SREE CHITRA TIRUNAL INSTITUTE FORMEDICAL SCIENCES AND TECHNOLOGY THIRUVANANTHAPURAM, KERALA

CORRELATION BETWEEN PULSATILITY INDEX IN TRANSCRANIAL DOPPLER AND POST STROKE OUTCOMES IN PATIENTS WITH ACUTE LACUNAR STROKES

Thesis submitted in partial fulfilment of the rules and regulations for

DM Degree Examination of

Sree Chitra Tirunal Institute for Medical Sciences and Technology

By

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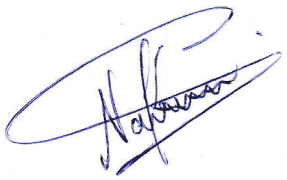
DECLARATION

I, Dr. Naveen Kumar. P, hereby declare that this project was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.



Thiruvananthapuram,
Date: 30-7-2021

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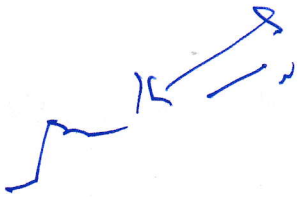
Forwarded :

The candidate, Dr. Naveen Kumar. P, has completed the project under my guidance.



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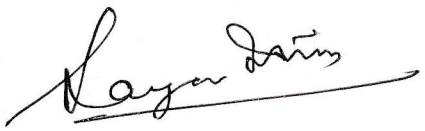
The candidate, Dr. Naveen Kumar. P, has carried out the minimum required project.



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Dr. Naveen Kumar. P

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SYNOPSIS

Background and purpose:

Lacunar infarcts, a manifestation of cerebral small vessel disease (cSVD) is associated with poor post-stroke functional outcomes and depression. Pulsatility index (PI), calculated using Transcranial Doppler(TCD) estimates the downstream cerebral microcirculatory resistance. We aimed to determine whether changes in PI correlates with post-stroke outcomes with respect to neurological deficits, disability and depression, following an acute lacunar stroke.

Materials and Methods:

Patients aged 18-80 years within 2 weeks of onset of an acute lacunar stroke were recruited. Baseline and 3 month NIHSS, mRS and BDI-2 scores were collected. PI was calculated from both Middle Cerebral Arteries and used to correlate with outcomes at 3 months.

Results:

Among the 45 patients enrolled, the mean PI was 1.3. The mean scores of NIHSS, mRS and BDI-2 at baseline were 5.6(SD=3.4), 3.4(SD=0.9) and 7.3(SD=7.1) respectively. At 3 months, the mean scores of NIHSS, mRS and BDI-2 were 1.7(SD=2.1), 1.4(SD=1.25) and 5.4(SD=5.1) respectively. Patients with PI ≥1.3 were more likely to have higher stroke severity, poor functional and depression scores both at baseline and at 3 months follow up. The severity of

leukoaraiosis did not seem to influence the outcomes at 3 months. The baseline NIHSS scores correlated significantly with the 3 month NIHSS and BDI-2 scores.

Conclusion:

Patients with elevated PI had more deficits, poorer mRS and depression scores at all points of evaluation. There was no influence of PI on the rate of change of scores over time. The severity of the stroke deficits at baseline influences the post stroke outcomes at 3 months.

INTRODUCTION

INTRODUCTION

Cerebral small vessel disease (cSVD) is a disorder of the cerebral microcirculation involving perforating arterioles, capillaries and venules that can present as ischemic as well as a hemorrhagic stroke, cognitive impairment, depression, gait difficulty and bladder symptoms(1). They have a spectrum of imaging manifestations that are better defined by Magnetic Resonance Imaging of the brain. Lacunar strokes, which constitute about 20% of ischemic strokes(2), are thought to be caused by cerebral small vessel disease are defined by infarcts occurring in subcortical regions (deep gray matter structures like basal ganglia, thalamus, brainstem, subcortical white matter and cerebellar white matter) due to occlusion of perforating vessels with infarct size less than 15mm in brain MRI(3). The white matter hyperintensities (WMH) seen in Magnetic resonance Imaging (MRI), called leukoaraiotic changes, are thought to be a sequelae of cerebral Small Vessel Disease (cSVD). Previous studies have shown that leukoaraiotic changes in brain MRI were associated with poor post-stroke functional outcomes, recurrent strokes, cognitive impairment, depression and mortality(4).

Post stroke depression is a common problem that is often overlooked. Studies have shown that approximately one-third of patients experience depression at some point after the stroke(5), and the number may increase to one half if the follow up is extended to 10-15 years(6). The frequency of post stroke depression is maximum in the first year and subsequently declines thereafter. Depression causes poor long term functional outcomes, higher mortality and often interferes in the rehabilitation and

recovery of the stroke patient and it is recommended to actively screen, diagnose and treat depression in every stroke patient(7).

Transcranial Doppler (TCD) is a non-invasive modality that can be used to estimate the resistance of the cerebral microcirculation as a surrogate marker. Pulsatility index (PI), calculated using TCD study has been shown to estimate the downstream cerebral microcirculatory resistance and this has been shown to correlate with white matter disease estimated by MRI(8).

In the context of acute lacunar stroke, increased PI has been found to predict infarct volume (9)with positive correlation and baseline white matter changes were found to predict depression in patients with lacunar stroke(10).

However, whether microcirculatory disturbances in cSVD, as reflected by a deranged PI in Transcranial Doppler (TCD) could serve as prognosticating factor for post stroke neuropsychological and functional recovery, has not been studied before.

The current study was undertaken to address this lacunae and to look for a correlation between PI in TCD and post stroke outcomes following acute lacunar strokes.

We hypothesized that elevated Pulsatility Index (PI) in Transcranial Doppler (TCD), which is a true surrogate marker for cerebral small vessel disease can predict post-stroke outcomes in terms of neurological deficits, disability and depression following acute lacunar strokes.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Stroke is the second leading cause of death and third leading cause of disability worldwide(11). In India, the incidence of stroke ranges between 105-152 per 1,00,000 persons per year with a prevalence of 44-559 per 1,00,000 persons based on review of studies in the last two decades in different parts of the country(12).

Lacunar strokes:

Small vessel disease strokes is one among the five subtypes of ischemic stroke, with lacunar stroke being its typical example, accounting for 15-28% of all ischemic strokes depending on the population studied(13–15). Fisher analysed lacunes and described the histopathological features of a lacunar stroke as early as 1969(16). Depending on the infarct location, lacunar stroke can manifest as various syndromes- the five most classical being pure motor hemiparesis, pure sensory stroke, sensorimotor stroke, ataxic hemiparesis and dysarthria clumsy hand syndrome.

The criteria for a lacunar stroke is based on the definition used in the TOAST classification(3):

- Typical Lacunar syndrome presentation
- Absence of cortical signs such as aphasia, agnosia, apraxia, hemianopia, stupor, loss of consciousness, coma or seizures
- Brain imaging with CT or MRI being normal or showing a brainstem or subcortical hemispheric lesion that is less than 15mm in the

maximum diameter

- Potential cardioembolism should be ruled out
- No significant atherosclerotic disease as assessed by absence of >50% stenosis of ipsilateral extracranial arteries

Lacunar strokes were previously regarded as benign, having a better prognosis when compared to other etiologic subtypes. However a systematic review done later showed that the prognosis is better only in the first few years and by 5 years, 25% of the patients had died predominantly due to cardiovascular complications and 20% had a recurrent stroke(17). The prognosis with respect to the functional outcome was better when compared to other supratentorial infarcts, although patients with lacunar strokes were much likely to have asymptomatic progression of cerebral small vessel disease very early, making them prone for cognitive impairment, dementia, gait difficulty, disability and recurrent lacunar strokes.

Pathophysiology of cerebral small vessel disease:

Cerebral small vessel disease is characterised by involvement of perforating arterioles, capillaries and venules and is seen on imaging as white matter hyperintensities, microinfarcts, lacunes, microbleeds and perivascular spaces(18). The pathology of small vessel disease is attributed to lipohyalinosis, arteriosclerosis, fibrinoid necrosis of the vessels(19). The involvement occurs in 3 stages with lipohyalinosis first occurring in basal ganglia, then involving deep white matter, thalamus, cerebellum and leptomeningeal arteries and finally involving the brainstem(20). The calibre of small vessels is altered and the cerebral autoregulatory

capacity is impaired leading to low diastolic flow and subsequent changes in brain parenchyma including leukoaraiosis(21). Endothelial dysfunction contributes to the increased arterial stiffness, leading to elevated pulsatility in pulse waves(1). The blood brain barrier is disrupted much more in patients with lacunar strokes when compared with cortical strokes(22).

The pathology often extends beyond what is visible by brain imaging to involve normal appearing areas in brain MRI(23), as it involves the cerebral microcirculation that is beyond the resolution of conventional MRI. Often the white matter tracts which pass through the lesions undergo secondary axonal degeneration and it has been shown that acute infarcts can lead to remote cortical thinning(24). There occurs disruption of both structural and functional connectivity between the brain networks leading to impairment in functional performance, leading to the concept that small vessel disease could be viewed as a disconnection syndrome(25). cSVD makes a patient susceptible for both lacunar strokes as well as intracerebral hemorrhages.

Leukoaraiosis:

White matter hyperintensities (WMH) also known as leukoaraiosis are the most common imaging manifestations of cerebral small vessel disease. They are defined as areas of increased signal on T2 and FLAIR sequences in MRI, with decreased signal in Computed topography (CT) brain. Hypertension and advanced age are the strongest risk factors for the presence of leukoaraiosis especially in the context of a prior history of stroke. The presence of leukoaraiosis can be taken as an intermediate

surrogate marker of stroke and the type of ischemic stroke most consistently predicted by leukoaraiosis is lacunar stroke as the two share the same pathology(26).

It has been shown that presence of leukoaraiosis in patients with first ever lacunar stroke is associated with poor short term and long term functional outcomes, in the form of dementia, recurrent stroke risk and cardiovascular mortality(27). The volume of leukaraiotic changes was shown to be an independent predictor of clinical outcome after an acute ischemic stroke, that was shown to be significant even after adjusting for other factors like age, the volume of the infarct and the stroke severity(28). Severe leukoaraiosis was shown to independently predict morbidity and mortality, especially pneumonia, death, death from pneumonia and falls, independent of pre-existing neurologic deficits based on a longitudinal follow up study(29).

Impact of cerebral small vessel disease on outcomes:

A systematic review showed that the presence of white matter hyperintensities in patients with first ever lacunar stroke was associated with poor long term functional outcomes, cognitive impairment, dementia, recurrent stroke and also mortality, with linear dose response relationship noted between the severity of the white matter disease and the extent of cognitive impairment(4). Patients who develop stroke in the setting of a cSVD were more likely to have a poor functional outcome especially if they had pre-existing cognitive decline and higher stroke severity(30).

Another study reported that good blood pressure control was associated with reduction of WMH at 1 year follow up suggesting that there may be a component of

reversibility in these lesions translating into better clinical outcomes(31). The LADIS study(Leukoaraiosis and Disability study) showed that more severe age related white matter disease were correlated with poor balance, gait difficulty and decrease in walking speed, with regular physical activity improving mobility issues(32).

Post stroke depression:

This is defined as depression occurring in the setting of a clinically apparent stroke(33). It has a multifactorial pathophysiological basis which can be biological or psychosocial, with biological causes that respond better to pharmacological treatments and psychological causes that respond to psychotherapy and social interventions(7). The "vascular depression" hypothesis states that disruption of the prefrontal circuits involving the cortico-striato-pallido-thalamo-cortical circuits by single or multiple lesions is a major contributor to depression(34).

Depression after stroke is not just a psychosocial reaction to the new onset deficit and disability, as evidenced by studies which showed depression in patients with silent infarcts(35), white matter disease burden(34), Transient Ischemic Attacks(TIAs) and non-disabling minor strokes(36,37), patients with anosognosia(38). The severity of stroke, level of physical disability, prior history of depression and cognitive impairment were the most consistent predictors of post stroke depression across multiple studies(7).

Silent lacunar infarcts in the basal ganglia, thalamus, subcortical and deep white matter have been shown to increase the risk of depression and a total burden caused

by multiple infarcts were more often associated with post stroke depression than single infarcts occurring in these regions(39,40).

Pavlov et al, specifically assessed patients with first ever lacunar stroke and observed that baseline functional status, white matter disease burden and subsequent development of cognitive impairment were factors that predicted late onset depression(10).

Depression interferes with the physical rehabilitation, cognitive retraining and therapies, and also in the making of lifestyle and behavioural changes necessary to make maximal recovery from stroke. The presence of post stroke depression has an adverse bearing on the functional outcomes and this in turn leads to a vicious cycle between poor recovery and depression(41).

A 2013 systematic review by Bartoli et al(42), found that post stroke depression was associated with higher risk of mortality with a Hazard ratio of 1.5(1.02-1.26).

The latest recommendations from the AHA/ASA state that depression after stroke should be actively screened, and if present should be treated to maximize good recovery and functional outcomes(7).

Quantifying the white matter disease:

Cerebral small vessel disease increases the risk of dementia, recurrent stroke and mortality and hence methods to detect them early are required, to facilitate treatment for vascular risk factors. MRI is the conventional imaging modality that provides an objective assessment of the white matter disease burden that can be done using semi

quantitative scales or volumetry. Semi quantitative methods include using visual rating scales like ARWMC(43), Fazeka's(44) and Schelten's(45). Studies have shown good correlation between the two methods(46,47) and although volumetric methods could detect slight differences in white matter hyperintensities(48), they may not be available in many centers.

Transcranial Doppler:

Conventional MRI has limitations in the imaging of the cerebral microcirculation in that small infarcts are often missed. Although it gives a better impression of the white matter burden and the amount of infarcts, the hemodynamic status of the cerebral small vessels are not known. Moreover, to screen for cerebral small vessel disease using MRI alone has limitations in that it is expensive and not available in all centers. This has therapeutic implications also in that early detection of cSVD may enable institution of strict control of vascular risk factors and close monitoring to look for development of cognitive impairment, gait difficulty, recurrent stroke and associated morbidities.

Transcranial Doppler (TCD) is an inexpensive, portable, bed side, non-invasive modality of imaging that is increasingly used to assess the hemodynamic status of cerebral micro circulation(49) with good inter-observer reliability(50) and without any risk of radiation exposure. TCD provides physiologic parameters such as peak systolic velocity, end diastolic velocity and mean velocity from the assessed intracranial vessels.

Pulsatility index (PI) described by Gosling and King is a useful parameter to determine downstream vascular resistance in the cerebral microcirculation that is calculated by using the above TCD parameters(51). It is calculated as (systolic flow velocity- diastolic flow velocity) divided by mean flow velocity. PI was postulated to be flow and pressure independent marker of peripheral resistance(52).

The cerebral vascular bed is a low resistance high flow bed(53), and the small vessels are the major determinants of cerebrovascular resistance. Lacunar strokes were shown to be due to lipohyalinosis or microatherosclerosis of small vessels which increases the resistance of the small vessels, leading to a pulsatile flow. Higher the cerebral vascular resistance, higher will be the Pulsatility index. Pulsatility index can be calculated using TCD or MRI. Phase contrast MRI can also be used to estimate the velocity and flow in intracranial vessels which can then aid in the calculation of PI.

PI has been shown to be elevated with increasing age, hypertension and in recent stroke(54,55). Elevated PI determined in patients with acute lacunar strokes was shown to correlate with final infarct volumes and it may as well be a surrogate marker for the extent of ischemic injury(9). Previous studies have demonstrated that PI derived from TCD has shown a good correlation with white matter hyperintensities and that elevated PI was an independent predictor for cSVD(8). A MCA PI of $\geq$1.15 indicated combined hemispheric cSVD with 95 specificity. On the contrary, a study of healthy aged population showed that PI correlated with

severity of baseline WMH but was not predictive of progression of WMH when followed up, after adjusting for age and hypertension(56).

Pulsatility index has also been shown to be influenced by arterial stiffness and increased pulse pressure in the systemic circulation(57). The Rotterdam Scan study showed that increase aortic pulsatility due to arterial stiffness can promote progression of WMH(58).

In a study of 100 stroke patients with white matter changes, 86 of whom had an acute lacunar stroke and 50 controls, Xiong et al demonstrated that an MCA PI of 1.15 reliably distinguished those with and without WMH with a sensitivity and specificity of 74 and 82% respectively(59). Elevated PI with reduced mean velocities were found especially in those who were hypertensive for ≥5 years duration(60).

Increased PI had been found in diabetic patients related to microangiopathic changes(61), especially in the context of an acute lacunar stroke, making it a predictor for the same, when compared against diabetics without a lacunar stroke(62).

The pulsatility of small vessels is essential in facilitating cerebrospinal fluid(CSF)-interstitial fluid(ISF) exchange through enhancement of the glymphatic system that serves to remove Aβ, cell debris and other waste products. Altered pulsatility might interfere with these mechanisms, leading to cSVD(63). An increased PI was shown to predict cognitive impairment in hypertensive patients in a study(64). The MCA PI has been shown to predict cognitive impairment in patients with acute lacunar strokes and syndromes, when tested across a range of cognitive domains(65).

Transcranial Doppler PI has been shown to be elevated both in patients with Alzheimer's and Vascular dementia(66,67), but it can often distinguish between the two with PI values >2 SD higher than normal, noted in vascular dementia(68,69).

Whether an elevated PI can help in the prediction of post stroke functional outcomes and depression is not studied till now.

TCD is a useful investigative tool especially in resource poor settings where it can be used to screen for cSVD using Pulsatility index to enable in the early institution of preventive measures.

AIMS AND OBJECTIVES

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1. To determine whether a high Pulsatility Index in TCD correlates with post-stroke outcomes with respect to neurological deficits, disability and depression, following acute lacunar stroke.

MATERIALS AND METHODS

MATERIALS AND METHODS

Patients presenting to Neurology/Stroke services of SCTIMST who are diagnosed to have acute lacunar stroke were taken up for the study. We recruited consecutive patients who fulfilled inclusion and exclusion criteria. All the patients were recruited after an informed consent from the patient/care giver is obtained.

Inclusion Criteria:

1. Patients aged 18 to 80 years with acute or recent lacunar strokes (as per TOAST classification(1)
2. Evaluation within 2 weeks of stroke onset attending to Neurology, Stroke services, SCTIMST.
3. Imaging confirmation of acute lacunar stroke by MRI Brain.

Exclusion criteria:

1. Age < 18 or >80 years.
2. Patients with evidence for large vessel atherosclerosis (>50% stenosis of the extra or intracranial vessels with any of the imaging modalities)
3. Patients with large artery territory infarcts or major Intra-Cerebral Hemorrhage (ICH) at any point of time
4. Patients with prior psychiatric illness or cognitive impairment
5. Presence of heart failure/fever/ respiratory distress or any other medical condition that can interfere with the neuropsychological assessment of the patient.

6. Impaired level of consciousness or significant aphasia.

Recruitment of patients were be done by the principal investigator and the co-principal investigator. Hospital records were reviewed for eligibility. All eligible patients were recruited for the study.

Sample size:

Sample size determination was done and the number required for this study using a correlation coefficient 0.5 with a significance level of 0.05 and a power of 90% was 37 patients. Hence we proposed to collect 50 patients.

Methodology:

Patients attending to neurology, stroke services at SCTIMST with diagnosis of lacunar stroke were recruited in the study, after applying inclusion and exclusion criteria. Information regarding clinical, demographic & risk factors were collected. Baseline neurological and disability status at presentation to Neurology services were documented using National Institute of Health Stroke Scale (NIHSS) and modified Rankin's scale (mRS) respectively. Assessment of depression was done using Beck Depression Inventory-II (BDI-II) by a neuropsychologist. MRI Brain was done for all patients as part of stroke work up and leukoaraiotic changes were documented using Fazeka's grading.

All the patients underwent Transcranial Doppler (TCD) evaluation (Nicolet® Sonara® digital TCD system). Doppler signals from the main stem of the Middle Cerebral Artery (MCA) were obtained with a 2-MHz probe at a depth of 50 to 60 mm through the temporal window. For both MCA, the mean, systolic, and diastolic velocities were measured, and the Gosling Pulsatility Index (PI) was calculated

automatically as (systolic velocity - diastolic velocity)/mean velocity. Mean MCA-PI was calculated by averaging the MCA PI at a depth of 50 to 60mm of both temporal windows. Patients who had a good temporal window only on one side, had only the PI obtained on that side as the mean MCA-PI. Patients were followed up 3 months later and neurological outcome, disability status and depression were recorded using similar scales as previous.

Statistical analysis:

The data were analysed with the help of computer software MS Excel and SPSS 25 for windows. Qualitative and quantitative variables were presented as percentages or mean +/- standard deviation as defined appropriate, respectively. Bivariate analysis was undertaken to examine relationship of various factors with the final outcomes at 3 months. Mann Whitney and Spearman correlation were applied as appropriate to evaluate statistical significance.

Multivariate analysis using repeated measures ANOVA/ logistic regression were used including the variables deemed significant after bivariate analysis as appropriate to evaluate the independent and joint effects of the variables of interest on the outcome. Receiver Operating characteristic curves were used to explore if Pulsatility indices categorized into high and low were useful in predicting worse scores in NIHSS, mRS or BDI-2.

A p value of <0.05 was considered statistically significant. All p values were two tailed.

Ethical considerations:

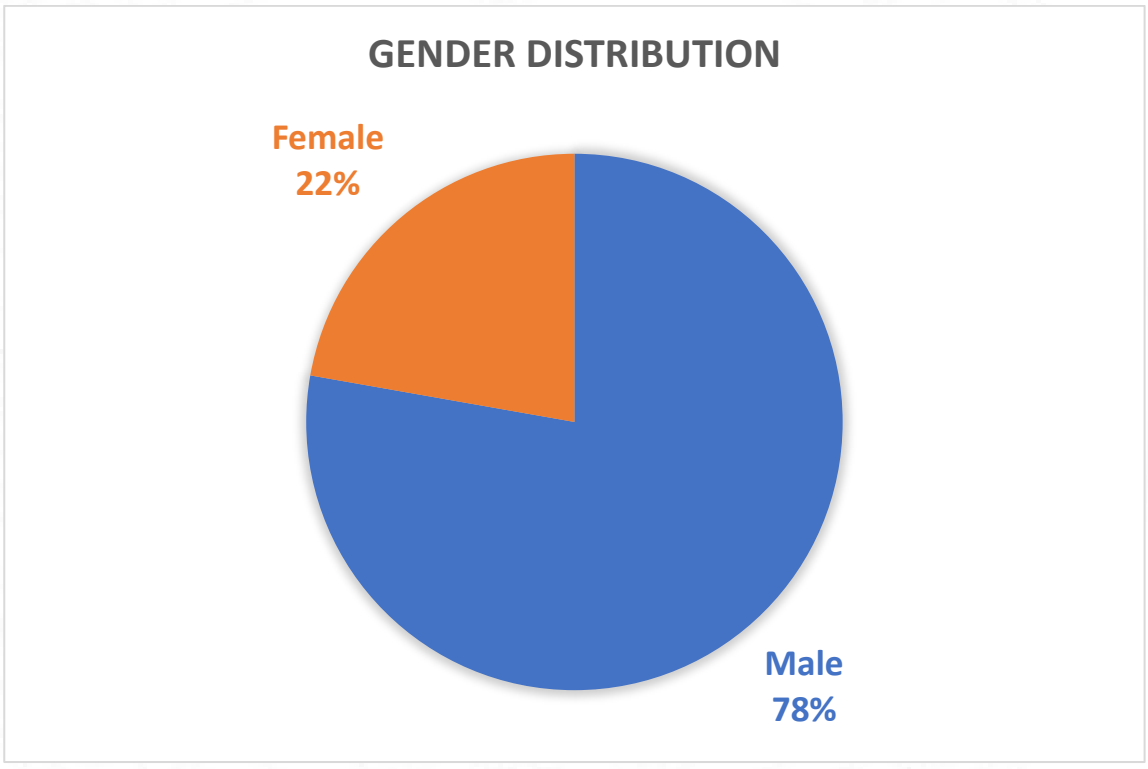
The study was approved by the Institute Ethics Committee (IEC). Written informed consent was obtained from all the participants prior to their inclusion.

RESULTS

RESULTS

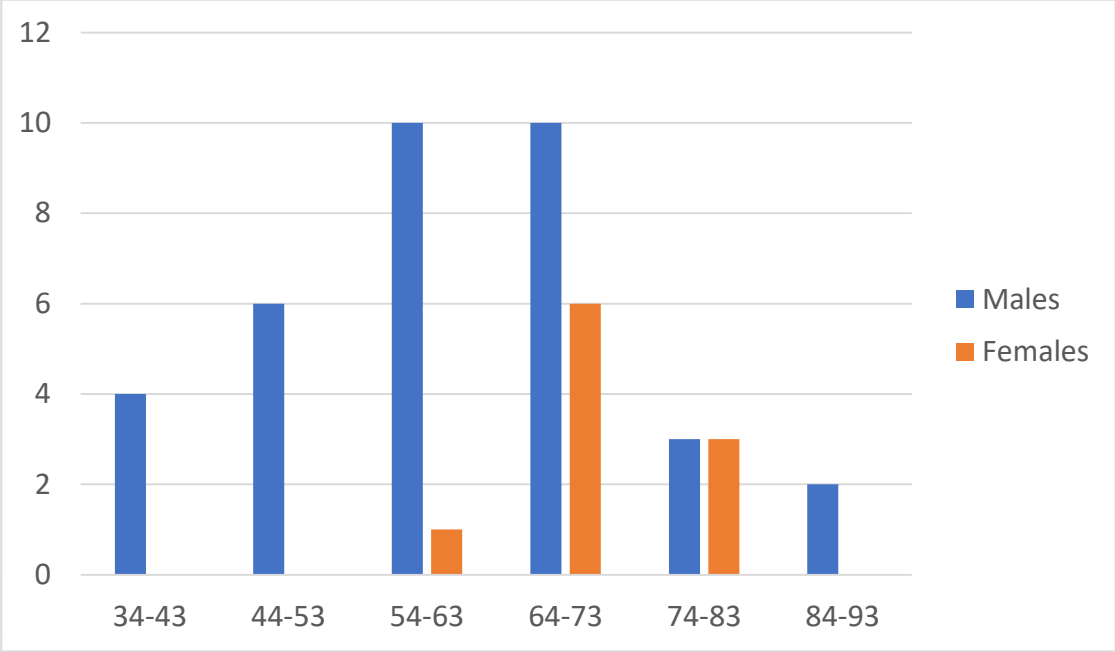
There were 52 patients who were admitted with acute lacunar strokes. 3 of them had no MRI brain at the time of stroke evaluation, 2 had poor temporal windows and 2 did not consent for the study. After applying inclusion and exclusion criteria, 45 patients were recruited in the study.

Fig. 1. Gender distribution of the study population



There were 35 males (78%) and 10 females (22%) in the study population.

Fig 2. Distribution of age and gender



Majority of the patients (78%) and all females (22%) were above the age of 53 years. The median age at onset of an acute lacunar stroke was 64 years (SD=11.8) with a range from 34-85 years.

The baseline characteristics of the population is depicted below.

Table 1. Risk factors in the study population

Risk factors	**Number (%)**
Hypertension	30 (66.67)
Diabetes	26 (57.7)
Dyslipidemia	11 (24.4)
Coronary artery disease (CAD)	6 (13.3)
Smoking-current or past	17 (37.7)

Most of the patients were hypertensives and diabetics.

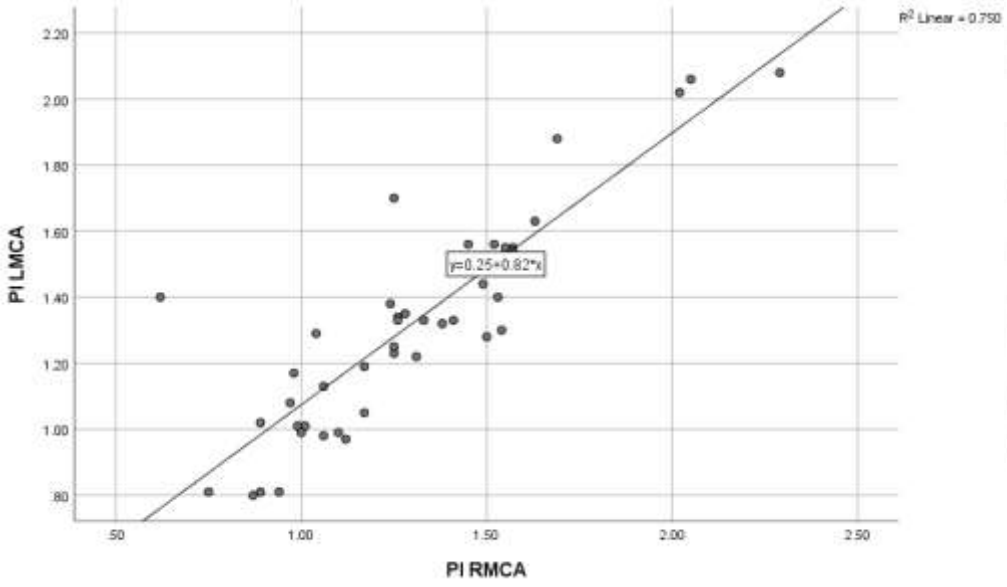
Table 2. Duration of risk factors in the study population

Duration of risk factors	**Mean years(SD)**
Hypertension	5.45 (7.3)
Diabetes	5.73 (8.3)
Dyslipidemia	1.63 (4.5)
Coronary artery disease (CAD)	0.69 (2.5)
Smoking-Pack years	4.27 (9.3)

The mean duration of diabetes and hypertension were > 5 years in the study population.

Pulsatility indices (PI) were obtained from right and left MCA and the mean PI was taken for each patient.

Fig 3. Correlation between right and left pulsatility indices



There was a significant correlation between PI measured from right and left MCA, r=0.828 (P<0.001). Similarly there was a significant correlation between the Mean velocities obtained from right and left MCA, r=0.514 (P<0.001).

The mean PI in our study population was 1.3(SD=0.32).

The mean values of NIHSS, mRS and BDI-2 at baseline were 5.6(SD=3.4), 3.4(SD=0.9) and 7.3(SD=7.1) respectively.

The mean values of NIHSS, mRS and BDI-2 at 3 months were 1.7(SD=2.1), 1.4(SD=1.25) and 5.4(SD=5.1) respectively.

Table 3. Depression scores severity at baseline and at 3 months.

BDI-2 categories	**Number=45(%)** **Baseline**	**Number=45 (%)** **3 months**
Minimal	38 (84.4)	40 (88.9)
Mild	5 (11.1)	4 (8.9)
Moderate	1 (2.2)	1 (2.2)
Severe	1 (2.2)	0

Depression was categorized as minimal (0-13), mild (14-19), moderate (20-28) and severe (30-63) as per the BDI-2 scores. Majority of the patients had minimal depression at baseline and at 3 months follow up.

The change between the baseline and 3 month scores of NIHSS, mRS and BDI-2 were assessed for each patient and their correlation with the mean PI was done using Pearson correlation coefficient.

Table 4. Correlation of mean PI with change in the NIHSS, mRS and BDI-2 scores.

	Change in NIHSS vs mean PI	**Change in mRS vs mean PI**	**Change in BDI-2 vs mean PI**
Correlation coefficient	0.229	-0.050	0.173
P value	0.131	0.746	0.257

There was no significant correlation between the mean PI and the change in outcomes across NIHSS, mRS or BDI-2 scores.

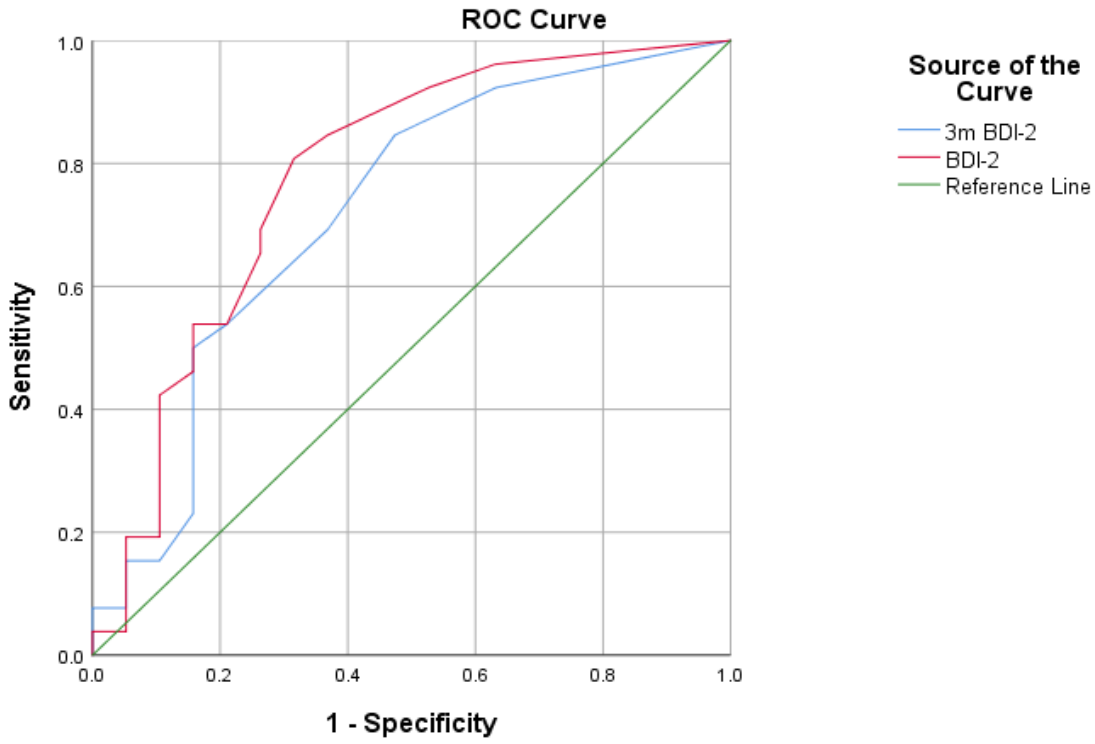
Since the mean PI was 1.3 in our study populations, the patients were categorized into those with PI <1.3 (low PI) and those with PI ≥1.3 (high PI).

19 patients had PI <1.3 and 26 patients had mean PI ≥ 1.3.

ROC analysis was done to determine the relationship of high and low PI categories with the NIHSS, mRS and BDI-2 scores at baseline and at 3 months.

It was found that those with higher PI were found to have significantly higher depression scores at baseline (P=0.002) and at 3 months (P=0.012) respectively.

Fig 4. ROC analysis for BDI-2 scores at baseline and at 3 months for those with high PI.



The area under the curve for BDI-2 at baseline was 0.778(P=0.002), and for 3 month BDI-2 it was 0.722 (P=0.012) respectively for those with PI ≥ 1.3.

ROC analysis showed no significant relationship between high and low PI categories with NIHSS and mRS scores both at baseline and at 3 months.

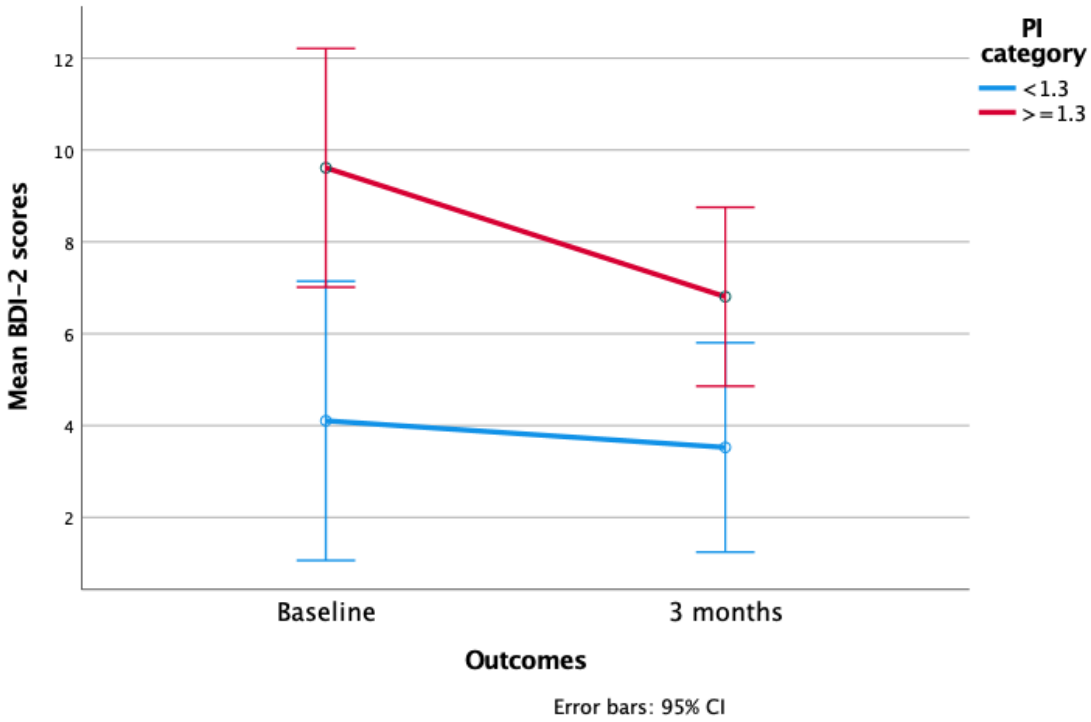
Table 5. The mean BDI-2 scores of those with high and low PI values.

		Mean	**SD**	**N**
Baseline BDI-2	PI <1.3	4.11	6.008	19
	PI ≥ 1.3	9.62	6.952	26
	Total	7.29	7.057	45
3 month BDI-2	PI <1.3	3.53	4.452	19
	PI ≥ 1.3	6.81	5.246	26
	Total	5.42	5.141	45

The mean baseline and 3 month BDI-2 scores were higher in the high PI group when compared to the low PI group.

Repeated measures ANOVA showed that between those with high and low PI there was significant differences in the BDI scores at baseline and at 3 months (P=0.014), but there was no significant differences when assessed within each group on the initial and final scores (P=0.10).

Fig 5. Interaction between BDI-2 scores when analysed by PI category.



A high PI value was found in those with higher BDI-2 scores both at baseline and at 3 months, but this did not influence the rate of decline in the scores at 3 months. Similar analysis were performed for NIHSS and mRS scores.

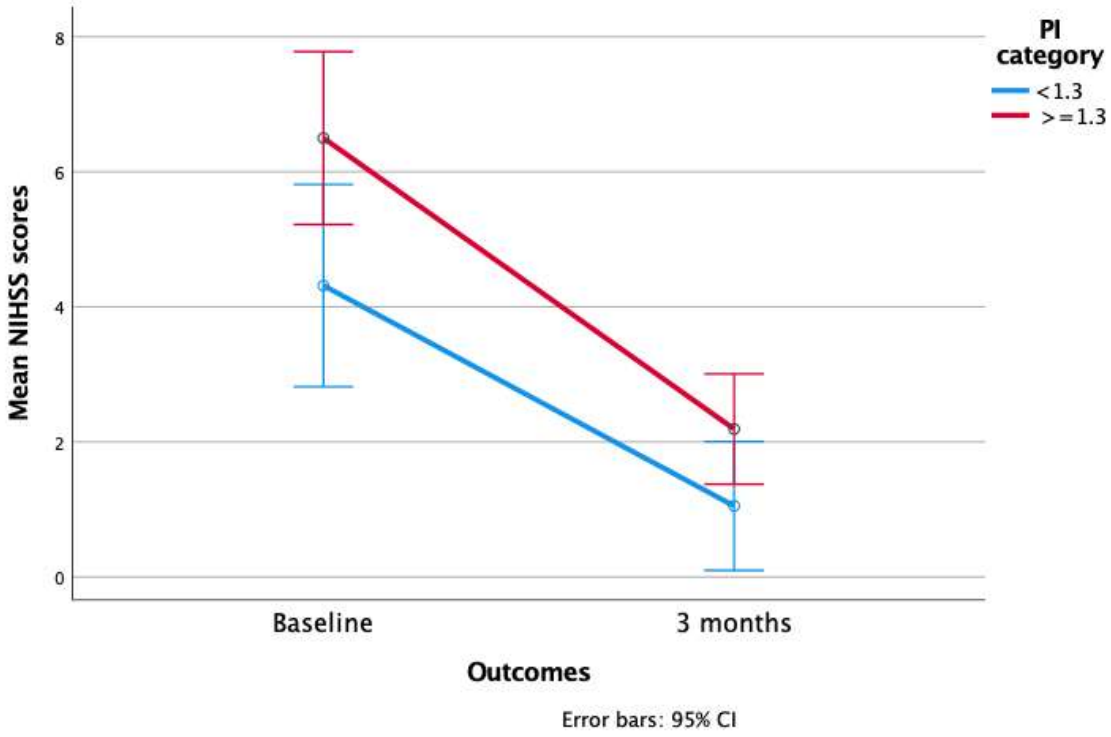
Table 6. The mean NIHSS scores of those with high and low PI values.

		Mean	**SD**	**N**
Baseline NIHSS	PI <1.3	4.32	2.829	19
	PI ≥ 1.3	6.50	3.501	26
	Total	5.58	3.381	45
3 month NIHSS	PI <1.3	1.05	1.682	19
	PI ≥ 1.3	2.19	2.298	26
	Total	1.71	2.117	45

The mean baseline and 3 month NIHSS scores were higher in the high PI group when compared to the low PI group.

Repeated measures ANOVA showed that between those with high and low PI there was significant differences in the NIHSS scores at baseline and at 3 months (P=0.024), but there was no significant differences when assessed within each group on the initial and final scores (P=0.209).

Fig 6. Interaction between NIHSS scores when categorized by PI category.



A high PI value was found in those with higher NIHSS scores both at baseline and at 3 months, but this did not influence the rate of decline in the scores at 3 months.

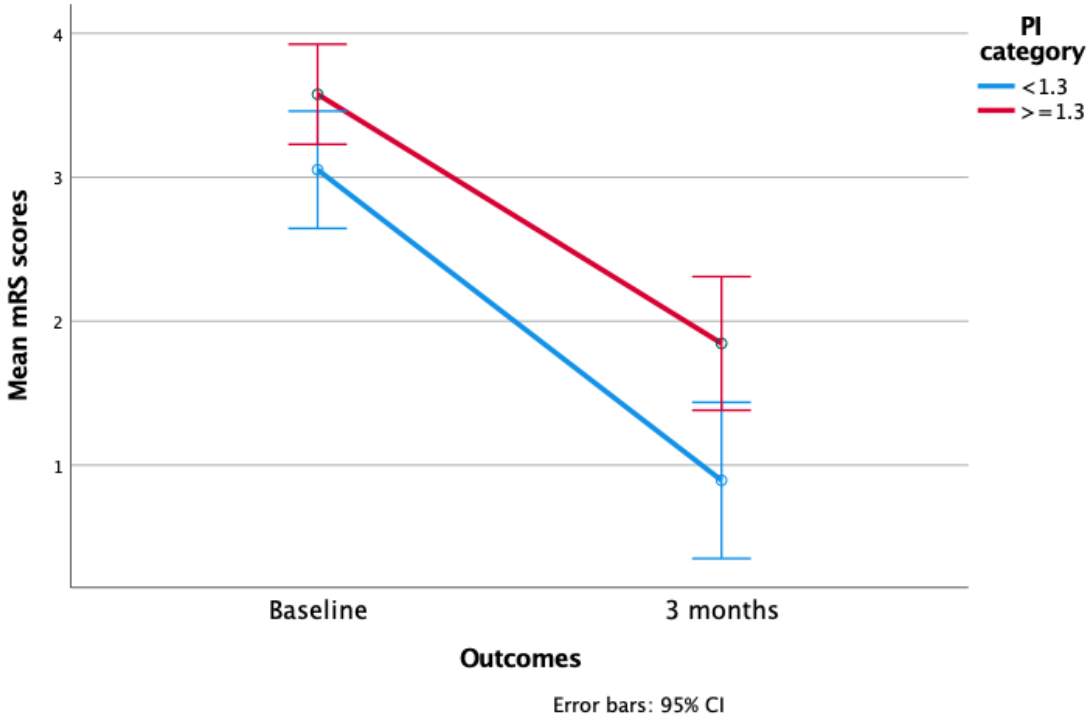
Table 7. The mean mRS scores of those with high and low PI values.

		Mean	**SD**	**N**
Baseline mRS	PI <1.3	3.05	1.026	19
	PI ≥ 1.3	3.58	0.758	26
	Total	3.36	0.908	45
3 month mRS	PI <1.3	0.89	1.049	19
	PI ≥ 1.3	1.85	1.255	26
	Total	1.44	1.253	45

The mean baseline and 3 month mRS scores were higher in the high PI group when compared to the low PI group.

Repeated measures ANOVA showed that between those with high and low PI there was significant differences in the mRS scores at baseline and at 3 months (P=0.003), but there was no significant differences when assessed within each group on the initial and final scores (P=0.298).

Fig 7. Interaction between mRS scores when categorized by PI category.



A high PI value was found in those with higher mRS scores both at baseline and at 3 months, but this did not influence the rate of decline in the scores at 3 months.

There were 16 patients(35.5%) who had grade 1, 11 patients(24.4%) with grade 2 and 8 patients (17.7%) with grade 3 Fazeka small vessel ischemic changes.

There was no correlation between those with Fazeka grade 2 or 3 small vessel ischemic changes when compared against those with Fazeka grade 0 or 1 small vessel ischemic changes with regard to 3 month NIHSS (P=0.179), 3 month mRS (P=0.443) and 3 month BDI-2 scores (P=0.105).

When the Fazeka grades (0-3) were compared against the change in scores of NIHSS, mRS and BDI-2 from baseline to 3 months, there was no significant

correlation obtained with respect to change in NIHSS (P=0.883), mRS (P=0.781), BDI-2 (P=0.528) scores respectively.

Table 8. Correlation of mean PI with other variables.

Correlation of mean PI with other variables	**Pearson Correlation**	**P value**
Hypertension	0.018	0.406
Diabetes	0.179	0.346
Leukoaraiosis (Fazeka grade 2,3)	0.040	0.792

There was no significant correlation of PI with regard to other variables like hypertension, diabetes, severity of leukoaraiosis.

Since the severity of baseline deficits could have an influence on the final outcomes at 3 months, we also looked into other variables that influenced the 3 month outcomes.

Table 9. Bivariate analysis of baseline predictors of 3 month outcomes with the P values.

	Number (%)	**3-month NIHSS P values**	**3 month mRS P values**	**3 month BDI-2 P values**
Female sex	10 (22)	0.657	0.352	0.038
Hypertension	30 (66.67)	0.462	0.390	0.103
Diabetes	26 (57.7)	0.049	0.057	0.982
Current smoking	12 (26.6)	0.568	0.367	0.603
Coronary artery disease	6 (13.3)	0.684	0.884	0.909
Peripheral vascular disease	1(2)	0.044	0.089	0.044
Dyslipidemia	11(24.4)	0.194	0.223	0.540
Prior stroke	10 (22.2)	0.111	0.381	0.111
Prior TIA	2 (4.4)	0.485	1.000	0.202
Past depression	2 (4.4)	0.182	0.315	0.085
Family history of CAD/stroke	4 (8.8)	0.285	0.525	0.041
Microbleeds	11 (24.4)	0.593	0.706	0.523
Old infarcts	8 (17.7)	0.411	0.611	0.969
Fazeka grade 2,3 changes	19(42.2)	0.179	0.443	0.105

Bivariate analysis showed that presence of diabetes was associated with 3 month NIHSS scores, and females were more often depressed at 3 months. However they lost significance in multivariate analysis. Peripheral vascular disease and family history of CAD/stroke were not considered for analysis because of very small number of patients in each category.

Table 10. Correlation of salient parameters with 3 month outcomes.

Variables		**3month NIHSS**	**3 month mRS**	**3 month BDI-2**
Age	Spearman Correlation	0.245	0.247	0.247
	P value	0.104	0.102	0.103
Hypertension Duration	Spearman Correlation	0.129	0.175	.381
	P value	0.400	0.249	0.010
Diabetes Duration	Spearman Correlation	0.287	.305	-0.026
	P value	0.056	0.042	0.867
Smoking Pack years	Spearman Correlation	-0.005	-0.040	0.017
	P value	0.972	0.796	0.913
CAD Duration	Spearman Correlation	0.069	0.023	-0.004
	P value	0.652	0.881	0.981
Dyslipidemia Duration (years)	Spearman Correlation	0.136	0.145	0.037
	P value	0.373	0.342	0.808

Variables		3month NIHSS	3 month mRS	3 month BDI-2
TCD Right MCA MV	Spearman Correlation	-0.007	0.013	-0.257
	P value	0.962	0.934	0.088
TCD Left MCA MV	Spearman Correlation	-0.093	-0.054	-0.136
	P value	0.543	0.725	0.372
PI Right MCA	Spearman Correlation	0.187	0.227	.300
	P value	0.219	0.133	0.045
PI Left MCA	Spearman Correlation	.302	.319	.346
	P value	0.044	0.033	0.019
NIHSS	Spearman Correlation	.468	.416	.533
	P value	0.001	0.004	0.000
mRS	Spearman Correlation	0.270	0.272	.308
	P value	0.073	0.070	0.040
BDI-2	Spearman Correlation	0.196	0.174	.816
	P value	0.196	0.253	0.000

The duration of hypertension, PI from each MCA, baseline NIHSS, mRS and BDI-2 scores had a significant correlation with BDI-2 scores at 3 months using bivariate analysis. The baseline NIHSS had a significant correlation with the 3 month NIHSS

and mRS scores. PI from left MCA alone also had a correlation with 3 month NIHSS and mRS scores. However this was not logically relevant as only the mean PI was used and moreover it lost its significance on multivariate analysis.

We performed multivariate analysis in 2 ways using

1. The actual NIHSS and mRS scores-using binary logistic regression
2. Categorizing them into low (0-3) and high (>3) NIHSS, good (0-2) and poor (>2) mRS at baseline-using repeated measures ANOVA.

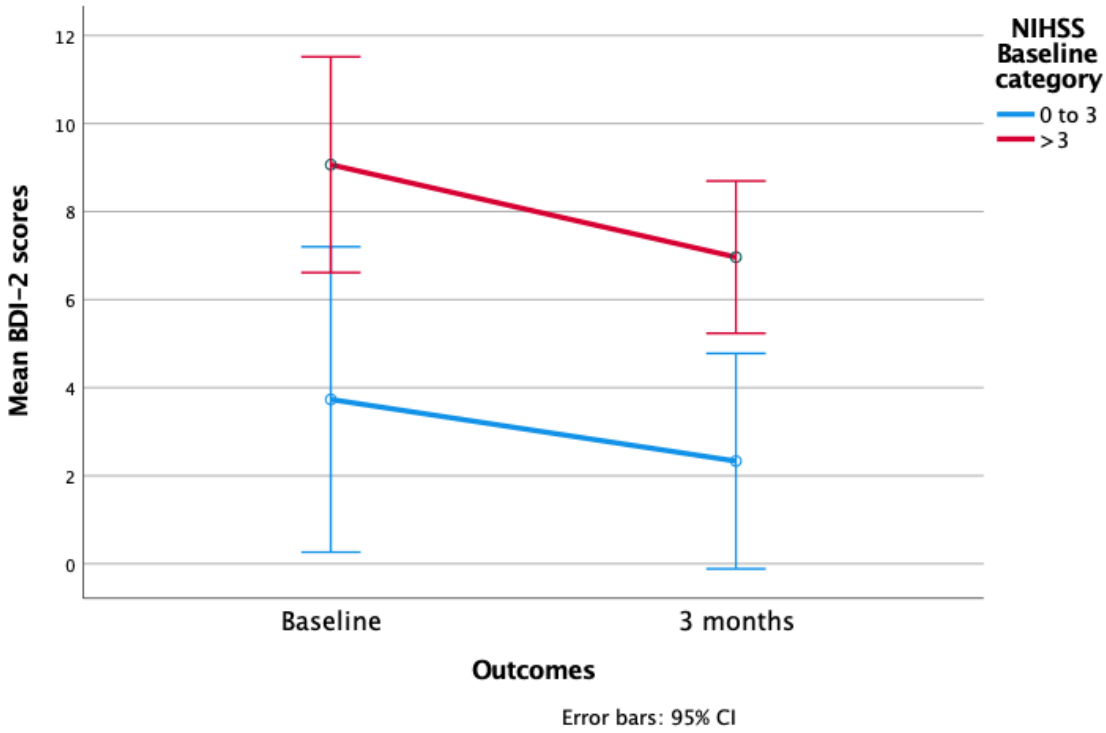
Binary logistic regression analysis was done using the variables deemed significant on bivariate analysis. It was found that only the baseline NIHSS predicted the 3 month BDI-2 scores ($P<0.001$). All other variables were removed iteratively because of low frequency or low effect size. Similarly, only the baseline NIHSS predicted the 3 month NIHSS scores ($P=0.05$).

The results of Repeated measures ANOVA are below.

Depression outcome:

The baseline NIHSS still had significant influence on the final BDI-2 scores (Wilks lambda $P=0.018$).

Fig 8. Interaction between BDI-2 scores when categorized by NIHSS as high or low categories.

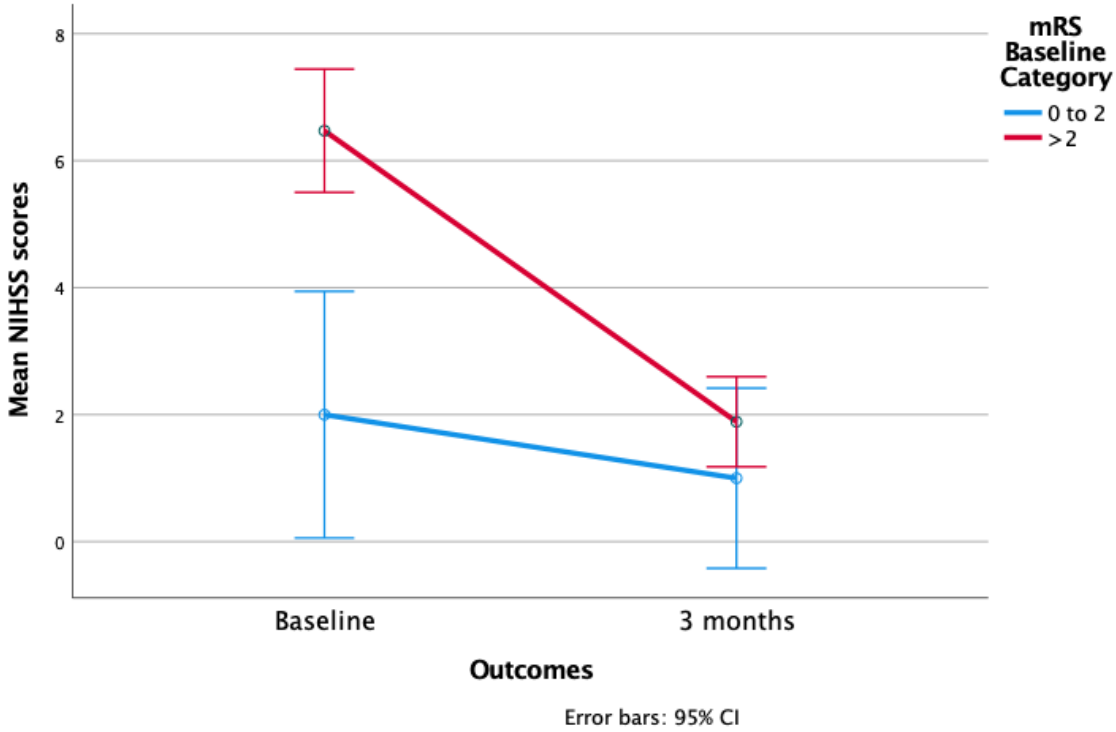


Those with severe post stroke deficits had higher depression scores on BDI-2 when compared against those with lesser deficits and this difference was maintained between the groups. However within either group the rate of decline in the BDI-2 scores was not significant.

Stroke severity outcome:

With regard to the stroke severity at 3 months, the baseline NIHSS score predicted the 3 month NIHSS score(P=0.05).

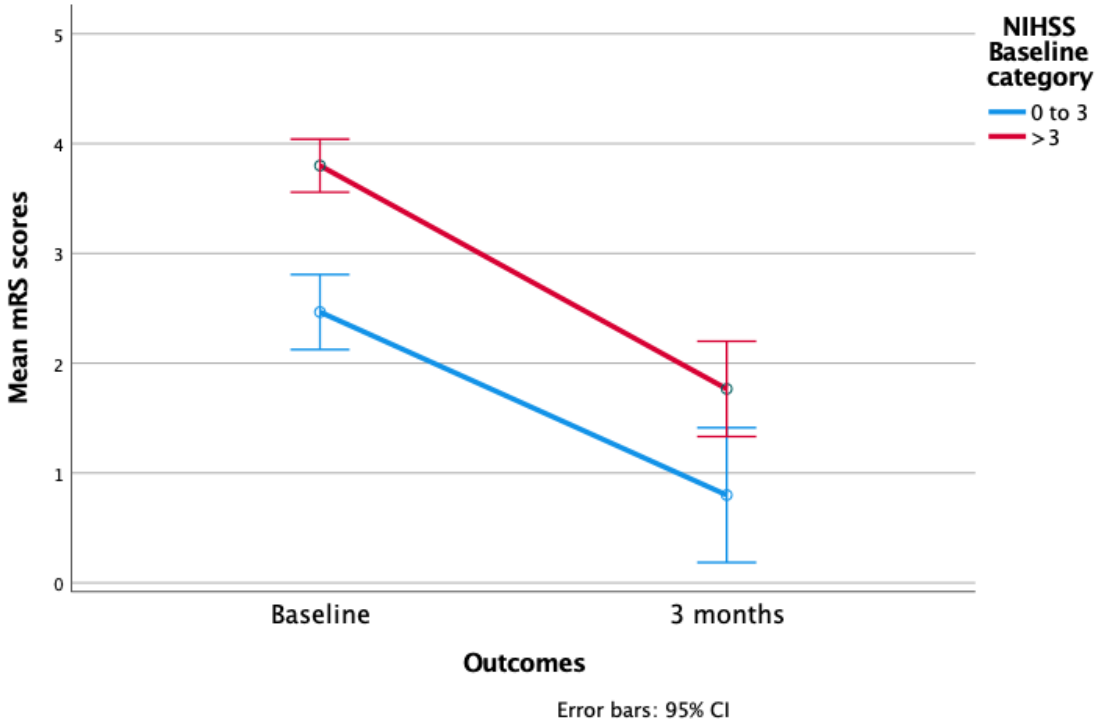
Fig 9. Interaction between NIHSS scores when categorized by mRS as high or low categories.



Those with higher mRS at baseline had higher NIHSS at 3 months when compared to those with low mRS. Also within subjects there was a significant decline in 3 month NIHSS scores in those with high mRS(Wilks lambda P<0.001).

Functional Outcome:

Fig 10. Interaction between mRS scores when categorized by high or low NIHSS.



With regard to functional outcomes at 3 months, those with higher deficits at baseline had a higher mRS at 3 months when compared against those who had lesser deficits at baseline(Wilks lambda P<0.001).

DISCUSSION

DISCUSSION

This prospective observational study was carried out in patients admitted with acute lacunar strokes in a Comprehensive Stroke Care centre of a tertiary care hospital in South India. We recruited 45 patients with acute lacunar strokes for our study, of which 35(78%) were males. About 67% were hypertensives, 58% were diabetics and 38% were current or past smokers, consistent with high prevalence of risk factors in this group. The mean duration of diabetes and hypertension was also more than 5 years in the study population.

Lacunar strokes are common in those with vascular risk factors like diabetes, hypertension and our results are in line with this well-known fact.

About 78% of the patients including all the females (22%) were above the age of 53 years, showing that majority of the acute lacunar strokes occur in elderly patients with risk factors. The median age at onset of an acute lacunar stroke was 64 years in our study population.

At presentation, the mean NIHSS and mRS were 5.6(SD=3.4) and 3.4(SD=0.9) respectively. Larger NIHSS scores are usually seen in major vessel occlusions often due to artery to artery or cardioembolic etiologies(70).

We used the Beck Depression inventory-2 to assess depression which has been previously validated with good interobserver variability. The mean depression score was 7.3(SD=7.1) and majority had minimal depression soon after the stroke, reinforcing that post stroke depression is often present and it needs to be actively sought and treated. Most of the patients had improvement in their deficits, with

improvement in depression scores at 3 months. Previous studies have shown that atleast one third of the stroke patients experience depression(5,6) which is influenced by the severity of the stroke, the physical disability in addition to prior history of depression and cognitive impairment(7).

We measured pulsatility indices from both MCA using TCD. The mean PI in our study population was 1.3 which is much higher than values for normal population PI of 0.5-1.19(51).

This is because we had elderly patients with multiple vascular risk factors that makes it prone for them to develop cerebral small vessel disease. White matter hyperintensities and lacunar strokes are manifestations of cerebral small vessel disease. These are shown to increase the resistance in the cerebral microcirculation which is reflected by an elevated PI measured using TCD. PI could therefore be taken as a true surrogate marker for resistance in the cerebral microcirculation.

There was a significant correlation between right and left MCA PI (r=0.828) and also between right and left MCA mean velocities (r=0.514) respectively.

Correlation of PI with risk factors:

There was no correlation of mean PI with hypertension or diabetes contrary to what is reported in the literature(54,55,61,62). Harris et al found only a weak correlation between PI and hypertension, that was probably due to the small sample size(64). Cho et al showed that elevated PI was found only in the group of patients who had hypertension for atleast 5 years compared with those with a lesser duration(60). In our study, among those who were hypertensive, only 53% had duration more than 5 years.

We did not find a correlation between PI and severity of leukoaraiosis. Previous studies have reported conflicting results with many showing a correlation(8,49,51,71–73) and others denying the same(56,74) after adjusting for confounders like age, hypertension.

Correlation of PI with post stroke outcomes:

We found that patients with PI ≥1.3 were more likely to have higher stroke severity, poor functional scores and worse depression scores both at baseline and at 3 months follow up. A higher PI at baseline reflects an already compromised cerebral microcirculation, which in turn portends more deficits and poor outcomes. These patients also had elevated scores of NIHSS, mRS and BDI-2 at 3 months follow up suggesting that baseline small vessel disease burden might delay the recovery after an acute lacunar stroke.

A previous study showed a correlation between low PI and good functional outcomes both in the acute phase and in short term however in the context of thrombolysis of an acute ischemic stroke(72). This study had included both large artery atherosclerosis and cardioembolic etiologies and hence those results could not be applied in the context of an acute lacunar strokes.

We also found that although there was a significant difference between subjects with elevated and low PI in terms of the scores at baseline and at 3 months, within subject groups there was no difference in the rate of eventual recovery regardless of high or low PI. This could mean that an elevated PI at baseline is a marker of the severity of the stroke at the onset and at short term follow up, however it may not influence the rate of change of the outcomes in the short term. This is due to a type 2 error and is

probably due to the limited sample size of our cohort. Although not attaining statistical significance, the graph of change in functional outcomes shows a trend of delayed recovery in patients with higher PI. Further studies with a larger population might likely detect a significant difference in the rate of improvement of outcomes between those with high and low PI.

Correlation of leukoaraiosis with 3 month outcomes:

The severity of the leukoaraiosis did not seem to influence the final outcomes at 3 months nor did those with high grade leukoaraiosis (Fazeka grade2 and 3) have lesser improvement at 3 months when compared to the baseline deficit. It has been shown that lacunar stroke is the most common ischemic stroke predicted by leukoaraiosis(26), and presence of leukoaraiosis in a patient with first ever lacunar stroke is associated with poor short term and long term outcomes with regard to cognition, recurrent stroke and cardiovascular mortality(4,27). Our results are similar to those of Wiszniewska et al, who did not report any influence of leukoaraiosis on stroke outcomes(75). The imaging finding of leukoaraiosis can have varied etiologies and may not reflect the actual functional hemodynamics of the cerebral microcirculation, which is better reflected by pulsatility index, a physiological surrogate marker. We also did not find a correlation between PI and leukoaraiosis in our study. Unlike leukoaraiosis, only an elevated PI was associated with poor baseline and 3 month post stroke outcomes in our study. We propose that an elevated PI is more reflective of the underlying functional status of cerebral small vessel disease than leukoaraiosis.

Correlation of baseline deficits with 3 month outcomes:

On bivariate analysis we found that the baseline NIHSS scores correlated significantly with the 3 month NIHSS, mRS and BDI-2 scores respectively and the baseline mRS and BDI-2 scores correlated significantly with the 3 month BDI-2 scores. However on multivariate analysis we found that only the baseline NIHSS scores correlated significantly with the 3 month NIHSS, mRS and BDI-2 scores. These results implicate that the severity of the deficits at baseline influences the outcomes at short term. This is line with previously reported studies(76–78). Mok et al showed that patients who develop stroke in the setting of cSVD were more likely to have poorer outcomes especially if they had higher baseline stroke severity and cognitive decline(30).

Strengths of the study:

1. This is the first prospective study to assess the utility of a pulsatility index measured using TCD to predict the stroke severity, functional outcomes and depression at baseline and at short term follow up in patients with acute lacunar strokes.
2. Our study population was a targeted group as we recruited only patients with acute lacunar strokes. The influence on PI due to proximal vessel narrowing and stroke of alternate etiologies were eliminated.
3. We also provide evidence that post stroke depression is often present in the context of an acute stroke and it needs to be actively screened and treated.

Limitations of the study:

1. The small sample size is a major limitation. One reason was due to the COVID 19 pandemic. We recruited only patients admitted with acute lacunar strokes. The COVID-19 pandemic limited the number of patients who were admitted with acute lacunar strokes. Most patients with acute lacunar strokes often have less deficits and may seek medical care in nearby local hospitals rather than be referred to a tertiary care centre like our institute. This could lead to a potential type 2 error which is the likely reason there was a lack of correlation of PI with the rate of change of outcomes. A larger cohort of such patients could give more insights into the relationship between PI and the rate of recovery after an acute lacunar stroke.
2. We did not measure PI from healthy controls which could have given us meaningful insights into the percentage of elevation of PI among patients with acute lacunar strokes.

CONCLUSIONS

CONCLUSIONS

1. Unlike leukoaraiosis, patients with an elevated Pulsatility Index had more severe neurological deficits, poorer functional outcomes and worse depression scores across all time points of evaluation in patients with an acute lacunar stroke.
2. Pulsatility index is a physiological indicator that reflects the microcirculatory dynamics and can better predict post stroke outcomes as compared to leukoaraiosis.
3. The severity of the deficits at baseline influences the post stroke outcomes at 3 months.

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APPENDIX

ABBREVIATIONS

ARWMC	: Age Related White Matter Changes
BDI-2	: Beck Depression Inventory-2
CAD	: Coronary Artery Disease
COVID-19	: COronaVirus Disease-19
cSVD	: cerebral Small Vessel Disease
HDL	: High Density Lipoprotein
LDL	: Low Density Lipoprotein
MCA	: Middle Cerebral Artery
MV	: Mean Velocity
MRI	: Magnetic Resonance Imaging
mRS	: modified Rankin Scale
NIHSS	: National Institute for Health Stroke Scale
PI	: Pulsatility index
PI LMCA	: Pulsatility Index Left Middle Cerebral Artery
PI RMCA	: Pulsatility Index Right Middle Cerebral Artery
WMH	: White Matter Hyperintensities
SD	: Standard Deviation
TCD	: Transcranial Doppler
TOAST	: Trial of Org 10172 in Acute Stroke Treatment trial

Data Collection Proforma in patients with Acute lacunar strokes

1. Personal Data:

1.1. Patient ID----------

1.2. Age ---------- years

1.4 Sex ---------- 1.Male 2.female

1.5. Educational status----------

2. Risk factors:(1=Yes, 2=No)

2.1. Hypertension---------- Duration in years

2.2. Diabetes mellitus--------Duration in years

2.3. Current smoking---------Pack years ----------

2.3a. Ex-Smoker----------Stopped ----------years back

2.3b.Tobacco chewing ----------

2.3c. Alcoholism----------

2.4. Coronary artery disease-------- Duration in years ----------Detected now ------

2.5. Peripheral vascular disease--------

2.6. Hyperlipidemia----------Duration in years----------Detected now----------

2.7. History of prior stroke --------Date of ictus----------

2.8. History of prior TIA----------Date of ictus----------

2.9. Patients on treatment ----------

2.9a. If yes, Type of treatment ----------

2.10 Depression in past----------

2.10a If yes. On treatment…….. drug(s)

2.11. Family history of stroke/CAD (first degree relatives) ---------- (Male<55yrs and Female <65 years of age

2.12 Family history of dementia (first degree relatives)----------

2.13 Family history of depression

3. Investigations:

3.1. Serum cholesterol----------

3.2. LDL--------

3.3. HDL----------

3.4. Serum triglycerides----------

3.5. Hb A1C----------

4. Imaging

4.1 CT scan ----------1.Normal.2. New infarct 3. Old infarct 4.Small vessel Ischemic changes 5.Not done

4.2MRI scan ----------1. DWI negative 2.DWI positive single lesion 3.DWI-Multiple lesions 4.Not done

4.2a Fazeka changes----------1. Present 2. Absent If present, specify----------

4.2b Microbleeds----------1. Present 2. Absent If present, specify

4.2c Old infarcts--------1. Present 2. Absent If present, specify

4.3 Transcranial doppler

4.3a Mean blood flow velocity 1. Right MCA--------- 2. Left MCA--------

4.3b Pulsatility index 1. Right MCA--------- 2. Left MCA----------

At admission:

1. NIHSS :
2. mRS:
3. BDI- 2 score:

3 months follow up:

1. NIHSS :
2. mRS:
3. BDI- 2 score:

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श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

22.08.2019

SCT/IEC/1397/JULY-2019

Dr. Naveen Kumar P
Senior Resident, Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Naveen Kumar,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "CORRELATION BETWEEN PULSATILITY INDEX IN TRANSCRANIAL DOPPLER AND POST STROKE OUTCOMES IN PATIENTS WITH ACUTE LACUNAR STROKES (IEC/1397)" on 26th July, 2019.

The following documents were reviewed:

Original submission

1. *Covering Letter addressed to the Chairperson, IEC, SCTIMST dated 27.06.2019 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Patient Information Sheet and Consent Form in English and Malayalam*
7. *CV of Principal Investigator and Co-Principal Investigators*

Revised submission

1. *Covering Letter addressed to the Chairperson, IEC, SCTIMST dated 12.08.2019 with checklist*
2. *TAC Approval Letter*
3. *IEC Application Form*
4. *Project Proposal*
5. *Proforma*
6. *Patient Information Sheet and Consent Form in English and Malayalam*
7. *Information Sheet and Consent Form for Legally authorized representative (LAR) in English and Malayalam*
8. *CV of Principal Investigator and Co-Principal Investigators*

The following members of the Ethics Committee were present at the meeting held on 26th July, 2019 at Noshir H Wadia Conference Hall, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
2.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
5.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

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