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The Pre-Lumbar puncture Intracranial Hypertension Scale (PLIHS): A practical scale to identify subjects with normal cerebrospinal fluid pressure in the management of idiopathic intracranial hypertension

Alberto Raggi [a,*], Stefania Bianchi Marzoli [b], Paola Ciasca [b], Gabriella Cammarata [b], Lisa Melzi [b], Luisa Chiapparini [c], Alessandra Erbetta [c], Elisa Ciceri [d], Giuseppe Faragò [e], Andrea Gioppo [f], Susanna Usai [g], Domenico D'Amico [g]

[a] Fondazione IRCCS Istituto Neurologico Carlo Besta, Neurology, Public Health and Disability Unit, Milano, Italy
[b] Istituto Auxologico Italiano IRCCS, Neuro-ophthalmology Center – Scientific Institute Capitanio Hospital, Milano, Italy
[c] Fondazione IRCCS Istituto Neurologico Carlo Besta, Neuroradiology Unit, Milano, Italy
[d] Fondazione IRCCS Istituto Neurologico Carlo Besta, Radiodiagnostic and Interventional Neuroradiology, Milano, Italy
[e] Papa Giovanni XXII Hospital, Neuroradiology Department, Bergamo, Italy
[f] ASST Santi Paolo e Carlo, P.O San Carlo, Radiologia II – Neurodiagnostica-Neurointerventistica, Milano, Italy
[g] Fondazione IRCCS Istituto Neurologico Carlo Besta, Neuroalgology Unit, Milano, Italy

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ABSTRACT

Background: Idiopathic Intracranial Hypertension (IIH) diagnosis requires lumbar puncture to measure cerebrospinal fluid (CSF) pressure. The Pre-Lumbar puncture Intracranial Hypertension Scale (PLIHS) is aimed to detect cases that will show raised or normal CSF opening pressure.

Methods: Retrospective analysis of records of patients who underwent lumbar puncture for suspect IIH. The target was CSF opening pressure $\geq$ 250 mmH2O, whereas a set of known neurological, neuro-ophthalmological and neuro-radiological parameters, plus obesity, were used as predictors in a logistic regression model. The PLIHS was based on significant predictors and a cut-off was validated using chi-squared test around CSF opening pressure $\geq$ 250 and $<$ 200 mmH2O.

Results: Records of 162 patients were included: CSF opening pressure was $<$200 mmH2O in 40 and $\geq$ 250 mmH2O in 95 patients; 85 fulfilled IIH diagnosis. PLIHS is based on Frisén grade 2 or higher papilledema, tinnitus, empty sella, perioptic subarachnoid space distension, and obesity. Score range is 0–7: correlation with CSF opening pressure is 0.508 ($p < .001$), and PLIHS score is different between subjects not diagnosed with IIH, and those diagnosed with IIH both with and without papilledema ($p < .001$). PLIHS score $\leq$ 2 identifies cerebrospinal fluid pressure $<$ 200 mmH2O; PLIHS score $\geq$ 3 identifies CSF opening pressure $\geq$ 250 mmH2O, IIH diagnosis, visual acuity $\leq$0.7, and optic nerve atrophy.

Conclusions: The PLIHS, can be used to identify patients who will particularly need LP, thus helping with the organization of the diagnostic work-up by optimising healthcare resources and potentially limit the likelihood to incur in LP-related adverse events.

Abbreviations: AUROC, Area Under the Receiver Operating Curve; BCVA, Best Corrected Visual Acuity; BMI, Body Mass Index; CSF, Cerebrospinal Fluid; GCC, Ganglion Cell Complex; IIH, Idiopathic Intracranial Hypertension; ln(OR), Log Odds; LP, Lumbar Puncture; MRV, Magnetic Resonance Venography; MD, Mean Deviation; OCT, Optical Coherence Tomography; OR, Odds Ratios; PLIHS, Pre-Lumbar puncture Intracranial Hypertension Scale; RNFL, Retina Nerve Fiber Layer thickness; TVO, Transient Visual Obscurations.

* Corresponding author at: Fondazione IRCCS Istituto Neurologico Carlo Besta, Neurology, Public Health and Disability Unit, Via Celoria 11, 20133 Milano, Italy.
E-mail addresses: alberto.raggi@istituto-besta.it (A. Raggi), s.bianchimarzoli@auxologico.it (S. Bianchi Marzoli), p.ciasca@auxologico.it (P. Ciasca), g.cammarata@auxologico.it (G. Cammarata), l.melzi@auxologico.it (L. Melzi), luisa.chiapparini@istituto-besta.it (L. Chiapparini), alessandra.erbetta@istituto-besta.it (A. Erbetta), elisa.ciceri@istituto-besta.it (E. Ciceri), gfarago@asst-pg23.it (G. Faragò), andrea.gioppo@asst-santipaolocarlo.it (A. Gioppo), susanna.usai@istituto-besta.it (S. Usai), domenico.damico@istituto-besta.it (D. D'Amico).

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1. Introduction

Idiopathic intracranial hypertension (IIH) is a relatively rare neurological condition caused by raised cerebrospinal fluid (CSF) pressure in absence of space-occupying lesions, which occurs predominantly in young women and obese subjects [1–3]. The pillars of IIH diagnosis are papilledema, and CSF opening pressure on lumbar puncture (LP) in lateral decubitus ≥250 mmH2O, normal CSF composition and neurological examination, and absence of any mass or structural lesion. Clinical presentation of IIH is highly variable, and signs of symptoms such as sixth nerve palsy, empty sella, flattening of the posterior aspect of the globe, distention of the perioptic subarachnoid space, and transverse venous sinus stenosis are also included among alternative markers of diagnosis [2]. The threshold for raised CSF pressure has been debated, as a value of 250 mmH2O or higher is not universally accepted in reason of the considerable diurnal CSF pressure fluctuations [4]. In fact, the IIH Treatment Trial Consortium study included also patients with CSF pressure between 200 and 250 mmH2O provided that the following findings suggestive of IIH were identified: pulse-synchronous tinnitus; sixth nerve palsy; grade II papilledema; no evidence of pseudopapilledema; transverse sinus stenosis or collapse on MRV; partially empty sella with unfolded perioptic nerve CSF spaces [5]. Finally, the identification of a "normal" CSF pressure value is variable as well: three studies addressed normative values for CSF opening pressure, and found average CSF pressure values of 155, 170 and 193 mmH2O [6–8].

LP, which essential in IIH diagnosis, is an invasive procedure which may be associated to complications, including back ache, nerve root irritation, hearing disturbances, and post-dural puncture headache [9]. The latter requires specific management, from bed rest, hydration and use of specific medication, up to the surgical closure of the dural gap [10–12]. A retrospective study on 969 patients who underwent diagnostic LP showed that 5% developed post-dural puncture headache, and one-fourth of them had to be treated with epidural blood patch [13]. LP might therefore determine an increase utilization of health services, and it is contraindicated in presence of local skin infection and high risk of bleeding [14]. In some cases, LP may be not necessary, as normal CSF opening pressure is a potential outcome of LP despite the presence of some symptoms and signs suggesting IIH. However, the information on non-diagnosis rates among suspect IIH cases is poorly reported in scientific literature.

We performed a recognition of literature reviews addressing signs and symptoms that are associated to IIH, and considered 16 reviews published between 1995 and 2020 [1,15–29]. The results of this literature analysis, although not systematic, show that three neuro-ophthalmological, three neurological, and five neuro-radiological signs or symptoms, and obesity were described as associated to IIH in at least two documents. Neuro-ophthalmological signs and symptoms were transient visual obscuration (TVO) [1,16,19–21,24,26,29], visual field defect [26,29], and papilledema [1,17,20,23,25–28]; neurological ones were headache [1,16,21,23,25–29], tinnitus [16,17,19–21,23–26,28,29], and dizziness/vertigo [1,19,28]; neuro-radiological ones were empty/partially empty sella, perioptic subarachnoid space distension, optic nerve tortuosity, flattening of the posterior aspect of the globe, and transverse sinus stenosis or collapse, all included in three reviews [15,20,22]; obesity was reported in four reviews [18,25,27,28]. Therefore, besides those signs and symptoms that are indicative of IIH diagnosis, the set of elements that suggest the utility of submitting a patient to the diagnostic workout for IIH is clearly wider. One of the problems with this amount of variables is that not all of them are systematically addressed: in particular, transverse sinus stenosis requires magnetic resonance venography (MRV). The sensitivity of such a procedure is dependent on technical factors, and sensitivity and specificity higher than 90% in identifying IIH have been reported [30], and it is of importance as it lays the foundation for the possibility to use venous sinus stenting, a procedure with good efficacy and favourable safety profile [31].

What is not systematically addressed in the literature is the procedure for the systematic selection of the best candidate for LP, which is of importance to limit the potential impact of its complications. The purpose of this study was to develop a practical scale for clinicians, the Pre-Lumbar puncture Intracranial Hypertension Scale (PLIHS), aimed to identify those patients who are likely to have a CSF opening pressure ≥ 250 mmH2O, which are therefore likely to be diagnosed with IIH, and those with pressure < 200 mmH2O, which therefore will not be diagnosed with IIH.

2. Methods

The development of PLIHS was based on the selection of candidate variables which have been reported in the literature as associated to IIH, and that were then tested in a retrospective study. Such a retrospective analysis was carried out on clinical records of patients with suspected IIH admitted at the division of Neuroalgology of the Neurological Institute Carlo Besta of Milan between January 2010 and May 2021. In case of multiple hospital admissions in our centre, we took into consideration the record referred to the first one. Patients' consent on the use of clinical data for research purposes was acquired at the time point of admission: an explicit mention on the possibility that clinical data are used for research purpose was written in admission documentation, and patients could opt either to agree or disagree on this. For this retrospective analysis, records of patients who explicitly agreed were revised.

IIH was suspected when at least two of the following signs and symptoms or neuro-radiological findings coexisted: TVOs, visual field defect, papilledema; headache, tinnitus, dizziness/vertigo, sixth cranial nerve palsy; empty/partially empty sella, perioptic subarachnoid space distension, optic nerve tortuosity, flattening of the posterior aspect of the globe, and transverse sinus stenosis or collapse. The choice of these signs and symptoms was defined to take into account both diagnostic ones as well as those that, although not considered as diagnostic (e.g. headache or TVOs), were reported as associated to IIH in previous literature reviews [1,15–29]. The final diagnosis of IIH was based on Friedman criteria [2].

Inclusion criteria were age greater of 18 years, CSF pressure measurement, completeness of neurological, neuro-ophthalmological and neuro-radiological parameters. We excluded patients who presented increased intraocular pressure, refractive error equal or greater of 6 dioptres, optic disc drusen, optic dysplasia or retinopathy, and patients who showed optic neuropathy with or without disc swelling unrelated to IIH. Pregnant women and patients with contraindications to MRI or MRV were also excluded.

All the studied variables were obtained during the in-patient hospitalization, through a standard multidisciplinary program, which included neurological examination, body mass index (BMI) calculation, complete neuro-ophthalmological evaluation and brain MRI and MRV. Neuro-ophthalmological examination included Standardized Automated Perimetry (SAP, Humphrey 30–2) and Optical Coherence Tomography (OCT: OptoVue-RTVue) measurements of the peripapillary Retina Nerve Fiber Layer thickness (RNFL) and the Ganglion Cell Complex (GCC).

MRI scans were performed either on 1,5 T (Philips Achieva Healthcare, Eindhoven, the Netherlands; Siemens Avanto, Erlangen, Germany) or 3 T MRI (Philips Achieva Healthcare, Eindhoven, the Netherlands) using spin echo T1 and turbo spin echo T2- weighted images, fluid attenuated inversion recovery, targeted study for orbital regions with T1 and T2 Fat Suppression sequences, and Phase Contrast venous angiography.

CSF pressure was measured by x-ray guided LP performed in the left lateral decubitus position with the knees and the neck flexed (legs and neck being approximately 20°-30° flexion, which enabled maintaining the lateral decubitus position during the procedure), avoiding Valsalva manoeuvre. A 20-gauge standard needle (quincke needle with a bevel tip) was inserted into the subarachnoid space at the L3-L4 or the L4-L5

interspace. Patients were not allowed to eat or drink from the previous midnight, acetazolamide, furosemide or topiramate therapy was suspended at least 72 h before the procedure; anticoagulants were switched to heparin, which was suspended 48 h before the procedure.

2.1. Variables and measurements

The primary endpoint was CSF opening pressure, the target of the predictive model being pressure ≥ 250 mmH2O. Best corrected visual acuity (BCVA) ≤0.7 using Snellen chart, and optic nerve atrophy, determined by OCT measurement of RNFL or GCC ≤90 μm, and IIH diagnosis (with and without papilledema) were used as secondary endpoints for PLHIS.

A total of 13 parameters were considered as predictors of CFS opening pressure ≥ 250 mmH2O. There were three neuro-ophthalmological parameters: subjective visual disturbances defined as TVOs, visual field defects defined as arcuate or generalized depression with mean deviation higher than −3.00 dB, and papilledema grade 2 or greater according to Frisén scale [32]. There were four neurological parameters: headache with an average frequency higher than four days/month in the previous trimester, tinnitus, dizziness/vertigo, and sixth cranial nerve palsy. There were five neuro-radiological parameters: empty sella (including also partially empty sella), perioptic subarachnoid space distention, optic nerve tortuosity, flattening of the posterior aspect of the globe, bilateral or unilateral transverse venous sinus stenosis or collapse. Finally, obesity status, defined by BMI ≥ 30, was included.

2.2. Data analysis

Descriptive statistics were employed to report distribution of each sign, at the whole sample level, and also by diving patients for CSF opening pressure (<200 mmH2O, 200–250 mmH2O, ≥250 mmH2O) and IIH diagnosis matching: group differences were tested with Chi-Squared test.

Logistic regression was performed to select relevant predictors of CFS opening pressure ≥ 250 mmH2O and build PLIHS. First, in order to select candidate predictors, each of the selected variables was tested in univariable logistic regression, and variables with significance at $p < .10$ level were retained for the multivariable analysis. We then applied a stepwise backward procedure which enabled excluding variable based on their level of significance: at each step, the less significant was excluded, until only variables showing a significant association with $p < .05$ were retained. The goodness of fit of the final model was assessed through Cox&Snell and Nagelkerke pseudo-R^2 and through the c-statistic, i.e. the area under the receiver operating curve (AUROC) for the predicted versus the actual data: c-statistic coefficient higher than 0.8 indicates a strong model.

The significant predictors were rated after rounding their log odds (ln (OR)) to the closest absolute even number to constitute the PLIHS score, which is based on the sum of items scores. We relied on ln(OR), rather than odds ratios (OR) to define PLIHS score, as the sum of ln(OR) is expected to more accurately predict the outcome rather than the sum of ORs [33].

To determine PLIHS cut-off score for CFS opening pressure ≥ 250 mmH2O, we relied on the AUROC procedure, and identified the score that was associated to the best sensitivity and specificity. To test whether the same cut-off also predicted normal pressure, we tested whether score below the cut-off showed the best sensitivity and specificity for CFS pressure < 200 mmH2O.

Three different approaches were used to validate the PLIHS and its the cut-off score. First, we tested the correlation between PLIHS scale score and CSF pressure using Pearson's correlation (significant at $p < .05$). Second, we addressed whether PLIHS scored differently between patients not matching IIH diagnosis, and those matching the diagnosis of IIH with and without papilledema: one-way ANOVA, with Bonferroni post-hoc test, was used to test such difference. Third, we assessed whether the cut-off score was associated to CSF pressure ≥ 250 mmH2O, to CSF pressure < 200 mmH2O, to formal IIH diagnosis according to Friedman criteria, to optic nerve atrophy determined by OCT measurement of RNFL or GCC ≤90 μm, and to BCVA ≤0.7 at Snellen's chart. To address such associations, the chi-squared test and odds ratios (ORs) with 95%CI were used.

3. Results

A total of 165 records of adult patients with clinically suspected IIH were available analysed, and since LP was not performed in three patients who refused the procedure, 162 cases (131 females) were included. In total 85 received a definite IIH diagnosis, and these patients' average CSF pressure was 345 mmH2O (95%CI 323–367): 22 of those with IIH diagnosis (25.9%) did not have papilledema. Mean age was 39.1 years (95% CI: 37.1–41.0), with no difference between subgroups based on CSF pressure and IIH diagnosis. Average BMI was 30.2 (95% CI: 29.2–31.2). Table 1 reports the distribution of signs and symptoms across the three groups with CFS pressure < 200 mmH2O, between 200 and 249 mmH2O, and ≥ 250 mmH2O.

Table 2 reports information on logistic regression used to build the PLIHS scale. Based on univariate regression analysis, the following variables were excluded: visual field defect, headache, sixth cranial nerve palsy, dizziness, and optic nerve tortuosity, thus leaving eight candidate predictors. The final model had a strong predictive power (C-Statistic = 0.85; 95% CI 0.78–0.91) and showed five significant predictors: Frisén grade 2 or higher papilledema, OR 6.5, ln(OR) 1.88, PLIHS score 2; tinnitus, OR 4.8, ln(OR) 1.57, PLIHS score 2; empty sella, OR 2.5, ln(OR) 0.92, PLIHS score 1; perioptic subarachnoid space

Table 1
Variables distribution across sample.

	All patients (N = 162)	CSF Pressure ≤ 200 mmH2O			P-value
		<200 mmH2O (N = 40)	200–249 mmH2O (N = 27)	≥250 mmH2O (N = 95)	
TVO	106 (65.4%)	20 (50.0%)	16 (59.3%)	70 (73.7%)	0.023
Visual field defect	63 (38.9%)	16 (40.0%)	8 (29.6%)	39 (41.1%)	0.554
Papilledema (Frisén grade II or higher)	83 (51.0%)	11 (27.5%)	9 (33.3%)	63 (51.2%)	<0.001
Headache >4 days/month	129 (79.6%)	34 (85.0%)	20 (74.1%)	75 (78.9%)	0.535
Sixth cranial nerve palsy	11 (6.8%)	1 (2.5%)	2 (7.4%)	8 (6.8%)	0.454
Tinnitus	36 (22.2%)	4 (10.0%)	2 (7.4%)	30 (31.6%)	0.003
Dizziness/ Vertigo	16 (9.9%)	1 (2.5%)	6 (22.2%)	9 (9.5%)	0.029
Empty/Partially empty sella	107 (66.0%)	17 (42.5%)	14 (51.9%)	76 (80.0%)	<0.001
Perioptic subarachnoid space distension	115 (71.0%)	20 (50.0%)	16 (59.3%)	79 (83.2%)	<0.001
Optic nerve tortuosity	76 (46.9%)	16 (40.0%)	18 (66.7%)	42 (44.2%)	0.071
Flattening of the posterior aspect of the globe	58 (35.8%)	7 (17.5%)	8 (29.6%)	43 (45.3%)	0.007
Transverse sinus stenosis or collapse	99 (61.1%)	18 (45%)	15 (55.6%)	66 (69.5%)	0.023
Obesity status (BMI ≥30)	78 (48.1%)	7 (17.5%)	14 (51.9%)	57 (60.0%)	<0.001

Notes. Data are reported as frequencies and percentage by group. CSF, Cerebrospinal Fluid; IIH, Idiopathic Intracranial Hypertension; BMI, Body Mass index; TVO, Transient Visual Obscuration.

Table 2
Univariable and multivariable regression models predicting CSF pressure ≥ 250 mmH2O.

	Univariate analysis		Multivariate analysis (initial model)		Multivariate analysis (final model)	
	OR (95% CI)	P-value	OR (95% CI)	P-value	OR (95% CI)	P-value
TVO	2.4 (1.2–4.7)	0.009	1.7 (0.7–4.1)	0.217		
Visual field defect	1.2 (0.7–2.4)	0.501				
Papilledema (Frisén grade II or higher)	4.6 (2.4–9.1)	<0.001	5.7 (2.4–13.7)	<0.001	6.5 (2.8–15.0)	<0.001
Headache >4 days/month	0.9 (0.4–2.0)	0.797				
Sixth cranial nerve palsy	2.0 (0.5–7.7)	0.334				
Tinnitus	4.7 (1.8–12.1)	0.001	4.9 (1.6–14.8)	0.005	4.8 (1.6–14.2)	0.005
Dizziness/Vertigo	0.9 (0.3–2.5)	0.838				
Empty sella	4.6 (2.3–9.3)	<0.001	2.5 (1.0–6.5)	0.052	2.5 (1.0–6.3)	0.049
Perioptic subarachnoid space distension	4.3 (2.1–8.7)	<0.001	2.6 (0.9–7.3	0.079	2.8 (1.1–7.4)	0.034
Optic nerve tortuosity	0.8 (0.4–1.4)	0.412				
Flattening of the posterior aspect of the globe	2.9 (1.4–5.8)	0.003	1.4 (0.5–3.5)	0.491		
Transverse sinus stenosis or collapse	2.3 (1.2–4.5)	0.010	0.8 (0.3–2.0)	0.672		
Obesity (BMI ≥30)	3.3 (1.7–6.4)	<0.001	4.5 (1.9–10.5)	0.001	4.2 (1.9–9.6)	0.001

Notes. Cox & Snell pseudo R-Squared 0.34; Nagelkerke pseudo R-Squared 0.45; C-Statstic 0.85 (95% CI: 0.78–0.91). CSF, Cerebrospinal Fluid; BMI, Body Mass index; TVO, Transient Visual Obscuration; OR, Odds Ratio; 95% CI, 95% Confidence Intervals.

distension, OR 2.8, ln(OR) 1.04, PLIHS score 1; obesity, OR 4.2, ln(OR) 1.44, PLIHS score 1.

PLIHS score range is 0–7 and the corresponding score for each item is shown in Table 3. Fig. 1 shows the distribution of PLIHS scores across patients with different opening CFS pressure levels, and it shows a clear gradient across scores: lower PLIHS scores are associated to lower CSF pressure, and higher score are associated to higher CSF pressure (Chi-Squared test 68.5, $p < .001$). PLIHS score positively correlated with opening CSF pressure ($r = 0.508$, $p < .001$). Table 4 shows the result of one-way ANOVA testing CSF pressure and PLIHS differences between patients not diagnosed and those diagnosed with IIH, with and without papilledema. Both CSF pressure and PLIHS showed difference, with all post-hoc test being significant: patients diagnosed with IIH without papilledema were in an intermediate position both for CSF pressure and PLIHS score.

AUROC analyses showed that PLIHS score ≥ 3 had a sensitivity of 87.4% and specificity of 65.5% for the identification of CSF pressure ≥ 250 mmH2O (AUROC = 0.84; 95%CI 0.78–0.90), and that PLIHS score ≤ 2 had a sensitivity of 82.7% and specificity of 71.2% for the identification of CSF pressure < 200 mmH2O (AUROC = 0.83; 95%CI 0.76–0.90).

Table 5 reports the validation of the cut-off score of PLIHS scale. Patients with PLIHS score ≥ 3 showed increased likelihood of having CSF pressure ≥ 250 mmH2O, of being appointed with IIH diagnosis, and of having optic nerve atrophy and BCVA ≤0.7 compared to those with PLIHS score ≤ 2. Conversely, those with PLIHS score ≤ 2 had higher likelihood of having CSF pressure < 200 mmH2O compared to those with PLIHS score ≥ 3.

Table 3
The PLIHS scale.

Papilledema	No papilledema or Frisén grade I	0
	Papilledema with Frisén grade II or higher	2
Tinnitus	No tinnitus	0
	Evidence of Tinnitus	2
Sella Turcica	Normal Sella	0
	Empty or Partially empty Sella	1
Perioptic subarachnoid space	Normal space	0
	Evidence of distension	1
BMI Level	Normal weight	0
	Obesity (BMI ≥30)	1
Total PLIHS score		(sum of items)

Notes. PLIHS, Pre-Lumbar puncture IIH Scale; BMI, Body Mass index.

4. Discussion

We developed the PLIHS, a scale for clinical practice aimed to detect patients that will most likely show raised or normal CSF opening pressure (i.e. ≥250 mmH2O or < 200 mmH2O), with a clear impact on IIH diagnosis. The scale is based on five elements that can be evaluated in patients with suspect IIH before they undergo LP procedure, namely: Frisén grade 2 or higher papilledema and tinnitus (both scored 2), empty sella, perioptic subarachnoid space distension, and obesity defined by BMI ≥ 30 (all scored 1). PLIHS scores' range is 0–7: it is well correlated with CSF opening pressure, and differentiates between subjects not diagnosed with IIH, and those diagnosed with IIH both with and without papilledema. Patients with PLIHS score ≤ 2 will likely have normal CSF opening pressure, whereas those with score ≥ 3 will likely have CSF opening pressure ≥ 250 mmH2O, IIH diagnosis, BCVA ≤0.7 at Snellen's chart and evidence of optic nerve atrophy at OCT.

Non-invasive approaches to the definition of raised CSF pressure have been proposed, in particular the use of ultrasounds to measure optic nerve sheath diameter. Such a technique showed significant associations with raised CSF pressure [34–36], and cut-off scores for CSF pressure > 250 mmH2O were 6.3 mm [36] and 5.2 mm [37]. However, ultrasound is a technique that is operator-dependent and requires specific skills. Such non-invasive approaches (including, in addition to ultrasounds, others such as tympanometry, near-infrared spectroscopy or visual-evoked potentials) are not reliable enough, they are not inexpensive and require

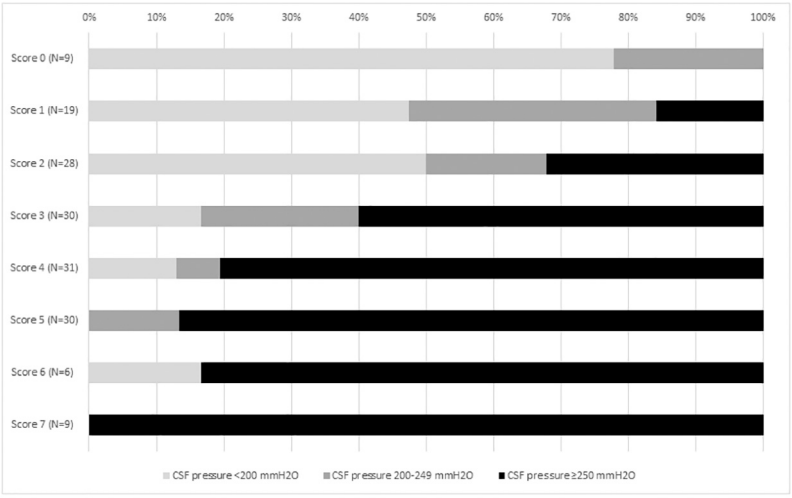

Fig. 1. distribution of single PLIHS score in relation to CSF pressure (≤200, 200–249, and ≥ 250 mmH2O).
Notes. PLIHS, Pre-Lumbar puncture IIH Scale; CSF, Cerebrospinal Fluid.

Table 4
One-way ANOVA for CSF pressure and PLIHS scale across patients with no IIH diagnosis, IIH diagnosis without papilledema, and IIH diagnosis with papilledema.

	NO IIH diagnosis ($N = 77$)	IIH without papilledema ($N = 22$)	IIH with papilledema ($N = 63$)	F (p)
CSF pressure	193 (183–204)	305 (283–328)	358 (330–387)	76.7 (<0.001)
PLIHS score	2.2 (1.8–2.5)	3.3 (2.9–3.8)	4.7 (4.4–5.1)	62.3 (<0.001)

Notes. Data are reported as means and 95% Confidence Intervals. PLIHS, Pre-Lumbar puncture IIH Scale; CSF, Cerebrospinal Fluid.

Table 5
Chi-Squared analysis of PLIHS cut-off score in relation to CSF pressure thresholds (<200 and ≥ 250 mmH2O), formal IIH diagnosis, optic nerve atrophy and visual acuity.

		PLIHS score 0–2	PLIHS score 3–7	Chi-Squared (p-value)	OR (95% CI)
CSF pressure ≥ 250 mmH2O	NO	44 (78.6%)	23 (21.7%)	48.9 (<0.001)	13.2 (6.0–29.0)
	YES	12 (21.4%)	83 (78.3%)		
CSF pressure < 200 mmH2O	YES	37 (66.1%)	15 (14.2%)	45.3 (<0.001)	11.8 (5.4–25.6)
	NO	19 (33.9%)	91 (85.8)		
Diagnosis of IIH	NO	49 (87.5%)	28 (26.4%)	54.8 (<0.001)	19.5 (7.9–48.1)
	YES	7 (12.5%)	78 (73.6%)		
Optic Nerve Atrophy	NO	46 (82.1%)	67 (63.2%)	6.2 (0.013)	2.7 (1.2–5.9)
	YES	10 (17.9%)	39 (36.8%)		
BCVA <0.7	NO	22 (39.3%)	24 (22.6%)	5.0 (0.025)	2.2 (1.1–4.5)
	YES	34 (60.7%)	82 (77.4%)		

Notes. Data are reported as frequencies and percentages. PLIHS, Pre-Lumbar puncture IIH Scale; CSF, Cerebrospinal Fluid; IIH, Idiopathic Intracranial Hypertension; BCVA, Best Corrected Visual Acuity; OR, Odds Ratio; 95% CI, 95% Confidence Intervals.

additional diagnostic procedures [38–41]: therefore, LP is still essential for IIH diagnosis.

Not all patients presenting with signs and symptoms suggestive of IIH will receive a definite IIH diagnosis based on Friedman criteria. In previous studies [42–45], the rates of non-diagnosis varied between 41% and 80% and, taken together, these findings suggest that 56.2% of patients with suspect IIH (i.e. 136 out of 242 comprised in the four aforementioned studies) did not receive formal IIH diagnosis (in our study the same figure was 47.5%, i.e. 77 out of 162 patients). It has to be considered that, across studies, the definition of suspected IIH may be variable and the rate of diagnosis non-confirmation, although poorly reported, stress the importance of a pre-LP screening procedure. PLIHS is therefore a viable procedure to define suspect IIH cases and might help in the organization of the diagnostic work-up: on one side, by postponing LP in those cases with low PLIHS score; on the other side, as a scientifically-based frame of reference for proposing LP to those patients that might not be prone to carry it out. Thus, the use of PLIHS would help optimising healthcare resources and potentially limit the likelihood to incur in LP-related adverse events. In fact, post-dural headache, requires few days of bed rest, and therefore delay in hospital discharge, eventually workdays loss, drug administration and, in the most severe cases, surgical procedures. However, in deciding whether to postpone LP or not, clinicians should be always aware of the diagnostic relevance of LP, not only for pressure measuring, but also for detecting other possible causes of elevated CSF pressure, such as neuroinflammation, infections or tumour cells. Moreover, some outliers might exist: in our series, 12.5% of those with score 0–2 (actually, all with score 2) received IIH diagnosis. Therefore, in case a clinician decides to postpone LP, a short-term follow-up has to be planned.

A minority of patients receive the diagnosis of IIH without papilledema: in previous studies, the rate of such diagnosis ranged between 2.5% and 22.7% [43,46–49] (in total, 39 out of 512 patients, corresponding to 7.6% of patients included in the five aforementioned studies). Generally, IIH patients without papilledema show lower opening CSF pressure, more frequently present migraine with aura, and show important diurnal CSF pressure fluctuations [50]. Diagnosing IIH

without papilledema is challenging and such a specific condition might be much more prevalent than expected [51,52]. In our study, 79 patients out of 162 (49%) did not present with papilledema, and the diagnosis of IIH without papilledema was made in 22 out of 85 patients matching IIH diagnosis (i.e. 25.9%). PLIHS scale score in patients with IIH without papilledema was significantly lower compared to those with papilledema, and higher compared to those not receiving IIH diagnosis (the difference being higher than one point on average in both cases). Such an intermediate position is consistent with CSF pressure: the difference was around 50 mmH2O between the two groups of patients, and around 110 mmH2O between patients with IIH without papilledema and those not diagnosed with IIH.

We decided to test PLIHS ability to identify CSF pressure < 200 mmH2O in addition to pressure ≥ 250 mmH2O, because our aim was to identify also those cases in which LP might be postponed or even reasonably avoided. There are some important reasons for this. It has been shown that variability exists in the measurement of CSF pressure related to factors, such as age, gender and BMI, with males, people with higher BMI and adults (compared to elderly) showing higher CSF opening pressure [53,54], patients' position [55–57], and Valsalva manoeuvres [58]. As diurnal fluctuations are well known [58–60], it has been shown that cases with borderline values higher than 200 mmH2O may benefit from long-term monitoring [50]. Moreover, the upper bound of normative values for CSF opening pressure exceeded 200 mmH2O in two studies [6,7]. As IIH cannot be diagnosed if CSF pressure is below 200 mmH2O, targeting CSF pressure level below this threshold is viable for the purpose of identifying cases that will not be diagnosed with IIH. These patients might be proposed to postpone LP and be closely monitored for clinical and radiological parameters.

We did not find any association with headache presence. It has historically been reported as a common feature of IIH [1,59,61–63], but is has a very heterogeneous phenotype: it may be unilateral, throbbing or pounding, and the associated migraine-like symptoms can be common as well [60,64]. However, it is difficult to address a specific "typical" headache disorder that is associated to IIH, and migraine-like headache, eventually associated with photophobia, may be confounding in the diagnostic procedure. The third International Classification of Headache Disorders [10] defines headache attributed to elevated CSF pressure (code 7.1) as either a new condition, or as the worsening of a pre-existing primary headache, but with a poor clinical definition, the most relevant aspect being the onset in temporal relation to intracranial hypertension or its discovery, and its relieving after reduction of CSF pressure. No characterization of such headache is given, which on the contrary happens for headache attributed to IIH (code 7.1.1), where the fact that such a secondary headache may mimic the features of chronic migraine or chronic tension-type headache is stated. However, such kind of headaches are secondary ones: in our series we accounted for headache irrespectively of the fact that it was secondary to IIH or increased CSF pressure, or an aggravation of pre-existing a primary one. Such an approach to headache definition was, in our opinion a successful one and reinforces the importance of PLHIS, which can be a valid aid in the diagnostic workup of suspect IIH cases, irrespectively of the presence of any associated headache disorder.

Some limitations should be acknowledged. First, our analysis is based on a single centre, with a long-lasting close collaboration between headache specialists, neuro-radiologists, neuro-ophthalmologists and psychologists, and a clearly defined multidisciplinary pathway for suspect cases workup: these aspects might have brought to a "natural selection" of clinical variables. Second, since the definition of IIH suspects is based on the clinical practice of our centre, our results may be not entirely comparable to those of others. A consequence of these two limitations might be the high rate of patients diagnosed with IIH without papilledema: we cannot exclude that such high rate might be due to the fact that we employed a definition of suspect cases that goes well beyond the presence of papilledema, sixth cranial nerve palsy and radiological findings. Third, we excluded patients with confounding optic nerve head issues and pregnant females (although none of the patients meeting inclusion criteria was pregnant). This might, at least in part, reduce the applicability of PLIHS to real world situations in which pregnancy and increased intraocular pressure, relevant refractive errors, optic disc drusen, optic dysplasia, retinopathy, and optic neuropathy unrelated to IIH may present. Fourth, some patients were under IIH treatment at the time point of admission to our centre which, being a third-level one, is often attended by patients diagnosed elsewhere. Patients with previously diagnosed IIH are submitted to the whole diagnostic path (i.e. inclusive of LP) if either LP was performed at least 12 months before or if the LP was not performed, and therefore the diagnosis was only suspected (if not misappointed) based on clinical, radiological and neuro-ophthalmological findings. As a mitigation strategy for lowering the impact of treatments on CSF opening pressure, acetazolamide, furosemide or topiramate therapy was suspended at least 72 h before the procedure. However, we cannot completely exclude that some clinical effect persisted. The same applies to body weight variation, either in terms of loss or gain.

4.1. Conclusions

In conclusion, we presented the development and validation of the Pre-Lumbar puncture Intracranial Hypertension Scale (PLIHS), a practical scale aimed to detect patients that are expected to have CSF pressure ≥ 250 mmH2O and < 200 mmH2O. PLIHS score is calculated on the basis of five clinical markers that are part of the normal clinical workup for IIH diagnosis and that are commonly detected before patients are submitted to LP: Frisén grade 2 or higher papilledema and tinnitus (all with score 2), empty sella, perioptic subarachnoid space distension, and obesity defined by BMI ≥ 30. Patients with PLIHS score ≤ 2 will likely have normal CSF pressure, whereas those with score ≥ 3 will likely have CSF pressure ≥ 250 mmH2O, IIH diagnosis, BCVA ≤ 0.7 and optic nerve atrophy. PLIHS correlates well with CSF pressure, and showed to differentiate not only diagnosis matching, but also between patients diagnosed with IIH with and without papilledema.

PLIHS might therefore help with the organization of the diagnostic work-up: it may help identifying patients for whom LP may eventually be postponed, for whom a short-term follow up of neurological, neuro-radiological and neuro-ophthalmological parameters has to be planned; at the same time, it may be useful also in presenting the need for LP out to those patients that might not be prone to carry it out. Thus, the use of PLIHS would help optimising healthcare resources and potentially limit the likelihood to incur in LP-related adverse events.

Declaration of competing interest

The authors declare that there are no conflicts of interest in relation to this article.

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