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NARRATIVE REVIEW

Non-invasive intracranial pressure estimation in the intensive care unit: narrative review of methods and clinical applications

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Abstract: Despite invasive methods are the gold standard for intracranial pressure (ICP) measurement, several non-invasive techniques (nICP) have been proposed as surrogate, although their use remains insufficiently recognized in clinical practice. These include transcranial Doppler blood flow velocity assessment (arterial or venous), optic nerve sheath diameter (ONSD), automated pupillometry, measurement of skull expansion and compliance, brain imaging, double-depth ophthalmic artery blood flow velocity, and ultrasound time-of-flight. The main limitations of all indirect methods are calibration and zeroing, which constrain the absolute accuracy of non-invasive ICP monitoring. For transcranial Doppler-based methods, the 95% limits of agreement are approximately ± 7–15 mmHg, while for ONSD-based techniques they range from ± 7–10 mmHg. Improved predictive accuracy may be achieved by combining different modalities and applying advanced signal analysis techniques. Importantly, in patients with acute brain injury, nICP can complement invasive monitoring by guiding patient selection for urgent monitoring, facilitating brain assessment in moderate traumatic brain injury, and assisting management in patients with coagulopathy. In the general intensive care population, nICP may provide valuable information after cardiac arrest, liver failure, and sepsis. In the emergency department, early detection of intracranial hypertension helps prevent missing the "golden hour" of brain care. Finally, nICP is particularly relevant in low-resource settings, where intensive care facilities are limited.

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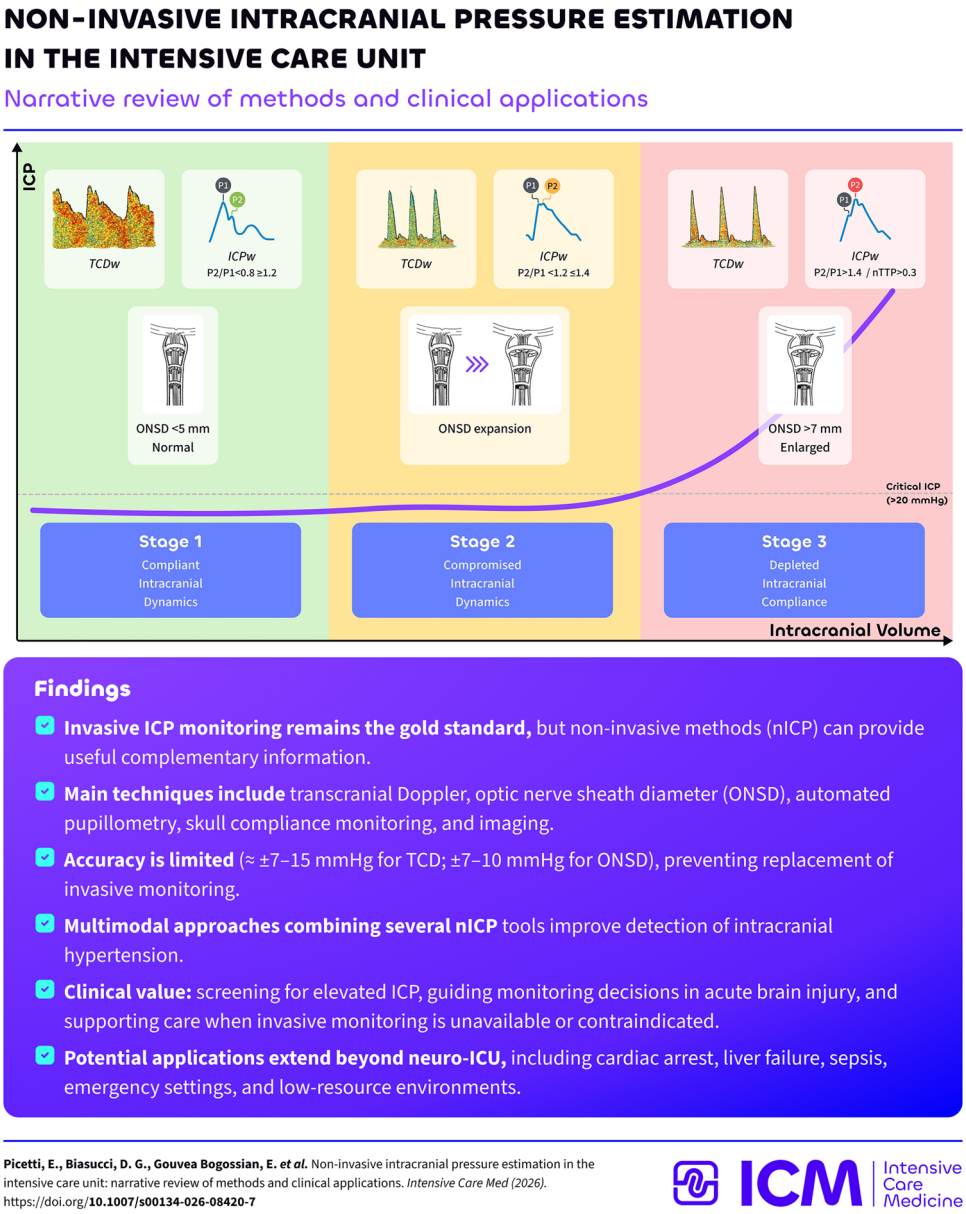
Graphical abstract:



Keywords: Non-invasive intracranial pressure, Outcome, Intensive care medicine, Secondary brain damage, Brain ultrasound, Automated pupillometry

Introduction

Intracranial hypertension (IH) after acute brain injury (ABI) is an important cause of secondary brain damage and remains a matter of continuous investigation [1]. It is widely recognized that intracranial pressure (ICP) is 'more than the number'; therefore, its continuous monitoring should be considered as a mandatory tool to avoid additional brain insults, resulting from a hyperdynamic course of ICP (plateau waves, sudden refractory hypertension, changes in arterial partial pressure of carbon dioxide ($PaCO_2$), etc.) [1]. Despite the lack of a positive Level-I evidence on outcome in traumatic brain injury (TBI), ICP monitoring is generally considered of paramount importance in the neuro-intensive care setting [2–5]. Invasive methods

(i.e., intraparenchymal and external ventricular drain (EVD) systems) are considered the gold standard for ICP measurement and treatment [6]. However, in some settings (e.g., low-income countries, austere environments, etc.), these systems are not immediately and easily available. Moreover, patients may have contraindications for invasive tools (i.e., infections, coagulopathy) or may not completely meet indications for insertion. This has induced many authors to focus their efforts, over the last decades, on the study of non-invasive ICP (nICP) estimators [7, 8]. A variety of non-invasive tools have been proposed, each with different levels of accuracy, availability, and feasibility (Table 1) [8]. Although none of these modalities has demonstrated sufficient accuracy to replace invasive ICP monitoring (mainly due to lack of calibration and zeroing), several have shown potential to complement invasive measurements. Rather than serving as substitutes, non-invasive tools provide additional, clinically relevant information regarding the risk and likelihood of IH. Importantly, they may also add value even when invasive ICP monitoring is in place, by contributing complementary physiological insights that support clinical decision-making across a range of settings [9]. Importantly, high sensitivity and high specificity are generally mutually exclusive. For example, a highly sensitive approach will result in many patients undergoing invasive monitoring unnecessarily, whereas a highly specific strategy risks missing patients with elevated ICP. This review aims to provide clinicians involved in the care of critical care patients [e.g., emergency physicians, general intensive care unit (ICU) physicians, neurosurgeons, etc.] with an updated overview on the methodology and clinical applications of nICP monitoring tools.

Take-home message

Although invasive intracranial pressure (ICP) monitoring tools remain the gold standard for diagnosing and managing intracranial hypertension, non-invasive methods (nICP) can provide valuable support in specific conditions.

Each nICP method has specific own strengths, methodological limitations and variable accuracy; therefore, a combination of different complementary tools is warranted to raise or exclude the suspicion of intracranial hypertension.

Methods for non-invasive ICP estimation

Transcranial Doppler: pulsatility index and diastolic flow velocity formula

Transcranial Doppler (TCD) ultrasound offers a portable, bedside method to measure cerebral blood flow (CBF) velocities in basal intracranial arteries, most commonly the middle cerebral artery (MCA). Because ICP alters intracranial compliance and distal cerebrovascular resistance, mainly due to changes in cerebral perfusion pressure (CPP), TCD waveform variations, especially in diastolic flow and pulsatility, have been studied extensively as non-invasive surrogates to estimate ICP and CPP in critically ill patients (Fig. 1). The cranial vault is a fixed-volume compartment in which arterial inflow, venous outflow, cerebrospinal fluid (CSF) and brain tissue volume interact, resulting in modulation of ICP. An increase in ICP reduces CPP, decreasing downstream vascular resistance (in patients with intact autoregulation mechanism) and increases critical closing pressure (CrCP), and preferentially diminishes diastolic flow. These hemodynamic changes modify the shape of the arterial velocity waveform recorded by TCD; systolic peaks may be preserved or even slightly increased, while end-diastolic velocities (EDV or FVd) fall, producing greater waveform pulsatility that can be quantified by the pulsatility index (PI) [10]. As TCD records peak systolic velocity (PSV), EDV, and time-averaged mean velocity (MV or FVm) from basal cerebral arteries, PI is calculated as (PSV − EDV)/MV. The PI mathematically can be described as a complex function of CPP, arterial blood pulse pressure, cerebrovascular resistance, compliance, and heart rate [11]. Therefore, PI is modulated by systemic hemodynamics (acute mean arterial pressure (MAP) changes, heart rate), arterial properties (stiffness, atherosclerosis), ventilatory status ($PaCO_2$), vasoactive drugs, and operator/acoustic window variability. These confounders can change PI independently of true CPP and ICP. For example, in case of vasospasm, PI may be altered by arterial narrowing rather than IH. As such, multivariable regression and machine-learning models that combine continuous waveform features with systemic inputs [MAP, $PaCO_2$/end-tidal CO_2 ($ETCO_2$), heart rate] and patient factors (age, vascular comorbidity) may improve classification of elevated ICP and sensitivity to therapeutic responses [12]. The TCD-PI presents a sensitivity and specificity of 0.74 for an optimal cut-off value of 1.28 [9] (ESM 1). Another quantitative nICP estimation from TCD can be performed using empirical formulas combining systemic arterial pressure with Doppler flow velocities. A commonly applied two-step method [13, 14] estimates non-invasive CPP (nCPP) from the ratio of FVd to FVm, then derives nICP from MAP:

$$nCPP = MAP \times \left(\frac{FVd}{FVm}\right) + 14$$

$$nICP = MAP - nCPP.$$

Table 1 Summary of different commercially available bedside non-invasive ICP methods with pros, cons availability, limitations, costs

Technique	Principle	Cut-offs for IH/ IH indicators and sensitivity/specificity	Pros	Cons	Commercial information[a]	
Automated pupillometry	Quantifies pupillary parameters, such as size, constriction and dilation velocities, and light response latency	NPi ≤ 3 suggests brainstem injury, possibly due to cerebral herniation Sensitivity = 0.68 and specificity = 0.68 for an optimal cut-off value of 3.96 [ESM 1]	Eliminates the subjectivity and inter-observer variability inherent in manual pupillary assessment. The Neurologic Pupillary index -NPi- provides an objective and aggregated score that has shown a strong correlation with outcomes in acute brain injury patients	Pupillometry may not detect more subtle or early ICP changes The exact cause of pupillary abnormalities (direct nerve injury versus ICP-related compression versus medication effect) still requires comprehensive clinical evaluation and can be challenging in cases of polytrauma or complex neurological conditions	Several providers. (NPi is a proprietary parameter from a single provider)	Low cost but disposable lens are intended for limited scans; not restricted to use by a specific professional
Optic nerve sheath diameter ultrasound	Ultrasound can assess the optic nerve sheath, which expands with increased ICP	Nerve sheath ≥ 6 mm indicates IH Sensitivity = 0.83 and specificity = 0.83 regarding an optimal cut-off value of 5.9 mm [ESM1]	This procedure can be carried out by both nurses and physicians. It requires training to achieve competency	Serial monitoring is employed. The literature reports different cutoffs and approaches to assess intracranial hypertension. The effects of clinical interventions remain to be established	Several providers	One-time device purchase. No disposables
Skull microdeformation	ICP waveforms can be reproduced from micrometric detection of skull pulsation synchronized with each heartbeat	P2/P1 ratio ≤ 0.8 rules out IH (sensitivity 0.92, specificity 0.19) [2]. P2/P1 ratio ≥ 1.4 indicates IH (sensitivity 0.11, specificity 0.90) [2]. Can be reinforced with a TTP ≥ 0.3 (sensitivity 0.16, specificity 0.92) [2]. A ML model can estimate ICP values with an error of nearly 3 mmHg	Allows continuous monitoring in real time; good temporal resolution to observe responses to clinical interventions. Not restricted to use by a specific professional	Patients who are highly agitated may be unsuitable candidates for scanning	Single provider	Affordable, requires a monthly digital subscription, no disposables
TCD – PI	The device uses Doppler shift to calculate blood velocity and applies color coding to indicate flow direction and insonation angle	PI ≥ 1.4 with diastolic velocities ≤ 20 cm/s indicate IH Sensitivity = 0.74 and specificity = 0.74 regarding an optimal cut-off value of 1.28 [ESM1]	Allows multiple additional diagnostics, as brain death, arterial stenosis, emboli and the overall cerebral hemodynamic panorama	Only physicians may perform this procedure, which requires extensive training for competency. Multiple central and systemic variables influence its parameters	Several providers	One-time device purchase. No disposables

Table 1 (continued)

Technique	Principle	Cut-offs for IH/ IH indicators and sensitivity/specificity	Pros	Cons	Commercial information[a]	
TCD—nICP formula	Uses TCD blood flow velocity and ABP signal	nICP > 25 mm Hg can be considered as a threshold for intracranial hypertension Sensitivity = 0.70 and specificity = 0.70 with an optimal cut-off value of 19.6 mmHg [ESM1]	Allows continuous monitoring of ICP- mean value, respiratory, pulse and vasogenic waves	Absolute error around 9.5 mm Hg	Several providers	One-time device purchase. No disposables

CSF, cerebrospinal fluid; CT, computed tomography; CTP, CT perfusion; CTxe, Xenon CT; EEG, electroencephalogram; ICP, intracranial pressure; IH, intracranial hypertension; MRI, magnetic resonance imaging; NIRS, near-infrared spectroscopy; PI, pulsatility index; TTP, time-to-peak; ML, machine learning; TCD, transcranial Doppler; ABP, arterial blood pressure; nICP, non-invasive intracranial pressure

[a] Most hospitals have Ultrasound/TCD/EEG already, hence is less the purchase of the machine, but more the indirect cost of provider time/interpretation, etc., that might be rate-limiting, versus new purchase of a new system

These equations provide a physiologically intuitive link between systemic pressure, Doppler-derived flow distribution, and estimated ICP, being useful for trend detection and Doppler data integration into clinical decision pathways. The TCD-nICP presents a sensitivity and specificity of 0.70 for an optimal cut-off value of 19.6 mmHg [9] (ESM 1). Many studies have evaluated the validity of TCD-derived nICP. The Invasive Versus Non Invasive Measurement of Intracranial Pressure in Brain Injury Trial 2 (IMPRESSIT-2) validated the role of TCD assessments as a screening tool to exclude clinically relevant IH in ABI patients, showing high negative predictive value (NPV) compared with simultaneous invasive ICP monitoring, and reinforcing the importance of standardized acquisition and experienced operators [15]. Acoustic window failure and poor image/measurement quality may also limit applicability in a subset of patients. Mid-range ICP values remain the zone of greatest uncertainty; TCD-derived methods are most reliable for trend detection and for identifying extreme states (very low EDV or diastolic flow reversal) rather than providing precise single-point ICP numbers [16]. In order to optimize clinical use of these non-invasive techniques, TCD-nICP and PI should be integrated into a multimodal monitoring strategy including: (1) standardized TCD exams with concurrent MAP and $PaCO_2$ documentation; (2) interpretation of PI and nCPP/nICP trends alongside neurological examination and imaging; and (3) contemporary use of other devices such as pupillometry and electroencephalogram (EEG). This strategy may help reserve invasive ICP monitoring when precise numeric ICP values are required for management decisions. Another useful rule may be adopted at the bedside: if during TCD examination PI is greater than 1.5, without arterial hypotension and hypocapnia, these findings suggest that ICP is elevated. The B-ICONIC consensus proposes a set of 34 recommendations (32 of which were strong) designed to assist clinicians managing TBI patients using nICP systems plus clinical assessment, in the presence or absence of brain imaging [9]. One of the strong recommendations is the use of at least two different nICP methods integrated into the clinical exam and imaging, when available [9]. In case of severe IH, TCCD can detect changes indicative of compromised CBF progressing towards cerebral circulatory arrest (i.e., reverberating flow, systolic spikes, and disappearance of previously registered flow) and consequent brain death [17].

Transcranial Doppler: other advanced methods for nICP estimation

Transcranial Doppler ultrasonography remains a central modality for nICP estimation, with modern work converging on three physiologically and analytically distinct

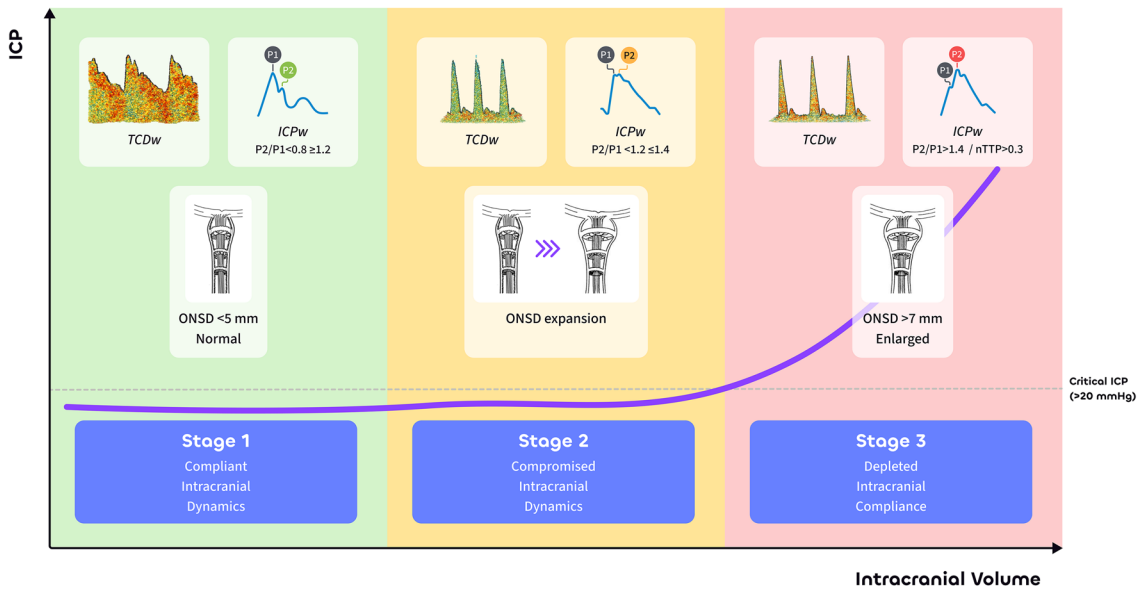


Fig. 1 Multimodal staging of intracranial compliance along the intracranial volume–pressure curve. The colored bands depict three compliance stages; the purple curve shows the exponential rise in ICP with increasing intracranial volume. The dashed horizontal line marks a commonly used clinical action level (ICP > 20 mmHg). Stage 1—compliant intracranial dynamics (green). Typical ICP waveform (ICPw) from brain4care (B4C) (with P1 ≥ P2; screening range P2/P1 ≈ 0.8–1.2. TCD waveform (TCDw) shows preserved diastolic flow without marked pulsatility. Optic nerve sheath diameter (ONSD) usually < 5 mm. Stage 2—compromised intracranial dynamics (yellow). P2 approaches or slightly exceeds P1; screening range P2/P1 ~ 1.2–1.4. ONSD shows interval expansion (~ 5–7 mm) or upward trend. TCDw often shows increased pulsatility compared with Stage 1. Stage 3—depleted intracranial compliance (pink). P2 > P1 with P2/P1 > 1.4 and nTTP > 0.30, consistent with low compliance and a higher likelihood of intracranial hypertension. ONSD > 7 mm is shown as a supportive marker. TCDw illustrates pronounced pulsatility. Abbreviations: B4C, brain4care; ICPw, intracranial pressure-related pulse morphology (P1 percussion peak; P2 tidal peak); nTTP, normalized time-to-peak; TCDw, transcranial Doppler waveform; ONSD, optic nerve sheath diameter. The direct associations between modalities are conceptual rather than definitive (i.e., despite increased ICP or reduced compliance, only some modalities may show signs of increased ICP depending on patient-specific circumstances)

strategies. Mathematical models that derive nICP from arterial blood pressure–flow relationships, including nCPP formulations, have been widely investigated [18, 19]. Although initial studies [19] suggested potential utility as screening tools, prospective validation has never been conducted. Generally, these methods cannot provide a reliable estimate of ICP values and serve only as high-NPV "rule-out" screening tools [15, 20]. Machine-learning and deep-learning methods represent the most promising evolution to date. By leveraging full arterial waveforms, arterial pressure, and electrocardiogram (ECG) timing, these models learn complex, nonlinear ICP-flow relationships unavailable to analytical formulas. Recent work (conducted, however, in a short series of patients) using domain-adversarial neural networks has achieved mean absolute errors near 3.9 mmHg, outperforming all previous TCD-based techniques and demonstrating improved detection of IH [21]. However, these tools are not universally available. A complementary venous approach using TCD focuses on deep cerebral venous outflow [22], particularly the straight sinus and basal veins. Venous TCD has shown good correlation with invasive ICP ($r = 0.54$), with further improvement when combined with optic nerve sheath diameter (ONSD) ($r = 0.81$) [23]. Despite this strong physiological signal, its clinical translation is hindered by operator dependency and technical difficulty [21, 22]. Overall, currently available approaches demonstrate the expanding utility of TCD for trend monitoring and risk stratification [15]. TCCD is also useful for the visual assessment of midline shift facilitating early diagnosis and treatment in patients with a significant intracranial mass effect [24]. Studies indicate that TCD-based nICP methods show 95% limits of agreement ranging from ± 7 mmHg to as high as ± 15 mmHg [25]. Invasive ICP probes, considering Food and Drug Administration (FDA) requirements, must instead adhere to a strict accuracy of ± 2 mmHg in the range of 0–20 mmHg. However, no TCD-based method currently matches the accuracy, reliability, or treatment-guiding capability of invasive ICP monitoring.

Optic nerve sheath diameter

Optic nerve sheath diameter ultrasonography is a nICP surrogate that takes advantage of the direct continuity of the optic nerve sheath (ONS), the CSF, and the meninges with the brain [25–28]. This network allows ICP

transmission into the ONS [25]. The ONS bulb, around 3 mm behind the globe, is the most sensitive part to ICP changes [27], which is likely due to its looser trabecular meshwork without rigid septa or pillars found in the rest of the sheath [28] (Fig. 1). However, several methodological limitations must be considered when interpreting ONSD measurements. Prolonged exposure to IH may alter the elastic properties of the optic nerve sheath, potentially affecting its ability to return to baseline dimensions. In adults, ONSD values are generally considered normal below approximately 5.2 mm and suggestive of enlargement when exceeding 5.8 mm; however, fixed cutoffs should be interpreted with caution. In the case of values between 5.2 and 5.8 mm, we suggest considering clinical picture, neuroimaging, other nICP tools, and eventually early repetition of the ONSD measurement. For ONSD-based techniques, the 95% limits of agreement range from ± 7–10 mmHg [29] which, as mentioned above, contrast with FDA requirements for invasive ICP probes. The ONSD ultrasonography presents a sensitivity and specificity of 0.83 for an optimal cut-off value of 5.9 mm [9] (ESM 1). The ONSD is also influenced by individual anthropometric characteristics, and several studies recommend normalization to eyeball diameter and/or optic nerve diameter to improve accuracy. To optimize visualization of the optic nerve trajectory, the CLOSED [Color Doppler–Low power examination–Optic disk clarity–Safety (short examination duration)–Elevate frequency–Dual measurements] protocol advocates the use of color Doppler to identify the central retinal artery and vein within the nerve [30]. In addition, many studies do not clearly specify whether the internal ONSD (ONSDint), i.e., measuring only the subarachnoid space, or the external ONSD (ONSDext), i.e., including the dural sheath, is assessed [31]. These two approaches differ substantially, with a reported mean discrepancy of approximately 22%, which limits inter-study comparability when not explicitly defined [32]. As with all ultrasound-based techniques, inter-observer variability represents an important source of measurement error. Accordingly, it is recommended to perform repeated measurements and to confirm consistency, typically defined as less than a 10% difference between values. Furthermore, ocular ultrasound should always adhere to the ALARA (As Low As Reasonably Achievable) principle to minimize acoustic exposure to the retina and lens [31]

Given these limitations, ONSD is often most informative when used for serial assessments in the same patient, comparing changes over time rather than relying on a single absolute value. Despite methodological heterogeneity, multiple meta-analyses have demonstrated that ONSD ultrasonography has good diagnostic performance for detecting intracranial hypertension, with reported sensitivities ranging from 86 to 92%, specificities from 78 to 90%, and overall diagnostic accuracy between 0.87 and 0.93 in both traumatic and non-traumatic neurocritical care populations [31, 33–35]. Recommendations to improve the utility of ONSD include: (1) following a standardized imaging and measurement checklist [36], (2) avoiding artifacts [37], (3) using machine learning to automate measurements [38], and (4) using a multimodal approach to evaluate ICP, including TCD, pupillometry, and ONSDint cut-off > 6 mm [9]. This method requires a linear probe (without adjunctive software installation), which is generally easy to find worldwide. However, this method is not always feasible after TBI because eye accessibility might not be possible.

Automated pupillometry

Automated pupillometry allows objective and comprehensive assessment of the pupillary light response (PLR) providing pupil size, percentage of pupillary constriction (%C), constriction velocity (CV), maximum contraction velocity (MCV), dilation velocity (DV), and latency response [39]. Some pupillometers also provide pupil indexes like the neurologic pupil index (NPi) and the quantitative pupillometry index (QPi), which integrate the above-mentioned parameters with a score from 0 to 5 (an NPi or a QPi < 3 is considered abnormal) (Fig. 1). Automated pupillometry presents a sensitivity and specificity of 0.68 for an optimal cut-off value of 3.96 [9] (ESM 1). Altered PLR, such as changes in pupil size and reactivity, reflects midbrain compression caused by uncal herniation, ischemia, hemorrhage, or edema [39–41]. As such, PLR parameters may be altered in case of IH with associated midbrain and/or oculomotor nerve compression. In fact, studies have reported abnormal NPi values preceding the diagnosis of uncal herniation in ABI patients [42, 43] while a significant, clinically relevant decrease in NPi often accompanies sustained episodes of IH [44, 45]. However, third cranial nerve or brainstem compression is not always present in case of elevated ICP. In fact, most cohort studies reported only a weak, clinically insignificant association between NPi reduction and ICP elevation [46–50], while a few demonstrated a moderate inverse correlation between NPi and ICP [44, 51, 52]. Moreover, Petrosino et al. demonstrated an overall lack of association between concomitant repeated NPi and invasive ICP values [50]. Therefore, as suggested by the B-ICONIC consensus, the NPi alone to assess ICP is unreliable and should only be applied in conjunction with other non-invasive methods and clinical picture to identify IH [9]. Additionally, other parameters such as CV, DV, %C, and pupil size may have a role in the nICP evaluation [41, 43, 53, 54], despite being less studied than NPi.

Non-invasive estimation of intracranial compliance

The skull may extend when ICP rises; this extension is very small but can be monitored using high-precision electronic devices. One of them is the brain4care (B4C) system, a novel non-invasive cranial extensometer designed for continuous, real-time monitoring of ICP wave (ICPW) morphology, intracranial compliance (ICC), and ICP estimation [55–60]. Technically, the B4C is a wearable device detecting beat-to-beat micrometric skull deformations from ICP variations with high sensitivity (< 0.2 µm) [61]. The proprietary algorithm extracts key ICPW parameters like the P2/P1 ratio and the time-to-peak (TTP), validated to show strong agreement with invasive measures in several single-center observational studies [55–58, 60, 62, 63]. A P2/P1 ratio of 0.8 has a 92% sensitivity to ICP rise above 20 mmHg, whereas a P2/P1 ratio of 1.4 and a TTP of 0.3 demonstrate a 90% specificity [60]. An integrated machine learning model also enabled nICP estimation with promising accuracy, which will be a possible additional information automatically provided by this system in the near future [64]. Normal values of P2/P1 ratio should be < 0.8 and TTP below 0.3 in both adult and pediatric populations. These values can increase with age and in women, with the P2/P1 ratio reaching up to 1.2 [65, 66]. Clinical studies show that a P2/P1 ratio above 1.4 is associated with a higher risk of IH [60]. These ratios relate non-linearly to ICP and may decrease after ICP reaches a critical level [63]. Initial clinical studies show broad applications of this novel methodology, which include detecting ICP elevations, assessing IH, cerebral autoregulation [67], cerebrospinal compliance [61], and brain compensatory reserve [61], providing prognostic insights to achieve better outcomes [49, 62, 68]. Its high NPV for ruling out IH makes it a valuable screening tool [60, 62]. Enhanced prognostic capabilities are observed when B4C is combined with TCD [59]. The system can capture waveforms similarly to invasive methods in patients, regardless of skull condition, including fractures, craniotomy, or craniectomy [55]. However, ICP waveform applicability when the bone flap is absent still needs further assessment [69]. The system monitors all intracranial volumes, serving as a proxy for evaluating intracranial dynamics. Changes in ICP wave patterns indicate that resistance to blood or cerebrospinal fluid flow in the brain is increased [61]. Future research on B4C should focus on extensive validation through large-scale, multicenter prospective studies across diverse patient populations to strengthen generalizability and to confirm its accuracy in various clinical scenarios. Technological advancements are crucial, including improving algorithms for ICP estimation. Clinically, future studies should investigate the system's impact on patient outcomes by guiding personalized therapies, optimizing ICP management, supporting mechanical ventilation weaning, etc.

Other methods

Neuroimaging, particularly computed tomography (CT), may show radiological signs of IH (e.g., midline shift, basal cistern effacement, and/or presence of space-occupying lesions) [70, 71]. The MRI imaging-derived elastance index (derived from the ratio of pressure to volume change) shows a promising correlation with ICP [72]. Moreover, both techniques can be utilized to estimate ONSD [73]. The presence of IH with a normal CT scan of the brain is a classic presentation of idiopathic intracranial hypertension [74]. In this regard, subtle signs of chronic high pressure are empty sella (flattening of the pituitary gland), dilatation of the optic nerve sheaths, or slit-like ventricles. Unfortunately, CT and MRI are time-consuming methods not easily useful for repeated bedside assessments.

The EEG can show changes related to IH and associated cerebral ischemia such as frequency slowing, reduced amplitude, or background disorganization [75, 76]. However, the EEG requires interpretation by trained personnel and is frequently influenced by sedative medications [75].

Intracranial pressure increments are transmitted to the optic nerve and retinal veins, inducing swelling of the optic disc and venous collapse [77]. These signs, if analyzed with a simple portable ophthalmoscope, are subjective and not always specific [77]. The optical coherence tomography (OCT) and the OCT-angiography (OCTA) can provide more objective and detailed assessments [77]. These devices are difficult to transport to the patient's bedside and require pharmacological pupil dilation (which can affect the neurological assessment for some time) [77]. A small pilot study was recently published regarding a portable instrument, but more data are needed on the applicability and reliability of this tool in daily clinical practice [78].

Intracranial components (brain, blood, and CSF) have different acoustic properties. A change of the content of these components, inside the acoustic path, influences the total acoustic characteristics of the intracranial media [79, 80]. The time-of-flight (TOF) analysis, which accounts for cranial tissue impedance, requires a specialized equipment and is not widely available in clinical practice [79, 80].

Pressure exerted from the CSF within the skull is transmitted to the perilymph within the inner ear [79, 81]. Therefore, an increase in ICP leads to a proportional increase in peri-lymphatic pressure, which can be measured non-invasively by the tympanic membrane

displacement [79, 81, 82]. More studies are necessary to validate this technique in daily clinical practice.

Another nICP measurement method is based on a two-depth high-resolution transcranial Doppler insonation of the ophthalmic artery. The artery is used as a natural pair of scales, in which the intracranial segment of the artery is compressed by ICP and the extracranial segment is compressed by extracranial pressure (Pe) applied to the orbit. The blood flow parameters in both ophthalmic artery segments are approximately the same when Pe = ICP. A specialized monitor has been constructed and tested clinically [83].

Clinical applications

Neuro-intensive care (when ICP is available)

In patients with severe TBI or SAH, nICP assessment may primarily help to refine patient selection for invasive monitoring (Fig. 2). Only about one-third of TBI patients who meet guideline-based monitoring criteria ultimately develop sustained IH [84]. Similarly, in SAH, EVDs are often placed for altered consciousness or hydrocephalus, although significant brain edema may also occur in the absence of CSF accumulation [85]. In ischemic or hemorrhagic stroke, decisions regarding ICP monitoring are usually based on hematoma or infarct size, yet international practices remain highly variable and potential survival implications have been reported [86, 87]. Earlier identification of candidates for direct ICP monitoring based on nICP assessment may facilitate timely recognition of midline shift before herniation and potentially support optimal decisions regarding brain imaging, neurosurgical intervention or escalation of medical therapy. Non-invasive monitoring may help identify such complications and/or discuss the personalized implementation of invasive monitoring. Furthermore, nICP assessment may support timely decision-making in moderate TBI or other at-risk patients who do not fulfill formal criteria for invasive monitoring, enabling earlier identification of candidates for ICP monitoring with higher accuracy. In cases of unclear decreased consciousness, nICP may help determine whether an emergency CT is necessary or whether alternative diagnoses (e.g., delirium) or diagnostics (e.g., EEG) should be prioritized first. Also, nICP is particularly valuable when invasive monitoring is contraindicated or unsafe, such as in the presence of coagulopathy (e.g., polytrauma), anticoagulation (e.g., hemorrhagic stroke), or dual antiplatelet therapy (e.g., SAH treated with intracranial stents), as it would allow safe interim surveillance until definitive monitoring becomes feasible. Finally, in patients already undergoing invasive monitoring, concurrent nICP assessment may contribute to individualized treatment thresholds and strategies (e.g., quantifying the tolerability of the brain to a specific ICP value rather than protocol-driven care based on fixed thresholds, hyperemia contributing to IH, etc.) (Fig. 3).

There is currently no evidence that pre-screening patients with non-invasive methods prior to invasive ICP probe placement is cost-effective or improves outcomes. In the Benchmark Evidence from South American Trials: Treatment of Intracranial Pressure (BEST-TRIP) trial [84], the group managed with imaging- and clinical-based strategies underwent more brain-specific diagnostics and interventions, without significant difference in 6-month survival or neurological outcome. In some situations, rapid placement of an invasive probe might simply be more convenient.

In some cases, the implementation of non-invasive tools was found to be associated with unintended adverse effects. For example, Hollingworth et al. [88] reported worse long-term outcomes in centers that used routine TCD screening in addition to the standard of care, compared to those that did not, in a cohort of over 2.000 aSAH patients.

General ICU population: cardiac arrest, liver failure, mechanical ventilation, sepsis

In the general ICU population, brain injury may arise from distinct mechanisms and is increasingly recognized as a key determinant of outcome (ESM 1) [89–92]. Following cardiac arrest, global ischemia–reperfusion induces a primary insult that is subsequently aggravated by secondary brain injury caused by IH [93], easily overlooked in the absence of proper nICP methodology. In conditions such as acute respiratory failure (ARF), liver failure, sepsis, or during mechanical ventilation, secondary brain injury can develop due to systemic derangements or elevated intrathoracic pressures, even in the absence of ABI at admission [94–101]. In this context, non-invasive neuromonitoring tools, such as ONSD ultrasonography, TCD/transcranial color-coded duplex (TCCD), and automated pupillometry, provide complementary information on ICP, cerebral perfusion, autoregulation, and brainstem function. These techniques complement each other by capturing different aspects of cerebral physiology: vascular resistance, edema, and brainstem reflexes. Following cardiac arrest, ischemia–reperfusion injury triggers cytotoxic and vasogenic edema, impaired autoregulation, and, in some cases, IH [93]. The CBF decreases immediately after the return of spontaneous circulation (ROSC) but generally normalizes within 72 h, with more pronounced reductions in severe hypoxic–ischemic encephalopathy (HIE) [102, 103]. Transcranial Doppler-derived indices, including PI and estimated CPP, reflect intracranial compliance and perfusion after ROSC. In a recent study, a PI ≥ 1.49 was

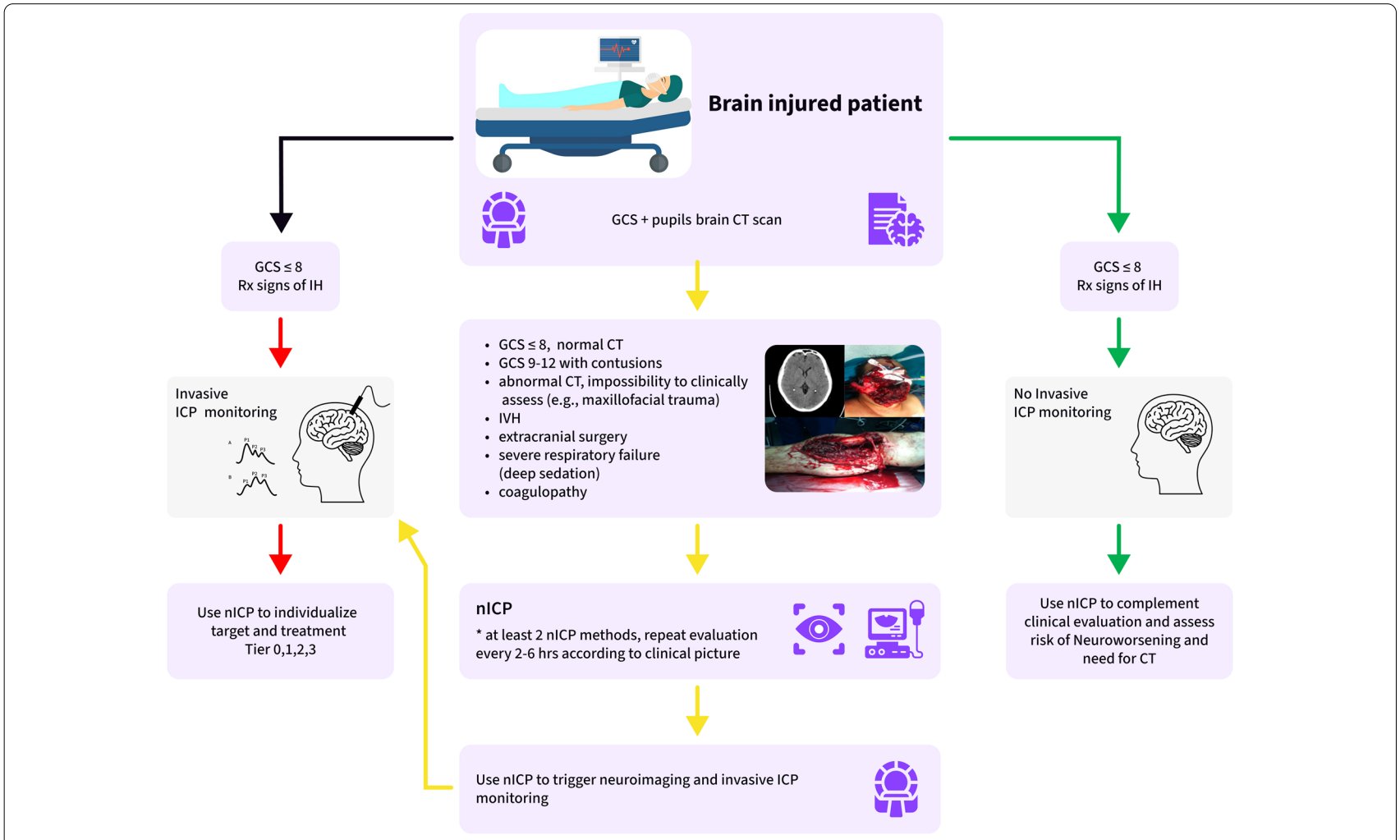


Fig. 2 Potential use for the application of non-invasive intracranial pressure monitoring (nICP) tools in patients with acute brain injury when ICP is available. After initial assessment (Glasgow Coma Scale, GCS, and neuroimaging), in patients with severe brain injury (i.e., GCS < 9), nICP could help to better select patients for invasive intracranial pressure (ICP) monitoring, or to monitor those with contraindications to invasive ICP, or to individualize ICP thresholds for therapeutic interventions. In mild-to-moderate injury, nICP might help to identify patients with the highest risk of intracranial hypertension, risk of neuro-worsening and need for imaging and invasive tools. Abbreviations: TBI = traumatic brain injury, IH = intracranial hypertension, nICP = non-invasive intracranial pressure; GCS, Glasgow Coma Scale; CT, Computed Tomography; IVH, intraventricular haemorrhage

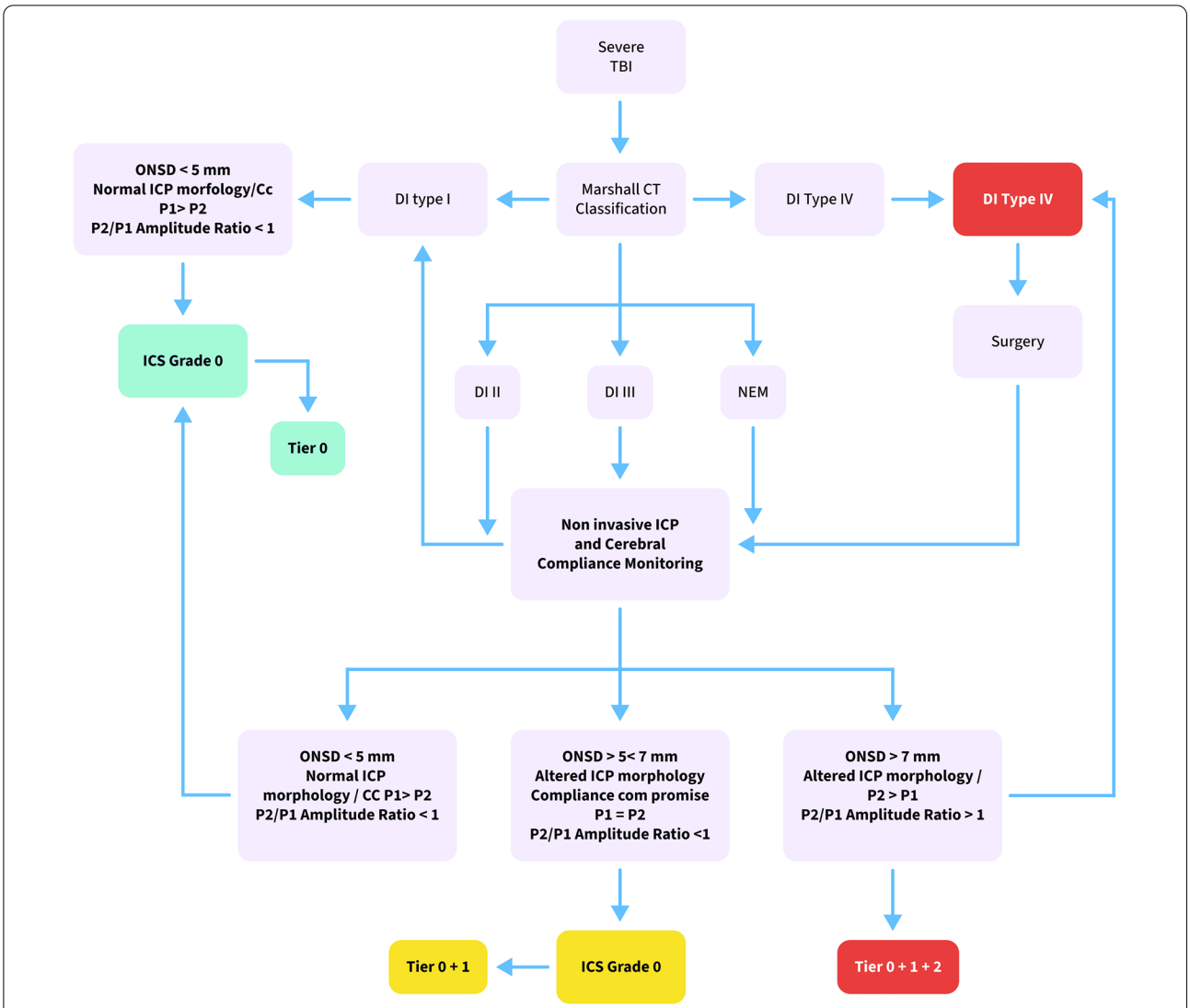


Fig. 3 PARADIGM Protocol (supported by intracranial compartment syndrome and developed with computed imaging scan findings (Marshall's classification*) and non-invasive neuromonitoring, for the management of acute brain injured patients when invasive ICP is not available. TBI: traumatic brain injury; DI: diffuse injury; ICP: intracranial pressure; CC: cerebral compliance; ICS: intracranial compartment syndrome; NEML: non-evacuated mass lesion; ONSD: optic nerve sheath diameter. *Marshall LF, Marshall SB, Klauber MR, van Berkum Clark M. A new classification of head injury based on computerized tomography. J Neurosurg. 1991; 75(Suppl): S14–20

significantly associated with poor neurological outcome [104]. In another prospective study, TCD-based ICP estimation showed a significant, albeit moderate, correlation with invasive ICP and a high predictive value for IH [97]. In the same study, ONSD demonstrated the strongest correlation with invasively measured ICP and an excellent accuracy in detecting IH [105]. The PLR assessed through quantitative pupillometry is a reliable prognostic marker after ROSC. A NPi ≤ 2 within 6 h after cardiac arrest strongly predicts poor neurological outcome [106, 107], with persistence at 72 h being highly specific [108, 109]. Thus, quantitative pupillometry complements EEG and somatosensory-evoked potentials in neuro-prognostication [110].

Cerebral edema and IH are devastating complications of acute liver failure, with an incidence of approximately 30% [111, 112]. Invasive ICP is contraindicated in the case of coagulopathy, making non-invasive approaches the safest alternative in this setting. In adults, ONSD and PI have shown limited diagnostic accuracy, whereas TCD-derived nICP demonstrated excellent performance with a high NPV [113]. In children, ONSD has been shown to predict mortality [114], and prospective data indicate that an ONSD > 4.55 mm

reliably identifies raised ICP, while failure to reduce it below 4.6 mm within 24 h predicts poor outcomes [115]. These modalities may also guide timely escalation of interventions, including osmotherapy or ammonia-lowering treatments.

The complex interplay between the brain and lungs has critical implications in ARF patients. Hypercapnia and hypoxemia directly influence CBF, with TCD/TCCD-derived FVm and PI providing reliable bedside correlations with oxygen content and $ETCO_2$ [116–120]. The impact of positive end-expiratory pressure (PEEP) on ICP and CPP is influenced by the lung recruitability and the cerebral autoregulation status. When PEEP induces alveolar overdistension, the subsequent rise in intrathoracic pressure may increase ICP and reduce CPP. Conversely, when PEEP promotes effective alveolar recruitment, oxygenation can improve without increasing intrathoracic pressure, thereby minimizing harmful cerebral effects [97–99, 121–124]. The TCD/TCCD assessment enables clinicians to identify deleterious responses—such as elevated PI or nICP and reduced CBF—and to guide individualized PEEP titration [121]. The application of prone positioning (PP) may add further challenges: in the acute respiratory distress syndrome (ARDS), even in the absence of ABI, standard PP has been associated with increased PI, which can be mitigated by a 30° reverse-Trendelenburg 'head-up' PP [125]. Similarly, in ARDS patients with ABI, tailoring head inclination during PP guided by TCD monitoring may help to mitigate ICP increase [126, 127]. Some non-invasive tools (e.g., TCCD, pupillometry, etc.) could be useful for neuromonitoring in patients undergoing extracorporeal membrane oxygenation support [128].

The TCD-derived nCPP (i.e., estimated CPP) was found to be reduced in one-third of a cohort of 132 septic patients; however, these alterations were not associated with the development of sepsis-associated encephalopathy (SAE) or with in-hospital mortality [129]. In contrast, an ONSD > 5.2 mm has shown high predictive value for SAE [130]. Moreover, TCD is essential for assessing cerebral autoregulation which is an independent predictor of SAE [131].

Generally, it is important to underline how none of the described methods has been validated specifically in these populations; most development and validation studies focus on TBI cohorts. Further studies should be performed in these settings.

Pre-hospital and emergency department settings (potential applications before to arrive in the ICU)

The very early phase following an acute cerebral insult can critically influence patient outcomes, particularly in the presence of IH, which, if unrecognized, may rapidly progress to fatal neurological deterioration. In the prehospital setting, where invasive ICP monitoring is not available, non-invasive assessment techniques could potentially play a fundamental role in the early identification of IH. Initial patient evaluation primarily focuses on detecting clinical features suggestive of raised ICP, including headache, nausea, vomiting, and visual disturbances. Suspicion should be further heightened in the presence of reduced level of consciousness, abnormal pupillary light reflexes, systemic arterial hypertension with widened pulse pressure, tachycardia followed by bradycardia, and irregular respiratory patterns [132, 133]. However, it is important to recognize that classical signs such as pupillary abnormalities, arterial hypertension, and bradycardia have limited sensitivity for identifying IH in the prehospital environment, particularly in the early stages [134, 135].

For the rapid assessment of comatose patients, automated pupillometry could represent a valuable first-line tool. It allows objective, quantitative evaluation of bilateral pupillary light reflexes within a few seconds, providing insight into midbrain function, and can be repeated frequently without operator dependency. In the subsequent minutes, either at the scene, during ambulance transport or in the emergency department, additional complementary non-invasive assessments can be performed. Available non-invasive cranial extensometers offer practical advantages in these settings, as they do not require a physician or specialized operator and allow hands-free application. Once installed, reliable signal acquisition can be achieved within approximately one minute. Importantly, this technology enables continuous or intermittent monitoring over prolonged periods, assessing intracranial compliance through waveform analysis. This could allow early detection of IH, monitoring of its progression, evaluation of responses to therapeutic interventions, and longitudinal comparisons over time. Ultrasound-based techniques, although examiner-dependent, could also be implemented early; ONSD measurement and TCD/TCCD could provide valuable information. Unilateral ONSD enlargement may suggest ICP gradients, whereas bilateral enlargement is more consistent with acute and severe IH [136, 137]. TCD/TCCD enable indirect estimation of ICP through parameters such as PI and FVd, while insonation of the MCAs offers a rapid overview of global cerebral hemodynamics and remains particularly useful in the evaluation of acute stroke [136, 137]. Although more studies are needed in these settings to draw reliable recommendations, the use of nICP tools, in experienced hands and integrated with clinical and radiological examination [138–140], could facilitate timely recognition of IH allowing early intervention. Early IH detection, even before imaging, could

allow clinicians to mitigate the risk of cerebral herniation during patient transport or positioning and to prevent secondary brain injury related to inadequate sedation, uncontrolled arterial pressure, or inappropriate $PaCO_2$ levels. Future research should also focus on the broader integration of portable, non-invasive monitoring technologies into prehospital and emergency care pathways. At present, insufficient data are available regarding the utilization of nICP methods in the prehospital setting making future study on this topic auspicable. However, the use of non-invasive tools must not slow down the execution of brain CT scans which play a key role in the assessment of these patients in the acute phase. Non-invasive tools can potentially be useful in polytrauma TBI patients needing emergent extracranial surgery for bleeding control. In these difficult situations their application should not interfere with life-saving interventions and would require extremely trained and coordinated personnel. This topic should definitely be the subject of further studies in the future.

Low-income countries: when invasive ICP monitoring is not available

Traumatic brain injury remains a major health concern worldwide, with therapeutic strategies and prognosis varying according to resource availability [141]. In limited resource settings, neuro-intensive care faces major challenges, particularly where advanced neuromonitoring tools, such as invasive ICP, are unavailable [142, 143]. In this scenario, clinicians traditionally rely primarily on neurological examination and neuroimaging, as shown by different protocols [i.e., the Imaging and Clinical Examination (ICE) protocol, the Consensus REVised ICE (CREVICE) protocol, and the Beyond One Option for Treatment of Traumatic Brain Injury: A Stratified Protocol (BOOTStraP)] [84, 144–147]. In particular, the ICE and the CREVICE protocols have been validated in clinical practice and are associated with improved neurological outcomes [145, 146]. However, clinical assessments are often late indicators of IH (e.g., posturing, arterial blood pressure fluctuations, etc.), limiting timely and targeted interventions. Brain CT scan, when available, assists in detecting mass effect, midline shift, basal cisterns status, or hydrocephalus, but its use is constrained by high costs, limited availability, and the risks associated with the transport of critically ill patients [140, 148]. Consequently, non-invasive neuromonitoring has emerged as a practical, affordable, and useful alternative [143, 149]. However, in this regard, we await new studies regarding nICP in low-resource settings and the validation in clinical practice of the recently published B-ICONIC consensus [9]. As recommended, some methods may be more useful when applied repeatedly within the same patient. This may partly explain why their use often remains limited to experienced users in specialized settings rather than translating into broader benefit for less specialized and less resource-intensive centers. Moreover, individually, several methods have yielded negative results, underscoring the nuanced background knowledge required for appropriate use and interpretation. Until invasive ICP monitoring becomes universally accessible, non-invasive neuromonitoring optimization and basic neurocritical care knowledge appear to be useful tools for improving neurological outcomes in poor resource settings.

Most currently available nICP monitoring approaches do not provide truly continuous precise measurements. Instead, they primarily aim to predict whether a predefined (invasive) ICP threshold is exceeded. However, over the past decade, research has repeatedly demonstrated that fixed ICP thresholds are unlikely to be universally valid [150]. Increasing evidence suggests that outcome prediction is better captured by the cumulative "ICP dose", reflecting both the magnitude and duration of ICP elevation. To date, none of the proposed nICP monitoring strategies appears to address this paradigm shift or to account for the temporal dimension of ICP burden.

Large studies capturing the effect of specific interventions (e.g., hyperosmolar therapy) on nICP parameters are lacking. This is an area of research that should be implemented in the future.

Other (austere environment)

Guidelines have traditionally been created to manage ABI patients in optimally resourced environments. Organizations, like the Brain Trauma Foundation (BTF), now recognize that resource stratification efforts must be a part of guidelines going forward to better serve patients worldwide [151]. In modern combat casualty care, we face not only the challenge of providing the best possible care to patients with brain injuries, despite limited resources, but also that of providing it under fire [151, 152]. In this case, weight and volume are key factors, as a limiting factor is the carrying capacity of military medics' backpacks. Recent years have seen important advancement in technologies that hold promise for bridging the gap of optimizing care when invasive ICP measurements are not feasible [151]. Point-of-care testing for blood-based biomarkers and hand-held portable spectroscopy devices may assist the diagnosis of TBI and, in particular, the detection of intracranial blood when CT scanning is not available [153–155]. Non-invasive ICP tools could be useful in this scenario. In particular, the automated pupillometry has been introduced as a possible monitoring tool in the recently published "Joint Trauma System Clinical Practice Guideline" on the "Traumatic Brain Injury

Management and Basic Neurosurgery in the Deployed Environment" [152]. Specifically, a NPi < 3 in one or both eyes may be related to IH [152]. More efforts are needed in this area, especially to improve the monitoring and subsequent treatment of TBI patients in austere environments. Especially in battlefield, rapid evacuation ("load and go") may be lifesaving, compared to prolonged on-site assessment with nICP devices. This aspect warrants further studies.

Conclusions

Over the past decades, substantial progress has been made in the recognition and prediction of raised ICP without the need for direct monitoring. These advances have converged into the development of nICP estimation techniques, which have gained increasing interest as safe, inexpensive, bedside, and readily available tools to support the management of patients with or at risk of IH. Although their intrinsic limitations, mainly limited accuracy, prevent them from being reliable substitutes for invasive systems, these techniques can be effectively employed when invasive methods are unavailable or contraindicated, and as complementary tools to improve the understanding of intracerebral dynamics. Further research is needed to provide evidence on the impact of therapeutic strategies guided by non-invasive monitoring, particularly when integrated with neurological examination and radiological assessment.

Supplementary Information
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Conflict of interest
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