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Review Article

The role of optic nerve sheath ultrasonography in increased intracranial pressure: A systematic review and meta analysis

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ABSTRACT

Objectives: To review the optimal diagnostic cut-off of ultrasonographic optic nerve sheath diameter (ONSD) in the diagnosis of increased intracranial pressure (IICP).

Methods: A systematic search was conducted of available studies assessing the use of ONSD ultrasonography in patients with suspected IICP. Meta-analysis of diagnostic accuracy of ultrasonographic ONSD was performed using a bivariate model of random effects to summarize pooled sensitivity and specificity. A summary receiver operating characteristics (SROC) curve was plotted. Accuracy measures associated with ONSD cut-off and predefined covariates were investigated with meta-regression.

Results: We included 38 studies, comprising a total of 2824 patients. A total of 21 studies used invasive techniques as a reference standard estimation of IICP and meta-analysis revealed a pooled sensitivity of 0.90 (95% CI 0.85–0.93) and specificity of 0.87 (95% CI 0.80–0.91). Optimal ONSD cut-off values ranged between 4.1 mm and 7.2 mm. Meta-regression analysis showed that ONSD cut-off values of 5.6 to 6.3 mm were associated with higher pooled specificity compared to cut-off values of 4.9 to 5.5 mm (0.93, 95% CI 0.85–0.97 vs. 0.78, 95% CI 0.65–0.87; $p = 0.036$).

Conclusions: Ultrasonography of ONSD shows a high diagnostic accuracy for IICP, with high pooled sensitivity and specificity. Additionally, larger cut-off values seem to significantly increase specificity without compromising sensitivity, which support their use as optimal ONSD cut-off. The overall high sensitivity of ultrasonographic ONSD suggests its usefulness as a screening tool for IIC, which may provide an estimate of when invasive methods are warranted.

Clinical relevance: ONSD ultrasonography is a fast and cost-effective method with a high diagnostic accuracy to detect IICP. The optimum ONSD cut-off hasn't been established before, but we suggest the 5.6 to 6.3 mm range as the best for the diagnosis of IICP.

1. Introduction

Intracranial pressure assessment and monitoring is critical in the management of several neurological and neurosurgical scenarios. Imbalances in central nervous system (CNS) fluid dynamics can result in increased intracranial pressure (IICP) requiring prompt identification and management which impacts clinical outcome [1]. But invasive techniques of intracranial pressure monitoring, including serial lumbar punctures and invasive intracranial pressure monitoring devices, have significant risks, namely postprocedural infection or hemorrhage [2–4]. A reliable non-invasive neuroimaging technique to accurately detect IICP could revolutionize clinical approach to these patients.

Abbreviations: AUC, Area Under the Curve; CI, Confidence Interval; CNS, Central Nervous System; EVD, External Ventricular Drain; IICP, Increased Intracranial Pressure; IPP, Intraparenchymal Probe; LP, Lumbar Puncture; ONSD, Optic Nerve-Sheath Diameter; PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analysis; SROC, Summary Receiver Operating Characteristic; RR, Relative Ratio; TBI, Traumatic Brain Injury.

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The optic nerve-sheath complex is an important CNS structure in the retrobulbar compartment of the orbit, which is continuous with the subarachnoid fluid space, thus allowing the cerebral spinal fluid to extend around these structures [5,6]. Variations in intracranial pressure lead to changes in the CNS fluid space and consequently to changes in the fluid content inside the optic nerve-sheath. Therefore, pressure oscillations may be reflected in the optic nerve-sheath diameter (ONSD) [7].

Ultrasonography of the retrobulbar compartment is an accessible, fast, and low-cost technique that can assess ONSD [8,9]. Previous studies have reported a correlation between ONSD and intracranial pressure [10,11], and several meta-analyses have revealed overall high diagnostic accuracy of ONSD in the diagnosis of IICP [7,12–15]. However, these reviews have generally been focused on the ultrasonographic accuracy and used widely varying ONSD cut-offs without comparing ONSD thresholds and their accuracies [12,14]. One review study suggested an optimum cut-off value of 5.0 mm [7], while other found a CI between 5.6 and 6.1 mm [16]. Overall, optimal ONSD cut-off varies widely across studies [10,17,18], and consensus is still lacking about the optimal threshold to diagnose IICP.

This systematic review of the literature aims to describe the optimal cut-off of the ONSD and its accuracy for the detection of elevated intracranial pressure [11,15].

2. Material and methods

This manuscript was developed according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [19,20]. The review protocol was previously published in the international prospective register of systematic reviews (PROSPERO) [21].

2.1. Search strategy

We systematically searched MEDLINE and CENTRAL from inception (1966 and 1996, respectively) until December 2021. In addition, the reference lists from the identified articles were crosschecked in order to identify any further potentially eligible studies. Studies written in English, Spanish or Portuguese were included.

The research strategy developed for all databases combined the terms intracranial hypertension and ultrasonographic optic nerve sheath diameter. The detailed query included: ([Intracranial Hypertension] OR [Raised Intracranial Pressure] OR [Elevated Intracranial Pressure] OR [Increased Intracranial Pressure] OR [pseudotumor cerebri] OR [Papilledema]) AND ([ONSD] OR [Optic Nerve Sheath Diameter] OR [Optic nerve ultrasound] OR [Optic Nerve Ultrasonography] OR [Ocular Ultrasound] OR [Transorbital Sonography]). A reviewer screened titles and abstracts according to our inclusion and exclusion criteria. A second reviewer will solve unclear abstracts.

2.2. Selection criteria

We selected studies assessing the ultrasonographic ONSD cut-off and its accuracy to diagnose IICP. The study population included patients of any age group and demographic with suspected intracranial hypertension. For review purposes, all reference standard for diagnosis of IICP were accepted for inclusion, namely CT, MRI, lumbar puncture (LP), invasive intraparenchymal probe (IPP) or external ventricular drain (EVD). For the meta-analysis of diagnostic accuracy, only studies that used direct intracranial pressure measurement through invasive techniques (LP, EVD or IPP) were included. Studies with insufficient accuracy data to reconstruct contingency tables were excluded. All study designs, except for case reports and selected case series were included. Full texts review was done by 2 independent reviewers, and any disagreements were resolved through discussion with a third reviewer to reach a final decision.

2.3. Effect measures

The study outcomes were: (1) the diagnostic test accuracy of ONSD ultrasonography for IICP, and (2) the determination of the optimal ONSD cut-off for the diagnosis of IICP in the adult population. Effect measures of diagnostic test accuracy were calculated, namely pooled sensitivity and specificity and diagnostic odds ratio.

2.4. Data extraction

Data was extracted from the individual included reports onto a previously piloted form, containing: (1) study characteristics, including authors, journal, year of publication, study design, setting, inclusion and exclusion criteria, sample size, ultrasonography procedure (probe, sonographer and measurement technique), and reference standard; (2) participant characteristics, including demographics and baseline characteristics; (3) outcome results, namely optimal ONSD cut-off, true and false positives, true and false negatives, and effect measurements of diagnostic accuracy (sensitivity, specificity, likelihood ratios, odds ratio).

2.5. Quality assessment

The Quality Assessment of Diagnostic Accuracy Studies-2 tool [22] was used to evaluate risk of bias, tailored to suit the review question. Signalling questions were used to assess the following domains: patient selection, index test, reference standard and flow and timing. Risk of bias was assessed across each of the 4 domains and applicability across the first 3 domains. A study was rated as having an overall high risk of bias if one or more domains were judged as high-risk.

2.6. Synthesis methods and analysis

Descriptive synthesis of included studies and analysis of main outcome variables was performed. We performed a meta-analysis of the studies using invasive intracranial pressure measurement as a reference standard for IICP. Diagnostic effect measures were obtained from 2×2 contingency tables to calculate sensitivity and specificity, with respective 95% confidence intervals (95% CI). A bivariate random-effects model was used, and forest plots were generated for graphical representation. We constructed summary receiver operating characteristic (SROC) models and calculated the area under the curve (AUC).

We calculated the weighted median of the optimal ONSD cut-offs across the included studies in the adult population and performed a meta-regression of the diagnostic accuracy of ultrasonography to determine the relative ratio (RR) of pooled sensitivity and specificity associated with predefined covariates: ONSD cut-off value (4.9–5.5 mm vs. 5.6–6.3 mm), etiology of suspected IICP (traumatic vs. non-traumatic) and reference standard (invasive vs. non-invasive).

We quantified heterogeneity of the included studies using the inconsistency index (I^2). The presence of publication bias was assessed by analysing funnel plot asymmetry constructed using the Deeks' model [23]. Statistical significance was set at $p < 0.05$. All analysis were performed using Stata version 16.1 (StataCorp LLC, Texas).

3. Results

3.1. Characteristics of selected studies

Database searching identified 1319 records which fulfilled initial keyword searches, of which 38 studies, comprising a total of 2824 patients, were included in this review. The study flowchart, according to PRISMA guidelines, is presented in Fig. 1.

Of the 38 included reports, a total of 21 studies used invasive techniques with direct measurement of intracranial pressure as a reference standard for estimation of IICP. Overall, most studies assessed the

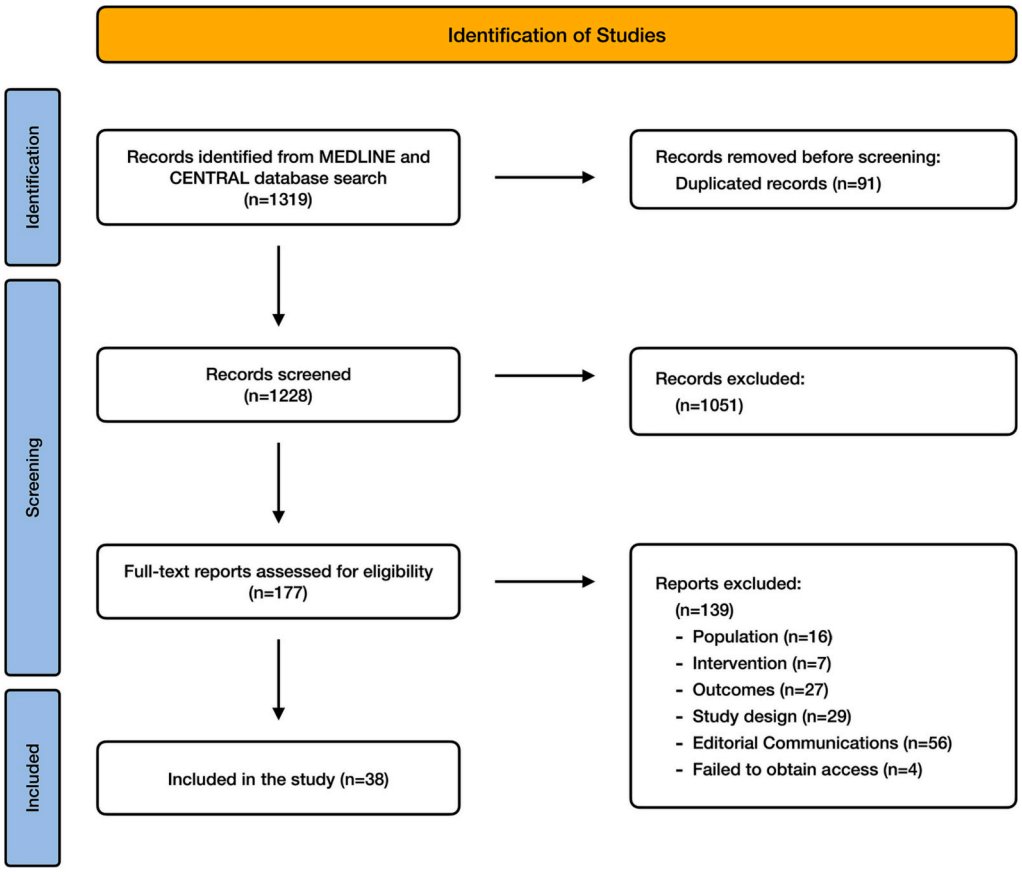

Fig. 1. Flowchart representation of selection process according to PRISMA guidelines.

optimal ONSD cut-off for IICP diagnosis [10,17,18,24–44], however 10 studies used a predefined cut-off of 5 mm [45–54]. There were 4 studies in pediatric population [55–58], of which 2 had invasive monitoring as reference standard for IICP and all calculated the optimal cut-off for detecting IICP. The characteristics of the selected studies, including the optimal ONSD cut-off, ultrasonography technique and reference standard for the diagnosis of IICP, are listed in Table 1. Quality assessment revealed a low risk of bias on 32 studies, with 14 rated as low risk on all domains, and an overall high-risk of bias on 6 studies (1 pediatric). Detailed criteria assessment is available in Supplemental Table 1.

A total of 10 studies included patients with traumatic brain injury (TBI), 16 with non-traumatic and 9 studies had a mixed traumatic and non-traumatic population. The exact distribution could not be assessed, since not every study specified the etiology of suspected IICP for the entire population. However, there were included at least 1154 patients (41%) in whom TBI was suspected to be the cause of IICP. Other etiologies included: (1) intracranial hemorrhage, (2) suspected idiopathic intracranial hypertension, (3) stroke, (4) intracranial infection disorders and (5) brain tumours.

Twenty-one studies comprising 1245 patients (40%) had invasive IPP, EVD or LP as a reference standard. The threshold for IICP diagnosis varied between studies, both in cut-off value and in measurement unit. Most studies ($n = 14$) used mmHg as a reference unit and set a threshold of >20 mmHg. A total of 7 studies used cmH_2O, which was set at >20 cmH_2O, with a single study using >25 cmH_2O. The most common IICP threshold for studies using continuous pressure monitoring devices (IPP or EVD) was >20 mmHg, with one study setting the threshold at >22 mmHg and two studies with EVD reporting in cmH_2O instead of mmHg (Table 1). In 16 studies the reference standard to detect IICP were non-invasive CT or MRI, assessing a total of $n = 1515$ patients (54%).

Ultrasonography for ONSD assessment was homogeneously performed using a linear ultrasound probe, but frequencies varied between studies with 7.5 MHz being the most common. Additionally, there was a wide variation in the sonographers' specialty and training periods. ONSD assessment was performed in most studies ($n = 12$) by emergency medicine physicians, followed by radiologists in 6 studies. Sonographer training varied significantly across studies, from lengths of time of 1 week [50] up to 10 years of neurosonologic experience [10]. Other studies classified training according to number of previous ONSD assessments performed and included training periods as short as 5 examinations [48]. All studies performed axial measurements of the ONSD, occasionally in combination with sagittal or coronal measurements, and usually performed multiple measurements of each optic nerve sheath (Table 1).

3.2. Diagnostic accuracy

Summary estimates of sensitivity and specificity for individual studies are represented in Fig. 2. The pooled sensitivity and specificity for the 21 studies using invasive techniques as reference standard for IICP diagnosis were 0.90 (95% CI 0.85–0.93) and 0.87 (95% CI 0.80–0.91), respectively. Additionally, the positive and negative likelihood ratios were 6.59 (95% CI 4.59–9.46) and 0.11 (95% CI 0.07–0.17), and the diagnostic odds ratio was 59.50 (95% CI 31.88–111.04).

The summary receiver operating characteristic (SROC) curve had an AUC of 0.95 (95% CI 0.92–0.96). The summary estimate of pooled sensitivity and specificity as well as the 95% confidence and prediction regions are represented in the SROC model (Fig. 3).

There was low to moderate among-study heterogeneity according to I^2 (Fig. 2). Funnel plots constructed using the Deeks' model showed no evidence of asymmetry suggestive of publication bias ($p = 0.45$, Fig. 4).

Table 1
Characteristics of the selected studies.

	Study	Year	Study design	Sample size	ONSD cut-off (mm)	Ultrasonography technique (position / plane)	Probe / sonographer's specialty	Etiology of suspected IICP	Reference standard
Studies with direct invasive monitoring of ICP[a]	Geeraerts et al	2007	Prospective	31	5.9	Supine 20° / Axial, Sagittal	Linear 7.5 / Anesthesia	TBI	**IPP (20 mmHg)**
	Geeraerts et al	2008	Prospective	37	5.9	Supine 20° / Axial, Sagittal	Linear 7.5 / Anesthesia	TBI, SAH, ICH, Stroke	**IPP (20 mmHg)**
	Kimberly et al	2008	Prospective	15	5.0	Supine / Axial	Linear 10–5 / Emergency	TBI (27%), ICH (73%)	**EVD (20 cmH_2O)**
	Moretti et al	2009a	Prospective	53	5.2	Supine / Axial, Sagittal	Linear 7.5 / NA	ICH (43%), SAH (57%)	**IPP/EVD (20 mmHg)**
	Moretti et al	2009b	Prospective	63	5.2	Supine 30–45° / Axial, Sag.	Linear 7.5 / NA	Primary ICH (46%), SAH (54%)	**IPP/EVD (20 mmHg)**
	Rajajee et al	2011	Prospective	65	4.8	Supine / Axial	Linear 13–6 / Neurosurgery	SAH, TBI, ICH, Tumour	**IPP/EVD (20 mmHg)**
	Frumin et al	2014	Prospective	27	5.2	Supine / Axial	Linear 5–10 / Emergency	ICH (37%), SAH (33%), TBI (22%)	**EVD (20 mmHg)**
	Nabeta et al	2014	Prospective	66	5.0[b]	Supine / NA	Linear 7.5 / Infectious	Infectious meningitis	**LP (20 cmH_2O)**
	Bolesch et al	2015	Prospective	36	5.7	Supine / Axial	Linear 17–5 / NA	IIH	**LP/EVD (20 cmH_2O)**
	Mehrpour et al	2015	CS	32	5.9	Supine / Axial, Sagittal	Linear 7.5 / Neurology	IIH	**LP (20 mmHg)**
	Wang et al	2015	CS	279	4.1	Supine / Axial, Sagittal	Linear 9–3 / Emergency	Infectious, Stroke, Tumour	**LP (20 cmH_2O)**
	del Saz-Saucedo et al	2016	Prospective	30	6.3	Supine / Axial	Linear 11–4.8 / Neurosonology	IIH	**LP (25 cmH_2O)**
	Irazuzta et al	2016	Prospective	13	4.5[c]	Supine / Axial	Linear 13–6 / Pediatric	IIH	**LP (20 cmH_2O)**
	Jeon et al	2017	Prospective	62	5.6	Supine / Axial	Linear 13 / Neurosurgery	ICH (61%), SAH (21%)	**EVD (20 mmHg)**
	Soliman et al	2018	Prospective	40	6.4	Supine / Axial	Linear 10–20 / Critical	TBI	**IPP (20 mmHg)**
	Agrawal et al	2019	Prospective	20	6.2	Supine 30° / Axial, Coronal	Linear 13–6 / Fellows	SAH (35%), ICH (25%)	**IPP/EVD (20 cmH_2O)**
	Mohson et al	2019	Prospective	40	5.0[b]	Supine / Axial	Linear 12–7.5 / NA	NA	**LP (20 mmHg)**
	Agrawal et al	2020	Prospective	120	7.2	Supine / Axial	Linear 13–6 / NA	TBI	**IPP (22 mmHg)**
	Robba et al	2020	Retrospective	100	5.3	Supine 30° / Axial, Sagittal	Linear 7.5 / Intensive	TBI	**IPP/EVD (20 mmHg)**
	Sharawat et al	2020	Prospective	30	4.0[c]	Supine / Axial, Sagittal	Linear 6–13 / Radiology	Infectious (67%),Metabolic (10%)	**IPP (20 mmHg)**
	Qiao et al	2021	Retrospective	86	4.9	Supine / NA	NA / Emergency	TBI	**IPP/EVD (20 mmHg)**
Studies with non-invasive monitoring of ICP	Blaivas et al	2003	Prospective	35	5.0[b]	Supine / Axial, Sagittal	Linear 10 / Emergency	Intracranial hemorrhage	CT
	Tayal et al	2007	Prospective	59	5.0[b]	Supine / Axial	Linear 7.5 / Emergency	TBI	CT
	Goel et al	2008	Prospective	100	5.0[b]	Supine / Axial, Sagittal	Linear 7.5 / Radiology	TBI	CT
	Le et al	2009	Prospective	64	4.5[c]	Supine / Axial	Linear 8–5 / Emergency	TBI, Infectious, Metabolic	CT/LP/EVD
	Major et al	2011	Prospective	26	5.0[b]	Supine / Axial	Linear 7.5 / Emergency	TBI (54%), Non-TBI (46%)	CT
	Amini et al	2013	Prospective	222	4.9	Supine / Axial	Linear 7.5 / Emergency	TBI	CT
	Qayyum et al	2013	Prospective	24	5.0[b]	Supine / Axial	Linear 7.5 / Emergency	TBI (54%), Tumour (21%),	CT
	Shirodkar et al	2014	Prospective	60	4.7	Supine / Axial	Linear 10 / Radiology	NA	CT/MRI
	Aduayi et al	2015	Prospective	80	5.2	Supine / Axial	Linear 7.5 / Radiology	TBI (56%), Stroke (25%), Tumour	CT
	Golshani et al	2015	Prospective	131	5.0[b]	Supine / Axial	Linear 7.5 / NA	IIH	CT
	Lee et al	2016	Prospective	108	5.5	Supine / Axial, Sagittal	Linear 13–6 / Radiology	ICH (83%), Stroke (10%)	CT/MRI
	Salahuddin et al	2016	Prospective	102	5.7	Supine / Axial	Linear 10–7.5 / Critical	Infectious, Vascular	CT
	Rehman Siddiqui et al	2018	Prospective	48	4.0–4.5[c]	Supine 30° / Axial	Linear 7.5 / Intensive	Infectious (56%), TBI (15%)	CT/MRI

(*continued on next page*)

Table 1 (*continued*)

Study	Year	Study design	Sample size	ONSD cut-off (mm)	Ultrasonography technique (position / plane)	Probe / sonographer's specialty	Etiology of suspected IICP	Reference standard
Naldi et al	2019	Prospective	46	5.6	Supine 30° / Axial	Linear 7.5 / Neurology	ICH	CT
Mathews et al	2020	Prospective	175	5.0[b]	Supine 30° / Axial	Linear 10 / Emergency	TBI	CT
Kaur et al	2021	CS	100	5.0[b]	Supine / Axial	Linear 10–13 / NA	TBI	CT
Kim et al	2021	Prospective	199	5.3	Supine / Axial	Linear 4–12 / Emergency	NA	CT

CS: cross-sectional study; EVD: external ventricular drain; ICH: intracranial hemorrhage; ICP: intracranial pressure; IICP: increased intracranial pressure; IIH: idiopathic intracranial hypertension; IPP: invasive intraparenchymal probe; LP: lumbar puncture; NA: not available; ONSD: optic nerve sheath diameter; SAH: subarachnoid hemorrhage; TBI: traumatic brain injury.

[a] Studies with direct invasive monitoring of ICP as reference standard (highlighted). Only these studies were included in the meta-analysis of diagnostic accuracy.

[b] Study with predefined ONSD cut-off of 5.0 mm for diagnosis of IICP. Excluded from optimal ONSD analysis.

[c] Study in pediatric population. Excluded from optimal ONSD analysis.

3.3. ONSD measurements and optimal cut-off

Individual optimal ONSD cut-offs were calculated from receiver operating characteristic (ROC) curve analysis in 24 studies in the adult population (4 studies in pediatric population were excluded from this analysis). In the adult population, the weighted median was 5.3 mm (interquartile range: 4.9–5.6 mm and 10–90 percentile range: 4.1–6.3 mm). The minimal optimal ONSD cut-off identified was 4.1 mm, in a large Asian cohort with mixed traumatic and non-traumatic disorders and using LP as reference standard for IICP. The maximum ONSD cut-off was 7.2 mm in a study of patients with traumatic brain injury and using IPP with threshold of 22 mmHg as a reference standard for IICP.

Summary estimates of ultrasonographic ONSD associated with cut-off values within the 75–90 percentile range (5.6–6.3 mm) compared to cut-off values within the 25–75 percentile range (4.9–5.5 mm) revealed a similar pooled sensitivity (4.9–5.5 mm: 0.87 vs. 5.6–6.3 mm: 0.89) and a higher pooled specificity in studies with larger cut-off values (4.9–5.5 mm: 0.82 vs. 5.6–6.3 mm: 0.89, Fig. 5a). The SROC curves stratified by ONSD cut-off (Fig. 5b) showed a higher AUC in the 5.6–6.3 mm cut-off range (0.95, 95% CI 0.93–0.97) compared to the 4.9–5.5 mm cut-off (0.93, 95% CI 0.90–0.95).

3.4. Meta-regression and optimal ONSD cut-off

A meta-regression analysis to estimate the relative sensitivity and specificity of IICP diagnosis associated with ONSD cut-off and adjusting

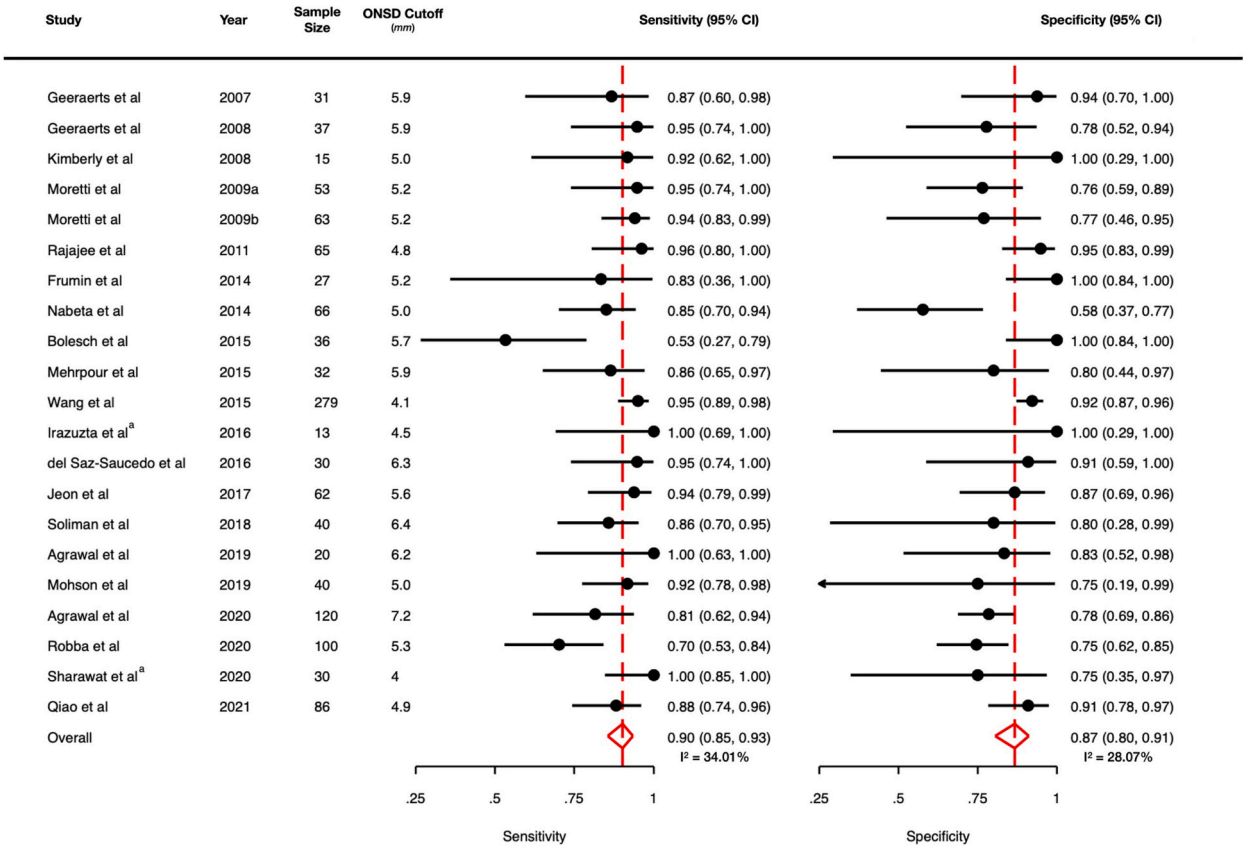

Fig. 2. Forest plot of pooled sensitivity and specificity of ultrasonographic ONSD for diagnosis of IICP.
[a]Study in pediatric population.
IICP: increased intracranial pressure; ONSD: optic nerve sheath diameter.

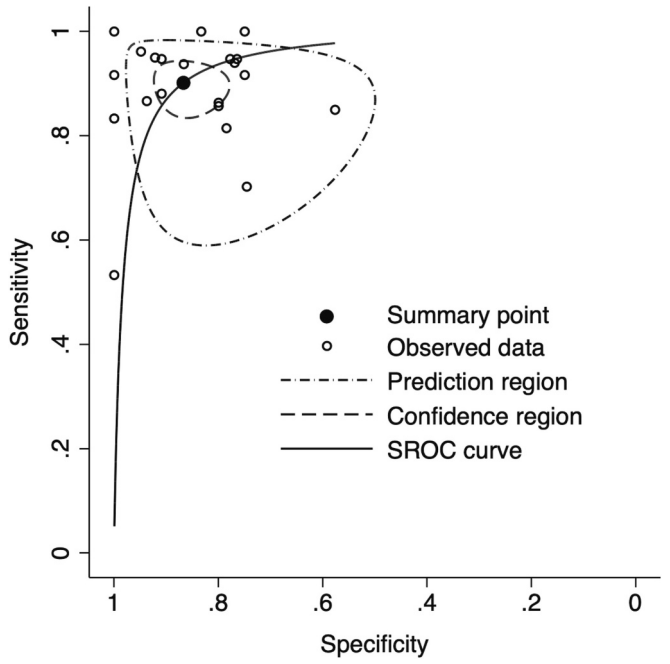

Fig. 3. Summary receiver operating characteristic curve of the diagnostic performance of ultrasonographic ONSD.
Summary receiver operating characteristic (SROC) curve. Each hollow point represents the sensitivity and specificity for the corresponding study. The black circle represents the summary point showing a pooled sensitivity of 90% (95% Cl, 85% to 93%) and specificity of 87% (CI, 80% to 91%). The summary point is surrounded by a dashed line representing the 95% confidence region, The 95% prediction region is represented by the dotted and dashed line. ONSD: optic nerve sheath diameter; SROC: summary receiver operating characteristic.

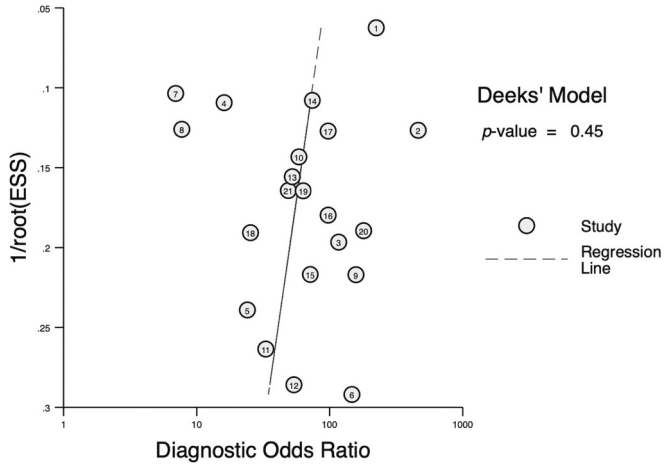

Fig. 4. Funnel plot asymmetry test for publication bias using Deek's model.

for etiology and reference standard was performed (Table 2). Ultrasonographic ONSD accuracy was independently associated with the ONSD cut-off and reference standard.

Studies with ONSD cut-off of 5.6–6.3 mm had a significantly higher specificity than studies with ONSD cut-off of 4.9–5.5 mm (0.93, 95% CI 0.85–0.97 vs. 0.78, 95% CI 0.65–0.87; $p = 0.036$). Similar pooled sensitivity was found across ONSD cut-off values.

Non-invasive studies had a higher sensitivity for IICP diagnosis than invasive studies (0.97, 95% CI 0.94–0.99 vs. 0.87, 95% CI 0.78–0.93; $p = 0.014$). Also, studies including patients with traumatic brain injury had lower pooled specificity for IICP diagnosis than studies with non-traumatic patients, however this association did not reach statistical significance (0.79, 95% CI 0.65–0.88 vs. 0.93, 95% CI 0.85–0.97; $p = 0.050$).

4. Discussion

Our findings demonstrate that ONSD ultrasonography is an accurate diagnostic tool for the detection of IICP, with a pooled sensitivity and specificity of 0.90 (95% CI 0.85–0.93) and 0.87 (95% CI 0.80–0.91), respectively. Additionally, this is the first review describing an independent association of cut-off values in the adult population with the diagnostic accuracy of ultrasonographic ONSD. Larger cut-off values of 5.6 to 6.3 mm were associated with higher pooled specificity (0.93, 95% CI 0.85–0.97 vs. 0.78, 95% CI 0.65–0.87; $p = 0.036$) compared to smaller cut-off values of 4.9 to 5.5 mm, while pooled sensitivity was similar across both cut-off values.

Two previous meta-analyses including a small number of studies found a pooled sensitivity of 0.90 and a specificity of 0.85 [12,13]. One large scale review assessing all non-invasive imaging methods for IICP diagnosis found similar sensitivity and specificity but concluded that a unified ONSD cut-off is missing [15]. Finally, a review of ultrasonographic ONSD including a larger number of heterogeneous studies in adult and pediatric population found a sensitivity of 0.97 in patients with traumatic brain injury and 0.92 in patients with non-traumatic brain injury [7]. Overall, previous reviews have similarly reported an overall high sensitivity and specificity of ultrasonographic ONSD for the detection of IICP in patients with suspected IICP, however no significant association of ONSD cut-off with the diagnostic accuracy was previously reported [12–15].

Optimal ONSD cut-off values reported in the literature are heterogeneous and no consensus exists about the definitive ONSD to diagnose IICP [16]. In our review, 10 studies used a predefined 5.0 mm as the optimal cut-off [45–54], and the remaining found a wide range of optimal cut-off values extending from 4.1 mm to 7.2 mm [17,31]. Despite ONSD ultrasonography high sensitivity and specificity, the lack of a consistent and narrow ONSD range to diagnose IICP may limit its clinical application. One previous meta-analysis reported an optimal ONSD cut-off value of 5.0 mm, however pediatric studies were included in the cut-off estimation which may have underestimated the cut-off value [7]. Additionally, 5.0 mm is often considered to be within the normal ONSD range in healthy individuals [59,60]. A recent review and meta-analysis found 5.82 mm (95% CI 5.58–6.06 mm) as the mean ONSD for IICP detection, however no diagnostic accuracy tests were conducted [16]. Our meta-regression analysis in the adult population describes a previously unreported finding that ONSD cut-off values of 5.6–6.3 mm are more specific for the diagnosis of IICP compared to smaller values of 4.9–5.5 mm, which is consistent with the previously reported mean ONSD values [16].

There was considerable heterogeneity between studies which used invasive and non-invasive reference standards, assessing direct intracranial pressure and indirect IICP signs, respectively. Our review methodology accounted for these potential differences by only including, in the meta-analysis, studies with direct invasive measurement of intracranial pressure. However, invasive techniques also varied between studies and used different thresholds for IICP, ranging from 20 cmH_20 (≈15 mmHg [54]) to 22 mmHg. Current guidelines set IICP diagnosis threshold at 20–22 mmHg [54–56], which is higher than most of the included studies and may result in underestimation of the ONSD for IICP diagnosis. The variability in intracranial pressures thresholds may justify the wide range optimal cut-off values identified. The etiology of suspected IICP was also a source of heterogeneity between studies, with both traumatic and non-traumatic patients being included. To mitigate this, we explored this heterogeneity in a meta-regression model adjusted for ONSD cut-off, etiology, and reference standard, which revealed that studies using non-invasive techniques had higher sensitivity than studies using invasive techniques, which could be explained by the overlap of non-invasive techniques with

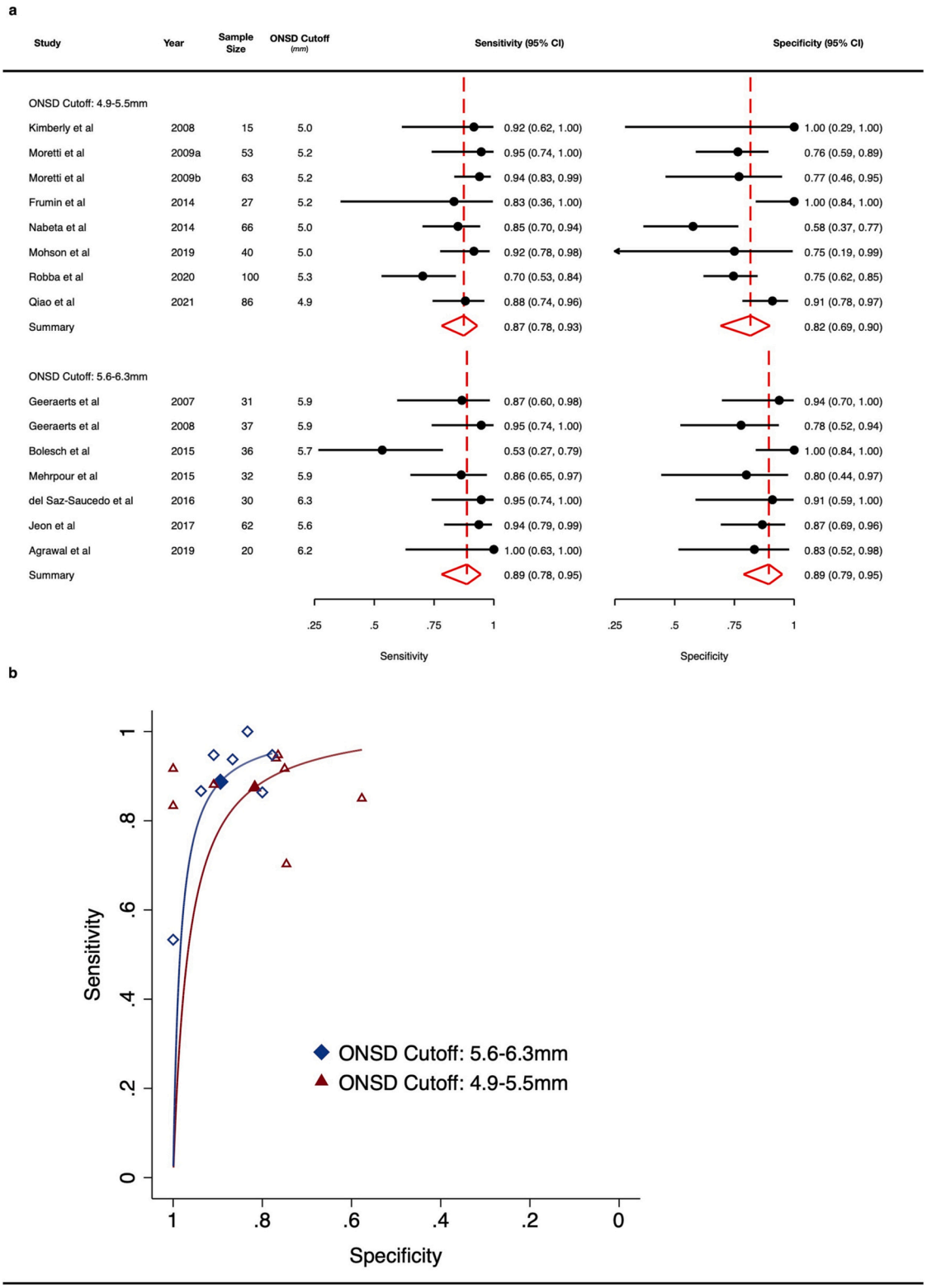

Fig. 5. Forest plot and SROC curve of sensitivity and specificity for the diagnosis of IICP by ONSD cut-off.
(a). Forest plot of sensitivity and specificity of ultrasonographic ONSD in the diagnosis of IICP. Comparison of ONSD cut-offs (4.9–5.5 mm vs. 5.6–6.3 mm).
(b) SROC curve showing a pooled sensitivity and specificity for IICP diagnosis across ONSD cut-off.
IICP: increased intracranial pressure; ONSD: optic nerve sheath diameter; SROC: summary receiver operating characteristic.

ultrasonography, given that increased ONSD is one of the indirect IICP signs in CT and MRI [61,62], which themselves have a reduced sensitivity and specificity compared to invasive techniques in the diagnosis of IICP [15]. Also, the meta-regression model also showed a higher specificity for IICP in studies with traumatic brain injury compared to non-traumatic etiologies, which did not reach statistical significance,

Table 2
Meta-regression analysis of ultrasonographic ONSD for IICP diagnosis.

	Summary estimates					
	Sensitivity (95% CI)	Relative ratio	*p*-value	Specificity (95% CI)	Relative ratio	*p*-value
ONSD Cut-off						
4.9–5.5 mm	0.95 (0.90–0.98)			0.78 (0.65–0.87)		
5.6–6.3 mm	0.92 (0.84–0.97)	0.974 (0.90–1.05)	0.514	0.93 (0.85–0.97)	**1.19 (1.01–1.40)**	**0.036***
Etiology						
Traumatic	0.91 (0.81–0.96)			0.93 (0.85–0.97)		
Non-traumatic	0.96 (0.91–0.98)	1.05 (0.96–1.15)	0.257	0.79 (0.65–0.88)	0.85 (0.72–1.00)	0.050
Reference Standard						
Invasive (EDV, IPP, LP)	0.87 (0.78–0.93)			0.86 (0.75–0.92)		
Non-invasive (CT, MRI)	0.97 (0.94–0.99)	**1.11 (1.02–1.21)**	**0.014***	0.86 (0.77–0.92)	1.01 (0.88–1.16)	0.910

EVD: external ventricular drain; ICH: intracranial hematoma; IICP: increased intracranial pressure; ICP: intracranial pressure; IPP: invasive intraparenchymal probe; LP: lumbar puncture; NA: not available; ONSD: optic nerve sheath diameter; SAH: subarachnoid hemorrhage; TBI: traumatic brain injury.
* Statistically significant relative ratio of sensitivity/specificity in meta-regression analysis.

which could be related to a rapid increase in intracranial pressure in traumatic patients and is consistent with previous reports of higher mean ONSD in traumatic patients [16].

Other factors significant sources of heterogeneity were the differences in ultrasonography procedure (probe and measurement techniques), and in the sonographers' specializations and duration of training. Our review showed differences in ultrasonography procedure, as studies used ultrasound probes with different frequencies, which may influence the ONSD assessment and the determination of the accurate outlines of the optic nerve sheath [60,63]. Additionally, even though patient supine positioning was consistent, head elevation varied across studies and was not always reported, which may affect generalisability of ONSD cut-off findings, because previous studies have shown that intracranial pressure rises in supine position compared to head elevation or upright position [64,65]. Similarly, the significant variability in duration of sonographer's training is expected to impact the accuracy of ONSD assessment. Finally, the information available about patient's characteristics was used to prevent overlapping cohorts, however exclusion of partial overlap of cohorts from different studies could not be guaranteed. These sources of heterogeneity were important limitations of our review and could not be included in meta-regression due to lack of granularity in the data. Therefore, further studies are needed with more homogenous criteria to accurately determine the optimal ONSD cut-off and its diagnostic accuracy.

5. Conclusion

Our findings indicate that ultrasonography of ONSD is an accurate diagnostic test for IICP, with an overall high sensitivity and specificity. Due to its high sensitivity, ONSD ultrasonography can be a reliable test for ruling out IICP and stratifying the decision of whether invasive measurement of intracranial pressure is necessary. Furthermore, a cut-off range of 5.6 to 6.3 mm was identified as the most specific for diagnosis of IICP, with no significant impact on sensitivity. Therefore, our study supports the use of this this range as the optimal ONSD cut-off for IICP diagnosis. Overall, ONSD ultrasonography is a fast and accessible technique which may be useful in the screening of patients with suspected IICP, however the significant heterogeneity between included studies suggests the need for further standardized studies.

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Declaration of Competing Interest

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jns.2023.120853.

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