

# Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> Combined with Optic Nerve Sheath Diameter in Predicting Elevated Intracranial Pressure of Patients with Traumatic Brain Injury in Prehospital Setting

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**Purpose:** To investigate a correlation between the central venous minus arterial CO<sub>2</sub> pressure to arterial minus central venous O<sub>2</sub> content ratio (Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub>) combined with optic nerve sheath diameter (ONSD) in predicting prehospital elevated intracranial pressure (ICP) in traumatic brain injury (TBI) patients.

**Patients and Methods:** This was a prospective observational study of all adult TBI patients from the surgical intensive care unit who underwent invasive ICP monitoring between January 2023 and December 2023. Using a Delica MVU-6300 machine with 14–5 MHz linear probe to measure ONSD. We drew blood samples for arterial and central venous blood gases to measure and calculate the following indicators such as Pcv-aCO<sub>2</sub>, Ca-cvO<sub>2</sub>, and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> ratio. ONSD and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> were recorded during the first 3 days after admission. Simultaneous ICP values were gained from the invasive monitoring. Associations between ONSD, Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> and simultaneous ICP were explored by Spearman correlation analysis. We constructed an ROC curve to identify the ONSD and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> cutoff for the evaluation of elevated ICP.

**Results:** We included 54 patients aged mean 57.13 (standard deviation 4.02) years and 24 (44%) were male. A significant correlation was observed between ONSD and ICP ( $r = 0.74$ ,  $P < 0.01$ ). The AUC was 0.861 (95% CI: 0.727–0.951), with a best cutoff value of 5.62 mm. Using a cutoff of 5.62mm, ONSD had a sensitivity of 92.8%, specificity of 80.4%. The Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> ratio also significantly correlated with ICP ( $r = 0.70$ ,  $P < 0.01$ ). The AUC was 0.791 (95% CI: 0.673–0.889). The optimal Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> value for predicting elevated ICP was 1.98 mmHg/mL. Using a cutoff of 1.98 mmHg/mL, Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> had a sensitivity of 87.3%, specificity of 77.2%. The AUC for ONSD combined with Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> was 0.952 (95% CI: 0.869–0.971), which had a sensitivity of 95.1%, specificity of 93.9%.

**Conclusion:** Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> combined with ONSD performed best in predicting elevated intracranial pressure of patients with TBI in a prehospital setting. Our findings provide a crucial tool to improve earlier management of these patients in prehospital care, where the availability and utilization of invasive monitoring is limited. It could lead to significant changes in how TBI patients are monitored and treated before reaching a hospital.

**Keywords:** intracranial pressure, traumatic brain injury, Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub>, optic nerve sheath diameter, prehospital

## Introduction

Traumatic brain injury (TBI) remains a major health-care problem; 69 million people suffer from TBI each year worldwide.<sup>1–3</sup> TBI disability rate and fatality rate top all trauma types.<sup>4</sup> Previous study and literature have demonstrated an in-hospital mortality of 18%,65% for moderate and severe TBI, respectively.<sup>5</sup> Secondary brain injury is a pathophysiologic injury including intracranial hematoma, cerebral edema and increased intracranial pressure (ICP),

leading to poor outcome. Early detection and subsequent prompt management of elevated ICP can be used for improving neurological outcomes and controlling mortality of TBI.<sup>6,7</sup>

At present, invasive ICP monitoring is recognized as the standard of care for diagnosis of elevated ICP.<sup>8–10</sup> However, restricted by equipment and the highly invasive nature with relevant comorbidity restricted its use to prehospital setting.

Ultrasound measurement of the optic nerve sheath diameter (ONSD) is a noninvasive ICP monitoring techniques, which can be performed quickly effective in predicting increased ICP.<sup>11</sup> Meanwhile, this method allows dynamic real-time monitoring of ICP during prehospital settings. Elevated ICP is transmitted to the subarachnoid space surrounding the optic nerve, leading to expansion of the optic nerve sheath, which can be detected by ultrasound.<sup>12</sup> Each measurement can be performed in bedside, reproducible and easy to learn. These characteristics are particularly important in the prehospital setting.

Secondary brain injury is closely related to cerebral hypoperfusion and ischemia, which begins to appear at the early stage of trauma, and results in cerebral edema. When cerebral edema occurs, the subsequent increase in ICP aggravates cerebral ischemia. The ratio of central venous to arterial CO<sub>2</sub> pressure to arterial minus central venous O<sub>2</sub> content (Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub>) as a marker of anaerobic metabolism, which can reflect the oxygen metabolism of cerebral tissues in real time.<sup>13,14</sup> Previous studies have confirmed that this ratio is more accurate than the central venous oxygen saturation and lactate levels, reflecting the state of oxygenation.<sup>15,16</sup> Furthermore, recent studies have demonstrated that there was a significant difference between cerebral perfusion pressure and ICP at different levels of brain oxygen.<sup>17</sup> Therefore, the state of brain oxygen is closely related to ICP. Importantly, Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> as a method of assessing cerebral oxygenation, each parameter can be quickly performed by emergency medical personnel at the bedside.

However, to our knowledge, no studies have validated whether a monitoring protocol informed by ONSD combined with Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> can improve the accuracy of elevated ICP diagnosis in TBI patients, especially in a prehospital setting. Unlike invasive monitoring, this combination can be performed in prehospital setting, unlimited by specialized equipment and easily performed by physician. If the findings are confirmed, it will provide meaningful ideas to address effective prehospital monitoring of intracranial pressure and significantly advance the field of TBI management.

The aim of the study was to explore Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> combined with ONSD in predicting prehospital elevated ICP in TBI patients. We will take this new method to improve diagnostic accuracy and better management strategies for TBI patients, ultimately enhancing patient outcomes.

## Materials and Methods

### Study design

This is a prospective observational study of patients with TBI who underwent invasive ICP monitoring in our surgical intensive care unit. This study was approved by the Ethics Committee of the First People's Hospital of Changde, Hunan Province, China (Register: YX-2023-417-01). Written informed consent was obtained from the patient's family. All clinical studies comply with the principles of the Declaration of Helsinki.

### Participant Selection Criteria

Patients were enrolled between January 2023 and December 2023. Patients aged >18 years with severe TBI (Glasgow Coma Scale [GCS] score ≤8) and those with arterial and central venous catheters were eligible for this study. Those who experienced significant ocular trauma were excluded.

### Data Collection Procedures

The total sample size was calculated using the formula based on sensitivity<sup>18</sup>. Previous studies demonstrated that the prevalence of TBI in the worldwide was 7.8%.<sup>1–3</sup> Raffiz<sup>11</sup> showed that the sensitivity and specificity of diagnosing elevated ICP by ONSD were 95.8% and 80.4%, respectively. Hence, with an absolute error of 10% and a type I error of 0.05, the minimum total sample size was 50.

We collected baseline information, including sex, age, admission GCS score, admission Injury Severity Score (ISS) and type of injury. All patients receive ventricular puncture. An external ventricular drain (EVD) catheter was inserted into the

ventricle and connected to a pressure transducer (Codman, USA). The ICP values were displayed on a monitor (Codman, 82–6635, USA). Elevated ICP was defined as ICP >20 mmHg (1 mmHg = 0.133 kPa). ONSD, Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> and the real-time ICP values were recorded at 0, 2, 6, 12, 24, 48, and 72 h after admission.

## ONSD and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> Measurement

The ONSD measurements were performed by two experienced physicians trained in specialized ultrasonography using a Delica MVU-6300 (Shenzhen, Guangzhou, China) machine with 14–5 MHz linear probe. The patient was placed in a relaxed supine position, and a linear ultrasound probe was placed gently over the closed upper eyelid until the image of the optic nerve was clearly displayed. ONSD measurements were recorded 3 mm behind the retina. Three ONSD measurements were obtained from each side, and the average of the six measurements was the final sheath value. The physician taking the ONSD measurement was blinded to the real-time ICP value.

We drew blood samples for arterial and central venous blood gases. Collect the following data such as arterial oxygen tension (PaO<sub>2</sub>), arterial oxygen saturation (SaO<sub>2</sub>), and ScvO<sub>2</sub>. The ratio was determined using the following formula: Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> = (PcvCO<sub>2</sub>-PaCO<sub>2</sub>)/(CaO<sub>2</sub>-CcvO<sub>2</sub>).

## Statistical Analysis

All statistical analyses were performed using SPSS software (version 20.0). Categorical variables are expressed as proportions with frequencies and percentages, and continuous variables are expressed as mean ±SD and medians with interquartile ranges (IQRs).

An independent sample two-tail Student's *t*-test was used to compare the ONSD and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> in patients with normal or elevated ICP, and the correlation between ONSD and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> with the simultaneous ICP value was analyzed by Spearman correlation. A receiver operating characteristic curve (ROC) was used to determine the optimal ONSD and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> cutoff points for the detection of ICP >20 mmHg (significance level was set to *P* <0.05, using 2-sided test).

## Results

### Characteristics of Study Subjects

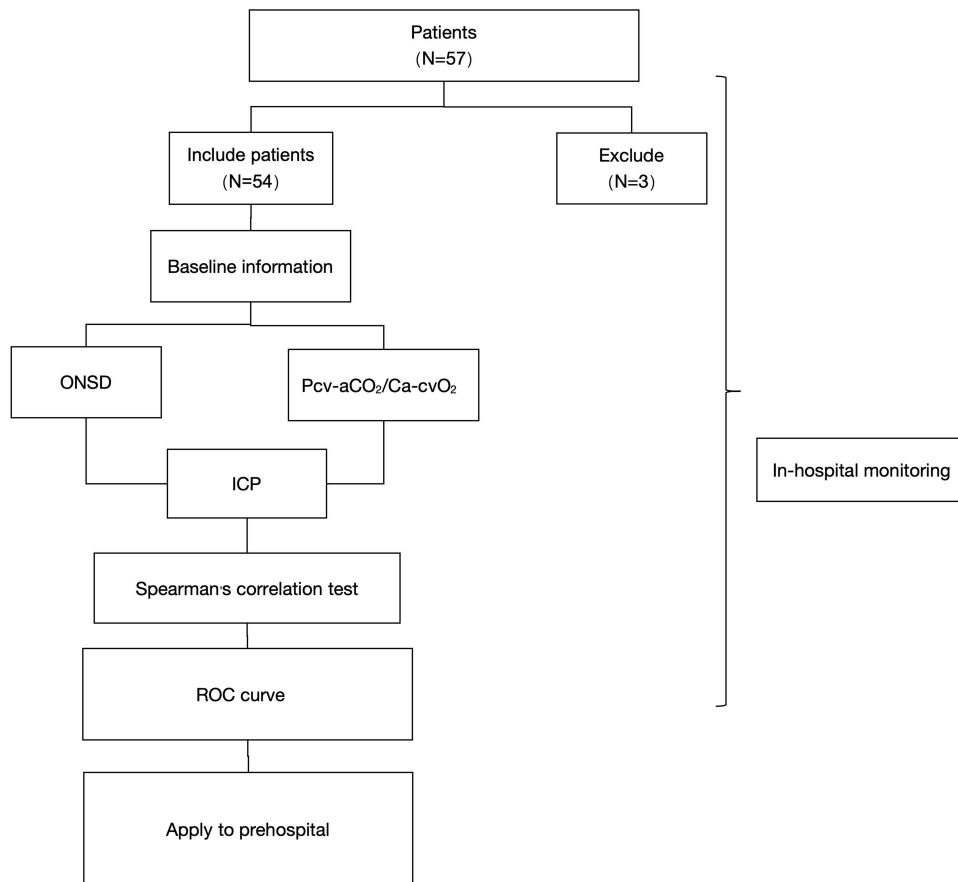
Table 1 shows the demographic and clinical characteristics of patients. There were 57 patients who completed Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> and ONSD measurements with invasive ICP monitoring during the study period. After the exclusion of three patients with orbital trauma, 54 were deemed eligible for analysis (Figure 1). The mean age of the patients was 57.13 ± 4.02 years. The number of men was 24 (44%). Thirty patients had elevated ICP, and 24 had normal ICP.

**Table 1** Demographic Data in the Normal and Elevated ICP Groups

	Overall (n=54)	ICP >20mmHg (n=30)	ICP ≤20 mmHg (n=24)	<i>P</i>
Age(years)	57.13±4.02	61.21±5.11	52.11±3.21	0.07
Male, n (%)	24 (44)	10 (33)	14 (58)	0.30
Type of injury				0.06
Traumatic brain injury only, n (%)	21 (39)	12 (40)	9 (38)	
Multiple injury, n (%)	33 (61)	18 (60)	15 (62)	
Glasgow coma score	7 (4, 10)	5 (3, 7)	8 (5, 11)	0.03*
Injury severity score	37 (21, 58)	39 (20, 61)	26 (17, 39)	0.01*
ONSD (mm)	5.33±0.44	6.51±0.62	4.99±0.51	0.02*
Pcv-aCO <sub>2</sub> /Ca-cvO <sub>2</sub> (mmHg/mL)	2.41±0.71	3.42±0.22	1.71±0.51	0.01*

**Notes:** \*Indicate statistical significance.

**Abbreviations:** ONSD, optic nerve sheath diameter; Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub>, the central venous minus arterial CO<sub>2</sub> pressure to arterial minus central venous O<sub>2</sub> content ratio; ICP, intracranial pressure.



**Figure 1** Flow chart of research. Flow chart illustrating inclusion and exclusion criteria.

**Abbreviations:** ONSD, optic nerve sheath diameter; Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub>, the central venous minus arterial CO<sub>2</sub> pressure to arterial minus central venous O<sub>2</sub> content ratio; ICP, intracranial pressure; ROC, receiver operating characteristic curve.

The mean overall ONSD was 5.33 ± 0.44 mm. The mean Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> of all participants was 2.41 ± 0.71 mmHg/mL. Patients with elevated ICP had significantly higher mean ONSD (6.51 ± 0.62 mm vs 4.99 ± 0.51 mm, P = 0.02) and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> (3.42 ± 0.22 mmHg/mL vs 1.71 ± 0.51 mmHg/mL, P = 0.01).

There were also significant differences in GCS (median [IQR], 5[3,7] vs 8[5,11]) and ISS (median [IQR], 39[20,61] vs 26[17,39]) between the elevated ICP and normal ICP groups.

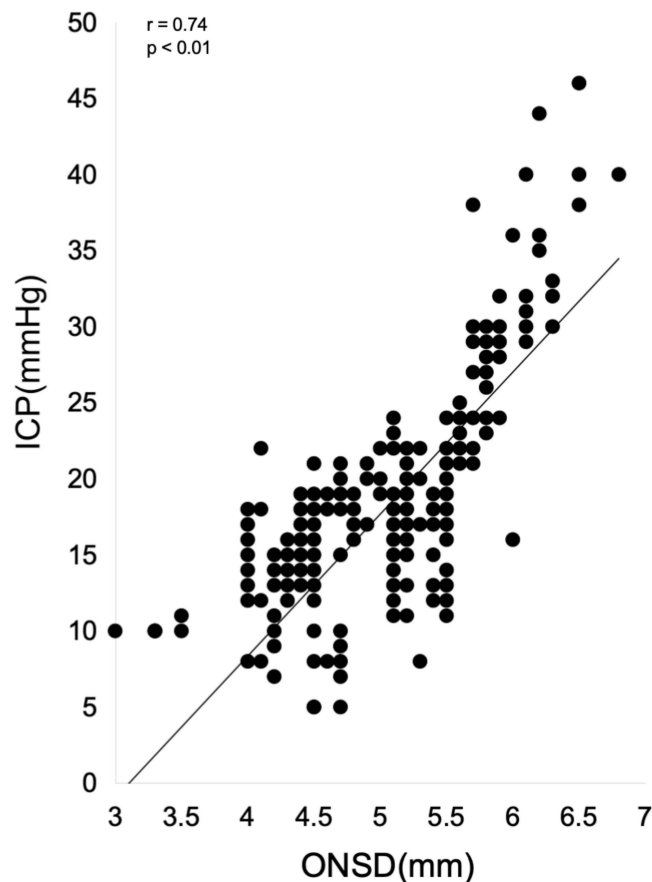
### Correlation Between ONSD, Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> and Invasive ICP Measurements

There was a linear association between ONSD and real-time ICP (r = 0.74, P < 0.01, Figure 2). There was a linear association between Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> and real-time ICP (r = 0.70, P < 0.01, Figure 3).

### ROC Curve

The ROC curve, which describes the ability of ONSD and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> to predict elevated ICP, illustrated that Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> combined with ONSD had maximum sensitivity and specificity (sensitivity 95.1% and specificity, 93.9%; area under the curve, AUC = 0.952, 95% CI: 0.869–0.971; Figure 4 and Table 2).

The AUC for ONSD diagnosis of ICP >20 mmHg was 0.861 (95% CI: 0.727–0.951, P = 0.007), with the best cutoff value of 5.62 mm (sensitivity, 92.8%; specificity, 80.4%). The AUC for Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> diagnosis of ICP >20 mmHg was 0.791 (95% CI: 0.673–0.889, P = 0.020), with a best cutoff value of 1.98 mmHg/mL (sensitivity 87.3%; specificity 77.2%).



**Figure 2** Linear association between ONSD and real-time ICP. Illustrating scatter plot of ONSD and ICP. **Abbreviations:** ONSD, optic nerve sheath diameter; ICP, intracranial pressure.

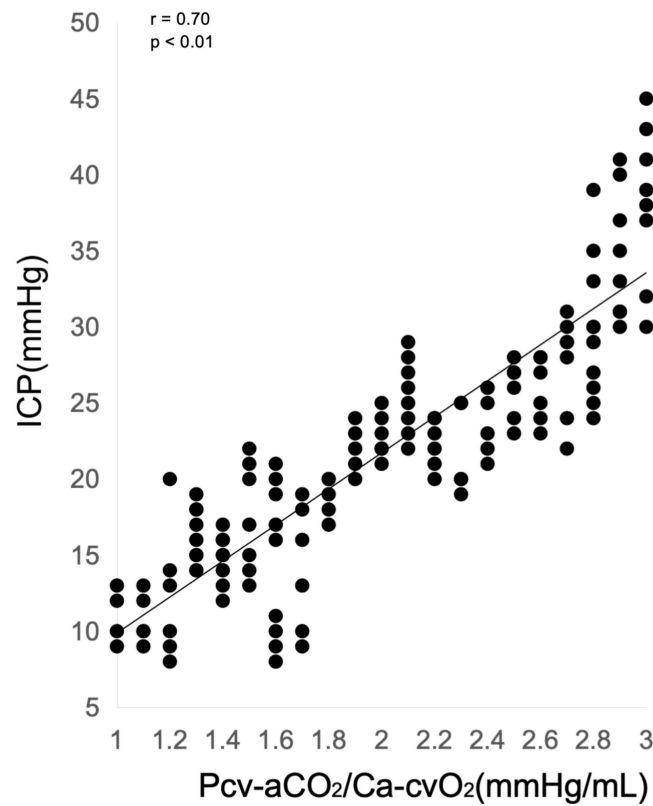
## Discussion

Elevated ICP leads to a high rate of disability and fatality in patients with TBI, which is considered an acute situation associated with poor clinical outcomes. Therefore, early diagnosis and effective treatment of elevated ICP are important for the management of patients with TBI in emergency situations.<sup>19</sup>

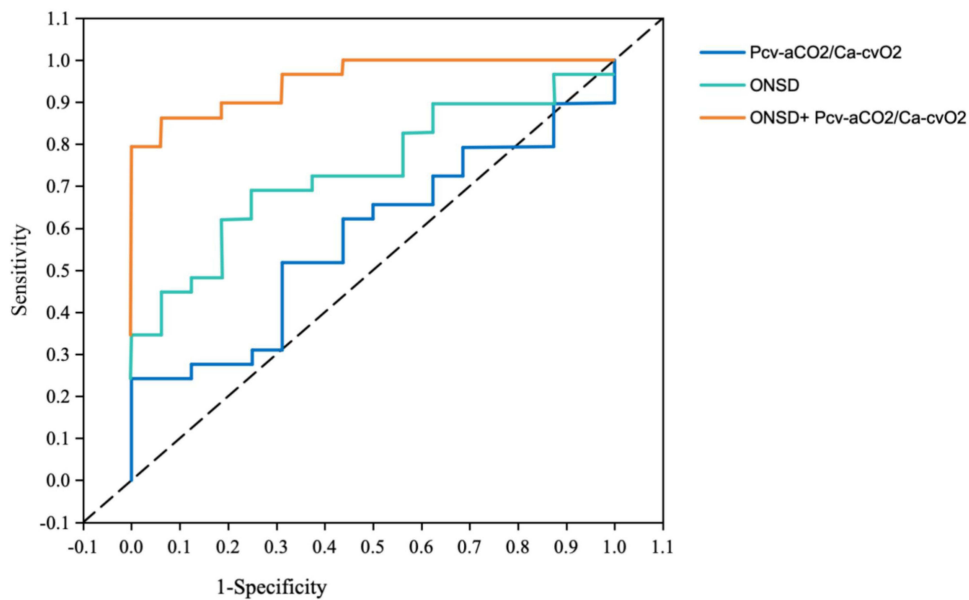
Invasive ICP monitoring is the gold standard for evaluating elevated ICP, and the fourth edition of the guidelines for the management of severe TBI recommends this technique as an important part of the management of TBI patients.<sup>2</sup> Importantly, early diagnosis and timely intervention of elevated ICP are critical to the management of TBI, particularly in the prehospital setting. However, invasive ICP monitoring cannot be performed in prehospital setting due to limited resources and lack of surgical availability.

Our study aimed to find a non-invasive technique for the detection of elevated ICP in the prehospital setting. Ultrasound measurement of ONSD to predict elevated ICP is noninvasive, simple, quick and easy to perform. These features can be particularly successfully applied in prehospital setting. Unlike the previous study,<sup>19</sup> we combined ONSD with Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> to assess cerebral oxygenation and ICP to provide a suitable method for the management of ICP in patients with TBI.

Our study confirmed the linear correlation between ONSD and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> and the real-time measurement of ICP via invasive monitoring in patients with TBI. Moreover, our study also established that both ONSD and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> can be utilized to successfully identify elevated ICP in patients with TBI. Therefore, our results suggest that ONSD combined with Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> is a critical tool for providing useful information regarding ICP in prehospital settings.



**Figure 3** Linear association between Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> and real-time ICP. Illustrating scatter plot of Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> and ICP.  
**Abbreviations:** ICP, intracranial pressure; Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub>, the central venous minus arterial CO<sub>2</sub> pressure to arterial minus central venous O<sub>2</sub> content ratio.



**Figure 4** ROC curve of ONSD, Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> and ONSD combined with Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> for diagnosis of ICP >20 mmHg. Illustrating the ROC of ONSD, Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> and ONSD combined with Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> in predicting ICP >20 mmHg in TBI patients.  
**Abbreviations:** ROC, receiver operating characteristic curve; ONSD, optic nerve sheath diameter; Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub>, the central venous minus arterial CO<sub>2</sub> pressure to arterial minus central venous O<sub>2</sub> content ratio; ICP, intracranial pressure.

**Table 2** Sensitivity and Specificity of ONSD and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> for Diagnosing Elevated ICP in Patients with TBI

Variable	AUC (95% CI)	Sensitivity	Specificity
Model with one variable			
ONSD	0.861 (0.727,0.951)	92.8	80.4
Pcv-aCO <sub>2</sub> /Ca-cvO <sub>2</sub>	0.791 (0.673,0.889)	87.3	77.2
Model with two variables			
ONSD+Pcv-aCO <sub>2</sub> /Ca-cvO <sub>2</sub>	0.952 (0.869,0.971)	95.1	93.9

**Abbreviations:** AUC, Area under the curve; 95% CI, 95% confidence interval; ONSD, optic nerve sheath diameter; Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub>, the central venous minus arterial CO<sub>2</sub> pressure to arterial minus central venous O<sub>2</sub> content ratio; ICP, intracranial pressure; TBI, traumatic brain injury.

Compared to traditional invasive ICP monitoring techniques, ONSD combined with Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> could accurately predict elevated ICP (AUC = 0.952). Our study has shown that ONSD combined with Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> is more sensitive and specific in assessing elevated ICP in TBI patients. Moreover, unlike invasive monitoring, this dual approach is suitable for assessing elevated ICP in the prehospital setting and could lead to better identification of elevated ICP, potentially allowing for timely interventions that could prevent secondary brain injuries. Meanwhile, both ONSD and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> are non-invasive and fewer comorbidities compared to traditional invasive ICP monitoring techniques. Indeed, multimodal monitoring reflects a growing trend in critical care to utilize various parameters for a more comprehensive assessment of patient status. This approach may lead to improved decision-making and patient management strategies during prehospital setting.

Currently, prehospital physicians rely more on vital signs such as pupil, blood pressure, heart rate, and clinical experience to identify patients with suspected elevated ICP due to lack of ICP monitoring devices. Therefore, it is challenging to take rapid initiation of treatments such as osmotherapy during prehospital setting. The integration of ONSD measurements with Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> offers a potentially new method for assessing cerebral oxygenation and ICP, to guide the use of mannitol in patients with TBI during prehospital setting. Our study provides a new method to address the problem of rational use of mannitol in the prehospital management of patients with TBI and avoiding cerebral hypoperfusion due to incorrect use of mannitol. Furthermore, our findings address a gap in the literature regarding the effectiveness of combining ONSD and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> for ICP monitoring and significantly advance the field of TBI treatment, which could be helpful for timely interventions and improved patient outcomes.

The optic nerve sheath has elastic ability. When ICP increases, the optic nerve sheath and surrounding elastic structure expand, causing ONSD to expand.<sup>20</sup> Previous research has reported a significant positive relationship between magnetic resonance imaging measurement of ONSD and invasive ICP.<sup>21</sup> However, this tool cannot be applied in prehospital settings due to the lack of appropriate equipment and the complexity of the environment. Sonographic measurement of ONSD is relatively easy, with readily available equipment making it a promising method for predicting raised ICP in patients with TBI during prehospital setting. In vitro optic nerve experiments reported that for every 1 mmHg increase in ICP, the ONSD expanded by 0.025 mm.<sup>22</sup> Our findings also demonstrated a good relationship between the ICP via invasive monitoring with the ONSD value. It is similar to prior prospective observation study that the ONSD of children was significantly related to simultaneous ICP.<sup>23</sup> Using the ROC curve we identified that ONSD for the evaluation of elevated ICP of the area under the curve (AUC) was 0.861. Our study showed that the ONSD cutoff point was 5.62 mm to identify elevated ICP (sensitivity, 92.8%; specificity, 80.4%). Meanwhile, a prospective blinded observation study concerning the accuracy of ONSD in a heterogeneous group of patients with different acute brain injury.<sup>24</sup> Their findings demonstrated that ONSD is the only independent predictor of elevated ICP regardless of diagnosis. It suggests that the predictive value of ONSD was not related to the varying severities of acute brain injury. Moreover, in some of the systemic diseases that lead to neurological complications, including cardiac arrest/coma and intraoperative complications, ONSD is a good predictor of poor prognosis associated with increased ICP.<sup>25,26</sup>

Moreover, we take some measures to control the bias of ONSD measurement. First, operator inexperience and error may confound the ability to assess the intrinsic value of the technique itself. Based on this, we have trained emergency medical personnel according to standardized protocols for measurement. Emergency medical personnel have become proficient in the measurement of ONSD to ensure accuracy of results. Second, three ONSD measurements were obtained from each side, and the average of the six measurements was the final sheath value, to minimize variability. However, the optimal ONSD cutoff point for identifying elevated ICP remains unknown, extending from 5.0 mm to 5.9 mm.<sup>27,28</sup> Genetic differences are one of the factors that may influence the cutoff points.<sup>29</sup>

The physiological rationale for ICP management in patients with TBI is to maintain cerebral oxygenation and ensure adequate cerebral perfusion pressure and cerebral blood flow (CBF) to prevent secondary brain injury.<sup>30</sup> However, whether a correlation exists between ICP and cerebral oxygenation level remains unclear. Pelah et al<sup>17</sup> found a relationship between brain oxygen (PbtO<sub>2</sub>), CBF, and ICP in patients with TBI, which demonstrated that an optimal ICP level is associated with favorable brain oxygenation and improved CBF. However, PbtO<sub>2</sub> requires medical equipment and support from the neurosurgery department, which is not suitable for the prehospital setting. In our study, we used Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> as a method for prehospital monitoring of cerebral oxygenation in patients with TBI. Unlike PbtO<sub>2</sub>, each of the Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> parameters can be quickly obtained from arterial and central venous blood gases in prehospital setting. The physicians in our study were proficient in the technique of arterial and central venous catheter insertion and were able to ensure the accuracy of the results. Furthermore, Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> is largely influenced by cardiac output,<sup>31</sup> and the patients included in our study were mostly in normal cardiac output, with little variability in patients. Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> evolved from the respiratory quotient (RQ) formula, RQ = carbon dioxide production (VCO<sub>2</sub>)/oxygen consumption (VO<sub>2</sub>), which was used to assess the tissue perfusion state and levels of anaerobic metabolism. High ratio suggests increased anaerobic metabolism in the brain tissue.<sup>32,33</sup> Within the first few hours following TBI, cerebral ischemia and hypoxia are associated with an acute increase in oxygen consumption, leading to increased ICP. However, whether Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> reflects the level of ICP remains unclear. This study is one of the few that explores the significance of Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> in the diagnosis of elevated ICP. Our finding demonstrated a significant relationship between ICP and Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> ( $r = 0.70$ ;  $P < 0.01$ ). Using the ROC curve, we identified that the AUC of Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> for evaluating elevated ICP was 0.791. The optimal cutoff point of Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> for predicting elevated ICP was 1.98 mmHg/mL (sensitivity 87.3% and specificity 77.2%). Therefore, our study suggests that Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> can be used to detect ICP levels in patients with TBI. Furthermore, the AUC values were 0.952 for integration of Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> with ONSD (sensitivity is 95.1% and specificity is 93.9%).

Our findings demonstrated that the combination of the two parameters could improve the sensitivity and specificity of the detection in elevated ICP. The BOOST-3 trial<sup>34</sup> showed that, adopting the PbtO<sub>2</sub> plus ICP monitoring model, neurological outcomes were better than those with ICP monitoring alone in patients with TBI. The present study suggests that ONSD combined with Pcv-aCO<sub>2</sub>/Ca-cvO<sub>2</sub> is important for improving the accuracy of elevated ICP diagnosis in patients with TBI, which could help identify the elevated ICP during prehospital setting. These results highlight the importance of multimodal neuromonitoring in the management of TBI patients.

In the future, we will explore whether 30-day survival rates are associated with these parameters and explore the integration of these parameters with cerebral perfusion pressure or end-tidal carbon dioxide to enhance the monitoring of TBI patients. Furthermore, we will investigate these predict complications associated with TBI, including cardiac dysfunction and kidney failure.

There are some limitations to our study. First, the marked variability of ONSD needs to be considered, particularly in the distensibility of ONSD is different in individuals. ONSD may not be able to shrink when the ICP is extremely high (70 mm Hg).<sup>35</sup> It seemed that ONSD cannot be considered as a surrogate for invasive ICP monitoring when ICP is extremely high and may influence the cutoff points of ONSD to detect elevated ICP. For this reason, the TBI patients with extremely high ICP should be excluded to better evaluate the relationship between ONSD and invasive ICP. Second, interobserver variability is an important aspect restricting the widespread adoption of this method. This will yield inconsistent results of ONSD measurement. Therefore, ONSD measurements should be performed by experienced operators, to minimize intraoperator variability. Third, this is a single-center study, not allowing us to generalize our

findings to other settings. Multi-center studies would provide a broader perspective and validate the results across different populations. Fourth,  $P_{cv-aCO_2}/Ca-cvO_2$  is affected by cardiac output. In conditions of high cardiac output, the ratio may be normal.<sup>31</sup> Finally, the external factors such as autoregulation, vessel compliance, and mean arterial pressure (MAP) may influenced on ICP.<sup>36</sup>

## Conclusion

Given the high stakes associated with TBI and the need for timely interventions, our study focus on prehospital settings is particularly relevant. The combinations of both ONSD and  $P_{cv-aCO_2}/Ca-cvO_2$  were effective in predicting the intracranial hypertension with higher sensitivity and specificity than that for either alone. This novel method is critical to monitor and guide treatment in prehospital setting and enhance the ability to detect elevated ICP in patients who are often comatose and difficult to assess in prehospital environments. It could lead to significant changes in how TBI patients are monitored and treated before reaching a hospital, which is highly relevant and can have significant implications for patient outcomes.

## Disclosure

The authors report no conflicts of interest in this work.

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