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REVIEW ARTICLE

The Impact of Invasive Brain Oxygen Pressure Guided Therapy on the Outcome of Patients with Traumatic Brain Injury: A Systematic Review and Meta-Analysis

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Abstract

Traumatic brain injury (TBI) is a major public health burden, causing death and disability worldwide. Intracranial hypertension and brain hypoxia are the main mechanisms of secondary brain injury. As such, management strategies guided by intracranial pressure (ICP) and brain oxygen ($PbtO_2$) monitoring could improve the prognosis of these patients. Our objective was to summarize the current evidence regarding the impact of $PbtO_2$-guided therapy on the outcome of patients with TBI. We performed a systematic search of PubMed, Scopus, and the Cochrane library databases, following the protocol registered in PROSPERO. Only studies comparing $PbtO_2$/ICP–guided therapy with ICP-guided therapy were selected. Primary outcome was neurological outcome at 3 and 6 months assessed by using the Glasgow Outcome Scale; secondary outcomes included hospital and long-term mortality, burden of intracranial hypertension, and brain tissue hypoxia. Out of 6254 retrieved studies, 15 studies ($n = 37{,}245$ patients, of who 2184 received $PbtO_2$-guided therapy) were included in the final analysis. When compared with ICP-guided therapy, the use of combined PbO_2/ICP–guided therapy was associated with a higher probability of favorable neurological outcome (odds ratio 2.21 [95% confidence interval 1.72–2.84]) and of hospital survival (odds ratio 1.15 [95% confidence interval 1.04–1.28]). The heterogeneity (I^2) of the studies in each analysis was below 40%. However, the quality of evidence was overall low to moderate. In this meta-analysis, $PbtO_2$-guided therapy was associated with reduced mortality and more favorable neurological outcome in patients with TBI. The low-quality evidence underlines the need for the results from ongoing phase III randomized trials.

Keywords: Head injury, Cerebral oxygenation, Mortality, Glasgow outcome scale, Multimodal neuromonitoring

Introduction

Traumatic brain injury (TBI) is an important cause of death, disability, and high socioeconomic burden worldwide, with an annual incidence estimated between 27 and 69 million cases [1, 2]. The cornerstone of the intensive care management of these patients is to minimize secondary brain injuries. Important causes of secondary brain injury are cerebral edema, hemorrhage, and hyperemia promoting intracranial hypertension, which, if left untreated, can lead to brain hypoxia, herniation, and/or

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brain death [3]. Indeed, intracranial hypertension is associated with mortality and poor neurological outcome in patients with TBI [4]. Therefore, most guidelines recommend monitoring and treatment of intracranial pressure (ICP) in this setting [5, 6], even though this strategy alone may not be sufficient to improve patients' prognosis [7].

Another important mechanism of secondary brain injury, which is also associated with poor outcome after TBI, is brain hypoxia [8, 9]. Importantly, brain hypoxia can occur in the absence of elevated ICP and/or low cerebral perfusion pressure (CPP) [10]. A multimodal approach that includes invasive brain tissue oxygenation ($PbtO_2$) monitoring may help optimize and individualize brain hemodynamics and improve cerebral oxygen delivery in this setting [11]. Indeed, there are three ongoing randomized clinical trials (RCTs) investigating the effect of $PbtO_2$-guided therapy on the outcome of patients with TBI (i.e., BONANZA, ACTRN12619001328167; BOOST-3, NCT03754114; and OXY-TC, NCT02754063). Previously, two meta-analyses [12, 13] have been conducted to explore the impact of $PbtO_2$-guided therapy after TBI. However, since then, few large observational studies [14, 15] and at least one RCT [16] were published. Moreover, most of these studies are retrospective or observational [12, 13, 17–20] and RCTs were underpowered to detect differences in outcome [16, 17, 21]. Therefore, a new, updated systematic review and meta-analysis would be of interest to summarize the current evidence while waiting for the conclusions of ongoing RCTs.

Methods

We adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis guidelines [22]. The protocol of this study was registered with the International Prospective Register of Systematic Reviews (PROSPERO) and last edited on the 11th of April 2022 (CRD42021295223).

Data Sources and Study Selection

We conducted a systematic review and meta-analyses of both retrospective and prospective observational studies, interventional studies, and RCTs. The PubMed/Medline, Scopus, and Cochrane library databases were searched on April 2022 and May 2022, including publications of adult human studies without date or language restriction. The research strategy is shown in the Supplemental Electronic Material S1. The Cochrane library Population Intervention Comparison Outcome (PICO) research terms were *population* "Traumatic Brain Injury" OR *intervention* ("Neurological Monitoring Regime" OR "Oxygenation Monitoring") OR *outcome* ("Raised Intracranial Pressure" OR "Mortality" OR "Glasgow Outcome Scale").

We considered the following criteria for study inclusion: (1) full-length reports published in peer-reviewed journals; (2) RCT, interventional studies, observational cohorts, case control studies of adult human patients; (3) studies that included $PbtO_2$ monitoring (in addition to ICP monitoring) and management protocol guided by $PbtO_2$; (4) studies that included outcomes measures (i.e., hospital mortality, mortality at 3 months, neurological outcome at 3 and 6 months, and the incidence of intracranial hypertension) in patients with TBI. Studies conducted in children, healthy volunteers, or animal models were excluded. Editorials, commentaries, letters to editor, opinion articles, reviews, meeting abstracts, and case reports were also excluded. When multiple publications of the same research group or center described case series with potential overlap, the more recent publication, if eligible, was considered. We also included into the systematic review a recent study from our group, which was concomitantly submitted with the present work and subsequently published [23].

The main investigators (AD, EGB, FST) performed the study selection process, including the initial search for the identification of references, the selection of potentially relevant titles for review of abstracts, and, among these, the choice for review of the full-length reports. All selections were decided by consensus.

Data Extraction and Study Quality Assessment

The main investigators (AD, EGB, FST) independently extracted information from the selected articles by using a standardized data collection system. The following data fields were collected (when available): study location, period of enrollment, patient enrollment criteria, number of patients enrolled, critical values in the $PbtO_2$, rates of mortality, unfavorable neurological outcome, and intracranial hypertension in the intervention (combined $PbtO_2$/ICP and CPP–guided therapy) group and in the control group (ICP/CPP–guided therapy.) To assess the methodological quality of the studies, we used the Cochrane risk of bias tool (risk of bias 2) [24] for randomized trials, the Risk of Bias in Nonrandomized Studies of Interventions tool [25] for interventional nonrandomized studies, and the Newcastle–Ottawa Quality Assessment Scale [26] for cohort and case control studies. This assessment was performed by two independent reviewers (EGB and AD), and in case of discordant analysis, a third investigator (FST) made the final decision. Overall, a study was considered as "low" risk of bias if each single component of tools described above was classified as "low."

We determined the level of evidence by using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) classification system [27].

Outcomes

The primary outcome of the meta-analysis was the occurrence of favorable neurological outcome, favorable neurological outcome was defined as a Glasgow Outcome Scale of 4–5 or an extended Glasgow Outcome Scale of 5–8 [28]. Secondary outcomes were mortality rate, burden of intracranial hypertension (defined as the dose and duration of an ICP > 20 mm Hg), and burden of tissue hypoxia (defined as dose and duration of a $PbtO_2$ below the hypoxic threshold, as reported in each study), whenever this was collected. Predefined analyses were performed in subgroups of studies: (1) RCT only and (2) observational studies only.

Statistical Analysis

We performed the meta-analysis by using the fixed effect inverse variance method. The results were pooled together in a forest plot. We computed pooled odds ratio (OR) with 95% confidence intervals (CIs) for dichotomic outcomes and pooled mean difference with 95% CIs for continuous variables. Heterogeneity was assessed by means of the I^2 statistic, which reflects the amount of between-study heterogeneity over and above the sampling variation and is robust to the number of studies and choice of effect measure. We assessed the potential of publication bias through funnel plot generation. We performed all analyses by using Review Manager version 5.3.

Results

Study Selection

A total of 15 studies from 6245 record identified after the initial search were included in the final analysis, resulting in 37,245 studied patients, of whom 2184 received $PbtO_2$-guided therapy (Fig. 1).

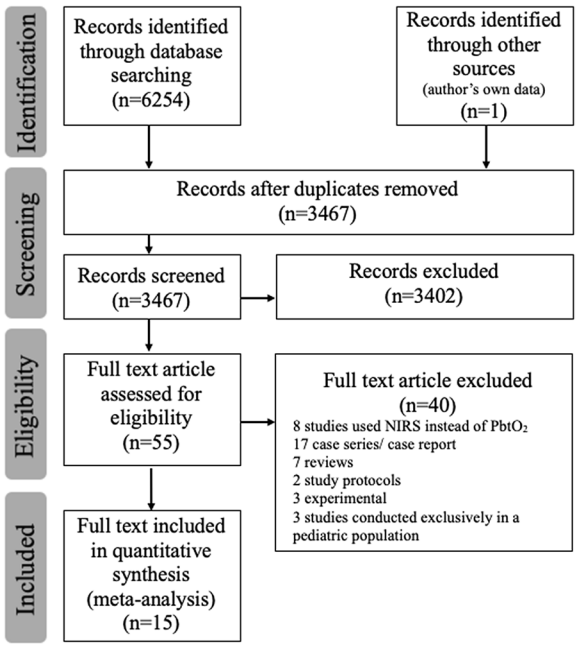

Fig. 1 Preferred reporting items for systematic reviews and meta-analysis (PRISMA) flow diagram of the search results for original studies and selection of eligible trials. NIRS, near infrared spectroscopy, $PbtO_2$, brain tissue partial pressure of oxygen

Study Characteristics

The characteristics of the selected studies are summarized in Table 1. We identified four RCTs, one prospective study, and ten retrospective studies. The risk of bias for RCTs was "some concern" in three studies and low in one (Table 2). For cohort and case control studies, the risk of bias was high in two, moderate in eight, and moderate to low in one (Table 3). The level of evidence assessed by the GRADE scale was moderate in all RCTs and in one prospective observational study (Tables 2, 3). The other observational studies were graded as "low quality" of evidence. The studies targeted an ICP < 20 mm Hg, a $PbtO_2$ > 10–25 mm Hg, and a CPP > 50–70 mm Hg; the most frequently used thresholds for $PbtO_2$ and CPP were > 20 mm Hg and > 60 mm Hg, respectively (Table 1) [15, 17–19, 21, 29–33]. The duration of intracranial hypertension and tissue hypoxia that triggered an intervention was reported in five studies: three studies used an ICP threshold of > 20 mm Hg for more than 5 min [16, 20, 34], whereas one study used an ICP > 20 mm Hg for 2 min [18]. Regarding tissue hypoxia, two studies used a $PbtO_2$ < 20 mm Hg for 5 min [16, 34], whereas one used a $PbtO_2$ < 15 mm Hg for 5 min [30]. General management of patients included in the selected studies was reported in 13 studies (Supplemental Table S1).

Neurological Outcome at 3 and/or 6 Months

We identified four studies that reported data on neurological outcome at 3 months. The pooled OR was 2.46 (95% CI 1.64–3.69) in favor of using combined $PbtO_2$/ICP–guided therapy, with a low heterogeneity of the studies ($I^2 = 0$; Fig. 2a) regarding the desired outcome, as shown in Fig. 2a. We also identified eight studies that reported neurological outcome at 6 months; the pooled OR was also 2.07 (95% CI 1.50–2.84) in favor of using $PbtO_2$/ICP–guided therapy, with a low heterogeneity of the studies ($I^2 = 0$; Fig. 2b) regarding the desired outcome. When all studies were combined, the OR for improved neurological outcome was 2.21 (95% CI 1.72–2.84;

Table 1 Summary of the characteristics of the studies included in the qualitative and quantitative analysis

References	Study characteristics	Study population	Physiological targets	Main results
Komisarow et al. [14]	Multicenter Retrospective USA 2008–2016	Adult GCS < 9 Exclusion criteria: survival < 24 h	Not reported	ICP group: $n = 34{,}155$ PbtO2/ICP group: $n = 134$ Patients who underwent $PbtO_2$ monitoring had a lower mortality rate than patients monitored with ICP only
Hoffman et al. [15]	Multicentric Retrospective with propensity score matching 2:1 USA 2013–2017	Adult GCS < 9	ICP < 20 mm Hg CPP > 60 mm Hg $PbtO_2$ > 20 mm Hg	ICP group: $n = 3266$ $PbtO_2$/ICP group: $n = 155$ In the propensity score cohort, patients with $PbtO_2$ had lower mortality rates than others $PbtO_2$ monitoring was associated with decreased odds of mortality but higher odds of unfavorable outcome at discharge
Wang et al. [32]	Single center RCT China 2017–2020	Adult GCS 4–8	ICP < 20 mm Hg CPP > 60 mm Hg $PbtO_2$ > 20 mm Hg	ICP group: $n = 36$ $PbtO_2$/ICP group: $n = 34$ ICP was lower in the ICP/$PbtO_2$ group and patients in this group had better neurological outcome at 3 and 6 months
Green et al. [31]	Single center Retrospective USA 2007–2009	Adult GCS < 9 Exclusion criteria: survival < 24 h	ICP < 20 mm Hg CPP > 60 mm Hg $PbtO_2$ > 20 mm Hg	ICP group: $n = 37$ patients $PbtO_2$ group: $n = 37$ patients Both groups had similar percentage of time spent with ICP > 20 mm Hg Mortality and functional status at discharge (GOS) were similar between groups
Narotam et al. [19]	Single center Prospective cohort with historical controls USA 1998–2006	Adult ISS > 15	ICP < 20 mm Hg CPP > 60 mm Hg $PbtO_2$ > 20 mm Hg	ICP group: $n = 41$ patients $PbtO_2$/ICP group: $n = 139$ patients The $PbtO_2$ group was associated with a risk reduction of 37% of mortality rate The $PbtO_2$ group had a higher probability of a favorable neurological outcome at 6 months
Spiotta et al. [18]	Single center Retrospective USA 2000–2004	> 15 years of age GCS < 9 ISS > 15 Exclusion criteria: Brain death; bilateral fixed dilated pupils; penetrating TBI, previous CNS disease or TBI; SBP < 90 mm Hg or $SatO_2$ < 90%	ICP < 20 mm Hg CPP > 60 mm Hg $PbtO_2$ > 20 mm Hg	ICP group: $n = 53$ patients $PbtO_2$/ICP group: $n = 70$ patients Both groups had similar daily mean ICP and CPP values Lower mortality rate and lower probability of poor neurological outcome at 3 months in the $PbtO_2$ group compared with the ICP group
Meixensberger et al. [35]	Single center Prospective (Interventional group from 1996 to 2000 compared to an observational cohort from a previous study 1993 to 1996) Germany 1993–2000	Adult GCS < 9 Exclusion criteria: multiple traumas	ICP < 20 mm Hg CPP > 70 mm Hg $PbtO_2$ > 10 mm Hg	ICP group: $n = 40$ patients $PbtO_2$/ICP group: $n = 53$ patients Lower occurrence of intracranial hypertension in the $PbtO_2$ group $PbtO_2$ was consistently higher in the $PbtO_2$ guided therapy group No significant differences between groups regarding outcomes

Table 1 (continued)

References	Study characteristics	Study population	Physiological targets	Main results
Stiefel et al. [20]	Single center Retrospective USA 2000–2002	Nonpenetrating TBI GCS < 8 ISS of 16 Exclusion criteria: SBP < 90 mm Hg $SatO_2$ < 93% Bilateral fixed and dilated pupils	ICP < 20 mm Hg CPP > 60 mm Hg $PbtO_2$ > 25 mm Hg	ICP group: *n* = 25 $PbtO_2$/ICP group: *n* = 28 Similar daily mean ICP and CPP values The hospital mortality rate was lower in the $PbtO_2$ group
Martini et al. [29]	Single center Retrospective USA 2004–2007	Adult GCS < 9	ICP < 20 mm Hg CPP > 60 mm Hg $PbtO_2$ > 20 mm Hg	ICP group: *n* = 506 patients $PbtO_2$/ICP group: *n* = 123 The incidence of intracranial hypertension and hospital mortality rate was numerically higher in the $PbtO_2$ group compared with the ICP group but not statistically significant
Adamides et al. [30]	Single center Prospective study (observational arm: fist 10 consecutive patients; interventional arm: next 20 consecutive patients) with a nested matched case control 1:1 Australia 2003–2005	Adult GCS score < 9 Within 48 h from injury Exclusion criteria: GCS score = 3 with fixed and dilated pupils and cardiac arrest at the scene	ICP < 20 mm Hg CPP > 60 mm Hg $PbtO_2$ > 20 mm Hg	ICP group: *n* = First 10 consecutive patients (monitored with $PbtO_2$ but not treated) $PbtO_2$/ICP group: Next 20 consecutive (received monitoring and treatment guided by $PbtO_2$) Matched control ICP group: *n* = 18 (no $PbtO_2$ monitoring) The mean duration of brain hypoxic episodes was lower in the $PbtO_2$ group compared with the ICP group No statistically significant differences in outcome
Okonkwo et al. [16]	Multicenter RCT USA Time period not specified	Nonpenetrating TBI > 14 years old GCS < 9 Motor score ≤ 5 Exclusion criteria: imminent brain death, hemodynamic instability, respiratory failure, no possibility of inserting the monitors or $PbtO_2$ monitor	ICP < 20 mm Hg CPP 50–70 mm Hg $PbtO_2$ > 20 mm Hg	ICP group: *n* = 62 (monitored with $PbtO_2$ but no treated based on it) $PbtO_2$/ICP group: *n* = 57 $PbtO_2$ guided therapy resulted in less episodes of brain hypoxia compared to ICP/CPP–guided strategy Outcome analysis showed trend toward lower mortality and better outcomes in the $PbtO_2$ group
Barrit et al. [23]	Single center Retrospective with a nested genetic matched case control Belgium 2012–2019	Adult GCS < 9 Exclusion criteria: Imminent death	ICP < 20 mm Hg CPP 60–70 mm Hg $PbtO_2$ > 20 mm Hg	Matched case control study ICP group: *n* = 35 PbtO2/ICP group: *n* = 35 ICP Cohort study: ICP group: *n* = 71 $PbtO_2$ group: *n* = 35 Patients monitored with $PbtO_2$ had lower incidences of intracranial hypertension No statistically significant differences in outcomes

Table 1 (continued)

References	Study characteristics	Study population	Physiological targets	Main results
Lin et al. [17]	Multicentric RCT Taiwan 2009–2010	Patients aged between 17–70 years old GCS 4–12 Exclusion criteria: GCS = 3, fixed and dilated pupils, hemodynamic/respiratory instability, multiple traumas, stay < 24 h in institution, limitations of care	ICP < 20 mm Hg CPP > 60 mm Hg $PbtO_2$ > 20 mm Hg	ICP group: $n = 27$ $PbtO_2$/ICP group: $n = 23$ Patients managed with $PbtO_2$ had lower ICP and higher CPP values than others No statistically significant differences in outcome
McCarthy et al. [33]	Single center Retrospective USA 2005–2008	Adult GCS < 9	ICP < 20 mm Hg CPP > 60 mm Hg $PbtO_2$ > 20 mm Hg	ICP group: $n = 64$ $PbtO_2$/ICP group: $n = 81$ No statistically significant differences in outcome
Lee et al. [21]	Single center RCT Taiwan 2006–2007	Patients aged between 12 and 70 years old Nonpenetrating TBI GCS 4–8 Exclusion criteria: pregnant women; multiply injured patients; and those with any previous disabling neurologic disease	ICP < 20 mm Hg CPP > 60 mm Hg $PbtO_2$ > 20 mm Hg	ICP group: $n = 16$ I CP group + mild hypothermia: $n = 15$ PbtO2/ICP group + mild hypothermia: $n = 14$ Similar ICP and outcome between ICP + hypothermia and $PbtO_2$ + hypothermia groups

CNS, central nervous system, CPP, cerebral perfusion pressure, GCS, Glasgow Coma Scale, GOS, Glasgow Outcome Scale, ICP, intracranial pressure, ISS, injury severity score, $PbtO_2$, brain tissue partial pressure of oxygen, RCT, randomized clinical trial, $SatO_2$, arterial oxygen saturation, SBP, systolic blood pressure, TBI, traumatic brain injury

Fig. 2c). The funnel plots of this analysis are presented in the Supplemental Fig. S1, panels a–c.

When considering only RCTs, combined $PbtO_2$/ICP–guided therapy was associated with a higher probability of favorable neurological outcome (pooled OR 2.10 [95% CI 1.36–3.25]; Supplemental Fig. 2a). Similarly, when considering only observational studies, combined $PbtO_2$/ICP–guided therapy was associated with a higher chance of overall favorable outcome (pooled OR 2.26 [95% CI 1.67–3.07]; Supplemental Fig. 2b).

Hospital Survival and Survival at 6 Months

Specific data on hospital survival were reported in nine studies. Combined $PbtO_2$/ICP–guided therapy increased the probability of hospital survival (pooled OR 1.15 [1.04–1.28]) but not at 6 months (1.20 [0.75–1.92]), when compared with ICP-guided therapy (Fig. 3a, b). Overall, $PbtO_2$-guided therapy increased the chance of survival (OR 1.15 [1.04–1.27], Fig. 3c). The funnel plots are presented in the Supplemental Fig. S1, panels d–f.

ICP and $PbtO_2$ Values

Patients who underwent $PbtO_2$/ICP–guided therapy experienced lower mean ICP values than patients who underwent ICP-guided therapy; the mean difference was − 2.87 (− 3.46 to − 2.27) mm Hg. The forest and funnel plots of this analysis are presented in the Supplemental Fig. S3. However, the occurrence of intracranial hypertension was similar between the two groups ($n = 9$ studies). No meta-analysis was possible for this outcome, as definition and reporting of intracranial hypertension significantly varied across the studies (i.e., episodes of intracranial hypertension, time spent with ICP > 20 mm Hg, occurrence of intracranial hypertension at least once); in addition, specific etiologies of intracranial hypertension were not described (i.e., hyperemia, edema with oligemia, or hydrocephalus).

Only three studies compared $PbtO_2$ values between groups [16, 30, 35]. In these studies, the treating physicians were blinded to the $PbtO_2$ value in the control group (i.e., ICP-guided therapy) or $PbtO_2$ was implemented but not used to guide therapy. In the RCT reporting $PbtO_2$ in the two groups [16], there was a significant reduction of the burden of brain hypoxia in the $PbtO_2$-guided group, when compared with the ICP-guided strategy [16]. In the other two studies [30, 35], there was a trend toward a lower burden of brain hypoxia in the patients receiving $PbtO_2$-guided therapy, although this did not reach statistical significance. The most used strategies to improve $PbtO_2$ were correct positioning of the head, fever avoidance, treatment of intracranial hypertension, induced hypertension (i.e., vasopressors), red blood cells transfusions, changes in ventilatory settings and in the inspired

Table 2 Quality of evidence (GRADE) and of the risk of bias assessment by using the Cochrane ROB tool 2 for randomized clinical trials

References	Randomization process	Deviation from the intended interventions	Missing outcomes data	Measurement of the outcome	Selection of the reported results	Overall ROB	Quality of level GRADE
Wang et al. [32]	Some concern	Some concern	Low	Low	Low	Some concern	Moderate
Okonkwo et al. [16]	Low	Low	Low	Low	Low	Low	Moderate
Lee et al. [21]	Some concern	Low	Low	Low	Low	Some concern	Moderate
Lin et al. [17]	Some concern	Low	Some concern	Low	Low	Some concern	Moderate

GRADE, Grading of Recommendations, Assessment, Development and Evaluation system, ROB, risk of bias

Table 3 Quality of evidence (GRADE) and risk of bias analysis assessed by the Newcastle–Ottawa scale for observational studies (cohort or case control studies)

References	Selection of cases	Comparability of cohorts	Exposure and outcome	Overall risk of bias	Quality of level GRADE
Stiefel et al. [20]	3	1	3	Moderate	Low
Spiotta et al. [18]	3	1	3	Moderate	Low
Meixenberger et al. [35]	3	1	3	Moderate	Low
Narotam et al. [19]	3	0	2	High	Low
Martini et al. [29]	4	0	2	Moderate	Low
Green et al. [31]	3	0	3	Moderate	Low
Komisarow et al. [14]	4	1	3	Moderate to low	Low
McCarthy et al. [33]	3	0	2	High	Low
Barrit et al. [23]	2	1	3	Moderate	Low
Adamides et al. [30]	3	1	3	Moderate	Moderate
Hoffman et al. [15]	3	1	3	Moderate	Low

GRADE, Grading of Recommendations, Assessment, Development and Evaluation system

fraction of oxygen (FiO_2), or increased sedation and analgesia levels. We also performed a quantitative analysis of the proportion of time that $PbtO_2$ values were below the hypoxic threshold, as reported in each study, comparing the two strategies. We found a reduction of 10% (95% CI 6–14%) in the time spent below the hypoxic threshold in the group treated with a $PbtO_2$/ICP–guided therapy, when compared with the group treated with ICP-guided therapy alone (Supplemental Fig. S4). However, this result was mainly driven by one study [16].

Discussion

This systematic review and meta-analysis investigated the impact of $PbtO_2$-guided therapy on the outcome of patients with severe TBI. We found that this approach was associated with better neurological outcome and reduced hospital survival, when compared with the standard ICP-guided therapy. Moreover, ICP levels were lowered with the implementation of a protocolized strategy that included $PbtO_2$ monitoring. However, the evidence of the existing literature was low to very low.

The cornerstone of neurological monitoring in patients with TBI remains clinical evaluation [36]; however, physiological monitoring can help clinicians understand the pathophysiological mechanisms of brain injury and detect neurological deterioration earlier, especially in sedated or comatose patients, as well as to individualize treatments [37]. Identifying the cause and the underlying pathophysiological pathway of intracranial hypertension can help clinicians to select specific therapies (i.e., ventriculostomy for hydrocephalus, hyperventilation for hyperemia, or osmotherapy for cerebral edema), as highlighted in a recent review [38]. In this setting, a combination of invasive and noninvasive monitoring tools would be the most effective way to identify different phenotypes of intracranial hypertension. $PbtO_2$ monitoring is a safe and reliable technique [39] that can be included as a part of a multimodal monitoring strategy in this setting; $PbtO_2$ is a regional monitor of the pool of oxygen available in the brain interstitial space, which depends on the balance between oxygen delivery (i.e., cerebral blood flow, hemoglobin, and arterial oxygenation), consumption (i.e., brain metabolism, mitochondrial

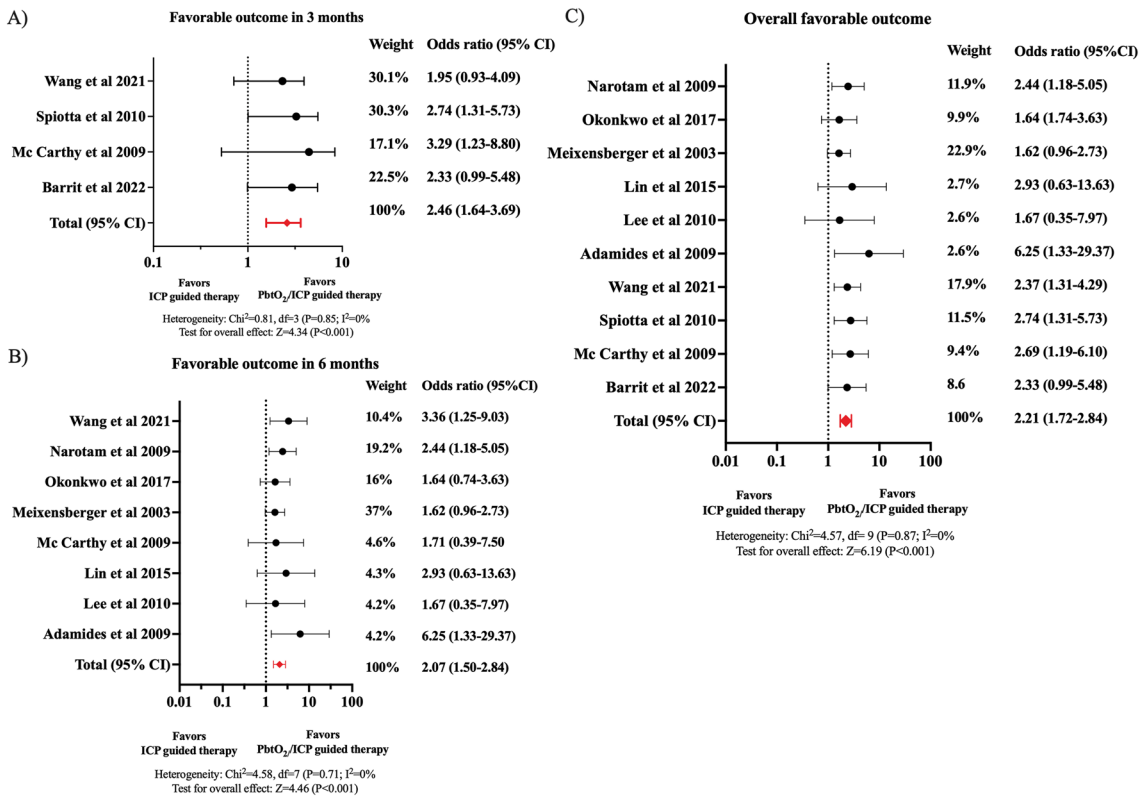

Fig. 2 Forest plot for favorable neurological outcome at 3 months (**a**) and 6 months (**b**) and overall (**c**). The horizontal bars represent 95% confidence intervals (CIs). ICP, intracranial pressure, $PbtO_2$, brain tissue partial pressure of oxygen

function, body temperature) and extraction (i.e., blood–brain barrier and microcirculation) [40].

Because brain tissue hypoxia is associated with poor outcome after TBI [8, 9, 41–44], optimizing $PbtO_2$ could lead to better functional recovery and survival rates. In fact, six observational studies [15, 18, 19, 30, 31, 33] and one RCT [32] included in this systematic review have shown a statistically significant benefit regarding neurological function when $PbtO_2$ was integrated in clinical management; all other studies also showed a nonstatistically significant trend toward better neurological recovery, which in the pooled analysis led to a two-times higher probability of favorable neurological outcome when $PbtO_2$-guided therapy was used. Additionally, six studies showed a significant improvement of survival, whereas one study [29] reported a nonstatistically significant trend toward lower hospital death in patients treated with $PbtO_2$-guided therapy.

The lack of benefit in some studies can be explained by several factors: (1) normalizing $PbtO_2$ may not always improve alterations of brain metabolism [45–48]; (2) $PbtO_2$ is a regional device, and an adequate $PbtO_2$ reading in one specific cerebral area may not reflect or detect tissue hypoxia in the entire brain oxygenation level; (3) therapies used to optimize $PbtO_2$, such as sedation, transfusion, fluid administration, and vasopressors, may have some adverse effects that can negatively impact outcomes, be associated with lung injury and cardiac overload, and lead to prolonged mechanical ventilation and prolonged intensive care unit stay [49–53]. Moreover, therapeutic protocols based on $PbtO_2$ and ICP could require different interventions and are not homogenous. For research purposes, the adherence to a recent consensus that provided a multistep approach to improve both intracranial pressure and brain oxygenation [54] in patients with TBI could facilitate comparison between studies, improve data reporting, and help generate more robust evidence. However, in the clinical practice, this approach offers initial physiological targets and treatment strategies, which should be therefore individualized to each patient accordingly. Interestingly, the lack of benefit on mortality at 6 months may be explained by the relevant role of brain tissue hypoxia on the occurrence of "early" mortality, whereas long-term mortality would be more influenced by demographic factors (i.e., age), the severity of injury (i.e., Glasgow Coma Scale on admission) and the number of complications over the intensive care unit and hospital stay [55–57].

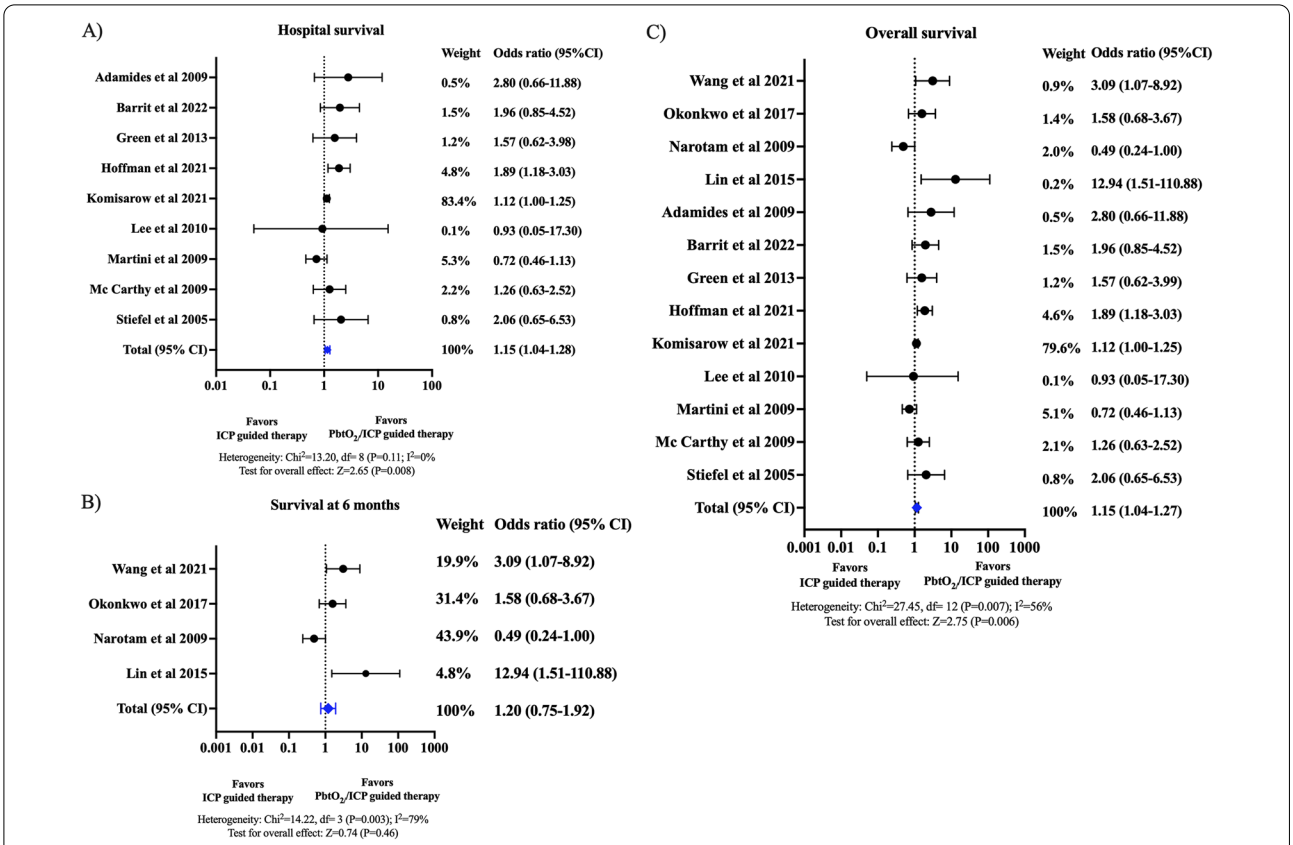

Fig. 3 Forest plot for hospital survival (**a**), 6-month survival (**b**), and overall mortality (**c**). The horizontal bars represent 95% confidence intervals (CIs). ICP, intracranial pressure, $PbtO_2$, brain tissue partial pressure of oxygen

Importantly, long-term mortality after TBI is higher than in the general population and is usually attributable to external causes and less frequently to cardiovascular or respiratory diseases and neoplasms [58].

An important caveat in the interpretation of these findings is the decision to monitor patients with TBI with $PbtO_2$, in particular for nonrandomized studies, which could vary according to the treating physician. Most centers tend to monitor patients with moderate to severe TBI on admission or those who will later deteriorate (i.e., Glasgow Coma Scale score < 8) [37]. However, moribund patients or those with extremely severe neurologic injury (i.e., Glasgow Coma Scale score of 3, bilateral nonreflective pupils, suspicion of brain death) and those with severe systemic injuries (i.e., hemodynamic instability, severe respiratory failure, cardiac arrest on presentation) were often excluded in the selected studies, which would limit the generalizability of these findings in this patient population. In clinical practice, selecting the patient who would most likely benefit from $PbtO_2$ monitoring (at least in the first 48 h after admission) can be challenging. Future research should focus on identifying patients' baseline characteristics associated with a beneficial gain in terms of outcomes of implementing a $PbtO_2$-guided strategy to help guide and individualize the decision to insert this monitoring tool.

Our study has several limitations. First, the quality of evidence assessed by the GRADE system was predominantly low. Second, several studies presented with a moderate risk of bias or raising some concerns, thereby reducing the strength of our findings. Third, few studies reported individual patient data, which have limited adjustment for confounders. Fourth, the decision to use $PbtO_2$ monitoring in observational studies might suggest the presence of some selection bias and might have influenced the final results. Fifth, only one article reported the reference point used for CPP calculation (i.e., Monroe's foramen or at the level of the heart). Sixth, the duration of time with elevated ICP, low CPP, and low $PbtO_2$ that triggered interventions and a detailed protocol of patients' management was not consistently reported in the studies and varied according to local practices. Seventh, the number of patients excluded for each study due to the initial TBI severity as well as the data regarding withdrawal of life support were scarcely reported, and this could have influenced our conclusions. Eighth, probe location was not considered when performing this analysis.

Conclusions

This systematic review and meta-analysis showed that $PbtO_2$-guided therapy may improve neurological outcome and hospital survival after TBI. Clinicians may consider adding $PbtO_2$ monitoring to the management of patients with severe TBI. Three ongoing RCTs assessing the impact of $PbtO_2$/ICP–guided therapy, compared with ICP-guided therapy, on the outcome of patients with TBI will help to define the optimal strategy. For future research, investigators should provide more detailed and homogenous data on probe location, thresholds, and therapeutic algorithms to better understand the role of $PbtO_2$-guided strategy in patients with brain injury.

Supplementary Information
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Author contributions
AD, EGB, and FST conceived the study; AD, SM, and MAB performed the screening and selected the articles for the systematic review. AD, EGB, and FA extracted the data from the articles; EGB and FST conducted the statistical analysis. AD, EGB, and FST wrote the first draft of the article; FA, SS, SM, and MAB revised the text for intellectual content. All authors read and approved the final manuscript.

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