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Objective triaging of traumatic brain injury patients with a novel machine learning powered near-infrared spectroscopy-based biomarker at different time-intervals post injury

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1. Introduction

Traumatic Brain Injury (TBI) is considered to be one of the primary causes of death and disability, with around 69 million new cases reported globally.[1] The disease burden is high in High-Income as well as Low- and Middle-Income Countries (LMICs). The data by The Centers for Disease Control and Prevention (CDC) USA, reported 1.5 million people succumbing to TBI every year, with around 223,135 hospitalizations due to TBI in 2019, 64,362 TBI-related deaths in 2020 and 80,000 to 90,000 TBI-related long-term disabilities.[2–4] Similarly, in India, about 1.5–2 million TBI cases are reported annually, of which 1 million people succumb to death. The outcome is similar in other South Asian countries, including Indonesia, where around 90% of the prehospital trauma-related deaths were attributed to head trauma.[5] In sub-Saharan Africa, TBI incidences are expected to reach 14 million per year by 2050.[6]

TBI is also highly prevalent in military and sports personnel. With a high probability of exposure to explosives, blast injury alone accounts for about 60% of all military-related TBI and about 80% of mild TBI (mTBI).[7] A report by U.S. armed forces reported close to 453,919 traumatic brain injuries from 2000 to 2021, of which 17.7% were severe injuries.[8] High burden of TBI is also reported in sports-related injuries. Approximately 20% of high school athletes participating in contact sports experience concussions annually, as reported by a sports medicine concussion program.[9]

Moderate to severe TBI often get medical attention within the golden period. The real challenge lies with the diagnosis and management of mTBI. According to CDC statistics, more than 80% of TBI cases are mild, i.e., asymptomatic, or mildly symptomatic at the time of injury.[10] 50% of these patients develop symptoms belatedly ranging from weeks to months after the trauma. However, if these patients do not get timely medical attention, approximately 15% of them develop persistent, moderate to severe disabling problems.[11]

Glasgow Coma Scale (GCS) has been the most preferred triaging test for the severity of TBI. GCS of 13–15 is considered mild TBI, comprising about 70–90% of all TBI cases. Since GCS alone was found to be insufficient for accurate classification, new guidelines were laid down by the World Federation of Neurological Societies (WFNS), the European federation of Neurosurgeons (EFNS), and World Health Organization (WHO) Collaborating Center Task Force to include other risk factors like loss of consciousness, post-traumatic amnesia, drowsiness, and headache to name a few.[12] However, this complicates the initial diagnosis

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and treatment of mTBI. A timely and correct diagnosis is crucial for effectively managing TBI. The primary injury that causes tissue damage in the brain and results in impaired cerebral blood flow cannot be undone; however, a secondary injury can be averted if the injury is attended to at an early stage. Studies have shown that mortality can be reduced significantly if the treatment is initiated within the first 4 h of injury.[13–15]

Another challenge is delayed hematoma, commonly seen in patients on antithrombotic therapy. Patients who suffer trauma while on anticoagulation therapy may be at a higher risk for delayed intracranial hemorrhage (ICH) after an initial negative head Computed Tomography (CT) scan.[16] These patients are often kept on observation, and the CT is repeated after 24 h or are advised to return after 24 h.

In order to counter the challenges and enable early detection, there is a need for an easy-to-use, objective assessment to determine the presence of an intracranial bleed even in the absence of any clinical symptoms and absence of information regarding risk factors. CEREBO® (developed by Bioscan Research Pvt. Ltd.) is one such portable, non-invasive, near-infrared-based, point-of-care device that detects ICH at an early stage by calculating the Intracranial tissue optical index (ITOI) in patients with a history of TBI (Fig. 1a). This study aims to report the temporal efficacy of machine learning-powered near-infrared spectroscopy (mNIRS) based ITOI by considering CT scan as the gold standard in detecting traumatic ICH in the first 72 h, further stratified into different time intervals post-injury, irrespective of the severity of TBI.

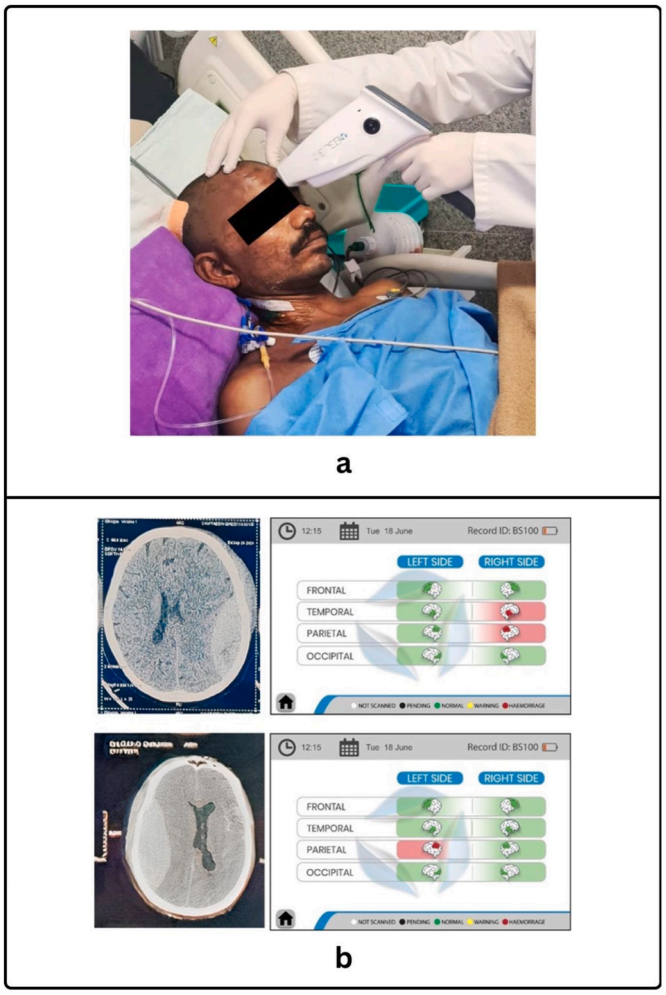

Fig. 1. 1a - The novel mNIRS device in use; 1b - The result display screen of the device in comparison with the CT output. The participants showed a positive hemorrhage in the mNIRS scan which was confirmed with the CT result.

2. Material and methods

A cross-sectional, prospective, double-blinded single-center study was carried out at the Trauma Emergency Medicine department of All India Institute of Medical Sciences (AIIMS), Bhopal, India, from March 1 to May 2, 2022. A total of 200 patients were brought to the Trauma Emergency Medicine department in the study period. Fig. 2 demonstrates the protocol of the participant selection of the study.

The research included participants of both sexes of all ages visiting the Trauma Emergency Medicine department of AIIMS with a suspected head injury and were recommended for a head CT scan. However, a majority (79%) were males due to road traffic accidents being commonly reported in the male population. Participants with severe scalp lacerations, active bleed, notable hematoma outside the skull, abnormal skull conditions or any other condition that would hinder the placement of the device were excluded. Subjects with a medical history of neurologic diseases such as tumors, infarcts, strokes, and pregnant women were not included. Participants who were critically ill or required immediate surgical intervention were also excluded.

21 participants were not included - 11 of them did not fulfill the criteria for inclusion while the other 10 were found to have chronic hematoma, cerebral or linear bleed, postoperative hematomas, tumors, cerebral venous thrombosis, and intraventricular hemorrhage based on the findings from the CT scans, leaving 129 available for analysis. Hence, 129 consecutive patients who were suspected with a head injury and fulfilled the predetermined inclusion and exclusion criteria and referred for a CT scan were enrolled in the study. The participants were examined with the novel biomarker ITOI and CT scan of the head for presence of ICH. All the accessible lobes were scanned in no particular

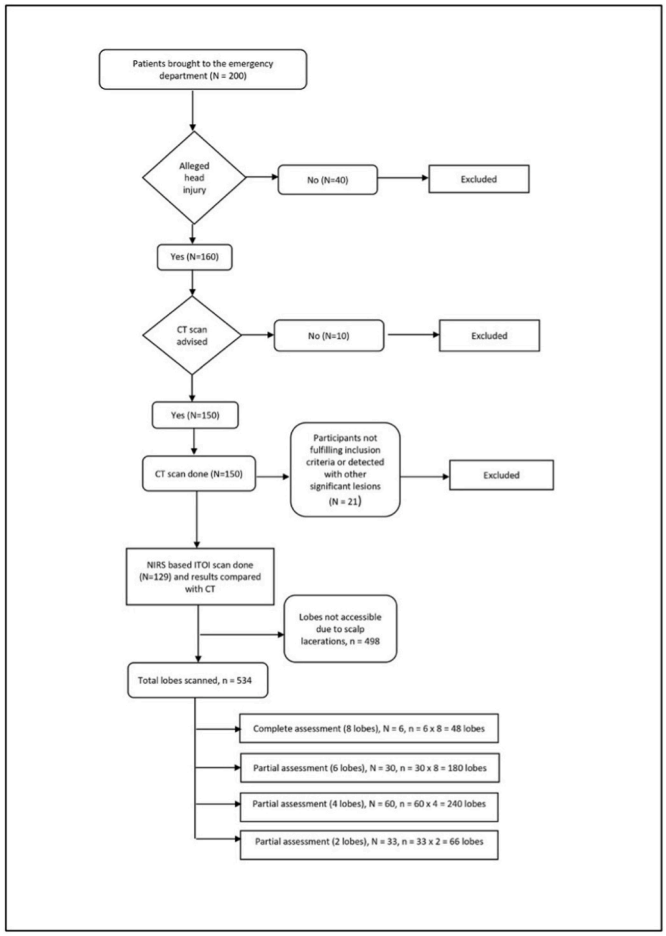

Fig. 2. Protocol of the study for patient selection and lobe assessment.

order. The study adhered to the principles of declaration of Helsinki. Prior to commencing the test, participant's nearest kin provided a written informed consent. Ethical approval for the study was obtained from the Institutional Ethics Committee of AIIMS Bhopal dated December 16, 2021. It was registered prospectively with the Clinical Trials Registry of India on February 10, 2022, under trial registration number "CTRI/2022/02/040208".

The study participants were evaluated based on the following CT parameters.

1. Presence or absence of hemorrhage in the CT
2. Hematoma location: Frontal left, temporal left, parietal left, occipital left; Frontal right, temporal right, parietal right, occipital right.
3. Time from injury to mNIRS tool assessment: 0–4 h (TICS1), 4–12 h (TICS2), 12–72 h (TICS3).
4. Type of hematoma: Epidural, Subdural, Subarachnoid, Intracerebral or Contusion.
5. Volume of hematoma (in cc).
6. Depth of hematoma from the outer surface of the skull (in cm).
7. Other parameters that were considered: GCS, cause of injury, symptoms following the injury, and recommended treatment (conservative or surgical).

The head CT scans were evaluated by a neuroradiologist blinded to the result of the mNIRS system and vice versa. However, the biostatistician was not blinded to the CT and mNIRS scan results allowing her to perform the statistical analysis. If the hematoma extended beyond one location, volumes at individual locations were determined.

The diagnostic performance or classification accuracy of mNIRS based ITOI to classify the participants into the hemorrhagic or non-hemorrhagic class was further analyzed by categorizing the participants according to the time duration between the injury and the time of the mNIRS scan (TICS) into the following three groups -

a) TICS1: The time duration between the injury and the mNIRS scan between 0 and 4 h;
b) TICS2: The time duration between the injury and the mNIRS scan from 4 to 12 h;
c) TICS3: The time duration between the injury and the mNIRS scan from 12 to 72 h.

2.1. Principle of the novel mNIRS based ITOI in intracranial bleed detection

The novel mNIRS based ITOI is an adaptive machine learning technology that presents an analytical advantage over simple ratio-metric analysis. The novel machine learning-powered optical device uses the near-infrared range of the electromagnetic spectrum. NIR light is able to penetrate the scalp, skull, and brain to detect an extravascular bleed non-invasively. To detect intracranial bleed objectively, the NIRS probes are placed on the surface of the scalp to measure the absorption. Near-infrared light is emitted from one end of the probe, passing through the intracranial tissues, where it is either scattered or absorbed. In the presence of hemorrhage, the hemoglobin concentration increases. Thus, the extravascular blood absorbs more NIR light in comparison to the brain tissue in absence of hematoma. The novel mNIRS system employs real-time noise cancellation and feature extraction algorithms that analyzes the NIRS signals and generates validated "Data Point pairs of Input and Output" (DPIO) signals. These validated DPIO are then fed to an automated machine learning classification algorithm to perform a linear regression and generate a specific tissue optical index (STOI) (or m-score) for each brain site that is scanned. ITOI is calculated by the logarithmic ratio of STOIs of two contralateral lobes. Absolute value of ITOI of 0.1 or greater indicates a positive hemorrhagic lobe.[17] This analytical approach eliminates the impact of outliers on the final assessment.

The probes of this tool are designed to be placed on eight specified contralateral locations, 2 frontal, 2 temporal, 2 parietal and 2 occipital.[17,18] It is a self-guided device which allows the operator to evaluate the subject with minimal training. Once the operator places the device on the participant's scalp and presses the trigger button, all the data process is automatic. A buzzer and an indicator light notify the operator about the completion of the scan. In case of any operational error, the device notifies the operator about the same and also guides the operator towards corrective steps. The scanning process for each site takes around 5 s, and the average duration for completing tasks, from scanning to result generation, is approximately 10 s for the frontal and temporal lobes, and roughly 16 s for the parietal and occipital lobes. Consequently, examining the entire head using the mNIRS device takes less than a minute.[19] The mNIRS based ITOI detects traumatic ICH within 72 h from the injury of more than 2 cc of volume and at a distance of 3–3.5 cm from the outer surface of skull.

2.2. Statistical analysis

All the data concerned with the baseline demographics, injury, clinical findings, CT and the mNIRS findings was compiled and analyzed using SPSS IBM Version 21 (Chicago, IL, USA). p-values <0.05 at 95% confidence interval was considered to be statistically significant. Sensitivity, specificity, accuracy, positive and negative likelihood ratios, and Youden's J index were computed by counting the true positives, true negatives, false positives, and false negatives in comparison to the results of the gold standard (head CT scan) to compute the clinical efficacy in detecting ICH. Given the study's primary focus on evaluating the screening tool's performance with an emphasis on reliability and minimizing false negatives, the false positive rate and false negative rate were chosen as relevant metrics. Additionally, likelihood ratios, which are independent of the prevalence of the disease, were computed. These likelihood ratios are considered robust global measures of the diagnostic performance of a test. The use of likelihood ratios in the study helps overcome the limitation of being influenced by disease prevalence, allowing for a more comprehensive and accurate assessment of the screening tool's diagnostic capabilities.

To assess the accuracy of mNIRS based ITOI to determine whether each subject had an intracranial hemorrhage or not (subject-wise analysis), the following procedure was implemented:

Firstly, for each subject, the mNIRS device generated multiple ITOI results that corresponded to 2–8 brain lobes or sites, which were categorized as either "RED" or "GREEN" based on the coding system (Fig. 1b). In this system, "RED" represented "TRUE", indicating the presence of hemorrhage, and the color "GREEN" represented "FALSE", indicating the absence of hemorrhage.[17]

Subsequently, the multiple ITOI results obtained in the previous step were processed for each subject using an "OR" function. This function involved comparing the different results and assigning an outcome based on the following rules: if both results were "RED", the outcome was deemed "TRUE"; if both results were "GREEN", the outcome was deemed "FALSE"; and if one result was "RED" and the other was "GREEN", the outcome was still considered "TRUE".[17]

By following these steps, the classification of each subject as either hemorrhagic subject or a non-hemorrhagic subject was determined based on the generated ITOI results.

To evaluate the classification accuracy of mNIRS-based ITOI in determining whether each lobe was hemorrhagic or non-hemorrhagic (lobe-wise analysis), the procedures undertaken are mentioned below.

Firstly, each lobe scanned was treated as an individual sample for analysis purposes. This allowed for a detailed examination of each lobe.[17]

Next, the mNIRS device generated the ITOI result for each lobe, categorizing it as either "RED" or "GREEN". In this coding system, the color "RED" was designated as "TRUE", indicating the presence of a

hemorrhage, while the color "GREEN" was designated as "FALSE", signifying the absence of a hemorrhage.[17]

The head CT scan provided a similar assessment for each individual lobe, assigning a "TRUE" or "FALSE" value to indicate the presence or absence of a hemorrhage, respectively. Finally, the ITOI result obtained in the second step was compared with the corresponding CT scan result from the third step for each scanned lobe. This comparison allowed for a comprehensive evaluation of the agreement or discrepancy between the mNIRS-based ITOI and the CT scan in determining the hemorrhagic or non-hemorrhagic status of each specific lobe or brain site.[16]

Using a significance criterion of $\alpha = 0.05$ and a statistical power of 00.80, the sample size was calculated according to the estimated specificity (Sp) of 76% and a prevalence (p) of 83% derived from a pilot study conducted in 2021 with a sample size of $n = 44$.[18] This pilot study aimed to assess the diagnostic accuracy of mNIRS-based ITOI in detecting intracranial hemorrhages. The minimum sample size required to detect a 10% difference from the presumed Sp value was determined to be $n = 116$. As a result, the sample size of $n = 129$ is adequate for evaluating the clinical efficacy (sensitivity and specificity) of mNIRS-based ITOI in detecting hemorrhages.

3. Results

Of 129 subjects and 1032 sites or lobes evaluations, 534 (51.74%) sites were accessible (Fig. 2). No adverse events were reported. Table 1 summarizes the demographic characteristics in the three study groups along with the injury details. 45% of the study participants reported in TICS1, while 25.6% and 29.5% were reported in TICS2 and TICS3. respectively. The mean (standard deviation) age of the study participants was 35.19 (SD 16.9) years with the maximum number of participants in the middle age group between 26 and 60 years of age (58.91%). The GCS of 14–15 is reported in 84.5%, 9–13 in 10.85% and 3–8 in 4.65% study participants. The commonest cause of injury in all the three study groups was found to be road traffic accidents. Fig. 3 shows the distribution of hematoma in different lobes of the brain with the temporal lobe showing the greatest number of hematomas reported (50%). In this study, epidural hematoma was the most common type of hematoma reported (34.38%) (Fig. 4).

A strong positive correlation was seen between the ITOI and the depth of hematoma, r (205) = 0.913, $p < 00.000$ and between the ITOI and the volume of hematoma, r (205) = 0.782, $p < 00.000$ (Table 2), when the hemorrhagic and non-hemorrhagic lobes were coded as "1" and "0" respectively. This was further strengthened by the multivariate regression analysis showing a positive statistically significant relation between the ITOI and the depth of hematoma and between the ITOI and the volume of hematoma, demonstrated in Table 3.

Fig. 5 establishes that a significant difference exists in the ITOI of the hemorrhagic lobes and non-hemorrhagic lobes in all the 3 temporal groups. An ITOI less than 0.1 was seen consistently for all the non-hemorrhagic lobes in all the three groups. Table 4 shows the ITOI computed for the hemorrhagic lobes and the non-hemorrhagic lobes in the three categories - TICS1, TICS2 and TICS3.

The ITOI exhibits a strong level of reliability in objectively determining the presence or absence of hematoma, as indicated by its high sensitivity, specificity, accuracy, positive likelihood ratio, negative likelihood ratio, and Youden's J index in classifying subjects as hemorrhagic or non-hemorrhagic (Table 5). The minimum bleed volume detected was 1 cc at a depth of 6 mm and a bleed volume of 30 cc was detected at maximum depth of 21 mm (Table 6).

Table 7 summarizes the data across all temporal groups for each lobe scanned. The overall sensitivity, specificity, and accuracy (lobe-wise analysis) was found to be 94% (CI 79–99%), 90% (CI 88–93%) and 91% (CI 88–93%) respectively. The ITOI demonstrates high performance across all temporal groups with a sensitivity of 100% up to 12 h since injury and 87% for 12–72 h post-injury due to the false negatives. 2 false negatives were reported in this group; one was in a child (3 years old)

Table 1
Demographic characteristics of study participants.

	Characteristics	TICS1[a] 0–4 h n = 33	TICS 2[a] (4–12 h) n = 58	TICS3[a] (12–72 h) n = 38
Participants	Males	$n = 26$ (78.8%)	$n = 46$ (79.3%)	$n = 30$ (78.9%)
	Females	$n = 7$ (21.2%)	$n = 12$ (20.7%)	$n = 8$ (21.1%)
	Age in years: Mean (SD)	39.03 (19.17)	35.52 (16.33%)	31.26 (15.46)
Cause of Injury	Fall	$n = 8$ (24.2%)	$n = 10$ (17.2%)	$n = 9$ (23.7%)
	RTA	$n = 25$ (75.8%)	$n = 43$ (74.1%)	$n = 28$ (73.7%)
	Assault/Violence	–	$n = 5$ (8.6%)	$n = 1$ (2.6%)
GCS	13–15	$n = 28$ (84.8%)	$n = 52$ (89.7%)	$n = 33$ (86.8%)
	9–12	$n = 2$ (6.1%)	$n = 4$ (6.9%)	$n = 4$ (10.5%)
	8 or less	$n = 3$ (9.1%)	$n = 2$ (3.4%)	$n = 1$ (2.6%)
Treatment	Conservative	$n = 31$ (93.9%)	$n = 57$ (98.3%)	$n = 37$ (97.4%)
	Surgical	$n = 2$ (6.1%)	$n = 1$ (1.7%)	$n = 1$ (2.6%)
Skin Type	Type 2	$n = 2$ (6.1%)	$n = 1$ (1.7%)	$n = 4$ (10.5%)
	Type 3	$n = 3$ (33.3%)	$n = 18$ (31%)	$n = 11$ (28.9%)
	Type 4	$n = 12$ (36.4%)	$n = 27$ (46.6%)	$n = 13$ (34.2%)
	Type 5	$n = 8$ (24.2%)	$n = 12$ (20.7%)	$n = 10$ (26.3%)
Time from injury to mNIRS scan in minutes: Mean (SD)		126 (0.05)	436 (0.1)	631 (1.81)
Symptoms	LOC	$n = 14$ (42.4%)	$n = 32$ (55.2%)	$n = 27$ (71.1%)
	Headache	$n = 14$ (42.4%)	$n = 19$ (32.8%)	$n = 7$ (18.4%)
	Blurred Vision	$n = 4$ (12.1%)	$n = 5$ (8.6%)	$n = 4$ (10.5%)
	Pain in and around eyes	–	$n = 1$ (1.7%)	$n = 3$ (7.9%)
	Vomiting/ Dizziness	$n = 15$ (45.5%)	$n = 18$ (31%)	$n = 19$ (50%)
	Seizures	–	$n = 2$ (3.4%)	$n = 1$ (2.6%)
	Bleeding from ear	$n = 6$ (18.2%)	$n = 8$ (13.8%)	$n = 6$ (15.8%)
	Bleeding from nose	$n = 3$ (9.1%)	$n = 13$ (22.4%)	$n = 5$ (13.2%)
	Others	$n = 6$ (18.2%)	$n = 17$ (12.1%)	$n = 5$ (13.2%)

[a] TICS1 (Time from injury to scan - 0 to 4 h); TICS2 (Time from injury to scan - 4 to 12 h); TICS3 (Time from injury to scan - 12 to 72 h).

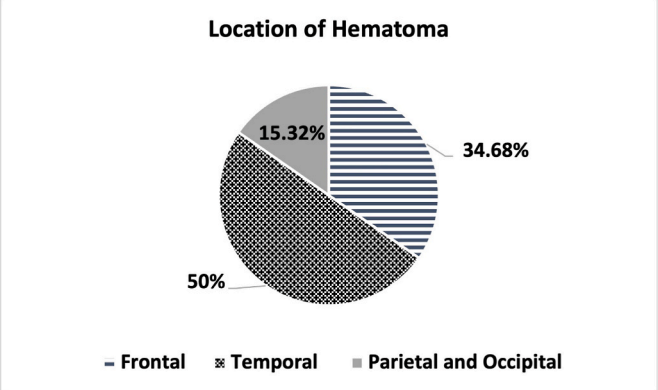

Fig. 3. Hematoma Distribution based on the location.

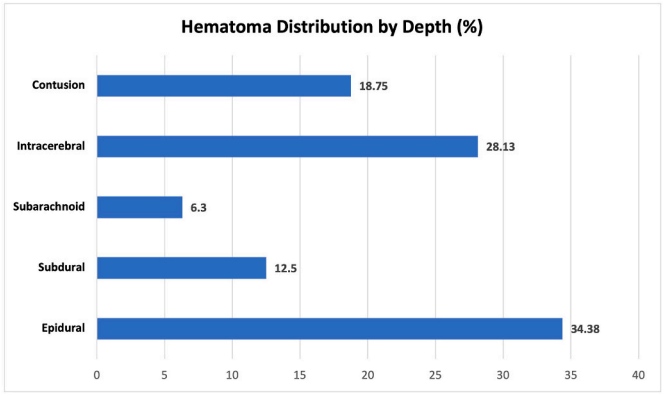

Fig. 4. Hematoma Distribution based on the type of the intracranial hemorrhage.

Table 2
Pearson coefficient between ITOI[a] and other variables – Volume, Depth and location of hematoma and age, gender, and skin type of the study participants.

	r	*p* value
Volume	0.782	0.000
Depth	0.913	0.000
Location	0.061	0.385
Age	0.172	0.013
Gender	−0.098	0.159
Skin Type	0.028	0.689

[a] ITOI – Intracranial Tissue Optical Index.

Table 3
Multivariate Regression showing the relation between ITOI[a] and volume and depth of hematoma.

	Coefficients	*P*-value	Lower 95%	Upper 95%
Intercept	0.009	0.278	−0.008	0.027
Volume	0.005	0.000	0.003	0.007
Depth	0.190	0.000	0.169	0.211

[a] ITOI – Intracranial Tissue Optical Index.

where the participant was uncooperative thus generating a false result. The other had an intracranial bleed less than 2 cc in volume. Thus, the sensitivity to detect ICH with a bleed volume of 2 cc or more was 97%. The specificity across the three groups ranged from 88 to 93% due to varying numbers of false positives. A total of 48 false positives were reported, of which 95% were due to presence of cerebral oedema or presence of hematoma in the adjacent lobe.

4. Discussion

The present study demonstrated the clinical efficacy of the mNIRS system to detect ICH within 72 h post-injury. An excellent sensitivity (94%) was reported to detect ICH including epidural, subdural, subarachnoid, intracerebral and contusion. Of the total participants, 6.2% were found to be false positives due to the presence of cerebral oedema. For lobe-wise analysis, 62.5% of false positives had a hemorrhagic adjacent lobe (a non-hemorrhagic left parietal lobe was diagnosed as hemorrhagic by the mNIRS scan due to the adjacent hemorrhagic left temporal lobe) and the other 33.33% had cerebral oedema. The other 4.17% lobes were scanned 72 h post-injury. Cerebral oedema can be devastating if left untreated. The oedema should be controlled to prevent further injury, and complications such as increased intracranial pressure. This study demonstrated the clinical utility of ITOI to detect ICH as well as cerebral oedema across the temporal groups.

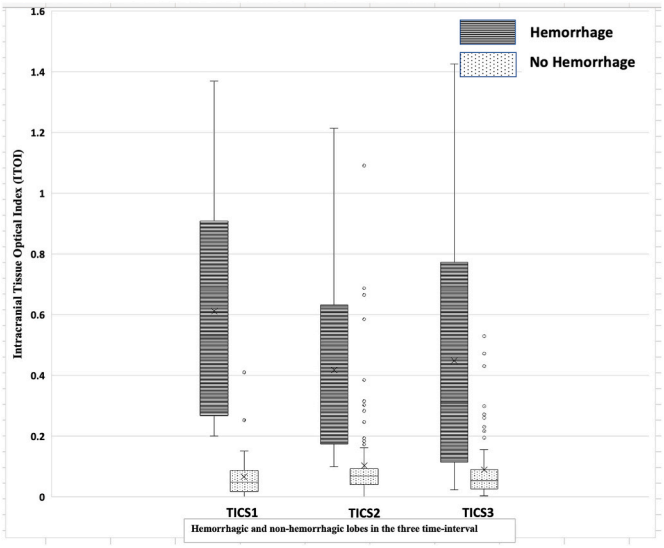

Fig. 5. Box and Whisker Plot showing the distribution of data in all the three categories – (a) TICS1; (b) TICS2; (c) TICS3. (*TICS1: Time from injury to scan: 0–4 h; TICS2: Time from injury to scan: 4–12 h; TICS3: Time from injury to scan: 12–72 h)

Table 4
The Intracranial Tissue Optical Index for the hemorrhagic and non-hemorrhagic lobes: Mean (Standard Deviation) for the three categories – TICS1, TICS2 and TICS3. A statistically significant difference was seen between the means the hemorrhagic and non-hemorrhagic lobes in all the three study groups, $p < .000$.

	Hemorrhagic Lobe ITOI	Non-Hemorrhagic Lobe ITOI	T stat
TICS1	0.6 (0.4)	0.06 (0.05)	7.96**
TICS2	0.13 (0.36)	0.09 (0.07)	5.46**
TICS3	0.18 (0.43)	0.06 (0.05)	6.22**

*ITOI – Intracranial Tissue Optical Index, TICS1 (Time from injury to scan - 0 to 4 h); TICS2 (Time from injury to scan - 4 to 12 h); TICS3 (Time from injury to scan - 12 to 72 h), **$p < .000$.

Table 5
Performance of the mNIRS based ITOI to detect traumatic intracranial hemorrhage (Subject-wise Analysis).

Statistical parameters	Overall $n = 129$
Accuracy	92 (81–100%)
Sensitivity	96 (81–100%)
Specificity	90 (83–95%)
FPR[a]	0.1 (0.05–0.17)
FNR[a]	0.04 (0–0.19)
PLR[a]	9.82 (5.43–17.78)
NLR[a]	0.04 (0.01–0.28)
Youden's J Index	0.86

To calculate these statistical parameters, the True positives (TP), true negatives (TN), false positives (FP) and false negatives (FN) were counted and the following formulas were applied.
Sensitivity = TP/(TP + FN;, Specificity = TN/(TN + FP); Accuracy = (TP + TN)/(TP + TN + FP + FN); FPR = FP/(FP + TN); FNR = FN/(FN + TP); PLR = Sensitivity/(1-Specificity); NLR = (1-Sensitivity)/Specificity; Youden's J Index = (Sensitivity + Specificity)-1.

[a] FPR – False Positive Ratio, FNR – False Negative Ratio, PLR – Positive Likelihood Ratio, NLR – Negative Likelihood Ratio. The number in the bracket gives the 95% confidence interval calculated using the clopper Pearson exact method.

Table 6
Mean Volume and Range of the Hematoma bleed volume at different depths.

	Mean Volume (cc)	Range
Epidural	14	1–46
Subdural	3.9	2–5 mm[a]
Intracerebral	25.6	1.9–70
Contusion	4.41	1.3–11

[a] Range in Subdural represents the varying thickness of the hematoma due to unavailability of the bleed volume as they were found to be patchy.The bleed volume of Subarachnoid hematoma could not be determined as they were found to be dispersed and thus were immeasurable.

Table 7
Performance of the mNIRS based ITOI to detect traumatic intracranial hemorrhage at different time intervals (Lobe-wise Analysis).

Statistical parameters	Overall n = 534	TICS1[a] (0–4 h) n = 132	TICS2[a] (4–12 h) n = 230	TICS3[a] (12–72 h) n = 172
Accuracy	91 (88–93%)	93 (88–97%)	91 (87–95%)	88 (82–92%)
Sensitivity	94 (79–99%)	100 (63–100%)	100 (66–100%)	87 (60–98%)
Specificity	90 (88–93%)	93 (87–96%)	91 (86–94%)	88 (82–93%)
FPR[a]	0.1 (0.07–0.12)	0.07 (0.03–0.12)	0.09 (0.05–0.13)	0.12 (0.07–0.17)
FNR[a]	0.06 (0–0.14)	0	0	0.13 (0–0.29)
PLR[a]	9.8 (7.38–13.02)	13.78 (7.34–25.85)	11.05 (7.28–16.78)	7.16 (4.49–11.41)
NLR[a]	0.07 (0.02–0.26)	0	0	0.15 (0.04–0.55)
Youden's J Index	0.85	0.93	0.91	0.75

To calculate these statistical parameters, the True positives (TP), true negatives (TN), false positives (FP) and false negatives (FN) were counted and the following formulas were applied.
Sensitivity = TP/(TP + FN;, Specificity = TN/(TN + FP); Accuracy = (TP + TN)/(TP + TN + FP + FN); FPR = FP/(FP + TN); FNR = FN/(FN + TP); PLR = Sensitivity/(1-Specificity); NLR = (1-Sensitivity)/Specificity; Youden's J Index = (Sensitivity + Specificity)-1.

[a] FPR – False Positive Ratio, FNR – False Negative Ratio, PLR – Positive Likelihood Ratio, NLR – Negative Likelihood Ratio, TICS1 – Time from injury to scan - 0 to 4 h); TICS2 (Time from injury to scan - 4 to 12 h); TICS3 (Time from injury to scan - 12 to 72 h). The number in the bracket gives the 95% confidence interval calculated using the clopper Pearson exact method.

The mortality and morbidity associated with delayed detection can be prevented significantly with accurate triaging. Although imaging techniques like CT and MRI scans can efficiently diagnose ICH, their deployment for periodic screening has its limitations including non-portability, multiple radiation exposure, high cost of scanning, manpower, and lack of experts for image interpretation, to name a few. This burdens the healthcare infrastructure. The mNIRS based ITOI can overcome these challenges since it is a rapid and portable system. The minimum bleed volume detected in this study was 1 cc. The ITOI can be monitored in patients under observation to evaluate for the development of the bleed so that the hematoma can be detected at an early stage and the neuro-intervention can be initiated. Also, because the technology is near infrared based, it can be used multiple times on a patient without causing any harm.

Unlike traditional imaging methods, the mNIRS-based ITOI offers a much more budget-friendly option for patients. This cost advantage makes mNIRS a more accessible and economically feasible choice for a broader range of patients, ensuring that financial constraints do not hinder their ability to receive critical medical evaluations. The affordability of mNIRS contributes to a more sustainable and equitable healthcare system, reducing the financial burden on patients while maintaining accuracy and efficiency in detecting ICH. In the present study, out of the total non-hemorrhagic participants, the mNIRS system correctly classified 90% of them. Thus, the radiation exposure as well as the cost of scanning these patients with traditional imaging devices could have been prevented in 90% of study participants. Hence, the cost-effectiveness of the ITOI system facilitates early detection and intervention, ultimately leading to improved clinical outcomes for patients.

Traditionally, the triaging of TBI has been based on GCS scoring along with various risk factors to be referred for neuroimaging. However, as discussed, a significant proportion of patients appear to be apparently asymptomatic resulting in a high number of false negatives at an early stage. A perfect score of 15 cannot conclude the absence of a hemorrhage or a possible development of post-concussive syndrome. As a result, for immediate detection of asymptomatic focal and diffuse TBI, more detailed indices are required. These valid indices will effectively increase the efficacy of therapeutic strategies in TBI patients.[20] Secondary brain injuries take place within the first few hours post-trauma. Thus, if the ICH is detected early, it can help to reduce the associated neurological worsening. The novel mNIRS system is an easy-to-use self-guided device that can provide early information about the brain condition after TBI, by evaluating the cerebral autoregulation in the early post-traumatic period. As the device does not need expert interpretation, the paramedic staff will be able to operate it with minimal training. The training requires only 30 min of time, and the device can then be used to supplement GCS. This will enhance the efficacy of the screening procedure, thereby allowing objective assessment and providing accurate triaging to mTBI patients even in low-resource rural locations or in austere health centers.

Many studies have reported the use of NIRS devices with ranging sensitivity to diagnose ICH thus establishing the efficacy of NIRS in TBI. Few studies have reported a high sensitivity of 93% in detecting hematoma more than 25 cc and 100% more than 75 cc in volume.[21,22] The mNIRS based ITOI has proven very effective to diagnose a bleed as small as 2 cc with over 90% sensitivity and a high Youden's J index demonstrates its capability to detect all the types of hematomas. Additionally, in comparison to the other available NIRS devices, this mNIRS system is incorporated with an advanced machine learning algorithm that requires zero calibration to scan irrespective of the patient's age, gender, or skin color. The algorithm negates the effect of these factors on the output thus making it an operator-friendly device.

This study has limitations, including the lack of ITOI to evaluate the evolving bleed. Future studies are needed to perform more evaluations through the monitoring phase in the same subject at different time intervals to better estimate the diagnostic accuracy in individuals and the association with changes in the ITOI and to further investigate the predictive accuracy of the ITOI with bleed evolution. Another limitation is the restricted number of operators and the possibility of human error considering the analysis and assessment was done by singular clinicians; although the device is very easy to learn and use, studies are currently underway to study inter-operator variability.

5. Conclusion

In this diagnostic study, the objective ITOI generated by mNIRS system at its core classified participants with intracranial bleeding at different time intervals post-injury with high accuracy. The patented device is easy to use and can be adopted as a complementary tool in current clinical practice to aid in detecting the ICH in mild TBI patients among all age groups and genders. The ease of learning and use will therefore facilitate the incorporation of the novel mNIRS powered device into existing standard assessments of traumatic brain injury to aid in clinical diagnosis.

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CRediT authorship contribution statement

Sumit Raj: Conceptualization, Writing – original draft, Dr. **Radha Sarawagi Gupta:** Formal analysis, Validation, Prof. **Rajesh Malik:** Writing – review & editing, Dr. **Md Yunus:** Investigation, Methodology, Dr. **Pradeep Chouksey:** Project administration, Writing – review & editing. **Adesh Shrivastav:** Conceptualization, Supervision, Dr. **Manoj Nagar:** Writing – review & editing, Dr. **Amit Agrawal:** Writing – original draft.

Declaration of competing interest

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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Abbreviation List

CT –: Computed Tomography
EFNS –: European federation of Neurosurgeons
GCS –: Glasgow Coma Scale
ICH –: Intracranial Hemorrhage
ITOI –: Intracranial Tissue Optical Index
mNIRS –: Machine learning powered Near Infrared Spectroscopy
STOI –: Specific Tissue Optical Index
TBI –: Traumatic Brain Injury
TICS1 –: Time from Injury to Scan: 0–4 h
TICS2 –: Time from Injury to Scan: 4–12 h
TICS3 –: Time from Injury to Scan:12–72 h
WFNS –: World Federation of Neurological Societies
WHO –: World Health Organization