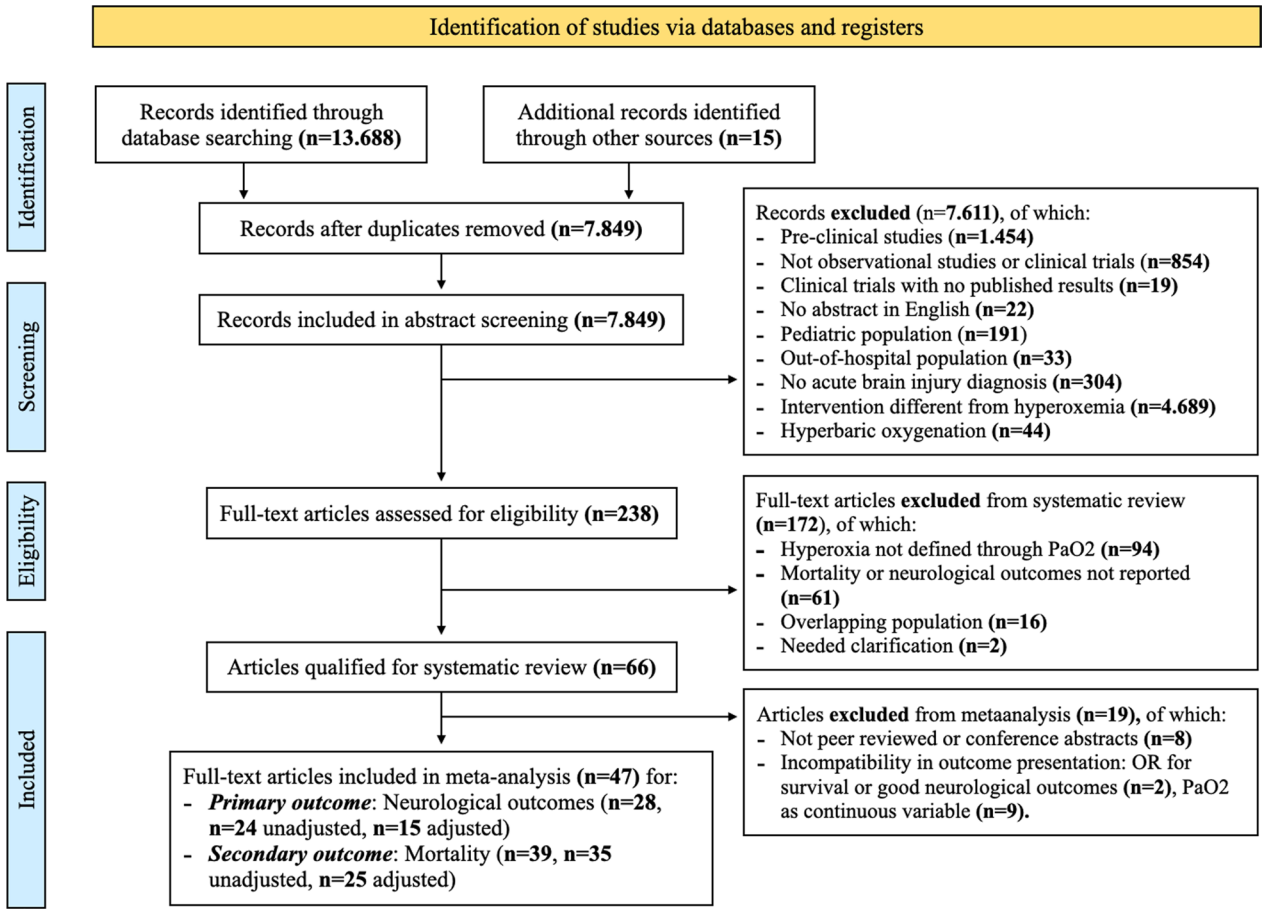


Fig. 1 PRISMA flowchart diagram for identification and selection of studies. Excluded studies are listed in Table S3 in the Supplement

for the unadjusted and 85,632 for the covariate-adjusted analyses, respectively).

Of the 66 studies, 1 was a RCT (1.5%), 33 were multicenter retrospective cohort studies (50%), 8 (12.1%) were multicenter prospective cohorts and 24 (36%) were single-center studies. Admission diagnosis was PCA for 26 studies, TBI for 15 studies, SAH for 7 studies, ABI for 3 studies, IS for 2 studies and ICH for 2 studies. A total of 43 studies (65.1%) had more than 6 points in the NOS tool for risk of bias assessment with more than 1 point in each domain, or had a Rob2 score "low-some concerns", being classified as "good" (Table S4 and S5 in the Supplement).

The definition of hyperoxemia varied among studies: 36 used PaO_2 thresholds of 200 mmHg or higher, while 27 used 300 mmHg or higher. A total of 42 studies (63.6%) used "normoxemia" as control group, 21 used "no hyperoxia" (31.8%) and in 5 the control group was "not defined". The only RCT included used "restrictive" versus "liberal" oxygenation targets. Neurological outcome scores were measured at hospital discharge (15 studies), at 3 months (5 studies) or at than 6 months or longer (8 studies). The score used for neurological outcome was related to admission diagnosis; the majority of PCA studies used CPC, TBI studies used GOS/GOSE and IS/ICH used mRS. Timing of mortality assessment varied from hospital discharge to 6 months (6 studies).

Primary outcome: Poor neurological outcomes

The quantitative synthesis for primary outcome included 28 studies (26,252 patients). The unadjusted OR meta-analysis, which included 24 studies (16,635 patients), showed an increase in poor neurological outcomes with hyperoxemia (OR 1.296, 95% CI 1.040–1.616, p = 0.02). Subgroup analysis revealed a greater effect in patients with SAH (OR 2.692, 95% CI 1.909–3.796) and IS (OR 2.031, 95% CI 1.287–3.207) (Fig. 2). The covariate-adjusted meta-analysis showed similar results (OR 1.295; 95% CI 1.143–1.467, Figure S1 in the Supplement). Effect size was greater in ischemic stroke and subarachnoid hemorrhage patients. Heterogeneity among studies was substantial (I^2 76.54%). The overall funnel plot

Table 1 Characteristics of the studies included in the systematic review

Study details		Population		Exposure					Outcomes	
Author, year	**Study design**	**Diag-nosis**	**Study size**	**Ventila-tion**	**Type of PaO_2**	**Time of PaO_2 (hours after admission)**	**Hyperoxemia definition (PaO_2 mmHg)**	**Comparator (PaO_2 mmHg)**	**Mortality (time)**	**Poor Neurological outcome (scale/time)**
Alali 2020 [36]	PC/M	TBI	417	NA	Average	24 h	> 100, > 150, > 200*, > 250, > 300, > 350	80–100	6 months	GOSE/6 months
Asher 2013 [37]	RC/M	TBI	193	NA	Highest	72 h	> 200, > 250*, > 300, > 350, > 400, > 487	60-value	HD	NA
Awad 2023 [38]	RC/M	PCA	9735	IV	Lowest	1 h	> 100*, > 150, > 225, > 300	60–100	1 month	NA
Bellomo 2011 [39]	RC/M	PCA	12,108	IV/NIV	Lowest	24 h	> 300	60–300	HD	NA
Bolduc 2016 [40]	RC/M	PCA	265	NA	NA	NA	> 300	< 300	NA	CPC 3–5/NA
Brenner 2012 [41]	RC/M	TBI	1547	NA	Average	24 h	> 200	100–200	HD	GCS < 9/HD
Chang 2019 [42]	RM/M	PCA	291	IV	First	24 h	> 300	60–300	NA	CPC 3—5/HD
Davis 2009 [43]	RC/M	TBI	3420	NA	First	1 h	> 487	110–487	NA	NA
Davis 2023 [44]	RC/M	TBI	1322	NA	Specific time	30 min	> 400	80–400	HD	GOS < 3/HD
Ebner 2019 [45]	PC/M	PCA	939	IV	Highest	36 h	> 300	60–300	NA	CPC 3–5/6 months
Ebner 2020 [46]	RC/M	PCA	2153	NA	Highest	24 h	> 300	60–300/< 300	NA	CPC 3–5/HD
Elmer 2015 [47]	RC/M	PCA	184	IV	Specific time	24 h	> 300*, > 100	60–100	HD	CPC 5/HD
Fallenius 2016 [48]	RC/M	ICH	3033	IV/NIV	First	24 h	> 97.5, > 150	< 97.5	6 months*/ICU, HD	NA
Fujita 2017 [49]	RC/M	TBI	129	IV	NA	24 h	Continuous	NA	6 months	GOS < 3/6 months
Fukuda 2019 [50]	RC/M	SAH	197	IV/NIV	Average	24 h/6 days	> 200, > 250*	< 200, < 250*	NA	GOS 1–3/HD
Gaieski 2012 [51]	RC/M	PCA	111	NA	Average	24 h	Continuous	NA	NA	NA
Grensemann 2022 [52]	RC/S	SAH	282	IV	Average	14 d	85–93, 93–228*	78–85	1 month	GOS 1–3 or DCI/3 months
Helmerhorst 2015 [53]	RC/M	PCA	5258	IV	Lowest	24 h	> 300	60–300	HD	NA
Humaloja 2019 [54]	RC/M	PCA	1110	NA	First	NA	> 120, > 300*	60–120	1 year	CPC 3–5/1 year
Humaloja 2021 [55]	RC/M	PCA	8290	IV	Lowest	24 h	> 137	61–137	1 year	Permanent disability or death/1 year
Ihle 2013 [56]	RC/M	PCA	957	IV	Lowest	24 h	> 300	60–300	HD	NA
Izawa 2022 [57]	RC/M	PCA	16,013	NA	First	Intra-arrest	> 300	60–300	NA	CPC 3–5/1 month or HD [first]
Janz 2012 [58]	RC/S	PCA	170	NA	Highest	24 h	> 310	< 310	HD	CPC 3–5/Discharge

Table 1 (continued)

Study details		Population		Exposure					Outcomes	
Author, year	**Study design**	**Diag-nosis**	**Study size**	**Ventila-tion**	**Type of PaO_2**	**Time of PaO_2 (hours after admission)**	**Hyperoxemia definition (PaO_2 mmHg)**	**Comparator (PaO_2 mmHg)**	**Mortality (time)**	**Poor Neurological outcome (scale/ time)**
Jeon 2014 [59]	RC/S	SAH	252	IV	Average	14 days	> 173	< 173	NA	mRS 4–6/3 months
Johnson 2017 [60]	RC/M	PCA	544	NA	Specific time	1,6,12*,24,48 h	> 300	60–300	HD	CPC 3–5/HD
Kang 2021 [61]	RC/S	PCA	97	NA	Average	6, 24 h	> 150	75–150	NA	CPC 3 to 5/24 h
Kahn 2021 [62]	RC/S	TBI	309	IV	Specific time	24 h	> 120	60–120	ICU, HD*	GOS < 4/HD
Kiguchi, 2016 [63]	RC/M	PCA	678	NA	First	NA	> 300	< 300	1 month	CPC 3–5/1 month
Kilgannon 2010 [64]	RC/M	PCA	6326	IV/NIV	First	24 h	> 300	60–300	HD	NA
Kilgannon 2011 [65]	RC/M	PCA	4459	IV	First	24 h	Continuous	NA	HD	NA
Lang 2016 [66]	RC/M	SAH	432	IV	Average	24 h	> 150	97.5–150	3 months	GOS 1–3/3 months
Lee 2014 [67]	RC/S	PCA	213	IV/NIV	Average	48 h	> 156.7	< 116.9, 116.9–134.9*, 134.9–156.7	HD	CPC 3–5/HD
Li 2019 [68]	RC/S	SAH	244	NA	Highest	24 h	> 200	< 200	3 months	GOS 1–3/3 months
López 2019 [69]	RC/S	IS	333	IV	First	NA	> 120	< 120	3 months	mRS 3–6 or 4–6*/3 months
Matta 2022 [70]	RC/S	PCA	144	NA	First	6 h, 24 h	> 100, > 200	< 100, < 200	1 month	CPC/1 month
McGuigan 2020 [71]	RC/M	PCA	23,625	IV	Lowest	24 h	> 100	60–100	HD	NA
Mckenzie 2021 [72]	RC/M	PCA	491	IV	Average	24 h*, 48 h, 72 h	> 180	180–100	HD	NA
Nelskyla 2013 [73]	RC/S	PCA	119	IV/NIV	Highest	24 h	> 300	< 300	1 month	NA
O Briain 2018 [74]	RC/M	TBI	24,148	IV	Lowest	24 h	> 300	60–300	HD	NA
Oh 2014 [75]	RC/S	PCA	792	NA	Specific time	2 h	> 300	60–300	HD	CPC 3–5/HD
Patel 2018 [76]	RC/S	PCA	167	IV	Specific time	Intra-arrest	> 300*, > 160, > 92	60–92*	HD	NA
Peluso 2020 [77]	RC/S	PCA	356	IV	Highest	24 h	> 300	< 300	ICU	CPC 3–5/3 months
Popovic 2014 [78]	RC/S	TBI	49	IV	First	NA	> 200	100–200	24 h, 48 h, HD	GOS 1–3/HD
Rai 2011 [79]	RC/S	PCA	88	NA	NA	NA	> 300	60–300	NA	NA
Raj 2013 [80]	RC/M	TBI	1,116	IV	Lowest	24 h	> 100	75–100	6 months*, ICU, HD	
Reynolds 2021 [81]	RC/S	SAH	345	NA	Highest	72 h	Continuous	NA	HD	NA
Rezoagli 2022 [5]	RC/M	TBI	1084	IV	Highest, average	24 h, 7 days	Continuous	NA	6 months	GOSE 1–4/6 months
Rincon 2014 TBI [82]	RC/M	TBI	1212	IV	First	NA	> 300	60–300	HD	NA

Table 1 (continued)

Study details		Population		Exposure					Outcomes	
Author, year	**Study design**	**Diag-nosis**	**Study size**	**Ventila-tion**	**Type of PaO_2**	**Time of PaO_2 (hours after admission)**	**Hyperoxemia definition (PaO_2 mmHg)**	**Comparator (PaO_2 mmHg)**	**Mortality (time)**	**Poor Neurological outcome (scale/ time)**
Rincon 2014 ABI [83]	RC/M	ABI	2894	IV/NIV	First	NA	> 300	60–300	HD	NA
Rincon 2015 [84]	RC/M	ICH	1388	IV	First	24 h	> 300	60–300	HD	NA
Robba 2022 PCA [15]	PC/M	PCA	1418	IV	Highest	72 h	> 300*, > 195	60–300*, 60–195	ICU*, Hospital discharge	mRs 4–6/6 months
Robba 2023 ABI [1]	PC/M	ABI	1407	IV/NIV	First	24 h	> 120*, > 300	80–120	HD*, ICU	NA
Roberts 2018 [85]	PC/M	PCA	280	IV	Highest	6 h	> 300	< 300	HD	mRS > 3/HD
Russell 2017 [86]	RC/M	TBI	266	IV	Highest	24 h	Continuous	NA	HD	GCS/HD
Sadaka 2013 [87]	RC/S	PCA	56	NA	First	24 h	> 250	60–250	NA	CPC 3—5/HD
Sadaka 2012 [88]	RC/S	TBI	169	NA	First	24 h	> 245	60–245	NA	GCS 1–3
Schmidt 2022 [89]	RCT	PCA	789	IV	All times	120 h	98–105	68–75	3 months	CPC 3–4/HD
Spindleboek 2013 [90]	RC/M	PCA	145	IV/NIV	First	24 h	> 300	60–300	HD	CPC 3–5/HD* or 1 month
Vaahersalo 2014 [91]	PC/M	PCA	409	IV	Average	24 h	> 225	75–150	NA	CPC 3–5/1 year
Vrettou 2023 [92]	PC/M	TBI	910	IV/NIV	Lowest	4 h	> 400, > 250*, > 100	< 100	1 month	GOSE 1–4/6 months
Wang 2015 [93]	RC/S	PCA	550	IV/NIV	First	24 h	> 300	60–300	HD	CPC 3–5/HD
Wang 2017 [94]	RC/S	PCA	9176	NA	First, last, highest*	24 h	> 300	60–300	HD	NA
Weeden 2021 [95]	RC/M	TBI	3699	IV	Lowest	24 h	> 300	60–300	6 months*, ICU, HD, 12 months, 24 months	GOSE1 -4/6 months*, 12 months, 24 months
Yokoyama 2019 [96]	RC/S	SAH	196	IV	Highest	24 h	> 120*, > 200, > 300	60–120	> 120 vs 60–120	mRS 3–6/HD
Youn 2018 [97]	RC/S	PCA	187	NA	Average	0–24 h*, 0–6 h, 6–24 h	> 100, > 150, > 200*, > 250, > 300	< 100, < 150, < 200*, < 250, < 300	NA	CPC 3–5/6 months
Young 2012 [98]	RC/M	IS	2643	IV/NIV	Lowest	24 h	> 341	< 69, 69–83, 83–93, 93–103, 103–117, 117–140, 140–174, 174–226**, 226–341, < 341***	HD	NA

ABI: Acute brain injury, AUC: Area Under the Curve, Cont: Continuous variable, CPC: Cerebral Performance Category, DCI: Delayed Cerebral Ischemia, GOS: Glasgow Outcome Scale, GOSE: Glasgow Outcome Scale Extended, HD: Hospital discharge, ICH: Intracerebral hemorrhage, ICU: Intensive care unit discharge, IS: Ischemic stroke, IV: Invasive ventilation, M: Multicentre, mRS: modified Rankin Score, NA: Not available, NIV: Non-invasive ventilation, PC: Prospective cohort, PCA: Post-cardiac arrest, RC: Retrospective cohort, RCT: Randomized controlled trial, ROSC: Return of spontaneous circulation, S: Single center, SAH: Subarachnoid hemorrhage, TBI: Traumatic brain injury, Values marked with (*) are those defined as primary objectives of each study. Values marked as (**) represent those used for unadjusted meta-analysis (if different)

(See figure on next page.)

Fig. 2 Effect of hyperoxemia on poor neurological outcomes in patients with ABI. Forest plot for the meta-analysis based on unadjusted ORs for poor neurological outcomes in hyperoxemia *versus* no hyperoxemia in patients in ABI (n = 24 studies, 16,635 patients). The boxes show the effect estimates from the individual studies. The size of the boxes is inversely proportional to the size of the result study variance. The diamonds represent pooled results in each subgroup and overall analysis; the length of horizontal lines across the boxes and the width of the diamonds illustrates the 95% CI. The gray vertical line at one is the line of null effect, and the red vertical line shows the pooled effect estimate of the whole analysis. ABI: Acute brain injury, CI: confidence interval, ICH: Intracerebral hemorrhage, IS: Ischemic stroke, OR: odds ratio, PCA: Post-cardiac arrest, SAH: Subarachnoid hemorrhage, TBI: Traumatic brain injury

showed slight asymmetry though the Egger test did not reach statistical significance (p = 0.078) (Figure S2 in the Supplement). One study, Humaloja 2021, included in the covariate-adjusted analysis, used a different measure of outcome ("permanent disability"); for this reason, a sensitivity analysis without this study was conducted (Figure S8).

Secondary outcome: Mortality

The quantitative synthesis for secondary outcome included 39 studies (105,589 patients). The unadjusted OR meta-analysis for mortality, which included 35 studies with 98,207 patients, demonstrated a statistically significant association between hyperoxemia and increased mortality (OR 1.13; 95% CI 1.002–1.282) (Fig. 3). Similar to neurological outcomes, the effect size was greater in ischemic stroke and subarachnoid hemorrhage patients, as well as in studies which included ABI of different causes. The covariate-adjusted OR meta-analysis showed similar overall results (OR 1.143, 95% CI 1.007–1.296) (Figure S3 in the Supplement). Heterogeneity among studies was substantial (I^2 88.04%). The initial funnel plot showed some asymmetry, which was supported by a borderline-significant Egger test (p≈0.048), indicating potential small-study effects. However, a trim-and-fill analysis did not identify any imputed studies, suggesting that classical publication bias may not be driving the observed asymmetry; instead, it could reflect genuine differences between smaller and larger studies (Figure S4 in the Supplement).

Group subanalysis and meta-regression

To explore the factors which may influence the correlation between arterial hyperoxemia and poor outcomes, group subanalysis was performed (Fig. 4). Studies with a lower risk of bias ("good" *versus* "not good") showed a trend towards greater effect size (p = 0.3 for neurological outcomes, p = 0.08 for mortality). Regarding time of outcome measure, there was a trend toward a higher effect size in studies considering short-term outcomes (less than 3 months or less than 6 months) *versus* long-term outcomes, where this effect seems to be lost, both in neurological outcomes (p = 0.94 and p = 0.08, respectively) and mortality (p = 0.125). (Figures S5 and S6 in the Supplement).

Regarding the type of PaO_2 measure, there is a trend towards a greater effect size when "average" PaO_2 is considered, both for neurological outcomes and mortality ($p = 0.09$ and $p = 0.20$ for group differences, respectively). No subgroup differences exist according to type of ventilatory support in either outcome ($p = 0.48$ and $p = 0.82$), although IV group shows a lower intra-group heterogeneity. Finally, evidence is inconsistent regarding subgroup analyses for PaO_2 for hyperoxemia and control group definition. While in mortality meta-analysis we found a trend towards a greater effect size in studies with higher thresholds ($p = 0.32$ for $PaO_2 >= 300$ mmHg, p = 0.73 for $PaO_2 >= 200$ mmHg), this effect is opposite in neurological outcomes ($p = 0.134$ and $p < 0.05$, respectively). Subanalyses according to control group definition do not find a statistically significant difference between using "normoxemia" and "no hyperoxemia" in either neurological outcomes or mortality, but "normoxemia" studies group reflect lower intra-group heterogeneity (Figures S5 and S6 in the Supplement).

To investigate potential sources of high heterogeneity, we performed a meta-regression analysis in univariate and multivariate settings with the same stratifying variables used in the subgroup analyses (Figure S7 in the Supplement). In the association between hyperoxemia and poor neurological outcomes, moderators "principal diagnosis" and "hyperoxemia as $PaO_2 \geq 200$ mmHg" substantially reduced *tau* and I^2, suggesting that these moderators explain some of the observed heterogeneity (Table S7 in the Supplement); particularly, the definition of hyperoxia markedly influenced the adjusted overall estimate (OR = 2.24, p < 0.001) (Table S6 in the Supplement). In the multivariate analysis, including all moderators significantly reduced heterogeneity from I^2 76.54% to 57.43% (model 8, Table S8 in the Supplement). In the meta-analysis for mortality, no individual moderators were found to significantly modify the association between hyperoxemia and mortality, with a high remaining heterogeneity in univariate models ($I^2 > 85\%$) and significant residual QQQ tests (p-value < 0.001, Tables S9 and S10 in the Supplement). Moreover, most overall odds ratios remained nonsignificant (OR close to 1) or

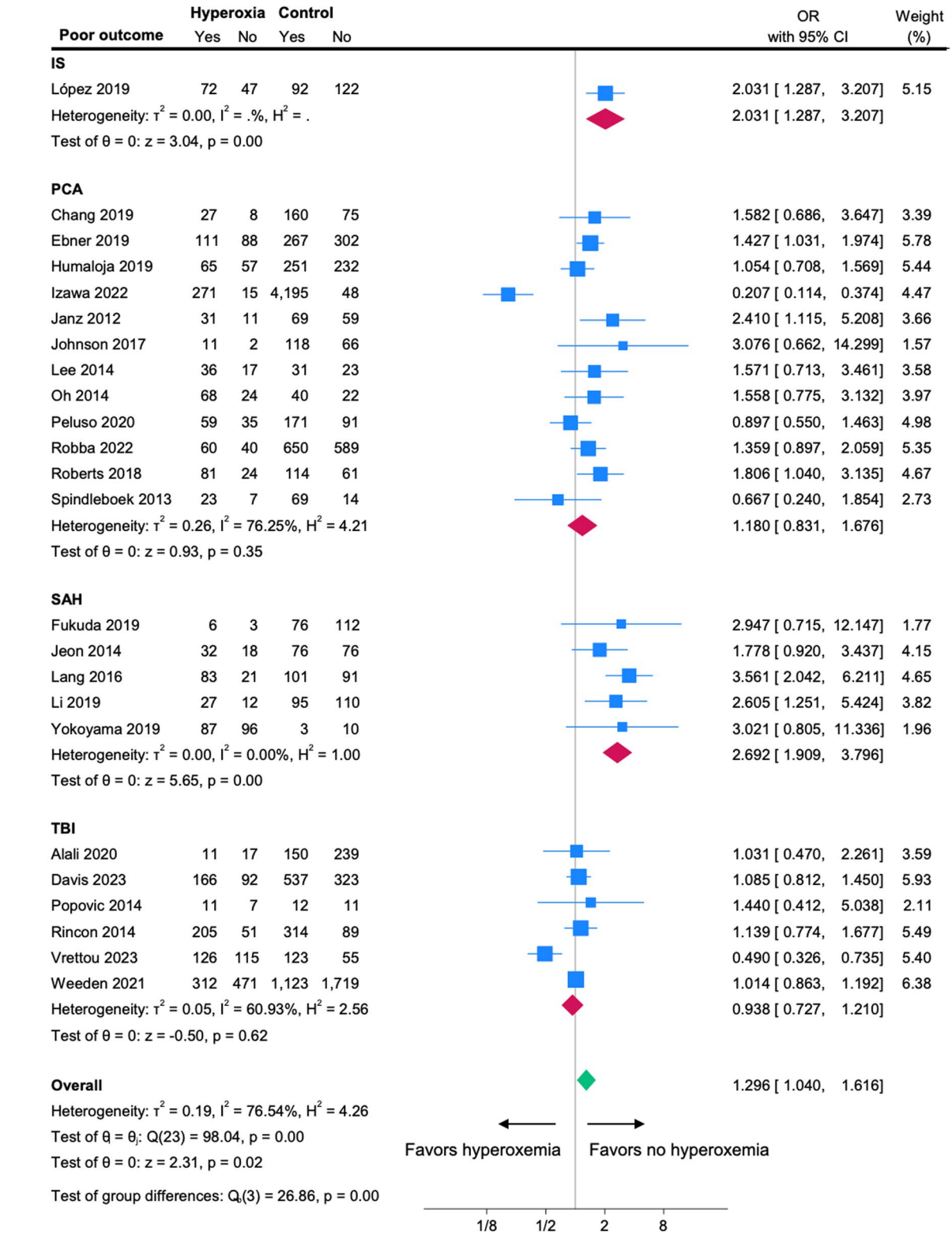


Fig. 2 (See legend on previous page.)

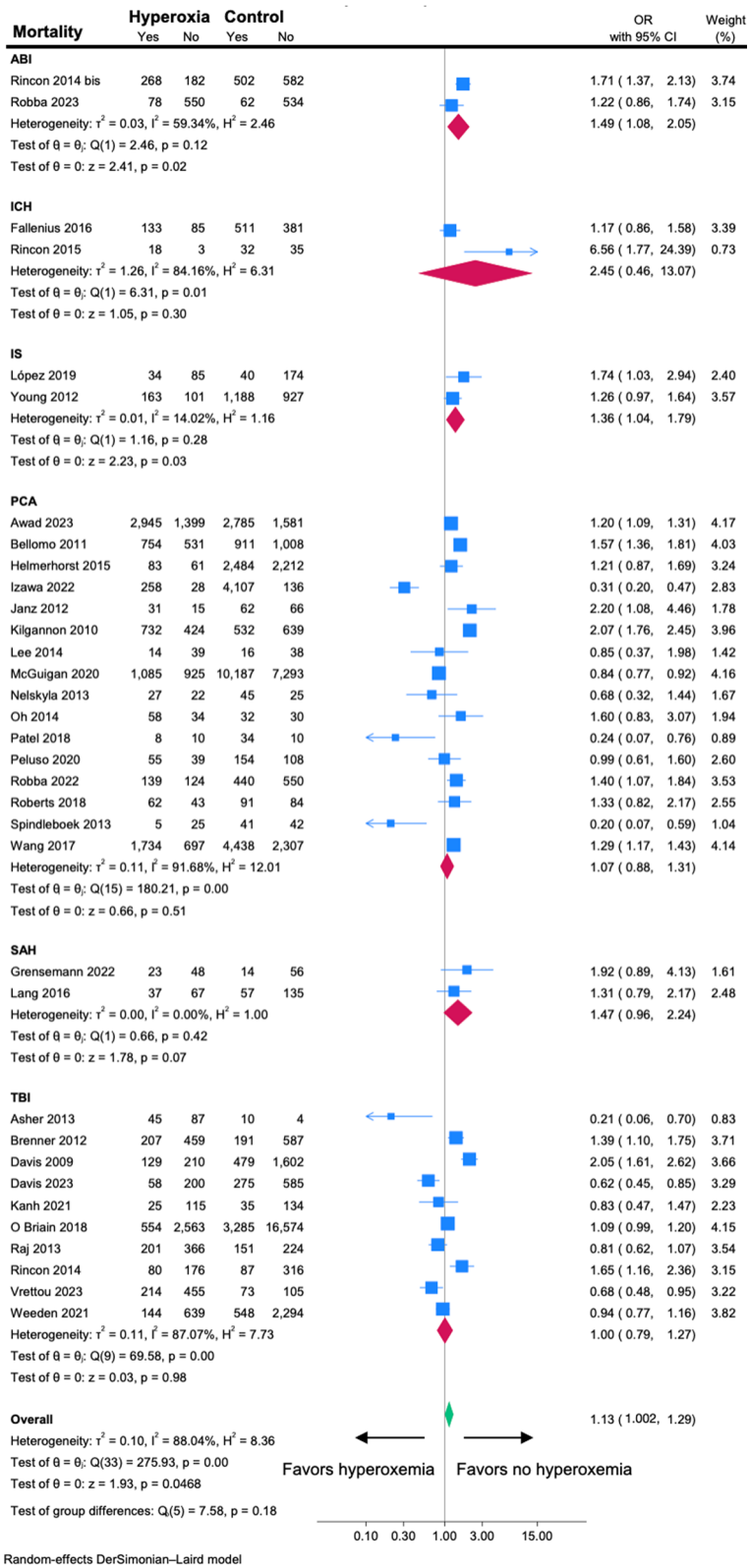


Fig. 3 Effects of hyperoxemia on mortality in patients with ABI. Forest plot for the meta-analysis based on unadjusted ORs for mortality in hyperoxemia *versus* no hyperoxemia in patients in ABI (n = 35 studies, 98,207 patients). ABI: Acute brain injury, CI: confidence interval, ICH: Intracerebral hemorrhage, IS: Ischemic stroke, OR: odds ratio, PCA: Post-cardiac arrest, SAH: Subarachnoid hemorrhage, TBI: Traumatic brain injury

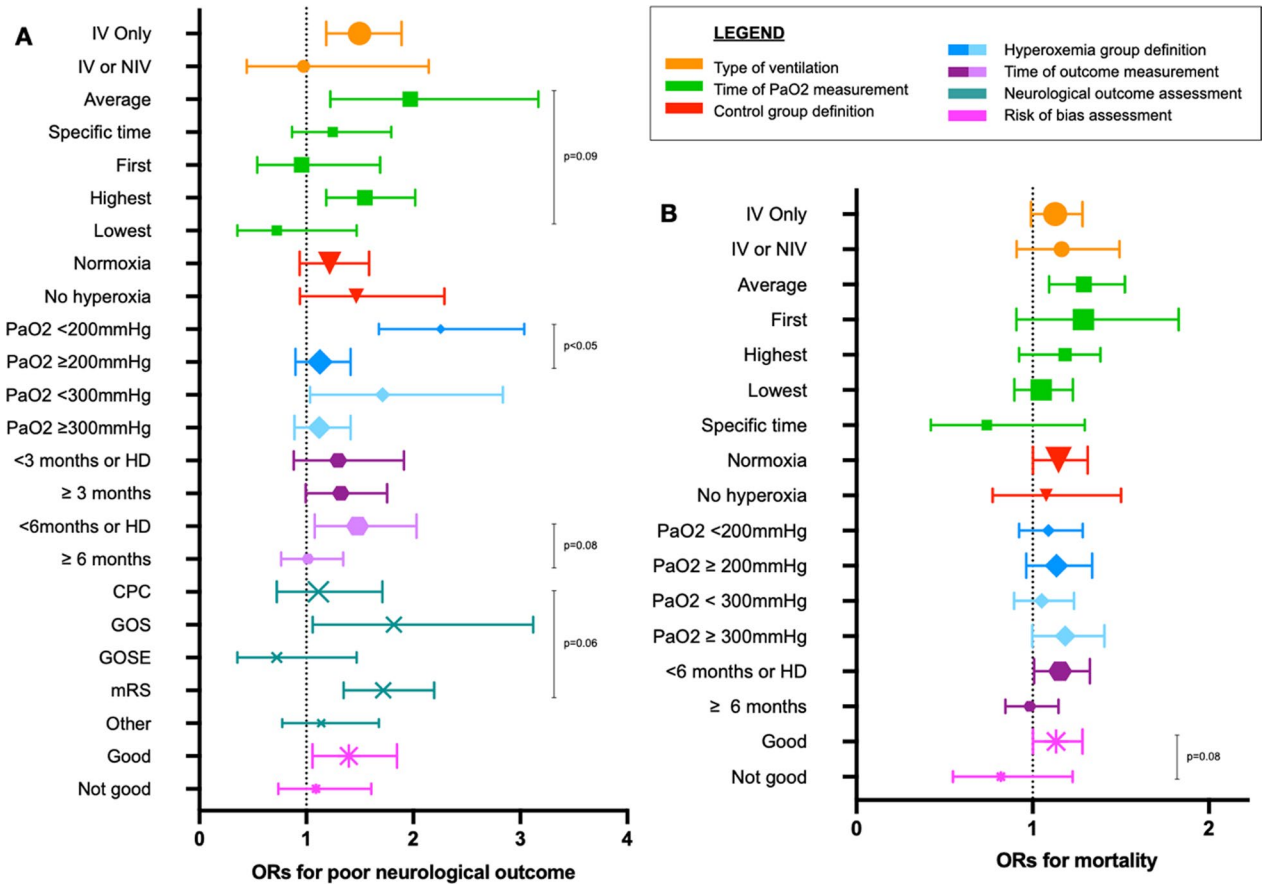


Fig. 4 Group subanalysis for association of hyperoxemia and poor outcomes. (**A**) Forest plot of unadjusted ORs for hyperoxemia and poor neurological outcomes classified by different criteria: risk of bias, neurological outcome scale, time of outcome evaluation, hyperoxemia definition, control group definition, type and time of PaO_2 measure, type of ventilatory support. (**B**) Forest plot of unadjusted ORs and for mortality classified by different criteria: risk of bias, time of outcome evaluation, hyperoxemia definition, control group definition, type and time of PaO_2 measure, type of ventilatory support. P-values < 0.1 for intra-group comparisons are shown. Horizontal lines represent 95% CIs; size of the symbols are proportional to the number of studies (see Figures S5 and S6). HD: hospital discharge, IV: invasive ventilation, NA: not available, NIV: non-invasive ventilation, NOS: Newcastle Ottawa Scale, PaO_2: arterial partial pressure of oxygen

encompassed wide confidence intervals. One exception was the combined model including mortality ≥ 6 months and hyperoxia > 300 mmHg (model 7, Table S11 in the Supplement), where the adjusted overall OR reached 2.53 (95% CI 1.01–6.31, p = 0.047).

Discussion

In this meta-analysis of 46 observational studies and 1 RCT we found evidence that hyperoxemia is associated with worse functional outcomes and increased mortality following acute brain injury. To our knowledge, this is the most up-to-date investigation into the effects of hyperoxemia, incorporating data from over 100,000 patients, primarily drawn from high-quality observational studies. Furthermore, it is the first to focus specifically on brain injured patients, while also providing a thorough subgroup analysis to examine the unique characteristics of each diagnosis individually. The prior publication of the study protocol in a peer-reviewed journal reinforces the methodological rigor of this work. This is the first review in the field to present both unadjusted and covariate-adjusted ORs, with consistent results in pooled estimates. Our statistical analysis is enhanced by the application of group subanalysis and meta-regression to thoroughly identify sources of heterogeneity, which improves the robustness of our findings.

Our findings are in line with experimental evidence of the harmful effects of supraphysiological oxygen tension on the damaged brain. It is well known that hyperoxemia causes vasoconstriction via interference with prostaglandin release or inactivation of nitric oxide [99, 100]. As a consequence, cerebral blood flow is reduced [101] and secondary brain damage appears. High levels of oxygen trigger production of reactive oxygen species (ROS),

inducing a proinflammatory response with a negative impact on altered blood–brain barrier and brain edema, notably after reperfusion [102]. The effect on mortality can be explained by the adverse effects of oxygen on the cardiovascular system, with a decrease in cardiac output due to increase afterload and coronary vasoconstriction [103, 104]; and the respiratory system, with altered hypoxic vasoconstriction reflex, increased pulmonary arterial pressures and immune-mediated acute lung injury [105].

The prevalence of hyperoxemia (defined as PaO_2 > 120 mmHg) in the TBI subgroup may be as high as 50%, according to recent works [5]. In our analysis, hyperoxia did not significantly alter mortality in TBI patients. This is in line with previous findings in a substudy from the ENIO database (included in the ABI subgroup in the present study) [1] and might be explained by the beneficial effects of supplemental oxygen on intracranial pressure control, the improved oxygen delivery through altered blood–brain barrier and a metabolic shift towards aerobic pathways [80]. Moreover, higher baseline PaO_2 decreases the risk of hypoxemia episodes, which are a well-known cause of secondary brain injury, according to IMPACT score [106]. In a large recent European study from CENTER TBI [5], exposure to hyperoxemia was associated with 6-month mortality and poor outcome; however, the study used FiO_2 and PaO_2 indistinctly and analyzed PaO_2 as a continuous variable.

In the PCA subgroup we found a non-significant trend towards a positive correlation between hyperoxemia and poor outcomes; when using covariate-adjusted estimates, this association turned statistically significant, both for neurological outcomes and mortality. A previous meta-analysis of observational studies [23] could not demonstrate this association. Authors attributed this lack of effect to the high number of out-of-hospital cardiac arrest (OHCA) patients, which were subject to greater heterogeneity in early management [23]. Moreover, we have to consider that mortality in PCA is frequently attributable to withdrawal of life-sustaining therapies, which introduces another source of heterogeneity. One of the benefits of using covariate-adjusted ORs is the possibility to limit bias due to heterogeneous populations; in fact, most studies considered relevant covariates such as setting of cardiac arrest (OHCA *versus* in-hospital), presence of shock, bystander resuscitation or initial rhythm. Regarding mortality, our results are aligned with those of two previous meta-analysis [13, 22] of observational studies; however, the only meta-analysis of RCT did not find significant differences [107]. Interestingly, the number of episodes of hypoxemia was significantly higher in the restrictive therapy, which could be a potential bias to consider [107]; in fact, another high-impact RCT in this population, the HOT OR NOT trial, was terminated early due to episodes of hypoxemia in the "normoxemia" (objective SpO_2 92–94%) arm [19]; this incident highlights the limitations of RCTs in an emergency context and emphasizes the role of meta-analyses in establishing clinical evidence. The BOX trial, included in this study, could not demonstrate differences in a composite outcome of mortality and poor neurological outcome between liberal and restrictive oxygen targets [89].

Poor neurological outcomes were significantly associated with hyperoxemia in SAH patients, which is coherent with previous analyses [23]. Experimentally, local vasoconstriction and increased amounts of oxidized hemoglobin associated with hyperoxemia can cause well-known complications of SAH, such as delayed cerebral ischemia (DCI) [50, 108]. However, the effect on mortality of SAH and ICH patients was not statistically significant, similar to some previous studies [1]. In this review, only 2 studies provided data for IS, with a significant detrimental effect of hyperoxemia in both. In the largest RCT in IS, a subgroup of patients showed a decrease in survival upon administration of 3L/min oxygen compared to no therapy; however, the general population also showed a transient improvement of clinical deficits with higher oxygen [109]. Disease severity should be considered as a potential cofounder in the stroke subgroup. Yokoyama et al. [96] only found an association between hyperoxemia and poor outcomes in Hunt and Hess grades I to III, suggesting that milder presentations are at greater risk; similarly, a detrimental effect on survival was found upon treatment with additional oxygen on the subgroup of patients with minor or moderate strokes only [109].

The diverging definitions of hyperoxemia and control groups is a non-neglectable source of heterogeneity. Although severe hyperoxemia is commonly defined at 300 mmHg, recent studies have established that the harmful effects of hyperoxemia start from a PaO_2 as low as 195 mmHg [15] or even 156 mmHg [1]. The group subanalysis for different PaO_2 thresholds revealed a trend towards a greater deleterious effect of higher PaO_2 cut-offs ($>=200$ mmHg and $>=300$ mmHg) in the mortality studies; however, this association is not true for neurological outcome studies. Most studies considering PaO_2 as a continuous variable are aligned with more harmful effects as PaO_2 increases [5, 50, 81, 86]. However, the fact that we used threshold PaO_2, instead of mean or maximum PaO_2 in the hyperoxemia group, precludes this study from establishing a linear correlation between PaO_2 and effect size.

Some studies may seem to contradict the fact that even mild hyperoxemia can be linked to worse outcomes finding, but thorough analysis uncovers a notable degree of

heterogeneity. For example, McKenzie et al. [72] found that mild to moderate hyperoxemia (100–180 mmHg) was better than normoxemia (60–100 mmHg); however, according to some studies included in our analysis, their "hyperoxemia" group could be classified as "no hyperoxemia". Similarly, Alali et al. [36] correlated mild levels of hyperoxemia (PaO_2 >200–250 mmHg) with better functional outcomes; nonetheless, these beneficial effects were lost in more extreme thresholds when PaO_2 exceeded 300 mmHg, which stands as cutoff point in most of our included studies. The EXACT trial [20], which randomized patients to lower (SpO_2 90–94%) vs higher (SpO_2 99–100%) targets in PCA patients, found more hypoxemic events and a trend towards higher mortality in the restrictive SpO_2 group; however, the median PaO_2 in the liberal oxygenation group was near 114 mmHg, which would fall within the "no hyperoxemia" group in most of studies in our meta-analysis. Comparably, some of our subanalysis found no difference is found between studies using "normoxemia" and "no hyperoxemia" as control group; it could be argued that "no hyperoxemia" group does not always contain hypoxemic patients and mean or minimum PaO_2 should be analyzed within each to limit bias in this regard. "Normoxemia" studies show lower heterogeneity than "no hyperoxemia" studies, although no significant differences are found on effect size.

Regarding ventilation status, some individual studies have compared the effects of hyperoxemia in mechanically ventilated patients versus non-mechanically ventilated patients, such as Fallenius et al. [48], who found that hyperoxia was only detrimental in non-mechanically ventilated patients. Although we did not find significant differences, we found less heterogeneity in the *"invasive ventilation"* subgroup, which suggests a more rigorous study design. Of note, the effect of ventilation mode may be more relevant in studies measuring FiO_2 instead of PaO_2, such as the HYPERS2 trial [110]. In our analysis, studies using "average" PaO_2 tend to be associated with greater effects of hyperoxemia. While average PaO2 could be the most appropriate outcome, it does not consider the time spent within each level of hyperoxygenation; for this reason, time-weighted average PaO_2 [47, 50, 97] or the area under the curve of PaO_2 [15] could stand as the most precise definition. Regarding time of outcome measure, we found that the greater size of effect concentrated in studies measuring short-term outcomes (< 3 or 6 months). On the one hand, long-term outcomes tend to reflect more reliable results in neurological improvement, given the potential for functional recovery during the first year [111]; on the other, we should consider that main causes of death attributable to hyperoxemia, such as cardiovascular events or lung injury, occur during the first month, and long-term outcomes (≥ 6 months) may be more prone to nonresponse bias [1, 15, 48].

The main limitation of our work is that it is based on observational studies, which precludes evidence of a causal relationship. Only 1 RCT could be included due mostly to the definition of hyperoxemia by means of SpO_2 titration, but also to the use of hyperbaric oxygenation or the inclusion of non-ABI patients. Secondly, a considerable limitation is that we consider only all-cause mortality as secondary outcome; in addition, mortality due to cardiovascular causes, duration of mechanical ventilation or incidence of acute respiratory distress syndrome merit attention in future investigations. Another limitation of the study is the use of ABI as a diagnosis subgroup; even though this might obscure the effect of certain patient subgroups on the subanalysis, some studies did not provide sufficient data to include patients divided by principal diagnosis [55, 83]. Heterogeneity is the third shortcoming of our work, which we addressed through meta-regression analysis. Both univariate and multivariate meta-regression revealed high variability in the observed effects; notably, diagnosis and definitions of hyperoxemia were significant contributors to the heterogeneity. The inclusion of moderators was able to significantly decrease heterogeneity in neurological outcomes, but not mortality outcomes, emphasizing the need for robust methodological consistency in hyperoxemia studies. The persistent high heterogeneity underscores the likelihood that additional unmeasured clinical variables or study design factors might be driving outcome differences; future research incorporating patient-level data or more standardized definitions of hyperoxemia, alongside more uniform outcome assessments, may be necessary to clarify whether specific subgroups or timing windows are associated with an altered mortality risk from hyperoxia exposure. In this regard, the fact that "normoxemia" show lower heterogeneity than "no hyperoxemia" studies, similarly to "invasive ventilation" versus "non-invasive or invasive ventilation" studies, may suggest higher methodological rigor and supports this study design for future works. To evaluate the association between PaO2 thresholds and effect size, maximum or mean PaO2 in the two groups should be used, although most studies did not report these data. Lastly, publication bias cannot be excluded, particularly in neurological outcome analyses, although adjusting for moderators and trim and fill method aimed at limiting this concern. Quality of evidence assessed by GRADE methodology was classified as low.

Conclusions

Hyperoxemia is associated with poor neurological outcomes and higher mortality in acute brain injury. In neurological outcomes, this association may be stronger in patients with ischemic stroke and subarachnoid hemorrhage, although more robust studies are needed. The described effects are greater in the short term *versus* the long term, and when global measures of oxygenation are used *versus* time-specific measures. Our results suggest the importance of carefully adjusting oxygenation strategies in neurocritical ICUs and motivate the design of studies to investigate PaO_2 thresholds specific to patients with acute brain injury.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05387-7.

Supplementary material 1.

Acknowledgements
We would like to thank MedStats (Philadelphia, USA) and Eduardo Nunez for his help with statistical analysis.

Author contributions
NRG and CR are first co-authors, RB and FST are last co-authors. NRG and RB initially conceived the study. BM, ARZ, MPG performed abstract screening. ARP and FP performed full-text screening and data collection. MGP, JC, AM and LG assessed risk of bias of the included studies. LP supervised statistical analysis. NRG and CR produced the first draft of the study which was consecutively discussed with FST and RB. The definitive manuscript was approved by all authors.

Funding
This project was conducted without receiving any specific funding.

Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Anesthesiology and Critical Care. Hospital, Clínico Universitario de Valencia. Avda, Blasco Ibáñez 17, 46010 Valencia, Spain. [2]INCLIVA Research Institute. Avda Menéndez y Pelayo, 4 Accesorio, 46010 Valencia, Spain. [3]Present Address: Faculty of Medicine. Avda Department of Surgery, University of Valencia, Blasco Ibáñez 15, 46010 Valencia, Spain. [4]Anaesthesia and Intensive Care, IRCCS Policlinico San Martino, Genova, Italy. [5]Present Address: Department of Surgical Sciences and Integrated Diagnostics, University of Genoa, Genoa, Italy. [6]Griffith University School of Medicine and Dentistry, Southport, QLD, Australia. [7]Present Address: Service Des Soins Intensifs, Hôpital Universitaire de Bruxelles, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium.

Received: 5 February 2025 Accepted: 24 March 2025
Published online: 23 April 2025

References

1. Robba C, Battaglini D, Cinotti R, Asehnoune K, Stevens R, Taccone FS, et al. Individualized Thresholds of Hypoxemia and Hyperoxemia and their Effect on Outcome in Acute Brain Injured Patients: A Secondary Analysis of the ENIO Study. Neurocrit Care. 2023 Jun 15;
2. Godoy DA, Murillo-Cabezas F, Suarez JI, Badenes R, Pelosi P, Robba C. "THE MANTLE" bundle for minimizing cerebral hypoxia in severe traumatic brain injury. Crit Care. 2023;27(1):13.
3. Carney N, Totten AM, O'Reilly C, Ullman JS, Hawryluk GWJ, Bell MJ, et al. Guidelines for the Management of Severe Traumatic Brain Injury. Fourth Edition Neurosurgery. 2017;80(1):6–15.
4. Nolan JP, Sandroni C, Böttiger BW, Cariou A, Cronberg T, Friberg H, et al. European resuscitation council and european society of intensive care medicine guidelines 2021: post-resuscitation care. Intensive Care Med. 2021;47(4):369–21.
5. Rezoagli E, Petrosino M, Rebora P, Menon DK, Mondello S, Cooper DJ, et al. High arterial oxygen levels and supplemental oxygen administration in traumatic brain injury: insights from CENTER-TBI and OzENTER-TBI. Intensive Care Med. 2022;48(12):1709–25.
6. Itagaki T, Nakano Y, Okuda N, Izawa M, Onodera M, Imanaka H, et al. Hyperoxemia in Mechanically Ventilated, Critically Ill Subjects: Incidence and Related Factors. Respir Care. 2015;60(3):335–40.
7. Yan EB, Satgunaseelan L, Paul E, Bye N, Nguyen P, Agyapomaa D, et al. Post-traumatic hypoxia is associated with prolonged cerebral cytokine production, higher serum biomarker levels, and poor outcome in patients with severe traumatic brain injury. J Neurotrauma. 2014;31(7):618–29.
8. Oddo M, Levine JM, Mackenzie L, Frangos S, Feihl F, Kasner SE, et al. Brain hypoxia is associated with short-term outcome after severe traumatic brain injury independently of intracranial hypertension and low cerebral perfusion pressure. Neurosurgery. 2011;69(5):1037–45.
9. McHugh GS, Engel DC, Butcher I, Steyerberg EW, Lu J, Mushkudiani N, et al. Prognostic value of secondary insults in traumatic brain injury: results from the IMPACT study. J Neurotrauma. 2007;24(2):287–93.
10. Singer M, Young PJ, Laffey JG, Asfar P, Taccone FS, Skrifvars MB, et al. Dangers of hyperoxia. Crit Care. 2021;25(1):440.
11. Young PJ, Hodgson CL, Rasmussen BS. Oxygen targets. Intensive Care Med. 2022;48(6):732–5.
12. Damiani E, Donati A, Girardis M. Oxygen in the critically ill. Curr Opin Anaesthesiol. 2018;31(2):129–35.
13. Damiani E, Adrario E, Girardis M, Romano R, Pelaia P, Singer M, et al. Arterial hyperoxia and mortality in critically ill patients: a systematic review and meta-analysis. Crit Care. 2014;18(6):711.
14. Cumpstey AF, Oldman AH, Martin DS, Smith A, Grocott MPW. Oxygen Targets During Mechanical Ventilation in the ICU: A Systematic Review and Meta-Analysis. Crit Care Explor. 2022;4(4): e0652.
15. Robba C, Badenes R, Battaglini D, Ball L, Sanfilippo F, Brunetti I, et al. Oxygen targets and 6-month outcome after out of hospital cardiac arrest: a pre-planned sub-analysis of the targeted hypothermia versus targeted normothermia after Out-of-Hospital Cardiac Arrest (TTM2) trial. Crit Care. 2022;26(1):323.
16. Panwar R, Hardie M, Bellomo R, Barrot L, Eastwood GM, Young PJ, et al. Conservative versus liberal oxygenation targets for mechanically ventilated patients a pilot multicenter randomized controlled trial. Am J Respir Crit Care Med. 2016;193(1):43–51.
17. Jakkula P, Reinikainen M, Hästbacka J, Loisa P, Tiainen M, Pettilä V, et al. Targeting two different levels of both arterial carbon dioxide and arterial oxygen after cardiac arrest and resuscitation: a randomised pilot trial. Intensive Care Med. 2018;44(12):2112–21.
18. The ICU-ROX Investigators and the Australian and New Zealand Intensive Care Society Clinical Trials Group*. Conservative Oxygen Therapy during Mechanical Ventilation in the ICU. New England Journal of Medicine. 2020 Mar 12;382(11):989–98.
19. Young P, Bailey M, Bellomo R, Bernard S, Dicker B, Freebairn R, et al. HyperOxic therapy OR NormOxic therapy after out-of-hospital cardiac

arrest (HOT OR NOT): a randomised controlled feasibility trial. Resuscitation. 2014;85(12):1686–91.
20. Bernard SA, Bray JE, Smith K, Stephenson M, Finn J, Grantham H, et al. Effect of lower vs higher oxygen saturation targets on survival to hospital discharge among patients resuscitated after out-of-hospital cardiac arrest. JAMA. 2022;328(18):1818.
21. Robba C, Poole D, McNett M, Asehnoune K, Bösel J, Bruder N, et al. Mechanical ventilation in patients with acute brain injury: recommendations of the European society of intensive care medicine consensus. Intensive Care Med. 2020;46(12):2397–410.
22. Helmerhorst HJF, Roos-Blom MJ, van Westerloo DJ, de Jonge E. Association between arterial hyperoxia and outcome in subsets of critical illness. Crit Care Med. 2015;43(7):1508–19.
23. Hirunpattarasilp C, Shiina H, Na-Ek N, Attwell D. The Effect of hyperoxemia on neurological outcomes of adult patients: a systematic review and meta-analysis. Neurocrit Care. 2022;36(3):1027–43.
24. You J, Fan X, Bi X, Xian Y, Xie D, Fan M, et al. Association between arterial hyperoxia and mortality in critically ill patients: A systematic review and meta-analysis. J Crit Care. 2018;47:260–8.
25. Ni YN, Wang YM, Liang BM, Liang ZA. The effect of hyperoxia on mortality in critically ill patients: a systematic review and meta analysis. BMC Pulm Med. 2019;19(1):53.
26. Dewan MC, Rattani A, Gupta S, Baticulon RE, Hung YC, Punchak M, et al. Estimating the global incidence of traumatic brain injury. J Neurosurg. 2019;130(4):1080–97.
27. Olesen J, Gustavsson A, Svensson M, Wittchen H-U, Jönsson B. The economic cost of brain disorders in Europe. Eur J Neurol. 2012;19(1):155–62.
28. Lucas-Noll J, Clua-Espuny JL, Lleixà-Fortuño M, Gavaldà-Espelta E, Queralt-Tomas L, Panisello-Tafalla A, et al. The costs associated with stroke care continuum: a systematic review. Health Econ Rev. 2023;13(1):32.
29. Romero-Garcia N, Robba C, Monleon B, Ruiz-Zarco A, Ruiz-Pacheco A, Pascual-Gonzalez M, et al. Neurological outcomes and mortality of hyperoxaemia in patients with acute brain injury: protocol for a systematic review and meta-analysis. BMJ Open. 2024;14(7): e084849.
30. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg. 2010;8(5):336–41.
31. Zhang J, Yu KF. What's the relative risk? JAMA. 1998;280(19):1690.
32. Higgins JPT. Measuring inconsistency in meta-analyses. BMJ. 2003;327(7414):557–60.
33. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;12: i4919.
34. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;28: l4898.
35. Brozek JL, Canelo-Aybar C, Akl EA, Bowen JM, Bucher J, Chiu WA, et al. GRADE Guidelines 30: the GRADE approach to assessing the certainty of modeled evidence—An overview in the context of health decision-making. J Clin Epidemiol. 2021;129:138–50.
36. Alali AS, Temkin N, Vavilala MS, Lele AV, Barber J, Dikmen S, et al. Matching early arterial oxygenation to long-term outcome in severe traumatic brain injury: target values. J Neurosurg. 2020;132(2):537–44.
37. Asher SR, Curry P, Sharma D, Wang J, O'Keefe GE, Daniel-Johnson J, et al. Survival advantage and PaO2 threshold in severe traumatic brain injury. J Neurosurg Anesthesiol. 2013;25(2):168–73.
38. Awad A, Nordberg P, Jonsson M, Hofmann R, Ringh M, Hollenberg J, et al. Hyperoxemia after reperfusion in cardiac arrest patients: a potential dose–response association with 30-day survival. Crit Care. 2023;27(1):86.
39. Bellomo R, Bailey M, Eastwood GM, Nichol A, Pilcher D, Hart GK, et al. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. Crit Care. 2011;15(2):R90.
40. Bolduc B, Riker R, Threlkeld K, Walker-Elders A, McCrum B, Dziodzio J, et al. No association of early hemodynamic factors and oxygenation with outcome in cardiac arrest survivors undergoing therapeutic hypothermia. Neurocrit Care. 2012;17:S108.
41. Brenner M, Stein D, Hu P, Kufera J, Wooford M, Scalea T. Association between early hyperoxia and worse outcomes after traumatic brain injury. Arch Surg. 2012;147(11):1042.
42. Chang WT, Wang CH, Lai CH, Yu HY, Chou NK, Wang CH, et al. Optimal arterial blood oxygen tension in the early postresuscitation phase of extracorporeal cardiopulmonary resuscitation: a 15-year retrospective observational study*. Crit Care Med. 2019;47(11):1549–56.
43. Davis DP, Meade W, Sise MJ, Kennedy F, Simon F, Tominaga G, et al. Both hypoxemia and extreme hyperoxemia may be detrimental in patients with severe traumatic brain injury. J Neurotrauma. 2009;26(12):2217–23.
44. Davis DP, McKnight B, Meier E, Drennan IR, Newgard C, Wang HE, et al. Higher oxygenation is associated with improved survival in severe traumatic brain injury but not traumatic shock. Neurotrauma Rep. 2023;4(1):51–63.
45. Ebner F, Ullén S, Åneman A, Cronberg T, Mattsson N, Friberg H, et al. Associations between partial pressure of oxygen and neurological outcome in out-of-hospital cardiac arrest patients: an explorative analysis of a randomized trial. Crit Care. 2019;23(1):30.
46. Ebner F, Riker RR, Haxhija Z, Seder DB, May TL, Ullén S, et al. The association of partial pressures of oxygen and carbon dioxide with neurological outcome after out-of-hospital cardiac arrest: an explorative International cardiac arrest registry 20 study. Scand J Trauma Resusc Emerg Med. 2020;28(1):67.
47. Elmer J, Scutella M, Pullalarevu R, Wang B, Vaghasia N, Trzeciak S, et al. The association between hyperoxia and patient outcomes after cardiac arrest: analysis of a high-resolution database. Intensive Care Med. 2015;41(1):49–57.
48. Fallenius M, Raj R, Reinikainen M, Bendel S, Skrifvars MB. Association between high arterial oxygen tension and long-term survival after spontaneous intracerebral hemorrhage. Crit Care Med. 2016;44(1):180–7.
49. Fujita M, Oda Y, Yamashita S, Kaneda K, Kaneko T, Suehiro E, et al. Early-stage hyperoxia is associated with favorable neurological outcomes and survival after severe traumatic brain injury: a post-hoc analysis of the brain hypothermia study. J Neurotrauma. 2017;34(8):1565–70.
50. Fukuda S, Koga Y, Fujita M, Suehiro E, Kaneda K, Oda Y, et al. Hyperoxemia during the hyperacute phase of aneurysmal subarachnoid hemorrhage is associated with delayed cerebral ischemia and poor outcome: a retrospective observational study. J Neurosurg. 2021;134(1):25–32.
51. Gaieski DF, Grossestreuer AV, Perman SM, Leary M, Donnino MW, Cocchi MN, et al. Neither hypoxia nor hyperoxia is associated with mortality in a cohort of postarrest patients. Circulation. 2012;126:A198.
52. Grensemann J, Mader MMD, Westphal M, Kluge S, Czorlich P. Hyperoxia is dose-dependently associated with an increase of unfavorable outcomes in ventilated patients with aneurysmal subarachnoid hemorrhage: a retrospective cohort study. Neurocrit Care. 2022;37(2):523–30.
53. Helmerhorst HJF, Roos-Blom MJ, van Westerloo DJ, Abu-Hanna A, de Keizer NF, de Jonge E. Associations of arterial carbon dioxide and arterial oxygen concentrations with hospital mortality after resuscitation from cardiac arrest. Crit Care. 2015;19(1):348.
54. Humaloja J, Litonius E, Efendijev I, Folger D, Raj R, Pekkarinen PT, et al. Early hyperoxemia is not associated with cardiac arrest outcome. Resuscitation. 2019;140:185–93.
55. Humaloja J, Skrifvars MB, Raj R, Wilkman E, Pekkarinen PT, Bendel S, et al. The association between arterial oxygen level and outcome in neurocritically ill patients is not affected by blood pressure. Neurocrit Care. 2021;34(2):413–22.
56. Ihle JF, Bernard S, Bailey MJ, Pilcher DV, Smith K, Scheinkestel C. Hyperoxia in the intensive care unit and outcome after out-of-hospital ventricular fibrillation cardiac arrest. Critical Care Resusc: J Australas Acad Critic Care Med. 2013;15(3):186–90.
57. Izawa J, Komukai S, Nishioka N, Kiguchi T, Kitamura T, Iwami T. Outcomes associated with intra-arrest hyperoxaemia in out-of-hospital cardiac arrest: a registry-based cohort study. Resuscitation. 2022;181:173–81.
58. Janz DR, Hollenbeck RD, Pollock JS, McPherson JA, Rice TW. Hyperoxia is associated with increased mortality in patients treated with mild therapeutic hypothermia after sudden cardiac arrest*. Crit Care Med. 2012;40(12):3135–9.
59. Jeon SB, Choi HA, Badjatia N, Schmidt JM, Lantigua H, Claassen J, et al. Hyperoxia may be related to delayed cerebral ischemia and poor outcome after subarachnoid haemorrhage. J Neurol Neurosurg Psychiatry. 2014;85(12):1301–7.

60. Johnson NJ, Dodampahala K, Rosselot B, Perman SM, Mikkelsen ME, Goyal M, et al. The association between arterial oxygen tension and neurological outcome after cardiac arrest. Ther Hypothermia Temp Manag. 2017;7(1):36–41.
61. Kang C, Jeong W, Park JS, You Y, Min JH, Cho YC, et al. Different stratification of physiological factors affecting cerebral perfusion pressure in hypoxic-ischemic brain injury after cardiac arrest according to visible or non-visible primary brain injury: a retrospective observational study. J Clin Med. 2021;10(22):5385.
62. Khan R, Alromaih S, Alshabanat H, Alshanqiti N, Aldhuwaihy A, Almohanna SA, et al. The impact of hyperoxia treatment on neurological outcomes and mortality in moderate to severe traumatic brain injured patients. J Crit Care Med. 2021;7(3):227–36.
63. Kiguchi T, Kitamura T, Yamada T, Hayakawa K, Yoshiya K, Abe Y, et al. Arterial hyperoxia associated with better survival among resuscitated patients with out-of-hospital cardiac arrest. Circulation. 2016;134:A17174.
64. Kilgannon JH, Jones AE, Parrillo JE, Dellinger RP, Milcarek B, Hunter K, et al. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. JAMA. 2010;303(21):2165.
65. Kilgannon JH, Jones AE, Parrillo JE, Dellinger RP, Milcarek B, Hunter K, et al. Relationship between supranormal oxygen tension and outcome after resuscitation from cardiac arrest. Circulation. 2011;123(23):2717–22.
66. Lång M, Raj R, Skrifvars MB, Koivisto T, Lehto H, Kivisaari R, et al. Early moderate hyperoxemia does not predict outcome after aneurysmal subarachnoid hemorrhage. Neurosurgery. 2016;78(4):540–5.
67. Lee BK, Jeung KW, Lee HY, Lee SJ, Jung YH, Lee WK, et al. Association between mean arterial blood gas tension and outcome in cardiac arrest patients treated with therapeutic hypothermia. Am J Emerg Med. 2014;32(1):55–60.
68. Li KC, Tam CWY, Shum HP, Yan WW. Impact of hyperoxia and hypocapnia on neurological outcomes in patients with aneurysmal subarachnoid hemorrhage: a retrospective study. Crit Care Res Pract. 2019;6(2019):1–8.
69. López HV, Vivas MF, Ruiz RN, Martínez JR, Navaridas BGV, Villa MG, et al. Association between post-procedural hyperoxia and poor functional outcome after mechanical thrombectomy for ischemic stroke: an observational study. Ann Intensive Care. 2019;9(1):59.
70. Matta S. DP, PL, de LD, MS. Association between arterial hyperoxia after return of spontaneous circulation (ROSC) in out-of-hospital cardiac arrest (OHCA) and prognosis. Resuscitation 2022 175 (S78) Supplement 1. 2022;
71. McGuigan PJ, Shankar-Hari M, Harrison DA, Laffey JG, McAuley DF. The interaction between arterial oxygenation and carbon dioxide and hospital mortality following out of hospital cardiac arrest: a cohort study. Crit Care. 2020;24(1):336.
72. Mckenzie N, Finn J, Dobb G, Bailey P, Arendts G, Celenza A, et al. Non-linear association between arterial oxygen tension and survival after out-of-hospital cardiac arrest: a multicentre observational study. Resuscitation. 2021;158:130–8.
73. Nelskylä A, Parr MJ, Skrifvars MB. Prevalence and factors correlating with hyperoxia exposure following cardiac arrest – an observational single centre study. Scand J Trauma Resusc Emerg Med. 2013;21(1):35.
74. Briain Ó, Diarmuid, et al. Early hyperoxia in patients with traumatic brain injury admitted to intensive care in australia and new zealand: a retrospective multicenter cohort study. Neurocritical care. 2018;29:443–51.
75. Oh YT, Kim YH, Sohn YD, Park SM, Shin DH, Hwang SY, et al. Early hyperoxemia may not increase mortality after cardiac arrest: a pilot study. Clin Exp Emerg Med. 2014;1(1):28–34.
76. Patel JK, Schoenfeld E, Parikh PB, Parnia S. Association of Arterial Oxygen Tension During In-Hospital Cardiac Arrest With Return of Spontaneous Circulation and Survival. J Intensive Care Med. 2018;33(7):407–14.
77. Peluso L, Belloni I, Calabró L, Dell'Anna AM, Nobile L, Creteur J, et al. Oxygen and carbon dioxide levels in patients after cardiac arrest. Resuscitation. 2020;150:1–7.
78. Popovic VV, Pelcl T, Lesjak VB, Strnad M. Impact of pre-hospital oxygenation and ventilation status on outcome in patients with isolated severe traumatic brain injury. Signa Vitae. 2014;9(1):42.
79. Rai M, Bhavnani S, Engles D, Ramu B, Chua NY, Khalili AH, et al. Does hyperoxia impact cardiac arrest survivors treated with therapeutic hypothermia? Circulation. 2011;124:A10507.
80. Raj R, Bendel S, Reinikainen M, Kivisaari R, Siironen J, Lång M, et al. Hyperoxemia and long-term outcome after traumatic brain injury. Crit Care. 2013;17(4):R177.
81. Reynolds RA, Amin SN, Jonathan SV, Tang AR, Lan M, Wang C, et al. Hyperoxemia and cerebral vasospasm in aneurysmal subarachnoid hemorrhage. Neurocrit Care. 2021;35(1):30–8.
82. Rincon F, Kang J, Vibbert M, Urtecho J, Athar MK, Jallo J. Significance of arterial hyperoxia and relationship with case fatality in traumatic brain injury: a multicentre cohort study. J Neurol Neurosurg Psychiatry. 2014;85(7):799–805.
83. Rincon F, Kang J, Maltenfort M, Vibbert M, Urtecho J, Athar MK, et al. Association between hyperoxia and mortality after stroke. Crit Care Med. 2014;42(2):387–96.
84. Rincon F, Vibbert M, Urtecho J, Athar MK, McBride W, Jallo J, et al. Hyperoxia is associated with higher case-fatality in ventilated patients with intra-cerebral hemorrhage. Crit Care & Shock. 2015;18(61–71):2015.
85. Roberts BW, Kilgannon JH, Hunter BR, Puskarich MA, Pierce L, Donnino M, et al. Association between early hyperoxia exposure after resuscitation from cardiac arrest and neurological disability. Circulation. 2018;137(20):2114–24.
86. Russell DW, Janz DR, Emerson WL, May AK, Bernard GR, Zhao Z, et al. Early exposure to hyperoxia and mortality in critically ill patients with severe traumatic injuries. BMC Pulm Med. 2017;17(1):29.
87. Sadaka F, Kendra R, Doerr D, Hindia J. Association between hyperoxia and outcome in post-cardiac arrest patients treated with hypothermia. Crit Care Med. 2013 41:12 (A114) SUPPL.
88. Sadaka F, Sermadevi V, Iqbal M, O'Brien J, Wood MP, Scheitler-Ring KM. Association between arterial hyperoxia and outcome in patients with traumatic brain injury. Neurocrit Care. 2012;17:1–337.
89. Schmidt H, Kjaergaard J, Hassager C, Mølstrøm S, Grand J, Borregaard B, et al. Oxygen Targets in Comatose Survivors of Cardiac Arrest. N Engl J Med. 2022;387(16):1467–76.
90. Spindelboeck W, Schindler O, Moser A, Hausler F, Wallner S, Strasser C, et al. Increasing arterial oxygen partial pressure during cardiopulmonary resuscitation is associated with improved rates of hospital admission. Resuscitation. 2013;84(770–5):76.
91. Vaahersalo J, Bendel S, Reinikainen M, Kurola J, Tiainen M, Raj R, et al. Arterial blood gas tensions after resuscitation from out-of-hospital cardiac arrest. Crit Care Med. 2014;42(6):1463–70.
92. Vrettou CS, Giannakoulis VG, Gallos P, Kotanidou A, Siempos II. Effect of different early oxygenation levels on clinical outcomes of patients presenting in the emergency department with severe traumatic brain injury. Ann Emerg Med. 2023;81(3):273–81.
93. Wang CH, Huang CH, Chang WT, Tsai MS, Lu TC, Yu PH, et al. Association between early arterial blood gas tensions and neurological outcome in adult patients following in-hospital cardiac arrest. Resuscitation. 2015;89:1–7.
94. Wang HE, Prince DK, Drennan IR, Grunau B, Carlbom DJ, Johnson N, et al. Post-resuscitation arterial oxygen and carbon dioxide and outcomes after out-of-hospital cardiac arrest. Resuscitation. 2017;120:113–8.
95. Weeden M, Bailey M, Gabbe B, Pilcher D, Bellomo R, Udy A. 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. 2021;34(2):441–8.
96. Yokoyama S, Hifumi T, Kawakita K, Tamiya T, Minamino T, Kuroda Y. Early hyperoxia in the intensive care unit is significantly associated with unfavorable neurological outcomes in patients with mild-to-moderate aneurysmal subarachnoid hemorrhage. Shock. 2019;51(5):593–8.
97. Youn CS, Park KN, Kim SH, Lee BK, Oh SH, Jeung KW, et al. The cumulative partial pressure of arterial oxygen is associated with neurological outcomes after cardiac arrest treated with targeted temperature management. Crit Care Med. 2018;46(4):e279–85.
98. Young P, Beasley R, Bailey M, Bellomo R, Eastwood GM, Nichol A, et al. The association between early arterial oxygenation and mortality in ventilated patients with acute ischaemic stroke. Crit Care Resusc. 2012;14(1):14–9.

99. Johnston AJ, Steiner LA, Gupta AK, Menon DK. Cerebral oxygen vasoreactivity and cerebral tissue oxygen reactivity. Br J Anaesth. 2003;90(6):774–86.
100. Zhilyaev SYu, Moskvin AN, Platonova TF, Gutsaeva DR, Churilina IV, Demchenko IT. Hyperoxic vasoconstriction in the brain is mediated by inactivation of nitric oxide by superoxide anions. Neurosci Behav Physiol. 2003;33(8):783–7.
101. Bulte DP, Chiarelli PA, Wise RG, Jezzard P. Cerebral Perfusion Response to Hyperoxia. J Cereb Blood Flow Metab. 2007;27(1):69–75.
102. Lee PJ, Choi AMK. Pathways of cell signaling in hyperoxia. Free Radic Biol Med. 2003;35(4):341–50.
103. Guensch DP, Fischer K, Yamaji K, Luescher S, Ueki Y, Jung B, et al. Effect of hyperoxia on myocardial oxygenation and function in patients with stable multivessel coronary artery disease. J Am Heart Assoc. 2020. https://doi.org/10.1161/JAHA.119.014739.
104. Thomas A, van Diepen S, Beekman R, Sinha SS, Brusca SB, Alviar CL, et al. Oxygen supplementation and hyperoxia in critically ill cardiac patients. JACC Adv. 2022;1(3):100065.
105. Hanidziar D, Nakahori Y, Cahill LA, Gallo D, Keegan JW, Nguyen JP, et al. Characterization of pulmonary immune responses to hyperoxia by high-dimensional mass cytometry analyses. Sci Rep. 2020;10(1):4677.
106. Steyerberg EW, Mushkudiani N, Perel P, Butcher I, Lu J, McHugh GS, et al. Predicting outcome after traumatic brain injury: development and international validation of prognostic scores based on admission characteristics. PLoS Med. 2008;5(8): e165.
107. Macherey-Meyer S, Heyne S, Meertens MM, Braumann S, Hueser C, Mauri V, et al. Restrictive versus high-dose oxygenation strategy in post-arrest management following adult non-traumatic cardiac arrest: a meta-analysis. Crit Care. 2023;27(1):387.
108. Foreman B. The pathophysiology of delayed cerebral ischemia. J Clin Neurophysiol. 2016;33(3):174–82.
109. Singhal AB, Benner T, Roccatagliata L, Koroshetz WJ, Schaefer PW, Lo EH, et al. A pilot study of normobaric oxygen therapy in acute ischemic stroke. Stroke. 2005;36(4):797–802.
110. Asfar P, Schortgen F, Boisramé-Helms J, Charpentier J, Guérot E, Megarbane B, et al. Hyperoxia and hypertonic saline in patients with septic shock (HYPERS2S): a two-by-two factorial, multicentre, randomised, clinical trial. Lancet Respir Med. 2017;5(3):180–90.
111. Macdonald RL. Delayed neurological deterioration after subarachnoid haemorrhage. Nat Rev Neurol. 2014;10(1):44–58.

Publisher's Note