Received: 2 June 2022 | Revised: 5 September 2022 | Accepted: 23 September 2022

DOI: 10.1111/jon.13062

JOURNAL OF NEUROIMAGING
THE OFFICIAL JOURNAL OF THE AMERICAN SOCIETY OF NEUROIMAGING
WILEY

TECHNOLOGY UPDATE

Optic nerve sheath diameter in intracranial hypertension: Measurement external or internal of the dura mater?

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Funding information
Stockholm Region Innovations Fund; Angeby Foundation

Abstract

Background and Purpose: Optic nerve sheath diameter (ONSD) is a promising metric to estimate intracranial pressure (ICP). There is no consensus whether ONSD should be measured external (ONSDext) or internal (ONSDint) of the dura mater. Expert opinion favors ONSDint, though without clear evidence to support this. Adjustments of ONSD for eye diameter (ED) and optic nerve diameter (OND) have been suggested to improve precision. We examined the diagnostic accuracy of ONSDext and ONSDint for estimating ICP, unadjusted as well as adjusted for ED and OND.

Methods: We performed an observational cohort study, measuring ONSDext and ONSDint in patients with invasive ICP monitoring at Karolinska University Hospital in Stockholm, Sweden. We used ONSDext and ONSDint unadjusted as well as adjusted for ED and for OND. We compared the area under the receiver operator characteristics curve (AUROC) for these methods. Thresholds for elevated ICP were set at ≥20 and ≥22 mmHg, respectively.

Results: We included 220 measurements from 100 patients. Median ONSDext and ONSDint were significantly different at 6.7 and 5.2 mm ($p = .00$). There was no significant difference in AUROC for predicting elevated ICP between ONSDext and ONSDint (.67 vs. .64, $p = .31$). Adjustment for ED yielded better diagnostic accuracy (AUROC, cutoff, sensitivity, specificity) for ONSDext/ED (.76, .29, .81, .62) and ONSDint/ED (.71, .24, .5, .89).

Conclusions: ONSDext and ONSDint differ significantly and are not interchangeable. However, there were no significant differences in diagnostic accuracy between ONSDext and ONSDint. Adjustment for ED may improve diagnostic accuracy of ONSD.

KEYWORDS
cerebral edema, critical care, intensive care, intracranial pressure, optic nerve sheath diameter, sonography, ultrasound

INTRODUCTION

Elevated intracranial pressure (ICP) is a serious complication to cerebral insults. It is treated aggressively in neurointensive care to avoid secondary ischemic insults. Invasive monitoring of ICP is therefore recommended in current guidelines for treatment of severe traumatic brain injury (TBI). It is also a common modality of monitoring in subarachnoid hemorrhage and large intracerebral hematomas.[1,2] Still,

invasive ICP monitoring is associated with risks, particularly infection and bleeding, and there is a lack of high-level evidence supporting these recommendations.[3,4] Several brain pathologies associated with cerebral edema and elevated ICP are not routinely monitored with invasive ICP measurement. Noninvasive methods to screen for elevated ICP could potentially improve care for many patients. Such techniques could inform decisions on transfer to neurosurgical centers and initiation of invasive ICP monitoring.[5,6]

Sonographic measurement of the optic nerve sheath diameter (ONSD) is among the most well-researched and most promising noninvasive methods of ICP estimation. It shows excellent diagnostic accuracy in many studies.[7] It does, however, have some important limitations. Importantly there is no consensus on whether the ONSD should be measured external (ONSDext) or internal (ONSDint) of the dura mater. Both of these methods have been used in different previous studies. Though several experts recommend ONSDint, there is very little evidence supporting this recommendation.[8] There are only a few previous studies comparing the diagnostic accuracy of these two measurement methods and they are inconclusive.[9,10] A previous study performed by our research group showed a significantly better interrater reliability for ONSDext.[11] Furthermore, intersubject variability in ONSD baseline is another concern. Two suggestions to remedy this are to correct ONSD for eye transverse diameter (ETD), using the formula ONSD/ETD,[12] or to correct for optic nerve diameter (OND), using the formula ONSD – OND.[13] To our knowledge, we have performed the largest observational cohort study yet that estimates diagnostic accuracies in identifying elevated ICP for both ONSDext and ONSDint, with and without corrections for eye diameter (ED) and OND.

METHODS

Patients

We included adult patients, sedated or unconscious and treated with invasive ventilation and invasive ICP monitoring, in the Intensive Care Unit at the Karolinska University Hospital in Stockholm. We excluded all patients with ocular trauma, known ocular disease, or limited ultrasound access to the eyes. Due to the circumstances of the Covid-19 pandemic with a heavy clinical workload, we used a convenience sample. We included all patients eligible and available for a measurement session when an ONSD operator was on duty and available. Enrollment took place between October 2020 and May 2022.

Ethical considerations

The study was conducted in accordance with the Helsinki declaration and was approved by the Swedish Ethical Review Authority, record number 2020–03004. In the studied cohort, it was not feasible to obtain written, informed consent. We informed next of kin about study participation and gave them mandate to withdraw participation on behalf of the patient.

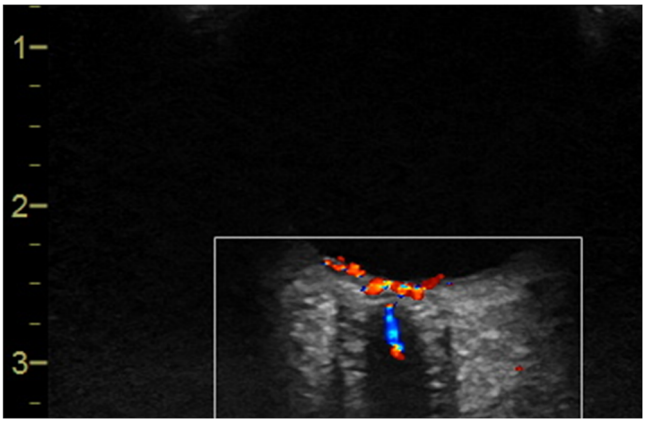

FIGURE 1 Color doppler of retinal artery. Image of ONSD with color doppler of the retinal artery and vein as an aide to identify the nerve and its direction properly. Red represents blood flow upward in the image (artery) and blue represents blood flow downward in the image (vein). Image from Pansell et al.,[11] reproduced under the Creative Commons License (CC BY-NC 4.0)

Data collection

ONSD measurements were gathered by two operators. We used a measurement protocol that yielded excellent inter- and intrarater reliability in a previous study by our research group.[11] We used the General Electrics GE Vivid S70 machine with a linear 11L probe. Power was reduced by 17 dB, which yields a Mechanical Index <0.23. Frequency was set at 10 MHz. These settings yield high-quality images without exposing the eyes to high levels of energy, in accordance with the as low as reasonably achievable principle, and adhere to the American Food and Drug Administration guidelines for ocular ultrasound.[14] We captured short video sequences and removed the probe in between. These video sequences were searched for optimal frames for measurement after image acquisition. We utilized color doppler to identify the central retinal artery and vein, as an aide to properly identify the optic nerve and its direction and to avoid faulty measurement of artefacts (Figure 1). Depth was set at 40 mm and focus at 30 mm. Images were collected from the transversal and the sagittal view for each eye.

ICP was noted at onset of image acquisition. If ICP fluctuated more than ±2 mmHg throughout the image acquisition, the measurement session was aborted. Images were gathered in both the transversal and sagittal views for each eye. Operators were not blinded to ICP during image acquisition. Measurements were performed post-image acquisition with operators blinded to ICP at the time of image acquisition. The ONSD was measured 3 mm behind the retina. We measured ONSDint, ONSDext, and OND in the same images and ED in images separately optimized for this (Figures 2 and 3). For measurement of ED, the largest possible image of the eye was chosen. Due to its spherical form, shadowing at the edges of the eye can occur when using a linear probe (Figure 3A). In our protocol, we use the ellipse tool to estimate ED when it is difficult to visualize the eye completely. This is illustrated in Figure 3B. The ellipse is fitted to the curvature of the retina and

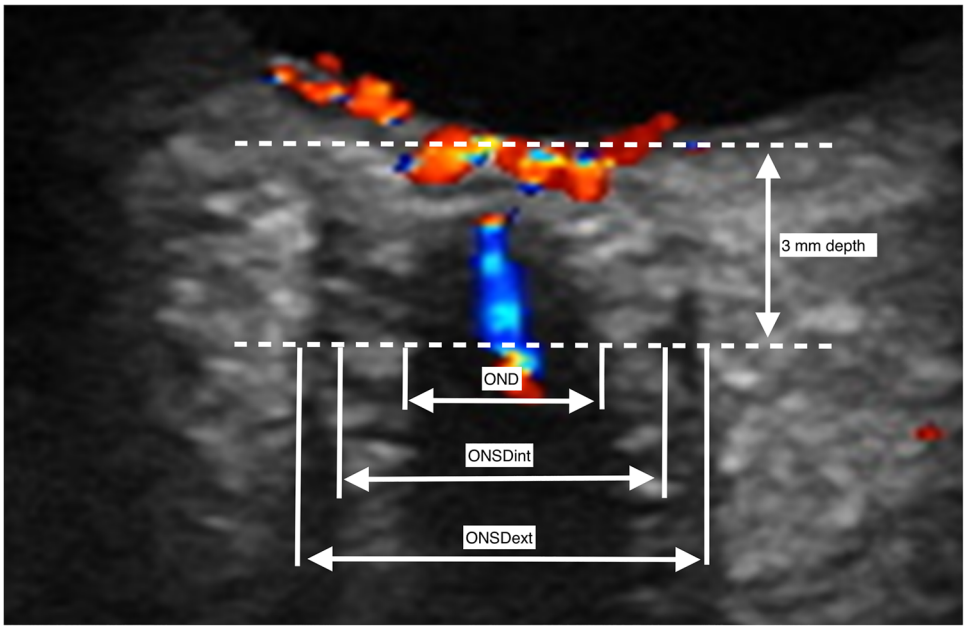

FIGURE 2 Measurement points: All measurements performed at a depth of 3 mm behind the retina. OND, optic nerve diameter; ONSDint, optic nerve sheath diameter internal of the dura mater; ONSDext, optic nerve sheath diameter external of the dura mater. Color doppler shows central retinal artery and vein: red represents blood flow upward in the image (artery) and blue represents blood flow downward in the image (vein). Image from Pansell et al.,[11] reproduced under the Creative Commons License (CC BY-NC 4.0)

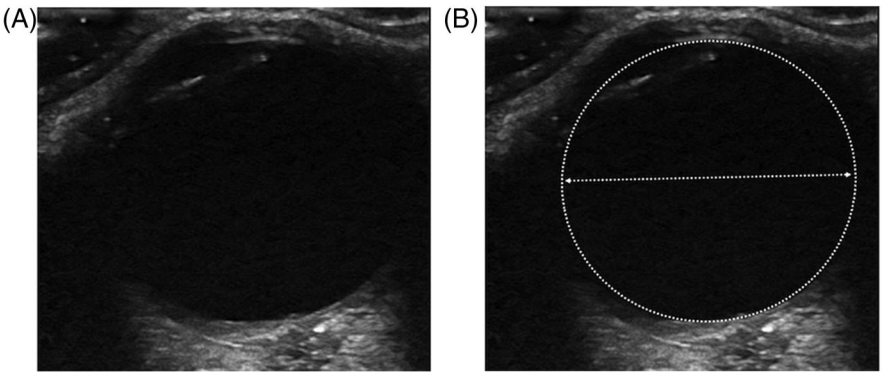

FIGURE 3 Measurement of eye diameter. (A) Image optimized to show the largest possible section of the eye. Due to the spherical shape, there is often shadowing on the sides as shown in this image. (B) Usage of the ellipse tool to estimate eye diameter. The ellipse is adjusted to follow the curvature of the retina as well as the anterior wall of the eye. The diameter of the ellipse is then used as an estimate of the diameter of the eye, assuming a near symmetrically spherical shaped eye.

the anterior wall of the eye. Assuming a near spherical shape of the eye, the ED then is estimated as the diameter of the ellipse. Measurements were performed in both transversal and sagittal views in both eyes. Analyzed measurements are mean values calculated from all four views. Data on age, sex, diagnosis, comorbidities, and treatment were gathered from electronic charts.

Statistical analysis

Correlation between ONSDext and ONSDint was estimated with linear regression. We performed separate receiver operating characteristics (ROC) analyses for elevated ICP with ONSDext, ONSDint, ONSDext/ED, ONSDint/ED, ONSDext – OND, and ONSDint – OND each set as independent variables. Elevated ICP was set as the dependent variable and defined at two different thresholds: at 20 mmHg to comply with most previous studies of ONSD for ICP estimation[7] and at 22 mmHg to comply with more recent TBI guidelines.[2] The ROC analyses were based on a logistic regression analysis with robust standard errors to compensate for the different amounts of data contributed by each patient. Logistic regression analyses were performed twice for each model, for the two different thresholds for elevated ICP. We performed Youden analyses for the optimal cutoff to identify elevated ICP with our respective predictors, and recorded sensitivities

TABLE 1 Descriptive data for the studied cohort

Demographics ($N = 100$)	
Male, *n*/*N* (%)	54
Median age (interquartile range)	57 (43; 65)
Intensive care unit diagnosis	
Subarachnoid hemorrhage, *n*/*N* (%)	41
Traumatic brain injury, *n*/*N* (%)	23
Intracerebral hematoma, *n*/*N* (%)	12
Other, *n*/*N* (%)	24
Modality of ICP monitoring	
Intraventricular, *n*/*N* (%)	71
Intraparenchymal, *n*/*N* (%)	29
Medications	
Propofol infusion, *n*/*N* (%)	78
Opioid infusion, *n*/*N* (%)	81
Midazolam infusion, *n*/*N* (%)	32
Pentothal infusion, *n*/*N* (%)	6
Norepinephrine infusion, *n*/*N* (%)	78
Comorbidities	
Cardiovascular disease, *n*/*N* (%)	10
Asthma/chronic obstructive pulmonary disease, *n*/*N* (%)	8
Diabetes, *n*/*N* (%)	10
Chronic intracranial hypertension, *n*/*N* (%)	4

Note: Descriptive data for the studied cohort.
Abbreviations: *n*, number of patients; *N*, total number of patients.

and specificities at these cutoffs. All analyses were performed in Stata v14.2.

RESULTS

We included 100 patients of which 46 were female. See Table 1 for baseline data of the cohort. We performed a total of 220 measurements with each patient contributing between one and seven measurements. Forty measurements (18.2%) contributed by 29 patients (29%) were performed at ICP ≥20 mmHg. Twenty-six measurements (11.8%) contributed by 18 patients (18%) were performed at ICP ≥22 mmHg. There were missing data on comorbidities in 4 patients (4%).

Median ONSDext and median ONSDint were significantly different at 6.7 mm (interquartile range [IQR] 6.3; 7.1) and 5.2 mm (IQR 4.9; 5.5), respectively ($p = .00$). ONSDext and ONSDint were highly correlated ($R2 = .79$, $p = .00$; Figure 4). With an ICP threshold of ≥20 mmHg, logistic regression yielded an odds ratio (OR) of 2.6 (95% confidence interval: 1.5; 4.8, $p = .00$) for ONSDext and 3.1 (1.2; 7.9, $p = .02$) for ONSDint. With an ICP threshold of ≥22 mmHg, logistic regression yielded an OR of 2.8 (1.4; 5.7, $p = .00$) for ONSDext and a borderline significant OR of 3.2 (1.0; 10.3, $p = .05$) for ONSDint.

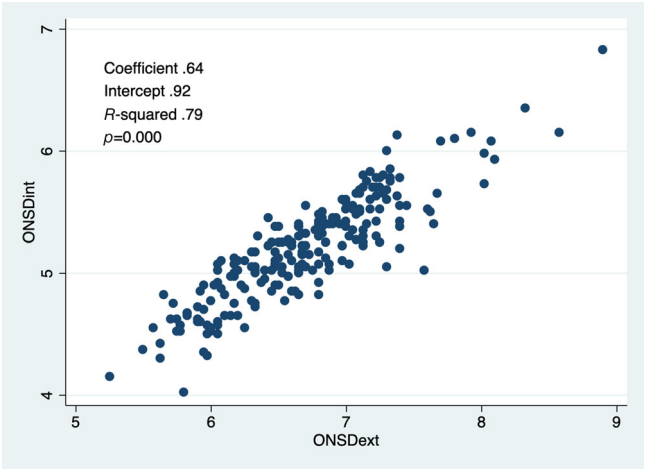

FIGURE 4 Association between ONSDext and ONSDint. Scatter plot of the association between ONSDext and ONSDint. ONSDext, optic nerve sheath diameter measured external of the dura mater; ONSDint, optic nerve sheath diameter measured internal of the dura mater

ONSDext yielded slightly but not significantly better AUROC than ONSDint, at an ICP threshold of 20 mmHg (.67 vs. .64, $p = .35$) as well as at an ICP threshold of 22 mmHg (.67 vs. .64, $p = .31$; Table 2 and Figure 5). Adjustment for ED resulted in significantly better AUROC for ONSDext versus unadjusted ONSDext (AUROC .76 vs. .67, $p = .02$) and a borderline significantly better AUROC for ONSDint versus unadjusted ONSDint, with ICP threshold set at ≥22 mmHg. Adjusting for ED also yielded a nonsignificant trend toward better AUROCs with ICP threshold set at ≥20 mmHg, for both ONSDext and ONSDint (Tables 2 and 3). Optimal cutoffs and corresponding sensitivities and specificities for all predictors, estimated with Youden analyses and at ICP thresholds of ≥20 and ≥22 mmHg, are presented in Table 4.

With ICP threshold set at 22 mmHg, ONSDext/ED yielded an optimal cutoff (Youden) at .29 with sensitivity .81, specificity .62, positive predictive value (PPV) .21, negative predictive value (NPV) .95, and negative likelihood ratio (LR−) .31. ONSDint/ED yielded an optimal cutoff (Youden) at .24 with sensitivity .50, specificity .89, PPV .30, NPV .90, and LR− .56. Figure 6 illustrates predicted probabilities of ICP ≥22 mmHg as a function of ONSDext, ONSDint, ONSDext/ED, and ONSDint/ED, based on logistic regression.

DISCUSSION

This study addresses possible areas of methodological improvement in ONSD sonography for noninvasive assessment of increased ICP. ONSDext/ED and a threshold of ≥22 mmHg for elevated ICP yielded an AUROC of .76 and predicted probabilities of elevated ICP increasing with increasing ONSDext/ED. The very high NPV of .95 alongside a poor PPV corroborates previous findings by Youm et al. that ONSD adjusted for ED primarily is useful as a rule-out tool.[10]

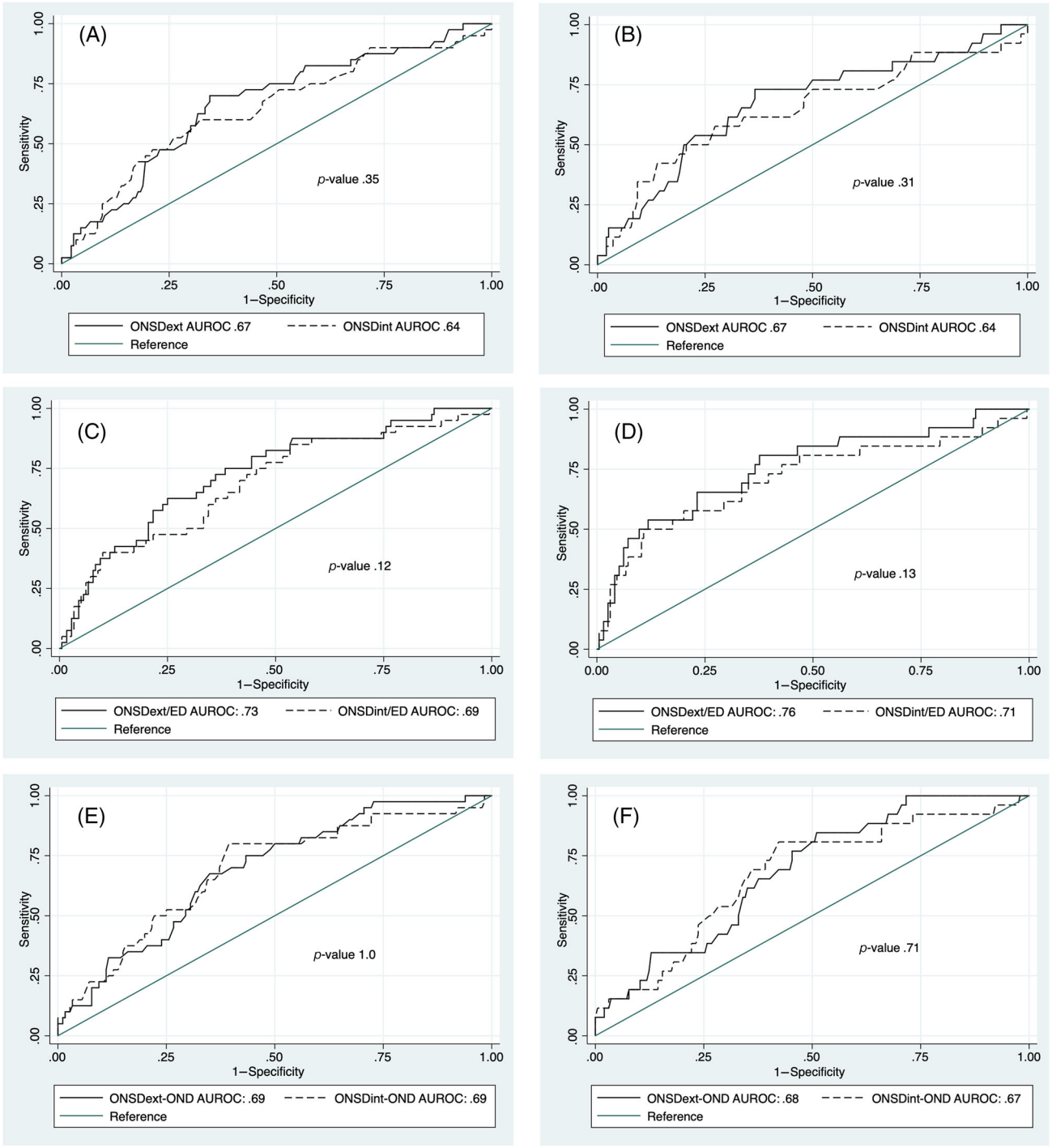

FIGURE 5 AUROC for ONSDext versus ONSDint at an ICP threshold of (A) ≥20 mmHg and (B) ≥22 mmHg. AUROC for ONSDext/ED versus ONSDint/ED at an ICP threshold of (C) ≥20 mmHg and (D) ≥22 mmHg. AUROC for ONSDext – OND versus ONSDint – OND at an ICP threshold of (E) ≥20 mmHg and (F) ≥22 mmHg. ICP, intracranial pressure; AUROC, area under the receiver operator characteristics curve; ONSDext, optic nerve sheath diameter measured external of the dura mater; ONSDint, optic nerve sheath diameter measured internal of the dura mater; ONSDext/ED, optic nerve sheath diameter measured external of the dura mater divided by eye diameter; ONSDint/ED, optic nerve sheath diameter measured internal of the dura mater divided by eye diameter; ONSDext – OND, optic nerve sheath diameter measured external of the dura mater minus optic nerve diameter; ONSDint – OND, optic nerve sheath diameter measured internal of the dura mater minus optic nerve diameter

TABLE 2 Comparison of AUROC for various ONSD measurement methods at different ICP thresholds

	ICP threshold ≥20 mmHg			ICP threshold ≥22 mmHg		
	ONSDext	ONSDint	*p*-value	ONSDext	ONSDint	*p*-value
Unadjusted ONSD	.67	.64	.35	.67	.64	.31
ONSD/ED	.73	.69	.12	.76	.71	.13
ONSD – OND	.69	.69	.99	.68	.67	.71

Abbreviations: AUROC, area under the receiver operator characteristics curve; ICP, intracranial pressure; ONSDext, optic nerve sheath diameter measured external of the dura mater; ONSDint, optic nerve sheath diameter measured internal of the dura mater; ONSD/ED, optic nerve sheath diameter divided by eye diameter; ONSD – OND, optic nerve sheath diameter minus optic nerve diameter.

TABLE 3 Comparison of AUROC for ONSD with/without adjustment for ED, at different ICP thresholds

	ICP threshold ≥20 mmHg			ICP threshold ≥22 mmHg		
	ONSD	ONSD/ED	*p*-value	ONSD	ONSD/ED	*p*-value
ONSDint	.64	.69	.21	.64	.71	.05
ONSDext	.67	.73	.07	.67	.76	.02

Abbreviations: AUROC, area under the receiver operator characteristics curve; ICP, intracranial pressure; ONSDext, optic nerve sheath diameter measured external of the dura mater; ONSDint, optic nerve sheath diameter measured internal of the dura mater; ONSD/ED, optic nerve sheath diameter divided by eye diameter.

There were no significant differences in diagnostic accuracy between unadjusted ONSDext and unadjusted ONSDint at either threshold of ≥20 or ≥22 mmHg. There was a nonsignificant trend toward better AUROC with ONSDext. This trend was consistent through both ICP thresholds and in unadjusted ONSD as well as ONSD adjusted for ED. Our study does not provide conclusive evidence favoring one method over the other and may have been underpowered to answer this question. Still, by showing a significant difference between ONSDext and ONSDint, it shows the importance of standardizing ONSD methodology to one of these methods. Furthermore, the current study suggests that adjustment of ONSD for ED increases diagnostic accuracy.

To our knowledge, this is one of very few studies to compare ONSDext to ONSDint in the same cohort of ICP-monitored patients. One similar previous study included 50 patients and reported an AUROC favoring ONSDext but did not report on statistical significance of this finding.[10] With twice the sample size and data reported on the level of statistical significance, we believe that our study increases the knowledge base necessary to address the unresolved issue of ONSDext versus ONSDint. One other previous study in patients without invasive ICP monitoring and elevated ICP diagnosed by clinical and radiological signs compared diagnostic accuracy of ONSDext compared to ONSDint, showing significantly better AUROC for ONSDext. The majority of patients classified with elevated ICP were brain-dead, while the majority of the controls were healthy test subjects and only a minority of the controls were patients on mechanical ventilation. Therefore, we believe that those results need to be interpreted with caution due to the likely extreme difference in ICP between the healthy subjects and the brain-dead subjects. When the healthy subjects were removed, the difference was nonsignificant.[9]

Our study brings new light to the suggestion of adjusting ONSD for ED or OND. It is previously known that ONSD is associated with ED in healthy subjects.[15] There is a hypothesis that correction of ONSD

TABLE 4 Optimal cutoff according to Youden analysis for all predictors, with ICP thresholds set at ≥20 or ≥22 mmHg

	ICP threshold ≥20 mmHg				ICP threshold ≥22 mmHg			
	Cutoff	Sens	Spec	AUROC	Cutoff	Sens	Spec	AUROC
ONSDext	6.8	.68	.66	.67	6.8	.69	.63	.67
ONSDint	5.3	.60	.68	.64	5.4	.50	.74	.64
ONSDext/ED	0.295	.62	.75	.73	0.289	.81	.62	.76
ONSDint/ED	0.217	.85	.47	.69	0.240	.50	.89	.71
ONSDext – OND	3.8	.68	.65	.69	3.5	.81	.49	.68
ONSDint – OND	2.1	.72	.62	.69	2.1	.73	.60	.67

Note: Optimal cutoff estimated by Youden analyses for all predictors, with ICP thresholds set at ≥20 or ≥22 mmHg.
Abbreviations: AUROC, area under receiver operator curve; ICP, intracranial pressure; ONSDext, optic nerve sheath diameter measured external of the dura mater; ONSDint, optic nerve sheath diameter measured internal of the dura mater; ONSDext/ED, optic nerve sheath diameter measured external of the dura mater divided by eye diameter; ONSDint/ED, optic nerve sheath diameter measured internal of the dura mater divided by eye diameter; ONSDext – OND, optic nerve sheath diameter measured external of the dura mater minus optic nerve diameter; ONSDint – OND, optic nerve sheath diameter measured internal of the dura mater minus optic nerve diameter.

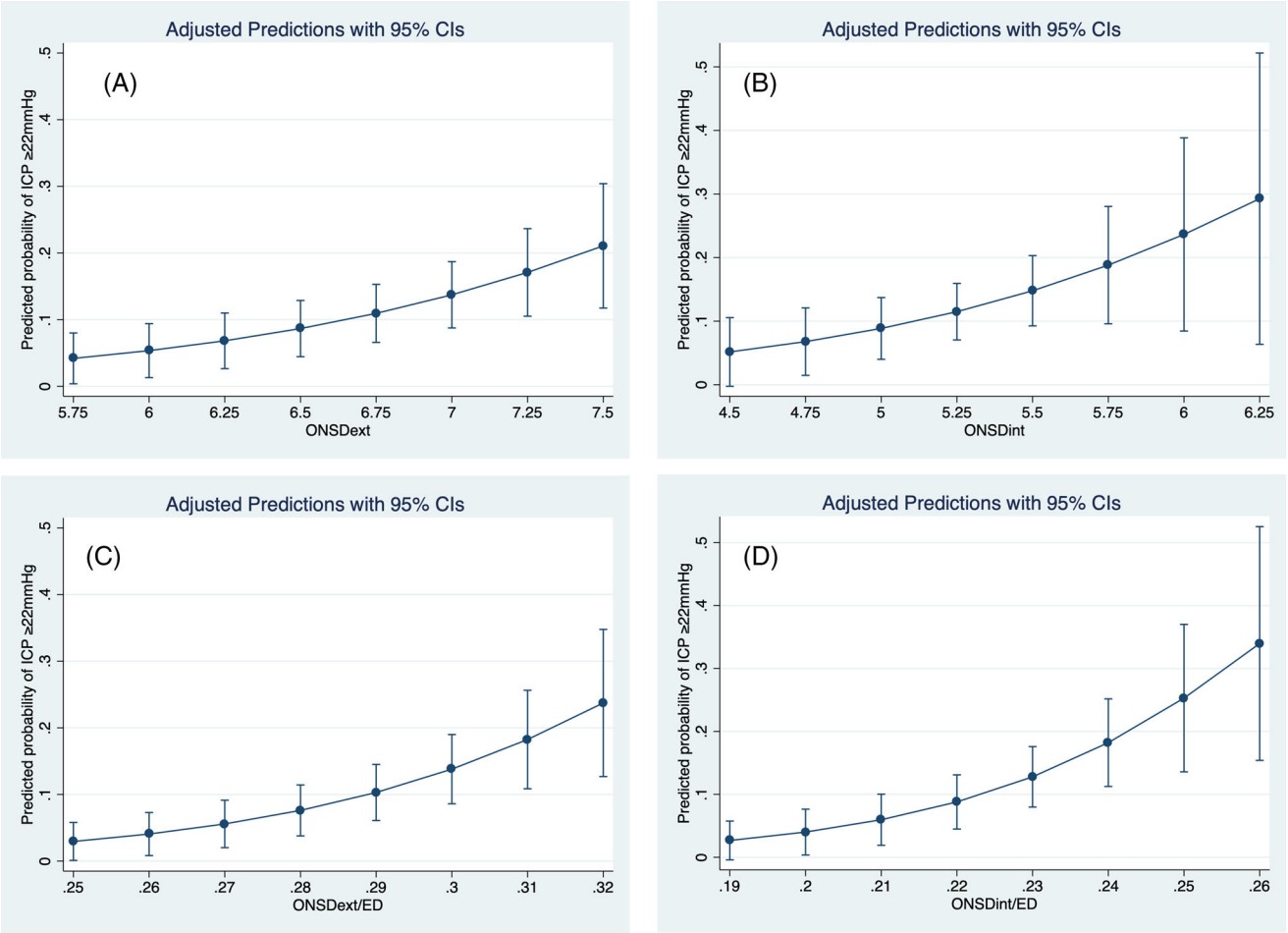

FIGURE 6 Predicted probabilities of ICP ≥22 mmHg as a function of (A) ONSDext, (B) ONSDint, (C) ONSDext/ED, and (D) ONSDint/ED. CI 95%, confidence interval; ICP, intracranial pressure; ONSDext, optic nerve sheath diameter measured external of the dura mater; ONSDint, optic nerve sheath diameter measured internal of the dura mater; ONSDext/ED, optic nerve sheath diameter measured external of the dura mater divided by eye diameter; ONSDint/ED. optic nerve sheath diameter measured internal of the dura mater divided by eye diameter

for ED should adjust for interindividual baseline variability. This has been tested with promising results for ONSD sonography but only in sample sizes of 50 and 52 patients.[10,12] With a larger sample size of 100 patients, our study yielded significantly better AUROC for ONSDext/ED compared to unadjusted ONSDext and a borderline significantly better AUROC for ONSDint/ED compared to unadjusted ONSDint. It should be noted that in our protocol, we measure ED in the transverse as well as the sagittal plane. Therefore, instead of using the previously used acronym ETD (eyeball transverse diameter), we use ED for the average of transverse and sagittal diameter. We could not replicate the promising results achieved by correcting for OND in a previous pilot study.[13]

In comparison to a recent meta-analysis exhibiting a pooled AUROC of .93 for diagnosing elevated ICP with ONSD sonography,[7] our AUROCs are lower. One possible reason for this is that our cohort may be more heterogenous than the cohorts that the AUROCs were pooled from in the meta-analysis. We included patients with a mix of different pathologies with different techniques of ICP monitoring. The Swedish population also is ethnically diverse and ethnicity has been proposed as a factor in interindividual baseline variability of ONSD,[16] possibly adding further heterogeneity to our cohort.

The only two previous studies comparing interrater reliability for ONSDext and ONSDint both reported a higher intraclass correlation for ONSDext.[10,11] In our experience, ONSDext is often more clearly delineated than ONSDint in the sonographic image. If ONSDint is more difficult to measure, and therefore more prone to measurement error, this may explain the better interrater reliability for ONSDext. This may also explain the nonsignificant trend toward better AUROC with ONSDext, and the wider confidence intervals for OR with ONSDint in our current study.

There are several limitations to our study. With the small effect size observed, there may be differences in AUROC that we were not able to detect with a sample size of 100 patients. There is an inherent assumption in our design that ICP is uniform throughout the brain since we used binocular average of ONSD as predictor of ICP. If ONSD changes more rapidly or more profoundly ipsilateral to a lesion, as has been previously shown,[17] this assumption may be questionable. Operators were not blinded to ICP during image acquisition and may have

remembered ICP when performing ONSD measurements on gathered images. The ONSD operators were experienced intensive care unit (ICU) nurses and patients in our ICU are aggressively treated for elevated ICP. This cannot be performed without the operators inferring from the clinical context that the patient has an elevated ICP. We therefore did not believe that blinding during image acquisition could be credibly achieved. We did, however, not perform measurements on the gathered images immediately at the bedside but afterward, without information about ICP at time of image acquisition. Though we cannot rule out that the operator performing the measurements remembered ICP at time of image acquisition, we believe this to be as close to blinding that was achievable during the circumstances.

The lower AUROCs in our study compared to many previous studies warrant discussion. We followed a strict measurement protocol with proven excellent interrater reliability.[11] We believe that the image quality resulting, as displayed in Figures 1 and 2, is very high and we are confident in the internal validity of our study. Still, given the heterogeneity of our material we suggest caution in implementation of cutoffs and indicators of diagnostic accuracy based on this study. We also caution that reported cutoffs are a statistical construct from Youden analyses. The "optimal" cutoff is a matter of clinical judgment, taking into consideration whether sensitivity or specificity is the more important in any given context. We therefore suggest that predictive probabilities of elevated ICP as a function of a given predictor, as exemplified in Figure 6, may be of greater utility than static cutoffs in clinical practice of ICP estimation. There are situations in which it is preferable to underdiagnose and other situations in which it is preferable to overdiagnose. The usage of a single "optimal" cutoff does not allow for this. We therefore believe that predictive probabilities based on continuous predictors can result in better informed clinical decisions, tailored to the specific patient. Still, we would caution the clinician that the predictive probabilities reported are dependent on the pretest probability specific to our cohort. They are likely to differ in another cohort. We also point out that the curve is steeper for ONSDint than for ONSDext, and for ONSDint/ED than for ONSDext/ED. This could be interpreted as though ONSDint and ONSDint/ED have better diagnostic capabilities. It is therefore important to note the much wider confidence intervals associated with ONSDint and ONSDint/ED, suggesting that the clinician should be less confident in predictions based on these measurements. Finally, the excellent NPV for ONSDext/ED at an ICP threshold of ≥22 mmHg is partially dependent on the low 11.8% rate of ICP ≥22 mmHg. The LR− of .31 may be more informative if using ONSDext/ED as a rule-out tool in cohorts with pretest probabilities that are either unknown or differ significantly from ours.

In conclusion, we believe that ONSD adjusted for ED is a reasonably good predictor of elevated ICP. ONSDext and ONSDint did not show significantly different diagnostic accuracies for elevated ICP. There was a nonsignificant trend toward higher diagnostic accuracy for ONSDext but more research is needed. Still, we believe that these results in the light of previous studies[9–11] may provide valuable information to the discussion on whether ONSDext or ONSDint should be the preferred method for ONSD sonography. Finally, the significant difference between ONSDext and ONSDint shows that they are not interchangeable. ONSD sonography is in need of standardization, preferably based on further and larger studies.

ACKNOWLEDGEMENTS AND DISCLOSURES

We would like to thank the following people for their valuable contributions: Andreas Hvarfner, MD; Head of Intensive Care and Neurointensive Care, Karolinska University Hospital Solna; David Nelson, MD, Associate Professor, Karolinska University Hospital Solna; Viveca Hambäck Hellkvist, Intensive Care Specialist Nurse and Research Nurse, Karolinska University Hospital Solna; and Pia Zetterqvist, Intensive Care Specialist Nurse and Research Nurse, Karolinska University Hospital Solna. The authors declare no conflict of interest.

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How to cite this article: Pansell J, Bell M, Rudberg P, Friman O, Cooray C. Optic nerve sheath diameter in intracranial hypertension: Measurement external or internal of the dura mater? J Neuroimaging. 2023;33:58–66.
https://doi.org/10.1111/jon.13062