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Role of Transcranial Doppler Ultrasound as a Predictor of Outcome in Severe Traumatic Brain Injury and Its Correlation with Glascow Coma Scale and Full Outline of Unresponsiveness Score

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Abstract
Introduction: *Traumatic brain injury(TBI) is a major public health problem. It is considered to be one of the leading causes of death and disability worldwide. After TBI cerebral blood flow (CBF) becomes extremely low approaching ischemic thresholds. Concurrently, cerebral blood flow velocities become strongly correlated to CBF itself post injury. Identification of such hemodynamic disturbances can be used to predict outcome in severe TBI when measured immediately post-injury using Transcranial Doppler (TCD). TCDpermits non invasive assessment of different CBF velocities as well as pulsatility index (PI). Abnormal measurement of such indices is believed to correlate to poor outcome.*
Methods: *120 patients with severe TBI, according to GCS, underwent TCD within 24 hours post trauma. Middle cerebral artery (MCA) velocities and pulsatility index, as well as other clinical and neuro imaging data, were recorded and accordingly patients were divided into 3 groups: patients with normal TCD measurements, patients with hypoperfusion and patients with vasospasm. Hypoperfusion was defined by meeting two out of three criteria: mean flow velocity (MFV) of MCA< 35cm/sec, End diastolic velocity (EDV) of MCA<20cm/sec, PI>1.4. Vasospasm was defined as MFV>120 cm/sec. Outcome was evaluated using the Glasgow Outcome Scale extended(GOSE) at 3 months, as well as in-hospital mortality.TCD measurements were also correlated to GCS and FOUR score.*
Result: *There was a significant correlation between PI and GOSE at 3 months. There was also significant correlation between PI and mortality. However, different MCA velocities did not show any correlation with GOSE or mortality. Strong negative correlation was recognized between PI and GCS and FOUR scores.*
Conclusion: *Pulsatility index, when measured within the first 24 hours post-trauma, is considered a good predictor of mortality as well as functional outcome at 3months. Abnormal pulsatility index values correlate with the severity of injury (in terms of GCS and FOUR scores).*
Key Words: *Critical; Trauma; Injury; Transcranial; Doppler.*

Introduction

Traumatic brain injury (TBI) is a major cause of death and disability, contributing to around 30% of all injury deaths.(1).It can lead to a variety of secondary conditions that might cause functional limitation, or disability eventually affection quality of life (2).Injury related health effects influences social interactions, safety concerns, skill behaviour and performance. All of this have its repercussions on the patients themselves, their relatives and eventually society (3).

It is well accepted that neurological outcome after TBI depends on the severity of initial injuries and the extent of secondary brain damage such as ischemia and hypoxemia[4]. After TBI, CBF becomes extremely low and near the ischemic threshold. At the same time, CBF velocities correlate with CBF itself. Accumulating interstitial edema can further compromises CBF and aggravates secondary ischemic insults [5]. Prevention and treatment of such secondary injuries are considered cornerstone in modern TBI management [6,7].

Transcranial Doppler (TCD) was first described in 1982 [8]. Itoffers a noninvasive real-time assessment of different CBF velocities, by insonating cerebral arteries, mainly middle cerebral artery, through thin bone windows, over extended time periods with high temporal resolution. Its main advantage over other imaging modalities is that it is relatively inexpensive, repeatable. It is also considered convenient to patients admitted to intensive care units (ICU) due to its portability thus allowing continuous bedside monitoring of these patients[9]

It is hypothesized that prediction of management outcome in severe TBI is possible by TCD. By recording MCA blood flow velocities as well as calculating PI, it is possible to assess the outcome since abnormally low or high flow velocities and abnormally high PI are a result of post-traumatic hemodynamic changes that could affect the prognosis. The aim of the work in the present study was to assess the predictive value of TCD in patients with severe TBI (at 3 months) and correlate its measurements with GCS and FOUR score.

Since its introduction, GCS has been used in prediction of morbidity and mortality in neurological patients and is considered the gold standard against which newer scales are compared [10,11]. However, it includes some limitations like inability to assess verbal response in intubated patients, and it does not include any clinical indicators of brainstem responses like corneal, papillary reflexes and breathing patterns [10,11]. FOUR score was designed to overcome the limitations of GCS and is now considered a powerful predictor of in-hospital mortality, functional outcome and overall survival in neurological patients [12,13], It may even be a better scale than GCS in predicting outcomes in TBI patients and mortality [14].

In this study, TCD measurements were recorded in patients with severe traumatic brain injury within 24 hours of admission. These values were then correlated with mortality as well as GOSE assessed at 3 months. To assess the severity of injury, TCD values were also correlated to GCS and FOUR scores.

Aim of the Work

The aim of the work was to assess the predictive value of early TCD in patients with severe TBI in terms of mortality and GOSE at 3 months, and also to correlate different TCD measurements with GCS score and FOUR score.

Material and Methods

This is an observational prospective cohort study which was conducted on 120 patients with severe TBI and who arrived within 24 hours of injury. A signed written informed consent was obtained from patient relatives as well as local ethical committee approval.

Inclusion Criteria

- Adult (≥ 18 years old).
- Patients with severe traumatic brain injury with GCS ≤ 8.

Exclusion Criteria

1. Patients admitted ≥ 24 hours after TBI.
2. Patients presented by out of hospital cardiac arrest or in-hospital cardiac arrest before performing the TCD.
3. Pregnant females.
4. Refusal to be involved in the study by patient's relatives.
5. Inability to obtain adequate ultrasound window.
6. Temporal bone fracture or transcalvarial brain herniation.

7. Open head injuries or patients in need for surgical intervention.
8. Loss of follow up.

For every eligible patient the following data were collected:

1) Demographic data including age (years) & sex.
2) Complete medical history and mechanism of trauma.
3) Acute physiology and chronic health evaluation (APACHE II) score [15] on admission.
4) GCS on admission to the ICU after primary respiratory and hemodynamic stabilization [16].
5) FOUR score on admission to the ICU after primary respiratory and hemodynamic stabilization [17].
6) Characteristics of Computerized Tomography (CT) scan of the head using The Rotterdam CT classification model. [18]
7) New Injury Severity Score (NISS) [19]:
   The NISS was calculated based on the 3 most severe injuries, regardless of body region, had their score squared and added together to produce the NISS score.
8) TCD ultrasonography was performed within the first 24 hours, immediately after hemodynamic and respiratory stabilization according to the following protocol:[20]

- All patients in the study were managed using the same medical management principles of traumatic brain injury which aimed at preventing secondary brain injuries such as:[21]

- Hypotension (SBP<90 mm Hg).
- Hypoxemia (Pao2 < 60 mm Hg or O2 saturation < 90%).
- Hypo or Hypercapnia (PaCo2 35-45).
- Anemia (Hg<100 g/L or hematocrit < 0.30).

- The examination was done using S probe (3S phased array probe, Norway); Vivid 3 device (General Electric®, Norway).
- Standing behind the head of the patient, the 2MHz ultrasound transducer was placed over the temporal area just above the zygomatic arch and in front of the tragus of the ear and oriented slightly upward and anteriorly.
- A red color signal (i.e. flow towards the probe) at a depth between 40-65mm represented the flow in the ipsilateral M1 MCA. The angle and position of insonation was adjusted to provide the highest quality Doppler signal.
- By applying pulsed wave on the insonated segment, the systolic (PSV) and diastolic (EDV) velocities were measured and recorded on US machine.
- Mean flow velocity (MFV) was then calculated using the formula: (PSV+ (EDVx 2))/3.
- Pulsatility index (PI) was calculated using the formula: (PSV-EDV)/ MFV.[22]
- The right and left MCA were explored and data were recorded on the ultrasound machine.
- The following data were collected at the time of the TCD study[23]:

- $PaCo_2$ in Arterial blood gases (ABG) 15 minutes before the study.
- Blood pressure: systolic, diastolic and mean in mmHg.
- Heart rate (Beats/min)
- Hemoglobin level.
- Temperature (°C) at the time of the study using an axillary thermometer.
- GCS at the time of examination just before the TCD study.
- Capillary glucose level (mg/dL)

Hypoperfusion was diagnosed, based on previous studies, if two of the following criteria were met:[24,25]

- Mean flow velocity of MCA < 35 cm / sec
- Diastolic velocity< 20 cm / sec
- Pulsatility index > 1.4

Based on previous studies, Vasospasm was diagnosed if MFV> 120 cm/ sec. [26,27]

Enrolled Patients were prospectively followed up for:

- Primary endpoint:
- Glasgow outcome score extended (GOSE) at 3 months [28].
  - Patients who remained hospitalized were evaluated in person. Those who were discharged were assessed by telephone.
  - The assessment was carried out using the structured interview for the GOSE, with questions covering the following aspects: (1) consciousness; (2) independence inside and outside the house; (3) resumption of normal social roles; and (4) residual symptoms interfering with daily life.
  - For the final prediction model GOSE was dichotomized as unfavorable (score 1-4) versus favorable (score 5-8)
- ICU and In-hospital Mortality.

Statistical Analysis

- Data are presented as median with interquartile range (IQR) for continuous variables and as frequencies and percentages for categorical variables.
- Pearson's correlation coefficients (r) [29] were calculated to test the relation between TCD and other clinical variables.
- A binary logistic regression analyses[30] were performed to reveal the odds ratios of clinical variables in predicting the primary outcome measures. Variables that showed statistically significant result under univariate analysis were entered into a multivariate analysis to identify independent predictors of outcome measures. Discrimination of the logistic models was assessed by calculating the area under receiver operating characteristic (ROC) curve.[31]The best cut-off point was chosen as that one which maximizes the Youden index (sensitivity + specificity - 1). Comparing the areas under ROC curves (AUC) was performed using the nonparametric technique described by DeLong et al.[32]
- A linear regression analyses[29] were performed to reveal the relation between clinical variables and the MV days and hospital LOS. Variables that showed statistically significant result under univariate analysis were entered into a multivariate analysis to identify independent predictors of outcome measures.
- Data were analyzed by SPSS 21.0 for Windows (SPSS Inc., Chicago, Illinois, USA) and ROC curve analyses were performed by MedCalc Version 15.8.0.0 (Frank Schoonjans, Mariakerke, Belgium). All hypotheses were constructed two-tailed and $p \leq 0.05$ was considered significant

Results

One hundred and twenty patients, who were admitted to Alexandria Main University Hospital, were studied from July 2015 to January 2017. General characteristics of the patients are presented in (Table 1). The median age of the patients was 37 with IQR 30-43. There were 104 males (86.7%) and 16 females (13.3%). The median values of heart rate, temperature, mean blood pressure, hemoglobin and glucose, for all patients and according to the 3 different groups based on TCD measurements, are shown in table 1. No statistical significance was found between these variables in the 3 groups

Table (1): Demographic, Clinical and laboratory Data.

		All Patients (n = 120)	Normal (n = 68)	Hypoperfusion (n = 41)	Vasospasm (n = 11)	p
Age (years)		37 (30 – 43)	36.5 (29.2 - 43.7)	38 (30.5 - 42)	35 (29 - 39)	0.744
Heart Rate (beats/min)		115 (104 – 122)	115 (103.5 - 122.7)	113 (102 - 120.5)	117 (106 - 123)	0.664
Temperature (°C)		38 (37.9 - 38.5)	38 (37.90 - 38.50)	38.1 (37.8 - 38.5)	38.2 (37.8 - 38.5)	0.922
Mean BP (mmHg)		100 (93 – 103)	99.2 (93.3 - 104.6)	100 (93.3 - 103.3)	96.7 (90 - 101.7)	0.746
Haemoglobin(g/dl)		11 (10 – 11)	11 (10 - 11.8)	10.8 (10 - 11.5)	10.7 (9.7 - 11.6)	0.360
Glucose (mg/dl)		154 (137 – 177)	151.5 (135.2 - 173.7)	156 (138.5 - 180)	166 (143 - 184)	0.381
Sex	Male	104 (86.7%)	58 (85.3%)	36 (87.8%)	10 (90.9%)	0.849
	Female	16 (13.3%)	10 (14.7%)	5 (12.2%)	1 (9.1%)	
Mechanism of Trauma	RTA	85 (70.8%)	47 (69.1%)	31 (75.5%)	7 (63.6%)	0.802
	Fall	25 (20.8%)	16 (23.5%)	6 (14.6%)	3 (27.3%)	
	Assault	10 (8.3%)	5 (7.4%)	4 (9.8%)	1 (9.1%)	

BP= Blood Pressure, pCO2= Partial Pressure of Carbon dioxide, RTA= Road Traffic Accident
Data are presented as median (interquartile range) and analyzed byKruskal Wallis Test or as frequency (%) and analyzed by Chi-Square test
* p is significant ≤ 0.05

For all patients, the median GCS score as well as FOUR score was 6. The median APACHE-II Score was 17, while the median Rotterdam CT score was 3. The median NISS for all patients was 29. When compared to those with abnormal measurements, Patients with normal TCD values had higher scores regarding the GCS score and the FOUR score but lower values for APACHE-II score, Rotterdam score and New ISS which were statistically significant. (Table 2)

Table (2): Scoring systems for each group.

	All Patients (n = 120)	Normal (n = 68)	Hypoperfusion (n = 41)	Vasospasm (n = 11)	P
GCS Score	6 (5 – 7)	7 (6 - 8)	5 (4 - 5)	5 (5 - 6)	< 0.001*
FOUR Score	6 (4 – 8)	8 (7 - 8)	4 (3 - 5)	4 (4 - 6)	< 0.001*
APACHE-II Score	17 (15 – 21)	15.5 (13 - 18)	19 (17 - 22)	22 (19 - 25)	< 0.001*
Rotterdam CT Score	3 (2 – 3)	2 (2 - 3)	3 (3 - 4)	3 (3 - 3)	< 0.001*
New ISS	29 (25 – 34)	25 (18 - 31)	34 (32 - 41)	29 (27 - 34)	< 0.001*

GCS= Glasgow Coma Scale, FOUR= Full Outline of Unresponsiveness, APACHE-II=Acute Physiology and Chronic Health Evaluation II, CT= Computed Tomography, ISS= Injury Severity Score
Data are presented as median (interquartile range) and analyzed byKruskal Wallis Test
* p is significant ≤ 0.05

Based on TCD measurements of MCA; 68 patients had normal measurements (56.6%), 41 patients had hypoperfusion (34.2%) and 11 patients developed vasospasm (9.2%). Table 3 illustrates the median systolic, diastolic and mean flow velocities for the middle cerebral artery as well as the pulsatility index for the three different groups.

Table (3): Transcranial Doppler data for each group.

	All Patients (n = 120)	Normal (n = 68)	Hypoperfusion (n = 41)	Vasospasm (n = 11)	p
Systolic Velocity (cm/sec)	86.3 (75.6 - 99.2)	88 (80.0 - 97.2)	74.2 (68.4 - 84.3)	194 (187.5 - 198.6)	< 0.001*
Diastolic velocity (cm/sec)	31.2 (18.8 - 41.3)	38.45 (30.7 - 41.8)	18.3 (17.3 - 18.9)	88.3 (81.4 - 91.4)	< 0.001*
Mean velocity (cm/sec)	49.9 (38.9 - 59.3)	54.3 (48 - 61.3)	37 (34.7 - 39.8)	121.8 (120.9 - 124.9)	< 0.001*
Pulsatility index	1.09 (0.92 - 1.46)	0.97 (0.86 - 1.11)	1.52 (1.46 - 1.66)	0.85 (0.78 - 0.97)	< 0.001*

Data are presented as median (interquartile range) and analysed byKruskal Wallis Test
* p is significant ≤ 0.05

Of the 68 patients with normal TCD measurements, 57 patients had a good outcome at 90day-GOSE assessment. Only one patient died in this group. Only 7 patients in the hypoperfusion (41 patients) had good GOSE assessment. Eighteen patients died in this group. Similarly, only 4 patients in vasospasm group (11 patients) had good outcome at 90day-GOSE assessment. Three patients died in this group. The overall results are summarized in (table 4), and shown in figure 1.

Table (4): Primary Outcome Measures.

		All Patients (n = 120)	Normal (n = 68)	Hypoperfusion (n = 41)	Vasospasm (n = 11)	P
In-Hospital mortality		22 (18.3%)	1 (1.5%)	18 (43.9%)	3 (27.3%)	< 0.001*
90-day GOSE	Good (5 - 8)	68 (56.7%)	57 (83.8%)	7 (17.1%)	4 (36.4%)	< 0.001*
	Poor (1 - 4)	52 (43.3%)	11 (16.2%)	34 (82.9%)	7 (63.6%)	

GOSE= Extended Glasgow Outcome Score
Data are presented as frequency (%) and analyzed by Chi-Square test
* p is significant ≤ 0.05

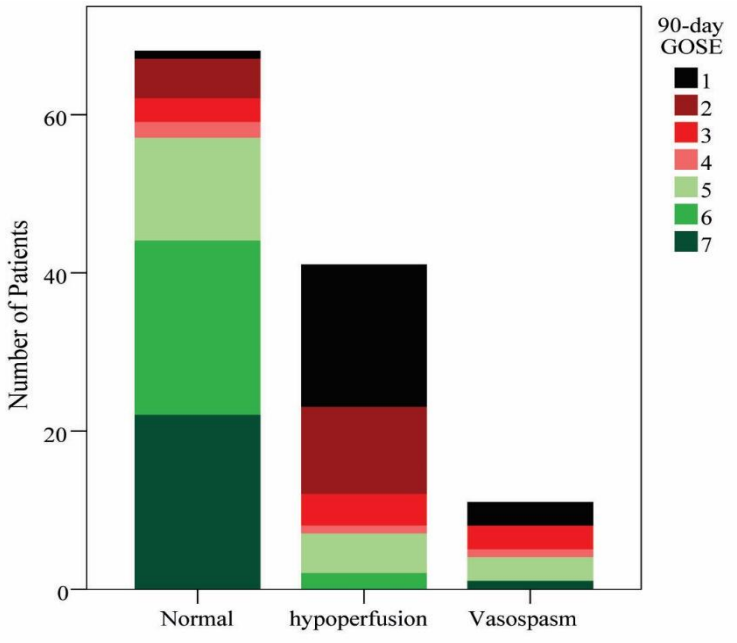

Figure 1: Distribution of GOSE at 90 day among study population.

Table 5 depicts the correlation between TCD measurements and the other scoring systems. There was no correlation between systolic, diastolic, or mean flow velocities and different scoring systems. However, Pulsatility index showed moderate negative correlation with GCS score and FOUR score, moderate positive correlation with Rotterdam CT score and new ISS, but weak positive correlation with APACHE-II score. (Figures 2-3)

Table (5): Correlation between TCD data and scoring systems.

		APACHE-II Score	GCS Score	FOUR Score	Rotterdam CT Score	New ISS
Systolic velocity	r	0.104	- 0.003	- 0.041	0.004	- 0.101
	p	0.086	0.970	0.660	0.970	0.270
Diastolic velocity	r	0.112	0.153	0.120	- 0.177	- 0.124
	p	0.224	0.095	0.193	0.052	0.074
Mean velocity	r	0.158	0.082	0.046	- 0.095	- 0.171
	p	0.085	0.372	0.616	0.300	0.062
Pulsatility index	r	0.197	- 0.464	- 0.459	0.499	0.436
	p	0.031*	< 0.001*	< 0.001*	< 0.001*	< 0.001*

APACHE-II=Acute Physiology and Chronic Health Evaluation II, GCS= Glasgow Coma Scale, FOUR= Full Outline of Unresponsiveness, CT= Computed Tomography, ISS= Injury Severity Score, r= correlation coefficient

* *p* is significant ≤ 0.05

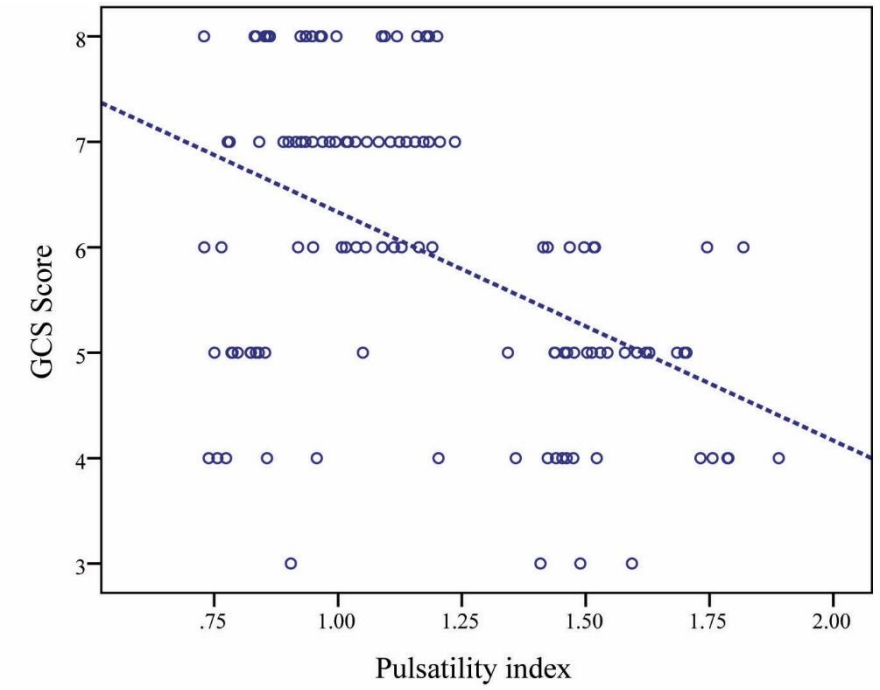

Figure 2: Scatter plot for the correlation between GCS Score and Pulsatility index.

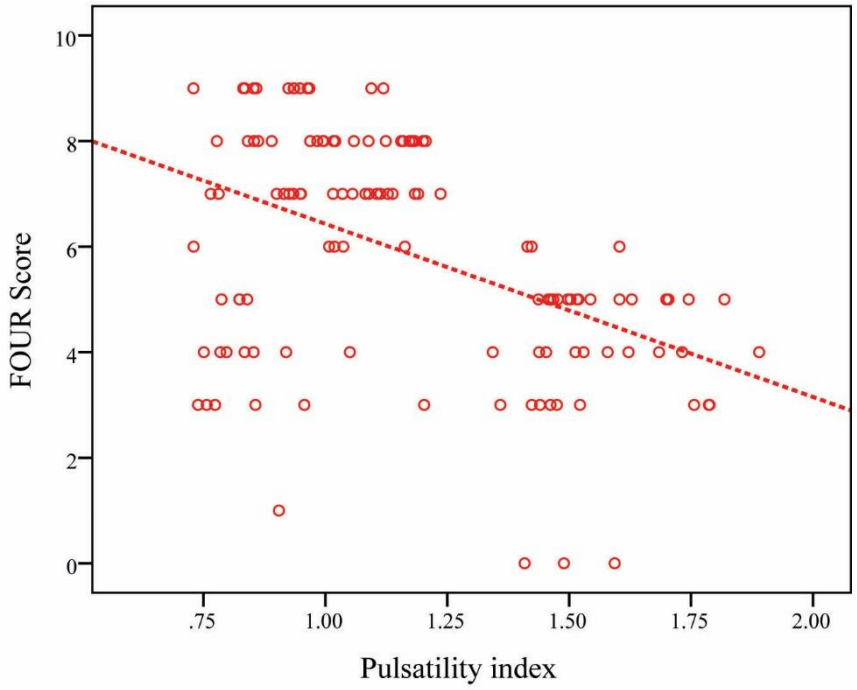

Figure 3: Scatter plot for the correlation between FOUR Score and Pulsatility index.

Prediction of in-hospital mortality:

Under univariate regression analysis, only the pulsatility index, out of all the TCD variables, showed statistically significant results with OR of 39.46 (95% CI; 6.81 - 228.67). Likewise, GCS score, FOUR score, APACHE-II score, Rotterdam CT score and new ISS showed statistically significant results. (Table 6)

After adjustment in the multivariate regression analysis, the Pulsatility index remained an independent predictor of in-hospital mortality alongside the GCS score, the FOUR score and the APACHE-II score , with an OR of 15.85 (95% CI; 2.18 - 115.26).

When assessing discrimination, the AU-ROC for mortality using the pulsatility index was 0.760 (95%CI; 0.674 -0.833) which is considered to be good. GCS and FOUR score showed the highest AU-ROC (0.827; 95% CI; 0.748 - 0.890) and (0.809; 95% CI;0.727 - 0.875) respectively (Figure 4). Interestingly, when we compared AU-ROC using PI to that of GCS and FOUR score, the differences were not significant. The best cut-off value for prediction of mortality by the pulsatility index was 1.36 with a sensitivity of 81.8% and a specificity of 78.6%.

Table (6): Prediction of in-hospital Mortality

	Univariate analyses	Multivariate analyses	ROC Curves analyses
	OR (95% CI)	OR (95% CI)	AUC (95% CI)
GCS Score	0.34 (0.20 - 0.56)	0.41 (0.20 - 0.84)	0.827 (0.748 - 0.890)
FOUR Score	0.52 (0.38 - 0.70)	0.59 (0.38 - 0.92)	0.809 (0.727 - 0.875)
APACHE-II Score	1.25 (1.11 - 1.42)	1.21 (1.02 - 1.43)	0.738 (0.650 - 0.814)
Rotterdam CT Score	2.99 (1.69 - 5.29)	0.92 (0.38 - 2.23)	0.761 (0.674 - 0.834)
New ISS	1.11 (1.04 - 1.19)	1.00 (0.91 - 1.10)	0.730 (0.642 - 0.807)
Pulsatility index	39.46 (6.81 - 228.67)	15.85 (2.18 - 115.26)	0.760 (0.674 - 0.833)

ROC= receiver operating characteristic, OR= Odds Ratio, CI= Confidence Interval, AUC= Area under the ROC Curve, GCS= Glasgow Coma Scale, FOUR= Full Outline of Unresponsiveness, APACHE-II=Acute Physiology and Chronic Health Evaluation II, CT= Computed Tomography, ISS= Injury Severity Score

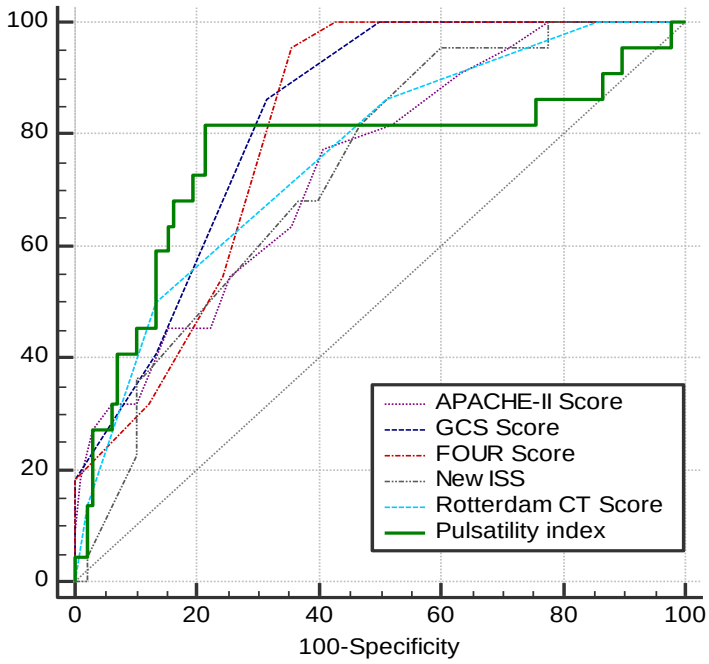

Fig (4): ROC curves comparing GCS Score, FOUR Score, APACHE-II Score, Rotterdam CT Score, New ISS, Pulsatility index in predicting in-hospital Mortality

Prediction of GOSE at 90 days:

Using univariate regression, pulsatility index, unlike TCD velocities, showed statistically significant results with OR 21.5 (95%CI; 5.42 - 85.39) (Table7). Likewise, the GCS score, the FOUR score, the APACHE-II score, the Rotterdam CT score and the new ISS were statistically significant

Under the multiple regression analysis, the pulsatility index was less significant with OR 3.89 (95% CI; 0.36 - 41.66). Only the GCS score and the FOUR score were independent predictors of 90 days-GOSE (Table 7)

The AU-ROC of 90d-GOSE using Pulsatility index was 0.685, 95% CI; 0.594-0.767. This was not statistically significant when compared to AU-ROC using the NISS with P value of 0. 579. However, it was statistically significant when compared to AU-ROC using each of GCS score, FOUR score, Rotterdam score and APACHE-II score (Table 7 Figure 5). The best cut-off value for prediction of 90day-GOSE by the pulsatility index was 1.24 with a sensitivity of 65.3% and a specificity of 89.7%

Table (7): Prediction of 90-day Neurologic Outcome

	Univariate analyses	Multivariate analyses	ROC Curves analyses
	OR (95% CI)	OR (95% CI)	AUC (95% CI)
GCS Score	0.11 (0.05 - 0.24)	0.15 (0.06 - 0.41)	0.940 (0.881 - 0.975)
FOUR Score	0.20 (0.12 - 0.36)	0.23 (0.11 -0.51)	0.950 (0.895 - 0.982)
APACHE-II Score	1.45 (1.26 - 1.67)	1.23 (1.01 -1.51)	0.831 (0.752 - 0.893)
Rotterdam CT Score	8.38 (3.84 - 18.28)	1.81 (0.69 - 4.75)	0.865 (0.790 - 0.920)
New ISS	1.11 (1.05 - 1.17)	0.91 (0.82 - 1.02)	0.722 (0.633 - 0.800)
Pulsatility index	21.50 (5.42 - 85.39)	3.89 (0.36 - 41.66)	0.685 (0.594 - 0.767)

ROC= receiver operating characteristic, OR= Odds Ratio, CI= Confidence Interval, AUC= Area under the ROC Curve, GCS= Glasgow Coma Scale, FOUR= Full Outline of Unresponsiveness, APACHE-II=Acute Physiology and Chronic Health Evaluation II, CT= Computed Tomography, ISS= Injury Severity Score

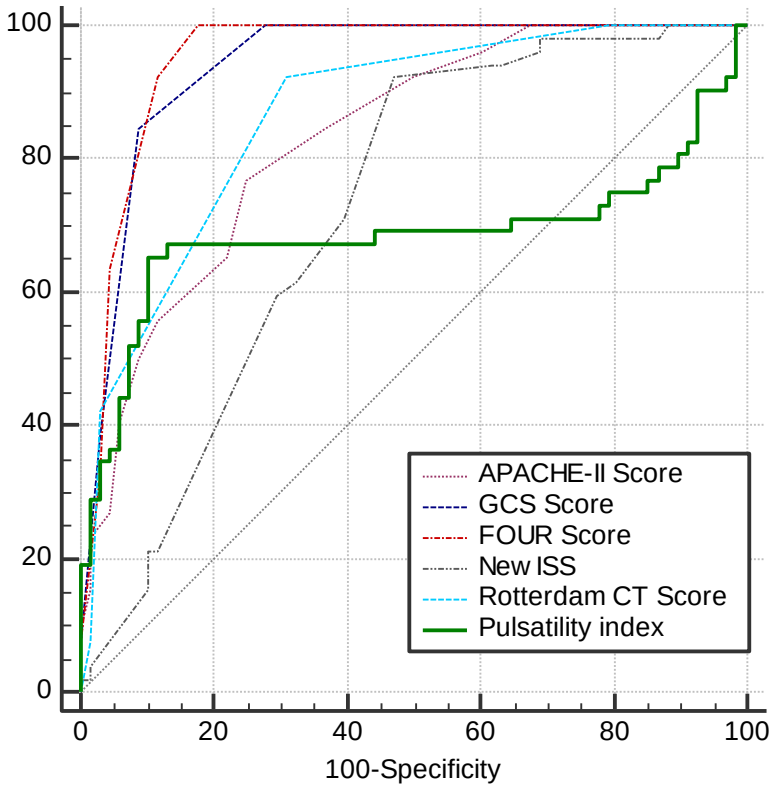

Fig (5): ROC curves comparing GCS Score, FOUR Score, APACHE-II Score, Rotterdam CT Score, New ISS, Pulsatility index in predicting 90-day neurologic outcome

Discussion

Sixty eight patients had normal measurements (56.6%). Of these, 57(83.8%) patients had good outcome, eleven patients (16.2%) had poor outcome and one patient died. Similarly, Ziegler et al[33] studied 255 patients, 45% of which had normal measurements. Of these 80% had a good outcome, 14% died and 5% had poor outcome.

41 patients (34%) had hypoperfusion, 18 of which died (43.9%), 34 patients (83%) had poor outcome and 18 patients (43.9%) died. Santbrink et al[24] had a 63% incidence of hypoperfusion, 26% of which died and 70% had poor outcome. Ziegler et al[33] however, had a 35% incidence of hypoperfusion, 98.6% of which died. This reflects the poor outcome of patients who developed hypoperfusion immediately post-injury.

In this study eleven patients (9%) had vasospasm, 3 patients died (27.3%) and 4 patients had good outcome (36.4%) and 7 patients had poor outcome (63%). Ziegler et al[33] reported that 27% of patients had vasospasm, 45% of which had a good outcome, 31.9% died and 23% poor outcome. However only 8 patients developed vasospasm on the first day. Santbrink et al[24] had a 17% incidence of vasospasm, most of which started on the second or the third day after trauma.

Gender and age relation to outcome

In the present study there was no significant difference between gender and poor outcome. This observation was in agreement with a systematic review to assess outcome in patients with moderate and severe traumatic brain injury where 9 studies found no relation between gender and outcome in multivariate analysis.[34] Also recently Melero et al studied 629 patients with severe TBI and demonstrated that gender is not an independent predictor for poor outcome after severe TBI.[35] Similarly there was no relation between age and poor outcome in the present study. In the literature, the prognostic value of age in severe TBI is inconclusive. Several trials found no relationship between age and come. Others found that older age was related to a worse outcome. In contrast, a single study demonstrated

an inverse relationship; an older age was associated with better outcome.[34]

Predictors of mortality

The overall mortality in the present study was 21 patients (18.3%). Only one patient died from group 1 (normal TCD measurements), 18 patients died from group 2 (hypoperfusion group) (44%) and 3 patients died from group 3 (vasospasm group) (27%). Ziegler et al[33] showed that the overall mortality rate was 42.7% whereas the mortality in hypoperfusion group and vasospasm group were 98.6% and 31.9% respectively. The difference in mortality in hypoperfusion group could be explained by the fact that Ziegler included patients requiring surgical interventions, hence, affecting the outcome.

Regarding the TCD values in predicting mortality, the results showed no association between the measured TCD velocities and mortality, however pulsatility index, which is calculated using the different velocities measured by TCD, was a significant predictor to hospital mortality in both univariate and multivariate analyses, with OR of 39.46 (CI; 6.81 - 228.67) and 15.85 (CI; 2.18 - 115.26) respectively and a good AU-ROC (0.760, 95%CI; 0.674 - 0.833).

When compared to AU-ROC using GCS and FOUR score, there was no significant difference (P; 0.4, 0.5 respectively) which demonstrates the significance of PI on mortality. Santbrink et al[24] studied 57 patients with severe traumatic brain injury and correlated TCD measurements to mortality found out that low flow velocity state defined as MFV<35 and high pulsatility index had a strong association with mortality in univariate analysis with OR of 3.9 (95% CI; 1.2-13), however this was less significant in multivariate analysis with OR of 2.1 (95%CI; 0.33-14). A notable difference from the current study is that Santbrink et al [24] included patients with intracranial mass lesions that required operative interventions, this type of patients was excluded from our study, and this could explain the variability in the outcome. In another study conducted by Moreno et al[36] on 125 patients with severe TBI, PI > 2.3 correlated with 100% mortality rate. To our knowledge, no further studies correlated PI with mortality in severe TBI patients.

There was a significant correlation between GCS score with mortality in both univariate and multivariate analysis with an AU-ROC of 0.827 (0.748 - 0.890) with a cut-off GCS score of 5. This is comparable to the systematic review done by Husson et al[34] to assess the prognosis after moderate and severe traumatic brain injury where lower GCS on admission correlated with poor outcome. Also Grigorakos et al studied 621 patients with severe traumatic brain injury and showed that mortality rate was higher for GCS score lower than 6.[37] Another multivariate analysis of 748 patients with severe traumatic brain injury demonstrated that mortality was higher with lower GCS with OR of 3.97.[38]

Similar to GCS score, FOUR score was found to be an independent factor of mortality with an AU-ROC of 0.809 (0.727 - 0.875) with a cut-off FOUR score of 5. Sadaka et al[39] studied FOUR score in traumatic brain injury and illustrated that it is an important predictor of in-hospital mortality as well as functional outcome at hospital discharge as well as the overall survival. Not only did he find an association between FOUR score and mortality but they also compared the FOUR score to GCS. Sadaka et al[39] enrolled 51 patients and demonstrated that AU-ROC for FOUR score was 0.85 compared to 0.83 for GCS. Likewise, Seyed et al [40] illustrated an AU-ROC of 0.92 for FOUR score compared to 0.96 for GCS score in predicting mortality in traumatic patients. In the present study, when we compared AU-ROC for GCS and FOUR score there was no statistical difference between both (P= 0.295).

This result here suggests that, when used within the first 24 hours of TBI, PI can be used, in conjunction with GCS and FOUR score, in predicting mortality following severe TBI.

Predictors of GOSE at 90 days

The pulsatility index values in the present study, unlike the TCD velocity measurements, were

correlated to the GOSE at 90 days. In a systematic review conducted by Husson et al,[34] the evidence for the predictive value of pulsatility index was strong, unlike the prognostic value of blood flow velocities where the evidence was inconclusive.

PI values in this study has been shown to predict unfavorable outcomes at 3 months with an odds ratio of 21.5 (CI; 5.42-85.39). However, on multivariate analysis, this association was less significant. (OR: 3.89). This observation is consistent with previous studies correlating PI with outcome. Moreno et al[36] illustrated that poor outcomes (GOS 1-3) were associated with significant rise in MCA PI (1.56, P< 0.001) whereas a PI < 1 identified 71% of patients with good outcome (GOS 4-5).However, PI was statistically significant in both univariate and multivariate analysis (OR: 8.5, 21.4 respectively). They also concluded that MFV is significantly related to the patient's outcome but only in univariate analysis. The differences in the results could be explained by the following observations; firstly Moreno et al [36] used shocked patients in the multivariate analysis, such patients are expected to have abnormally low flow velocity and altered PI measurements, consequently affecting the outcome results. Secondly they included patients with intracranial mass lesions requiring surgical evacuation, a type of patients excluded in our study, which similarly is expected to affect the outcome. Thirdly he assessed the patients at 6 months.

Likewise, a study done by Splavski et al[41] on 30 patients with severe TBI showed statistically significant negative strong correlation between PI values and outcome (r= -0.722, P< 0.01). However, a weak correlation was noticed between MCA flow velocity and outcome (r= 0.136), P<0.01).

Santbrink et al[24] addressed that low flow velocity state (MFV<35 and high pulsatility index) were associated with poor outcome in univariate analysis (OR=3.9, 95%CI; 1.2-13) but again this was less significant in multivariate analysis (OR=1.2,95%CI; 0.25-5.9).

When AU-ROC for GOSE was assessed at 3 months using PI and compared to that using GCS score and FOUR score, AU-ROC using PI was considered to be acceptable (0.68 at 3 months), although still weaker than that measured by GCS and FOUR score. (0.94 and 0.95 respectively).

TCD measurements and their correlations with GCS and FOUR scores

Pulsatility index showed moderate negative correlation with GCS and FOUR score with correlation coefficient of -0.464 and -0.459 (P<0.001) respectively. (Table 6) .This means that patients with lower GCS and FOUR scores are expected to have an abnormally high PI. Since GCS score, and lately FOUR score, are considered valuable tools in determining the severity of TBI patients, as illustrated in previous studies, [10-14] their correlation with PI denotes that the later is deemed valuable in assessing the progression of the injury and can help reflect the neurological status of the severely injured TBI patients.

It is worth mentioning that Novkoski et al[42] assessed the correlation between GCS and intracranial cerebral perfusion and concluded that there was a positive correlation between GCS and CPP (p<0.016). This means that PI indirectly correlates with CPP, thus monitoring of PI may be of value in follow-up of these patients as it may reflect cerebral hemodynamics that occur post injury.

Notably the pulsatility index showed also significant correlations with other scores that have established prognostic values in TBI. This include Rotterdam CT score, New ISS and APACHE-II. [43,44,45] Hence, pulsatility index could be of value if included among the current armamentarium for assessment and prognostications of TBI.

The essential finding in this study is that disturbance in cerebral hemodynamics created early after severe traumatic brain injury could serve as a predictor of outcome. There was obvious strong correlation between PI values and mortality and GOSE assessment at 3 months. This result was reinforced by the negative correlation between PI and GCS score and FOUR score, which reflects the correlation between PI and the

severity of injury. TCD velocities, however, did not show any significant correlation with patient's mortality or GOSE outcome.

The shortcomings of the present study can be summarized in the following points; assessment of the outcome of patients for a longer period (e.g. 6 months or 1 year) and correlating them with their outcome at 3 months would give a stronger evidence about the benefit of early GOSE assessment. Also a larger number of patients are required to confirm the prognostic value of TCD when used in combination with other models. Another limitation is that the value used in defining pulsatility index in the current study differs from that used in some of the previous papers. This is due to the fact that there is no true definition of normal values for transcranial Doppler measurements so far in the literature. This in-turn may cause difficulty when interpreting data or when comparing between the results of different studies previously conducted on that particular matter.

Conclusion

There is an association between pulsatility index, when measured within the first 24 hours of admission, and mortality as well as functional outcome at 3 months. Abnormal pulsatility index values correlate with the severity of injury (in terms of GCS score and FOUR score).

Declarations

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