Relationship of Optic Nerve Sheath Diameter and Intracranial Hypertension in Patients with Traumatic Brain Injury

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Abstract

Background: to study the association between optic nerve sheath diameter (ONSD) and intracranial pressure (ICP) in patients with moderate-to-severe brain injury. Patients and Methods: A retrospective cohort study of traumatic brain injury (TBI) patients was conducted between 2010 and 2014. Data were analyzed and compared according to the ICP monitoring cutoff values. Outcomes included intracranial hypertension (ICH) and mortality. Results: A total of 167 patients with a mean age of 33 ± 14 years, of them 96 had ICP monitored. ICP values correlated with ONSD measurement (r = 0.21, P = 0.04). Patients who developed ICH were more likely to have higher mean ONSD (P = 0.01) and subarachnoid hemorrhage (SAH) (P = 0.004). Receiver operating curve for ONSD showed a cutoff value of 5.6 mm to detect ICH with sensitivity 72.2% and specificity 50%. Age and ICP were independent predictors of inhospital mortality in multivariate model. Another model with same covariates showed ONSD and SAH to be independent predictors of ICH. Simple linear regression showed a significant association of ONSD with increased ICP (β = 0.21, 95% confidence interval 0.25–5.08, P = 0.004). Patients who developed ICH were more likely to have higher mean ONSD (P = 0.03). Conclusions: ONSD is a simple noninvasive measurement on initial CT in patients with TBI that could be a surrogate for ICP monitoring. However, further studies are warranted.

Keywords: Computed tomography, intracranial pressure, optic nerve sheath diameter, traumatic brain injury

Introduction

Severe traumatic brain injury (TBI) is associated with higher rates of morbidity and death.[1,2] Notably, up to 40% of the severe TBI survivors sustain long-term disabilities and around less than half of patients recover with a favorable neurologic outcome at 1-year period.[3,4] There are several factors that might influence the prognosis of TBI, including age, gender, severity of injury, secondary insults, initial Glasgow Coma Scale (GCS), the motor score, pupil reactivity, type of lesion, and intracranial pressure (ICP).[5,6]

Elevated ICP is an important indicator of the worse outcomes and mortality in patients with severe TBI.[7] Early diagnosis and management of cerebral perfusion have a positive impact on outcomes in TBI patients. However, monitoring of ICP with intraventricular catheter is an invasive procedure which might have risk of infection and technical difficulties.[8] The estimation of optic nerve sheath diameter (ONSD) has been suggested as an effective indirect method in the assessment of ICP.[9,10] Several investigators have identified a strong relationship between ONSD and ICP on ultrasonography.[11-13] However, ultrasonography needs technical expertise for such assessments. Therefore, noninvasive measurement of ICP using ONSD from a readily available computed tomography (CT) scan could be of value in the initial evaluation of TBI patients with suspected intracranial hypertension (ICH).[14-16] To date, only few studies have examined the prognostic implications of ONSD in patients with severe TBI. Therefore, this study aims to evaluate the potential association of ONSD measured by the initial CT scan (first CT head taken on admission of patient to hospital and trauma resuscitation unit) and the invasively

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How to cite this article: Al-Hassani A, Strandvik G, Abayazeed S, Ahmed K, El-Menyar A, Mahmood I, et al. Relationship of optic nerve sheath diameter and intracranial hypertension in patients with traumatic brain injury. J Emerg Trauma Shock 2020;13:183-9.
measured ICP in patients with moderate-to-severe TBI. Furthermore, we aim to find a potential correlation between the initial ONSD values and hospital mortality (i.e., whether the ONSD serves as an initial predictor of poor outcome in the absence of ICP monitoring).

**Patients and Methods**

This is a retrospective chart review of moderate-to-severe TBI patients over the age of 18 years admitted to the Trauma intensive care unit (ICU) at Hamad General Hospital (HGH). Patients who had penetrating head trauma, no initial head CT scan, or significant facial trauma affecting the orbits or orbital cavity were excluded. Data were queried from the trauma registry database over a 5-year period from January 2010 to December 2014. Data included baseline patients’ characteristics, mechanism of injury, and pupillary reactivity. Clinical and laboratory findings, initial vital signs, admission GCS, injury severity score (ISS), and head CT scan findings (such as subarachnoid or intraventricular hemorrhage, basal cistern compression, cortical sulcus effacement, midline shift of more than 5 mm on the initial CT, or herniation). The ONSD on initial CT scan and after 48 h (if available), ICP monitoring, and initial ICP values (within 1 h of CT scanning), neurosurgical intervention, mechanical ventilation, length of hospital and ICU stay, and inhospital mortality were also analyzed. This study follows the STROBE Checklist [Supplementary Table 1].

Moderate-to-severe TBI is defined according to the ATLS (10th edition) as GCS ≤12. The ICU management protocol for patients with severe TBI in our institution is based on the Brain Trauma Foundation guidelines.[17] This protocol aims to minimize the ICP by using a tiered management approach including intravenous sedation, neuromuscular paralysis, osmolar therapy (mannitol and/or hypertonic saline), and hyperventilation. ICP was continuously measured by the ICP monitoring system in selected severely injured patients, low GCS <8, based on neurosurgeon discretion and abnormal CT scan findings (brain edema, midline shift, intracranial hemorrhage). Some patients were not considered suitable for direct ICP monitoring based on the clinical assumption that the head injury was unsalvageable.

For patients who received an ICP monitor, an increase in ICP above 20 mmHg for >5 min without stimulation triggers an active intervention. Invasive intracranial monitoring can detect changes of ICP continuously, and direct measurement techniques may offer therapeutic options such as intraventricular drainage of cerebrospinal fluid (CSF).

Optic nerve sheath is continuous with the meninges of the central nervous system and is encased within the subarachnoid membrane. In the setting of increased ICP and limited intracranial compliance, CSF located in the subarachnoid space accumulates in the optic nerve sheath thereby widening its diameter.[18]

Optic nerve sheath diameter measurement

Three independent radiologists (SN, NA, and ZA) examined all CT scans of the included cases. The radiologists were blinded for the demographics, baseline characteristics, and injury severity. The ONSD was measured from 1.5 mm thick axial sections of the Head CT scan with a Display Field of Vision of 220 mm, displayed on 1024 × 1024 matrix. The pixel size was 0.21 mm. The ONSD was measured 3 mm behind the globe as described by Legrand et al.[15] The measurement was obtained using electronic calipers from one side of the optic nerve sheath to the other at a section through the center of the optic nerve. The ONSD for both the optic nerves was determined in mm and the mean value was calculated for each patient and used for analysis. The protocol was approved by the Institutional Review Board at Hamad Medical Corporation, Doha, Qatar (IRB# 15439/15), and granted a waiver of consent.

**Statistical analysis**

Data were presented as percentage, mean (± standard deviation), median and range, when applicable. Data were analyzed to look for any association between ONSD among ICP-monitored survivors, ICP-monitored deceased, and non-ICP-monitored unsalvageable TBI cases. Comparison between respective groups was performed using Student’s t-test for continuous variables, and Pearson Chi-square test was used to compare proportions for categorical variables. Pearson correlation coefficient was calculated between ICP and ONSD. Receiver operating characteristic curves were used to determine the sensitivity, specificity, and cutoff level of ONSD for the risk of developing ICH (ICP >20 mmHg). Multivariate logistic regression model was performed to identify predictors of inhospital mortality in ICP monitored cases after adjusting for potential covariates. Data were expressed as odds ratios (OR) with the corresponding 95% confidence intervals (95% CI). To specifically link hypertensive ICP and the variation in ONSD, a threshold of ≥20 mmHg was considered to distinguish between ICH and normotension, according to the recommendations of the Trauma Foundation International Guidelines.

Other indicators of ICH were midline shift and mass effect which were noted as confirmation to the change in ONSD to detect elevated ICP. Two multivariate linear regression models were performed to determine the relationship between increased ICP, ONSD, and CT head findings (midline shift and mass effect). A significant difference was considered when the two-tailed P < 0.05. Data analysis was carried out using the Statistical Package for the Social Sciences version 18 (SPSS Inc., Illinois, USA).

**Results**

During the study period, a total of 946 patients sustained TBI which necessitated admission to the Level I trauma center. Of these, 167 patients with moderate-to-severe TBI were included; 96 had neuroinvasive ICP monitoring based on clinical and radiological findings. Seventy-one patients were considered initially “unsalvageable TBI” based on clinical presentation and subsequent CT scan findings (i.e., fixed and dilated pupils, absent brainstem reflexes, devastating CT brain findings). The overall mean age of patients was 32.9 ± 13.9 and 97.6% were...
The frequent mechanism of TBI included motor vehicle crashes (34.7%) and fall from height (23.4%). All patients had their initial brain CT within the first few hours of admission to the hospital. In all patients the ICP device was inserted within 60 (+7) minutes, except for the six patients who had the ICP inserted at the time of surgery approximately more than 60 min from time of initial head CT. Initial ICP values were documented.

Baseline characteristics of the cohort are presented in Table 1.

Twenty-four (14.4%) patients underwent neurosurgical evacuation of intracranial hematoma (a craniotomy for evacuation of space-occupying lesion). The most frequent initial CT scan findings included traumatic subarachnoid hemorrhage (SAH) in (28.7%), subdural hemorrhage (21.0%) and epidural hemorrhage (10.8%), and midline shift (32.3%). The mean ONSD was 5.8 ± 0.8 mm and the mean ICP was 20.3 ± 12.8 mmHg. The median length of ICU and hospital stay were 10 days (1–85) and 13 days (1–211), respectively. The ICU mortality rate among ICP monitor cases was 15.6% (15 patients).

In comparison to ICP-monitored cases, those in non-ICP unsalvageable group were more likely to be older in age and to have higher head AIS, ISS, and higher frequency of midline shift on CT scan (P < 0.05 for all). Table 2 shows characteristics and complications in patients who underwent ICP monitoring.

Nonsurvivors were 4 years older, had significantly lower GCS at emergency department (ED) (P = 0.03), higher mean ICP (P = 0.04), and a trend of frequent ARDS (P = 0.001) as compared to survivors. The two groups did not differ significantly for ISS, frequency of tracheostomies, mean ONSD, mechanical ventilation, and ICU length of stay. There was a weak positive correlation between ICP and ONSD (r = 0.21, P = 0.04). To specifically link hypertensive ICP and variation in ONSD, a threshold of ≥20 mmHg was used to distinguish between ICH and normotension, according to the recommendations of the Trauma Foundation International Guidelines. Other indicators of ICH such as midline shift and mass effect were also noted as useful tools to detect elevations in ICP. Furthermore, Table 3 shows the association between ONSD measurements in patients with ICP less than or greater than 20 mmHg. Patients who developed ICH were more likely to have higher mean ONSD (P = 0.01) and had significantly higher proportion of SAH (P = 0.004) as compared to those who had normal ICP. Figure 1 shows examples of ONSD assessment.

A receiver operating curve (ROC) curve was plotted to assess the prognostic value of ONSD measurement which displayed an area under the curve for the ability to detect elevated ICP (>20 vs. ≤20 mmHg) of 0.65 (95% CI 0.54–0.76). Using a cutoff of 5.6 mm, ONSD had fair performance characteristics with a sensitivity of 72.2% and specificity of 50%.

### Optic nerve sheath diameter and mortality

The overall hospital mortality in ICP monitored cohort was 15.6%.

Figure 2 compares the ONSDs in survivors and nonsurvivors between ICP monitored group as well as non-ICP TBI patients. The mean ONSD did not differ significantly among the study

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Table 1: Overall clinical characteristics and outcomes in intracranial pressure monitored and unsalvageable to-severe brain injury cases

| Characteristic                          | Overall (n=167) | TBI with ICP monitor (n=96) | Non-ICP unsalvageable TBI (n=71) | P      |
|----------------------------------------|----------------|-----------------------------|----------------------------------|--------|
| Age (years), mean±SD                   | 32.9±13.9      | 30.5±13.3                   | 36.2±14.3                        | 0.009  |
| Male, n (%)                            | 163 (97.6)     | 95 (99.0)                   | 68 (95.8)                        | 0.18   |
| GCS ED, mean±SD                        | 4.2±2.6        | 4.5±2.9                     | 3.6±2.1                          | 0.04   |
| Head AIS, mean±SD                      | 4.3±0.9        | 4.0±0.9                     | 4.6±0.9                          | 0.001  |
| ISS, mean±SD                           | 28.9±9.4       | 26.3±8.5                    | 32.5±9.4                         | 0.001  |
| ONSD (mm), mean±SD                     | 5.8±0.82       | 5.7±0.9                     | 5.9±0.65                         | 0.30   |
| ICP (mmHg), mean±SD                    | 20.3±12.8      | 20.3±12.8                   | -                                | -      |
| ICP >20 (mmHg), n (%)                  | 36 (37.5)      | 37.5                        | -                                | -      |
| Pupil reactivity abnormalities, %      | 28.1           | 28.1                        | -                                | -      |
| Midline shift, n (%)                   | 54 (32.3)      | 22 (22.9)                   | 32 (45.1)                        | 0.002  |
| Mass effect, n (%)                     | 123 (73.7)     | 74 (77.1)                   | 49 (69.0)                        | 0.24   |
| Neurosurgical intervention, n (%)      | 24 (14.4)      | 24 (14.4)                   | 0 (0.0)                          | 0.001  |
| Tracheostomy, n (%)                    | 3 (1.8)        | 3 (3.1)                     | 0 (0.0)                          | 0.13   |
| Ventilatory days                       | 7.5 (1-28)     | 11 (1-27)                   | 5 (1-28)                         | 0.001  |
| ICU length of stay                     | 10 (1-85)      | 17 (2-85)                   | 4 (1-74)                         | 0.001  |
| Hospital length of stay                | 13 (1-211)     | 26 (1-211)                  | 4 (1-101)                        | 0.001  |
| Pneumonia, n (%)                       | 68 (40.7)      | 59 (61.5)                   | 9 (12.7)                         | 0.001  |
| Sepsis, n (%)                          | 19 (11.4)      | 16 (16.7)                   | 3 (4.2)                          | 0.01   |
| ARDS, n (%)                            | 7 (4.2)        | 4 (4.2)                     | 3 (4.2)                          | 0.89   |
| Mortality, n (%)                       | 86 (51.5)      | 15 (15.6)                   | 71 (100)                         | 0.001  |

SD: Standard deviation; ISS: Injury severity score; GCS: Glasgow Coma Scale; ED: Emergency department; ONSD: Optic nerve sheath diameter; ICP: Intracranial pressure; ARDS: Acute respiratory distress syndrome; ICU: Intensive care unit; TBI: To-severe brain injury; AIS: Acute ischemic stroke
Table 2: Comparison of injury characteristics and complications among intracranial pressure monitored (n=96) survivors and nonsurvivors

|                          | Survivors (n=81) | Nonsurvivors (n=15) | P    |
|--------------------------|-----------------|---------------------|------|
| Age (years), mean±SD     | 29.8±12.5       | 33.8±17.0           | 0.29 |
| ISS, mean±SD             | 25.8±8.7        | 28.7±6.9            | 0.23 |
| GCS ED, mean±SD          | 4.67±3.0        | 3.60±1.5            | 0.03 |
| Tracheostomy, n (%)      | 3 (3.7)         | 0 (0.0)             | 0.44 |
| Pupil reactivity abnormalities, % | 22.2 | 42.9 | 0.11 |
| SAH, n (%)               | 37 (45.7)       | 9 (60.0)            | 0.30 |
| SDH, n (%)               | 26 (32.1)       | 8 (53.3)            | 0.11 |
| Mid line shift, n (%)    | 16 (19.8)       | 6 (40.0)            | 0.08 |
| Mass effect, n (%)       | 60 (74.1)       | 14 (93.3)           | 0.10 |
| ONSD (mm), mean±SD       | 5.7±0.9         | 6.1±0.8             | 0.17 |
| ICP (mmHg), mean±SD      | 13.9±10.4       | 22.9±15.1           | 0.04 |
| Pneumonia, n (%)         | 52 (64.2)       | 7 (46.7)            | 0.20 |
| ARDS, n (%)              | 1 (1.2)         | 3 (20.0)            | 0.001|
| Sepsis, n (%)            | 14 (17.3)       | 2 (13.3)            | 0.70 |
| Ventilatory days         | 11 (1-25)       | 12 (1-27)           | 0.71 |
| ICU length of stay       | 18 (3-85)       | 14 (2-37)           | 0.19 |
| Hospital length of stay  | 30 (6-211)      | 13.5 (1-27)         | 0.001|

SD: Standard deviation, ISS: Injury severity score, GCS: Glasgow Coma Scale, ED: Emergency department, ONSD: Optic nerve sheath diameter, SAH: Subarachnoid hemorrhage, ICP: Intracranial pressure, SDH: Subdural hematoma, ARDS: Acute respiratory distress syndrome, ICU: Intensive care unit

Table 3: Association between optic nerve sheath diameter and intracranial hypertension (n=96)

|                    | ICP ≤20 (n=36) | ICP >20 (n=50) | P    |
|--------------------|----------------|----------------|------|
| Initial ONSD, mean±SD | 5.58±0.95     | 6.03±0.80      | 0.01 |
| Midline shift, n (%)  | 16 (26.7)     | 6 (16.7)       | 0.26 |
| Mass effect, n (%)    | 44 (73.3)     | 30 (83.3)      | 0.25 |
| Subarachnoid hemorrhage, n (%) | 22 (36.7) | 24 (66.7) | 0.004|
| SDH, n (%)            | 22 (36.7)     | 12 (33.3)      | 0.74 |

ICP: Intracranial pressure, ONSD: Optic nerve sheath diameter, SD: Standard deviation, SDH: Subdural hematoma

Multivariate analysis for predictors of inhospital mortality
Multivariable regression analysis after adjusting for age, admission systolic blood pressure, GCS ED, average ONSD, ICP, and head CT scan findings (midline shift, mass effect, and SAH) showed that age (OR 1.06, 95% CI 1.0–1.12, P=0.04) and ICP (OR 1.09, 95% CI 1.02–1.15, P=0.007) were the independent predictors of inhospital mortality in TBI patients [Table 4]. However, the increased odds of hospital mortality for ONSD (OR 1.32, 95% CI 0.59–2.95, P=0.49) did not reach statistical significance.

Multivariate analysis for predictors of intracranial hypertension
A second regression analysis utilizing the same covariates showed that the average ONSD (OR 1.95, 95% CI 1.10–3.48, P=0.02) and SAH (OR 3.30, 95% CI 1.25–8.65, P=0.01) were independent predictors of ICH after adjusting for relevant covariates [Table 4].

Table 5 demonstrates the linear relationship between ONSD and ICP using the simple (model A) and multivariable (models B) linear regression models. Simple linear regression (model A) demonstrated that ONSD was associated with increased ICP (β=0.21, 95% CI 0.25–5.08, P=0.03). However, the regression coefficient did not change substantially (β=0.22, 95% CI 0.15–5.92, P=0.03) after multivariable adjustment for the CT predictors of increased ICP (Model B) that resulted in a slight increase in R²=0.071. Therefore, no modification of effect measure observed on the relationship between ONSD and ICP by CT predictors of increased ICP.

Figure 1: Example of optic nerve sheath diameter assessment the retrobulbar area was zoomed, ONSD were measured in an axis perpendicular to the optic nerve. The ONSD was measured at a distance of 3 mm behind the eyeball, immediately below the sclera. a: (patient 1), b: (patient 2)

P = 0.02) and SAH (OR 3.30, 95% CI 1.25–8.65, P = 0.01) were independent predictors of ICH after adjusting for relevant covariates [Table 4].

**DISCUSSION**

The present study evaluates the ONSD measured on initial head CT scan in correlation to the initial ICP readings based on invasive ICP monitoring among moderate-to-severe TBI patients. It also evaluates the association between initial ONSD and mortality regardless of the ICP monitoring. In this study, higher ONSD value was found to correlate but weakly with the ICP, and this correlation was evident regardless of CT predictors of increased ICP. Moreover, ONSD and SAH were the independent predictors of ICH. We also observed that age
and elevated ICP were independently associated with in-hospital mortality. Consistent with our findings, increased ICP following severe TBI is a well-recognized phenomenon and is consistently associated with poor outcomes, and this relationship has been widely demonstrated in several studies.\textsuperscript{[10-23]} The placement of an invasive intracranial catheter, either intraparenchymal or intraventricular, allows accurate measurement of ICP and is recommended for the management of patients with a raised intracranial pressure.\textsuperscript{[1,2]} International guidelines for monitoring ICP in TBI patients recommend ICP insertion for all TBI patients with GCS <8.\textsuperscript{[23]} Organizations such as the Brain Trauma Foundation and The American Association of Neurological Surgeons endorsed the placement of an invasive catheter for ICP monitoring as standard of care in managing any patients at risk of ICH, especially in TBI.\textsuperscript{[1,4]} The assessment of risk elevated ICP is often clinical and radiological. A multicenter, controlled trial (BEST: TRIP) of severe TBI reported that the treatment based on invasive ICP monitoring was not found to be superior over noninvasive management using clinical examination and radiological findings.\textsuperscript{[24]} Therefore, ICP monitoring is debatable and might be associated with unfavorable outcomes in severe TBI patients.

Unfortunately, due to the lack of a reliable and reproducible noninvasive technique to measure ICP, use of invasive catheters is likely to continue in monitoring patients with suspected elevated ICP.\textsuperscript{[1]} However, the placement of invasive ICP monitoring devices is not without significant risk of infectious complications and poor functional independence.\textsuperscript{[25]}

The measurement of ONSD has emerged as a viable indirect assessment mode of intracranial pressure. A recent study suggested that bedside ultrasonographic measurement of ONSD is a non-invasive technique with high sensitivity and specificity to detect ICH among traumatic and nontraumatic neurosurgical patients.\textsuperscript{[23]} Moreover, ONSD significantly correlates with increased ICP and even detect immediate changes in ICP.\textsuperscript{[26]} Hence, ONSD measurement may be an invaluable adjunct in the management of TBI patients which may assist in deciding the injury severity and also assist in deciding appropriate management.

Furthermore, initial ONSD measurement might assist in triage of trauma patients, i.e., either to keep the patient at the referring center, or urgent referral to neurosurgery, or even to suggest the neurosurgeon at the referring center to proceed with an urgent craniotomy.\textsuperscript{[1]}

An experimental ultrasound study based on autopsies of the cadaveric donors without neurological injury, demonstrated cutoff values of 6.7 mm of ONSD which correlates well with the increased intracranial pressure.\textsuperscript{[27]} Notably, this study was not performed on trauma patients who have different hemodynamic status. Another case–control study of head trauma

\begin{table}
\centering
\caption{Multivariate logistic regression for the predictors of in-hospital mortality and intracranial hypertension in intracranial pressure-monitored cases}
\begin{tabular}{llllll}
\hline
Variables & \multicolumn{2}{c}{Inhospital mortality} & \multicolumn{2}{c}{Intracranial hypertension} \\
 & OR & 95\% CI & \(P\) & OR & 95\% CI & \(P\) \\
\hline
Age & 1.06 & 1.00-1.12 & 0.04 & 0.98 & 0.94-1.02 & 0.33 \\
SBP ED & 0.99 & 0.97-1.02 & 0.82 & 0.99 & 0.97-1.01 & 0.63 \\
GCS ED & 0.79 & 0.57-1.09 & 0.15 & 0.94 & 0.78-1.12 & 0.49 \\
Average ONSD (mm) & 1.32 & 0.59-2.95 & 0.49 & 1.95 & 1.10-3.48 & 0.02 \\
Midline shift & 2.50 & 0.46-13.46 & 0.28 & 0.34 & 0.09-1.22 & 0.10 \\
Mass effect & 1.91 & 0.18-19.81 & 0.58 & 1.80 & 0.53-6.04 & 0.34 \\
SAH & 1.04 & 0.24-4.39 & 0.95 & 3.30 & 1.25-8.65 & 0.01 \\
ICP (mmHg) & 1.09 & 1.02-1.15 & 0.007 & - & - & - \\
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\caption{Regression comparing two linear models with intracranial pressure as the dependent variable \((n=96)\)}
\begin{tabular}{llll}
\hline
Predictor variable & Model A & Model B \\
\hline
Average ONSD (mm) & \(\beta=0.21\), 95\% CI=0.25-5.08, \(P=0.03\) & \(\beta=0.22\), 95\% CI=0.15-5.92, \(P=0.03\) \\
Midline shift & - & \(\beta=0.107\), 95\% CI=−0.97-3.24, \(P=0.32\) & \\
Mass effect & - & \(\beta=0.14\), 95\% CI=0.01-10.79, \(P=0.17\) & \\
\(R^2\) & 0.047 & 0.071 & \\
Adjusted \(R^2\) & 0.037 & 0.040 & \\
\hline
\end{tabular}
\end{table}
versus non-trauma patients reported significantly higher ONSD values (7.0 ± 0.58) in TBI patients with ICH.[28] In our study, TBI patients who developed ICH were more likely to have higher mean ONSD (6.03 ± 0.80) as compared to normal ICP.

An earlier study has identified an ONSD of 5 mm as a cutoff point for raised ICP-based clinical or radiological findings.[29] As most studies evaluated ONSD on ultrasonography for detection of increased ICP in severe TBI patients, various cutoffs have been proposed ranging between 5.0 and 5.5 mm on ONSD for detecting raised ICP.[19,28,30] A recent prospective observational study by Raffiz and Abdullah[31] demonstrated that an ONSD cutoff of 5.205 mm on ROC analysis showed a high sensitivity and specificity (95.8% and 80.4%, respectively) for raised ICP (>20 mmHg). The authors also found a significant correlation among the ONSD values on sonography and ICP.

Measurement of ONSD on magnetic resonance imaging (MRI) has also been shown to correlate with increased ICP >20 mmHg, with ONSD-MRI cutoffs ranging between 5.5 and 5.8 mm.[15,32] Previous US and MRI studies also established a similar accuracy making the ability to measure ONSD potentially generalizable. However, the benefit of CT is that it is more widely available in trauma patients than MRI, easily reproducible, and does not require the imaging acquisition expertise of ultrasound.[33] Thus, our study has focused on ICP and ONSD-CT.

In terms of the predictive ability of elevated ICP, ONSD-CT in our study, showed a cutoff of 5.6 mm with 72.2% sensitivity and 50% specificity. Similar to our findings, a Canadian retrospective study for ONSD-CT identified a cutoff of 6.0 mm, with high sensitivity (97%), but lower specificity (42%).[34] The authors also demonstrated a linear relationship between ONSD-CT and ICP in patients with TBI and identified that ONSD measured on CT scan was independently associated with ICP and mortality. In addition, a linear relationship existed between ONSD-CT and ICP within the first 48 h of admission, although there was considerable variation around the linear prediction. This relationship persisted even after adjustment for features of increased ICP on CT (basal cistern compression, effacement, midline shift, and intracranial hemorrhage) based on the Rotterdam score.[15] Increased ICP following TBI is a well-recognized phenomenon and consistently associated with a poor outcome.[22,35] Similarly, in our series, age (OR = 1.06) and ICP (OR = 1.09) were found to be the significant independent predictors of inhospital mortality in TBI. Legrand et al.[15] presented a prospective cohort study of 77 patients with severe TBI which demonstrated an association between elevated ONSD on CT scan and mortality.

However, the increased odds of hospital mortality for ONSD measured on admission CT head scan (OR 1.32, \( P = 0.49 \)) did not reach statistical significance in our study. Notably, ONSD-CT was nonsignificantly higher for the nonsurvivors.

Furthermore, studies suggested that ONSD has discriminative potential for ICH in TBI.[36] In our analysis, the average ONSD and SAH were found to be the independent predictor of ICH. Our observations are in agreement with the previous studies, suggesting a significant independent association between ONSD in predicting elevated ICP.[16,37] Earlier studies demonstrated a significant linear relationship between initial ONSD and increased ICP in the first 48 h, suggesting a potential pathophysiological explanation for the relationship between mortality and increased ONSD. In line with these observations, we were able to demonstrate that ONSD was associated with increased ICP. In addition, no modifying effect has been observed on the relationship between ONSD and ICP by CT predictors (midline shift, or mass effect) of increased ICP. There are several limitations to our study. The sample size and retrospective nature of the study increase the risk of measurement bias. The ONSD was measured on the initial CT and the initial ICP readings were done within an hour of this finding. A smaller number of patients had ICP measured perioptatively, which could affect the results. Although findings showed an association between ONSD and ICH, this relationship is dynamic and may fluctuate within minutes as suggested by earlier ultrasound-based studies.[18,35] Thus, a study demonstrating a significant relationship between ICP and ONSD on CT is likely to require simultaneous invasive ICP monitoring during the CT scan, something which did not happen in our study. Importantly, the clinical utility of our findings needs to be interpreted with caution due to the large amount of variability and weakly positive nature of the linear prediction. ICH is a target of active therapy post-TBI to preserve an optimal CPP to provide adequate cerebral oxygen delivery. Thus, it is possible that patients with increased ICP received more active ICP lowering therapies which may not have been captured in our analysis. Unmeasured or residual confounders remain an alternate explanation for our findings, a limitation of all observational studies. The study lacks information on the functional outcomes in patients with TBI which is arguably more important than mortality. Finally, since our study’s inception, all current brain CT scans are being performed in one millimeter slices, enabling easier and more accurate measurement of ONSD.

**Conclusions**

ONSD is a simple noninvasive measurement in patients with moderate-to-severe TBI that has potential prognostic implications for discrimination of ICH. ONSD on initial CT in patients with moderate-to-severe TBI could be a surrogate for ICP. However, further studies are warranted to establish the relationship between ONSD on CT, mortality, and functional outcomes in TBI patients. Examining the changes in ONSD on CT after neurosurgical intervention is needed to establish a temporal relationship in a prospective analysis.

**Acknowledgments**

We would like to thank the National Trauma Registry team in the Trauma Surgery Section, HGH, Qatar.

**Financial support and sponsorship**

Nil.
Conflicts of interest
There are no conflicts of interest.

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## Supplementary Table 1: STROBE statement

| Item number | Recommendation                                                                 | Page number |
|-------------|--------------------------------------------------------------------------------|-------------|
| Title and abstract | (a) Indicate the study’s design with a commonly used term in the title or the abstract | 1           |
| Introduction | (b) Provide in the abstract an informative and balanced summary of what was done and what was found | 1           |
| Background/rationale | Explain the scientific background and rationale for the investigation being reported | 2, 3        |
| Objectives | State specific objectives, including any prespecified hypotheses | 3, 4        |
| Methods | Present key elements of study design early in the paper | 3           |
| Setting | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection | 3, 4        |
| Participants | (a) Give the eligibility criteria, and the sources and methods of selection of participants | 3, 4        |
| Variables | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable | 3, 4        |
| Data sources/measurement | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group | 3, 4        |
| Bias | Describe any efforts to address potential sources of bias | 4           |
| Study size | Explain how the study size was arrived at | 4           |
| Quantitative variables | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why | 4, 5        |
| Statistical methods | (a) Describe all statistical methods, including those used to control for confounding | 4, 5        |
| | (b) Describe any methods used to examine subgroups and interactions | 4           |
| | (c) Explain how missing data were addressed | -           |
| | (d) If applicable, describe analytical methods taking account of sampling strategy | -           |
| | (e) Describe any sensitivity analyses | -           |
| Results | (a) Report numbers of individuals at each stage of study - eg., numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed | 5           |
| | (b) Give reasons for non-participation at each stage | -           |
| | (c) Consider use of a flow diagram | -           |
| Descriptive data | (a) Give characteristics of study participants (eg., demographic, clinical, social) and information on exposures and potential confounders | 5, 6, tables |
| | (b) Indicate number of participants with missing data for each variable of interest | Tables |
| Outcome data | Report numbers of outcome events or summary measures | 7, 8        |
| Main results | (a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (. 95% confidence interval). Make clear which confounders were adjusted for and why they were included | 7, 8        |
| | (b) Report category boundaries when continuous variables were categorized | Tabs |
| | (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period | 7, 8        |
| Other analyses | Report other analyses done-eg., analyses of subgroups and interactions, and sensitivity analyses | Table, figure |
| Discussion | Summarise key results with reference to study objectives | 8-12        |
| Key results | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias | 12          |
| Limitations | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence | 8-12        |
| Interpretation | Discuss the general is ability (external validity) of the study results | 11, 12      |
| General is ability | Other information | Funding | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based | 13          |

An explanation and elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org. *Give information separately for exposed and unexposed groups