Noninvasive Evaluation of Intracranial Pressure by Transcranial Doppler Ultrasound in Patients With Traumatic Brain Injury

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Research article

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Abstract

Background

As a noninvasive monitoring measure, transcranial Doppler ultrasound (TCD) has been widely used to monitor the secondary brain injury in patients with traumatic brain injury (TBI). There are different physiological theories on the noninvasive assessment of intracranial pressure by TCD parameters, including ONSD and PI, which may cause that the change of ONSD and PI is not always synchronous with that of ICP. Therefore, the objective of this study was to investigate the relationship between PI or ONSD and ICP at different levels or in different periods after the operation, and the ability of prediction intracranial hypertension with these parameters in patients with TBI.

Methods

The clinical data of 68 patients with TBI were retrospectively analyzed. The statistical correlation analysis was performed to investigate the relationship between the PI or ONSD and ICP one week after the operation. Besides, the area under the curve (AUC) of ONSD or PI alone or a combination of them was calculated to determine the ability of intracranial hypertension.

Results

1. There was a correlation between ONSD and ICP ≥ 20 mmHg (r = 0.665, $p < 0.001$), ICP < 20 mmHg (r = 0.358, $p = 0.006$). The correlation still remained at ONSD ≥ 5 mm (r = 0.644, $p < 0.001$), but no correlation at ONSD < 5 mm ($p = 0.137$). 2. There was a strong correlation between PI and ICP at ICP of 15–20 mmHg (r = 0.705, $p < 0.001$), and ICP ≥ 20 mmHg (r = 0.716, $p < 0.001$). Nevertheless, it revealed a weak correlation at PI < 1.2 (r = 0.271, $p = 0.021$), PI ≥ 1.2 (r = 0.350, $p = 0.020$). In different period after the operation, there was a moderate correlation between ICP and PI on days 3, 4, and 5 (r = 0.508, $p < 0.001$), a strong correlation on days 6 and 7 after the operation (r = 0.645, $p < 0.001$). 3. For prediction intracranial hypertension with PI ≥ 1.2 or ONSD ≥ 5 mm alone or a combination of ONSD ≥ 5 mm and PI ≥ 1.2, the AUC value was 0.729 ($p < 0.001$), 0.900 ($p < 0.001$), and 0.943 ($p < 0.001$), respectively.

Conclusion

The correlation between the parameters of TCD, including ONSD and PI, and invasive ICP vary at different levels of ICP and in different periods in patients with TBI post-operation. It could also allow for a more accurate prediction of elevated intracranial pressure with a combination of ONSD ≥ 5 mm and PI ≥ 1.2.

Background

Invasive intracranial pressure (ICP) monitoring is the gold standard approach for evaluating intracranial pressure in patients with traumatic brain injury (TBI). ICP -directed therapy, which is recommended by the

guidelines for TBI treatment, can reduce the mortality of patients with severe TBI [1, 2]. Due to the number of complications of invasive ICP monitoring, including bleeding, iatrogenic infection, bacteria-free operating environment, and zero drift, its application was limited[3]. As a noninvasive monitoring measure, transcranial Doppler ultrasound (TCD) monitoring may help identify cerebral hypoperfusion in patients with TBI, who lack invasive ICP monitoring in community hospitals, emergency departments, or intensive care units. Target-directed therapy of cerebral blood flow measured by TCD can restore normal cerebral tissue perfusion within a short time, which is conducive to controlling secondary brain insults[4, 5].

The optic nerve sheath is the continuation of the cranial dura mater in the optic canal, which is about 2.2-5.0 mm in healthy adults. Increased ICP and enlarged ONSD are independent risk factors of the mortality in patients with severe TBI [6]. Therefore, ONSD can theoretically reflect the levels of ICP. Currently, there is still a lack of unified ONSD diagnostic criteria for intracranial hypertension, and the correlation between ONSD and ICP at different ICP levels have not yet been studied.

PI is an essential index for evaluating the compliance and elasticity of distal cerebral arterioles resistance, calculated by PI = (peak systolic velocity - end diastolic velocity) / mean flow velocity. PI is considered to keep pace with invasive ICP measurements when cerebrovascular autoregulation is lost [7]. Therefore, the increase of ICP may lead to the rise of cerebrovascular resistance, the progressive increase of PI, and the decrease of cerebral blood flow. However, different clinical research programs and objectives have different conclusions about the relationship between PI and invasive ICP, and the correlation between them at different ICP levels has not yet been studied.

Additionally, there are different physiological theories on the noninvasive assessment of intracranial pressure by TCD parameters, including ONSD and PI, which may cause that the change of ONSD and PI is not always synchronous with that of ICP. Besides, the majority of previous studies were qualitative rather than quantitative in evaluating intracranial pressure by ONSD or PI, which was of limited value in guiding treatment.

Thus, this research aimed to explore the relationship between the TCD parameters and ICP at different levels or in different periods after the operation, and the ability of prediction intracranial hypertension for ONSD or PI alone or a combination of them in patients with TBI during the first post-operative week.

Methods

Study Design and Patient Enrollment

This study retrospectively analyzed the clinical data of 68 patients with TBI treated at the intensive care unit of the Second Affiliated Hospital of Air Force Medical University between January 2018 and April 2019. Patients who presented with closed brain injury, age ≥ 16 years, time from onset to admission ≤ 4 h, craniectomy with invasive ICP monitoring, high-quality image of blood flow spectrum, and optic nerve sheath can be obtained by TCD, and the duration of ICP monitoring ≥ seven days were considered for inclusion. With a history of craniotomy, cerebral ischemic or hemorrhagic stroke, eyeball or optic nerve injury, endovascular

stent implantation for a cephalic and cervical vessel, and open head injury were excluded. The baseline characteristics of the patients are shown in Table 1.

Table 1 Baseline characteristics of the 68 patients with TBI

Characteristic	N(%) or median (IQR)
Total number (n,%)	68（100%）
Male sex (n,%)	46 (67.64%)
Age(y), mean ± SD	46.17 ± 16.87
GCS on admission,mean ± SD	6.59 ± 2.45
Time from onset to admission(h)（Median（P25,P75)	7 (5, 18.50)
Time from admission to operation(h)（Median（P25,P75)	13 (8, 28)
Mechanism of injury(n,%)	
Traffic accident injury	51(75.00%)
Falling injury	13 (19.12%)
Attack injury	4 (5.88%)
Cerebral hernia(n,%)	
Unilateral	25 (36.76%)
Bilateral	6(8.82%)
Cranial CT imaging(n,%)	
Cerebral contusion and laceration	35(51.47%)
Intracerebral hematoma	21(30.88%)
Subdural hematoma	7 (10.29%)
Epidural hematoma	3 (4.41%)
Subarachnoid hemorrhage	5 (7.35%)
Cerebral infarction	4 (5.88%)

Monitoring Protocol

All patients included in the study received neurocritical care management. The operation was performed by an associate chief surgeon with ten years of experience. For the surgery procedure[1], the surgeon removed the extradural hematoma, subdural hematoma, brain contusion during the operation, and the bone flap was removed for the external decompression.

ICP, a parenchymal probe (Codman, REF-826631, Johnson & Johnson Professional Inc., Raynham, MA, USA), was usually placed on the affected side or more severe side of brain injury and monitored continuously for seven days post-operation. When ICP ≥ 20 mmHg, the increase of intracranial pressure should be considered, and the practical strategy should be taken to maintain the ICP < 20 mmHg, CPP 60–70 mmHg.

Three qualified sonographers (all with > 5 years of experience) conducted TCD at least once a day or whenever necessary. The bilateral middle cerebral artery (MCA), through the temporal ultrasound window, was monitored using a portable 2-MHz pulsed TCD device (LOGIQ E9, General Electric Healthcare, Wauwatosa, WI, USA) [8]. Peak systolic velocity, end diastolic velocity, mean flow velocity, and PI were recorded simultaneously. According to these parameters, abnormal cerebral hemodynamics, including cerebral ischemia, hyperemia, and vasospasm, was diagnosed and corrected.

The ONSD measurement method was done as follows: the width of the optic nerve sheath was measured 3 mm behind the optic disc with a 7.5–10 MHz ultrasound probe. Each eye was measured twice, and the average value was taken for further analysis. The width of ONSD was 5.00 mm as the critical value of increasing ICP.

Statistical analysis

SPSS 24.0 (SPSS Inc., Chicago, IL, USA) and MedCalc (MedCalc ver. 19.0.4; MedCalc Inc., Mariakerke, Belgium) was used for statistical analyses. Graphs were constructed via GraphPad Prism Software for Science Version 4.0c (San Diego, CA). Analysis of agreement between the different evaluation methods of intracranial pressure was performed using the Bland-Altman statistical method. Continuous data were presented as means ± standard deviations, while the measurement data with non-normal distribution were expressed by means (P25, P75). The relationship between the two variables was analyzed by correlation analysis, and regression analysis was used to describe the estimation of measurable variables to unmeasurable variables. Multiple linear regression describes the linear relationship between continuous dependent variables and multiple independent variables. The area under the curve (AUC) of single and multiple factors was used to predict the diagnostic sensitivity. The difference between the correlation coefficients or the AUC values were compared using a parametric Z test. Two-sided *p*-values < 0.05 were considered statistically significant.

The research ethics committee of the Second Affiliated Hospital of Air Force Medical University approved this study (Grant number:2018113).

Results

The correlation between ONSD and ICP one week after the operation

In general, ONSD was strongly correlated with ICP during this period (r = 0.679, $p < 0.001$) ((Fig. 1). Furthermore, there was a strong correlation between ONSD and ICP ≥ 20 mmHg (r = 0.665, $p < 0.001$), but a weak correlation between them at ICP < 20 mmHg (r = 0.358, $p = 0.006$); the difference between the two

correlation coefficients was statistically significant (Z = 2.066, $p = 0.039$). Besides, when ONSD was stratified, there was a strong correlation between ICP and ONSD ≥ 5 mm (r = 0.644, $p < 0.001$), but without correlation at ONSD < 5 mm ($p = 0.137$).

The correlation between PI and ICP one week after the operation

Generally, PI was moderately correlated with ICP during this period (r = 0.458, $p < 0.001$) (Fig. 2). Moreover, when ICP was stratified, it revealed no correlation between PI at ICP < 15 mmHg ($p = 0.366$), but a strong correlation at ICP 15–20 mmHg (r = 0.705, $p < 0.001$) and ICP ≥ 20 mmHg (r = 0.716, $p < 0.001$); the difference between the two correlation coefficients was not statistically significant (Z = -0.078, $p = 0.938$). Besides, when PI was stratified, there was a weak correlation between them at PI < 1.2 (r = 0.271, $p = 0.021$), and PI ≥ 1.2 (r = 0.350, $p = 0.020$) respectively; we found no significant differences between these correlation coefficients (Z = -0.440, $p = 0.660$). There was no correlation between ICP and PI on days 1 and 2 after the operation ($p = 0.705$), while a moderate relationship between them was found on days 3, 4, and 5 (r = 0.508, $p = 0.001$), and a strong relationship on days 6 and 7 post-operation (r = 0.645, $p < 0.001$); the difference between the two correlation coefficients was not statistically significant (Z = -0.784, $p = 0.433$).

The ability of ONSD or PI alone or a combination of them to predict intracranial hypertension (ICP ≥ 20 mmHg) one week after the operation

Bland-Altman analysis of agreement between the different evaluation methods of intracranial pressure, there was no specific trend to cause the difference between the two observers (Fig. 3) (Table 2.).

Table 2 Bland-Altman analysis of agreement.

Analysis of agreement	mean difference, mmHg (95%CI)	repeatabilitycoefficient, mmHg (95% CI)	lower limit mmHg(95% CI)	upper limit mmHg(95% CI)	*p*value
ICP_{ONSD} and ICP_{PI}	4.48 (2.41-6.55)	20.75 (18.06-24.39)	-14.43 (-17.98--10.89)	23.39 (19.84-26.94)	0.001
ICP_{ONSD} and ICP_{PI} at intracranialhypertension	-2.58 (-3.46--1.70)	6.45 (5.04-8.97)	-6.67 (-8.19--5.14)	1.50 (-0.02-3.03)	0.001
$ICP_{ONSD+PI}$ and ICP_{ONSD} at intracranialhypertension	-6.85 (-8.00--5.72)	14.58 (11.57-19.72)	-12.62 (-14.59--10.65)	-1.09 (-3.07-0.88)	0.001

For prediction intracranial hypertension with PI ≥ 1.2 or ONSD ≥ 5 mm alone, the AUC value was 0.729 (95%CI: 0.623–0.834, $p < 0.001$) (Fig. 4), and 0.900 (95%CI: 0.831–0.969, $p < 0.001$) ((Fig. 5) respectively; the

difference between the two AUC values was statistically significant (Z = 2.647, $p = 0.008$). Further, a combination of ONSD ≥ 5 mm and PI ≥ 1.2 for predicting intracranial hypertension, the AUC value was 0.943 (95% CI: 0.866-1.000, P < 0.001) (Fig. 6). There was not statistically significant difference between the AUC value of a combination of ONSD ≥ 5 mm and PI ≥ 1.2 and ONSD ≥ 5 mm alone for predicting intracranial hypertension (Z = -0.819, $p = 0.413$).

Discussion

It was believed that the increase of ONSD could quickly and accurately reflect the rise of ICP. Maissan et al.[9] reported that when ICP increased to more than 20 mmHg during tracheotomy in 18 patients with TBI, ONSD rapidly expanded to more than 5 mm. If we consider that the longitudinal measurement of the ONSD width of 5.0 mm is the diagnostic threshold for intracranial hypertension [10, 11], this study found that ICP and ONSD had a strong correlation (r = 0.679, $p < 0.001$) during seven days post-operation. The correlation was stronger at intracranial hypertension than that at normal ICP level (r = 0.665 vs. r = 0.358, $p = 0.039$). Rajajee et al.[12] found that ONSD rapidly increased following the increase of ICP. Nevertheless, when ICP returned to normal levels, the ONSD remained to widen. This study also found a strong correlation between ICP and ONSD ≥ 5 mm (r = 0.644, $p < 0.001$), and no correlation at ONSD < 5 mm ($p = 0.137$). Hence, the higher the intracranial pressure corresponds to a stronger correlation between ONSD and ICP. When the intracranial pressure is decreased, the tension of dura in the cranial cavity is released, but the nerve sheath may still be in the state of expansion. So when the intracranial pressure is reduced or less than 20 mmHg, ONSD may not allow for the accurate evaluation of the ICP for a weak correlation between them. This conclusion suggested that the therapeutic measures based on the decrease of ONSD width might prolong osmotic drug use or other programs for ICP management.

So far, there are different conclusions about the relationship between PI and invasive ICP. Bellner et al.[13] reported that PI was correlated with ICP, when PI > 2.13 or < 1.2, it was deduced ICP > 22 mmHg or < 12 mmHg respectively. Moreover, Prunet et al.[14] found that TCD-PI could accurately and effectively predict intracranial hypertension in patients with TBI: the area under the curve was 0.901, the optimal threshold was 1.35, the sensitivity was 80%, and the specificity was 90%. On the contrary, de Riva et al.[15]argued that TCD-PI could not accurately predict ICP. It was influenced by cerebral perfusion pressure, heart rate, arterial pressure difference, cerebrovascular resistance, cerebral artery compliance, and cerebral vascular autoregulation function. The formula was put forward: $PI = \frac{a1}{CPPm} \times \sqrt{(RaCa)^2 HR^2 2\pi^2 + 1}$ ($a1$ is the pressure difference between systolic and diastolic pressure, *CPPm* mean arterial pressure, *Ra* vascular resistance, *Ca* vascular compliance, *HR* heart rate)[16].

In the present study, we found a moderate correlation between ICP and PI on the whole seven days post-operation (r = 0.458, $p < 0.001$). When the ICP was stratified, there were no significant differences between these correlation coefficients (r = 0.705 vs. r = 0.716, $p = 0.938$). Furthermore, the intensity difference of correlation coefficient between invasive ICP and PI no matter at PI < 1.2 or PI ≥ 1.2 was also no significant differences too (r = 0.271 vs. 0.350, $p = 0.660$). Additionally, the intensity difference of correlation coefficient between ICP and PI at an early stage or a late-stage post-operation was not statistically significant (r = 0.508

vs. r = 0.645, p = 0.433). Therefore, all the findings above mentioned, confirmed that PI should be regarded as a dynamic trend of ICP, rather than an absolute value of ICP. PI is not a pressure indicator, which may be affected by the severity of secondary brain injury, cerebrovascular autoregulation, intracranial pressure, and other factors[15]. So, we should carefully deduce the variation of ICP based on PI parameter in this case, and similarly, it does not mean that the higher intracranial pressure led to the stronger correlation between invasive ICP and PI.

The regression analysis of ONSD and PI evaluation intracranial hypertension was carried out in the present study. It showed that the AUC value of a combination of ONSD ≥ 5 mm and PI ≥ 1.2 for prediction intracranial hypertension was 0.943. Although there was not a statistically significant difference between the AUC value of a combination of ONSD ≥ 5 mm and PI ≥ 1.2 and ONSD ≥ 5 mm alone for predicting intracranial hypertension (p = 0.4119), it was a tendency to enhance the ability to predict intracranial hypertension and helpful for clinicians from qualitative to quantitative assessment of intracranial pressure[17]. Notwithstanding, considering the characteristics of patients and the level of intracranial pressure in this study, we should be comprehensively analysis of the clinical and imaging examination before intervention is taken based on the PI or ONSD.

There are several limitations in the present study that should be pointed out. First, we were not able to overcome the bias of observational research and the small number of patients with TBI included in this study. Second, TCD measurements, including ONSD, were intermittent; invasive parenchymal ICP monitoring was continuous, which may influence the effectiveness of this study. Third, TCD was performed by different physicians, which may lead to variability in performance and differences in data acquisition. Finally, our results showed a different strength correlation between ONSD and TCD-PI with ICP, respectively, which does not suggest that these indicators would replace invasive ICP monitoring in patients with TBI.

Conclusions

The correlation between the parameters of TCD, including ONSD and PI, and invasive ICP vary at different levels of ICP and in different periods in patients with TBI post-operation. Additionally, it could allow for a more accurate prediction of elevated intracranial pressure with a combination of ONSD ≥ 5 mm and PI ≥ 1.2.

Abbreviations

ICP
intracranial pressure; TCD:transcranial Doppler ultrasound; TBI:traumatic brain injury; PI:pulsatility index; ONSD:optic nerve sheath diameter; AUC:area under the curve

Declarations

Acknowledgments

Not applicable.

Author’contributions

Tao Chang collected the data and drafted the manuscript. Yanlong Yang and Zhen Qian revised the language and grammar of the manuscript. Zhen Qian and Qingbao Guo provided the clinical data and searched the literature. Lihong Li conceived and designed the experiments. All authors read and agreed to the final manuscript.

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Availability of data and materials

The datasets used and/or analyzed in the present study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The research ethics committee of the Second Affiliated Hospital of Air Force Medical University approved this study (Grant number:2018113).

Consent for publication

Not applicable.

Competing interests

The authors declare they have no potential conflicts of interest relevant to this research work.

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Figures

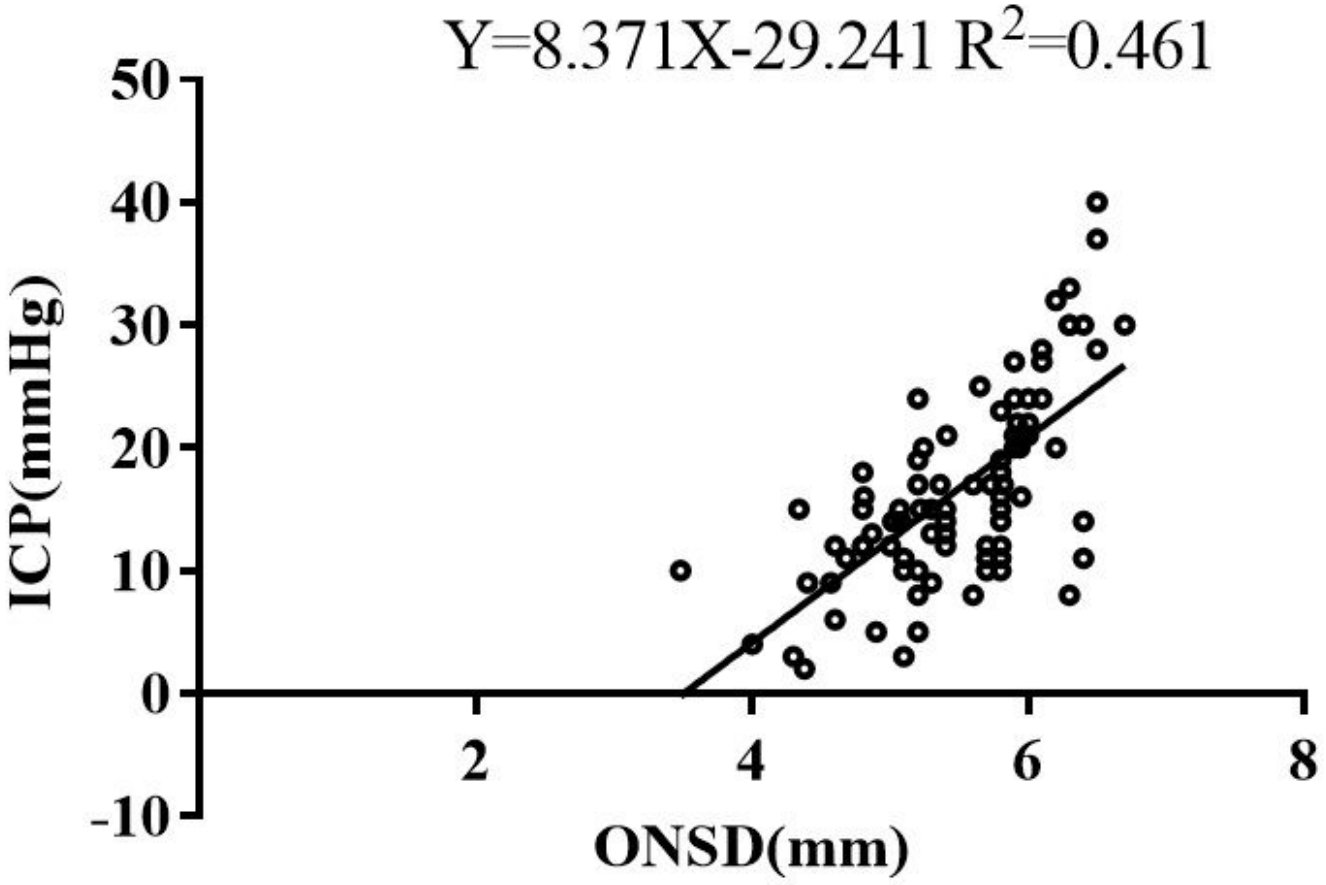

Figure 1

Scatter plots and linear regression between ICP and ONSD.

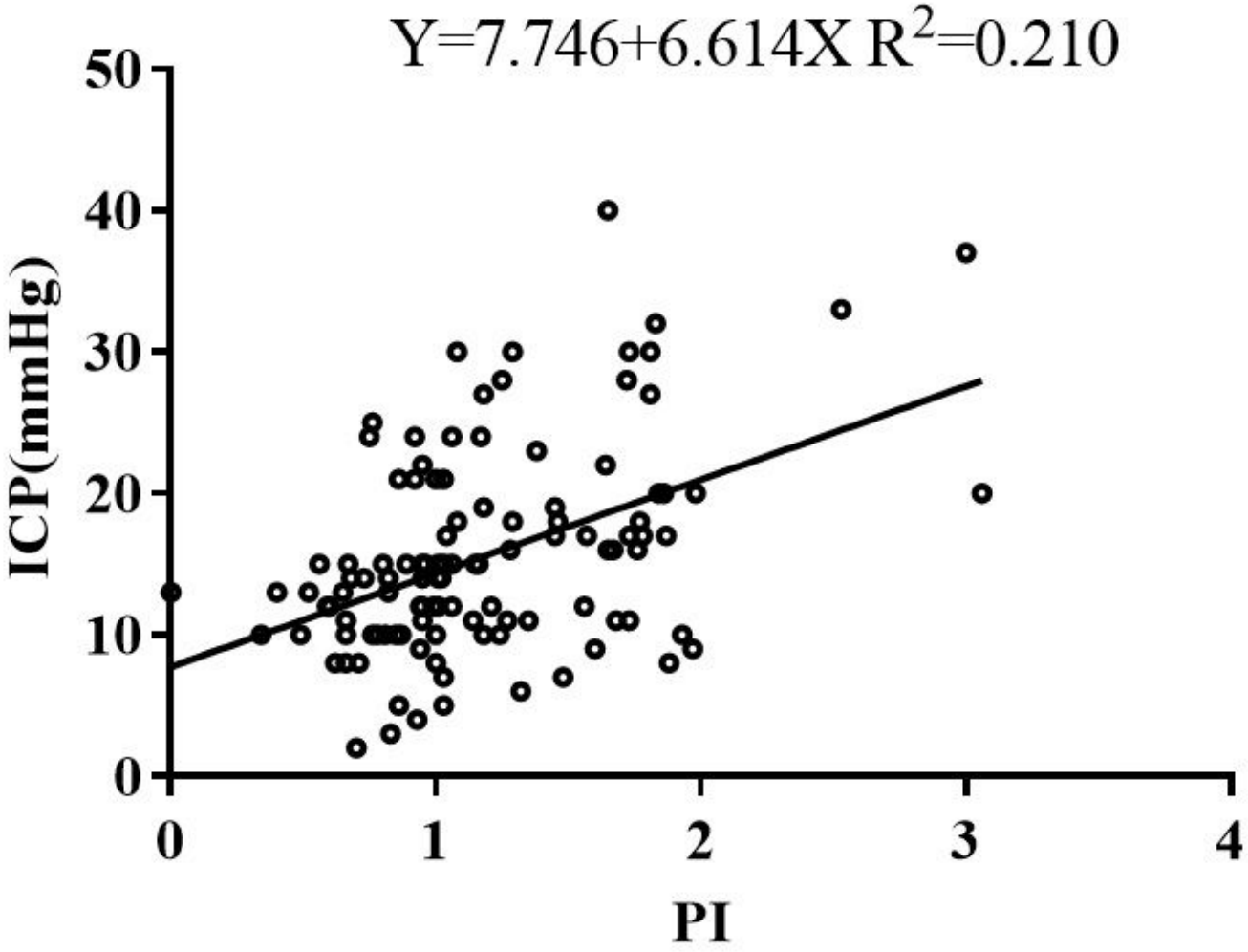

Figure 2

Scatter plots and linear regression between ICP and PI.

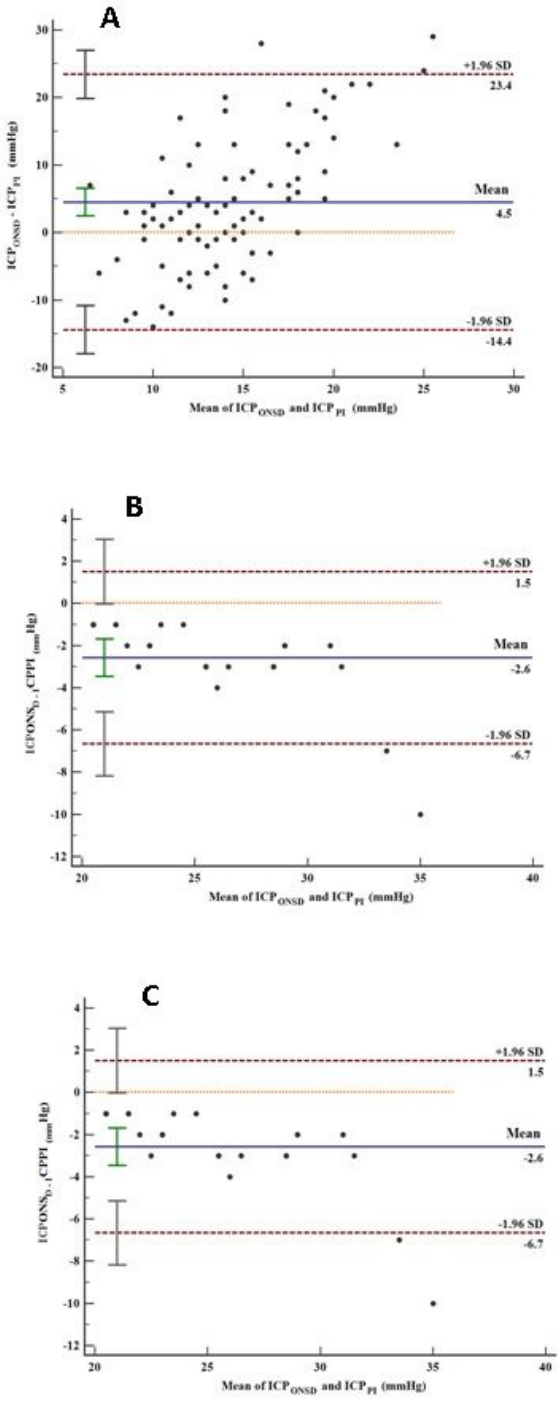

Figure 3

Bland-Altman analysis of agreement (A) intracranial pressure at ONSD ≥ 5mm and PI ≥ 1.2, (B) ICP≥20mmHg at ONSD ≥ 5mm and PI ≥ 1.2, (C) ICP≥20mmHg at a combination of ONSD ≥ 5mm and PI ≥ 1.2 and ONSD ≥ 5mm alone. Red dotted lines indicate 95% limits of agreement (1.96 SD); the solid blue lines in the middle represents the average value of the difference; the orange dashes lines represent the position where the average value of the difference is 0. There was no specific trend to cause the difference between the two observers. Abbreviations: SD, Standard Deviation.

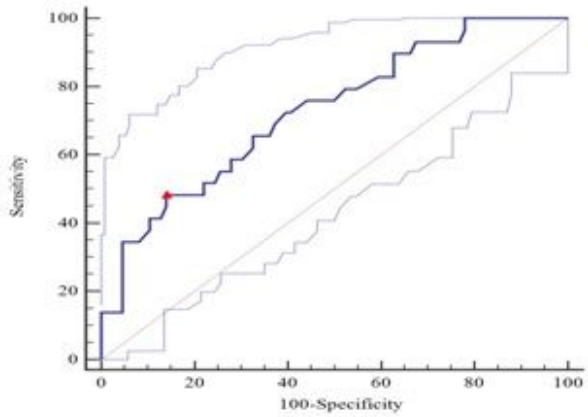

Figure 4

For prediction intracranial hypertension with PI ≥ 1.2, the AUC value was 0.729 (95%CI: 0.637 - 0.807; p < 0.001). Youden's index 0.343, sensitivity 0.483, specificity 0.860. △, the cut-off value corresponding to Youden index. Abbreviations: AUC, area under the curve; PI, pulsatility index.

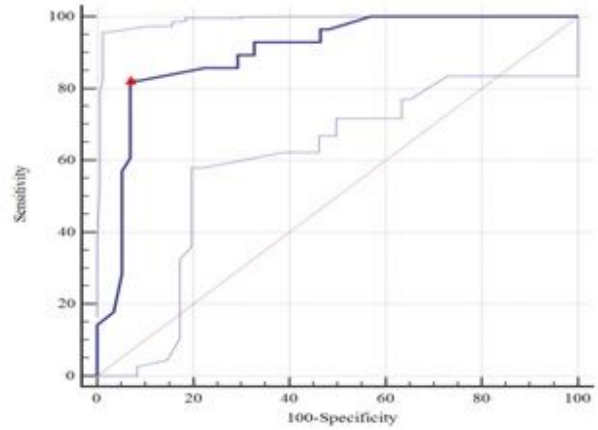

Figure 5

For prediction intracranial hypertension with ONSD ≥ 5mm, the AUC value was 0.900 (95% CI :0.816 - 0.954; p < 0.001). Youden's index 0.752, sensitivity 0.821, specificity 0.931. △, the cut-off value corresponding to Youden index. Abbreviations: AUC, area under the curve; ONSD, optic nerve sheath diameter.

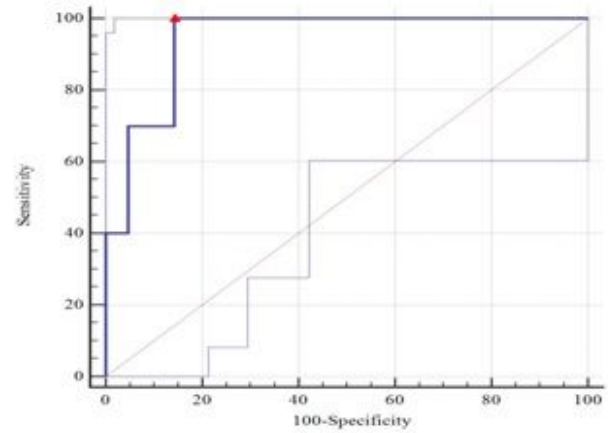

Figure 6

For prediction intracranial hypertension with a combination of ONSD ≥ 5mm and PI ≥ 1.2, the AUC value was 0.943 (95% CI: 0.796 - 0.994; p < 0.001). Youden's index 0.857, sensitivity 1.000, specificity 0.857. △, the cut-off value corresponding to Youden index. Abbreviations: AUC, area under the curve; ONSD, optic nerve sheath diameter; PI, pulsatility index.