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REVIEW

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Ultrasonography of optic nerve sheath diameter for detection of raised intracranial pressure: a systematic review and meta-analysis

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Abstract *Purpose:* To evaluate the diagnostic accuracy of ultrasonography of optic nerve sheath diameter (ONSD) for assessment of intracranial hypertension. *Methods:* Systematic review without language restriction based on electronic databases, with manual review of literature and conference proceedings until July 2010. Studies were eligible if they compared ultrasonography of ONSD with intracranial pressure (ICP) monitoring. Data were extracted independently by three authors. Random-effects meta-analysis and meta-regression were performed. *Results:* Six studies including 231 patients were reviewed. No significant heterogeneity was detected for sensitivity, specificity, positive and negative likelihood ratios or diagnostic odds ratio. For detection of raised intracranial pressure, pooled sensitivity was 0.90 [95% confidence interval (CI) 0.80–0.95; p for heterogeneity, $p_{het} = 0.09$], pooled specificity was 0.85 (95% CI 0.73–0.93, $p_{het} = 0.13$), and the pooled diagnostic odds ratio was 51 (95% CI 22–121). The area under the summary receiver-operating characteristic (SROC) curve was 0.94 (95% CI 0.91–0.96). *Conclusions:* Ultrasonography of ONSD shows a good level of diagnostic accuracy for detecting intracranial hypertension. In clinical decision-making, this technique may help physicians decide to transfer patients to specialized centers or to place an invasive device when specific recommendations for this placement do not exist.

Keywords Intracranial hypertension · Optic nerve sheath diameter · Ultrasonography · Meta-analysis · Systematic review · Accuracy

Introduction

Intracranial hypertension is a common life-threatening syndrome caused by a variety of neurological and non-neurological diseases. If left unchecked and untreated, intracranial hypertension can lead to catastrophic deterioration related to brain ischemia and brainstem herniation. Invasive intracranial devices remain the gold standard for intracranial pressure (ICP) measurement [1, 2]. However, this technique is invasive and not always feasible due to a lack of neurosurgeons or contraindications such as coagulopathy or thrombocytemia [3]. Moreover, ICP monitors can lead to complications such as hemorrhage [4] in 1.1–5.8% of cases [3], malfunction

[4] in 6.3–40% of cases [3] or infection [5] in 0–15% of cases [3] with a significantly increased risk of bacterial colonization after 5 days [6]. Intracranial hypertension is usually defined as ICP ≥20 mmHg.

Noninvasive methods such as neuroimaging and bedside tools have been developed for rapid assessment of risk of raised ICP when invasive devices are not available or are contraindicated.

Neuroimaging by computed tomography (CT) scan and magnetic resonance imaging can be used to predict intracranial hypertension, but these techniques are expensive, need long acquisition times, have limited availability, and require harmful patient transport. Furthermore, CT scan has poor performance for detection of raised ICP [7, 8].

Transcranial Doppler sonography may predict intracranial hypertension by detecting alterations of cerebral blood velocity [9, 10] and reflects more the level of cerebral perfusion pressure than the level of ICP. However, it requires expert hands, as unsatisfactory images are obtained in about 5% of patients when the temporal window is used [11].

Ultrasonography is becoming a simple bedside tool widely used in emergency units [12]. The equipment is widely available, and the cost is low. Ultrasonography of ONSD has been developed and suggested as a possible indicator of intracranial hypertension [13–15]. The optic nerve is part of the central nervous system and is surrounded by cerebrospinal fluid. Elevation in intracranial pressure is transmitted through this subarachnoid space, especially the retrobulbar segment [16]. The technique of ultrasonography of ONSD has been previously described and seems to be reproducible [17–19] (Fig. 1). The patient is placed in supine position at 20° to horizontal. A thick layer of gel is applied over the closed upper eyelid. The probe is placed only on the gel in the temporal area of the eyelid to prevent pressure being exerted on the eye. The position of the probe is adjusted to give a suitable angle for displaying the entry of the optic nerve into the globe. Two-dimensional mode is used, and ONSD is measured 3 mm behind the globe using an electronic caliper along an axis perpendicular to the optic nerve.

The aim of the present study is to summarize available evidence on the accuracy of ultrasonography of ONSD compared with invasive measurements of intracranial pressure by intraparenchymal or intraventricular devices for diagnosis of intracranial hypertension.

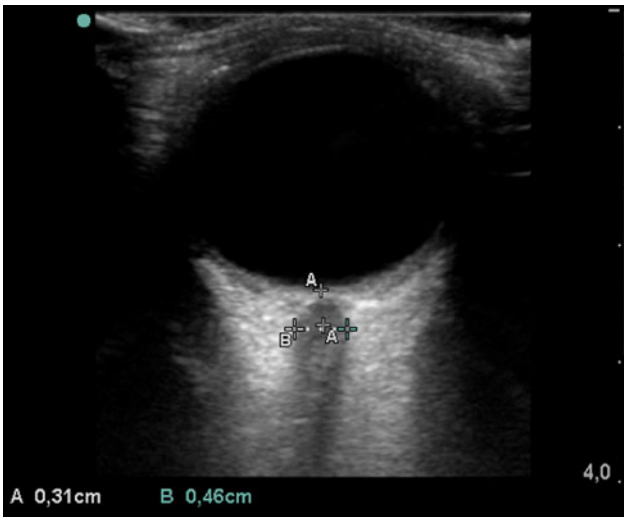

Fig. 1 Two-dimensional ocular sonography for measurement of optic nerve sheath diameter. *A* Depth from the retinal to the optic nerve, measured along the axis of the optic nerve. *B* ONSD measured at 3 mm depth, corresponding to the distance between the two external parts of the optic nerve sheath

Methods

Search strategy

We searched Medline using PubMed® interface, Embase®, Pascal Biomed®, Google Scholar®, and the Cochrane database from 1960 to July 2010. For the PubMed search, we used the following medical subject headings (MeSH) and free-text terms [20]: "brain injuries", "ultrasonography", "intracranial hypertension", "intracranial pressure", "optic nerve", "raised intracranial pressure", "myelin sheath", intraventricular catheter", "cerebrospinal fluid pressure" and "diagnosis", "sensitivity", "specificity", "predictive value", "likelihood ratio", "false positive" or "true positive". No language restrictions were applied. We also manually reviewed the reference lists of identified studies and scanned abstracts from recent (from 2005 to 2009) conference proceedings. Finally, we searched for ongoing trials on clinicaltrials.gov.

Study selection

Studies were eligible if they met the following criterion: assessing the diagnostic accuracy of ultrasonography of ONSD compared with intraparenchymal or intraventricular ICP monitoring. Studies were excluded if intraparenchymal or intraventricular ICP was not the reference standard. Eligibility was independently assessed by three authors (J.D., E.J., and M.M.). Differences were resolved by consensus.

Quality assessment

We used the QUADAS tool [21] to assess the quality of the studies. The quality of each article was assessed independently by three authors (J.D., E.J., and M.M.).

High-quality and low-quality studies were distinguished and grouped. Four primary criteria were used: (1) presence of an independent blind comparison with the gold standard; (2) the population studied included an appropriate spectrum of patients to whom the test would be applied in clinical practice; (3) sufficient description of ultrasonography of ONSD to allow reproducibility of the method; (4) a short delay (<1 h) between the two tests. High-quality studies had to fulfill all four criteria. Studies which did not fulfill these criteria were qualified as "lower-quality" studies.

Data abstraction

The first screening was performed by one investigator (J.D.) under supervision of the principal investigator (B.K.). Three authors (J.D., E.J., and M.M.) independently abstracted data on the characteristics of the studies, patient demographics, sample size, test methods, methodological quality, cutoff value, sensitivity, and specificity. Then, each author extracted data to construct a 2 × 2 contingency table. Disagreements were resolved by consensus and with the help of the principal investigator (B.K.).

Statistical analysis, detection, and management of heterogeneity

For each study and for detection of raised ICP, the sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio (indicator of global diagnostic performance [22]) were calculated from the 2 × 2 contingency table. We added 0.5 to each cell in any 2 × 2 table that contained one or more zero values [23]. We calculated 95% confidence intervals based on normal or Poisson approximations to the binomial distribution, as appropriate [24].

Sensitivity, specificity, positive and negative likelihood ratios, and diagnostic odds ratio were analyzed using Cochran's Q test in order to detect heterogeneity. p-Value <0.05 was considered as significant, thus showing heterogeneity. The I-squared (I^2) statistic [25] was also calculated to measure the percentage of variability between summary indices that was due to heterogeneity rather than chance. A study with $I^2 > 50\%$ was considered to have substantial heterogeneity.

We used the bivariate model for diagnostic meta-analysis to obtain overall sensitivity and overall specificity [26]. Besides accounting for study size, the bivariate model estimates and incorporates the negative correlation that may arise between the sensitivity and specificity of the index test within studies as a result of differences in test positive/negative threshold between studies. The bivariate model uses a random-effects approach for both sensitivity and specificity, which allows for heterogeneity beyond chance as a result of clinical and methodological differences between studies. This method allowed for construction of forest plots of sensitivity and specificity, Fagan's nomogram, and pre- and posttest probabilities graph. To present the results graphically, we plotted the individual and summary points of sensitivity and specificity in a summary receiver-operating characteristic (SROC) graph, plotting the index test's sensitivity on the y-axis against 1 – specificity on the x-axis. In addition, we plotted the 95% confidence region around the pooled estimates to illustrate the precision with which the pooled values were estimated (confidence ellipse of a mean) and to show the amount of between-study variation (prediction ellipse, the likely range of values for a new study). The area under the curve (AUROC) serves as a global measure performance. The following guidelines were suggested to interpret AUROC values: low for 0.5–0.7, moderate for 0.7–0.9, and high for >0.9 [27]. Publication bias was examined by constructing a funnel plot using the Egger regression model [28]. We drew a regression line on the funnel plot to test formally for funnel plot asymmetry [29]. p-Value inferior to 0.1 for the slope coefficient was considered to indicate significant asymmetry. We explored clinical heterogeneities by meta-regression [30] using the restricted maximum-likelihood estimation (REML) method. We defined a priori the

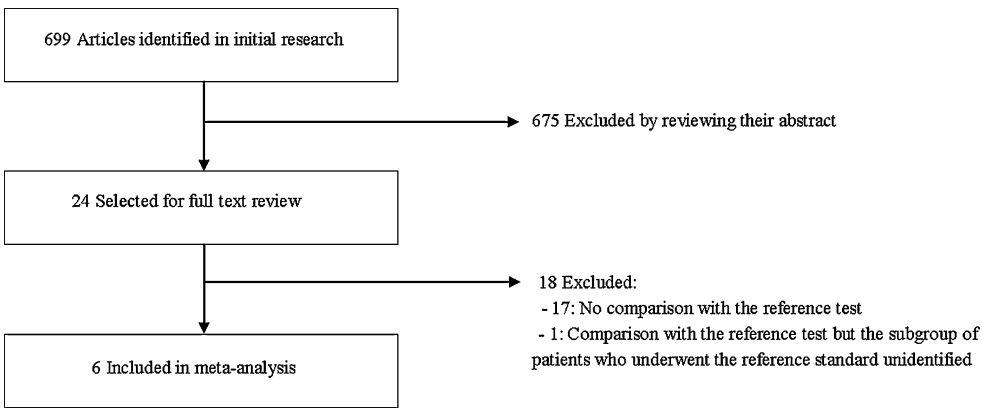

Fig. 2 Flowchart of study identification, inclusion, and exclusion for meta-analysis

Table 1 Characteristics of the studies included in the systematic review

Author	Year	Study design	Number of patients	Inclusion period	Pathology	Description of US of ONSD	Probe	Delay between ICP and ONSD	ICP monitors	Threshold	Quality
Geeraerts	2007	Cross-sectional	31	December 2005–June 2006	Traumatic brain injuries	3 mm behind the globe, supine position, two measurements for each eye (sagittal and transverse planes)	HP Sonos 5550, Hewlett Packard, Les Ulis, France 7.5-MHz linear probe	<1 h between the two tests	Intraparenchymal catheter	5.9 mm	12 items/14
Geeraerts	2008	Cross-sectional	37	May 2007–October 2007	Traumatic brain injuries (22) Subarachnoid hemorrhage (6) Intracranial hematoma (8) Stroke (1)	3 mm behind the globe, supine position, two measurements for each eye (sagittal and transverse planes)	HP Sonos 5550, Hewlett Packard, Les Ulis, France 7.5-MHz linear probe	Simultaneously	Intraparenchymal catheter	5.86 mm	13 items/14
Kimberly	2008	Cross-sectional	15	May 2006–December 2006	Traumatic brain injuries (4) Spontaneous intracerebral hemorrhages (11)	3 mm posterior to the orbit, patients in supine position, three measurements on each eye	Sonosite Micromax (Sonosite Inc., Bothell, WA) 10–5-MHz linear probe	Simultaneously	Extraventricular drain	5.0 mm	11 items/14
Moretti	2009/01	Cross-sectional	53	April 2007–March 2008	Intracranial hemorrhage	3 mm behind the globe, supine position, two measurements for each eye (sagittal and transverse planes)	Hitachi EUB 405, Hitachi Medical Corporation, Tokyo, Japan 7.5-MHz linear probe	<1 h between the two tests	Extraventricular drain (32) Intraparenchymal catheter (21)	5.2 mm	11 items/14
Moretti	2009/07	Cross-sectional	63	April 2007–March 2009	Primary intracerebral hemorrhage (29) Subarachnoid hemorrhage (34)	3 mm behind the globe, two measurements for each eye (sagittal and transverse planes)	Hitachi EUB 405, Hitachi Medical Corporation, Tokyo, Japan 7.5-MHz linear probe	Simultaneously	Intraventricular drain (39), intraparenchymal catheter (24)	5.2 mm	9 items/14
Soldatos	2008	Cross-sectional	32	October 2006–January 2008	Severe brain injury	3 mm behind the papilla, patients in supine position, repeated measurement in each eye	Philips HD11XE, Philips Medical Systems, Bothell, WA, USA 9-MHz linear probe	Simultaneously	Intraparenchymal catheter	5.7 mm	12 items/14

following clinical and design characteristics of a study's potential covariates: year of publication, pathology, ultrasonography probe, delay between the two tests, reference standard, and QUADAS quality. Analyses were performed using Stata 10.0 and MetaDisc [31].

Results

Six hundred ninety-nine articles were eligible for our systematic review. One ongoing study (MOONSTRIP: measurement of optic nerve sheath diameter in traumatic raised intracranial pressure) was also identified on clinicaltrials.gov. Among the eligible studies, 675 were excluded because the abstracts did not mention ultrasonography of ONSD and 17 were excluded because ultrasonography of ONSD was not compared with ICP monitoring [17, 32–46]. Finally, another study [47] was excluded because we were not able to distinguish the subgroup of patients who had the reference standard test. A total of six studies [48–53] were included in the meta-analysis (Fig. 2), including 231 patients. Table 1 shows patient and study characteristics of the included studies. The spectrum of pathologies (Table 1) included traumatic brain injuries (TBI), intracranial hemorrhages, and one stroke. All patients were older than 18 years old.

Out of 372 extracted data, 9 differences were found between authors regarding QUADAS quality. These differences were resolved by consensus. Overall, studies were of high quality according to the QUADAS tool. All studies used prospective study design and enrolled consecutive patients suspected for raised intracranial pressure. The asymmetry test for the funnel plot was not significant with a p value of 0.79 for the slope coefficient, which suggested symmetry in the data and low likelihood of publication bias (Fig. 3).

For each study, the sensitivity and specificity of ultrasonography of ONSD compared with intracranial pressure by intraparenchymal or intraventricular devices are shown in Fig. 4. The pooled sensitivity was 0.90 (95% CI 0.80–0.95, $p_{het} = 0.09$), and the pooled specificity was 0.85 (95% CI 0.73–0.93, $p_{het} = 0.13$). The pooled likelihood positive and negative ratios and their influence on posttest probabilities are shown in Fig. 5. No significant statistical heterogeneity was found for sensitivity, specificity, positive and negative likelihood ratios or diagnostic odds ratio ($p > 0.10$; $I^2 < 50\%$).

The pooled diagnostic odds ratio was 51 (95% CI 22–121), and the area under the SROC curve was 0.94 (95% CI 0.91–0.96) (Fig. 6).

Meta-regression analysis did not show a significant association between the characteristics of the study and the diagnostic odds ratio (Table 2).

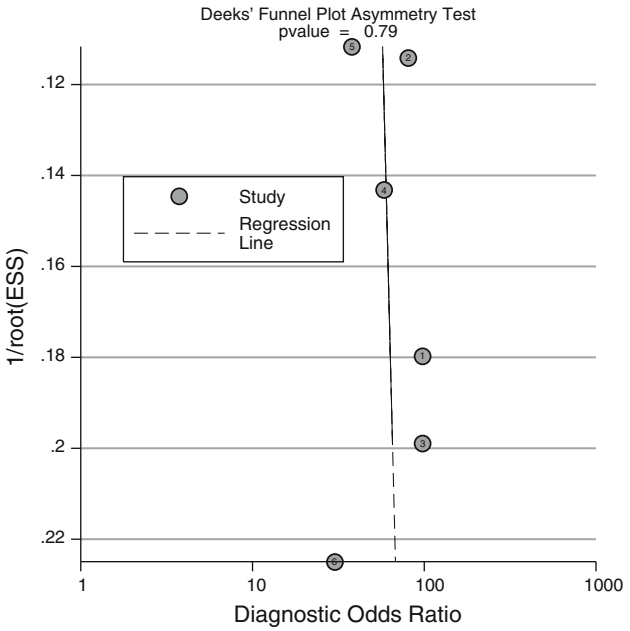

Fig. 3 Funnel plot of included studies. p-Value for the slope coefficient of the regression line is superior to 0.1, indicating that the funnel plot is symmetric with no evidence for publication bias

Discussion

In our systematic review, ultrasonography of ONSD showed good accuracy for detection of intracranial hypertension.

The pooled diagnostic odds ratio was 51 (95% CI 22–121). This means that, for ultrasonography of ONSD, the odds of positivity among patients with intracranial hypertension are 51 times higher than among patients without intracranial hypertension.

As regards ultrasonography of ONSD, clinicians should favor sensitivity rather than specificity. Indeed, when a test has high sensitivity, a negative result rules out the diagnosis. However, when a test has very high specificity, a positive result effectively rules in the diagnosis. As undetected raised ICP can lead to catastrophic outcomes, clinicians prefer a diagnostic test with high sensitivity for raised ICP detection. In our analysis, the pooled sensitivity was 0.90. Clinicians should therefore remember that, despite the good performance of ONSD ultrasonography for detection of raised ICP, 10% of patients with significant intracranial hypertension would not be detected, resulting in potentially incorrect management of these patients. However, the studies included in our analysis only concern TBI and intracranial hemorrhage. International guidelines for ICP monitoring in TBI patients exist [54]. In all TBI patients with Glasgow Coma Scale (GCS) $\leq$8, ICP monitoring is recommended [54]. We believe that ultrasonography of ONSD may help decision-making in cases for which there are no specific

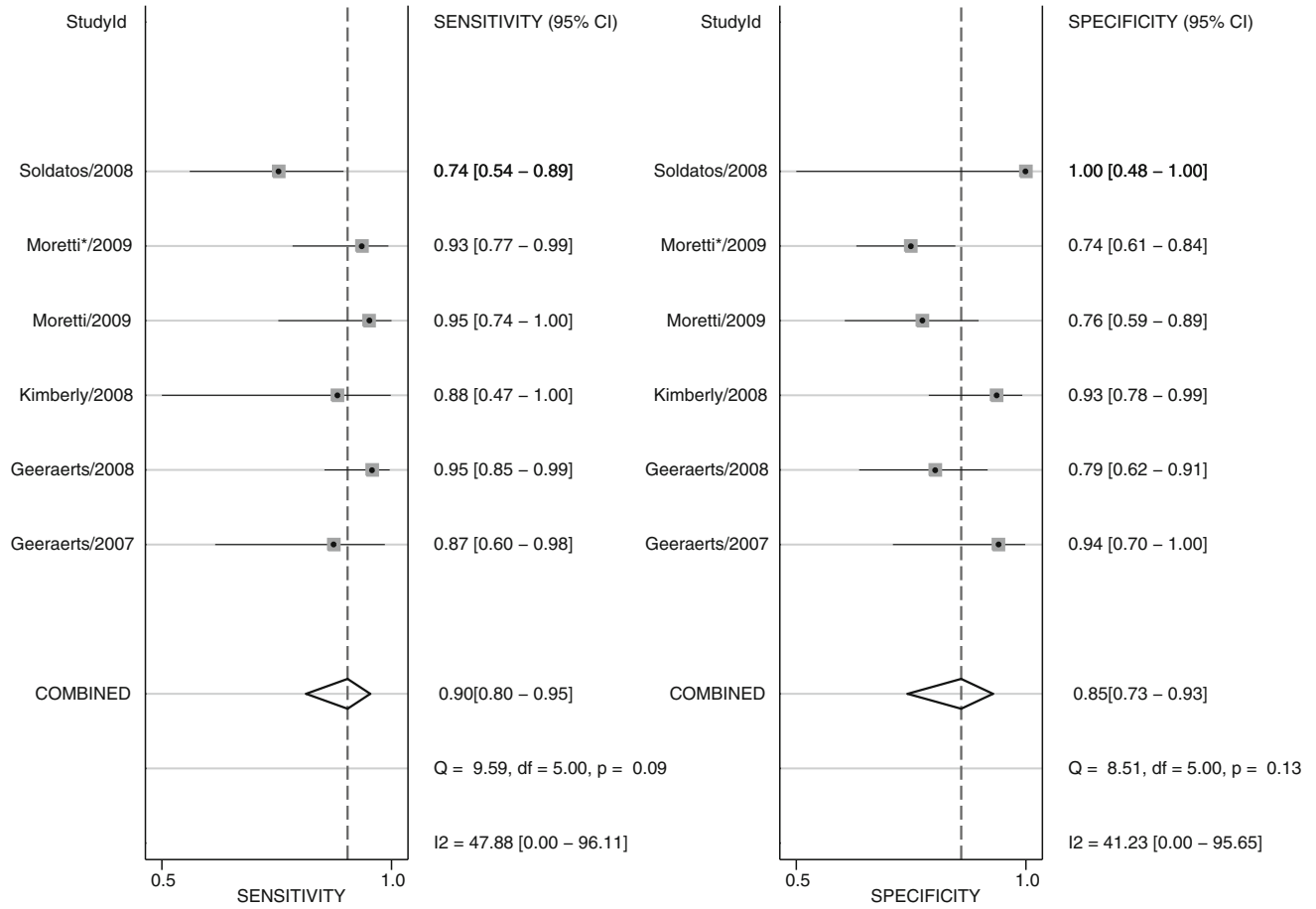

Fig. 4 Sensitivity and specificity of ultrasonography of ONSD for diagnosis of intracranial hypertension compared with ICP devices

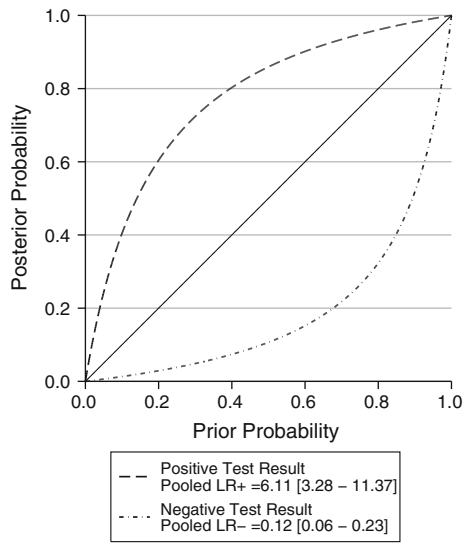

Fig. 5 Conditional probability plot of ultrasonography of ONSD for diagnosis of intracranial hypertension. *LR* Likelihood ratio

recommendations. Furthermore, we should keep in mind that interpretation of ultrasonography of ONSD should be combined with a set of clinical and radiological signs.

The clinical usefulness of ultrasonography of ONSD could also be evaluated by calculating positive and negative likelihood ratios. With a positive likelihood ratio above 1, the probability of the disease or condition being present goes up. When it is below 1, the probability of it being present goes down. When it is 1, the probability is unchanged. Furthermore, likelihood ratios allow clinicians to obtain posttest probabilities using Fagan's nomogram [55]. For instance, using the calculated likelihood ratios of ultrasonography of ONSD, a clinician who has clinically determined the pretest probability to be 50% can predict that the posttest probability will be 86% if the test is positive and 11% if the test is negative (Fig. 7). All posttest probabilities as a function of pretest probabilities are shown in Fig. 5, indicating good accuracy of ultrasonography of ONSD.

Ultrasonography of ONSD is certainly not intended to replace ICP monitoring using invasive devices, which are

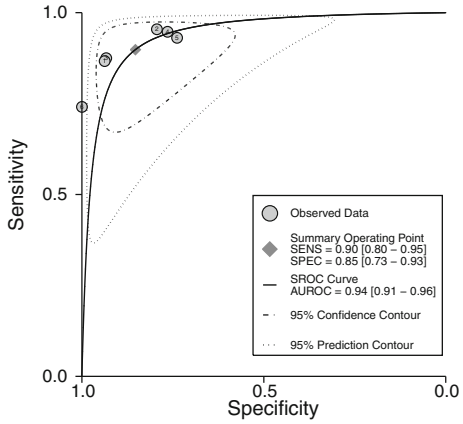

Fig. 6 SROC curve of ultrasonography of ONSD for diagnosis of intracranial hypertension compared with ICP devices. The area under the SROC curve provides an overall summary of test performance. AUROC was 0.94 (95% CI 0.91–0.96), indicating a good level of accuracy

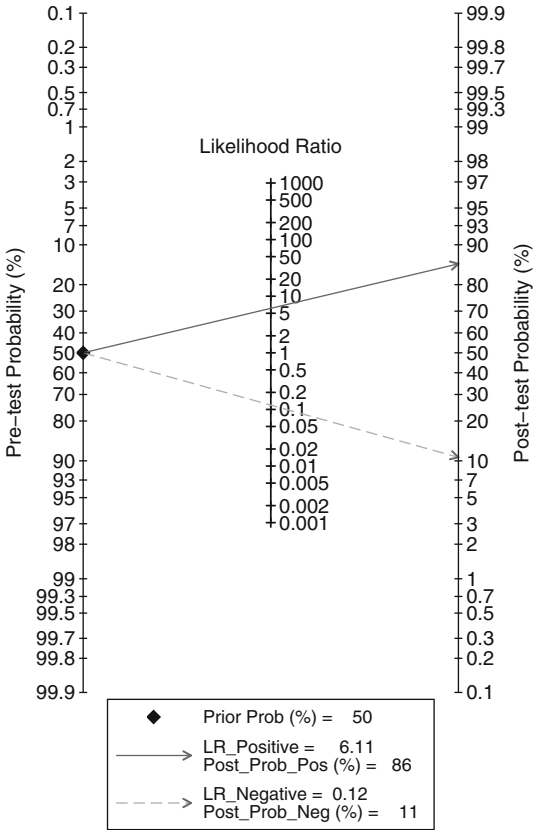

Fig. 7 Posttest probabilities as a function of pretest probabilities of ultrasonography of ONSD for diagnosis of intracranial hypertension

well codified in certain specific conditions. However, it could represent a useful tool when ICP monitoring is unavailable or contraindicated. This technique is reproducible, as shown in the studies included in our analysis, with median intraobserver reliability of 0.2 mm (0.1–0.5 mm) [53] and median interobserver reliability varying from 0.2 to 0.3 mm [48, 52, 53]. Bauerle et al. [56] also reported that the Pearson's correlation coefficient between two investigators was superior to 0.8 in both eyes. Unlike ultrasonography, ICP monitoring often requires the availability of neurosurgeons, who are not present in all medical centers [57, 58]. In addition, the average time from hospital admission to placement of ICP monitoring is frequently longer than 1 h. Therefore, ultrasonography of ONSD may allow for earlier management of intracranial hypertension when ICP monitoring is not available or before its placement. It could be also useful during long transportation times to better monitor acutely ill patients and to eventually institute a medical treatment. Ultrasonography is a simple tool available in all medical centers like transcranial Doppler sonography, but this latter requires a long experimentation time [11].

Tayal et al. [43] suggested that physicians with bedside sonographic experience may be able to learn ultrasonography of ONSD relatively quickly. They estimated that the learning curve for experienced sonologists may include as few as 10 subjects with three abnormal scan results, whereas for novice sonologists the number of scans needed may be closer to 25. This technique is not recommended in "non-specialized" units. In these settings, less specialized practitioners may gain false reassurance from a negative result, which could lead to inappropriate triage or delay in specialized care as there is a 10% false-negative rate.

Table 2 Meta-regression: estimated influence of study characteristics on diagnostic OR

Study characteristics	RDOR[a]	95% CI	*p*-Value
Year of publication (2009 versus 2008 or 2007)	1.95	0.07–51.96	0.56
Pathology (traumatic brain injuries versus other)	1.43	0.00–412.38	0.85
Ultrasonography probe (7.5-MHz linear probe versus other)	0.74	0.00–145.73	0.87
Delay between the two tests (simultaneously versus <1 h)	0.78	0.03–17.63	0.81
Reference standard (intraventricular device versus other)	0.56	0.00–77.97	0.74
QUADAS quality	0.73	0.04–12.44	0.75

[a] Relative diagnostic OR (RDOR) is <1 when studies with the characteristic produce a lower diagnostic OR, and >1 when the reverse is true

The relationship between ICP and ONSD variations needs more investigation. Geeraerts et al. [49] reported that there was a strong correlation ($r = 0.74$) between changes in ONSD measures and ICP variations.

Limits of the study

The main limit of this study is the lack of power, because there are only six included studies (231 patients). Summary results obtained from any meta-analysis can be misleading if publication bias exists [59]. Although we did not identify any unpublished studies, the funnel plot did not suggest the presence of publication bias in our review. Furthermore, no clinical or methodological heterogeneity was found using meta-regression. However, as our review includes few studies, we were not able to perform a sensitivity analysis. Also, the results of the meta-regression lack power and the potential for robust conclusions is clearly very limited. Meta-regression also has the same disadvantages as other observational studies, notably bias by confounding or the availability of data from original papers.

Clinicians certainly focus on the necessity to know the accurate cutoff value. This question could not be resolved in this study because of the use of different thresholds in the included studies. This is an important question to answer. Also, it could be resolved using meta-analytic methods on individual data and by constructing an ROC curve.

The accuracy of ultrasonography of ONSD in other settings or in patients who suffer from ocular trauma or ocular pathology such as chronic nerve atrophy or optic neuronitis remains unclear. These two conditions were clearly defined as exclusion criteria in all studies that we included in our review.

In conclusion, ultrasonography of ONSD shows a good level of diagnostic accuracy to detect intracranial hypertension in adult patients with TBI and intracranial hemorrhage. Clinicians would appreciate the clinical usefulness of this test and develop it in their intensive care units. A positive test is associated with a 51 times higher risk of intracranial hypertension. In clinical decision-making, this technique may help physicians decide to transfer patients to specialized centers or to place an invasive device when specific recommendations for this placement do not exist. The application of this technique in other clinical situations with intracranial hypertension, such as meningitis, severe encephalitis or valve dysfunction, requires further studies.

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