Transcranial Doppler as a screening test to exclude intracranial hypertension in brain-injured patients: the IMPRESSIT-2 prospective multicenter international study

Frank A. Rasulo1,2*, Stefano Calza3, Chiara Robba4, Fabio Silvio Taccone5, Daniele G. Biasucci6, Rafael Badenes7, Simone Piva1,2, Davide Savo8, Giuseppe Citerio6,9, Jamil R. Dibu10, Francesco Curto11, Martina Merciadri12, Paolo Gritti13, Paola Fassini14, Soojin Park15, Massimo Lamperti16, Pierre Bouzat17, Paolo Malacarne12, Arturo Chiaregato11, Rita Bertuetti1, Raffaele Aspide18, Alfredo Cantoni19, Victoria McCredie20, Lucrezia Guadrini1 and Nicola Latronico1,2

Abstract

Background: Alternative noninvasive methods capable of excluding intracranial hypertension through use of transcranial Doppler (ICP_tcd) in situations where invasive methods cannot be used or are not available would be useful during the management of acutely brain-injured patients. The objective of this study was to determine whether ICP_tcd can be considered a reliable screening test compared to the reference standard method, invasive ICP monitoring (ICP_i), in excluding the presence of intracranial hypertension.

Methods: This was a prospective, international, multicenter, unblinded, diagnostic accuracy study comparing the index test (ICP_tcd) with a reference standard (ICP_i), defined as the best available method for establishing the presence or absence of the condition of interest (i.e., intracranial hypertension). Acute brain-injured patients pertaining to one of four categories: traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH) or ischemic stroke (IS) requiring ICP_i monitoring, were enrolled in 16 international intensive care units. ICP_i measurements (reference test) were compared to simultaneous ICP_tcd measurements (index test) at three different timepoints: before, immediately after and 2 to 3 h following ICP_i catheter insertion. Sensitivity, specificity, positive (PPV) and negative predictive values (NPV) were calculated at three different ICP_i thresholds (> 20, > 22 and > 25 mmHg) to assess ICP_tcd as a bedside real-practice screening method. A receiver operating characteristic (ROC) curve analysis with the area under the curve (AUC) was used to evaluate the discriminative accuracy and predictive capability of ICP_tcd.

Results: Two hundred and sixty-two patients were recruited for final analysis. Intracranial hypertension (> 22 mmHg) occurred in 87 patients (33.2%). The total number of paired comparisons between ICP_tcd and ICP_i was 687. The NPV was elevated (ICP > 20 mmHg = 91.3%, > 22 mmHg = 95.6%, > 25 mmHg = 98.6%), indicating high discriminant accuracy of ICP_tcd in excluding intracranial hypertension. Concordance correlation between ICP_tcd and ICP_i was 33.3%.

*Correspondence: frank.rasulo@gmail.com
1 Department of Anesthesiology, Intensive Care and Emergency, Spedali Civili University Hospital, 25123 Brescia, Italy
Full list of author information is available at the end of the article

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Introduction
Intracranial hypertension is a common and severe complication of acute brain injury \([1]\). If diagnosis is delayed, intracranial hypertension can lead to brain herniation with compression of the brainstem and distortion of brain parenchyma and vessels, and ultimately death \([1]\). Both the presence of intracranial hypertension and its burden, defined as the total amount of time spent above different thresholds of intracranial pressure (ICP), have been correlated with poor outcome \([2]\). The reference standard for diagnosing intracranial hypertension is the invasive measurement of ICP using ventricular drains or cerebral catheters and microsensors placed through a burr hole drilled in the skull \([3]\). However, invasive ICP measurement may not be available in certain situations, such as in underserved rural areas, in developing countries with limited resources or in settings outside the intensive care unit (ICU) and neurosurgical departments \([4]\). In several conditions, such as liver failure, preeclampsia, encephalitis, meningitis and stroke, the role of invasive ICP monitoring is not well established or the risk–benefit ratio remains unclear \([5–9]\). Moreover, invasive insertion of intracranial transducers can result in important complications, including infection and hemorrhage \([10, 11]\). For these reasons, the presence of intracranial hypertension is often estimated based on noninvasive screening methods, including neurological examination, brain imaging or cerebral ultrasonography (i.e., optic nerve sheath diameter and transcranial Doppler, TCD) \([12]\). These screening tests are more easily accessible, less expensive and time-consuming, less invasive, and hence, less physically and psychologically discomfiting for patients. However, the diagnostic accuracy of these methods remains poorly defined. A TCD-derived formula to estimate cerebral perfusion pressure (CPPe) and ICP (ICPtcd) has been available for more than 20 years \([13, 14]\). In 2017, a multicenter pilot study (IMPRESSIT: Invasive vs. noninvasive Measurement of intracranial PRESSure in brain Injury Trial) reported that the ICPtcd threshold of 24.3 mmHg was associated with a 100% sensitivity and 100% negative predictive value (NPV) in excluding the presence of intracranial hypertension (ICP > 20 mmHg) \([15]\). Based on these preliminary findings, and to definitively answer whether ICPtcd represents an accurate noninvasive ICP measurement method, we designed a prospective, international, multicenter study to evaluate the discriminant accuracy of TCD in excluding intracranial hypertension in a broad and representative cohort of acute brain-injured patients.

Methods
Study design
This prospective, international, multicenter, diagnostic accuracy study is reported according to the Standards for Reporting of Diagnostic Accuracy Studies (STARD) guidelines (Additional file 1: Appendix 1) \([16]\) and involved comparing the index test, ICPtcd, with a reference standard (invasive ICP, ICPi), defined as the best available method for establishing the presence or absence of the condition of interest (i.e., intracranial hypertension). The study was unblinded, and the reference standard results were available to the performers of the index test.

ICPtcd measurement (index test). We used a method based on a mathematical model which comprises parameters derived from TCD flow velocities and arterial blood pressure, which is described in detail elsewhere \([13–15]\). Briefly, CPPe is first estimated as: MAP×FVd /FVm + 14, where MAP is the mean arterial blood pressure and FVd and FVm are, respectively, the MCA diastolic and mean blood flow velocities derived from the TCD measurements. ICPtcd is then calculated as: MAP–CPPe.

The insonation technique of the middle cerebral artery (MCA) was standardized across all sites: A low-frequency pulsed 2 MHz ultrasound probe was placed over the acoustic temporal window for insonation of the M1/M2 section of MCA at a depth ranging from 45 to 55 mm. The acoustic window ipsilateral to the side of the ICPi placement was preferred. Cerebral blood flow velocities were assessed by using either of two technologies, TCD or transcranial color-coded Doppler (TCCD). Regarding the various ultrasound machine companies, no limitations nor specifications were requested by the protocol since the ICPtcd method is based on a calculated formula derived from standard TCD parameters \([13, 14]\).
For each patient enrolled into the study, a total of three comparisons of ICPi and ICPtcd were made in three different time frames, as described previously in the IMPRESSIT pilot study (Fig. 1).

At TIME 1, ICPtcd was obtained shortly before performing the burr hole procedure and was compared to the first ICPi reading once the invasive probe was positioned. An effort was made to limit the cerebrospinal fluid leakage during intraventricular catheter placement which may cause changes in ICP. At TIME 2 and TIME 3, paired ICPtcd and ICPi were obtained immediately after TIME 1 and 2 to 3 h following the second reading. This later time lapse was chosen for two reasons: First, it was deemed necessary to permit any variations of cerebral hemodynamics induced by the ICPi device insertion maneuver to stabilize to a steady state; second, once the invasive device is inserted, a specific physiologically based time lapse becomes less relevant since any further variations in cerebral hemodynamics would automatically influence both the invasive and noninvasive measurement.

ICPi measurement (reference test)
The decision to insert invasive ICP monitoring was independent from the study protocol and was made by the physician in charge of the patient based on the international guidelines for TBI patients, and neurological signs (i.e., altered pupillary diameter and light reaction, altered reflex motor response), clinical course (i.e., rapid neurological worsening) and neuroradiological findings (midline shift, cerebral ventricles dilatation or compression, signs of transtentorial brain herniation, obliteration of the brainstem cisterns) for SAH, ICH and IS patients. Arterial blood pressure (ABP) was invasively monitored in order to obtain mean arterial pressure (MAP), and cerebral perfusion pressure (CPP) was calculated with the transducer placed at the tragus level.

ICPi was measured by means of either an intraparenchymal fiberoptic transducer (Codman, Johnson & Johnson Medical Ltd., Raynham, MA, USA, or Camino Laboratories, Integra LifeSciences, San Diego, CA, USA, RAUMEDIC) placed in the non-dominant frontal lobe, or a catheter inserted into the brain ventricles and connected to an external pressure transducer and drainage system (Codman, Johnson & Johnson Medical Ltd., Raynham, MA, USA).

Study population
Sixteen centers in seven countries, chosen for their high volume of brain-injured patients and for their expertise in the field of TCD monitoring, enrolled a convenience sample of adult (≥ 18 years) critically ill neurological patients who required invasive ICP monitoring, either using intraventricular, intraparenchymal or post-craniotomy/postsurgical catheters, for any of the following diagnostic categories: traumatic brain injury (TBI), subarachnoid hemorrhage (SAH), intracerebral hemorrhage (ICH) and ischemic stroke (IS).

Patients were excluded if they had an inaccessible or poor acoustic ultrasound window, cardiac or vascular disease which had the potential of causing hemodynamic variations affecting the TCD measurement (i.e., severe arrhythmia, severe cardiac valvular stenosis, moderate or severe cerebral vasospasm), or a craniotomy or craniec- tomy performed prior to the first time frame readings. Patients were also excluded if they required treatment for suspected intracranial hypertension or manipulation of arterial blood pressure between the first ICPtcd estimation and immediately before or during the first ICPi measurements in TIME 1.

Ethics approval
For the coordinating center of Brescia, Italy, the ethics committee approval was obtained on July 17, 2017 (NP-2762). The study approval was also obtained at each site.
from local regulatory boards before the study started. Written informed consent was obtained by family representatives. In the Italian centers, the requirement of informed consent was waived, because relatives are not regarded as legal representatives of the patient in the absence of a formal designation. Written informed consent was requested from all surviving patients if, and as soon as, they regained their mental competency.

**Outcome measures**

Intracranial hypertension in TBI patients was defined as ICPi above 22 mmHg and lasting for at least 10 min. Since definition of intracranial hypertension is not well established in SAH, ICH and IS, we also assessed the accuracy of ICPtcd with ICPi above 20 mmHg and above 25 mmHg [17].

**Data collection**

Given the focused nature of the study on diagnostic TCD accuracy, we collected a minimum number of parameters for parsimony, including demographic characteristics, cause of admission, neurological (Glasgow Coma Scale score) and neuroradiological severity (brain CT Marshall score), and type of device used to measure invasive ICP. De-identified data were extracted from electronic medical records and stored within the main database located at the coordinating center [18].

**Statistical analysis**

Sample size was calculated using an exact method, assuming a true sensitivity of ICPtcd of 90% with lower acceptable confidence limit of 10%, resulting in a requirement of 147 cases. Assuming a prevalence of intracranial hypertension equal to 30%, the total sample size was 490 patients [19].

Continuous variables are presented as mean (standard deviation, SD) or median and interquartile range (IQR), and discrete variables as counts and percentages. Concordance correlation coefficient between ICPtcd and ICPi was calculated using variance components, estimated through linear mixed model to account for repeated measurements [19]. A Bland–Altman plot accounting for replicated measurements was fitted to estimate potential bias and limits of agreement. Since the main scope of the study was to assess the TCD as a real-practice screening method to exclude intracranial hypertension, we focused on negative and positive predictive values (NPV, PPV) and also calculated false omission rate (1 – NPV), representing the proportion of patients who have the condition among those with a negative test (i.e., intracranial hypertension ruled out). This is an important measure of a model’s misclassification of events [20]. Description of the TCD attributes (ICPtcd) relative to the reference standard (ICPi) was determined by calculating sensitivity, specificity, and the areas under a curve (AUC), for each ICPi threshold at each time frame (TIME 1, TIME 2 and TIME 3) and averaged over all three time points (\(I_{1,2,3}\)). 95% confidence intervals (CI) were computed using bootstrapping (\(B = 2000\)). The best ICP thresholds were computed using the Youden criterion [21]. In case of missing or indeterminate index test or reference standard results, patients were excluded from the analysis. All tests were two-sided, and a p value of 0.05 was considered as the threshold for significance. The R software was used for statistical analysis (version 3.2.5, Free Software Foundation, Inc., Boston, MA, USA) [22]. Negative likelihood ratio (LR −) was used to evaluate the performance in ruling out the condition in the presence of a negative test (ICPtcd).

**Results**

**Study population**

Recruitment started on July 2017 and was interrupted April 2020 after 266 patients were enrolled given the rapid reduction in the recruitment rate from late February 2020 onward when cases of COVID-19 started to rise quickly in western countries. The number of patients recruited per center is presented in Additional file 2: Figure S1. Of 266 patients recruited, 178 (70.4) were males and 75 (29.6) were females. The mean age was 65 years (SD 24.8). Four patients were excluded due to protocol violation (missing or indeterminate index test or reference standard results), leaving 262 patients and a total of 687 paired ICPtcd and ICPi measurements performed (Fig. 2).

The main characteristics of the study population are presented in Table 1.

All 262 patients enrolled were investigated with both the index test (ICPtcd) and the reference standard (ICPi) with no protocol violation (Fig. 2, Additional file 3: Appendix 2).

**ICPtcd versus ICPi.**

The mean ICPi was 13.8 (SD 9.7) mmHg and intracranial hypertension (> 22 mmHg) occurred in 87 patients (33.2%). ICPtcd was higher than ICPi in 412 measurements (60%); details regarding intracranial hypertension according to different ICP thresholds (> 20 mmHg, > 22 mmHg and > 25 mmHg) are reported in Additional file 4: Table S1. NPV was high, 91.3%, 95.6% and 98.6% for ICPi threshold, respectively, of 20 mmHg, 22 mmHg and 25 mmHg, and 1-NPV was low, ranging from 9 to 2%, indicating high discriminant accuracy of ICPtcd in excluding intracranial hypertension with few model misclassifications of events. Data regarding the PPV, NPV, 1-NPV, sensitivity, specificity, accuracy, the positive and negative
Regarding negative likelihood ratio (LR-), this has a constant value of 0.3 across time, corresponding to a moderate performance in ruling out the condition, with an approximate 25% reduction in condition probability after a negative test (ICP$_{tcd}$).

The best measured ICP$_{tcd}$ threshold was 20.5 mmHg, corresponding to a sensitivity of 0.70 (0.41–0.93) and a specificity of 0.76 (0.70–0.81) with an AUC of 0.76 (95% CI 0.66–0.85) to predict intracranial hypertension.

The percentage of patients with ICP above and below the given thresholds of 20, 22 and 25 mmHg and NPVs and PPVs of the averaged time frames ($T_{1,2,3}$) at the same thresholds are presented in Fig. 3.

Furthermore, we also evaluated if there were any discrepancies regarding the descriptors of diagnostic accuracy of ICP$_{tcd}$ compared to ICP$_{i}$ at three different ICP$_{i}$ thresholds (20, 22 and 25 mmHg) in TBI versus non-TBI patients, and found no substantial differences (Additional file 6: Table S2).

Agreement between ICP$_{tcd}$ and ICP$_{i}$, estimated using concordance correlation coefficient, was 33.3% (25.6–40.5%) (Fig. 4a). Bland–Altman analysis yielded a mean bias (ICP$_{tcd}$–ICP$_{i}$) of -3.3 mmHg with limits of agreement comprised between $-26.1$ mmHg and $+19.5$ mmHg (Fig. 4b, Additional file 7: Figure S3).

When comparing relevant clinical variables (CPP, TBI vs non-TBI and GCS) in patients with concordant or discordant ICP$_{i}$ and ICP$_{tcd}$ readings, we found that CPP showed a significant trend, with lower values in false negative and higher values in false positives, compared to concordant readings. All measurements were

Table 1 General characteristics of the study population

| Type of brain injury | N° patients (%) | Score (Median (IQR)) | Type of device for ICP measurement N° (%) |
|---------------------|----------------|----------------------|-----------------------------------------|
| TBI                 | 135 (53.3)     | GCS 6 (4–7)          | EVD 12 (8.9)                             |
|                     |                | MARSHALL 3 (2–4)     | IP 113 (84)                              |
|                     |                |                      | SD 10 (7.4)                              |
| ICH                 | 36 (14.2)      | GCS 7 (4–8)          | EVD 26 (72)                              |
|                     |                | IP 10 (2.7)          | SD 0 (0)                                 |
| SAH                 | 75 (29.6)      | WFNS 4 (2–5)         | EVD 64 (85)                              |
|                     |                | FISHER 4 (3–4)       | IP 11 (13)                               |
|                     |                |                      | SD 0 (0)                                 |
| IS                  | 7 (2.8)        | NHSS 21 (20–23)      | EVD 3 (42.8)                             |
|                     |                |                      | IP 1 (14)                                |
|                     |                |                      | SD 3 (42.8)                              |

Bold abbreviations in the first column indicate type of brain injury. TBI, traumatic brain injury; SAH, subarachnoid hemorrhage; ICH, intracerebral hemorrhage; IS, ischemic stroke; GCS, Glasgow Coma Scale; WFNS, World Federation of Neurosurgical Societies; NHSS, National Health Stroke Scale. Bold abbreviations in the last column indicate the type of invasive intracranial pressure monitoring device: EVD, external ventricular drain; IP, intraparenchymal; SD, subdural. Italic values indicate number, and percentage, of devices inserted.

likelihood ratios and AUC for the three different ICP$_{i}$ thresholds during each separate and averaged time frame are reported in Table 2 and Additional file 5: Figure S2.
considering the average value over the three timings (Additional file 8: Table S3).

**Discussion**

In this prospective, international, multicenter study, we found that TCD reliably excluded intracranial hypertension in a variety of acute neurological injuries. Since TCD application is noninvasive, our results may have an impact on daily practice in situations where invasive ICP measurement is impractical or is not feasible. Of those cases identified as having normal ICP_{tcd}, 91% had normal ICP_{i} using a threshold of > 20 mmHg, 96% using a threshold > 22 mmHg and 99% using a threshold of > 25 mmHg. 

**Table 2** Descriptors of diagnostic accuracy of intracranial pressure measured with transcranial Doppler (ICP_{tcd}) compared to invasive ICP measurement (ICP_{i}) at three different ICP thresholds and three time frames (T1, T2 and T3)

| ICP thresholds | Time frames of ICP measurements | Averaged values of all three time frames |
|----------------|---------------------------------|----------------------------------------|
| Above 20 mmHg  |                                 |                                        |
| Optimal ICP threshold, mmHg | 16.5 (15.5–24.5) | 21.5 (16.5–27.0) | 21.5 (13.5–25.5) | 21.5 (12.5–24.5) |
| Sensitivity, %  | 75.8 (51.6–87.1) | 62.5 (42.5–80.0) | 65.9 (43.9–92.7) | 65.1 (44.2–90.7) |
| Specificity, %  | 66.0 (54.7–86.8) | 79.4 (65.8–90.5) | 78.4 (42.7–88.6) | 74.4 (40.2–88.1) |
| PPV, %          | 47.6 (40.0–63.0) | 38.4 (28.0–53.7) | 37.9 (25.4–51.6) | 32.6 (22.7–46.3) |
| NPV, %          | 87.4 (81.2–92.9) | 91.5 (88.1–95.0) | 90.9 (87.1–96.4) | 91.3 (88.2–95.7) |
| 1-NPV, %        | 12.6 (7.1–18.8) | 8.5 (5.0–11.9) | 9.1 (3.6–12.9) | 8.7 (4.3–11.8) |
| Accuracy, %     | 69.7 (61.5–79.2) | 76.6 (66.5–84.5) | 75.2 (50.9–82.7) | 72.5 (48.5–82.1) |
| PPV, %          | 2.2 (1.1–6.6) | 3.0 (1.2–8.4) | 3.0 (0.8–8.2) | 2.5 (0.7–7.6) |
| LR +            | 0.4 (0.1–0.9) | 0.5 (0.2–0.9) | 0.4 (0.1–1.3) | 0.5 (0.1–1.4) |
| AUC             | 73.3 (65.7–80.8) | 69.0 (58.4–79.7) | 73.0 (64.6–81.4) | 71.5 (63.1–80.0) |
| Above 22 mmHg   |                                 |                                        |
| Optimal ICP threshold, mmHg | 16.5 (15.5–23.5) | 20.5 (16.5–25.5) | 21.5 (14.5–25.5) | 20.5 (15.5–29.5) |
| Sensitivity, %  | 86.8 (62.3–96.2) | 71.0 (48.4–87.1) | 75.0 (53.1–93.8) | 70.4 (40.7–92.6) |
| Specificity, %  | 66.1 (57.1–86.9) | 77.9 (62.0–89.9) | 75.8 (51.5–87.6) | 71.9 (51.9–94.0) |
| PPV, %          | 45.0 (38.9–62.7) | 32.7 (23.1–48.2) | 32.6 (22.7–47.2) | 230.1 (16.2–50.0) |
| NPV, %          | 93.6 (87.6–98.1) | 94.6 (91.9–97.6) | 94.8 (91.7–98.4) | 95.6 (93.1–98.5) |
| 1-NPV, %        | 6.4 (9.1–14.9) | 5.4 (2.8–14.1) | 5.2 (1.6–8.3) | 4.4 (1.5–6.9) |
| Accuracy, %     | 71.5 (64.3–82.8) | 77.0 (64.4–86.2) | 75.2 (57.1–84.5) | 71.8 (55.3–89.7) |
| PPV, %          | 2.6 (1.5–7.3) | 3.2 (1.3–8.6) | 3.1 (1.1–7.6) | 2.5 (0.8–15.5) |
| LR +            | 0.4 (0.1–0.8) | 0.4 (0.1–0.8) | 0.3 (0.1–0.9) | 0.4 (0.1–1.1) |
| AUC             | 80.2 (73.8–86.7) | 74.1 (63.3–84.8) | 77.0 (68.4–85.6) | 75.6 (65.6–85.5) |
| Above 25 mmHg   |                                 |                                        |
| Optimal ICP threshold, mmHg | 22.5 (18.5–24.5) | 19.5 (17.5–28.5) | 17.5 (14.5–29.5) | 25.5 (19.5–29.5) |
| Sensitivity, %  | 78.1 (59.4–90.6) | 81.0 (52.4–95.2) | 78.9 (47.4–100.0) | 81.2 (56.2–100.0) |
| Specificity, %  | 76.7 (63.0–86.8) | 72.5 (63.3–91.7) | 69.6 (46.4–91.3) | 84.1 (63.8–95.1) |
| PPV, %          | 35.5 (26.5–48.1) | 22.2 (16.3–42.9) | 18.6 (13.0–38.9) | 23.1 (13.1–48.3) |
| NPV, %          | 95.2 (92.0–98.0) | 97.3 (94.7–99.3) | 97.2 (94.5–100.0) | 98.6 (96.8–100.0) |
| 1-NPV, %        | 4.8 (2.0–8.0) | 2.7 (0.7–5.3) | 2.8 (0.0–5.5) | 1.4 (0.0–3.2) |
| Accuracy, %     | 76.5 (65.6–84.6) | 73.2 (64.8–89.1) | 70.4 (50.0–88.5) | 83.6 (65.3–93.5) |
| PPV (sens/1−spec) | 3.4 (1.6–6.9) | 2.9 (1.4–11.5) | 2.6 (0.9–11.5) | 5.1 (1.6–20.5) |
| LR (1−sens/spec) | 0.3 (0.1–0.6) | 0.3 (0.1–0.8) | 0.3 (0.0–1.1) | 0.2 (0.0–0.7) |
| AUC             | 78.4 (69.7–87.0) | 76.2 (64.2–88.2) | 75.1 (63.7–86.5) | 83.2 (71.4–94.9) |

PPV, positive predictive value; NPV, negative predictive value; LR, likelihood ratio; AUC, area under the curve. Numbers indicate the estimated values via bootstrap (95% confidence interval).
practice in a patient with an intact skull for whom only clinical information is available.

To date, this study is the first to demonstrate the value of ICP <sup>tcd</sup> as a screening test to exclude intracranial hypertension in patients with acute brain injury. We found four single-center observational studies [23–26], of which three were prospective [24–26] and only one was multicenter study [15]. A recent meta-analysis [17] found a sixth retrospective, single-center study [27]. Accuracy of TCD was reported in terms of the screening test’s attributes relative to the reference standard, mainly as ROC analysis and AUC, and hence the usefulness of the test in clinical practice was not specifically addressed. Only one study in 21 patients with acute liver failure

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**Fig. 3** Percentages of patients with intracranial hypertension (IH) and negative (NPV) and positive (PPV) predictive values at the three intracranial pressure (ICP) thresholds. 

- **a** Percentage of patients with ICP above (red silhouette indicating IH) and below (green silhouette indicating normal ICP) the given ICP thresholds of 20, 22 and 25 mmHg.
- **b** NPV and PPV (%) of the averaged time frames (T<sub>1,2,3</sub>) at the three ICP thresholds (20, 22 and 25 mmHg). NPV = green silhouette indicating true negatives and grey silhouette indicating false negatives. PPV = red silhouette indicating true positives and grey silhouette indicating false positives.
reported that an ICP\textsubscript{tcd} > 18.55 mmHg had a NPV of 100\% (95\% CI 74\%-100\%) and a PPV of 56\% (95\% CI 34\%-75\%) for the detection of concurrent ICP\textsubscript{i} > 20 mmHg. [28] The authors concluded that ICP\textsubscript{tcd} may in fact be most useful as a screening tool to exclude intracranial hypertension. Two recent prospective studies found contrasting results in terms of diagnostic accuracy of TCD, with one study reporting good diagnostic test accuracy with 81\% sensitivity and 70\% specificity and the other reporting 0\% sensitivity and 74.4\% specificity for ICP\textsubscript{tcd} to detect ICP\textsubscript{i} > 20 mm Hg mmHg [28, 29]. None of these two studies assessed the predictive ability of TCD in excluding intracranial hypertension.

There is general agreement that sensitivity and specificity, which are important descriptors of the accuracy of a diagnostic test, should be applied only in the context of describing the screening test’s attributes relative to a reference standard [30]. With sensitivity and specificity, the main question addressed is: “Is the screening test adequate?”. The problem addressed is the fundamental “credentials” of the screening test [13]. However, if the main question is: “Do the results on the screening test correspond to the results on the reference standard?”, as should be in the context of real-practice screening, it is the screening test that is being assessed, and positive and negative predictive values are more appropriate and informative. In fact, diagnostic testing is used because clinicians want to know the probability of the condition existing or not existing. Since clinicians make decisions based on diagnostic test results and not necessarily on results of reference standards, positive and negative predictive values can be more important than sensitivity and specificity for clinical practice. If the test has a high NPV, there is a high probability that a patient does not have the pathological condition being investigated when the patient has a negative test. This is particularly relevant if the condition to be excluded is a life-threatening, time-dependent condition, such as acute intracranial hypertension, and invasive ICP monitoring is not available or is impractical. A recent study found that automated pupillometry performed in 23 patients with spontaneous intracerebral hemorrhage had high NPV in excluding intracranial hypertension [31]. In patients with acute liver failure, elevated ICP is an important cause of death and disability; ICP\textsubscript{tcd} may be helpful in these cases, because coagulopathy, which is always present, increases the risk of intracranial hemorrhage following monitor insertion [27]. During triage of polytrauma patients, ICP\textsubscript{tcd} may be helpful in prioritizing treatment when extracerebral lesions are also involved. In the general ICU population, especially in cardiac arrest patients or in metabolic coma and liver failure, ICP\textsubscript{tcd} can be an important tool for the early diagnosis and treatment of cerebral complications [32]. Another field where a noninvasive ICP monitoring technique would be most useful would be developing countries where access to hospitals with resources for invasive ICP monitoring is scarce [33, 34]. Finally, in patients at risk for intracranial hypertension, repeated

\[ \text{ICP}_\text{tcd} - \text{ICP}_\text{i} \]
TCD assessment is easily implemented and may represent the primary monitoring method if ICP_tcd remains low. If ICP_tcd indicates intracranial hypertension, further diagnostic modalities, including a prompt decision for invasive ICP monitoring, should be considered. A simple algorithm for application of ICP_tcd is provided in Fig. 5.

Of those measurements identified as having intracranial hypertension at ICP_tcd, 67.4% (53.7–77.3) had intracranial hypertension at ICP_i using a threshold of > 20 mmHg, 77.0% (50.0–83.8) using a threshold > 22 and 76.9% (51.7–86.9) using a threshold of > 25 mmHg. Reasons for this duality of ICP_tcd, an excellent screening test to exclude intracranial hypertension and a poor screening test to confirm it, remain speculative. Unlike a pressure transducer, TCD is a measurement of blood flow velocity and not a direct measurement of pressure and is greatly influenced by the ratio between FVd and FVm: the lower the ratio, the higher the ICP_tcd value. A low ratio may occur in the presence of true intracranial hypertension due to external vessel compression and increased resistance, but also in the case of normal ICP_i with decreased MAP and altered cerebrovascular autoregulation. In both cases, the transmural pressure (i.e., the “extra-mural” ICP minus the intramural arterial pressure) increases with a disproportionate reduction in FVd compared to FVm and, hence, a reduction in their ratio.

**Limitations**

Some study limitations are worth considering: First, as mentioned previously, recruitment stopped after 266 patients were enrolled; therefore, we did not reach the target sample size of 490 patients. Nevertheless, we believe that the number of patients recruited was sufficient enough to perform an adequate statistical analysis of our study aim; second, we do not have an exact number of patients screened among the 16 centers who took part in this study; third, we enrolled patients with different types of brain injury, including IS, SAH and ICH, for which ICP thresholds are

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**Fig. 5** Algorithm for noninvasive intracranial pressure monitoring through the use of transcranial Doppler (ICP_tcd). Once indication for ICP monitoring is decided, application of the invasive method (gold standard) is evaluated: if **NO** (invasive ICP monitoring not possible) for the presence of one or more of the reasons provided, ICP_tcd associated with brain imaging should be performed. *The result should not act as a deterrent for transferal towards a hospital with a Neurosurgical facility or to perform further brain imaging studies, instead ICP_tcd should be used as an adjunct capable of providing valuable information for the Clinician, if **YES** (invasive ICP monitoring possible), then burr hole and insertion of a catheter within the brain parenchyma should be performed. *However, brain ultrasound with transcranial Doppler may be useful in order to obtain surrogate information regarding brain hemodynamics through the evaluation of cerebral blood flow velocity.
not as well defined as for TBI; fourth, the study was unblinded and therefore correct reporting of paired ICPi and ICPtcd may have been imprecise; fifth, the incidence of intracranial hypertension was lower than in other series, which may limit the generalizability of results to other populations with more severe disease; sixth, hemodynamic instability during critical illness due to extracranial causes (sepsis, hemorrhage, etc.) may influence the correlation between true ICPi and ICPtcd leading to a probable disassociation between the two; and finally, as per study design, the patients’ outcome was not assessed, and hence, the impact of using TCD in reducing morbidity and mortality remains unanswered.

Despite the study limitations, the results in this study confirm the results obtained from our previous multicenter pilot IMPRESSIT-1 study, which showed a NPV of 100% in excluding intracranial hypertension at ICP thresholds of > 20 and > 22 mmHg, and at the best threshold value of 24.8 mmHg. [19] TCD screening test attributes relative to the reference standard were better than in the current study, with 100% sensitivity and 70% (95% CI 54.5–84.8%) specificity at ICP thresholds of > 20 and > 22 mmHg, and at the best threshold value of 24.8 mmHg. The technique remains operator-dependent, and among the 16 centers involved there may have been heterogeneity regarding the skills of the various sonographers. It must be stressed that as for any monitoring tool, correct training should be performed before implementation of the technique.

Nevertheless, TCD retained excellent screening performance, suggesting that its use to exclude intracranial hypertension in everyday clinical practice, where the presence of multiple sonographers represents a common situation, is feasible.

Conclusion
This study demonstrates that ICPtcd has a high NPV compared to ICPi in a variety of acute neurological conditions. As such, TCD may prove useful to exclude intracranial hypertension in situations where invasive methods cannot be used or are not available, and to screen at-risk patients for potential invasive ICP monitoring.

Abbreviations
ICU: Intensive care unit; AUC: Area under the receiver operating characteristic curve; ICP: Intracranial pressure; ICPi: Invasive intracranial pressure; ICPtcd: Transcranial Doppler measurement of intracranial pressure; TCD: Transcranial Doppler; CPP: Cerebral perfusion pressure; ABP: Arterial blood pressure; MABP: Mean arterial blood pressure; SAH: Subarachnoid hemorrhage; ICH: Intracerebral hemorrhage; TBI: Traumatic brain injury; IS: Ischemic stroke; ROC: Receiver operating characteristic; NPV: Negative predictive value; PPV: Positive predictive value; CI: Confidence interval.

Supplementary Information
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Consent for publication
All authors have provided their consent for publication.

Competing interests
The authors declare that they have no competing interests.

Author details
1 Department of Anesthesiology, Intensive Care and Emergency, Spedali Civili University Hospital, Brescia, Italy. 2 Department of Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy. 3 Unit of Biostatistics and Bioinformatics, Department of Molecular and Translational Medicine, University of Brescia, Brescia, Italy. 4 Policlinico San Martino, Dipartimento di Scienze Chirurgiche ed Integrate, University of Genoa, Genoa, Italy. 5 Department of Intensive Care, Erasme Hospital, Université Libre de Bruxelles, Brussels, Belgium. 6 Neurosurgical Intensive Care, Fondazione Policlinico Universitario “A. Gemelli”, IRCCS, Rome, Italy. 7 Department of Anesthesiology and Intensive Care, Hospital Clinic Universitari, University of Valencia, Valencia, Spain. 8 Neurointensive Care Unit, San Gerardo Hospital, ASST-Monza, Monza, Italy. 9 University of Milano-Bicocca, Milan, Italy. 10 Cerebrovascular Center of Neurological Institute, Cleveland Clinic, Abu Dhabi, United Arab Emirates. 11 Department of Neurointensive Care, Grande Ospedale Metropolitano, Niguarda, Milan, Italy. 12 Department of Anesthesiology and Critical Care, Azienda Ospedaliera Universitaria Pisana, Pisa, Italy. 13 Department of Anesthesiology and Critical Care, Papa Giovanni XXIII Hospital, Bergamo, Italy. 14 Department of Anesthesiology and Intensive Care, Legnano Hospital, Legnano, Italy. 15 Division of Critical Care Neurology, Columbia University Irving Medical Center, New York, USA. 16 Anesthesiology Institute, Cleveland Clinic, Abu Dhabi, United Arab Emirates. 17 Division of Anesthesiology and Intensive Care, Gironobles, France. 18 Anesthesia and Intensive Care Unit, Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy. 19 Neurointensive Care, ASST-SESTE-LAGHI, Varese, Italy. 20 Toronto Western Hospital, University Health Network, Toronto, ON, Canada.

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