SREE CHITRA TIRUNAL INSTITUTE FORMEDICAL SCIENCES AND TECHNOLOGY THIRUVANANTHAPURAM, KERALA

HIGH RESOLUTION MR VESSEL WALL IMAGING IN THE DIAGNOSIS OF INTRACRANIAL VASCULOPATHY DUE TO MIDDLE CEREBRAL ARTERY DISEASE

Thesis submitted in partial fulfilment of the rules and regulations for

DM Degree Examination of

SreeChitraTirunal Institute for Medical Sciences and Technology

By

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Month and Year of Submission: August 2020

Department of Neurology

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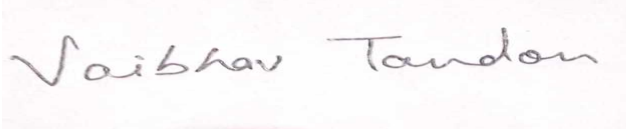
2018-2020

DECLARATION

I, Dr. Vaibhav Tandon, 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: 31-08-2020.

Dr. Vaibhav Tandon

Forwarded:

The candidate, Dr.Vaibhav Tandon, has completed the project under my guidance.

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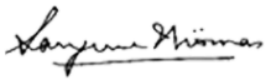
FORWARDED

The candidate, Dr Vaibhav Tandon has completed the minimum work required for the project.



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ACKNOWLEDGEMENT

I take this opportunity to express my sincere gratitude to **Dr.Sylaja P.N.,** Professor of Neurology, SCTIMST, my guide for the study, for her expert guidance, constant review, kind help and keen interest at each and every step of the study.

I am extremely thankful to **Dr Sapna EratSreedharan**, Associate Professor, Department of Neurology, **Dr.Kesavadas C**, Professor & Head of Department, IS&IR forhis valuable input and assistance to the study.

I am grateful to **Dr.Santhakumar**, Senior Resident, Department of IS&IR, SCTIMST, for his assistance in patient screening and recruitment.

I am thankful to the entire faculty, nursing staff in Epilepsy unit, and my colleagues for their valuable input and assistance to the study.

Last but not the least, I extend my gratitude to all my patients and their primary caregivers who participated in this study, without whose cooperation this study would not possible.

Dr. Vaibhav Tandon

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SYNOPSIS

BACKGROUND AND PURPOSE:

High resolution MR vessel wall imaging(VWI) can depict and characterize vessel wall pathology affecting intracranial circulation and helps in differentiating different types of vasculopathies. The purpose of the study was to differentiate intracranial pathologies involving Middle cerebral artery (MCA) and characterize the high risk plaques in intracranial atherosclerotic disease(ICAD).

MATERIALS AND METHODS:

Patients with MCA disease with ≥50% luminal narrowing confirmed by CT Angiography/MR TOF were prospectively enrolled. All the patients underwent high-resolution (3T) intracranial vessel wall imaging. The pattern of vessel wall thickening, high signal on T1-weighted images, juxtaluminal hyperintensity, remodelling, pattern and grade of enhancement were studied. The TOAST classification before and after VWI and the recurrence of ischemic events with imaging characteristics were analyzed.

RESULTS:

Thirty six patients with MCA disease were enrolled. The mean age was 49.53 years±15.61 years. After luminal imaging, according to TOAST classification15 out of 36 patients had stroke of undetermined etiology,23 patients had ICAD, 9 had vasculitis and 2 had partially occlusive thrombus in MCA. After vessel wall imaging,(77stenoocclusive lesions)etiology of stroke remained uncertain in only 2patients.The ability of VWI to bring a change in diagnosis was found to be significant. (p-value-0.009) .Of the 23 ICAD patients, 12 patients were found to have recurrent strokes., of which 9 had Grade 2 enhancement..Three patients with Grade 0 enhancement had no recurrence. Seven of the ICAD patients had type 2 thickening pattern, of which 6 had recurrence of ischemic events..Thus, the presence of Grade 2 contrast enhancement (*p* - 0.006) and type 2 wall thickening (*p* - 0.033) in ICAD showed a statistically significant association with recurrent ischemic events.

CONCLUSIONS:

High-resolution intracranial vessel wall imaging characteristics can help differentiate the etiology of stroke. The presence of Grade 2 enhancement and type 2 wall thickening in ICAD signifies vulnerable plaques which may provide valuable insights into risk stratification.

INTRODUCTION

INTRODUCTION

Stroke is currently the second leading cause of death worldwide. Ischemic heart disease and stroke together accounted for 15.2 million deaths (15–15.6 million) in 2015(1). Stroke is the commonest cause of chronic adult disability(2). Stroke affects 33 million individuals worldwide each year.

The importance of diagnosing the etiology of stroke was recognised as early as 1991(3)For secondary prevention of stroke, etiological diagnosis is very important since it has got implications in treatment and also in predicting stroke recurrence and final outcome.

For determining the etiology of stroke, conventional luminal imaging done by CT Angiography (CTA), MR Angiography (MRA) is used with Digital Substraction Angiography (DSA) used in limited situations. However, these approaches have a limited ability to differentiate vascular pathologies because they help in looking at the luminal characteristics alone.

Without detailed knowledge of plaque location, severity, and morphology, determination of stroke mechanism cannot be directly determined.

High resolution MRI Vessel wall imaging(VWI) may provide this information and has the potential to directly depict and characterize vessel wall pathology affecting intracranial circulation increasing diagnostic accuracy for vasculopathies with angiographic findings(4) and thus helps in differentiating different types of vasculopathies.

It is especially challenging due to small caliber and tortuosity of the intracranial vessels necessitating submillimeter spatial resolution and high field strength magnets.

It is a rapidly growing and evolving area of clinical and research interest that hold promise to improve diagnostic accuracy for intracranial vasculopathies.

Specific vessel wall thickening and enhancement patterns have been described in several conditions with similar angiographic findings enabling discrimination of these diseases that was not previously possible. In addition, variation in the plaque characteristics on vessel wall imaging can help predict high risk plaque and risk of recurrence of stroke.

Furtherstudies are needed to better define the role of VWI in predicting risk from intracranial vasculopathies and determining the best management approach.

REVIEW OF LITERATURE

HISTORICAL OVERVIEW

Evidence for first studies to evaluate the vessel wall using MRI dates back to 1982 when Nuclear magnetic resonance was used on surgically excised iliac artery atherosclerotic lesions(5). These studies provided correlation between plaque composition and MR signal characteristics. In 1990, Edelman et al found that using black blood technique was superior to assess the degree of luminal stenosis as compared to bright blood technique(6)Subsequently the "vulnerable plaque concept" was introduced by Naaghvi et al in 2003 according to which certain plaque characteristics can increase the likelihood of patient symptoms secondary to thrombus formation and embolization(7)These characteristics were enumerated as the presence and status of the fibrous cap, intra-plaque hemorrhage, presence and volume of lipid-rich necrotic core (LRNC), plaque neovascularity, ulceration, and fissuring. The presence of these events were associated with future cerebrovascular events.

The first study to assess the intracranial vessel walls on MRI was done in 1995. It was noticed that with age there was associated increase in the presence of contrast enhancement and this was thought to correlate with the presence of intracranial Atherosclerotic disease(8). Thirteen years later, Kulker et al showed similar enhancement in patients with vasculitis(9). The technique of intracranial vessel imaging has been

modified over the years and has evolved from luminal imaging to image the vessel wall in order to characterize a range of intracranial vasculopathies, including cerebral vasculitis, ICAD, RCVS, aneurysms, arterial dissections, and moyamoya disease (MMD) and syndrome (MMS)

High Resolution Intracranial vessel wall MRI (HRVWI) aims at achieving sufficient resolution and contrast such that the vessel wall and overlying tissue can be accurately assessed which can help to differentiate between intracranial vascular pathologies that were previously evaluated with luminal imaging.

Causes of Middle cerebral artery involvement

There are multiple causes of involvement of MCA in patients with stroke(10) and differentiation of these entities is important for differential diagnosis and treatment.

1) Intracranial atherosclerotic disease.
2) Artery to artery embolism
3) MCA dissection
4) Vasculitis- Primary or secondary

The features in HRVWI can be used to differentiate between different types of intracranial vasculopathies.

Study done by Klein et al(11) showed that the findings of vessel wall thickening and wall enhancement were observed in the areas corresponding to reduced arterial lumen and not found in normal MCA segments.

Swartz R.H., Bhuta S.S et al(12) studied intracranial arterial wall imaging and found that MRI VWI may be able to differentiate enhancement patterns of intracranial atherosclerotic disease, inflammation and other wall pathologies like dissection, Moya Moya disease.

A study done in Seattle by Mossa-Basha M, Hwang W.D. et al(13) studied the value of VWI in differentiating intracranial vasculopathic processes and showed that there was substantial inter-reader agreement for the assessment of lesional T2 hyperintensity, pattern of wall thickening and the presence, pattern and intensity of enhancement in MR Vessel wall imaging to determine the etiology of stroke.

HRvWI is able to characterize multiple imaging features of intracranial plaque in intracranial atherosclerotic disease (ICAD). It is also capable of diagnosing those lesions which are missed on luminal imaging as initial atherosclerotic lesions expand outward and thus can be missed on luminal imaging(14) as shown by study by Liu et al in which high resolution VWI was able to detect MCA stenosis greater than 50% with higher sensitivity than CTA using DSA as the gold standard.

Intracranial atherosclerotic disease

An atherosclerotic plaque is composed of Lipid core and a fibrous cap.(11) Atherosclerotic plaques in the intracranial circulation tend to present as eccentric and usually irregular wall thickening with or without luminal stenosis and variable enhancement(15). Eccentricity refers to a less than 360-degree vessel wall involvement or if the thickest part of the wall thickening is twice the thinnest part. Enhancement(11) can be graded as 0, 1, and 2, by comparing with the signal intensity of pituitary infundibulum; with grade 0 indicating enhancement similar to the intracranial arterial walls without plaque, and grades 1 and 2 indicating less or more enhancement than the infundibulum, respectively. Juxtaluminal T2 hyperintensity represents a fibrous cap, and the subjacent T2 hypointense area indicates the fatty core and the peripheral thin rim enhancement is due to increased vasa vasorum in the adventitia of the artery(16). The T2 hyperintense fibrous cap helps to differentiate ICAD from vasculitis and is 100% especially when there is eccentric enhancement of the vessels(17)

In addition to the diagnosis of cause of the narrowing being as ICAD, HRvWI also plays a role in differentiating symptomatic and asymptomatic plaques. In a study done by Dieleman et al, eccentric plaques were associated with asymptomatic disease and concentric

plaques were found with symptomatic disease and there was no association found with the presence of contrast enhancement and plaque vulnerability(18). In another study done by Fang Wu et al, it was found that the presence of high signal on T1 weighted images, Grade 2 contrast enhancement and >50% of circumferential thickening of the vessel wall are associated with symptomatic plaques(19). In a study done by Kim JM et al in South Korea, plaque enhancement from HRMRI was independently associated with stroke recurrence with Hazard ratio of 7.42(20). Another study characterising MCA plaques found that the degree of stenosis, the presence of plaque irregularity, presence of positive remodelling are predictors of symptomatic nature of the plaques(21)Qiao et al. observed a lack of contrast enhancement only in nonculprit plaques(22). Another study compared plaque enhancement in acute, subacute, and chronic phases of ischemic injury, and showed that the presence and strength of plaque enhancement decreased over time, showing a correlation between acute ischemic stroke and plaque enhancement (23) In addition, to find factors associated with contrast enhancement in vWI, a study done by Woo et al showed that patients with enhancement were more likely to have severe stenotic lesions and higher levels of total cholesterol, triglycerides, low-density cholesterol, Apo (b), and Apo (b)/Apo (a) lipoprotein ratio(24). Thus, presence and severity of enhancement is related to dyslipidemic conditions.

Xu et al (8) studied the prevalence of intraplaque hemorrhage in ICAD and its clinical significance using HR-MRI. Intraplaque hemorrhage was observed in 10.1% of patients with MCA stenosis. Furthermore, lesions with intraplaque hemorrhage were shown to be highly associated with ipsilateral strokes.

No contrast enhancement or hyperintensity is seen on MRVWI in artery-to-artery embolism.

Vasculitis

CNS vasculitis involves both small and large vessels of the brain. Whereas small vessels are not amenable to imaging by HRvWI, larger vessel walls can be characterised. Vessel wall enhancement as a diagnostic sign of vasculitis was first recognised by Kuker et al who proposed that wall thickening and contrast enhancement seen of post-contrast MRA images are frequent findings in patients with active vasculitis(11).With the advent of vessel wall imaging, these findings have been confirmed with better resolution and characterisation. MR HRvWI in vasculitis demonstrates concentric vessel wall thickening and enhancement but there have been reports of vasculitis resulting in eccentric vessel wall abnormalities.(25)In a study done by Obusez et al, it was shown that the presence of concentric wall thickening and enhancement can reliably differentiate between CNS vasculitis and

Reversible cerebral vasoconstriction Syndrome (RCVS)(26). A study done by Mandell et al showed similar results with patients not showing contrast enhancing vessel wall lesions during vessel wall imaging showed resolution of narrowing after 12 weeks suggesting RCVS rather than vasculitis(16). Also the presence of T2 hyperintensity is 100% specific for ICAD although its absence does not rule out the presence of atherosclerosis(14). Thus, HRvWI can assist or replace the more invasive methods of diagnosis of CNS vasculitis like meningo-cortical biopsy which has a diagnostic sensitivity of 50-60% and can help in early diagnosis of patients and contribute in improved functional outcome(27). A study done by Schuster et al identified that the use of HRvWI can also help to decide the appropriate invasive diagnostic modalities. They found that the patients diagnosed as vasculitis based on imaging had negative biopsy results because the disease process involved medium sized vessels which were less amenable to biopsy(28). Also Zeiler et al found that the yield of biopsies in suspected cases of vasculitis can be increased by directing the biopsy to the site of enhancement seen in vessel wall imaging. 8 out of 9 vessel wall imaging guided biopsies yielded positive results in their series of vasculitis patients(29).

Dissection

Vessel wall imaging can also help to diagnose dissection; early diagnosis of which can help prevent life-threatening complications. Digital subtraction angiography (DSA) has been considered as the gold standard for the diagnosis and follow-up of arterial dissection(30). However, it does not ensure the definitive diagnosis of dissection. Direct visualisation of vessel wall demonstrating intramural hematoma and intimal flap is a better technique(31). In addition, avoiding DSA can decrease the risk of iatrogenic dissections. The classical features of dissection are intimal plaque, double lumen and intramural hematoma. Previous studies have emphasised the role of intramural hematoma in diagnosis of dissection. An intramural hematoma appears T1 hyperintense and it could be difficult to differentiate this hematoma from an ICAD associated intraplaque hemorrhage. Moreover, mural haematomas show diverse signal intensity as the time progresses after stroke.In a study done by Miran Han from Korea, it was found that mural hematomas were detected in only half of the cases of dissection and that dissection flaps provide more direct evidence of dissection and are easily detectable on T1W contrast enhanced sequences(30).In cases of dissections which appear as only stenosis or occlusion on angiography, HRvWI can identify dissection segments by detecting thrombosed pseudoaneurysms and outer wall enlargement. In a case report by Kwak et al signifying the usefulness

of HRvWI in the diagnosis of isolated MCA dissection which showed intimal flap and tapered pseudolumen with intraplaque hemorrhage(32). The diagnosis of dissection was confirmed by DSA thus making HRvWI a non-invasive diagnostic study that is capable of detecting this condition when there is a high index of clinical suspicion. These results were reproduced by Gao et al in China in their case series of 8 patients with Middle cerebral artery dissection and it was found that HRvWI could directly display unequivocal findings of arterial dissection- namely intimal flap and intramural hematoma in 7 out of their 8 patients(33).

Since there is a paucity of studies on all vasculopathic process which involve the middle cerebral artery alone, the study was aimed at discussing the various HR VWI features and their ability to differentiate between the different vasculopathic processes and to determine the added diagnostic value in determining stroke etiology after luminal imaging. The study was also aimed to discuss the plaque features which can detect plaque vulnerability in the subgroup of patients having Intracranial Atherosclerotic disease.

OBJECTIVES OF THE STUDY

To analyse the role of high resolution MR vessel wall imaging in differentiating different types of Intracranial vasculopathies affecting the Middle cerebral artery

To identify high risk features of plaque predicting vulnerability in ICAD subgroup.

METHODOLOGY

The study was a prospective as well as retrospective study.

Inclusion criteria

- Patients who got admitted in first two weeks after the onset of acute ischemic stroke with initial vascular imaging showing MCA disease with >50% stenosis
- Only the patients who required additional evaluation in the form of MRI Vessel wall imaging as a part of etiological evaluation were taken up for the study.

Exclusion criteria

- Patients who presented with a duration of stroke more than 2 weeks
- Patients who had mRS score >4 were excluded from the study.

Demographic and clinical profile, vascular risk factors, were noted.The stroke severity and the imaging details were collected. The etiological classification was done according to the TOAST classification(34)into

- Large vessel atherosclerotic disease
- Cardioembolic
- Lacunar
- Stroke of other determined etiology
- Stroke of undetermined etiology

Patients in whom the vascular imaging showed 50 % or more stenosis of the MCA as seen by either CTA or MRA were included and HRVWI imaging was done. Patients were scanned on a 3T MRI system using a twenty four-channelled head coil. Our institute protocol consists of 3D TOF MRA, followed by whole brain 3D CUBE (GE healthcare, USA) sequences of T1 FS (fat saturation), T2 FS, PD, post contrast T1 FS. 3D TOF MRA acts as a localizer to assess the site of vessel narrowing. The entire HRVWI imaging could be done within 30 to 35 minutes, as per our protocol with good imaging resolution. Multiple tissue weightings like T1, T2, PD are used for better characterisation of the individual lesion. VRFA sequences were taken with good vessel flow and CSF suppression with pre-pulse DANTE (delay alternating with nutation for tailored excitation) echo train(35)Similarly, pre-pulse sequences like double inversion recovery or Motion-sensitized Driven-equilibrium were applied for better blood flow suppression(11,12)

The scan was read by a neuroradiologist who was blinded and a neurology resident and categorized into

- Pattern of disease
- Contrast enhancement
- T1W vessel wall thickening and T1W hyperintensity
- T2Wjuxtaluminal hyperintensity with surrounding hypointensity

- Wall remodeling

Characteristics	**ICAD**	**Vasculitis**	**Dissection**	**Partially occlusive thrombus**
Pattern of disease	Eccentric	Concentric	Eccentric	
Juxtaluminal T2 Hyperintensity	Present	Absent	Absent	Absent
Contrast enhancement	+	++	±	±
T1 hyperintensity	-	±	Intramural hematoma	-
Outer wall remodeling	++	-	±	-
Potential overlap in findings	Vasculitis	ICAD	ICAD	ICAD

After the HRvWI, the etiology of stroke was reclassified according to the TOAST classification and the pre and post MR Vessel wall imaging etiology of stroke was compared and the usefulness of MR Vessel wall imaging in better defining the etiology of stroke was analysed.

STATISTICAL METHODS

The data was analysed using SPSS version 26 software (SPSS Inc, Illinois, Chicago). Categorical variables were analysed in proportions and compared using Chi square test. Numerical variables were analysed using mean and Standard Deviation and compared using student T-test. $P < 0.05$ was considered to be statistically significant

RESULTS

This hospital based cohort study included patients admitted in comprehensive stroke care unit, SCTIMST within two weeks of onset of diagnosis of ischemic stroke during a four year time period (2014-2019). The patients having Middle cerebral artery territory stroke and luminal imaging showing >50% stenosis on the symptomatic side and those who needed HRvWI as a part of diagnostic work-up were included in the study.36 patients fulfilled the inclusion criteria and were included in the study.

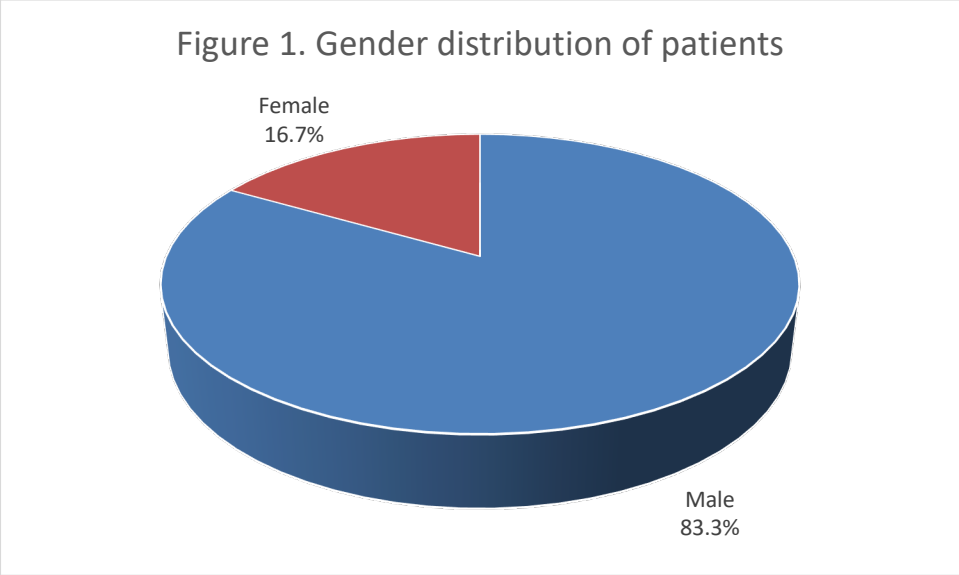
1. COHORT CHARACTERISTICS

1.1 Mean age-

Mean age of the patients admitted was 49.53 years ± 15.61 years.

1.2 Gender Distribution

In our study, there were 30 males and 6 females.(Figure 1)



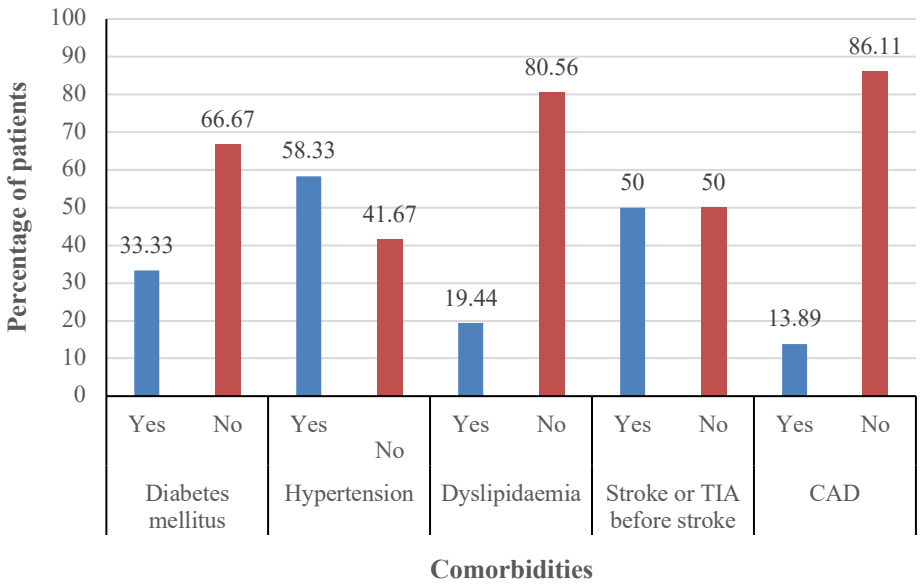
1.3 Risk factors

The various risk factors are summarized in Table 1.Hypertension was present in 21 patients, 12 patients were diabetic and dyslipidemia was present in 7 patients.5 patients had concomitant coronary artery disease and 18 patients had history of previous stroke.6 patients were smoker and 6 had history of alcohol intake.

Table 1. Risk Factor profile

Risk factors	n (%)
Hypertension	21 (58.3%)
Diabetes	12 (33.3%)
Dyslipidemia	7 (19.4%)
Coronary artery disease	5 (13.9%)
Previous stroke	18 (50%)
Smoking	6 (16.7%)
Alcohol intake	6 (16.7%)

Figure 2- Risk factor profile



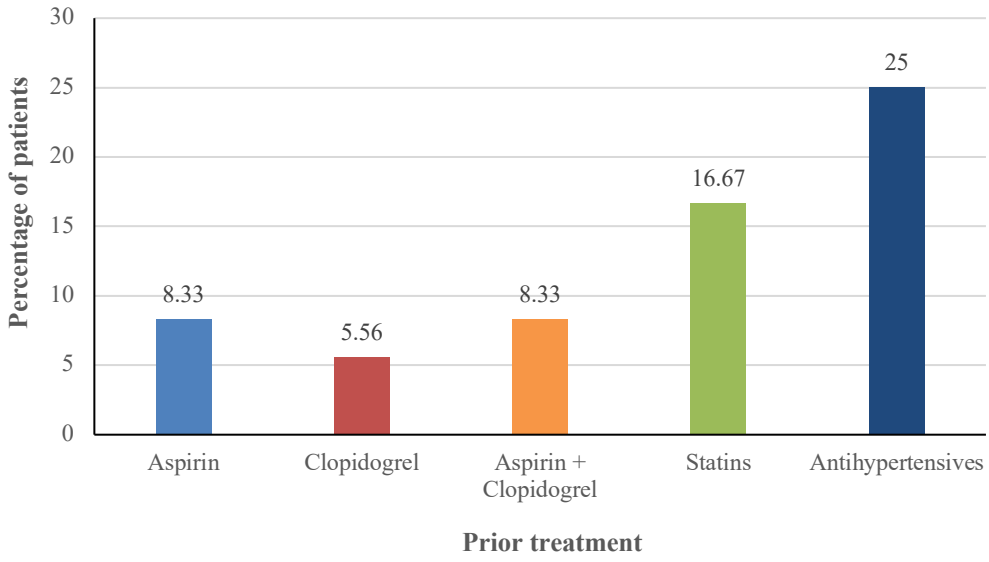
Treatment History

13 patients were on prior treatment before stroke onset and the rest were without treatment.(Table 2,Figure 3)

Table 2.Treatment history

Prior treatment		
Prior treatment	**No. of patients**	**Percentage of patients**
Taken	*13*	*36.11*
Aspirin	3	8.33
Clopidogrel	2	5.56
Aspirin + Clopidogrel	3	8.33
Statins	6	16.67
Antihypertensives	9	25
Not taken	*23*	*63.89*

Figure 3. Treatment history



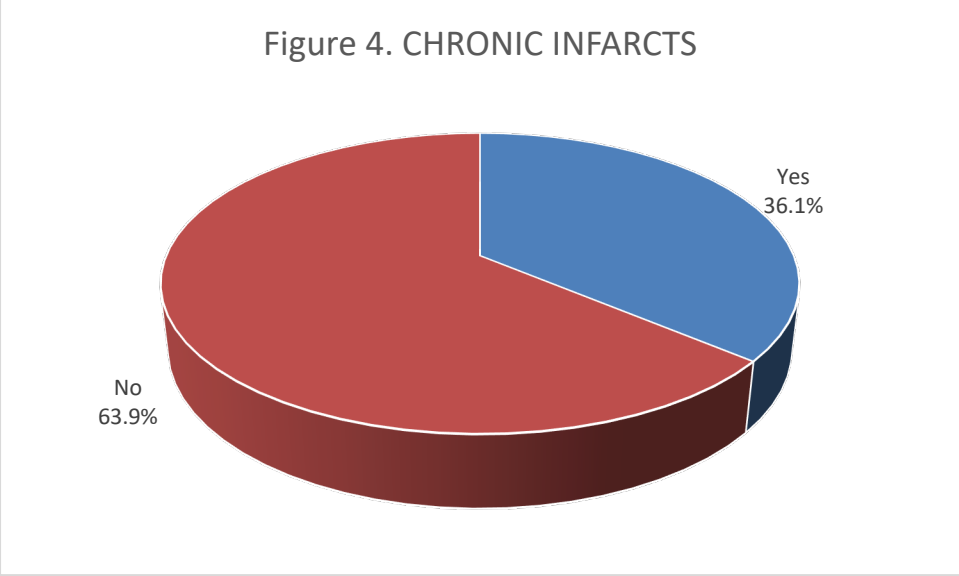
STROKE CHARACTERISTICS

15 patients had right MCA stroke and 21 patients had left MCA stroke. The presence of pattern of infarcts were studied in 33 patients by using MRI diffusion weighted imaging while 3 patients had presented with Transient Ischemic attack. The pattern of acute infarcts is summarized in table 3. 45.4% of patients had perforator territory infarcts, whereas cortical and mixed infarcts were present in 27.2% and 21.4% of patients respectively. Watershed infarcts were present in 6% of patients.

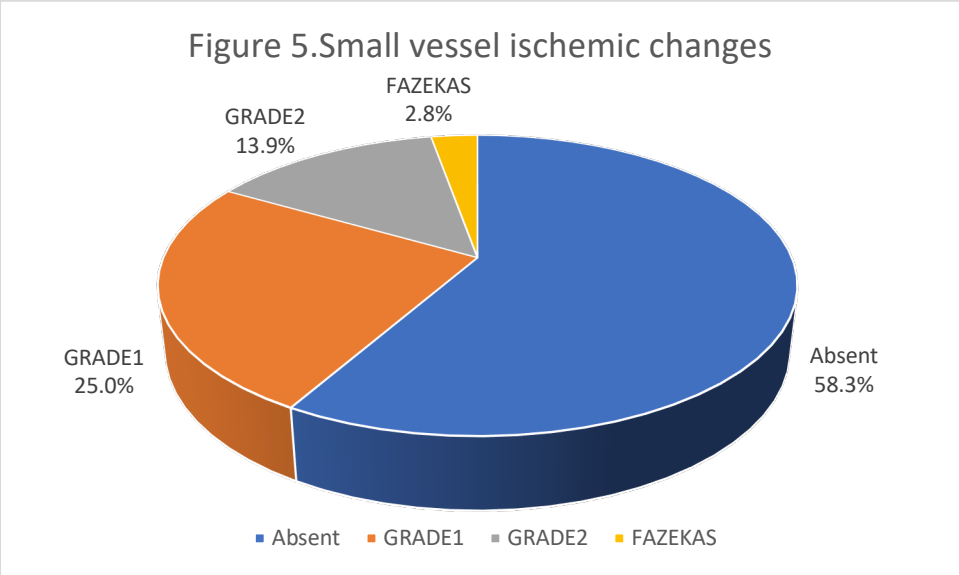
Table 3. Pattern of infarct

Infarct Pattern	Frequency	Percent
Cortical	9	27.2%
MCA Subcortical (Perforator territory)	15	45.4%
Watershed	2	6%
Mixed	7	21.4%
Total	33	100

The presence of chronic infarcts and small vessel ischemic changes are illustrated in Figure 4 and Figure 5 respectively.



Small vessel ischemic changes were seen in 15 patients. The distribution into Grade 1 to Grade 3 Fazeka Changes is shown below.



Cerebral microbleeds were seen in 2 patients and both were eventually diagnosed to be having Intracranial atherosclerotic disease. None of the vasculitis patients were detected to be having microbleeds.

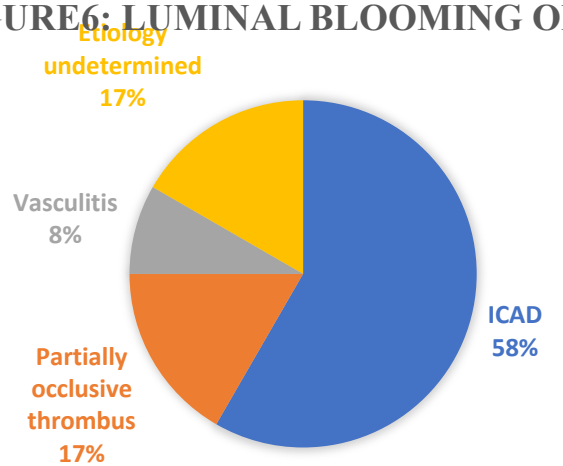
Luminal blooming was seen in 12 patients.(Table 4)

Table 4. Presence of Luminal blooming

LUMINAL BLOOMING ON SWI	Frequency	Percent
Yes	12	33.3
No	24	66.7
Total	36	100

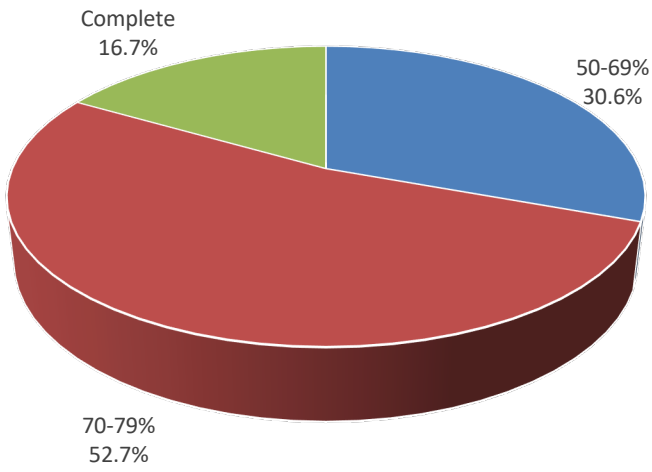
Out of these 12 patients, 7 were Intracranial atherosclerotic disease, 2 were Partially Occlusive thrombus, 1 was vasculitis and in 2 cases diagnosis could not be determined after vessel wall imaging.(Figure 6)

FIGURE6: LUMINAL BLOOMING ON SWI



Luminal imaging by CT/MR Angiography showed the degree of stenosis.(Figure 7)

Figure 7. Degree of stenosis



Site of stenosis

HRVWI done in 36 patients with Middle cerebral artery (MCA) disease showed that 20 patients had left sided and 15 had right sided stenosis which mainly involved the M1 MCA. Only a single patient had stenosis in Left M2 MCA. Asymptomatic vessel narrowing was also seen in other vessels in 16 patients with the total number of stenotic lesions being 77.

Characteristics of vessel wall at stenotic site of middle cerebral artery--

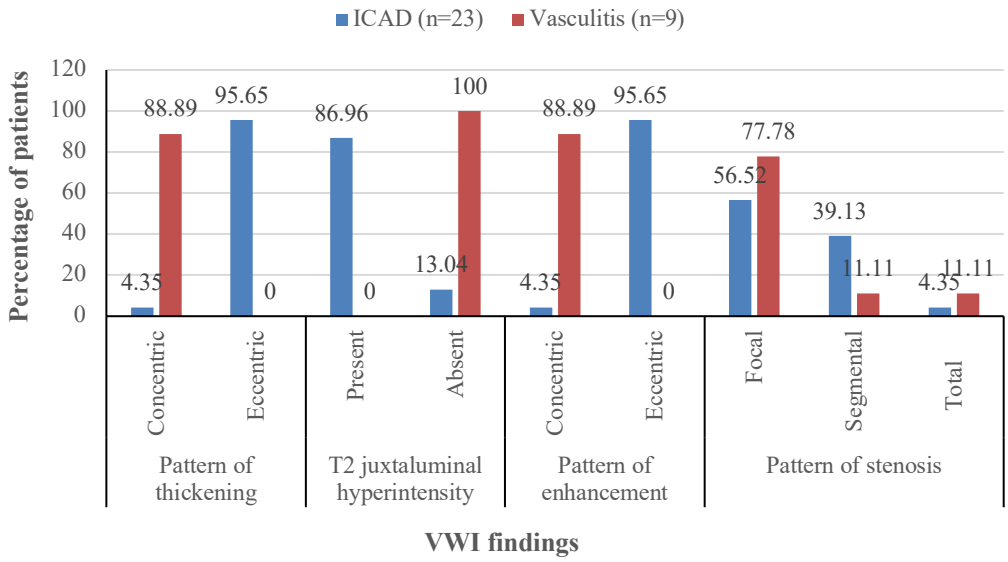
Pattern of thickening and stenosis was assessed along with the presence or absence of positive remodelling and T2 Heterogeneity. Post contrast enhancement of the stenotic vessel wall was also assessed. The findings are summarised in the table below.(Table 5) and illustrated in the figures below.(Figure 9-12)

Table 5. Characteristics of vessel wall at stenotic site

Pattern of thickening	**Frequency**	**Percent**
Normal	2	5.6
Concentric	10	27.8
Eccentric	24	66.7
T1 post contrast vessel wall enhancement	Frequency	Percent
Absent	2	5.6
DIFFUSE CONCENTRIC	10	27.8
FOCAL ECCENTRIC	24	66.7
Positive remodelling	Frequency	Percent
Present	25	69.4
Absent	11	30.6

Pattern of stenosis	Frequency	Percent
Focal	22	61.1
Segmental	12	33.3
Total	2	5.6
Total	36	100
T2 JUXTALUMINAL HYPERINTENSITY WITH SURROUNDING HYPOINTENSITY	Frequency	Percent
Present	22	61.1
Absent	14	38.9
Total	36	100

Figure 8. Summarising the various imaging findings by HRVWI



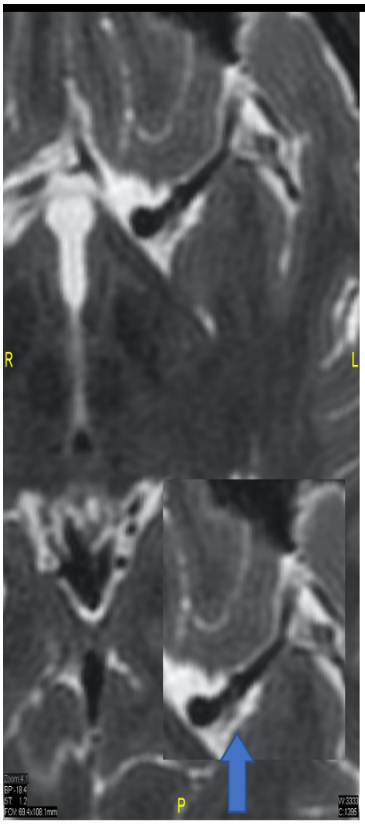


Fig 9

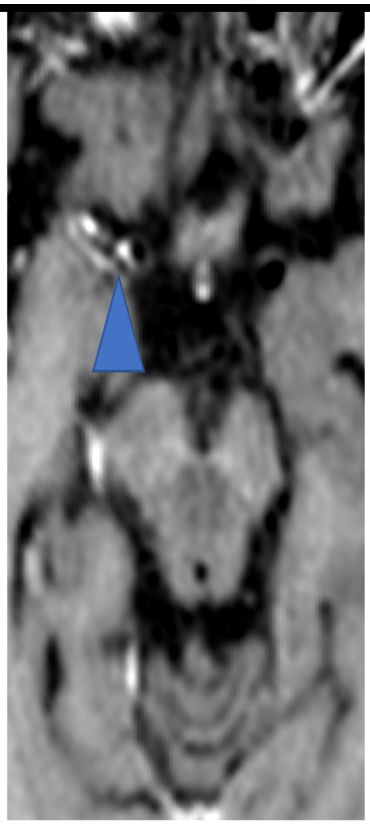


Fig 10

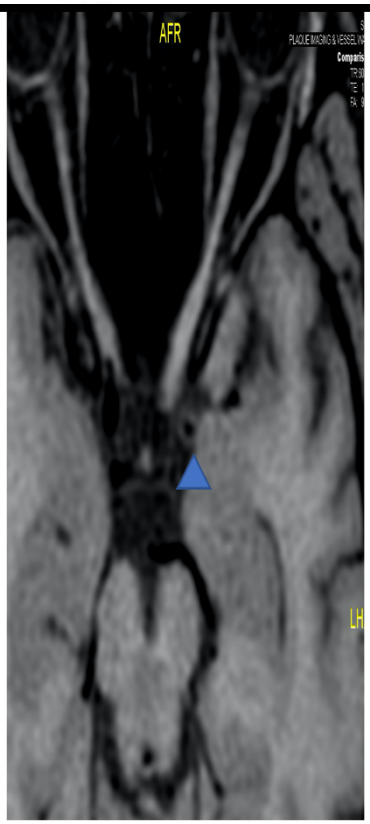


Fig 11

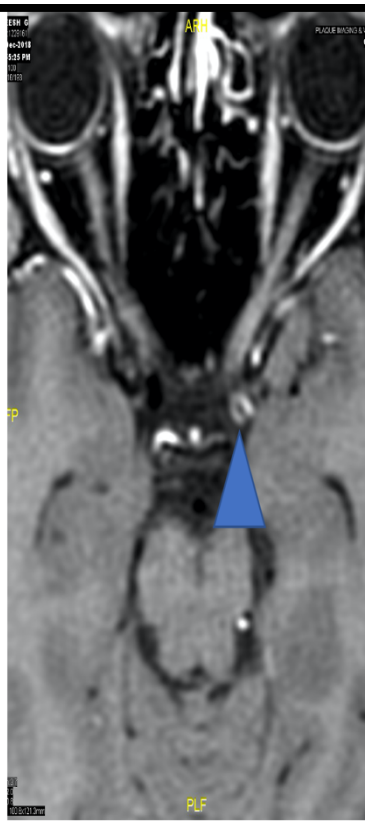


Fig 12

Figure 9:55 year old male presented with aphasia and right sided weakness.Left MCA M1 showed narrowing. HRVWI showing T2 Juxtaluminal hyperintensity

Figure 10:62 year old male presented with left sided weakness.Luminal imaging showed MCA M1 70% stenosis. HRVWI T1 post contrast sequence showing eccentric contrast enhancement

Figure 11:26 year old male presented with right sided weakness 1 week after chickenpox illness.Left MCA M1 showed narrowing. HRVWI showing T1 concentric thickening.

Figure 12:26 year old male presented with right sided weakness 1 week after chickenpox illness.Left MCA M1 showed narrowing. HRVWI showing T1 post contrast enhancement.

Final diagnosis after vessel wall imaging.(Table 8). 23/36 patients were ICAD, 9 had vasculitis, 2 were having partially occlusive thrombus and the etiology of 2 patients could not be determined after vessel wall imaging.

Table 6. Final diagnosis after vessel wall imaging.

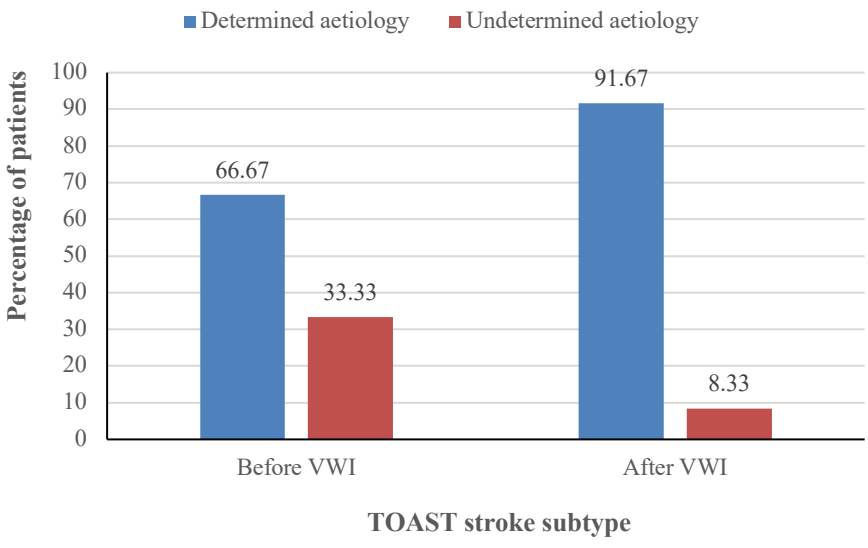
Final Diagnosis after VWI		
Diagnosis	**No. of patients**	**Percentage of patients**
ICAD	23	63.89
Vasculitis	9	25
Partially occlusive thrombus	2	5.56
Undetermined	2	5.56
Total	**36**	**100**

The value of vessel wall imaging in bringing a change to the diagnosis according to TOAST classification is illustrated below (Table 7, Figure 13).

Table 7: Comparison of TOAST classification before and after luminal wall imaging

TOAST classification			
TOAST stroke subtype	**Determined etiology N (%)**	**Undetermined etiology N (%)**	**p-value***
Before VWI	24 (66.67)	12 (33.33)	**0.0091**
After VWI	34 (91.67)	2 (8.33)	
Total	**36**	**100**	
*Calculated using chi-square test. P<0.05 considered statistically significant.			

Figure 13. Change in TOAST classification after vessel wall imaging



TOAST classification

Characteristic features of vessel wall in diagnosing vasculopathic processes.

The presence of eccentric wall thickening can reliably diagnose ICAD and concentric wall thickening can diagnose vasculitis and can distinguish it from ICAD and partially occlusive thrombus. However, eccentric wall thickening can also be seen in Occlusive thrombus and cannot be used to distinguish between ICAD and Partially Occlusive thrombus.

Table 8: T1 vessel wall thickening and its significance in diagnosing various intracranial vasculopathies

T1 VESSEL WALL THICKENING	Diagnosis						Total		Pair wise p value		
	ICAD		Vasculitis		Occlusive thrombus				ICD VS Vasculitis	Vasculitis VS Occlusive thrombus	ICAD VS Occlusive thrombus
	n	%	n	%	n	%	n	%			
Eccentric	22	95.7	0	0	1	50	23	67.6	**<0.001**	**0.003**	0.831
Concentric	1	4.3	8	88.9	0	0	9	26.5			
Normal	0	0	1	11.1	1	50	2	5.9			
Total	23	100	9	100	2	100	34	100			

Juxtaluminal T2 Hyperintensity with surrounding hypointensity

The following table illustrates that juxtaluminal T2 hyperintensity is present in 20 patients and was absent in 3 patients of ICAD and is absent in all patients of vasculitis and partially occlusive thrombus and its presence is thus a diagnostic indicator of underlying ICAD.(Table 9)

Table 9.T2 Juxtaluminal hyperintensity with surrounding hyperintensity in various vasculopathic processes and diagnostic significance

T2 juxtaluminal hyperintensity with surrounding hypointensity	Diagnosis						Total		p value
	ICAD		Vasculitis		Occlusive thrombus				
	n	%	n	%	n	%	n	%	
Present	20	87	0	0	0	0	20	58.8	**<0.001**
Absent	3	13	9	100	2	100	14	41.2	
Total	23	100	9	100	2	100	34	100	

T1 post contrast vessel wall enhancement

The presence of concentric enhancement can reliably diagnose vasculitis from ICAD. Partially occlusive thrombus can show eccentric contrast enhancement on post contrast T1 weighted imaging. This is illustrated by the table given below.(Table 10)

Table 10. T1 post contrast vessel wall enhancement and its diagnostic significance

T1 POST CONTRAST VESSEL WALL ENHANCEMENT	Diagnosis						Total		P-value
	ICAD		Vasculitis		Occlusive thrombus				
	n	%	n	%	n	%	n	%	
Absent	0	0	1	11.1	1	50	2	5.9	
Diffuse concentric	1	4.3	8	88.9	0	0	9	26.5	
Focal eccentric	22	95.7	0	0	1	50	23	67.6	<0.001
Total	23	100	9	100	2	100	34	100	

Positive remodeling

The ability of positive remodelling to differentiate between ICAD and vasculitis and partially occlusive thrombus was found to be statistically significant.(Table 11)

Table 11. Positive remodelling and its diagnostic significance

Positive remodelling	Diagnosis						Total		P value
	ICAD		Vasculitis		Occlusive thrombus				
	n	%	n	%	n	%	n	%	
Present	20	87	3	33.3	0	0	23	67.6	
Absent	3	13	6	66.7	2	100	11	32.4	<0.001
Total	23	100	9	100	2	100	34	100	

Grade of hyperintensity

The following table (Table 12) shows the comparison of Grade of hyperintensity between ICAD and vasculitis. 47.8% of ICAD patients had higher grade of hyperintensity as compared to 33.3% patients in vasculitis and the difference was not statistically significant.

Table 12. Grade of hyperintensity and association between ICAD and vasculitis.

Grade of HI	Diagnosis				Total		p
	ICAD		Vasculitis				
	n	%	n	%	n	%	
0	3	13.0	1	11.1	4	12.5	0.695
1	9	39.1	5	55.6	14	43.8	
2	11	47.8	3	33.3	14	43.8	
Total	23	100.0	9	100.0	32	100.0	

Pattern of stenosis

Pattern of stenosis was not found to be helpful to differentiate the etiology of stroke.

Table 13. Pattern of stenosis seen in various vasculopathic processes and its ability to differentiate between vasculopathies

Pattern of stenosis	Diagnosis						Total		p-value
	ICAD		Vasculitis		Occlusive thrombus				
	n	%	n	%	n	%	n	%	
Focal	13	56.5	7	77.8	1	50	21	61.8	0.570
Segmental	9	39.1	1	11.1	1	50	11	32.4	
Total	1	4.3	1	11.1	0	0	2	5.9	
Total	23	100	9	100	2	100	34	100	

Subgroup analysis

Intracranial atherosclerotic disease

In ICAD subgroup of patients, plaques were found to be superior in location in 61% of patients.(Table 14)

Table 14. Location of plaques in ICAD

Location of plaque	Frequency	Percent
Superior	14	60.9
Inferior	4	17.4
Anterior	4	17.4
Concentric	1	4.3
Total	23	100.0

In ICAD subgroup of patients, 12 patients were found to have recurrent events. Various risk factors of stroke recurrence were matched between the recurrent and non-recurrent groups.(Table 15)

Table 15. Risk factors of stroke recurrence and their comparison between the recurrence and non-recurrence groups

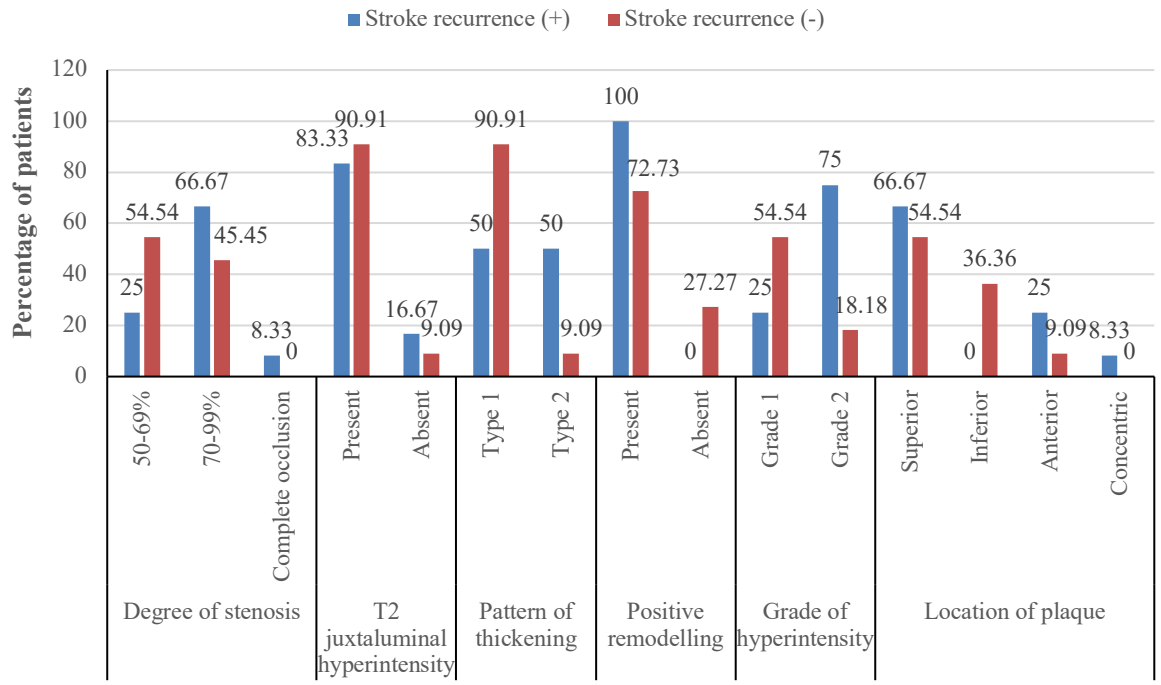
Factors associated with stroke recurrence			
Factors	**Stroke recurrence (+)**	**Stroke recurrence (-)**	**p-value**
N	12	11	
Age (in years), Mean ± SD	58.67 ± 9.31	57.09 ± 11.29	0.7169*
Gender, n (%)			
Males	11 (91.67%)	9 (81.82%)	0.4836#
Females	1 (8.33%)	2 (18.18%)	
Comorbidities, n (%)			
HTN	10 (83.33%)	9 (81.82%)	
DM	6 (50%)	5 (45.45%)	0.4114#
Dyslipidemia	2 (16.67%)	5 (45.45%)	
CAD	1 (8.33%)	4 (36.36%)	
Risk factors, n (%)			
Smoking	3 (25%)	2 (18.18%)	0.7642$
Alcohol	2 (16.67%)	2 (18.18%)	
HbA1c, n (%)			
<6.5%	5 (41.67%)	6 (54.54%)	
6.5-9%	4 (33.33%)	2 (18.18%)	0.6331#
9-10%	1 (8.33%)	1 (9.09%)	
>10%	1 (8.33%)	3 (27.27%)	
TC, Mean ± SD	162.5 ± 39.90	176.18 ± 78.10	0.5976*
LDL, Mean ± SD	102.75 ± 29.45	107.09 ± 52.39	0.8067*
HDL, Mean ± SD	38.75 ± 10.01	43.82 ± 6.46	0.1680*
TG, Mean ± SD	126.08 ± 50.42	121.64 ± 51.41	0.8365*
Mean SBP, Mean ± SD	155.33 ± 23.48	145.45 ± 15.59	0.2524*
Mean DBP, Mean ± SD	86.67 ± 9.71	88.27 ± 9.05	0.6876*

*Calculated using the student's t-test. #Calculated using the Chi-square test. $Calculated using the Fisher's exact test.P<0.05 considered statistically significant.

Imaging findings in ICAD patients with stroke recurrence are illustrated in the following table.66.6% of patients had 70-99% stenosis and positive remodeling was seen in all patients. T2 heterogeneity was seen in 83.33% of patients whereas high grade of post contrast hyperintensity was seen in 75% of patients.66.6% of patients had superior location of the plaque.(Table 16, Figure 14)

Table 16.Plaque characteristics of patients with recurrent strokes

Findings in ICAD patients with stroke recurrence (n=12)		
Findings	**No. of patients**	**Percentage of patients**
Degree of stenosis		
50-69%	3	25
70-99%	8	66.67
Complete occlusion	1	8.33
T2 juxtaluminal hyperintensity with surrounding hypointensity		
Present	10	83.33
Absent	2	16.67
Pattern of thickening		
Type 1	6	50
Type 2	6	50
Positive remodeling		
Present	12	100
Absent	0	0
Grade of hyperintensity		
Grade 1	3	25
Grade 2	9	75
Location of plaque		
Superior	8	66.67
Anterior	3	25
Concentric	1	8.33



Findings in ICAD patients with stroke recurrence and without stroke history

T1 hyperintensity

There was positive correlation between presence of T1 hyperintensity and luminal blooming on Susceptibility weighted imaging(Table 17)

Table 17. T1 hyperintensity and its association with Susceptibility weighted imaging

T1 hyperintensity	LUMINAL BLOOMING ON SWI				Total		p
	Yes		No				
	n	%	n	%	n	%	
Absent	0	0.0	7	43.8	7	30.4	**0.036**
Present	7	100.0	9	56.3	16	69.6	
Total	7	100.0	16	100.0	23	100.0	

Factors associated with stroke recurrence

Grade of hyperintensity and >50% circumferential thickening of vessel wall (Type II) were associated with significant association with stroke recurrence in our study group. It was also noted that the presence of higher duration of hypertension approached statistically significant association with recurrent strokes. The presence of T1 hyperintensity was not associated with stroke recurrence.(Table 18).High risk and low risk plaque features are illustrated in the figure below.(Figure 15)

Table 18. Factors associated with stroke recurrence and their significance

	Recurrent Stroke				Total		p
	Present		Absent				
	n	%	n	%	n	%	
Duration of Hypertension >5 years	7	70	9	100	16	84.2	0.073
Duration of Diabetes > 5years	5	83.3	5	100	10	90.9	0.338
HbA1C >9	2	18.2	3	27.3	5	22.7	0.611
Pattern of Thickening- Type II	6	50	1	9.1	7	30.4	**0.033**
Degree of stenosis >70%	9	75	5	45.5	14	60.9	0.147
Location- superior	8	66.7	6	54.5	14	60.9	0.552
Grade of HI Grade 2	9	75	2	18.2	11	47.8	0.006
Prior treatment	4	33.3	7	63.6	11	47.8	0.146
T1 Hyperintensity	9	75	7	63.6	16	69.6	0.554

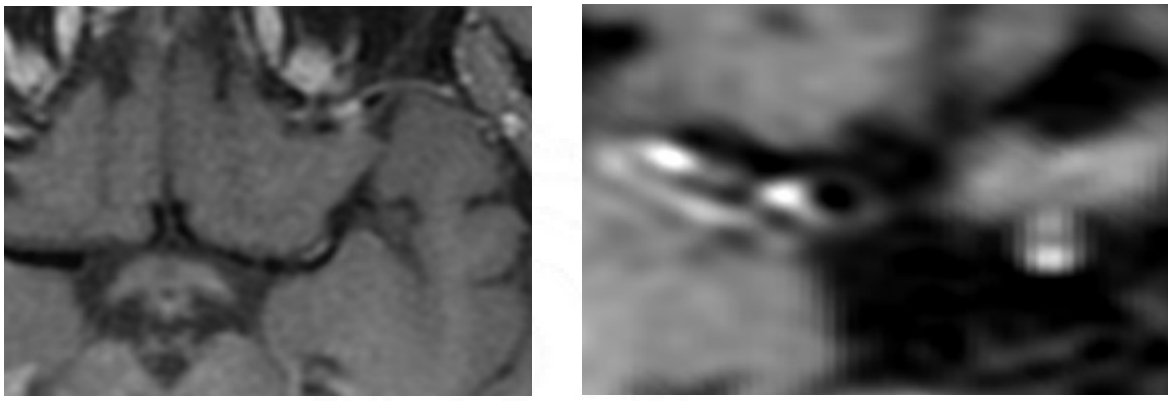


Figure 15: Showing comparison between Grade 1 and Grade 2 pattern of contrast enhancement. Patient 1 had a left MCA stroke and recovered whereas Patient 2 was readmitted with a worsening 1 week later.

Factors influencing Grade of Hyperintensity

Factors influencing Grade of hyperintensity were also studied including age and presence of hypertension or dyslipidemia. None of the associations were found to be statistically significant.(Table 19)

Table 19. Factors influencing Grade of Hyperintensity

	Grade of HI				p-value
	Higher grade (N=11)		Lower grade(N=12)		
	Mean	SD	Mean	SD	
AGE	60.73	9.221	55.33	11.436	0.225
Systolic blood pressure	149.45	15.546	151.67	25.949	0.805
Diastolic blood pressure	85.82	10.294	88.92	9.199	0.457
Total cholesterol	165	41.689	172.75	79.516	0.771
Low density lipoprotein	104.91	32.073	104.75	52.59	0.993
High density lipoprotein	39.91	10.454	42.33	7.878	0.54
Triglycerides	115	42.485	132.17	60.266	0.436

DISCUSSION

Our study provides insights into various vasculopathic processes, patterns of vessel wall involvement and assessment of the added benefit of HRVWI compared with current luminal diagnostic algorithms in the differentiation of nonocclusive vasculopathies, specifically ICAD, vasculitis and partially occlusive thrombus. It also helped to identify the features which can depict plaque vulnerability in intracranial atherosclerotic disease subgroup in 36 patients of acute ischemic stroke patients admitted in comprehensive stroke care centre at a tertiary care hospital in south India during a four year time period(2016-2019).

Previously, luminal imaging had served as the reference standard for the differentiation and characterization of nonocclusive vasculopathies. However, in the current study, luminal imaging alone could not definitively diagnose 5 cases of ICAD, 4 cases of vasculitis and one case of partially occlusive thrombus. After vessel wall imaging, the diagnostic accuracy increased from 66.6% to 91.6%. Our findings were in line with previous studies(25,26)(36)which showed that the addition of vessel wall imaging to luminal imaging significantly improves the diagnosis of etiology of stroke. In a study done by MossaBasha et al, the diagnostic accuracy of etiology increased from 43.5% after luminal imaging to (96.3%) when luminal+HRVWI were reviewed(11).

Our study also attempted to compare the HVWI appearances of ICAD,Vasculitis, and Partially occlusive thrombus. We found that using a contrast vWI protocol, following differences could be seen--- ICAD had eccentric, mild to moderately eccentric contrast enhancing lesions with heterogenous T2 appearance in addition to presence of positive remodelling.

This is in line with earlier research from Swartz et al,(37) in which the authors showed that patients suffering from atherosclerotic disease had focal, eccentric lesions compared with patients with other pathologies who had diffuse and concentric lesions. On the other hand, vasculitis had concentric thickening and concentric contrast enhancement with absence of T2 heterogeneity and positive remodelling which has been demonstrated previously. Previous literature(38) has described artery to artery embolism occlusions to be of normal thickness and non- contrast enhancing but can show concentric thickening and enhancement which was more commonly seen in patients treated with mechanical thrombectomy than medical therapy. In our study, one patient with a partially occlusive thrombus had eccentric thickening and mild eccentric contrast enhancement. The presence of underlying ICAD was ruled out by the absence of T2 heterogeneity and also absence of positive remodelling. So, our study signifies that partially occlusive thrombus, in

addition to showing normal or concentric thickening, can have eccentric thickening. Further studies with large sample size of partially occlusive thrombus are needed to further confirm this finding.

In a study done by Sung-Ho Ahn et al(39), atherosclerotic narrowing was focal whereas narrowing associated with vasculitis were non-focal. In our study, however, 7/9 patients of vasculitis were found to have focal stenosis. Although our HR-vasculitis patients did not show these characteristics findings, this can be explained by the fact that vasculitis may show variable pattern of the vessel wall involvement depending on the inflammatory status.

The analysis of the grade of hyperintensity between ICAD and vasculitis did not show any statistically significant difference.. This was in contrast to various studies which had shown that vasculitis was associated with higher grade of hyperintensity (40). This could be explained either by variable pattern of vessel wall involvement depending on the disease stage and due to the small sample size of patients in the vasculitis subgroup.

In the ICAD subgroup of 23 patients, plaques were found to be in superior location in 61% of patients. This is contrast to the previous study done by Wei-Hai Xu et al who in their study of location of MCA plaques and their clinical relevance showed that plaques were more

frequently located at the ventral and inferior wall as compared with the superior and dorsal wall(17). When symptomatic MCA plaques were considered, significantly more number of plaques were superior in location as compared to ventral and inferior location. Our study found that among 23 patients of ICAD, 61% had plaques in superior location which concurs with the study.

12/23 patients in ICAD subgroup had recurrent strokes in the symptomatic artery distribution. The role of vessel wall imaging in determining vulnerable plaque characteristics were studied. Our study did not find any significant correlation with the degree of stenosis and the chances of having recurrent stroke. This signifies the limitation of luminal imaging in accurately depicting the degree of stenosis in ICAD patients due to outward(positive) remodelling in ICAD lesions.

The association of contrast enhancement with symptomatic plaques is controversial. In a study done by Dieleman et al(18) in middle cerebral artery symptomatic plaques, no association was found between enhancement and symptomatic plaques. Lesion enhancement is a well established feature of plaque vulnerability in extracranial circulation but same could not be said for intracranial arteries as they have abundant vasa vasorum which can increase with age. However, not all elderly patients have been found to have enhancing walls which may suggest that that

different mechanisms are involved in the intracranial vessel wall enhancement. However, our study has shown definite correlation between higher grade of hyperintensity with stroke recurrence. The other risk factors for stroke such as age, presence of traditional vascular risk factors were not different between the recurrence and non-recurrence groups. These results are similar to the studies done by Fang Wu et al(41) and Gyung Ho Chung(18) who showed that the presence of Grade 2 enhancement is associated with increased recurrence of stroke. These results can provide valuable insights in risk stratification of stroke patients.

In addition to Grade 2 enhancement, thickening of the vessel wall with >50% circumferential thickening is associated with stroke recurrence which was similar to study done by Fang Wu et al(42). This suggests that type 2 thickening pattern may be a marker of more progressive and extensive plaques, which may easily develop into vulnerable plaques.

Controversy also exists for the presence of T1 hyperintensity in ICAD patients. Ryu et al. (43) have reported that T1 hyperintense foci were more frequently observed within the plaques of symptomatic stenosis than within the plaques of asymptomatic stenosis. However, Xu et al. (44)in their study of ICAD plaques reported that a hyperintensity band was observed in most of the MCA plaques, irrespective of symptoms.

Studies have shown that T1 Hyperintensity is an indicator of intra-plaque hemorrhage but in another study by Natori et al(44)Type 1 hyperintensity was believed to indicate the presence of lipid components in addition to IPH. In our study no difference of presence of T1 hyperintensity between stroke recurrence and non-recurrence groups was seen. However, a positive association was obtained between presence of T1 hyperintensity and SWI blooming. These two findings indicate that the presence of T1 hyperintensity in our patients is not only an indicator of intra-plaque hemorrhage but also indicates the presence of lipid components.

Strengths of the study

1) Vessel wall imaging data was reviewed by a trained neuroradiologist who was blinded to the clinical diagnosis of the patient.
2) All parameters assessed in vWI were defined according to accepted standards to ensure uniformity.

Limitations

Few limitations of the study include-

1) the small number of subjects
2) The lack of pathological verification of MCA stenosis.
3) No serial MRI examinations were performed in this study to monitor the progression of burden of the plaques.

CONCLUSIONS

- Our data provides insights into the various vasculopathic processes involving the middle cerebral artery.
- Our study was able to highlight the plaque characteristics and the ability of these characteristics to differentiate between various vasculopathic processes.
- Our study also highlighted that the confidence of diagnosis of various vasculopathic processes was more when vessel wall imaging was combined with luminal imaging than as compared to luminal imaging alone.
- Plaque characteristics on vessel of imaging which can suggest vulnerable plaques in Intracranial atherosclerotic disease patients are Higher grade of hyperintensity and Type II pattern of thickening.
- These findings have implications as the presence of these findings in asymptomatic plaques might suggest the chances of stroke and thus guide management.

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APPENDIX

LIST OF ABBREVIATIONS

HRvWI	High resolution vessel wall imaging
CTA	Computed Tomography angiography
MRA	Magnetic resonance angiography
DSA	Digital Subtraction Angiography
ICAD	Intracranial atherosclerotic disease
MMD	Moya-Moya Disease
IPH	Intra-plaque hemorrhage
TC	Total cholesterol
HDL	High density lipoprotein
LDL	Low density lipoprotein
TG	Triglycerides
DANTE	Delay alternating with nutation for tailored excitation
VRFA	Variable Refocussing Flip Angle
TOF	Time of Flight
SWI	Susceptibility Weighted Imaging
FS	Fat suppressed
RCVS	Reversible Cerebral Vasoconstriction Syndrome

Proforma

1.1. Name of the patient: ----------

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

1.3 Sex ---------- 1.Male 2.female

1.4. Date of admission. ----------

1.5. Date of symptom onset----------

2. Risk factors (1=yes, 2=No)

1. Hypertension---------- Duration in years ----------

2. Diabetes mellitus---------- Duration in years ---------

3. Current smoking---------- pack years ----------

4 Ex smoker……Stopped ----------years back

5. Drug addiction ----------

6. Alcoholism----------

7. Coronary artery disease-------- Duration in years ----------

8 Valvular heart disease--------- Duration in years ----------

9Congestive heart failure ---------- Duration in years ----------

10. Peripheral vascular disease--------

11. Hyperlipidaemia---------- Duration in years----------

12. Atrial fibrillation---------- Duration in years----------

13. Known carotid disease----------

14. Patients on treatment ----------

15 . If yes, Type of treatment ----------

3.Symptoms(1=yes, 2=No)

3.1. Visual disturbances ----------1.Amaurosis fugax 3.Hemianopia 4.Diplopia 5. Blurring of vision 6. None

3.2. Weakness ---------- 1. face alone 2.arm 3.leg 4.arm and leg 5. Face arm and leg 6.None

3.3. Numbness/paresthesia ----------

3.4. Speech disturbances ----------1.Aphasia 2.Dysarthria3. Both 4.None

3.5. Ataxia----------

4. Clinical Examination(1=yes, 2=No)

4.1. Pulse rate---------- (If Regular =1, Atrial fibrillation =2)

4.2. Blood pressure at ER Systolic---------- diastolic --------- (first documented BP)

4.3. Bruit ----------

4.4. Weakness ----------

4.5. Numbness----------

4.6. Cerebellar signs----------

4.7. Aphasia----------

4.8. Dysarthria ----------

4.9. Hemianopia----------

4.9.1. Hemispatial neglect ----------

4.9.2. Final impression----------

1. Right hemispheric 2.Left hemispheric

4.9.3 NIHSS at admission ----------

4.9.4. NIHSS at 24hours (if admitted on day of stroke or TIA onset) ----------

4.9.5. GCS on admission ----------

4.9.6. MRS prior to stroke ----------

4.9.6a.mRS at stroke onset----------

5. Investigations

5.1. Blood glucose in ER----------

5.2. Serum cholesterol----------

5.3. LDL--------

5.4. HDL----------

5.5. Serum triglycerides----------

5.6. ECG---------- 1.Normal 2.LVH 3.AF 4 Ischemic changes 4. Not done

5.7. Echo-trans thoracic ---------- 1.Normal 2.LV dysfunction 3.Mural thrombus 4. Valve disease 5.PFO 6.infective endocarditis7.Not done.

5.7a.If valve disease, specify ----------

6.Diagnostic imaging

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

6.1. A Territory ---------- 1. ICA 2.ACA 3.MCA-complete 4 MCA-Inf div 5 MCA sup div 6 MCA subcortical

6.1.B Dense artery sign -------1. MCA 2. PCA 3. Basilar 4.ACA.5.ICA 6.absent

6.2. CT angio neck ---------- 1.Normal 2.abnormal 3.not done

6.2.1. If abnormal, specify ----------

6.2.2. CT angio intracranial----------1.Normal 2.abnormal 3.not done

6.2.3. If abnormal, specify----------

6.3. MRI scan ---------- 1. DWI negative 2.DWI positive single lesion3.DWI – Multiple lesions 4.Not done

6.3.1. Arterial territory of acute infarct---------- 1.ICA 2.ACA 3.MCA-complete 4. MCA-Inf div 5. MCA sup div 6. MCA subcortical

6.4. MRA neck----------1.normal 2.abnormal 3.Not done

6.4.1. If abnormal specify----------

6.4.2. MRA intracranial----------1.normal 2.abnormal 3.Not done

6.4.3. If abnormal, specify ----------

6.5. Carotid Doppler----------1.normal 2.abnormal 3.Not done

6.5.1. If abnormal, specify ----------

6.6. DSA---------- 1.normal 2.abnormal 3.Not done

6.6.1. If abnormal specify ----------

6.7. Final impression on vessel status (symptomatic vessel) ---------- 1. <50% stenosis 2. Moderate stenosis (50-69%) 3.severe stenosis 4.arterial dissection 5.vessel occlusion 6.Normal

6.7.1. Vessel involved ---------- 1.MCA M1 2. MCA M2. -

6.7.2. Side of involvement of vessel ----------1.Right 2.Left 3.Bilateral

6.8 MR Vessel wall imaging---------- Findings

6.8.1 Wall remodeling------ 1. Positive 2. Negative

6.8.2 Wall thickening and enhancement 1. Concentric 2. Eccentric 3. No enhancement

6.8.3 Intimal flap 1. Present 2. Absent

6.9Stroke subtype----------1.large artery atherosclerosis 2.Cardioembolic.3Other Specific causes.4.Undetermined 5.lacunar

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)

SCT/IEC/1338/FEBRUARY-2019 *02.04.2019*

Dr. Vaibhav Tandon
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Vaibhav Tandon,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled "HIGH RESOLUTION MR VESSEL WALL IMAGING IN THE DIAGNOSIS OF INTRACRANIAL VASCULOPATHY DUE TO MIDDLE CEREBRAL ARTERY DISEASE (IEC/1338)" on 16th February, 2019.

The following documents were reviewed:

Original submission

1. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 28.01.2019 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 30.03.2019 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

The following members of the Ethics Committee were present at the meeting held on 16th February, 2019 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation wi Institution(s
1.	Dr. R V G Menon	M Tech, PhD	Male	*Lay Person (Chairman)*	*No*
2.	Dr. Rema M. N	MD	Female	*Basic Medical Scientist*	*No*
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	*Basic Medical Scientist*	*No*
4.	Dr. Harikrishna Varma PR	Ph.D(Materials Science)	Male	*Medical Technology*	*Yes*
5.	Dr. Christina George	MD Psychiatry	Female	*Clinician*	*No*
6.	Dr. S S Giri Sankar	LL.M. Ph.D.	Male	Legal Expert	*No*
7.	Dr. Aneesh V Pillai	BA. LLB (Hons.), LLM, Ph. D, SET (Law)	Male	Legal Expert	*No*
8.	Dr. P. Manickam	BSMS, MSc (Epid).,PhD	Male	Health Science Expert/ Social Scientist	No
9.	Mr. Satheesh Chandran	MSW, PGDPM	Male	Lay person/ NGO/ Social Scientist	No
10.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
11.	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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