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Review

Non-invasive intracranial pressure assessment in adult critically ill patients: A narrative review on current approaches and future perspectives

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HIGHLIGHTS

- Intracranial hypertension is a severe complication in acute brain injured patients worsening outcomes.
- Invasive measurement is the gold standard but it is not free from complication
- Some noninvasive methods are easily applicable at the bedside and could out intracranial hypertension effectively.

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ABSTRACT

Intracranial hypertension (IH) is a life-threatening complication that may occur after acute brain injury. Early recognition of IH allows prompt interventions that improve outcomes. Even if invasive intracranial monitoring is considered the gold standard for the most severely injured patients, scarce availability of resources, the need for advanced skills, and potential for complications often limit its utilization. On the other hand, different non-invasive methods to evaluate acutely brain-injured patients for elevated intracranial pressure have been investigated. Clinical examination and neuroradiology represent the cornerstone of a patient's evaluation in the intensive care unit (ICU). However, multimodal neuromonitoring, employing widely used different tools, such as brain ultrasound, automated pupillometry, and skull micro-deformation recordings, increase the possibility for continuous or semi-continuous intracranial pressure monitoring.

Abbreviations: IH, intracranial hypertension; ICU, intensive care unit; AI, artificial intelligence; CSG, cerebrospinal fluid; ICP, intracranial pressure; NICCU, neurointensive care unit; FOUR, Full Outline of UnResponsiveness; GCS, Glasgow Coma Scale; CT, computed tomography; MRI, magnetic resonance imaging; TBI, traumatic brain injury; TCD, transcranial color doppler; TCCD, transcranial color coded duplex sonography; MCA, middle cerebral artery; nCPP, non-invasive cerebral perfusion pressure; nICP, non-invasive intracranial pressure; FVm, mean flow velocity; FVd, diastolic flow velocity; CBF, cerebral blood flow; ICH, intra cerebral hemorrhage; PI, pulsatility index; MAP, mean arterial blood pressure; DBP, diastolic blood pressure; ONSD, optic nerve sheath diameter; ALARA, As Low As Reasonably Achievable; CrCP, critical closing pressure; ICPw, intracranial pressure waveform; TTP, time to peak; ICC, intracranial compliance; PLR, pupillary light reflex; ABI, acute brain injury; MAC, maximum amplitude constriction; PLRA, pupillary light reflex amplitude; CV, constriction velocity; DV, dilation velocity; NPi, neurological pupil index; CNNs, convolutional neural networks; LSTM, long-term recurrent neural network..

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Furthermore, artificial intelligence (AI) has been investigated to as a tool to predict elevated intracranial pressure, shedding light on new diagnostic and treatment horizons with the potential to improve patient outcomes.

This narrative review, based on a systematic literature search, summarizes the best available evidence on the use of non-invasive monitoring tools and methods for the assessment of intracranial pressure.

1. Introduction

Cerebral blood, cerebrospinal fluid (CSF), and brain parenchyma are the key players determining intracranial pressure (ICP), which is normally <15 mmHg in adults and < 6 mmHg in children [1].

Any change in volume to any component will induce a change in ICP as explained by the Monro-Kellie law: until a certain point, changes in the volume of one component can be compensated by changes of other components, normalizing ICP. When buffering capacity has been reached, ICP rises, leading to intracranial hypertension (IH) [2,3].

Severe IH impairs cerebral perfusion and in extreme cases could lead to brain death [4].

IH worsens clinical outcomes in critically ill patients irrespective of the cause. It is therefore important to rapidly recognize and treat it [5,6].

Traumatic brain injury (TBI) or intracranial bleeding are the most common causes, but many other conditions could be associated with IH such as septic encephalopathy [7].

The gold standard for IH monitoring is invasive an intracranial probe, especially indicated in case of severe acute brain injury; however, this is not without risks, some contraindications exist (for example severe coagulopathy or brain infection) and often it is not immediately available in non-neurointensive critical care units (NICCU) or in low-income countries [8].

For these reasons, research has focused on non-invasive tools that have become available and are used more frequently with the majority of critically ill patients as intermittent-semicontinuous or continuous monitoring, as shown in Fig. 1 [9].

The main aim of this review is to provide updated evidence on easily accessible tools that help clinicians detect IH non-invasively and to explore future perspectives for implementing IH monitoring with the help of AI.

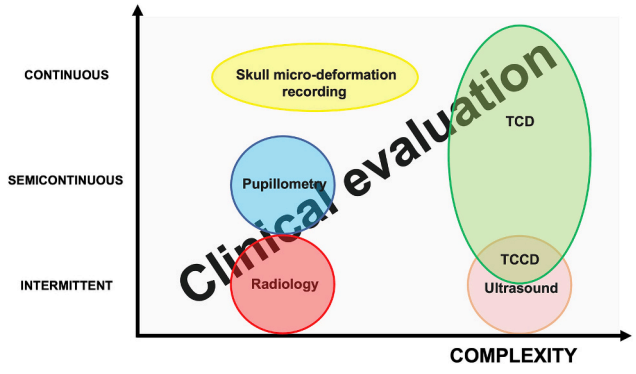


Fig. 1. Non-invasive tools potentially useful to determine if critically ill patients are developing intracranial hypertension.
Monitoring systems could be intermittent (i.e., they can be used for a limited period due to intrinsic properties), semi-continuous (if information is given for a certain period of time), or continuous if they can be put in action without interruption.
Another important aspect to consider is the technical skills required to interpret correctly data obtained through these monitors. While clinical evaluation is applicable by the majority of healthcare personnel, expertise is necessary to use TCD or TCCD when evaluating patients with suspected intracranial hypertension.
However, it must be said that intermittent systems, whether easy or complex, represent an excellent tool for screening for IH (especially for ruling it out).

2. Methods

This work was conceived as a narrative review, designed to synthesize current evidence on non-invasive intracranial pressure monitoring in critically ill adult patients. A systematic search of MEDLINE, Scopus, and Web of Science (WOS) databases was conducted covering the period from January 2000 to September 2024, using the following comprehensive set of keywords: "intracranial hypertension", "traumatic brain injury", "cerebral hemorrhage", "stroke", "brain herniation", "Cushing's triad", "pupillary abnormalities AND ICU", "neuromonitoring", "cerebral circulatory arrest", "transcranial doppler", "automated pupillometry AND ICU", "cerebral compliance" and "neurocritically ill patients". We considered only articles written in English and with abstracts available to the reader.

We included original prospective studies, meta-analyses, and observational studies published in English with accessible abstracts. Editorials, letters, case reports, preclinical studies, and studies involving non-human subjects were excluded.

Two authors (CD and DGB) retrieved the full texts of the relevant articles. All other related titles and abstracts were retrieved, and the full versions obtained. The reference lists of the included studies and review articles were manually searched to identify any additional relevant study. Full-text documents were initially assessed for relevance. Articles that were not relevant to the review aim were excluded from further analysis. In case of disagreement, a third author (LV) resolved the issue.

A secondary screening and selection of studies was based on relevance to the review aim and scientific quality, with consensus among the authors.

Although a systematic search was conducted, no formal risk-of-bias (RoB) assessment tool was applied, as this review does not follow the structure of a systematic review with quantitative synthesis or diagnostic accuracy analysis. In particular, the RoB 2.0 tool is specific to randomized controlled trials and would not be applicable to the range of study types included here. While the QUADAS-2 tool would be more appropriate for diagnostic accuracy studies, we opted not to use it given the narrative focus and the descriptive nature of our synthesis.

Standards for Reporting Qualitative Research Guidelines (SRQR EQUATOR Guidelines) were followed for this review.

3. Discussion

3.1. Clinical evaluation

Clinical examination is the cornerstone for assessing cerebral function in ICU patients [10]. Some clinical manifestations could be pathognomonic of the underlying clinical process (for example, left hemiplegia in case of right basal ganglia hemorrhage).

Level of consciousness, motor and sensory function, reflexes, and cranial nerve function (especially pupil size and light reflex) should be investigated [11].

The most commonly reported symptoms in patients with acute IH include headache, nausea, vomiting, and visual changes. As IH increases, level of consciousness and responsiveness decrease until deep coma occurs [12].

Irregular respiration, bradycardia and arterial hypertension in comatose patients, namely Cushing's triad, point to a medical emergency related to high ICP, potentially treatable with surgical procedure in the case of intracranial bleeding [13]. Yumoto et al., found that both

in traumatic adult and pediatric brain injury patients, high blood pressure and bradycardia are predictors of the requirement for immediate neurosurgical intervention to evacuate mass lesions [14].

These results were not confirmed by Avest et al., where in a large prehospital cohort of adult TBI patients, clinical signs of elevated ICP demonstrated a poor sensitivity for IH (36.8 %, 95 % IC 26.7–47.8 %) [15].

Pupil evaluation (size and response to light) might be indicative of the mechanism that causes IH; a unilateral mydriatic pupil unresponsive to direct or consensual light stimulus is potentially indicative of mass lesion that determines uncal herniation towards mesencephalon [16].

Bilateral mydriatic unresponsive pupils are indicative of extensive damage to the brainstem, and if corroborated by other signs and symptoms, they could raise suspicions of brain death [17].

However, the most severely brain-injured patients are frequently under sedation, muscular paralysis and mechanical ventilation. Therefore, some aspects of the clinical evaluation, such as the Glasgow Coma Scale, may not represent the severity of the brain damage. In this case, non-invasive tools may be helpful.

3.2. Pupillometry

Pupillary light reflex (PLR) examination is an essential part of the neurocritical patient evaluation; it provides information about brainstem function or injury, and helps guide clinical decisions [18,19].

PLR evaluation is safe, easy, and repeatable at the bedside with a recognized outcome predictive capability after acute brain injury (ABI) [19–22].

However, qualitative examination can include many inaccuracies due to interobserver variability, drug confounders, or ambient pollution [23].

Therefore, modern automated pupillometry has been developed, providing more accurate, reliable, and reproducible measurements [24]. The pupillometer provides several PLR parameters including latency, maximum constriction amplitude (MAC, the difference between initial and final pupillary diameters), pupillary light reflex amplitude (PLRA), constriction velocity (CV, MCA divided by the duration of the constriction), and dilatation velocity (DV, measured similarly to the CV).

NeurOptics developed the Neurological Pupil Index (NPi), a proprietary algorithm that compares the pupil diameters of patients with a normative model of pupil reaction, providing an objective and automated assessment of pupil parameters [25].

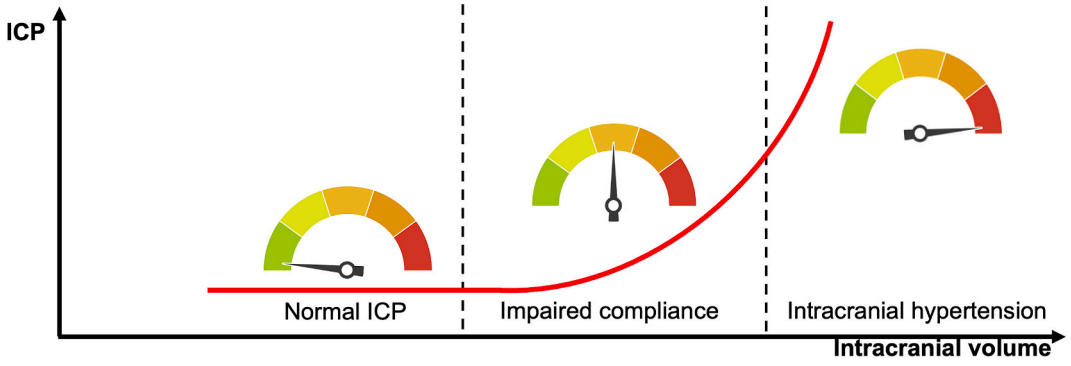
NPi considers PRL parameters and derived variables (e.g., percentage of change in pupil diameter and mean CV), grading the patient's pupillary response on an objective dimensionless scale ranging from 0 to 5. NPi <3.7, has been associated with increased intracranial pressure and poorer outcomes in critically ill patients as shown in Fig. 2 [26,27].

Pupillometry can be an important instrument in diagnosing transuncal herniation [28–30]. NPi measurements were found to be abnormal some hours before 73 % of herniation episodes, and they were useful in decreasing osmotic therapy in a small case series [31].

The diagnostic capability of PLR quantitative assessment in hospital-onset unresponsive patients was confirmed in another study in which NPi measurements, as well as enlarged pupillary size, were significantly associated with the development of brainstem herniation syndrome, with high specificity and negative predictive value for NPi <1.6 [32].

Taylor et al. studied quantitative PLR examination in 310 healthy volunteers and 26 patients with acute brain lesions. They found asymmetry in pupil size greater than 0.5 mm when ICP > 20 mmHg, and CV drop when ICP values rose over 20 mmHg in patients with midline shift and over 30 mmHg in patients with diffuse brain swelling without midline shift [33].

In another study, researchers used NPi (threshold <3) as a triage tool and guide for intervention (craniotomy or invasive ICP monitor



Tool	Normal findings	Modifications	
Clinical	GCS 15, normal pupils	headache, nausea, vomiting, focal signs	headache, nausea, vomiting, abnormal pupils, focal signs, coma, BD
Neuroradiology	patent basal cisterns, no MLS, no swelling	Effaced basal cisterns, ± MLS, swelling	Effaced basal cisterns, ± MLS, swelling, brain ischemia
TCD/TCCD	PI<1.2, FVm>30 cm/s, FVd>20 cm/s	PI>1.2, FVm>30 cm/s, FVd<20 cm/s, nICP*	PI>1.4, FVm<30 cm/s, FVd<20 cm/s, nICP*
ONSD	diameter < 5.5 mm	diameter > 5.5 mm	
Skull deformation	P1>P2, P2/P1<1.2, TTP<0.22	P2≥P1, P2/P1>1.2, TTP>0.22	P2>P1, P2/P1>1.2, TTP>0.22
Pupillometry	NPi>3	NPi<3.7, ↓CV, ↑latency	NPi<3.7, ↓CV, ↑latency

Fig. 2. Main alterations of non-invasive tools parameters during transition from normal ICP to intracranial hypertension.
In the upper part of the figure, it is represented the Monro-Kellie curve. In the lower part of the figure, there are tabulated main parameters changes obtained through non-invasive monitoring systems when a patient is experiencing low cerebral compliance or intracranial hypertension. Considering that no one tool is perfect in terms of sensitivity and sensibility, it is advisable to include most of them in order to adopt a multimodal neuromonitoring based decision.
Legend:GCS = Glasgow Coma Scale; BD = brain death; MLS = midline shift; TCD/TCCD = *transcranial doppler/transcranial color coded duplex; PI = pulsatility index; FVm = mean flow velocity; FVd = diastolic flow velocity; nICP = non-invasive estimation of ICP (please, refer to* Table 1 *for formulas); P1 = first peak; P2 = second peak; TTP = time to peak; NPi = neurological pupil index; CV = constriction velocity.*

placement) [34].

Ong et al. found NPi improvement after osmotic therapy in a cohort of neurocritically ill patients [35].

Fritz-Patrick et al. examined NPi trends over time in a cohort of consecutive patients with severe traumatic brain injury (TBI) who were monitored with a parenchymal ICP probe; among patients with IH, NPi showed a negative correlation with intracranial pressure, both during ICP rise, and after that, osmotherapy was given. The abnormal NPi values were more frequent in patients with refractory IH. Moreover, the cumulative burden of NPi <3 was associated with worse 6-month outcome (GOS 1–3) [36].

Antje Giede-Jeppe et al. have evaluated the use of automated pupillometry in predicting increased ICP in supratentorial intracerebral hemorrhage (ICH) patients and the correlation between CT indicators of ICH and pupillometry parameters [37]. The investigators found PLR parameters had high negative predictive values (97 %–99.2 %) for predicting IH. In addition, CT findings were correlated with the NPi, ICH volume and midline shift exhibited a significant correlation with the NPi. The authors concluded that automated pupillometry rule out ICH patients without IH, facilitating clinical management by saving invasive ICP monitoring or repetition of CT controls in those patients.

There is still limited evidence available on the role of quantitative pupillometer in acute ischemic stroke.

A retrospective study found that ipsilateral NPi abnormality, along with hemorrhagic conversion, was associated with malignant cerebral oedema in ischemic stroke patients treated with large vessel thrombectomy [38].

Moreover, Osman et al., using the ENDPANIC registry (a prospective database of pupillometer readings in neurological patients), found a significant correlation between septum pellucidum shift and NPi, CV and pupillary asymmetry (but not pupillary size) in patients with ischemic and hemorrhagic strokes [39].

Scala et al. found that several pupillometry parameters (a high percentage of pupil constriction, a low constriction velocity, high difference between these two parameters and NPi) were independent predictors of acute ischemic stroke, helping differentiate patients with ischemic stroke during the acute phase (≤72 h from symptoms onset) from healthy subjects [40].

Finally, the ORANGE study, a recent prospective, observational, multicenter cohort study, confirmed the clinical and statistical prognostic value of NPi for neurological outcome and mortality after acute brain injury. Specifically, two consecutive NPi measurements equal to 0 or a deterioration of the NPi to a value of 0 were linked to an elevated mortality risk and, in contrast, the risk of mortality did not increase when an NPi value of 0 recovered to a higher value. Moreover, NPi values falling between 3 and 4 demonstrated a significantly higher association with mortality risk compared to NPi values exceeding 4 [41].

Some limitations need to be acknowledged: pupil asymmetry could result from direct trauma to the eye or the transmission pathway of pupil reflex.

3.3. Neuroradiology

Brain imaging performed with computed tomography (CT) or magnetic resonance imaging (MRI) plays a crucial role in evaluating patients with suspected IH [42,43]. The CT scan is the standard imaging modality in trauma. The importance of a head CT scan at the baseline evaluation is fundamental to making a correct diagnosis, and can be used as the first guide to clinical management. In cases of traumatic brain injury, the CT scan result is the starting point in the decision algorithm [44]. Although radiation exposure is of concern, CT scans can be done quickly and permit real-time changes in management [45].

Furthermore, various CT findings have been suggested to be predictive of elevated ICP, including abnormal morphology of cisterns and ventricles, midline shift, the presence of subarachnoid blood or hematoma, herniation patterns, cortical sulcal effacement, and grey/white matter differentiation [43–46].

Among these neuroradiological signs, compression or abnormal basal cisterns have been identified as a main parameter correlating with IH [42,47–49].

However, other authors emphasized that normal basal cisterns do not exclude the presence of increased ICP. In a study of 57 children with severe TBI, Kouvarellis et al. found that 40 % with normal cisterns had at least 1 episode of ICP > 20 mmHg and 15 % had an average ICP > 20 mmHg [50]. Indeed, a normal CT scan cannot exclude the presence of an elevated ICP as there is a high possibility of false negative results.

Fernando et al. recently summarized all these aspects in a systematic review and metanalysis as reported in Table 1 [51].

MRI has the same clinical applications as a CT with regard to identifying and managing the pathology responsible for raised ICP. Nevertheless, MRI being costly and time-consuming, CT is the preferred diagnostic modality, especially in emergency situations [42].

In the last few years, radiomic analysis, is rapidly emerging as a new field of research. Radiomic analysis converts digital medical images into mineable high dimensional data via extraction of quantitative features and a subsequent data analysis can be used to support decisions. Radiomic features consist of first-order, second-order, and higher-order elements based on the distribution and relationship of pixel or voxel grey-levels in the image. Some authors have recently demonstrated that computed tomography radiological features analysis could effectively characterize IH, and that radiomic features, especially second-order features, can be used to evaluate ICP non-invasively compared with conventional methods [52,53].

Finally, the major limitation of neuroradiology is represented by the limited time-resolution: CT scans and MRI offer a picture only of what is happening at that moment in time.

3.4. Ultrasound

Ultrasound-based methods used to evaluate elevated intracranial pressure include:

- *trans*-Cranial Doppler (TCD) or Trans-Cranial Color-Coded Doppler (TCCD);
- Optic Nerve Sheath Diameter (ONSD); and
- combination methods

3.4.1. Trans-Cranial Doppler (TCD) and Trans-Cranial Color-Coded Doppler (TCCD)

TCD/TCCD of the middle cerebral artery (MCA) has been investigated as a potential non-invasive tool to assess cerebral perfusion pressure (nCPP) and intracranial pressure (nICP) or to risk-stratify patients who may benefit from invasive ICP monitor use.

Accurate evaluation of mean flow velocity (FVm) and diastolic velocity (FVd) allows cerebral hemodynamic description and cerebral blood flow (CBF) monitoring. As ICP increases and CPP decreases, there is a pronounced reduction in FVd first, and then in FVm, with a FVd/FVm ratio rapidly reducing to under approximately 0.6 [54,55].

When CPP decreases due to IH, FVd falls below 20 cm/s and FVm below 30 cm/s [55–58].

Based on the available evidence, TCD/TCCD-based methods to evaluate intracranial pressures include:

1. methods based on the relationships between the Pulsatility Index (PI) and ICP; and
2. methods based on the estimate of CPP.

3.4.1.1. Methods based on PI. PI, which normally equals 0.5–1.19, is calculated as the difference between systolic and diastolic flow velocities

Table 1
Sensitivity and specificity of noninvasive methods of investigation for elevated intracranial pressure.

Method	Authors	Sample size & Population	Diagnostic accuracy
Methods based on CT scan findings			
Midline shift>5 mm, asymmetrical or absent basal cisterns (ICP > 20 mmHg	Giede-Jeppe et al. [37]	23 ICH	Sensitivity 95.9 %, Specificity 61.8 %, PPV 9.1 %, NPV 99.7 %
Diffuse sulci effacement or obliteration of basal cisterns or midline shift>5 mm or transtentorial/uncal herniation (ICP > 20 mmHg)	Moulin de Moraes [45]	18 ABI	Sensitivity 100 %, Specificity 16.6 %, PPV 34 %, NPV 100 %
Ratio of CSF volume to the size of the intracranial vault (ICV) or volume inside the skull ≤0.034 (ICP > 20 mmHg)	Pappu et al. [46]	20 TBI	Sensitivity 100 %, Specificity 55.9 %
Open cisterns <15 mmHg	Kouvarellis et al. [50]	104 Pediatric TBI	Sensitivity 61.5 %, Specificity 52.5 %, PPV 35.6 %
Open cisterns <20 mmHg			Sensitivity 61.6 %, Specificity 57.9 %, PPV 59 %
Open cisterns <25 mmHg			Sensitivity 57.9 %, Specificity 59.3 %, PPV 73.3 %
Basal cisterns absent or compressed (ICP > 20 mmHg)	Fernando et al. [51]	619 TBI	Sensitivity 85.9 % Specificity 61 % Diagnostic odds ratio 9.55 (1.56–56.61)
Midline shift >0 mm (ICP > 20 mmHg)	Fernando et al. [51]	627 TBI	Sensitivity 80.9 %, Specificity 42.7 % Diagnostic odds ratio 3.16 (1.43–7.01)
Midline shift >5 mm (ICP > 20 mmHg)	Fernando et al. [51]	832 TBI	Sensitivity 49.4 %, Specificity 70 % Diagnostic odds ratio 2.28 (1.26–4.13)
Midline shift >10 mm (ICP > 20 mmHg)	Fernando et al. [51]	651 TBI	Sensitivity 20.7 %, Specificity 89.2 % Diagnostic odds ratio 2.16 (0.87–5.37)
Methods based on the relationships between the Pulsatility Index (PI) and ICP			
A	Moulin de Moraes et al. [45]	18 ABI	PI>1.28 Sensitivity 78.6 %, specificity 77.3 %, PPV 50 %, NPV 91.7 %.
$PI = \frac{FVs - FVd}{FVm}$	Moreno et al. [60]	125 (ICU)	Correlation between PI and ICP was R^2 = 0.96
			PI ≥1.56 was associated to poor outcome
	Bellner et al. [62]	81 (ICU)	Sensitivity and 99 % Specificity for a threshold of 20 mmHg
			Correlation between PI and ICP was R = 0.94
			Formula used was ICP = 10.93 9 PI - 1.28, with 83 %
	Robba et al. [63]	100 ABI in ICU	Sensitivity 81 %, Specificity 78 % for PI>0.97
	Zweifel et al. [64]	290 (ICU)	Correlation between PI and ICP was R = 0.31
	Behrens et al. [65]	10 (ICU)	Correlation between PI and ICP was poor: R^2 = 0.22
	De Riva et al. [66]	345 (ICU)	Correlation between PI and ICP was R = 0.70
Methods Based on the estimation of CPP (nCPP)			
B	Czosnyka et al. [69]	96 (ICU)	Correlation between nCPP and CPP was R = 0.73
$nCPP = MAP\ X\ \frac{FVd}{FVm} + 14\ mmHg$			The method had a high positive predictive value (94 %) for detecting low CPP (< 60 mmHg)
$nCPP = MAP\ X\ \frac{FVd}{FVm} + 14\ mmHg$	Schmidt et al. [70]	25 (ICU)	Highly specific for detecting changes over time (R^2 = 0.82) Error for nCPP estimation was less than 10 and 13 mmHg in 89 % and 92 % of the cases, respectively.
The value 14 mmHg is a calibration parameter established for traumatic brain injury patients.	Gura et al. [71]	47 (ICU)	Correlation between nCPP and CPP was R = 0.92
	Rasulo et al. [47]	262 (ICU)	NPV was high: 91.3 %, 95.6 % and 98.6 % for

(*continued on next page*)

Table 1 (*continued*)

Method	Authors	Sample size & Population	Diagnostic accuracy
			nICP thresholds of 20 mmHg, 22 mmHg and 25 mmHg, respectively 1-NPV was low, ranging from 9 to 2 %, indicating high discriminant accuracy of eICP in excluding intracranial hypertension
			Sensitivity 70 %, Specifcity 76 % or a threshold of 20.5 mmHg, with AUC of 0.76 (0.66–0.85) to predict intracranial hypertension
	O'Brien et al. [73]	23 (Pediatric ICU)	Correlation between CPP and nCPP was $R = 0.78$ In Bland-Altman plot, the bias or average discrepancy for all measurements was 3.7 mmHg with 95 % limits of agreement of −17 and + 25 mmHg
C ***nCPP = [(FVm/(FVm-FVd)] X (MAP – DBP) mmHg***	Edouard et al. [74]	20 (ICU)	During normocapnia nCPP and CPP were significantly correlated (slope 0.76; intercept +10.9; 95 % CI -3.5 to +25.4) During hypercapnia nCPP and CPP were correlated with increased discrepancy (slope 0.55; intercept +32.6; 95 % CI +16.3 to +48.9)
D ***nCPP = ABP X [0,734 - $\frac{0,266}{\sqrt{(CVR\ x\ Ca\ x\ HR\ x\ 2\pi)^2 + 1}}$] – 7026 mmHg*** ***CVR represents cerebrovascular resistance calculated as the ratio between MAP and FVm; Ca indicates the compliance of the cerebral arterial bed calculated as the ratio between amplitude of the first harmonic impulse of the cerebral arterial blood volume waveform (BV1) and the amplitude of the first harmonic impulse of the ABP waveform (a1); HR represents heart rate.***	Varsos et al. [75]	280 (ICU)	Correlation between nCPP and CPP was $R = 0.85$ AUC > 0.8
Methods based on ONSD measurements			
E ***nICP = 5.00 × ONSD − 13.92 mmHg***	Robba et al. [81]	64 (ICU)	Correlation between nICP and ICP was $R = 0.76$ AUC 0.91 (95 % CI, 0.88–0.95) to predict ICP ≥ 20 mmHg
F ***$nICP_{ONSD+FVsv}$ = 4.23 × ONSD + 0.14 × FV_{sv} − 14.51 mmHg***	Robba et al. [81]	64 (ICU)	Correlation between nICP and ICP was $R = 0.80$ AUC 0.93 (95 % CI 0.90–0.97) to predict ICP ≥ 20 mmHg
ONSD	Aletreby et al. [83]	619 (mixed ABI)	Sensitivity 90 %, Specificity 85 % Diagnostic odds ratio 46.7 (26.2–83.2)
ONSD > 5.3 mm ICP > 20 mmHg	Robba et al. [63]	100 ABI in ICU	Sensitivity 70 %, Specificity 75 %
ONSD > 5.2 mm	Moulin de Moraes et al. [45]	18 ABI	Sensitivity 71.4 %, Specificity 70.4 %, PPV 43.5 %, NPV 88.6 %
Methods based on skull micro-deformation detection			
P2/P1 ratio with cutoff 1.06	Moulin de Moraes et al. [96]	18 (stroke)	Sensitivity 100 %, Specificity 45.4 % PPV36.8 %, NPV 100 %
Time to Peak value 0.2	Moulin de Moraes et al. [96]	18 (stroke)	Sensitivity 85.7 %, specificity 50 % PPV 35.5 %, NPV 91.7 %
P2/P1 ratio with cutoff 1.13	Moulin de Moraes et al. [103]	69 (mixed ABI)	Sensitivity 93 %, specificity 60 % PPV 40 %, NPV 97 %
Methods based on automated pupillometry			

(*continued on next page*)

Table 1 (*continued*)

Method	Authors	Sample size & Population	Diagnostic accuracy
NPi ≤ 3.75	Pansell et al. [28]	26 aSAH	Sensitivity 65 %, Specificity 75 % PPV9.6 %, NPV 98.2 %
NPi ≤ 3.97	Pansell et al. [28]	10 ICH	Sensitivity 86 %, Specificity 58 % PPV 20.4 %, NPV 97.1 %
NPi ≤ 3.77	Pansell et al. [28]	19 TBI	Sensitivity 66 %, Specificity 60 % PPV 16.9 %, NPV 92.4 %
NPi ≤ 3.85	Pansell et al. [28]	65 mixed ICU	Sensitivity 70 %, Specificity 66 % PPV 13.4 %, NPV 96.7 %
Constriction velocity < 0.8 mm/s	Giede-Jeppe et al. [37]	23 ICH	Sensitivity 78.1 %, Specificity 65.5 %, PPV 8.3 %, NPV 98.7 %
% change of aperture < 10 %			
Dilation velocity < 0.2 mm/s			Sensitivity 66.7 %, specificity 66.3 %, PPV 7.4 %, NPV 98 %
Latency > 0.3 s			
(ICP ≥ 20 mmHg)			Sensitivity 35.6 %, Specificity 83 %, PPV 7.8 %, NPV 97 %
NPi < 4.1	Robba et al. [63]	100 ABI in ICU	Sensitivity 65 %, specificity 70 %

Abbreviations: *FVs peak systolic velocity, FVm mean flow velocity, FVd end diastolic velocity, PI Pulsatility Index, ICU Intensive Care Unit, ICP invasively measured intracranial pressure, R^2: Coefficient of determination, R Correlation coefficient, MAP mean arterial pressure, nCPP non-invasively estimated cerebral perfusion pressure, CPP measured cerebral perfusion pressure, nICP, non-invasively estimated intracranial pressure, AUC Area Under the Curve, DBP diastolic blood pressure, ABP arterial blood pressure, CVR cerebrovascular resistance, Ca compliance of the cerebral arterial bed, HR heart rate, ONSD optic nerve sheath diameter, FVsv straight sinus systolic flow velocity, NPi = neurological pupil index, P2/P1 ratio between second and first peak of intracranial pressure esteemed with Brain4care®.*

divided by FVm, as shown in Table 1-A [59].

ICP and PI have been shown to positively correlate during increases of ICP [60–63]. For this, PI values >1.4 may strongly suggest IH.

However, increased PI is not specific to IH [64,65]. For example, it is directly correlated to the amplitude of arterial blood pressure pulsation, so presence of an unknown aortic regurgitation will increase it [66].

Moreover, PI is also inversely proportional to CPP, so a decrease in CPP due to hypotension might also increase it. Furthermore, PI is influenced by $PaCO_2$, hypocapnia being responsible for PI increase, and hypercapnia for its decrease [66]. PI has been shown to be non-linearly correlated to cerebrovascular resistance and heart rate. In fact, bradycardia may account for a decrease in FVd, increasing PI. Then, vasodilation of the downstream vessels can cause a reduction in PI; conversely, vasospasm or stenosis may account for an increase in PI [67]. Moreover, PI can increase in advanced age [68].

As a practical guide for clinicians, a suspicion of elevated ICP at the bedside can be supported by a combination of elevated PI (> 1.4), low FVd (< 20 cm/s), and low FVm (< 30 cm/s).

3.4.1.2. Methods based on the estimation of CPP (nCPP). The second approach includes different methods primarily aimed at estimating CPP non-invasively (nCPP), based on the relationships between flow velocities, mean arterial pressure (MAP), and nCPP. These methods allow indirectly calculating nICP according to the formula:

nICP = MAP–nCPP

Czosnyka et al. demonstrated that a decrease in FVd is associated with a decreased nCPP according to eq. B shown in Table 1 [69].

This method has subsequently been tested by numerous studies [70,71], including in a multicenter prospective IMPRESSIT-2 study where it proved to be useful for ruling out IH [72].

However, when this formula was applied to a small study of 23 children with severe traumatic brain injury, it was not successful [73].

Edouard et al. proposed formula “C” in Table 1 to estimate nCPP [74]. This method was tested under stable conditions and during a $PaCO_2$ reactivity test. Estimated nCPP and measured CPP were correlated both in normocapnic condition and during hypercapnia, even if in the latter condition, an increased discrepancy between nCPP and CPP was found.

A further method developed by Varsos et al. is based on the concept of critical closing pressure (CrCP) [75], previously introduced by Nichol et al. [76]. CrCP derives from the sum of ICP and vascular wall tension (WT) and represents the minimum threshold of blood pressure allowed to prevent cerebral arteries from collapsing and cerebral blood flow cessation [77]. CrCP can be non-invasively assessed using TCD by comparing waveforms of FV and ABP. Given its relationship with the vasomotor tone of small blood vessels, CrCP can provide information on the state of cerebral hemodynamics and reflect changes in CPP according to formula “D” in Table 1 [78].

This method was tested in a cohort of 280 patients with traumatic brain injury in which nCPP was found to be correlated with measured CPP, with an estimation error of less than 10 mmHg in 83.3 % of cases [75]. The analysis of nCPP prediction at 3 different CPP thresholds (50, 60, and 70 mmHg) produced AUC values higher than 0.8 for all thresholds. The nCPP estimation based on the concept of CrCP was applied to a small study of 23 children with severe traumatic brain injury but was not successful [73].

3.4.2. Methods based on ONSD measurements

Ultrasound assessment of the optic nerve sheath diameter (ONSD) has recently been investigated as a tool to detect IH. The optic nerve is surrounded by the intraorbital subarachnoid space, and its anterior part is more distensible than the posterior [79]. Thus, an increase in ICP is transmitted along the optic nerve sheath, accounting for an accumulation of cerebrospinal fluid in its anterior portion, which determines a rapid increase in its diameters [80]. Robba et al. proposed equation “E,” reported in Table 1, for non-invasive estimation of nICP based on ONSD measurements, showing good correlation between measured ICP and nICP ONSD based [81].

According to different recent meta-analysis, ONSD values in the range of 4.80–6.30 mm have a robust prediction ability for IH, applying thresholds of both 20 mmHg and 25 cmH_20 [82,83]. However, possible cut-off values for the detection of IH, as well as the sonographic-based examination technique, show enormous variability [84]. Furthermore, during sonographic assessment of ONSD, optimal ultrasound frequency and mechanical power should be set and balanced to avoid any potential

damage to the ocular structures. Thus, the ALARA principles must be followed (Table 2) [85]. Therefore, to standardize the examination technique and increase safety, a bundle that includes using color-coded doppler of the ophthalmic artery has been proposed [86]. Furthermore, ONSD can increase in other conditions such as normal pressure hydrocephalus.

3.4.3. Methods based on the integration of TCCD and ONSD assessments

Robba et al. proposed a method for estimating nICP by combining ONSD measurement and the systolic flow velocity in the straight sinus using formula "F" described in Table 1 [81]. This combined method showed a statistically significant improvement in AUC values compared to the ONSD-only method. However, more data are needed.

3.5. Skull micro-deformation detection

Skull micrometric dilatation following changes in intracranial pressure has become public [87]. Following this discovery, it was demonstrated in experimental and then in clinical studies that skull micro-deformation slopes (Skw) follow brain pulsations and represent ICP waveform (ICPw) precisely [88–91]. Recently, a system named B4C that can capture, filter, amplify, and analyze Skw was built for clinical purposes (brain4care, São Carlos, Brazil) [92]. The B4C system presents real-time Skw analysis, providing the bedside clinician with numerical parameters such as the P2/P1 ratio and time-to-peak (TTP). The P2/P1 ratio is calculated estimating P1 and P2 amplitudes from Skw, whereas the TTP is the normalized percentage of time from the beginning of the pulse to its highest amplitude. A study among individuals without neurological conditions indicated an elevation of the P2/P1 ratio with aging and in menstruating women. However, for any age, it is unlikely to present P2/P1 ratio values persistently over 1.2.

These biomarkers were correlated with ICPw changes following intracranial compliance (ICC) reduction [93–95]. This system was validated in case series studies with neurocritical care patients under ICP invasive monitoring [96–98]. However, it is also valuable in identifying ICC impairment in patients with severe COVID-19, end-stage kidney disease, and children with hydrocephalus [99–101], and thus for general critical care or other non-acute situations.

The changes in ICPw (and their equivalent Skw) are based on the level with which ICP becomes noxious, respecting intra- and inter-individual variability. Therefore, it may not correspond to a predetermined ICP threshold. Notwithstanding, the studies correlating invasive ICP and B4C indicate the satisfactory power of its parameters (P2/P1 ratio and TTP) to rule out IH (ICP < 20 mmHg) due to its high negative predictive value and negative likelihood ratio [96,102,103]. The odds of IH occurring increase consistently the higher the P2/P1 ratio [102]. Among traumatic brain-injured patients, a P2/P1 ratio over 1.2 and TTP over 0.22 presented an AUC of 0.9 to indicate ICP > 20 mmHg. Another study with spontaneous brain hemorrhage patients observed similar results with a 1.1 cut-off for the P2/P1 ratio [96].

The management of severe neurological patients demands monitoring multiple brain pathophysiological events besides ICP. Accordingly, some studies were dedicated to investigating in which way the combination of different techniques can improve diagnostic power [104]. The combination of B4C with invasive ICP monitoring, or even with different transcranial Doppler parameters, demonstrated an improved prognostic power, rather than considering the same parameters separately [105]. These first clinical assays encourage further prospective and interventionist studies, with the aim of integrating multimodal non-invasive monitoring models into therapeutic strategies.

3.6. Artificial intelligence, intracranial hypertension and future directions

Recently, artificial intelligence (AI) has shown great potential in improving the diagnosis, monitoring, and treatment of IH through *deep learning* or *machine learning* models [106]. Indeed, in medicine, AI is emerging as a powerful tool capable of transforming information management and clinical decisions [107–109].

An example of the application of AI in the management of IH is Quachtran et al.'s study, which explores the use of *deep learning*, specifically "Convolutional Neural Networks (CNNs)", to detect IH by analyzing intracranial pressure traces [110]. The trained "CNN" model achieved an accuracy of 92.05 %, demonstrating the effectiveness of "CNNs" in detecting IH events.

Van Hal et al.'s 2024 study shows how AI can predict IH in patients with traumatic brain injury (TBI) [111]. The models adopted (especially those based on "neural networks" and "Gaussian processes"), using variables such as intracranial pressure (ICP) and mean arterial pressure (MAP), dependably predicted IH (AUC up to 0.94). Moreover, they have been externally validated, indicating their potential clinical applicability.

Fong et al.'s study of that year developed the I-CARE algorithm to predict IH in acute brain injury patients [112]. Using retrospective data from over 900 patients, the algorithm, which is a "supervised ensemble machine learning algorithm", successfully predicted IH values 30 min before the onset, basing the prediction on clinical variables such as ICP history, temperature, weight, serum creatinine, age, Glasgow Coma Scale, and hemodynamic parameters. This tool promises to revolutionize the management of IH, allowing clinicians to take proactive measures to prevent critical episodes.

Another recent article explores the use of algorithms for predicting mean intracranial pressure using "artificial neural networks" to support medical decisions [113]. This technology makes it possible to anticipate dangerous ICP trends, thus improving medical intervention and utilization of hospital resources. The use of "artificial neural networks" is therefore crucial in improving the clinical management of brain injury.

Guochang Ye et al.'s recent study demonstrated the effectiveness of a *machine learning*-based model for continuous prediction of intracranial pressure in traumatic brain injury patients [114]. The model, using a "long-term recurrent neural network", showed an average accuracy of 94.62 % in predicting IH events, with a sensitivity of 74.91 % and specificity of 94.83 %, outperforming traditional methods. This real-time predictive capability enables clinicians to anticipate and promptly manage critical changes in ICP.

Deep learning approaches have been used to derive non-invasive intracranial hypertension using extracranial common vital parameters recorded during ICU stay. These studies demonstrated interesting results that need further validation [115,116].

Despite the promising applications of AI in IH management, several challenges still exist. One of the main is the accuracy of the algorithms; these must be validated through large-scale clinical studies to ensure that they are safe and effective. Furthermore, the integration of these tools into everyday clinical practice requires adequate training for healthcare professionals.

Another challenge relates to data management: AI algorithms require large amounts of data to be trained and validated, raising concerns about patient privacy. It is crucial to develop solid policies and protocols to protect sensitive patient information.

Table 2
Summary of recommended settings for ultrasound measurement of ONSD.

Frequency	Acoustic output	Mechanical Index	Termal Index	Depth	Focus	Gain	PRF
10 MHz	max 25 %	≤0.23	≤1 °C	40 mm	25 mm	50–60 %	1 KHz

Abbreviations: *MHz megahertz, PRF pulse repetition frequency, KHz kilohertz.*

Finally, in the future, AI could be integrated with other emerging technologies, such as telemedicine and wearable devices, to improve the management of IH. Interdisciplinary collaboration between neurologists, engineers, and researchers will be crucial to fully exploit the potential of these technologies.

3.6.1. Limitations

The primary limitation of this work is its narrative design. Although a systematic search strategy was applied, the review does not follow the structure of a systematic review or meta-analysis. This approach was intentionally chosen due to the expected substantial methodological and clinical heterogeneity among the tools and studies examined. As a result, no formal quantitative synthesis or risk-of-bias assessment was performed. Tools such as RoB 2.0, which are designed for randomized controlled trials, and QUADAS-2, specific to diagnostic accuracy studies, were deemed inappropriate for the scope and aims of this review.

4. Conclusions

Intracranial hypertension represents a neurological emergency that should be rapidly recognized and treated to improve the patient's outcome.

Some non-invasive monitoring tools are available at the bedside, overcoming the limits of invasive intracranial monitoring (staff and material availability, expertise, and potential complications). There are transcranial doppler, automated pupillometry, and brain skull deformation devices demonstrated to be useful in critically ill patients. Considered together, they offer a valuable alternative, especially for ruling out IH and potentially changing daily clinical management [117].

Moreover, future data from AI and radiomics could increase the sensitivity of multimodal neuromonitoring in detecting IH and monitoring the response to the therapies administered.

CRediT authorship contribution statement

Cristian Deana: Writing – review & editing, Writing – original draft, Supervision, Resources, Project administration, Methodology, Conceptualization. **Daniele Guerino Biasucci:** Writing – review & editing, Writing – original draft, Validation, Methodology, Conceptualization. **Raffaele Aspide:** Writing – original draft, Visualization, Investigation. **Daniele Bagatto:** Writing – review & editing, Writing – original draft, Investigation, Formal analysis, Data curation. **Sergio Brasil:** Writing – original draft, Methodology, Investigation, Formal analysis. **Domenico Brunetti:** Writing – review & editing, Writing – original draft, Data curation. **Thomas Saitta:** Writing – review & editing, Writing – original draft, Methodology, Data curation, Conceptualization. **Mina Vapireva:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Christian Zanza:** Writing – review & editing, Writing – original draft, Methodology, Data curation. **Yaroslava Longhitano:** Writing – review & editing, Writing – original draft, Investigation. **Elena Giovanna Bignami:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Data curation. **Luigi Vetrugno:** Writing – review & editing, Writing – original draft, Validation, Supervision, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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