



REVIEW ARTICLE OPEN ACCESS

Intraindividual Optic Nerve Sheath Variation and Intracranial Pressure Changes: A Systematic Review and Meta-Analysis

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ABSTRACT

Background and Purpose: To review the existing evidence on multiple timepoint assessments of optic nerve sheath diameter (ONSD) as an indicator of intraindividual variation of intracranial pressure (ICP).

Methods: A systematic search identified studies assessing intraindividual variation in ICP through multiple timepoint measurements of ONSD using ultrasonography. Meta-analysis of studies assessing intraindividual correlation coefficients between ONSD and ICP was performed using a random effects model, and we calculated the weighted correlation coefficient for the expected change in ICP associated with variations in ONSD.

Results: A total of five studies, comprising 157 patients, were included in the review. ONSD was compared with invasive ICP measurement methods at multiple timepoints. Meta-analysis of intraindividual ONSD–ICP correlation demonstrated a correlation coefficient of 0.62 (CI: 0.50–0.71). Individual linear correlation analyses were performed in two of the studies, yielding correlation coefficients ranging from 0.79 to 1.00; however, widely variable individual slopes were found (1.51–41.43 mm/mmHg). ONSD variations ranged from 0.12 to 3.30 mm per 5 mmHg change in ICP, with a variation of 0.55 mm in adults with hypoxic brain injury and 0.77 mm in children with idiopathic intracranial hypertension.

Conclusions: Our findings indicate that ONSD significantly correlates with ICP, and longitudinal intraindividual assessment shows a predominantly linear correlation between both variables. A personalized ONSD–ICP correlation equation may enable accurate ICP prediction, making ONSD a useful tool for follow-up in patients with previous invasive ICP measurements, when adjusted to each patient's characteristics and pathologies.

1 | Introduction

Elevated intracranial pressure (ICP) is a neurological condition that may result in severe clinical outcomes, including cerebral ischemia and herniation of intracranial structures [1]. Therefore,

accurate and timely assessment of the ICP is of paramount importance in clinical scenarios that can result in intracranial hypertension, like traumatic brain injury, idiopathic intracranial hypertension, neoplasms, hydrocephalus, and stroke among others [2–4].

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Invasive ICP monitoring methods are currently the gold standard for ICP measurement, such as intraventricular or intraparenchymal catheters [5, 1, 4, 6–8]. While these invasive techniques provide precise and continuous ICP monitoring, they are associated with several limitations and complications, namely infectious and hemorrhagic procedural risks, technical challenges, and high resource intensity [7, 9, 10]. An accessible, noninvasive, low-cost, and accurate technique to determine ICP would improve the approach to patients with suspected intracranial hypertension [1, 9, 10].

The optic nerve is surrounded by a meningeal sheath filled with cerebrospinal fluid, which is continuous with the subarachnoid space of the CNS [11, 12]. Therefore, an increase in ICP results in a distension of the optic nerve sheath, increasing its diameter [11, 13–15]. The reliability of ultrasound measurement of optic nerve sheath diameter (ONSD) when compared to invasive methods for assessing ICP has recently been the subject of multiple studies and ongoing investigations. These studies have revealed a high diagnostic accuracy and very high sensitivity to detect increased ICP and suggest its potential use as a screening tool to stratify when invasive ICP measurement is needed [16–21].

Despite the ONSD association with ICP, little is known about the intraindividual relationship between ONSD and ICP, namely how a change in ICP correlates with the optic nerve sheath variation. It is unclear whether a specific variation in ONSD can accurately predict the individual ICP variation and how physiological characteristics and increased ICP etiologies affect it. A direct accurate correlation between changes in ONSD and fluctuations in ICP would be essential to obviate the need for invasive ICP techniques in the clinical context.

We aim to review the existing evidence on multiple timepoint assessments of ONSD as a marker for intraindividual variation of ICP.

2 | Methods

This manuscript was developed according to the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) guidelines [22, 23]. The review protocol was previously published in the international prospective register of systematic reviews (PROSPERO) [24].

2.1 | Study Selection

Selected studies assessed intraindividual variation of ICP associated with ONSD assessment at multiple timepoints. All study designs were included, except case reports. The study population included patients with intracranial hypertension assessed through invasive monitoring techniques. We included studies assessing the ONSD using ultrasonography. Studies were excluded if data on intraindividual ONSD measurements or ICP values were not reported or if the full-length report was written in a language other than English, Portuguese, and Spanish.

2.2 | Search Strategy

We conducted a systematic search on MEDLINE and Web of Science from inception until April 2024. Additionally, reference lists from identified articles were manually cross-checked for further potentially eligible studies. We accepted studies written in English, Portuguese, or Spanish.

Search strategy combined terms for (1) optic nerve sheath diameter, (2) intracranial pressure, (3) intraindividual correlations, and (4) ultrasonography. The detailed search query for both databases included the following combination of medical subject headings (MeSH) and free-text terms: (“optic nerve sheath diameter” OR “ONSD”) AND (“intracranial pressure” OR “ICP” OR “intracranial hypertension” OR “cerebrospinal fluid pressure” OR “intracerebral pressure”) AND (“longitudinal studies”[MeSH Terms] OR “longitudinal” OR “time point*” OR “timepoint*” OR “multiple measurements” OR “multiple exam*” OR “Multiple assessments” OR “serial examination” OR “linear correlation*” OR “real-time evaluation” OR “intra-individual”) AND (“Ultrasonography”[MeSH Terms] OR Ultraso* OR Sonog*).

Titles and abstracts yielded by the search were independently screened against the inclusion and exclusion criteria, and full-text reports were analyzed for inclusion by two reviewers (H.A., D.B.). Disagreements were solved by consensus or by another reviewer.

2.3 | Effect Measures

The main outcome of this study was the intraindividual correlation between the individual ONSD variation and the respective change in ICP.

2.4 | Data Extraction

Data were 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, and ultrasonography procedure (probe, sonographer, and measurement technique); (2) invasive ICP technique, namely technique, location, and type of monitoring; (3) participant characteristics, including demographics and comorbidities characteristics; and (4) outcome results, namely optimal ONSD and ICP measurements, linear or Spearman’s correlations, and time between measurements.

2.5 | Quality Assessment

One reviewer assessed the risk of bias using the “Quality Assessment of Diagnostic Accuracy Studies – 2” (QUADAS-2) tool [25]. Data verification was performed by a second reviewer. The reviewers evaluated on four domains: patient selection, index test, reference standard, and flow and timing. These domains were qualitatively classified as high or low risk of bias and as having high or low applicability concerns.

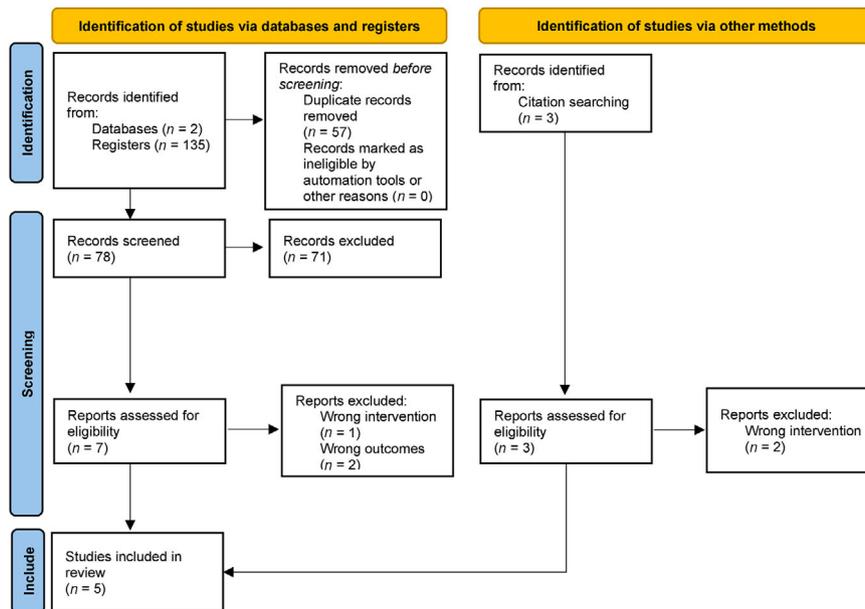


FIGURE 1 | Flowchart representation of selection process according to PRISMA guidelines.

2.6 | Strategy for Data Synthesis

Descriptive synthesis of included studies and analysis of main outcome variables were performed. We performed a meta-analysis of studies assessing intraindividual correlation coefficients between ONSD and ICP. A random-effects model was used, and forest plots were generated for graphical representation. We calculated the weighted correlation coefficient of the expected change in ICP associated with variations in ONSD across the included studies. Statistical heterogeneity between studies was assessed using the inconsistency index (I^2). Confidence intervals (CIs) were reported at 95%, and statistical significance was determined at an alpha level of 0.05. All analysis were conducted using STATA version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC, <https://www.stata.com>).

3 | Results

3.1 | Characteristics of Selected Studies

A systematic search of the MEDLINE and Web of Science databases yielded a total of 135 records based on the predefined keywords and MeSH terms. Following the screening process, five studies, assessing a total of 157 patients, were deemed eligible and were included in the review. Figure 1 details the flowchart of the study according to PRISMA guidelines.

Of the five studies, Kerscher, Schöni, et al. conducted a retrospective cohort study [26]. The remaining, Cardim et al., Chen et al., Geeraerts et al., and Kerscher, Zipfel, et al., were prospective cohort studies [27–30]. Kerscher, Schöni, et al.'s and Kerscher, Zipfel, et al.'s studies were conducted in pediatric populations, accounting for a total of 25 patients in this age group [26, 30]. All the cohorts included patients with proven or suspected symptoms of increased ICP (>20 mmHg) due to

variable etiologies, including traumatic brain injury, idiopathic intracranial hypertension, hypoxic brain injury, intracranial hematoma, subarachnoid hemorrhage, among others. Several invasive methods for ICP measurement were employed in the studies, including intraparenchymal devices in Geeraerts et al. [29] and Cardim et al. [27], while Chen et al. [28] and Kerscher, Zipfel, et al. [30] utilized lumbar puncture. Kerscher, Schöni, et al.'s study [26] used a combination of intraparenchymal devices, lumbar puncture, and extraventricular drainage for ICP measurement. The standard reference used to define elevated ICP varied between studies, with 20 mmHg being the most common threshold, used in Cardim et al. and Geeraerts et al.'s studies [27, 29]. Kerscher, Zipfel, et al. employed 18.50 mmHg (converted from 1 cmH₂O to ≈0.74 mmHg), and Chen et al. [28] used 200 mmH₂O as their studies' thresholds. Kerscher, Schöni, et al. [26] defined multiple ICP subgroups of 5, 10, 15, 20, 25, and 30 mmHg, without standardizing a reference for intracranial hypertension [31].

The characteristics of the selected studies, including the ultrasonography technique, invasive ICP measuring method, time-points, and mean ONSD, are described in Table 1. Quality and risk of bias assessment using QUADAS-2 revealed a low to moderate risk of bias across the five studies, which is detailed in Table 2.

The ONSD ultrasonographic measurement devices were linear probes operating at frequencies ranging from 5 to 14 MHz, and most studies [26, 28–30] provided or described good image acquisition. The ultrasound measurements were performed primarily in the transverse plane, with some studies incorporating additional vertical measurements, and all studies [26–30] considered the external limit of the dura mater for the ONSD. In most studies [26, 28, 30], patients were positioned supine with the head resting at 0° during the ONSD assessment. Cardim et al. [27] utilized a raised head position at 30°, and the ultrasound image quality was not described or provided. Geeraerts et al. [29] did not specify the patient's positioning.

TABLE 1 | Characteristics of the selected studies.

Study	Study design	Sample size and demographic	Invasive ICP method	Ultrasoundography technique (patient's position/plane)	Ultrasoundography probe (frequency/type/model)	Time between ICP and ONSD measurements			
						Number of timepoints	Time between each timepoint	Overall mean ONSD	
Geeraerts et al. [29]	Prospective	37, adults	IPP	NA/vertical and axial	7.5 MHz/linear	2	Immediate	24 h	5.99 ± 0.40 mm
Cardim et al. [27]	Prospective	11, adults	IPP	30°/vertical and axial	7 MHz/linear/Sonosite, USA	9	Immediate	~8 h (three times per day)	NA
Chen et al. [28]	Prospective	84, adults	LP	Supine/vertical and axial	14–5 MHz/linear, B-mode/Delica MVU-6300 (Shenzhen, Guangzhou, China)	2	<5 min	10 min	NA
Kerscher, Schöni, et al. [26]	Retrospective	10, children	IPP, external ventricular drainage, LP	Supine/axial	12 MHz/linear/NA	3	Immediate	3–4 days	5.35 ± 0.73 mm
Kerscher, Zipfel, et al. [30]	Prospective	15, children	LP	Supine/axial	12 MHz/linear/Epiq 5G US system; Philips Healthcare, Best, The Netherlands	2–7	<10 min	Before and immediately after LP with cerebrospinal fluid draining	6.5 ± 0.7 mm

Abbreviations: ICP, intracranial pressure; IPP, invasive intraparenchymal probe; LP, lumbar puncture; NA, not available.

TABLE 2 | Quality assessment of Diagnostic Accuracy Studies-2 for the selected studies.

Study	Year	Risk of bias				Applicability concerns		
		Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Geeraerts et al. [29]	2008	☺	☺	?	☺	☺	☺	☺
Cardim et al. [27]	2019	☺	☺	☺	☺	☺	☺	☺
Chen et al. [28]	2019	☺	?	☺	☺	☺	☺	☺
Kerscher, Schöni, et al. [26]	2020	?	?	☺	☹	☺	☺	☺
Kerscher, Zipfel, et al. [30]	2024	☹	☺	☺	☺	☺	☺	☺
		Low risk	☺	Unclear risk	?		High risk	☹

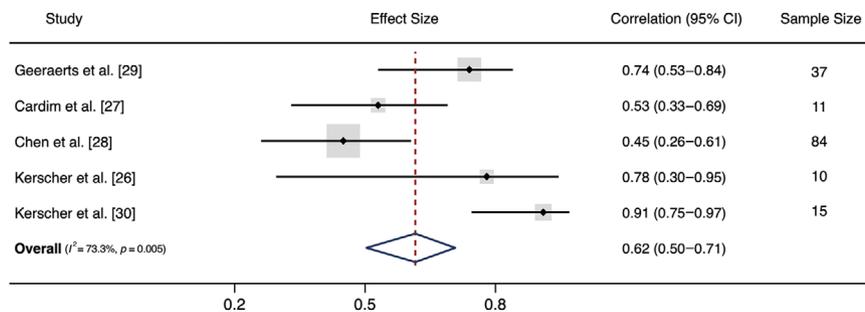


FIGURE 2 | Forest plot of correlation coefficient meta-analysis of the intraindividual correlation between ONSD and ICP. CI, confidence Interval.

All studies ensured the simultaneous measurement of ICP and ONSD, with intervals of less than 10 min between the two assessments [26–30]. Cardim et al., Kerscher, Schöni, et al., and Kerscher, Zipfel, et al. conducted measurements at three or more timepoints, allowing for a more comprehensive evaluation of the relationship between these two variables [26, 27, 30]. Geeraerts et al. [29] and Chen et al. [28] correlated the variation/delta ONSD (Δ ONSD) with the variation/delta ICP (Δ ICP) using two timepoints, while the remaining studies did individual linear correlations [28, 29].

3.2 | Intraindividual ONSD–ICP Correlation

A meta-analysis of intraindividual ONSD–ICP correlation coefficients revealed an overall mean correlation effect of 0.62 (CI: 0.50–0.71; Figure 2).

The correlation coefficients in the included studies ranged from 0.45 to 0.91. Cardim et al. [27] and Kerscher, Zipfel, et al. [30] used a repeated measures correlation (rmcorr); Geeraerts et al. [29] used a linear regression of ONSD and ICP changes (paired measurements per individual); and Kercher-Schöni et al. [26] and Chen et al. [28] used Pearson’s or Spearman’s correlations. Although these methods differ in statistical implementation, they all estimate the same parameter, the average intraindividual relationship between ONSD and ICP, independent of the variation between subjects. Geeraerts et al., Kerscher, Schöni, et al., and Kerscher, Zipfel, et al. all reported higher correlation coefficients

of 0.74, 0.78, and 0.91, respectively [26, 29, 30]. These three studies assessed participants of varying ages with different etiologies and ICP monitoring methods; however, all participants were assessed in a similar protocol, in supine position with their head at 0° [26, 29, 30]. Cardim et al. [27] and Chen et al. [28] reported lower coefficients of 0.53 and 0.45, respectively. Cardim et al. [27] studied patients with hypoxic brain injury in a 30° head-raised position, and, despite a lower correlation coefficient, they found ONSD to have the highest correlation with ICP compared to other noninvasive techniques. Chen et al. [28] did not specify the etiology of increased ICP, and their ICP measurement device had a maximum value of 400 mmH₂O (400 mmH₂O \approx 29 mmHg).

3.3 | Detailed ONSD Findings and ONSD–ICP Correlation Strength

The intraindividual linear correlation slopes between ONSD and ICP varied widely from patient to patient as seen in Figure 3. Studies by Cardim et al., Kerscher, Schöni, et al., and Kerscher, Zipfel, et al. displayed individual linear correlations graphics illustrating the association between ONSD and ICP [26, 27, 30]. Notably, Kerscher, Zipfel, et al. [30] provided individual linear correlation equations, with slopes ranging from 1.51 to 41.43. Despite this wide variation, the intraindividual correlations were nearly linear and had correlation coefficients ranging from 0.96 to 1.00 in Kerscher, Zipfel, et al. [30] and from 0.79 to 1.00 in Kerscher, Schöni, et al. [26]. The remaining studies did not provide individual correlation coefficients.

Slopes of ONSD–ICP intraindividual correlation

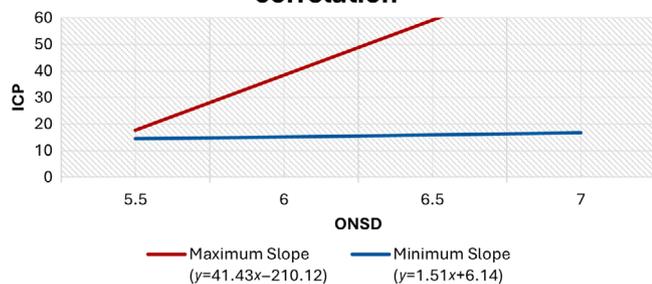


FIGURE 3 | Slope variation of ONSD–ICP intraindividual linear correlation.

The maximum ONSD measured was 8.2 mm, with the majority (>95%) of measures being under 7.0 mm, in both children and adults. The ONSD corresponding to a given ICP demonstrated substantial variability—for instance, an ICP value of 10 mmHg corresponded to ONSD measurements ranging from 5.0 to 7.1 mm across different patients. Additionally, the corresponding variation in ONSD for approximately 5 mmHg of ICP variation ranged from 0.12 to 3.3 mm. These different slopes and variations were observed across all studies, including in participants with the same comorbidities and etiologies for increased ICP.

The median ONSD in Cardim et al. [27] was 5.60 mm (5.50–6.30 mm) in adult patients with hypoxic brain injury. In Kerscher, Zipfel, et al. [30], the mean ONSD was 6.50 ± 0.70 mm, and Kerscher, Schöni, et al. [26] reported a mean ONSD of 5.35 ± 0.73 mm in their pediatric populations. In adults included in the Geeraerts et al. [29] study, the mean ONSD was 5.99 ± 0.40 mm. Cardim et al. [27] reported an average ONSD variation of 0.55 mm per 5 mmHg of ICP increase. Kerscher, Zipfel, et al. [30] found an average variation of 0.77 mm per 5 mmHg, with individual variations ranging from 0.12 to 3.30 mm. Chen et al. [28] described a mean ONSD variation of 0.11 mm and a mean ICP variation of 30 mmHg. The remaining studies did not provide specific linear equations or ONSD variation values for given ICP levels [26, 29]. Cardim et al. [27] studied adults with hypoxic brain injury, while Kerscher, Zipfel, et al. [30] focused on pediatric patients with idiopathic intracranial hypertension. Kerscher, Schöni, et al. [26] analyzed various pediatric conditions, finding that idiopathic intracranial hypertension had the strongest ONSD–ICP correlation ($r = 0.99$, $p < 0.01$), while hydrocephalus ($r = -0.13$) and craniosynostosis ($r = 0.31$) showed weaker correlations. This study also noted that ONSD correlated best with intracranial monitoring devices and worst with lumbar puncture. Geeraerts et al. [29] included adults requiring sedation, mechanical ventilation, and ICP monitoring, such as patients with traumatic brain injury, subarachnoid hemorrhage, and intracranial hematoma patients.

3.4 | Interindividual Correlation Between ONSD and ICP

Additionally, Geeraerts et al., Chen et al., Kerscher, Schöni, et al., and Kerscher, Zipfel, et al. assessed the interindividual correlation between ONSD and ICP as well, which yielded correlation

coefficients of $r = 0.50$, 0.52 , 0.71 , and 0.48 , respectively [26, 28–30]. These interindividual correlation coefficients were lower when compared to the intraindividual correlations in Geeraerts et al., Kerscher, Schöni, et al., and Kerscher, Zipfel, et al. [26, 29, 30]. Inversely, Chen et al. [28] found a higher interindividual correlation ($r = 0.48$) compared to the individual delta ONSD and delta ICP correlation ($r = 0.45$).

4 | Discussion

This is the first systematic review addressing the intraindividual relationship between ONSD and ICP to study whether it can be used as a monitoring tool for variations in ICP. Our findings demonstrated that ONSD variations were correlated linearly with ICP changes, with a meta-analysis of intraindividual ONSD–ICP correlation demonstrating an overall correlation of 0.62 (95% CI: 0.50–0.71). Additionally, our review showed that correlation coefficients varied among studies, ranging from 0.45 to 0.91, demonstrating heterogeneity between findings. The correlations were higher in the studies [26, 30] that included participants with idiopathic intracranial hypertension and were lower in Cardim et al. [27] and Chen et al. [28]. Cardim et al.’s [27] population were patients with hypoxic brain injury, and ONSD was measured with an elevation of the head of 30°. In Chen et al. [28], the ICP measuring device had a significant limitation of an upper maximum value of 400 mmHg. The ultrasound probes’ frequencies of Cardim et al., Geeraerts et al., and Chen et al. were less than 10 MHz [27–29], which has been described to affect the image resolution and could lead to technical measurement errors [15, 32]. These differences could justify the lower correlation found. Furthermore, substantial variability was observed among participants, who, despite showing very strong correlations between ONSD variations and ICP changes, had very different linear equation slopes. Slopes for individual linear equations ranged from 1.51 to 41.43 (Kerscher, Zipfel, et al. [30]). However, the intraindividual correlations were nearly linear and with high correlation coefficients, ranging from 0.79 to 1.00.

It is possible that individualized equations could be developed to predict ICP using ultrasound-measured ONSD [30]. Such equations, tailored to individual patient characteristics, could serve as valuable noninvasive tools for monitoring ICP in patients with prior invasive ICP assessments. However the ONSD–ICP relationship may not follow a purely linear correlation, as >95% of ONSD measurements fall below 7.00 mm, and studies have referred that at higher ICP levels, ONSD may not respond linearly [11, 33]. The optic nerve sheath contains collagen fibers in parallel arrangement, forming a surprisingly flexible dural tissue distinct from conventional dura mater [11, 34]. However, under elevated ICP, the optic nerve sheath collagen fibers, instead of the normal elastic response, undergo plastic deformation, possibly distorting the ONSD–ICP linear relationship, which has been seen in ex vivo patients [35]. Besides each patient’s physiological characteristics, several other factors could also influence ONSD measurements, including the underlying pathology, the duration of ICP elevation, ICP values, and intraocular pressure.

The interindividual correlation between ONSD and ICP has been described by several studies, with findings indicating moderate to significant associations, with variable correlation coefficients (r

values) ranging from 0.50 to >0.90, which suggested that ONSD is useful as a screening or monitoring tool in emergency medicine and critical care but cannot replace traditional invasive methods [33, 36–40]. In this review, the interindividual correlations yielded lower coefficients when compared with the intraindividual correlations, except in Chen et al. [28], which reflects the differences in baseline ONSD and ONSD–ICP relationships across patients and supports this challenge in creating a universal formula able to accurately predict ICP through ONSD [26, 27, 29, 30].

The strong ONSD–ICP intraindividual correlations in specific patients suggest that it may be better suited as a follow-up tool for monitoring ICP in patients with prior invasive ICP measurements or as a primary qualitative screening method, rather than a first-contact ICP predicting tool, given the considerable ONSD heterogeneity between individuals seen in this review. The patient's positioning during ONSD measurements influences the results and may have contributed to the observed heterogeneity [17]. Developing a model function according to the optic nerve sheath's biomechanical characteristics and adjusting it to each individual may enable an accurate ICP prediction. Further research and new tools, such as the Berhanu et al.'s and Xu et al.'s indexes [41, 42], are needed to characterize the individual ONSD–ICP curve behavior and how different pathologies and methods [43] can affect this correlation to validate the clinical utility between these variables.

This study has some limitations. First, there is a high heterogeneity in the results, likely attributable to the small number of studies included and their reduced sample sizes. Additionally, two of the studies were conducted by the same author, which might have introduced potential bias associated with partial overlapping in cohorts [26, 30]. Another limitation is that two of the studies ended up conducting the intraindividual analysis in a considerably smaller subpopulation of the total sample size, justified by only including the patients who had measurements in three or more timepoints, which might have resulted in significant selection bias. Another limitation is that in Chen et al.'s study [28], the upper limit measurable by the invasive ICP device was 400 mmH₂O. Additionally, potential unreported acute ICP increasing events in the studies with longer intervals between measurements [26, 27] could have influenced the observed correlations [35]. Technical aspects such as the patient's position, image quality, examiner's experience, frequency of the ultrasound probe, and the type of ICP monitor used could also have impacted the ONSD–ICP correlation [16, 17, 26, 43–45]. Despite these limitations, the findings of this review offer a foundation for future investigations aimed at integrating ONSD as a personalized ICP monitoring strategy and highlight the necessity of methodizing future ONSD studies, in order to further develop its potential utility.

Our findings suggest that ONSD is significantly correlated with ICP, and longitudinal intraindividual assessment shows a linear correlation between ONSD and ICP. These findings support the creation of an ONSD–ICP correlation equation, personalized to patient-specific characteristics, which may be able to monitor ICP accurately. Further studies in a larger population are needed to better establish a model to longitudinally predict ICP based on ONSD. Furthermore, research directed at investigating the variation in ICP per millimeter change of ONSD and investigate

the physiological limits of sheath distension is also necessary in order to examine the eventual nonlinear correlation between ONSD and ICP at higher pressures.

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The authors have nothing to report.

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Conflicts of Interest

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