The Role of Transcranial Doppler as a diagnostic tool for Septic Encephalopathy in Critically Ill Patients

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Abstract

Background: The acute phase of sepsis is often accompanied by sepsis-associated encephalopathy (SAE), which is highly associated with increased mortality. This work aimed to to evaluate the feasibility and efficacy of Transcranial Doppler (TCD) in assessing cerebral perfusion changes in septic patients and to determine its prognostic value in the outcome of these patients.

Methods: This case-control study included 100 Septic patients presenting with acute onset of disturbed conscious level, who were presented to critical care unit, Faculty of Medicine kasr alainy, Cairo University. They were divided into two equal groups: Group A included fully conscious patients with sepsis for less than 24 h., and group B included septic patients presented with acute onset of disturbed conscious level for less than 24 h. They underwent general and neurological examination, laboratory investigations and computed tomography of the brain was done on admission.

Results: Increase in PI at T0, RI at T0 , PI at T1, RI at T1 increase risk of encephalopathy with the following odds ratio 10.8, 11.5 & 20.2. PI, RI at T0 , PI & RI at T1 are statistically significant predictors of mortality among studied cases. Increase in PI at T0 , RI at T0 , PI at T1 and RI at T1 increase risk of death with the following odds ratio 31.5, 27.28 , 14.5 & 55.8.

Conclusions: Our findings suggest that TCD could be a valuable tool in the management of critically ill patients with suspected septic encephalopathy.

Keywords: Transcranial Doppler; Predictor; Septic Encephalopathy; Critically Ill Patients.

Introduction

Sepsis is a major cause of death in intensive care units worldwide. The acute phase of sepsis is often accompanied by sepsis-associated encephalopathy (SAE), which is highly associated with increased mortality [1]. SAE is the most common cause for encephalopathies in ICUs worldwide, affecting up to 50% of patients during the course of sepsis. A proven bacteremia even increases the incidence of SAE up to 70%. Patients with renal, liver, or multi-organ failure are more frequently affected than sepsis patients without organ complications [2].

The mortality rate of sepsis patients increases from 26% to 49% with SAE and is associated with higher values of the GCS, sequential organ failure assessment score (SOFA), and the APACHE II score. At hospital discharge, almost 45% of sepsis survivors show symptoms of long-term cognitive dysfunction [3]. The etiology of SAE is likely multi-factorial, and a number of pathomechanisms are involved in parallel, influence each other, and contribute to a varying degree to the development of SAE [4]. These factors may involve ischemic/hemorrhagic lesions, a compromised blood–brain barrier (BBB), neuroinflammatory processes, e.g., microglia activation and astrogliosis,changes in neuronal synaptic spine density, and dysregulation of neurotransmitter (gamma-aminobutyric acid, norepinephrine, serotonin, and dopamine pathways) [5].

The clinical presentation of SAE may already be present before sepsis criteria are fulfilled. Symptoms in the acute stage range from sickness behavior and delirium to coma and may later result in long-term cognitive impairment.symptoms include agitation, hallucinations, reduced concentration, and alteration of the sleep–wake cycle. Depending on the disease severity, patients may become somnolent or even comatose [6].

Transcranial Doppler (TCD) is a noninvasive ultrasound tool used to measure cerebral blood flow velocity in the major intracranial vessels. It is relatively inexpensive and reproducible, and its portability offers increased convenience over other diagnostic imaging methods, allowing continuous bedside monitoring of cerebral blood flow velocity, which is particularly useful in the intensive care setting [7]. It is an efficient method to evaluate cerebral perfusion in critically ill septic patients. Cerebral microcirculation alterations related to sepsis are characterized by a decrease in the density of perfused micro vessels, that can be related to an increase in cerebrovascular resistance. The pulsatility index (PI), as an indicator of

cerebrovascular resistance, has been found to be higher in septic patients, compared with normal controls or non-septic critically ill patients [8]

The aim of this study was to evaluate the feasibility and efficacy of Transcranial Doppler (TCD) in assessing cerebral perfusion changes in septic patients and to determine its prognostic value in the outcome of these patients.

Patients and Methods

This case-control study was conducted on 100 Septic patients of both sexes presenting with acute onset of disturbed conscious level (with normal computed tomography of the brain and with no acute metabolic insult) and with less than 24 h., who were presented to critical care unit, Faculty of Medicine kasr alainy, Cairo University from 1 march 2022 to 30 June 2023. Informed written consent was obtained from all participants' parents. The study was done after approval from the Ethics Committee on research involving human subjects of Faculty of Medicine kasr alainy , cairo University with IRB code: (MD-176-2022).

Exclusion criteria were age < 18 years old, known cerebral lesions (ischemic or hemorrhagic cerebrovascular event, neoplasm), cerebral infection, patient supported by intra-aortic balloon pump or ECMO, drug intoxication, known severe carotid stenosis (>70%), regnancy, hepatic, uremic and hypoglycemic brain insult.

Grouping

The participients were divided into two groups:

Group A (n=50): fully conscious patients with sepsis for less than 24 h., as a control group.

Group B (n=50): included septic patients presented with acute onset of disturbed conscious level (with normal computed tomography of the brain and excluding other causes of metabolic encephalopathy) for less than 24 h.

All studied cases were subjected to detailed history taking, including personal history (age, gender), past medical history (diabetes mellitus, hypertension, , asthma and cardiac disease), past surgical history included (history of any surgical procedures, history of medications), sources of sepsis, relevant microbiological results, and treatments, including administration of adrenergic and sedative agents, were recorded, general examination of vital signs (pulse, blood pressure, central venous pressure, respiratory rate and temperature) and head, neck, respiratory, cardiac, abdominal examination and neurological examination where the neurology status was evaluated in the first 24 h of sepsis diagnosis, using Glasgow Coma Scale (GCS) and full outline of UnResponsiveness (FOUR) score by the attending intensivists;, both scores were determined within the same hour [9, 10]

Laboratory investigations was conducted including complete blood count, C-Reactive protein, liver and kidney function tests, arterial blood gases, procalcitonine, serum lactate, and INR.

Imaging:

Computed tomography of the brain was done on admission. Blood velocity in the middle cerebral artery (VMCA) was measured with a 3-MHz TCD probe, going through the temporal bone window at both sides of the skull within the first day of sepsis. The values of the brain side with the mean VMCA were registered. We referred to day one by time zero T0. Three days later, the examination was repeated and parameter recorded and we referrd to day three by time one T1. During the examination, patients were placed in the supine position with a head elevation of no more than 30°. We calculated PI (PI = (velocity systolic-velocity diastolic)/ mean velocity) and cerebral blood flow velocity [11]. TCD was performed on the first day of admission after the normalization of systolic arterial blood pressure with or without vasopressors. An ultrasound machine (GE Logiq R P3) manufactured in the USA

with a 3-MHz TCD probe was used. The probe was directed through the temporal bone window on both sides of the skull. The temporal window was used to examine the middle cerebral artery. PI and RI were calculated as follows: (PI = (systolic velocity – diastolic velocity) / mean velocity), PI = (systolic velocity – diastolic velocity) / mean velocity, RI = systolic velocity – (diastolic velocity/systolic velocity).

We tested the predictive value of PI on the first day referred as PI T0 and the third day referred as PI T1 for encephalopathy patients and we correlated that an increased PI was related to relative microcirculation disturbances. We also calculated ICP by non invasive method derived from PI on the 1st and 3rd day T0 and T1 for encephalopathy patients. we also calculated CPP on the 1st and 3rd day T0 and T1.

Non invasive intra cranial pressure (nICP) derived by PI (PI ICP) was calculated according to a formula based on data described by Budohoski et al [12] (ICP PI=4.47•PI+12.68). According to Czosnyka et al. [13], non invasive cerebral perfusion pressure (nCPP) has been calculated as:(nCPP=ABPm•FVd/FVm+14)

The severity of illness was assessed with the sequential organ failure assessment score (SOFA) and Acute Physiology and Chronic Health Evaluation (APACHE) II scores [14]. All patients were followed up until discharged or death. The Length of ICU stay, duration of mechanical ventilation and mortality rate were recorded.

Study outcomes:

The primary outcomes included evaluating the role of TCD as diagnostic tool for sepsis associated encephalopathy, The secondary outcome parameters included, Relation between PI by TCD (and other TCD parameters) and outcome in septic patients.

Sample size calculation:

The sample size was calculated using G* power software version 3.1.9.2 and based on previous study done by Zidan et al. [15], which investigated Role of transcranial Doppler and FOUR score in assessment of sepsis-associated encephalopathy and reported large effect size between the two studied groups. So, with test family (t - tests), statistical test (Means: Wilcoxon-Mann-Whitney test (two groups)), type of power analysis (A priori: Compute required sample size - given α , power and effect size), input parameters , effect size= 1.07, α error= 0.01, power(1- β)= 0.99, resulting output parameter was total sample size of 92 (46 subject in each group). Allowing for possible data loss and drop out, the sample size was increased to 100 patients 50 in each group.

Statistical analysis:

Statistical analysis was done by SPSS v27 (IBM©, Armonk,NY,USA). Shapiro-Wilks test and histograms were used to evaluate the normality of the distribution of data. Quantitative parametric data were presented as mean and standard deviation (SD) and were analyzed by unpaired student t-test. Quantitative non-parametric data were presented as the median and interquartile range (IQR) and were analyzed by Mann Whitney-test. Qualitative variables were presented as frequency and percentage (%) and analyzed using the Chi-square test or Fisher's exact test when appropriate. A two-tailed P value < 0.05 was considered statistically significant. The Spearman's rank-order correlation is used to determine the strength and direction of a linear relationship between two non-normally distributed continuous variables and / or ordinal variables .Receiver operating characteristics curve (ROC curve) was used to calculate validity (sensitivity & specificity) of continuous variables with calculation of best cut off point .Predictive values and accuracy are assessed using cross tabulation. Binary

logistic regression was used to assess the effect of combination of more than 2 independent variables on dichotomous outcome using Stepwise / forward Wald / Enter technique .

Results

There was no statistically significant difference between studied groups as regard their age and sex. A statistically significant difference of respiratory distress frequency as primary causes of ICU admission between studied groups (P value =0.015). A statistically significant higher mean heart rate, respiratory rate and MAP among group B than group A (P<0.05).

Table 1

Table 1: Demographic characteristics and vital signs on aadmission among the studied groups

		Group A (n=50)	Group B (n=50)	test of significance
Age/years		57.90±3.97	59.46±8.26	t=1.20, p=0.23
Sex	**Male**	24(48.0%)	21(42.0%)	χ^2=0.36, p=0.69
	Female	26(52.0%)	29(58.0%)	
Vital signs	**MAP (mmHg)**	88.18±8.79	80.81±9.71	t=3.98, **p=0.001***
	HR (beats/min)	85.84±6.37	92.86±9.07	t=4.48, **p<0.001***
	RR (breath/min)	20.74±3.28	27.04±3.52	t=9.27, **p<0.001***
	Temperature (ºc)	37.65±0.45	37.69±0.69	t=0.36, p=0.72
	CVP (mmHg)	9.58±1.43	9.42±1.34	t=0.58, p=0.57

Data presented as mean ± SD or frequency (%), MAP mean arterial blood pressure , HR heart rate , RR respiratory rate , CVP: centeral venous pressure, t: Student t test, χ2=Chi-Square test, χ2=Chi-Square test , FET: Fisher exact test, *statistically significant.

Table 2 shows a statistically significant higher mean lactate, creatinine, urea, INR, PCT, CRP, WBCS, ALT, AST, total bilirubin and direct bilirubin among group B than group A (P<0.05). A statistically significant lower mean platelet count among group B than group A (P=0.001).

Table 2: Laboratory findings at admission between studied groups

	Group A (n=50)	Group B (n=50)	test of significance
Lactate (mg/dl)	1.88 ± 0.50	3.59±0.78	t=13.04, **p=0.001***
Platelet count (*10^9/L)	307.86±78.33	199.06±39.28	t=8.78,**p=0.001***
Hemoglobin(mg/dl)	12.92±1.38	12.42±1.66	t=1.65,p=0.102
Creatinine(mg/dl)	1.10±0.17	1.39±0.42	t=4.42,**p=0.001***

Urea(mg/dl)	31.82±4.77	48.84±13.31	t=8.51,**p=0.001***
INR	1.17±0.10	1.45±0.23	t=7.86,**p=0.001***
Albumin(gm/dl)	3.43±0.516	2.48±0.32	t=11.04,**p=0.001***
PCT (ng/mL)	5 (0.20-30.0)	30 (0.5-100)	z=5.51,**p=0.001***
CRP(mg/l)	138.5(50-247)	246 (89-345)	z=6.13,**p=0.001***
WBCS (*10^9/L)	14 (3.5-141)	18 (2.5-48)	z=4.09,**p=0.001***
ALT (IU/L)	32 (20-49)	52(35-130)	z=7.60,**p=0.001***
AST(IU/L)	28 (22-36)	46 (25-107)	z=7.61,**p=0.001***
Total bilirubin(mg/dl)	0.45 (0.30-1.45)	1.45 (1.2-2.66)	z=7.44,**p=0.001***
Direct bilirubin(mg/dl)	0.425 (0.10-1.2)	1.10 (0.80-1.9)	z=7.35,**p=0.001***

Dta presented as mean ± SD or median (range), INR International Normalized Ratio , CRP C Reacive protein, t:Student t test , Z:Mann Whitney U test *statistically significant ,WBCs white blood cells ,PCT procalcitonine , ALT Alanine transaminase, AST Aspartate transaminase, t:Student t test , Z:Mann Whitney U test *statistically significant.

Table 3 demonstrates a statistically significant higher mean APACHE score and SOFA score among group B than A. (P value p<0.001). Group B showed lower GCS and FOUR score . This is stastistacally significant (P value p<0.001). Death rate, mechanical ventilation and length of ICU stay were singifacntly higher in group B compared to group A (P<0.05).

Table 3: Comparison of clinical scores and outcome between studied groups

	Group A (n=50)	**Group B (n=50)**	**test of significance**
APACHE II score	15.22±3.1	25.52±6.3	t=10.38, **p<0.001***
GCS	15.0±0.0	12.78±0.5	t=16.10,**p<0.001***
FOUR score	15.98±0.1	11.96±0.5	t=14.06,**p<0.001***
SOFA score	6.28±2.0	11.22±2.2	t=11.68,**p<0.001***
30 Day mortality **Survived** **Died**	 47(94.0) 3(6.0)	 31(62.0) 19(38.0)	χ^2=14.92,**p<0.001***
MV duration (days)	4(3-6)	12(4-16)	Z=3.47,**P=0.001***
Length of ICU stay LOS (days)	7(5-15)	14(9-20)	Z=7.68,**P<0.001***

APACHE :Acute Physiology and Chronic Health Evaluation FOUR, Full Outline of UnResponsiveness; GCS, Glasgow Coma Scale; SOFA, sequential organ failure assessment, MV mechanical ventilation , NIV non invasive ventilation , LOS length of stay in intensive care, MC: Monte Carlo test , χ2=Chi-Square test , Z:Mann Whitney U test, t:Student t test , *statistically significant,

Table 4 illustrates statistically significant higher mean PSV, EDV , FV m , CPP at T0 & T1 among group A than group B.A statistically significant lower mean PI , ICP PI , RI at T0 & T1 among group A than group B.Within each of the studied groups; there is no statistically significant change in all studied parameters between T0& T1. A significant higher mean PI at T0, T1, mean ICP PI at T1 , mean RI at T0& T1 among died than survived cases.

Table 4: Comparison TCD indices between studied groups and correlation outcome and TCD indices

		Group A (n=50)	Group B (n=50)	test of significance (Student t test)
PSV	**T0**	97.87±24.16	75.11±23.82	t=4.74, **p<0.001***
	T1	97.85±23.86	75.62±22.79	t=4.76,**p<0.001***
EDV	**T0**	45.53±11.69	29.06±13.99	t=6.39,**p<0.001***
	T1	45.79±11.88	29.88±13.62	t=6.23,**p<0.001***
FV m	**T0**	62.99±15.31	43.57±15.13	t=6.38,**p<0.001***
	T1	63.18±15.16	43.80±14.84	t=6.46,**p<0.001***
PI	**T0**	0.84±0.12	1.21±0.20	t=11.39,**p<0.001***
	T1	0.83±0.126	1.21±0.224	t=10.41,**p<0.001***
ICP PI	**T0**	16.38±0.53	17.52±1.08	t=6.72,**p<0.001***
	T1	16.39±0.529	17.53±1.36	t=5.49,**p<0.001***
CPP	**T0**	78.34±8.06	67.68±9.85	t=5.93,**p<0.001***
	T1	78.62±7.88	68.23±10.30	t=5.66,**p<0.001***
RI	**T0**	0.53±0.052	0.65±0.069	t=9.94,**p<0.001***
	T1	0.52±0.052	0.65±0.074	t=10.15,p<0.001*
		Survived	**Died**	
PSV	**T0**	76.68±21.75	72.53±27.29	t=0.6,p=0.56
	T1	76.93±21.65	73.48±25.02	t=0.51,p=0.60
EDV	**T0**	29.25±10.56	28.74±18.63	t=.13,p=0.90
	T1	30.06±10.28	29.58±18.12	t=0.12,p=0.91
FV m	**T0**	45.03±13.97	41.19±16.98	t=0.87,p=0.39
	T1	45.69±13.71	40.71±16.43	t=1.16,p=0.25
PI	**T0**	1.11±0.15	1.37±0.17	t=5.50,**p=0.001***
	T1	1.08±0.16	1.41±0.17	t=6.87,**p=0.001***
ICP PI	**T0**	17.33±1.06	17.83±1.07	t=1.60,p=0.115
	T1	17.18±1.29	18.08±1.30	t=2.37,**p=0.02***
CPP	T0	69.44±9.85	64.81±9.40	t=1.64,p=0.108
	T1	69.24±9.54	66.58±11.52	t=0.88,p=0.38
RI	T0	0.625±0.06	0.695±0.06	t=3.97,**p=0.001***
	T1	0.607±0.06	0.712±0.05	t=6.71,**p=0.001***

PSV peak systolic velocity , EDV end diatolic velocity, FVm mean flow velocity , PI pulsatility index , ICP PI intracranial pressure calculated from pulsatility index, CPP cerebral perfusion pressure, RI resistive index, *Statistically significant.

There was statistically significant positive correlation between PI at T0 and length of ICU stay (r=0.341). RI at T0 and length of ICU stay (r=0.488). Mechanical ventilation duration and the following; PSV at T0 (r=0.78) , PSV at T1 (r=0.51) , EDV at T0 (r=0.55) , EDV at T1 (r=0.56) , FV m at T0 (r=0.46) , FV m at T1 (r=0.46) and RI at T0(r=0.53). Mechanical ventilation duration and delta change in PSV, EDV, FV m, PI , ICP PI, CPP and RI (p>0.05).

Table 5

Table 5: Correlation between length of ICU stay, MV duration and TCD, delta change in transcranial Doppler indices among studied cases

		Length of ICU Stay (days)	
		r	**P**
PSV	**T0**	-0.12	0.41
	T1	-0.10	0.48
EDV	**T0**	0.04	0.77
	T1	0.05	0.71
FV m	**T0**	-0.08	0.59
	T1	-0.08	0.60
PI	**T0**	0.34	**0.015***
	T1	0.27	0.06
ICP PI	**T0**	-0.12	0.42
	T1	0.02	0.88
CPP	**T0**	0.03	0.82
	T1	0.04	0.77
RI	**T0**	0.49	**<0.001***
	T1	0.26	0.07
		MV duration (days)	
		r	**P**
PSV	**T0**	0.78	**0.023***
	T1	0.51	**0.015***
EDV	**T0**	0.55	**0.009***
	T1	0.56	**0.006***
FV m	**T0**	0.46	**0.03***
	T1	0.46	**0.03***
PI	**T0**	0.38	0.08
	T1	0.31	0.16
ICP PI	**T0**	0.05	0.82
	T1	0.23	0.31
CPP	**T0**	-0.07	0.75
	T1	-0.17	0.44
RI	**T0**	0.53	**0.01***
	T1	0.27	0.23
Delta PSV		0.04	0.88
Delta EDV		-0.01	0.96
Delta FV m		0.27	0.23
Delta PI		-0.23	0.31
Delta ICP PI		-0.35	0.11
Delta CPP		0.02	0.93
Delta RI		0.22	0.34
Delta PSV		-0.08	0.59
Delta EDV		-0.03	0.85
Delta FV m		0.13	0.37
Delta PI		-0.17	0.24
Delta ICP PI		-0.09	0.54
Delta CPP		-0.06	0.59
Delta RI		0.26	0.07

PSV peak systolic velocity , EDV end diatolic velocity, FVm mean flow velocity , PI pulsatility index , ICP PI intracranial pressure calculated from pulsatility index, CPP cerebral perfusion pressure, RI resistive index, r: Spearman correlation co-efficient , *statistically significant

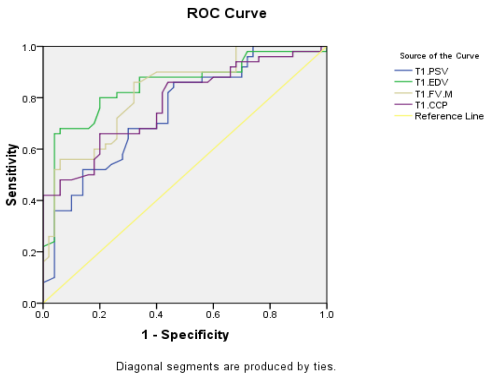
PI at T0 , RI at T0 , PI , RI at T1 are statistically significant predictors of encephalopathy among studied cases. Increase in PI at T0, RI at T0 , PI at T1, RI at T1 increase risk of encephalopathy with the following odds ratio 10.8, 11.5 & 20.2 , respectively. PI, RI at T0 , PI & RI at T1 are statistically significant predictors of mortality among studied cases .Increase in PI at T0 , RI at T0 , PI at T1 and RI at T1 increase risk of death with the following odds ratio 31.5, 27.28 , 14.5 & 55.8 , respectively. **Table 6**

Table 61: Binary logistic regression of transcranial doppler indices in predcition of encephgalopathy and moratlity at T0 , T1

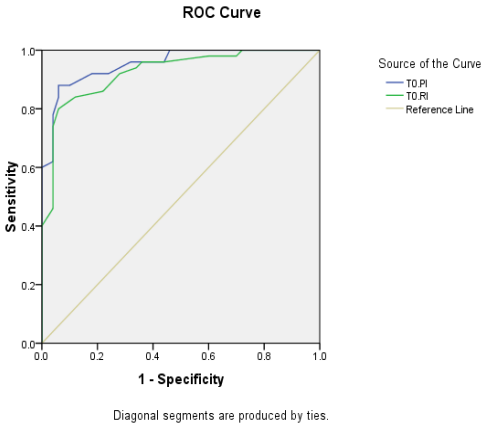
Predictors	B	p value	odds ratio	95.0% C.I.for odds ratio	
				Lower	Upper
Prediction of encephgalopathy					
T0.PSV	0.58	0.72	1.79	0.07	43.39
T0.EDV	0.21	0.95	1.23	0.002	620.86
T0.FV.M	-1.18	0.81	0.31	0.00	3854.71
T0.PI	26.62	**0.007***	10.8	8.6	15.0
ICP.PI T0	-5.87	**0.13**	0.01	0.00	.37
T0.CPP	0.07	0.5	1.08	0.87	1.33
T0.RI	28.41	**.007***	11.5	9.8	20.69
T1.PSV	0.01	0.89	1.01	0.85	1.21
T1.EDV	-0.08	0.40	0.93	0.77	1.11
T1.FV.M	-0.05	0.78	0.95	0.68	1.33
T1.PI	15.62	**0.002***	20.2	12.47	24.56
T1.ICP	-1.25	**0.24**	0.29	0.09	.93
T1.CCP	0.01	0.94	1.01	0.9	1.13
T1.RI	12.88	**0.019***	39.2	0.02	40.5
Prediction of mortality					
T0.PSV	-0.06	0.68	0.94	0.69	1.27
T0.EDV	0.03	0.88	1.03	0.73	1.46
T0.FV.M	0.12	0.74	1.12	0.56	2.24
T0.PI	14.95	**<.001***	31.5	7.6	35.6
ICP.PI T0	-0.94	0.20	0.39	0.09	1.65
T0.CPP	0.01	0.92	1.01	0.9	1.13
T0.RI	17.31	**<0.001***	27.28	10.4	30.2
T1.PSV	-0.06	0.58	.94	0.76	31.5
T1.EDV	0.24	0.18	1.27	0.9	24.5
T1.FV.M	0.003	0.99	1.01	0.62	35.4
T1.PI	7.28	**0.011***	14.5	1.41	15.8
T1.ICP	0.64	0.32	1.90	0.53	6.9
T1.CCP	0.11	0.07	1.12	0.99	10.5
T1.RI	45.47	**.029***	55.8	25.4	65.9

PSV peak systolic velocity , EDV end diatolic velocity, FVm mean flow velocity , PI pulsatility index , ICP PI intracranial pressure calculated from pulsatility index, CPP cerebral perfusion pressure, RI resistive index, *Statistically significant.

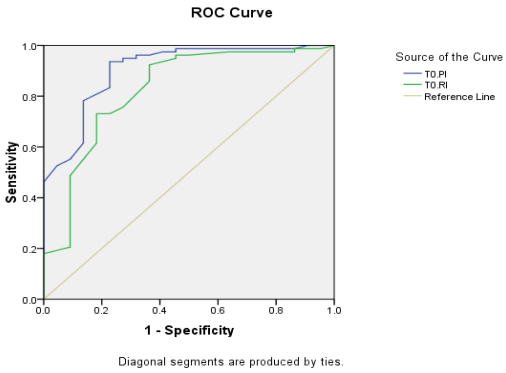
The best detected cut off points are as following ; 86.8,31.2 , 44.8, 58.9 , 1.3 ,19.6 & 0.8 . The highest sensitivity is detected for PI, RI at T0 (90% each) and the least is detected for PSV (80%). That area under ROC curve for PSV, EDV, FV m ,CCP, PI, ICP and RI at T1 in predcition of septic encephgalopathy in critically ill patients are good to excellent (AUC=0.777 to 0.942) . The best detected cut off points are as following ; 96.6 ,34.9 , 55.4, 52.9 , 1.3 , 20.1 & 0.8 . The highest sensitivity is detected for PI,RI at T1 (89% each) and the least is detected for EDV . The highest specificity is detected for PI at T1 (88%) and the least is detected for PSV at T1. The highest specificity is detected for PI at T0 (86%) and the least is detected for EDV at T0.That area under ROC curve for PSV, EDV, FV m ,CCP, PI, ICP and RI at T1 in predcition of septic encephgalopathy in critically ill patients are good to excellent (AUC=0.777 to 0.942) . The best detected cut off points are as following ; 96.6 ,34.9 , 55.4, 52.9 , 1.3 , 20.1 & 0.8 . The highest sensitivity is detected for PI,RI at T1 (89% each) and the least is detected for EDV . The highest specificity is detected for PI at T1 (88%) and the least is detected for PSV at T1. that area under ROC curve for delta PSV, EDV, FV m ,PI , ICP PI, CPP and RI in diagnosing critically ill patients s with septic encephalopathy are poor with no statistically significant difference in differentiation. **Figure 1**


ROC Curve
Sensitivity
1 - Specificity
Source of the Curve
T1.PSV
T1.EDV
T1.FV.M
T1.CCP
Reference Line
Diagonal segments are produced by ties.

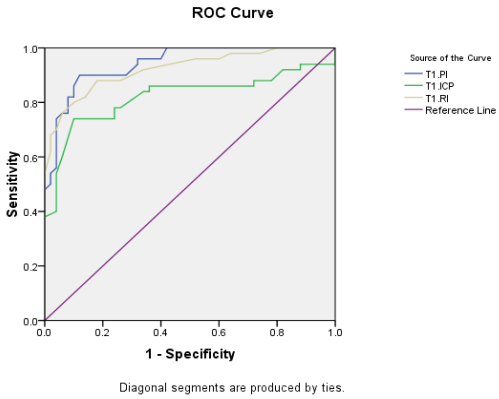
B


ROC Curve
Sensitivity
1 - Specificity
Source of the Curve
T0.PI
T0.RI
Reference Line
Diagonal segments are produced by ties.

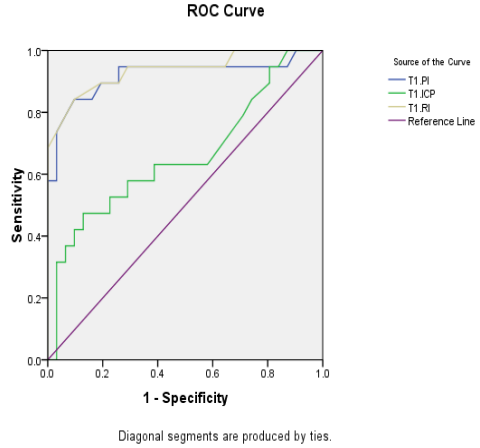
A


ROC Curve
Sensitivity
1 - Specificity
Source of the Curve
T0.PI
T0.RI
Reference Line
Diagonal segments are produced by ties.

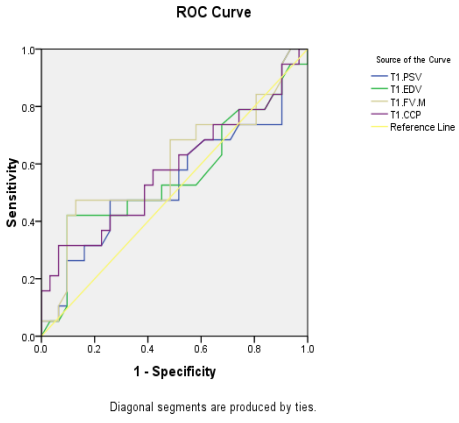
D


ROC Curve
Sensitivity
1 - Specificity
Source of the Curve
T1.PI
T1.ICP
T1.RI
Reference Line
Diagonal segments are produced by ties.

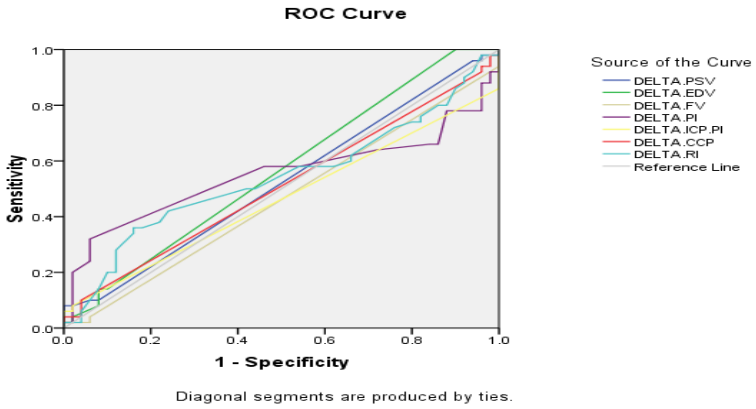
C


ROC Curve
Sensitivity
1 - Specificity
Source of the Curve
T1.PI
T1.ICP
T1.RI
Reference Line
Diagonal segments are produced by ties.

F


ROC Curve
Sensitivity
1 - Specificity
Source of the Curve
T1.PSV
T1.EDV
T1.FV.M
T1.CCP
Reference Line
Diagonal segments are produced by ties.

E



G

Figure 12: ROC curve for A:TCD indices at T0 in prediction of septic encephalopathy, B: transcranial doppler indices at T1 in predection of septic encephalopathy in critically ill patients, C: transcranial doppler indices at T1 in predection of septic encephalopathy in critically ill patients, D: transcranial doppler indices at T0 in predcition of mortality, E: transcranial doppler indices at T1 in predcition of mortality, F: transcranial doppler indices at T1 in predcition of mortality, G: delta change in transcrainal doppler indices in prediction of septic encephalopathy in critically ill patients

Discussion

Sepsis is a major cause of death in intensive care units worldwide. The acute phase of sepsis is often accompanied by sepsis-associated encephalopathy (SAE), which is highly associated with increased mortality [16].

Transcranial Doppler (TCD) is a noninvasive ultrasound tool used to measure cerebral blood flow velocity in the major intracranial vessels. It is relatively inexpensive and reproducible, and its portability offers increased convenience over other diagnostic imaging methods, allowing continuous bedside monitoring of cerebral blood flow velocity, which is particularly useful in the intensive care setting [17].

There was no statistically significant difference between studied groups as regard their age and sex. The mean age of group A is 57.90 ± 3.97 years versus 59.46 ± 8.26 years for group B. For group A, 52% are females versus 58% of group B.

Pierrakos et al. [8] examined about forty septic patients with transcranial doppler on the first and third day of sepsis diagnosis. The results showed that patients with high PI (>1.3) were older (72 ± 13 vs. 62 ± 16 years, p = 0.04).

A statistically significant difference of sepsis and respiratory distress frequency as primary causes of ICU admission between studied groups. Sepsis is detected among 50% versus 28% of group B & A, respectively. Respiratory distress was detected among 40% of group A versus 18% of group B. There is a statistically significant higher frequency of malignancy, chemotherapy, and other associated medial history among group B than group A.

Gai et al. [18] carried out a case contol study where among 72 patients with sepsis, there were 42 (58.3%) non-survivors and 30 (41.7%) survivors. The mean ages of the survivors and non-survivors were 71.07 ± 7.52 and 71.45 ± 6.89 years, respectively (P = 0.822)..

There was a statistically significantly higher mean APACHE score and SOFA score among group B than A. A statistically significant lower mean GCS and FOUR score among group B than A.

Zidan et al. [19]conducted a case control study including two groups. The first group included 58 adult patients with sepsis for fewer than 24 h, suffering from acute onset of disturbed conscious level (SAE) with normal computed tomography of the brain and with no acute metabolic derangement. The second group included 58 fully conscious patients suffering from sepsis for fewer than 24 h. The results showed that The GCS score area under the curve (AUC) was significantly higher compared with SOFA score (P<0.0001). The FOUR score AUC was significantly higher compared with SOFA score (P<0.0001).

Gai et al. [18] found mean APACHE II and SOFA scores were higher in the non-survivors than in the survivors (APACHE II, 22.67 ± 4.28 vs. 17.43 ± 3.17 and SOFA score, 10.62 ± 1.67 vs. 7.83 ± 2.29, respectively; P < 0.001 for both).

There was a statistically significant higher mean lactate, creatinine, urea, INR, PCT, CRP, WBCS, ALT, AST, HR, Total bilirubin, direct bilirubin among group B than group A. A statistically significant lower mean platelet counts among group B than group A.

Gai et al. [18] showed that C-reactive protein, and albumin level between both the groups. Compared with survivors, non-survivors experienced higher dose of norepinephrine. The lactate level showed significant difference between non-survivors and survivors (3.79 ± 1.05 mmol/L and 2.74 ± 0.92 mmol/L, respectively; $P < 0.001$).

Refaat et al. [20] highlighted that Hb and CRP was high in-patient group compared to healthy patients. Chen et al. [21] revealed that maximum bilirubin, maximum creatinine was significantly higher in the non-survivors; whereas the minimum hematocrit, minimum albumin, minimum hemoglobin, minimum platelet were significantly lower in the non-survivors. In addition, non-survivors were more likely to have liver disease and malignant tumors. Non-survivors had significantly higher initial lactate, maximum lactate, lactate load, and normalized lactate. There was a significant correlation between normalized lactate load and maximum lactate ($r = 0.850$, $p < 0.001$), and between normalized lactate load and initial lactate ($r = 0.794$, $p < 0.001$).

There was a statistically significant higher mean PSV, EDV, FV m, CPP, RI at T0 & T1 among group A than group B. A statistically significant lower mean PI, ICP PI, RI at T0 & T1 among group A than group B. Within each of the studied groups, there is no statistically significant change in all studied parameters between T0& T1 except for EDV increased from 29.06±13.99 to 29.88±13.62.

Ratnaparkhi et al. [22] carried out a cross-sectional analytical study recruiting two groups: Group I (with 54 neonates) - neonates with EONS and group II (with 69 neonates) - age-matched neonates without any signs of sepsis. The results showed that a statistically

significant difference exists in the median values of PSV, EDV, PI, and RI among neonates with sepsis and neonates without sepsis less than 0.05. There was a statistically significant difference between studied groups as regard outcome, mechanical ventilation frequency, Death rate, and Median length of ICU was higher among group B than group A.

Sakr et al. [23] highlighted that sepsis patients in intensive care unit length of stay were longer (6 [3–13] vs 2 [1–4] days, P <.001) in patients with than in those without sepsis. Intensive care unit mortality rates were 25.8% in patients with sepsis and 12.1% in those without (P <.001); hospital mortality rates were 35.3% vs 16.7%, P <.001). Intensive care unit and hospital mortality rates varied from 11.9% and 19.3% (Oceania) to 39.5% and 47.2% (Africa), respectively.

However, Algebaly et al.[24] found that they also had significantly higher frequency of cases with mechanical ventilation and shorter duration of ICU stay.

There was a statistically significant positive correlation between PI at T0 and T1 and length of ICU stay (r=0.341, 0.488). There was a statistically significant higher mean PI, ICP PI at T0, T1 among died than improved cases.

Sanz et al. [25] performed brain imaging of 49 pediatric septic shock patients, and the most frequent acute brain lesion patterns, found on neuroimaging, were ischemia and cerebritis (i.e., cerebral edema/damage in the clinical context of infection)

In the present study, it was found that area under ROC curve for PI and RI at T 0 in differentiating cases with septic encephalopathy from sepsis are excellent (AUC=0.953 & 0.925). The best detected cut off points are as following ; 1.315 & 0.682 , yielding sensitivities of 88.0 & 84% and specificities of 92% &88.0% , respectively .

Algebaly et al.[24] showed that PI and RI showed good performance as predictors of subsequent SAE development [area under the curve (AUC): 0.72 and 0.73, respectively.

In the present study, it was found that PI, RI at T0 , PI & RI at T1 are statistically significant predictors of mortality among studied cases .Increase in PI at T0 , RI at T0 , PI at T1 and RI at T1 increase risk of death with the following odds ratio 31.5, 27.28 , 14.5 & 55.8 , respectively.

Algebaly et al. [24] showed that PRISM score, FOUR score, PI, and RI were significant predictors of mortality in the univariate analysis. However, in the multivariate analysis, only PRISM score and RI remained significant. ROC curve analysis showed good performance of PI and RI as predictors of mortality at the end of follow-up.

The statistically significant variables included APACHE II score in Gai study were SOFA score, lactate, low PSV, EDV, and RI which evidenced to be the potential risk factors for mortality by the univariate analysis ($P < 0.05$) were used to establish a stepwise multivariate logistic regression model. However, only PSV was included in the model. Patients with higher PSV (100.8 cm/s) have a 70.5% lower chance of dying (OR = 0.295; 95% CI: 0.094–0.925) (survivors) than patients with lower PSV (78.92 cm/s). The ROC analysis showed that the AUC of PSV (0.99) was the largest among variables of the APACHE II score, SOFA score, lactate level, and EDV. The sensitivity, and specificity of PSV were 0.99, and 0.96, respectively [18].

Limitations: this study included small sample size, was single center cooperation, lack of follow up period. therefore, we recommend providing a larger sample size with multicenter cooperation to validate our results, providing follow up period (e.g. 6 months), and further research is recommended to validate the efficacy of TCD as predictor for septic encephalopathy in critically ill patients.

Conclusions:

PI and RI at both T0 and T1 were significantly associated with clinical outcomes, demonstrating promise as biomarkers for diagnosis, prognosis, and disease monitoring. PI and RI at T1 were excellent in differentiating patients with septic encephalopathy from those with sepsis, while PI and RI at T0 were excellent in predicting mortality. These findings suggest that TCD could be a valuable tool in the management of critically ill patients with suspected septic encephalopathy.

Financial support and sponsorship: Nil

Conflict of Interest: Nil

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List of abbreviation:

APACHE II	Acute Physiology and Chronic Health Evaluation II
AUROC	Area Under the Receiver Operating Characteristic
CT	Computed Tomography
CTA	Computed Tomography Angiography
EDV	End-Diastolic Velocity
FOUR	Full Outline of Unresponsiveness Score
GCS	Glasgow Coma Scale
HR	Heart Rate
ICA	Intracranial Carotid Artery
ICAS	Intracranial Atherosclerotic Stenosis
ICDSC	Intensive Care Delirium Screening Checklist
ICU	Intensive Care Unit
MCA	Middle Cerebral Artery
MCI	Mild Cognitive Impairment
MFV	Mean Flow Velocity
PCA	Posterior Cerebral Artery
PI	Pulsatility Index
PMD/TCD	Power Motion-Mode Transcranial Doppler
PSV	Peak Systolic Velocity
qSOFA	Quick Sequential Organ Failure Assessment
RI	Resistance Index
SAE	Sepsis-Associated Encephalopathy
SOFA	Sequential Organ Failure Assessment
TCD	Transcranial Doppler
VA	Vertebral Artery