CORRELATION OF CAROTID INTIMA-MEDIAL THICKNESS (CIMT) AND DISEASE ACTIVITY IN TAKAYASU ARTERITIS (c-CAT STUDY)

A dissertation submitted in partial fulfillment of DM- Branch II Cardiology Examination of the Tamilnadu Dr. MGR Medical University, Chennai, to be held in July/August 2010.

BONAFIDE CERTIFICATE

This is to certify that the work presented in this dissertation titled "**CORRELATION OF CAROTID INTIMA-MEDIAL THICKNESS (CIMT) AND DISEASE ACTIVITY IN TAKAYASU ARTERITIS (c-CAT STUDY)"** done towards fulfillment of the requirements of the Tamilnadu Dr. MGR Medical University, Chennai, for the DM- (Branch II) (Cardiology) examination to be conducted in July/August 2010, is a bonafide work of the candidate Dr. Sujith Thomas Chacko, Post-graduate student in the department of Cardiology, Christian Medical College,Vellore, under my guidance & supervision. This dissertation has not been submitted, fully or in part to any other board or university.

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DECLARATION

I, Dr. Sujith Thomas Chacko, hereby declare that this dissertation entitled "**CORRELATION OF CAROTID INTIMA-MEDIAL THICKNESS (CIMT) AND DISEASE ACTIVITY IN TAKAYASU ARTERITIS (c-CAT STUDY)"** has been prepared by me under the supervision and guidance of Dr. George Joseph M.D., D.M., FCSI, Professor, Department of Cardiology, Christian Medical College, Vellore. This is being submitted to Dr. M.G.R. medical university in partial fulfillment of regulations for the DM- (Branch II) (Cardiology) examination to be conducted in July/August 2010.

This dissertation has not been submitted by me either in part or in full on any previous occasion to any university or institution for the award of any degree or diploma.

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Dr.SujithThomas Chacko

CONTENTS

TITLE OF THE STUDY

CORRELATION OF CAROTID INTIMA-MEDIAL THICKNESS (CIMT) AND DISEASE ACTIVITY IN TAKAYASU ARTERITIS (c-CAT STUDY)

Correlation of CIMT and disease Activity in Takayasu Arteritis (c-CAT study)

ABSTRACT

Background: Clinical analysis of Takayasu Arteritis (TA) disease activity, response to treatment and detection of relapse remains suboptimal. The currently used NIH criteria demand an invasive procedure and have other limitations. B-mode carotid ultrasound is a safe, reliable and non-invasive method of measuring CIMT which may have a role as a marker of disease activity.

Objective: To assess correlation of Carotid Intima-Medial Thickness (CIMT) with disease activity in patients with Takayasu's arteritis (TA).

Methods: An observational study on 41 consecutive patients with TA seen in the Cardiology department from August 2008 to January 2010. Disease activity was assessed in these patients using (i) acute phase reactants- ESR, CRP (ii) NIH (National Institute of Health) criteria, & (iii) ITAS score (Indian Takayasu arteritis Activity Score. Angiographic extent of the disease was also assessed at enrollment. CIMT images were acquired with a high-end ultrasound system, at end diastole. CIMT were then measured in the proximal, mid & distal common carotid artery on both the left & right side.
CIMT was also measured in 30 healthy controls, of a similar age group as the study population.

Results: A total of 41 patients were studied. The male, female ratio was approximately 1:4. CIMT was increased in patients with Takayasu arteritis as compared to the controls. The mean CIMT among the study population was 0.85 ± 0.30, which was significantly higher than that of the controls which was 0.50 ± 0.06 ($p = 0.00$). Patients with active disease (CIMT = 1.05 ± 0.33) had higher values than those with inactive disease (CIMT = 0.73 ± 0.20). CIMT $\geq$ 0.80mm was found to have a statistically significant association with ESR $\geq$ 40mm in 1 hour, NIH score $\geq$ 2, and ITAS score $\geq$ 3. CIMT $\geq$ 0.80mm has a sensitivity of 86% & a specificity of 61% in the detection of active TA.

Conclusion:
Abnormal CIMT (CIMT $\geq$ 0.80mm) is an easily available & economical tool that can be used to reliably assess disease activity in patients with TA.

INTRODUCTION

Takayasu Arteritis (TA) is a chronic vasculitis of uncertain etiology involving the large elastic arteries. TA is widely recognized as a multifactorial disease, although a genetic factor has been suggested as its cause because of predominance in young females from the Orient. The disease onset is insidious, and prominent symptoms are nonspecific or absent in majority of the patients in the early stage. Moreover the clinical features differ with geographical location. Hence a high index of suspicion is needed to make the correct diagnosis. The gold standard to confirm the diagnosis is aortography. The course and prognosis of patients with TA show wide variation.

Detailed assessment of disease extent and activity are essential to follow both the long term outcome and the response to therapy in TA. Serological tests have proved unreliable in distinguishing active from quiescent disease. The main problem here is assessing activity in a disease where so much of the pathology is located in deep-seated vessels, progressing at a slow pace and not necessarily associated with any acute phase response. The need is to develop techniques that will allow activity to be assessed independently of acute clinical events, such as vessel occlusion. Non-invasive imaging currently is a promising tool for early diagnosis, detection of disease activity and monitoring response to treatment. Assessment of inflammation in the vessel wall by MRI or PET may allow reliable assessment of disease activity. However these techniques are expensive & are

not widely available. The establishment of a gold standard for activity should at least provide the necessary anchor for clinical studies.

An increase in Carotid Intimal Medial Thickness (CIMT) in inflammatory conditions such as rheumatoid arthritis, psoriatic arthritis, Behcet's disease and Takayasu's arteritis has been demonstrated. B-mode carotid ultrasound is a safe, reliable and non-invasive method of measuring CIMT. Therefore we undertook this study to evaluate the role of CIMT as a marker of disease activity, in patients with TA.

AIMS & OBJECTIVES

Aims:

1. To assess correlation of Carotid Intimal Medial Thickness (CIMT) with disease activity in patients with Takayasu's arteritis (TA).

Objectives:

1. To detect the association of an abnormal CIMT with the currently used parameters of disease activity, in patients with TA.

2. To assess the sensitivity & specificity of an abnormal CIMT (CIMT $\geq$ 0.80mm) to detect active TA.

3. To detect the cutoff point of CIMT that yields the best sensitivity & specificity to detect active disease, using the currently available parameters of disease activity.

REVIEW OF LITERATURE

Takayasu arteritis (TA) is classically described as a chronic, progressive, inflammatory, disease involving the large elastic arteries mainly the aorta and its major branches as well as the pulmonary artery and its branches. The inflammation leads to stenosis and occlusion of the involved artery or aneurysm formation or both. The arterial lesions can lead to secondary hypertension, retinopathy, cardiac involvement, cerebrovascular events, and premature death. The course and prognosis of patients with aortoarteritis show wide variation. In addition to substantial morbidity, mortality has been reported to be as high as 20% at 5 yrs[1]. A small percentage of patients experience a self-limiting monophasic inflammatory episode, which does not require chronic immunosuppressive therapy and does not progress to the occlusive stage.

History

The first description of this morbid condition was in 1830 by Yamamoto in Japan[17]. However, the first scientific presentation of Takayasu Arteritis was made in 1905 at the 12th annual meeting of the Japan Ophthalmology Society in Fukuoka by Mikito Takayasu describing a case of a 21-year old girl who showed a peculiar optic fundal finding - a peculiar wreathlike arteriovenous anastomosis around the papillae of the retina (Takayasu disease)[2]. In 1940 Ohta confirmed that this characteristic optic fundal feature resulted in ischemia due to the obstruction of cervical vessels[18]. This disease has come to

be called Takayasu Arteritis in honor of the first reporter. At that meeting both Dr. Ohnishi and Dr. Kagoshima both pointed out that in their patients no radial pulse could be palpated. In 1951, Shimizu and Sano summarized the clinical features of this "pulseless disease"[3]

Epidemiology

TA is rare, but most commonly seen in Japan, South East Asia, India, and Mexico. It is the third commonest vasculitis in childhood worldwide. A study of North American patients by Hall *et al* found the incidence to be 2.6/million/year[4]. TA is the most common cause of renovascular hypertension in India, China, Korea, Japan and other countries of South East Asia.

The disease commonly presents in the 2nd or 3rd decade of life, often with a delay in diagnosis from the onset of first symptoms of months to years. In one of the cohorts[5] (n = 107) 80% of patients were between 11 and 30 years, 77% had disease onset between the ages of 10 and 20 years. The time from onset of symptoms to diagnosis was 2 to 11 years in 78%. A study of 88 patients from India[1] found the age at symptom onset to be 24.0 ± 8.8 years and the age at diagnosis to be 28.3 ± 9.9 years. The National Institute of Health study by Kerr *et al* suggested that the delay in diagnosis was longer in juveniles, being up to four times that of adult patients[35]. However, data from India[6] looking at patients aged less than 18 years demonstrated a delay of only 2.5 to 5.5 months. This presumably reflects the higher incidence & hence increased clinical awareness.

The disease has a predilection for females with wide geographical variations; in Japan it is 8: 1, in Mexico 5: 1, in India 4: 1[7]and in Israel 1.2: 1. In a series by Panja et al[8] from India, F:M ratio was 6.4 : 1.

Pathology

Aortoarteritis is a panarteritis involving all the three layers of the arterial wall causing extensive intimal proliferation, inflammation of media and adventitia followed by marked fibrous scarring[9].

In the acute stage of large vessel vasculitis, adventitial vessels of the arterial walls (vasa-vasorum) become inflamed. The media is infiltrated by lymphocytes & occasional gaint cells with neovascularisation. Neovessels originate at the junction of the media and adventitia, and subsequently fan out to incorporate the entire media[10]. The intima becomes thickened, with depositions of mucopolysaccharides, smooth muscle cells, and fibroblasts.

The arteritis then progresses to a chronic sclerotic stage, with intimal and adventitial fibrosis and scarring of the media. Histologically there is round cell infiltration, cuffing of vasa vasorum and destruction of tunica media leading ultimately to gross fibrosis. In older cases, hyalinization of deeper layers of intima and dystrophic calcification can be seen. The appearance of aortic intima is closely related to the activity and duration of the disease. Circumferential intimal thickening, plaques and patches of raised intima are frequently seen on the inner surface of the aorta. In advanced stage, the aortic intima may

have ‘tree-bark’ appearance similar to that of luetic aortitis[11]. Skipped areas of aortic involvement are quite characteristic of aortoarteritis.

Aneurysm formation also occurs, as an abnormal response to mural stress because of inflammation, and may be exacerbated by increased volume, as with aortic regurgitation.

Infection, particularly, tuberculosis has been implicated in the pathogenesis of this disease. However a causal immunopathogenic relationship is still unclear.

Clinical Features

TA classically exhibits a triphasic pattern of expression consisting of a systemic non-vascular phase, a vascular inflammatory phase, and a quiescent, “burnt out” phase[4]. However, this classic presentation holds true only in a minority of patients because both inflammatory and fibrotic changes may coexist at one time owing to the chronic and recurrent nature of TA[12]. During the early systemic non-vascular phase, nonspecific systemic symptoms and signs predominate, albeit often unrecognised. The late phase is characterised by ischaemia, and symptoms secondary to arterial occlusion. Recurrent disease often occurs in new arterial territories, with the coexistence of active and quiescent disease.

Symptoms and signs include[13]

1) Fever, breathlessness, hemoptysis, headache, dizziness, vertigo, angina, chest wall pain and claudication pain.
2) Diminished or absent pulses in 84–96% of patients, resulting in discrepancies of blood pressure between limbs.

3) Hypertension in 1/3rd to 3/4^{ths} of patients. Marked narrowing of the aorta is associated with renovascular disease in up to 2/3rds with reduced aortic elasticity and aortic regurgitation in about 1/4th.
4) Vascular bruits in 4/5ths of patients, often multiple, and particularly affecting the carotids, subclavian, and abdominal vessels.
5) Aortic regurgitation resulting from dilatation of the ascending aorta, separation of the valve leaflets, and valve thickening in 20–24%
6) Takayasu retinopathy in up to 37% of patients whereas hypertensive retinopathy is seen in 1/3rd.
7) Congestive cardiac failure associated with hypertension, aortic regurgitation, and dilated cardiomyopathy
8) Coronary arterial disease is seen in 1/10th. Three types of disease is identified
   (a) stenosis or occlusion of ostia and proximal segments of coronary arteries
   (b) diffuse or focal coronary arteritis (diffuse involvement or "skip lesions")
   (c) coronary arterial aneurysms
9) Pulmonary artery involvement in 14–100% of patients, depending on the method used to assess pulmonary vasculature. Oligaemic lung fields on plain chest *x* ray correlate with pulmonary vasculopathy in approximately a third of cases. Pulmonary artery disease shows little correlation with the systemic pattern of arterial involvement.
10) Neurological features secondary to hypertension and/or ischaemia, including postural dizziness, seizures, and amaurosis

11) Other symptoms include dyspnoea, headaches, carotodynia, myocardial ischaemia, chest wall pain, and erythema nodosum.

Establishing the diagnosis

The American College of Rheumatology(1990) has established diagnostic criteria for Takayasu arteritis as follows[14]:-

1. Age of 40 years or younger at disease onset
2. Claudication of the extremities (Development & worsening of fatigue & discomfort in muscles of 1 or more extremity while in use, especially the upper extremity)
3. Decreased pulsation of one or both brachial arteries
4. Difference of more than 10 mmHg in systolic blood pressure between arms
5. Bruit audible on auscultation over one or both subclavian arteries or the abdominal aorta
6. Arteriographic narrowing or occlusion of the entire aorta, its primary branches, or large arteries in the upper or lower extremities that is not due to arteriosclerosis, fibromuscular dysplasia, or other causes.

Presence of at least 3 of these 6 criteria suggests the diagnosis of aortoarteritis, which have a sensitivity of 90.5% and a specificity of 97.8%.

The gold standard to confirm the diagnosis of Takayasu arteritis is however, aortography.

Modified version of Ishikawa diagnostic criteria for Takayasu arteritis[15]:

3 major criteria:

1. Left mid-subclavian artery lesion
2. Right mid-subclavian artery lesion
3. Characteristic signs & symptoms of at least 1 month duration

10 minor criteria:

1. ESR > 20mm/hr
2. Carotid artery tenderness
3. Hypertension
4. Aortic regurgitation or annulo-aortic ectasia
5. Pulmonary artery lesion
6. Left mid-Common Carotid artery lesion
7. Distal brachio-cephalic trunk lesion
8. Descending Thoracic aorta lesion
9. Abdominal aorta lesion
10. Coronary artery lesion

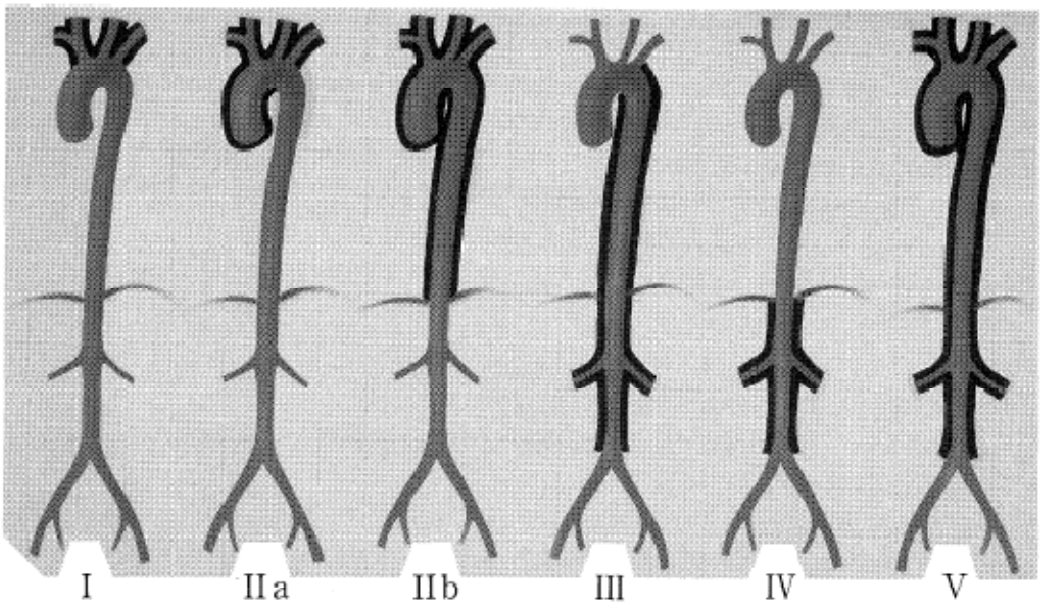
Presence of 2 major & 2 or 4 minor criteria suggest a high probability of TA, which has a diagnostic sensitivity and specificity of 92.5 and 95%.

Classification of Takayasu's arteritis

In 1994, the Xlth International Conference on Takayasu Arteritis established a new classification of angiographic findings as below[16] :-

Type	Vessel involvement
Type I	Branches from the aortic arch
Type IIa	Ascending aorta, aortic arch and its branches
Type IIb	Ascending aorta, aortic arch and its branches, thoracic descending aorta
Type III	Thoracic descending aorta, abdominal aorta, and/or renal arteries
Type IV	Abdominal aorta and/or renal arteries
Type V	Extensive involvement of whole length of aorta and/or its branches

Involvement of coronary or pulmonary arteries is designated as C (+) or P (+).

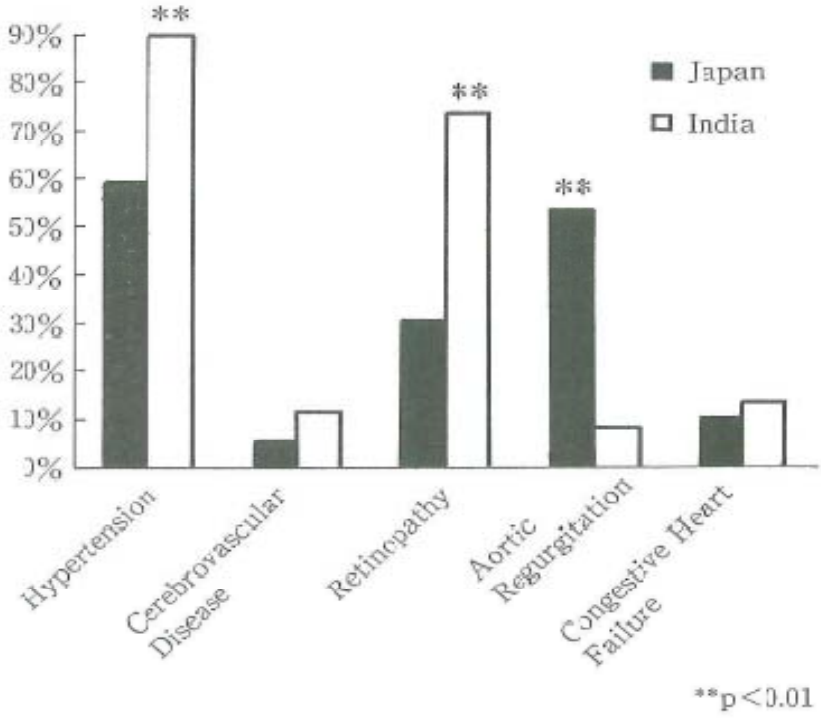


Varied Clinical Spectrum

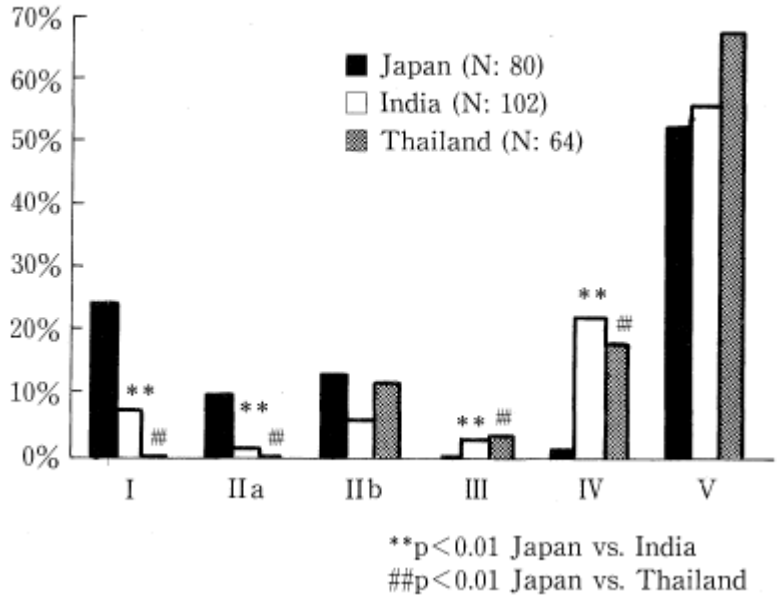
Takayasu Arteritis is more prevalent in Asian and South American nations. However the variable disease presentation between different populations is well illustrated by Moriwaki *et al* in their study of Indian and Japanese patients[16]. The Japanese patients (n = 80) were predominantly female (96%), presenting with dizziness, vertigo, pulselessness, more prolonged and severe inflammation, and more aortic regurgitation, reflecting involvement of the aortic arch and its main branches. This contrasted with the Indian patients (n = 102), 37% of whom were male. They tended to present with headache, hypertension, and left ventricular hypertrophy suggesting a high frequency of lesions in the abdominal aorta, including the renal arteries, leading to renovascular hypertension. However, most patients in both countries had diffuse disease.

Sen *et al.* and Chhertri *et al.* have reported a female to male ratio of 1.58:1 in Indian patients[17]. Indian male patients with TA have a higher frequency of hypertension and abdominal aorta involvement while female patients have a tendency towards involvement of aortic arch and its branches. The average age of the Indian patient presentation is in the third decade.

Frequencies of complicated diseases in Takayasu Arteritis between Japan & India[18].



Comparison of angiographic types in Takayasu Arteritis between Japan, India & Thailand[18]



Clinical Classification of Takayasu disease (as described by Ishikawa) & Prognosis

Severity of aortoarteritis: The patients are classified into four groups according to the presence and severity of four major complications at the time of initial assessment, as described by Ishikawa[20].

Group	*Clinical features*	*5yr survival rate from diagnosis*
1	Uncomplicated disease with or without involvement of the pulmonary arteries	100%
2	Aortoarteritis associated with one of the following complications: (a) retinopathy, (b) secondary hypertension, (c) aortic regurgitation (d) aortic or arterial aneurysm	
2a	Severity of the complication: mild to moderate	100%
2b	Severity of the complication: severe	70-80%
3	Aortoarteritis associated with two or more complications	70-80%

Complications of aortoarteritis:

A) Retinopathy: Estimation of the severity of Takayasu's retinopathy is made according to Uyama and Asayama's classification[21]

stage 1: dilatation of small vessels;

stage 2: microaneurysm formation;

stage 3: arterio-venous anastomoses;

stage 4: ocular complications.

The mild and moderate forms are identical with stages 1 and 2, respectively. The severe form is equivalent to stages 3 and 4.

B) Hypertension: values were graded according to[20]:

mild form : 140 to 159 mm Hg brachial systolic and/or 90 to 94 mm Hg diastolic,

or 160 to 179 mm Hg popliteal systolic and/or 90 to 94 mmHg diastolic;

severe form : ≥ 200 mm Hg brachial systolic and/or ≥ 110 mm Hg diastolic, or

≥ 230 mm Hg popliteal systolic and/or ≥ 110 mm Hg diastolic;

moderate form - between the mild and severe forms.

C) Aortic or arterial aneurysm: Severity of aneurysm of the aorta and its main branches was assessed by angiography. Severe aneurysm was defined as a diameter more than twice that of normal vessels. The reported incidence of aneurysms in Takayasu's disease varies from 2 to 14%[20].

D) Aortic regurgitation was estimated angiographically or clinically. Aortic regurgitation of grades 3 or 4 was defined as severe aortic regurgitation. The reported incidence of aortic incompetence in Takayasu's disease varies from 7% to 15%[20].

Other cardiac complications.

i) Mitral regurgitation was diagnosed and graded by clinical and/or angiographic examination.

ii) Cardiomyopathy was diagnosed when the patient had congestive heart failure or ventricular dysfunction out of proportion to the degree of hypertension, valvular incompetence, or coronary artery involvement.

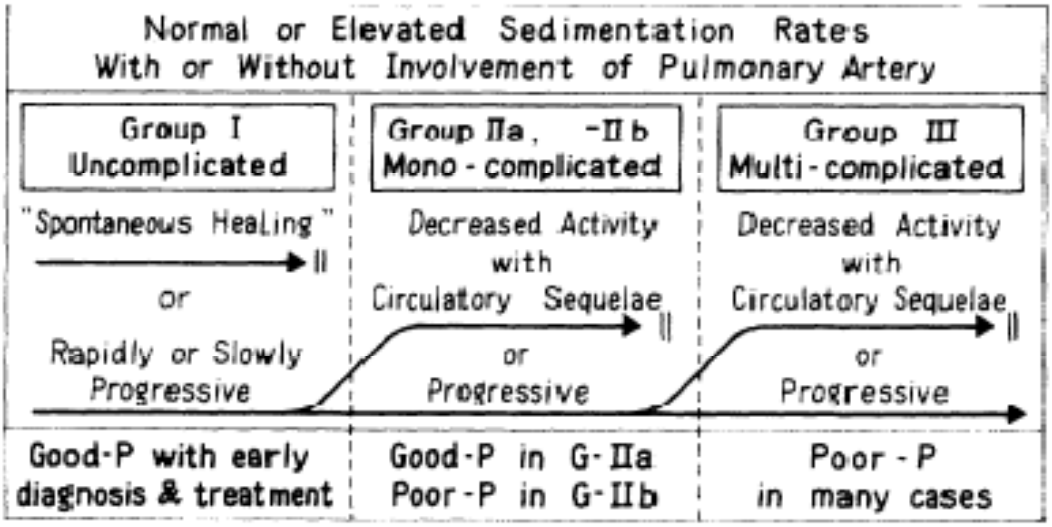
Natural History

TA usually extends for many years, with varying degrees of activity in the different lesions. TA classically exhibits a triphasic pattern of expression consisting of a systemic non-vascular phase, a vascular inflammatory phase, and a quiescent, "burnt out" phase[4]. However, this classic presentation holds true only in a minority of patients because both inflammatory and fibrotic changes may coexist at one time owing to the chronic and recurrent nature of TA. The natural history of TA often has two distinct phases - an active or pre-pulseless phase and a chronic or pulseless phase. Active phase may remit spontaneously in 3 months or may progress insidiously into the chronic phase. There can be exacerbations of activity during the chronic illness. Not all patients have a manifest acute phase and may present in chronic phase only. In the chronic phase, the inflammation leads to either stenosis or occlusion (85%) of the affected vessel, aneurysm formation (2%) or both (13%). Approximately 20% of patients have a monophasic and self-limited disease. TA in children tends to have a more aggressive course. One series[41] have shown a mortality rate as high as 35–40% by five years.

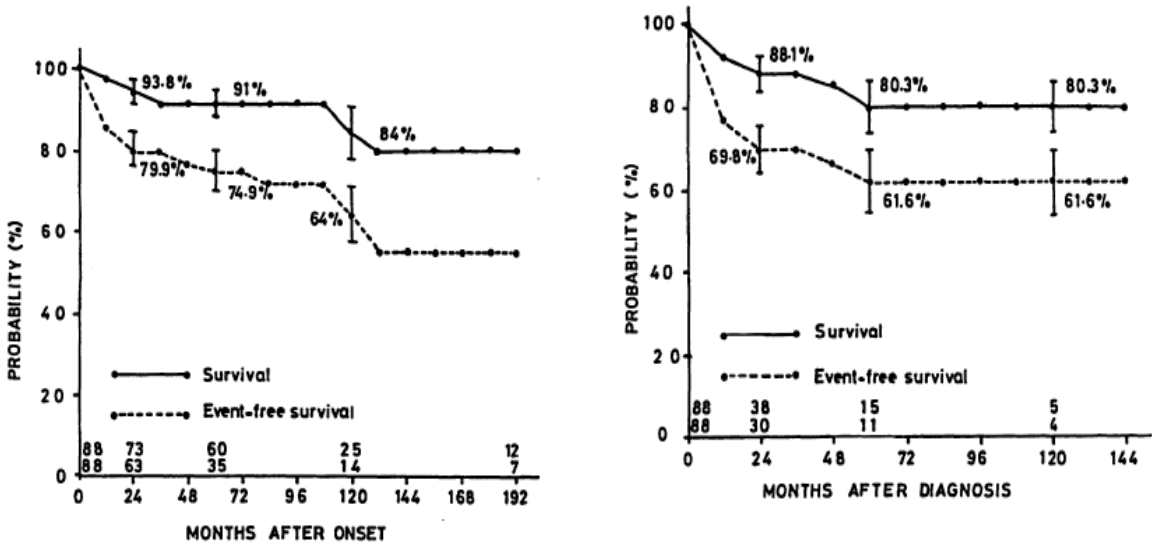
Prognosis:

Survival is worse by $1/6^{th}$ in those with hypertension as this may cause cardiac failure, stroke & renal failure. The experience from India[1] suggest that the cumulative survival at

five years after disease onset was 91%, after 10 years the figure was 84%, whereas event free survival figures were 74.9% and 64%, respectively. The main cause of death is cardiac failure secondary to hypertension or aortic regurgitation. Forty percent of deaths in the Indian cohort were the result of CHF[1]. Presence of a severe single complication (group 2B) or multiple complications (group 3), severe hypertension, cardiac involvement, and severe functional disability are useful in predicting premature death, premature event, or both on follow-up. Patients with none of these factors have a good long-term prognosis.



Natural history and clinical classification of occlusive thromboaortopathy (Takayasu's disease). P = prognosis.



Plot of actuarial survival and event free survival curves[1] after the A) onset of aortoarteritis B) diagnosis of aortoarteritis

Clinical imaging in TA

Considerable advances have been made in recent years in vascular imaging. Thus magnetic resonance imaging and angiography (MRI/MRA), computed tomography (CT) and CT angiography, positron emission tomography (PET), CT-PET and high-resolution ultrasound (US) are becoming more widely available for the investigation of patients presenting with symptoms suggestive of a large vessel vasculitis[22]

Conventional angiography

Percutaneous intravascular angiography has been the gold standard investigation for the diagnosis of TA, providing high quality images of the arterial lumen. Lesions often occur at or close to the point of origin of the primary branches of the aorta. Localized

narrowing or irregularity of the arterial lumen is the earliest lesions detectable by angiography, and these may proceed to stenosis or complete occlusion. Vessels may also be dilated or aneurysmal—either saccular or fusiform. One of the most characteristic angiographic findings is the presence of 'skip lesions', where stenoses, or less frequently aneurysms, alternate with segments of uninvolved blood vessel. Based on the location of vessel involvement, a five-type angiographic classification system was introduced. It is also important to note that intra-arterial angiography allows accurate assessment of central aortic pressures and imaging of the coronary arteries, which are not readily available with current non-invasive approaches[23].

Limitations of angiography: Despite its benefits, intraarterial angiography is invasive, may aggravate local disease and only provides data on luminal anatomy. This inability to evaluate changes in the arterial wall may result in a normal angiogram in patients with early phase disease. Furthermore, the nature of the procedure and the necessity for exposure to contrast media and radioactivity significantly limits its use as a tool for monitoring patients with TA.

Magnetic resonance imaging

Increasing use is being made of MRI/MRA in the diagnosis and management of TA. The combination of multiplanar cardiac MRI using T1- and T2-weighted sequences in coronal and oblique sagittal planes, combined with contrast-enhanced 3D MRA

has been reported to display equivalent diagnostic accuracy to invasive angiography. A specialized MR unit with a dedicated study protocol can provide a highly informative arterial survey of the vessels typically involved in TA including pulmonary arteries[24, 25]

Limitations of MR: MR remains time-consuming, operator-dependent and expensive. Furthermore, although MRI may reveal signs suggestive of vascular inflammation in TA, including arterial wall thickening, increased signal intensity and arterial wall oedema , no consistent correlation with disease activity or progression has been demonstrated . Although MR identified vessel wall oedema in 94% of patients with definite active disease and in 56% of those with apparent clinical remission, a consistent correlation between the oedema and disease progression could not be demonstrated[26]. It has also been reported that MR may occasionally overestimate the degree of stenosis in branch arteries, and that limitations in resolution may result in relatively poor imaging of distal aortic branches

High-resolution Doppler ultrasound (US)

Although widely available, the use of high-resolution Doppler US is relatively under investigated in TA. US may lead to an earlier diagnosis in patients presenting with TA, through detection of pre-stenotic lesions in the common carotid and subclavian arteries. US is particularly good for the assessment of common carotid arteries, where it is up to 10-fold more sensitive than MRI, displaying a resolution of 0.1–0.2mm[27]. In addition, Doppler US can be used for indirect measurement of arterial stiffness, which is commonly raised in patients with TA.

Sonographic findings can be divided into the following[28]: -

(i)Wall Thickening: This is the earliest finding in TA and is universally seen in all patients with aortoarteritis. There is uniform thickening of the wall of the vessels involved. The earliest wall thickening is seen in the SCAs, most commonly the left SCA. The arch of the aorta is also involved early; however, because of difficulty in visualization of the aortic arch, the presence of aortoarteritis is inferred from assessment of the major aortic arch branches. It is easier to assess the abdominal aorta and its branches. Measurement of abdominal aortic wall thickness is difficult because of the constant motion. In TA, long segments of diffuse, homogeneous, moderately echoic circumferential vessel wall thickening are found. This is seen more commonly in the CCA in TA and has been described as the "macaroni sign". It can be distinguished from arteriosclerosis, which is more inhomogeneous.

An increase in wall thickness is associated with secondary signs such as decreased pulsatility and loss of a normal triphasic flow pattern. The involved vessels reveal loss of the triphasic pattern, with a monophasic or biphasic parvus tardus type of spectral flow pattern. This type of pattern is also seen distal to an occlusion when there is reformation of vessels by collaterals, but wall thickening associated with dampened flow suggests the diagnosis of TA.

(ii)Luminal Narrowing or Stenosis: Luminal narrowing or stenosis is common in TA because of wall thickening, which leads to a decrease in the luminal diameter. This stenosis or narrowing is commonly seen as a long segment compared with atherosclerosis or fibromuscular dysplasia, in which the stenoses are commonly short segments.

(iii) *Luminal Dilatation and Aneurysms:* Luminal dilatation and aneurysms are not as common as narrowing. It is suggested to be due to inadequate supportive fibrous tissue or focal intima weakness. The aorta is most commonly affected, especially the thoracic and abdominal portions.

(iv) *Calcification:* Calcification is uncommon in aortoarteritis and more commonly seen in atherosclerosis.

(v) *Occlusions:* Occlusions are seen in the later stages of the disease

In TA, the typical lesion identified by US is a long, smooth, homogeneous concentric thickening of the arterial wall, whereas in contrast an atherosclerotic plaque is shown to be nonhomogeneous, often calcified and associated with an irregular vessel wall. Comparative studies have shown that results obtained with US correlate closely with angiography and MRA, with agreement in excess of 95% reported[27]. In addition, US may on occasion be more sensitive than angiography, through its ability to detect the intimal-media thickening associated with early lesions. The high resolution of Doppler US raises the possibility that it may also offer a means by which disease activity and response to treatment can be monitored[22].

Limitations of Doppler US imaging: Doppler US is highly operator-dependent and few centres have radiologists with sufficient vascular expertise. Furthermore, while imaging is optimal in the common carotid and vertebral arteries, assessment of the proximal subclavian and distal internal carotid arteries is limited by overlying tissues, and high-resolution US of the aorta is not yet available. As with the other forms of non-invasive imaging, US do not allow measurement of central aortic pressures. Finally, there is

insufficient data available to conclude whether or not US has a place in disease monitoring.

CT angiography

CT angiography has been used to assess patients with TA. CT allows detection of arterial wall thickening in the pre-stenotic phase and can help distinguish TA from atherosclerosis[30]. CT compared well with angiography in the analysis of lesions in the common carotid, subclavian and brachiocephalic arteries. However, there are insufficient data in the literature to decide whether CT has a place in disease activity monitoring, with conflicting results reported for the use of arterial wall enhancement as a means of analysis. Likewise, contrasting results have been reported for the use of CT in assessing changes in wall thickness following treatment.

Limitations of CT angiography: The main limitations associated with CT are the requirement for iodinated contrast administration and radiation exposure. The current resolution of CT is such that it is most effective in the assessment of the aorta and its proximal branches and offers relatively limited imaging of distal aortic branches

18F-Fluorodeoxyglucose positron emission tomography

Labelling of the glucose analogue deoxyglucose with Fluorine-18, a positron-emitting radionuclide, permits the identification of areas of high glucose metabolic activity. FDG uptake is related to both the metabolic rate of the cell and the abundance of glucose

transporters and although phosphorylated by hexokinase, FDG is not metabolized. The use of 18F-FDG-PET in pathology has been most widely studied in oncology. However, FDG uptake may also be increased at sites of inflammation and infection and although not as well characterized, 18F-FDG-PET is increasingly recognized to be a useful imaging modality in this setting. In TA, abnormal 18F-FDG-PET uptake is seen in the wall of large vessels (>4 mm), if vascular inflammation is present[22]. In two recently reported retrospective studies which explored the utility of 18F-FDG-PET scanning in TA, this test had a sensitivity of 92% and a specificity of 100%, with a positive predictive value of 100% and a negative predictive value of 85%[31]. The second study[32], comparing angiography, MRI and 18F-FDG-PET in six TA patients, suggested that 18F-FDG-PET is an important new clinical tool for the diagnosis of TA and that it may have a place in the monitoring of disease activity and response to treatment[31]. The principle advantage of 18F-FDG-PET is its ability to detect pre-stenotic disease in patients presenting with non-specific features commonly associated with early TA. Reduction in 18F-FDG-PET uptake at the site of aortitis has been correlated with both clinical improvement and a reduction in aortic wall thickness. In addition, a marked reduction in 18F-FDG-PET uptake at sites of inflammation following adequate immunomodulatory therapy has been demonstrated. Studies have made observations suggesting that 18F-FDG-PET scanning represents a sensitive means for the detection of persistent disease activity, in those patients who appear clinically to be in remission while having histological evidence for persistent vascular wall inflammation. Compared with disease activity assessed by the NIH criteria, F-18 FDG PET-CT had a sensitivity of 78% and a specificity of 87% to detect active disease[33]. The sensitivity of F-18 FDG PET-CT for detecting active disease

was higher in patients with higher erythrocyte sedimentation rate values. Although the specificity of F-18 FDG PET-CT was high, owing to the low sensitivity of the NIH criteria in detecting active disease, further prospective studies are needed.

Limitations of 18F-FDG-PET: First, it results in significant radiation exposure, is expensive and is limited to relatively few centres. Second, it lacks both histological confirmation of the findings in TA and a reliable standardized technique for quantification. Finally, 18F-FDG-PET may detect atherosclerosis, although this is more commonly seen in older patients and typically exhibits a vascular distribution distinct from TA. For example, TA typically affects the common carotid arteries while atherosclerosis is more typically seen in the internal carotid arteries. Moreover, an intense linear uptake of FDG is more characteristic of active vasculitis. Nevertheless, particularly in older TA patients it may prove difficult to distinguish between FDG uptake due to active TA or subclinical atherosclerosis.

As yet, 18F-FDG-PET scanning has only been shown to be of use in the diagnosis of TA. Prospective studies are required to confirm its utility as a tool for the assessment of disease activity and for monitoring. Likewise, data are needed on the outcome of patients whose 18F-FDG-PET scan suggests persistent disease activity, so as to establish whether they are more likely to suffer a disease flare or to develop progressive vascular lesions.

Assessing the disease activity in Takayasu arteritis

Activity of disease is the presenting manifestation in about 1/3rd of cases of aortoarteritis. About 10% of cases have activity throughout the course of the disease. Constitutional symptoms of fever, night sweats, malaise, headache, polyarthralgia or weight loss have been reported in 7 - 36% cases of active disease[34]. Detailed assessment of disease extent and activity are essential to follow both the long term outcome and the response to therapy in TA. Clinical analysis of TA disease activity, response to treatment and detection of relapse however, remains suboptimal.

1. Acute phase reactants as markers of disease activity:

Several studies have examined the acute phase response in Takayasu arteritis. Elevated erythrocyte sedimentation rate (ESR > 40mm in 1 hour) is considered as an indicator of active disease with or without constitutional symptoms like fever, polyarthralgia[35]. Mandalam et al in 1994 suggested that a persistently elevated ESR of more than 40mm in 1 hour is an indicator of disease activity, inflammation and disease progression[36]. Ishikawa[20] found that the erythrocyte sedimentation rate (ESR) was raised in 29 of 54 patients studied, with an equal distribution in the four disease categories. He suggested an ESR of > 20mm in 1 hour as an index of activity. Higher values were seen in the younger patients, declining with age, perhaps representing the natural history of the disease. Hall et al[4] found that the ESR was raised in three quarters of 32 cases, and that it showed an excellent correlation with treatment effect. However, Kerr et al[37] concluded that the ESR

was not a consistently reliable marker of disease course, being raised in 72% with active disease but also in nearly half of patients in clinical remission. In their study, 44% of arterial biopsy specimens obtained from patients with clinically inactive disease demonstrated vasculitis, suggesting that disease activity may be underestimated.

This inconsistency has led to a search for better serological markers.

A study reported in 1998[38] concluded that no known serological test was able to supplant vascular histopathology in determining disease activity. This study compared 29 patients (22 with clinically inactive disease and seven with clinically active vasculitis) with 26 healthy control volunteers; no serological test reliably distinguished healthy volunteers from patients with active disease. The markers assessed included ESR, C reactive protein (CRP), tissue factor, von Willebrand factor, thrombomodulin, and tissue plasminogen activator, in addition to various adhesion molecules. The numbers with clinically active disease were small and again may have been underestimated in the absence of histological assessment. ESR and CRP values were not directly compared. Although disease activity may not be discriminated by these markers at a single point in time, for individual patients the use of a given parameter longitudinally may still be of value.

2. ***Cytokines & Matrix MetalloProteinases (MMPs) as markers of disease activity***

Serum concentrations of the pro-inflammatory and chemotactic cytokines interleukin 1b (IL-1b), IL-6, and RANTES (regulated on activation, normal T cell expressed and secreted) have been assessed by enzyme linked immunoabsorbent assay. All of 18

patients studied[39] had increased concentrations of IL-6 and RANTES during active disease compared with healthy controls, and concentrations parallelled disease activity. These cytokines correlated with the ESR but not with CRP values. This lack of CRP correlation (CRP being driven by IL-1 and IL-6) was not adequately explained. The positive correlation with disease activity suggested that these cytokines may contribute to the vasculitis and raised the possibility of their use in monitoring disease and treatment. However, serum cytokine assays are not necessarily a reflection of tissue cytokine concentrations and may not accurately detect biologically active cytokine. Their use over and above the ESR remains to be established. Interleukin-18 levels were also found to correlate well with disease activity[40] & may prove to be a useful marker for monitoring treatment response.

In TA, the earliest change appears to be a granulomatous inflammation in the adventitia and outer layers of the affected arteries, followed by gradual progression to a panarteritis with inflammatory mononuclear cell infiltration. Histologically this is characterized by degeneration of the elastic lamella in the media of affected elastic arteries. The process eventually produces intimal thickening and scarring, and aneurysms form in the weakened arterial walls, particularly when the aorta itself is involved. In this process, proteases secreted from infiltrated cells are thought to play some role in the destruction of elastic fibers. Among the types of elastolytic proteinases, matrix metalloproteinases (MMPs) can be induced in response to cytokines implicated in a variety of inflammatory processes. MMPs comprise a family of calcium-dependent zinc endoproteinases and might pathologically participate in a variety of inflammatory responses. MMP-2, also

known as 72-kDa gelatinase, which can digest gelatin, type IV collagen, and elastin, is constitutively expressed in mesenchymal cells such as fibroblasts and smooth muscle cells. MMP-2 levels were higher in patients with TA than in healthy controls, regardless of disease activity, and that a high concentration of MMP-2 was helpful in diagnosing TA. MMP-3, also known as stromelysin A, is secreted mainly by fibroblasts and smooth muscle cells.12 MMP-9, or 90-kDa gelatinase, is produced by mononuclear cells, including neutrophils, macrophages, and T lymphocytes. Cytokines, including interleukin-6 and RANTES, which can accelerate the production of MMP-3 by mesenchymal cells and of MMP-9 by inflammatory cells, are secreted in inflammatory conditions and are reported to increase in patients with active-phase TA. A positive correlation was observed between both MMP-3 and MMP-9 levels and disease activity score, and the elevated levels of MMP-3 and MMP-9 improved when patients entered remission[41]. In addition, serum levels of TIMP-1 tissue inhibitor of metalloproteinase-1 (TIMP-1) were lower in TA patients than those in controls. The highest sensitivity and specificity were 800 and 100 ng/mL for MMP-2 and MMP-3, respectively. With these values, the sensitivity and specificity were 96% and 100%, respectively, for MMP-2 as a diagnostic marker and 91% and 100%, respectively, for MMP-3 as a disease activity marker. As to MMP-9 as an activity marker, cutoff values of 90 and 75 ng/mL gave sensitivity and specificity of 45.5% and 100%, respectively, and 63.6% and 81.8%, respectively[41]. In this respect, MMP-3 is a more suitable marker for disease activity than MMP-9, but the combination of MMP-3 and MMP-9 may allow us to estimate more accurate disease activity. Higher MMP-3/TIMP-1 ratios than in patients with remission

were also found in active TA. Thus, MMP-3/TIMP-1 ratio may also be a useful marker for disease activity[41].

3. National Institute of Health (NIH) criteria for disease activity:

By this, if 2 or more of the following features were present, the disease was considered to be active.

(1) Presence of systemic features/ constitutional symptoms such as fever, arthralgia, or musculoskeletal problems with no other cause identified;

(2) Elevated ESR;

(3) Presence of features of vascular ischemia or inflammation, such as claudication, diminished or absent pulse, bruit, vascular pain (carotodynia), or asymmetrical blood pressure in either upper or lower limbs (or both), and

(4) Typical angiographic features.

.New onset or worsening of each of the above-mentioned features was given a score of 1; a score of 2, 3, or 4 defined active disease[37]. Although this is the most commonly used score for assessing disease activity in TA, the nonvalidated status[43] & the low sensitivity[33] of the NIH criteria in detecting active disease is a matter of concern. The requirement for an angiographic examination also makes it cumbersome. The invasiveness and cumulative radiation toxicity of this procedure limit its use in monitoring disease progression.

4. ***Indian Takayasu Activity Score (ITAS) to assess disease activity:***

The Birmingham Vasculitis Activity Score (BVAS), a reliable indicator of disease activity for primary systemic vasculitis, lacks sensitivity for the large vessel vasculitides and is rarely useful for clinical practice. The main problem here is assessing activity in a disease where so much of the pathology is located in deep-seated vessels, progressing at a slow pace and not necessarily associated with any acute phase response. The need is to develop techniques that will allow activity to be assessed independently of acute clinical events, such as vessel occlusion. The standard tools, BVAS and Vasculitis Disease Index (VDI), do not perform well for the different disease pattern in TA where there is no simple test for disease activity[44].

At the Third International Conference on Giant Cell Arteritis and Polymyalgia Rheumatica held in Cambridge in July 2005, Dr Sivakumar, on behalf of the IRVAS group, presented a new clinical index of disease severity and extent in TA (the DEI-TAK) which uses the BVAS index as its template[45]. This DEI-TAK index is based on the findings from 143 Indian patients with Takayasu arteritis and contains 59 items in 11 organ-based scoring systems with emphasis on the cardiovascular system (19 items). The data sheet also includes an acute phase test and the physicians' global opinion on activity. It was in use to determine the extent and pattern of disease seen by rheumatologists in India. The DEI-TAK was revised by M.R Sivakumar, R.Misra, and P.A.Bacon in Sept 2007 and applied in patients with TA, as the Indian Takayasu Activity Score (ITAS). Each item is scored only if the abnormality is new or worse, within the past 3 months.

An ITAS score more than or equal to 3 suggest active disease.

The new Indian Takayasu Activity Score (ITAS) was validated[44] in a single referral centre where one investigator scored 177 patients and in a group exercise where 10 experienced physicians scored both paper and live cases. The ITAS score of recent disease, showed a strong correlation with the PGO (physicians' global opinion of disease activity). In the large series, the mean ITAS score in 13 ''active'' cases was 5.9; in grumbling disease (n= 45) the score was 3.2; in inactive disease (n= 36) the score was 0.9 ($p < 0.000$ by Anova). In the group exercise, ITAS intra-class correlation coefficient was 0.754 ($p<0.000$). ITAS again correlated significantly with PGO scored on a 10mm analogue scale across the range ($r= 0.502$, $p<0.000$). ITAS also had a strong correlation with BVAS ($r= 0.578$, $p<0.000$) but is a more sensitive assessment tool for TA[41]. An elevated ESR/CRP was associated with systemic disease but did not relate to any other score items. The DEI.Tak used to score relevant items occurring since the onset of disease provides a comprehensive damage index which confirmed the different disease pattern observed in TA in the large cross-sectional study. The authors concluded[44] that ITAS provides an index of activity that correlates with PGO and BVAS, and can be used in therapeutic studies in centres where cost restricts the use of MR and PET scans. However the DEI.Tak provides a useful tool for longer term outcome and epidemiological studies.

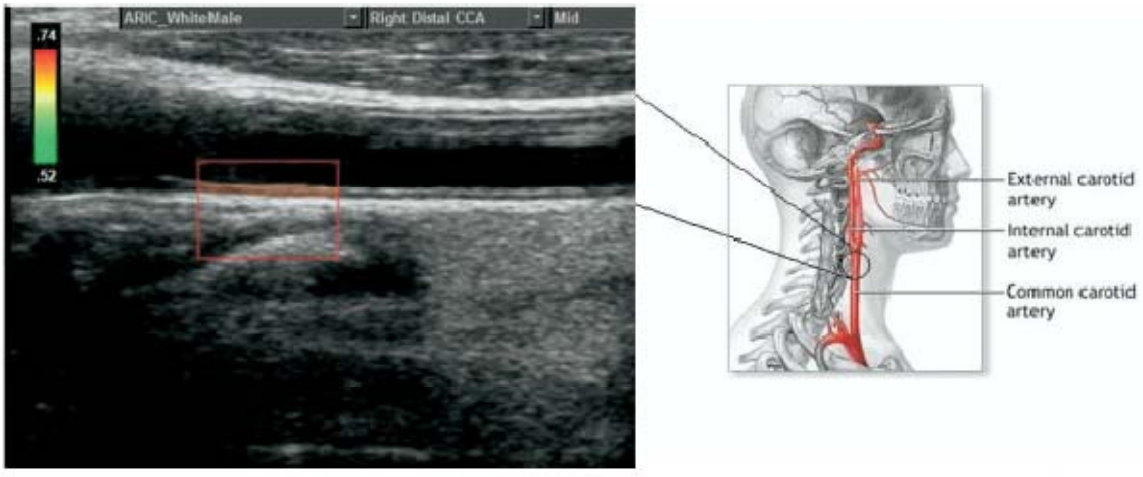
5. ***High resolution Doppler Ultrasound of Common Carotid arteries***

The use of high-resolution doppler UltraSound (US) is relatively under investigated in TA. US is particularly good for the assessment of common carotid arteries, where it is up to 10-fold more sensitive than MRI, displaying a resolution of 0.1–0.2mm[27]. In addition, Doppler US can be used for indirect measurement of arterial stiffness, which is commonly raised in patients with TA[45]. The high resolution of Doppler US raises the possibility that it may also offer a means by which disease activity and response to treatment can be monitored.

Park and colleagues studied the common carotid artery and based on the ESR, CRP and CT angiography findings they graded lesions identified active or inactive[47]. Using high-resolution US they report a common carotid arterial wall thickness of 2.5–5.0mm in active lesions compared with 1.1–2.0mm in lesions considered inactive, corresponding to a vessel diameter of 10mm or more in active disease and <7mm in inactive disease. Hence, they suggest that US may represent a means by which TA disease activity can be monitored. In addition, US has identified reductions in arterial wall thickness in response to treatment and following resolution of disease activity. However, although US is the most sensitive noninvasive method for detection of abnormalities in the common carotid arteries[48], further prospective studies are required to show convincingly that it can be of use in estimating disease activity and outcome.

6. Carotid Intimal-Medial Thickness (CIMT) as a marker of disease activity

A variety of methods are available for the assessment and imaging of vascular disease, with varying degrees of sensitivity. Central atherosclerosis is often measured with high-resolution carotid ultrasound for the presence of plaque, though the extent of carotid artery intima–media thickness (CIMT) conveys different, though possibly just as important, information. B-mode ultrasound is a safe, reliable and non-invasive method of measuring CIMT. The combined thickness of the intima and media can be measured in various sections of the carotid artery, although the common carotid artery appears to be the most reproducible and accurate area to assess. This is usually measured 1 cm below the bifurcation of the common carotid in order to accurately reassess the same area. The internal carotid is technically more difficult to assess but appears to correlate more closely with major atherosclerosis risk factors and pre-exisiting cardiovascular disease.



An increase in CIMT has been shown to correlate with cardiovascular risk factors such as smoking, high cholesterol and hypertension[49]. It has also been shown to be an independent predictor for subsequent myocardial infarction and stroke[51].

In addition, various studies have shown an increase in CIMT in inflammatory joint conditions such as RA and psoriatic arthritis[51, 52], along with other inflammatory conditions such as Behcet's disease and Takayasu's arteritis[53, 54.] There is emerging evidence that smoking influences CIMT in RA and that treatment with anti-tumour necrosis factors may have a beneficial effect on CIMT measurements. This suggests that these treatments may reduce cardiovascular risk. In the future, CIMT measurements could be used to assess cardiovascular risk of patients with rheumatic disease[54].

Amongst the parameters of vascular change, distensibility is sometimes quoted, presumably because it is easily visualized, which may or may not be synonymous with the more frequently described arterial stiffness, usually accepted to be impaired. There is sometimes a lack of clarity as to whether this is a primary phenomenon of rheumatic disease or a secondary consequence of cardiovascular disease once present. A consensus would accept, however, that arterial stiffness is increased in most chronic inflammatory diseases including not only post-menopausal females with RA but also in adolescents and young adults with SLE. Sometimes this may be site specific, and in RA it can be reduced by atorvastatin, particularly in patients with the most severe disease. Arterial stiffness can also be enhanced in vasculitis, including both Takayasu's arteritis[43]and giant cell arteritis.

Lande et al[55] report the first study of CIMT in hypertensive adolescents that corrects for the effects of body mass. They found that CIMT was greater in hypertensive subjects than in controls matched for age, gender, and BMI. Gonzalez et al[56] demonstrated that CIMT

measurements in young adults were 2.2%–3.1% greater in the right carotid artery than in the left. He suggested that the reproducibility of CIMT measurements is greatest when combining values from both carotid arteries and/or from the maximal and minimal arterial diameters.

Zienlinski et al[57] in their study of ultrasound examination of carotid arteries with intima media measurement in 18 patients (16 women and 12 men, aged 11-62) demonstrated that the mean IMT of the CCA in patients with Takayasu's disease was significantly higher than in controls(mean +/- SEM; 1.1+/- 0.1 vs 0.59 +/- 0.01mm). In healthy controls, the intima media thickness of the bulb was higher than that in the CCA (0.7 +/- 0.05 as 0.59 +/- 0.01).In patients with Takayasu's disease, that proportion was inversed (0.81 +/- 0.05 as 1.1 +/- 0.1mm). Higher intima media thickness found in the common carotid artery than in the bulb can raise a suspicion of Takayasu's arteritis.

Seth et al evaluated common carotid artery carotid intima–medial thickness (CCA–IMT) in 56 common carotid arteries (CCAs) in 28 healthy controls and 74 CCAs in 37 patients of TA[58]. They correlated these findings with the presence of activity as assessed by the National Institutes of Health (NIH) criteria. CCA–IMT was increased (> 0.8 mm) in 59% of the patients with TA. In patients with disease activity, the CCA–IMT was more than in those without activity (1.5 ± 0.16 vs. 0.9 ± 0.2 mm, $P < 0.005$). This is presumably because of ongoing inflammation causing abnormal thickening. Even among patients without active disease, CCA–IMT was more than in controls (0.9 ± 0.2 vs. 0.6 ± 0.1 mm,

$P < 0.05$) possibly due to a milder degree of inflammation or healing with fibrosis. All patients with angiographic carotid obstruction had increased CCA–IMT irrespective of whether they were active or not. However, in patients with angiographically normal carotid arteries, CCA–IMT was increased only among the patients who were active (1.4 ± 0.2 vs. 0.7 ± 0.04, $P < 0.05$). Abnormal CCA–IMT as marker of disease activity had a sensitivity of 82% and specificity of 60%. On excluding patients with increased CCA–IMT who had angiographic carotid stenosis (because the increase in CCA–IMT cannot be attributed entirely to activity alone in these patients), the specificity increased to 70%. They concluded that increased CCA–IMT is a reliable marker of active disease, especially in the absence of angiographically visible carotid disease[58].

Measurement of CIMT - Technical Considerations:

CIMT imaging requires methodic attention to carotid anatomy, ultrasound parameters, and a standardized measurement protocol. To begin the CIMT examination, the patient should be supine with the sonographer positioned at the head of the bed. The patient and sonographer should be comfortable during the examination with careful attention paid to safe, efficient, and ergonomic scanning positions to minimize the potential for injury. During the scan the patient should have minimal support under the neck to aid in neck extension and rotation that will aid in positioning of the carotid artery for optimal imaging. Linear-array transducer frequency is best between 8 to 12 MHz using

fundamental frequency only[50]. The far wall CIMT should be seen as a double line representing the lumen-intima and media-adventitia interface. The best image resolution is obtained when the ultrasound beam is perpendicular to the structure being imaged, which may require the sonographer to manipulate transducer, ie, heel-to-toe and/or rotation motions, to optimize the intima-media image.

Reliability and Reproducibility

The difference in thickness between a normal scan and an abnormal scan can be small and a common concern for those who have not previously performed CIMT measurement is whether the measurement is accurate and reproducible. Data from published research centers that have an expertise at performing CIMT have consistently shown that the measurement is highly reproducible, although this varies somewhat depending on sites measured, number of measurements, and whether mean or maximum values were used[50]. Newer semiautomated border detection programs are available that are less time-consuming and more reproducible for less experienced users. A recent study compared a novice reader with a reference laboratory using a semiautomated border detection program. The novice reader results were bioequivalent to the reference laboratory with small absolute differences (experienced 0.011 ± 0.004mm, novice 0.022 ±0.004 mm) in CIMT and high reproducibility (coefficients of variation: experienced 3.1%, novice 7.8%)[59].

Reproducibility of 2 major carotid intima-media thickness studies[50]:

Study	Reproducibility
Rotterdam study	SD between paired measurements of sonographers, & readers were -0.004 & 0.066.
Atherosclerosis Risk in Communities Study	Between - reader reliability coefficients ranging from 0.78 to 0.93 & coefficients of variation ranging from 13.1% to 18.3%

DESIGN & METHODOLOGY

Study design:

An observational study done in the department of Cardiology, CMCH, Vellore

Methodology:

Study Protocol

All consecutive patients with Takayasu Arteritis (TA) seen in the Cardiology department from August 2008 to January 2010 were enrolled in the study. Diagnosis was based on the American College of Rheumatology (1990) ACR criteria. Disease activity was assessed using (i) acute phase reactants- ESR, CRP (ii) NIH (National Institute of Health) criteria, & (iii) ITAS score (Indian Takayasu arteritis Activity Score) at enrollment. CIMT was measured in all these patients. Angiographic extent of the disease including involvement of the common carotids was also assessed at enrollment.

CIMT was also measured in 30 healthy controls, of a similar age group but with no evidence of systemic hypertension, diabetes mellitus, peripheral vascular disease or coronary artery disease.

CIMT measurement in the study

CIMT images were acquired with a high-end ultrasound system (iE-33) with an L 11–3 (Linear Array, 288 elements, 11.0 to 3.0 MHz) transducer (Philips Medical Systems). Patients were placed in a supine position using a 45° head rotation angle for acquisition. Acquisitions were obtained in a zoomed still frame at end diastole and images were stored digitally for off-line analysis. Long-axis images and cross-sectional images of the right and left common carotid artery were obtained with posterior, medial, and anterior transducer angulations. CIMT was measured on the fall wall of the right and left common carotid artery from long-axis images obtained with medial transducer angulation. CIMT were measured in the proximal, mid & distal common carotid artery on both the left & right side. The maximum diameter at sites where there was no plaque seen was measured. The means of the three CIMT values of the right & left common carotid artery were calculated separately. The CIMT value used for analysis in each patient was defined as the average of the mean CIMT of the right and left common carotid arteries. CIMT measurements were performed by the same sonographer who was unaware of the activity status of the disease at the time of measurement.

Outcome measures:

CIMT & its correlation with disease activity, in the whole group of patients with TA was the primary outcome measured. Demographic profiles, angiographic pattern of involvement, correlation of CIMT with angiographic involvement of carotid arteries were the secondary outcomes measured.

Statistical analysis:

Statistical analysis was done using SPSS Version17. Continuous variables were expressed as mean ± standard deviation. Continuous variables with skewed distributions were expressed as median and interquartile range. Distributions of CRP and ESR were skewed with a Galton's (*log-normal)* distribution. Hence they were analyzed on a log scale to obtain normal distribution. Categorical variables were expressed as counts (percentages) unless stated otherwise. Mann–Whitney *U* test. Differences between groups were compared using the Mann-Whitney U-test (non parametric) and t test (parametric) wherever appropriate. In brief, for groups with smaller sample sizes and non normal distribution, MannWhitney test was used and for groups with larger sample sizes with normal distributions, t test was used. For categorical variables, Mantel-Haenszel chi-square was used to test the significance of the linear relationship between two ordinal variables. Pearson's chi-square and Fisher exact tests were used, wherever appropriate, for comparison of categorical variables. Pearson and Spearman Rank Coefficient correlations were used wherever appropriate to measure of the strength of the associations between two variables. Using NIH and ITAS criteria as the gold standard, a sensitivity analysis of CIMT was performed. A ROC ("Receiver Operating Characteristic") curve was drawn to estimate the cut-off point for CIMT as a predictor of disease activity. All tests used were two-tailed and the $p<0.05$ value was considered statistically significant.

RESULTS

A total of 41 patients were studied. Out of this, angiographic data was available for 39 patients. Majority (75.6%) of the study population were females, in keeping with the pattern seen in TA. The male, female ratio was approximately 1:4. The baseline characteristics were as shown in Table 1. All the variables except CRP had a normal distribution pattern. Hence these were expressed both in the Mean ±SD & Median + Interquartile Range. Owing to the distribution pattern of CRP, the mean & median values were widely apart. The blood pressure recorded was the central aortic pressure.

Table 1: Baseline characteristics

Variable	**Mean ±SD**	Median + IQ Range
Age (years)	29 ±12	27 (22-34)
Female Sex *	31 (75.6)	
ESR (mm/hour)	35.46±27.26	30 (15-50)
CRP (mg/l)	14.03±15.87	7.69 (1.74-25)
Systolic Blood Pressure (mmHg)	142±27	142 (121-159)
Mean Blood Pressure (mmHg)	106±18	101 (95-113)

*Expressed as number and percentages

Table: 2: Distribution of NIH scores in the study population

NIH Score	Frequency	Percent	Cumulative Percent
0	12	29.3	29.3
1	14	34.1	63.4
2	13	31.7	95.1
3	2	4.9	100.0
Total	41	100.0	

Table: 3 Distribution of ITAS scores in the study population

ITAS Score	Frequency	Percent	Cumulative Percent
0	4	9.8	9.8
1	2	4.9	14.6
2	14	34.1	48.8
3	2	4.9	53.7
4	8	19.5	73.2
5	2	4.9	78.0
6	3	7.3	85.4
9	1	2.4	87.8
11	3	7.3	95.1
12	2	4.9	100.0
Total	41	100.0	

Table 2 shows that by NIH criteria, 15 patients ie 36.6% had active disease. Table 3 demonstrates that when ITAS scoring was used to define active disease, 21 patients ie 51.2% had active disease.

Table 4a: Distribution of angiographic types in the study population

	Frequency	Percent
I	11	26.8
IIa	2	4.9
III	2	4.9
IV	7	17.1
V	17	41.4
n/a	2	4.9
Total	41	100.0

Table 4b:

Distribution of angiographic types among men & women in the study population

Angiographic type	SEX		Total
	Female	Male	
I	10	1	11
IIa	0	2	2
III	1	1	2
IV	5	2	7
V	14	3	17
n/a	1	1	2
Total	31	10	41

By the angiography, the most common was type V (41.4%) followed by I (26.8%) & then type IV (17.1%). The arch vessels were involved in 62.85% of the cases whereas the infra-diaphragmatic abdominal aorta was involved in 51.21%. Extensive involvement of

the whole aorta & its branches were seen in 1 patient. There were no cases of type IIb disease. Coronary involvement was noted in 2 patients. Pulmonary angiogram was not done in these patients & hence the data regarding pulmonary artery involvement was not available. All the angiographic types except type III, which had an equal distribution, were more common in women than in men. Arch vessel involvement seems to be much more common in women than in men.

Table 5: CIMT values

CIMT in the study population (n = 41)

	Mean ±SD	Median + IQ Range
CIMT (Mean of both sides)	0.85 ± 0.30	0.83(0.60 – 0.98)
CIMT (Left)	0.87 ± 0.37	0.80(0.60 – 1.09)
CIMT (Right)	0.82 ± 0.33	0.71(0.58 – 0.96)

CIMT in the control population (n = 30)

	Mean ±SD	Median + IQ Range
CIMT (Mean of both sides)	0.50 ± 0.06	0.50(0.46 – 0.53)
CIMT (Left)	0.50 ± 0.06	0.50(0.47 – 0.53)
CIMT (Right)	0.51 ± 0.06	0.52(0.47 – 0.54)

Difference in the mean of two groups (Parametric- Independent samples t test)

	Patients	controls	p
CIMT	0.85 ± 0.30	0.50 ± 0.06	0.000

CIMT was increased in patients with Takayasu arteritis as compared to the controls (Table 5). The mean CIMT among the study population was 0.85 ± 0.30. This was significantly more than that of the controls which was 0.50 ± 0.06 (p = 0.00). Moreover, as shown in Table 6, patients with an active disease (Mean ± SD = 1.05 ± 0.33) had higher CIMT values than those with inactive disease (Mean ± SD = 0.73±.20). By the non-parametric- Mann Whitney U test, the difference in the mean of two groups was statistically significant (p = 0.001).

Table 6. CIMT in patients with active or inactive disease

	Mean ±SD	p value*	Median + IQ Range
Active (n= 15)	1.05±0.33	0.001	0.98 (0.86-1.29)
Inactive (n= 26)	0.73±20		0.68 (0.58-0.89)
Overall (n = 41)	0.85 ± 0.30		0.83(0.60 – 0.98)

* p value was obtained by the Non Parametric- Mann Whitney U test

Table7. Influence of Carotid Angiographic abnormality on CIMT

	Normal	Abnormal	p
CIMT, Right side	0.76± 0.29 (n = 32)	1.09±0.42 (n = 7)	0.037
CIMT, Left side	0.81± 0.34 (n = 27)	1.05±0.39 (n =12)	0.037
CIMT, Combined	0.79±0.31 (n = 59)	1.07±0.39 (n = 19)	0.002

When all the carotid vessels in the study population were assessed together, 59 common carotid arteries (75.6%) had a normal carotid angiogram & 19 common carotid arteries (24.4%) had a normal carotid angiogram. Moreover, as in Table 7 the CIMT values were significantly higher in common carotid arteries with abnormal luminogram than in the ones with a normal angiogram.

Table 8. Correlation of CIMT with age, ESR, CRP, ITAS & NIH

	Pearson's Correlation coefficient Rho(r)	p
CIMT log & CRP log	0.184	0.25
CIMT log & ESR log	0.301	0.05
CIMT & Age	0.100	0.53
CIMT & SBP	-0.198	0.22
CIMT & MBP	-0.300	0.06
CIMT & ITAS	0.506	0.001
CIMT & NIH	0.559	0.000

Table 8a. Correlation of ITAS with NIH Score

	Spearman's Correlation coefficient Rho(r)	p
ITAS & NIH	0.548	0.000

Analysis of correlations of mean CIMT with the different variables of disease activity – ESR, CRP, NIH & ITAS, (Table 8) showed that there was a moderate, statistically significant correlation with ESR, NIH & ITAS scores. The correlations with CRP, age & Blood pressure were however not significant. Correlation analysis as shown in Table 8a also showed a significant correlation between the 2 scores – NIH & ITAS.

Strength of association of CIMT ≥ 0.80mm with the variables of disease activity were evaluated by the Mantel - Hansel linear by linear association chi square test. CIMT ≥ 0.80mm was found to have a statistically significant association with ESR ≥ 40mm in 1 hour (Table 9a), NIH score ≥ 2(Table 9c), & ITAS score ≥ 3(Table 9d). But the association with CRP was not significant (Table 9b).

Table 9. CIMT association with markers of disease activity

CIMT association with ESR, CRP, NIH & ITAS by the Mantel Haensel linear by linear association chi square test: -

Table 9a:

		ESR		Total
		< 40	≥ 40	
	CIMT < 0.8	17	1	18
	CIMT ≥ 0.8	13	10	23
Total		30	11	41

p Value=0.007

Table 9b:

		CRP		Total
		< 6	≥ 6	
	CIMT < 0.8	9	9	18
	CIMT ≥ 0.8	10	13	23
Total		19	22	41

p Value=0.681

Table 9c:

		NIH		Total
		< 2	≥ 2	
	CIMT < 0.8	16	2	18
	CIMT ≥ 0.8	10	13	23
Total		26	15	41

P Value=0.003

Table 9d:

		ITAS		Total
		<3	≥ 3	
	CIMT < 0.8	15	3	18
	CIMT ≥ 0.8	5	18	23
Total		20	21	41

P Value=0.000

The strength of association was also tested in patients with angiographic arch vessel involvement. The result of this is shown in Table 10. Even in these 27 patients, a statistically significant association was demonstrable between CIMT ≥ 0.80mm with ESR ≥ 40mm in 1 hour (Table 10a), NIH score ≥ 2(Table 10c), & ITAS score ≥ 3(Table 10d) but not with CRP(Table 10b).

Table 10. CIMT association with markers of disease activity, among patients with angiographic arch vessel involvement

Table 10a

		ESR		Total
		< 40	≥ 40	
	CIMT < 0.8	10	0	10
	CIMT ≥ 0.8	7	10	17
Total		17	10	27

P Value = 0.003

Table 10b

		CRP		Total
		< 6	≥ 6	
	CIMT < 0.8	4	6	11
	CIMT ≥ 0.8	7	10	17
Total		11	16	27

P Value = 0.953

Table 10c

		NIH		Total
		< 2	≥ 2	
	CIMT < 0.8	10	0	10
	CIMT ≥ 0.8	6	11	17
Total		16	11	27

P Value = 0.001

Table 10d

		ITAS		Total
		<3	≥ 3	
	CIMT < 0.8	9	1	10
	CIMT ≥ 0.8	3	14	17
Total		12	15	27

P Value = 0.000

Table 11. Sensitivity(Sn) and specificity(Sp) of CIMT to detect active disease

Gold Std	CIMT measure	Sn	Sp	LR (+)	LR (-)	PPV	NPV
NIH	CIMT ≥ 0.80mm	86%	61%	2.20	0.23	0.57	0.88
ITAS	CIMT ≥ 0.80mm	86%	75%	3.44	0.19	0.78	0.83

Sn: Sensitivity; Sp: Specificity;

LR (+): Positive likelihood ratio; LR (-): Negative likelihood ratio

PPV: Positive Predictive Value; NPV: Negative Predictive Value

NIH criteria are one of the most commonly used criterions to assess disease activity or response to treatment in patients with TA. Hence using the NIH criteria as the gold standard to detect active disease, sensitivity(Sn) and specificity(Sp) of CIMT ≥ 0.80mm to detect active disease was calculated. Based on these likelihood ratios were also calculated, as shown in Table 11. Thus CIMT ≥ 0.80mm has a sensitivity of 86% & a specificity of 61% which increases to 86% & 75% when ITAS is used as the gold standard.

Table12. Influence of carotid angiographic abnormality on sensitivity and specificity of CIMT

	Carotid Angiogram		Total
	Normal	Abnormal	
CIMT < 0.80mm	37	3	40
CIMT ≥ 0.80mm	22	16	38
Total	59	19	78

Sensitivity = 84%; Specificity = 63%;

Positive Predictive Value = 0.42; Negative Predictive Value = 0.93

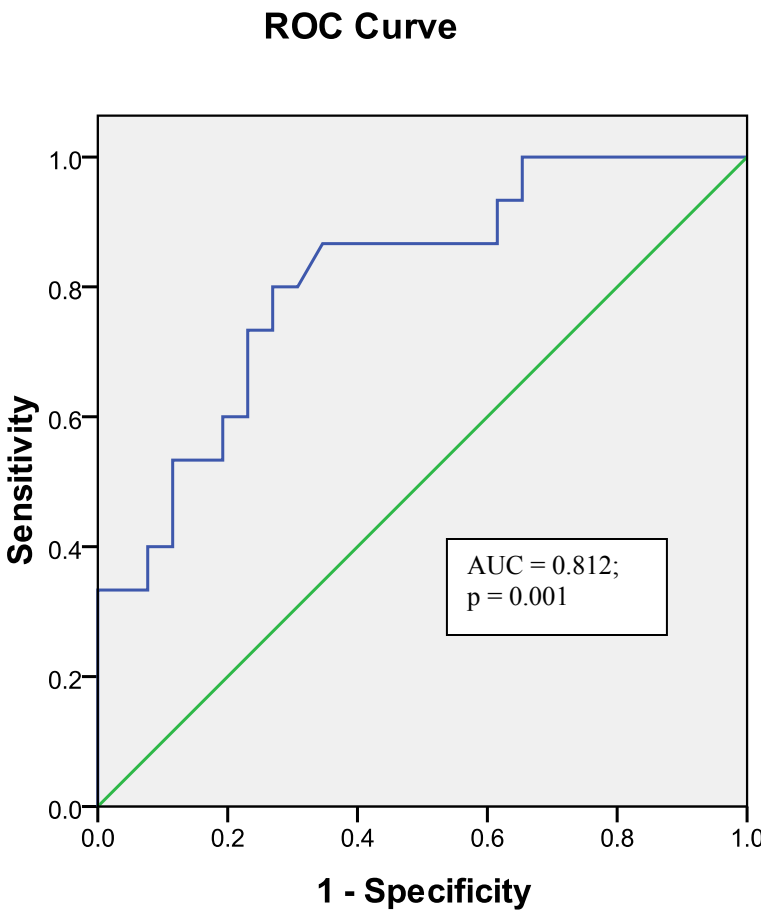
Likelihood ratio for a Positive test = 2.27; Likelihood ratio for a Negative test = 0.253

Thus as per Table 12, a CIMT ≥ 0.80mm in a patient with TA increases the pretest probability of having an abnormal carotid angiogram.

ROC analysis:

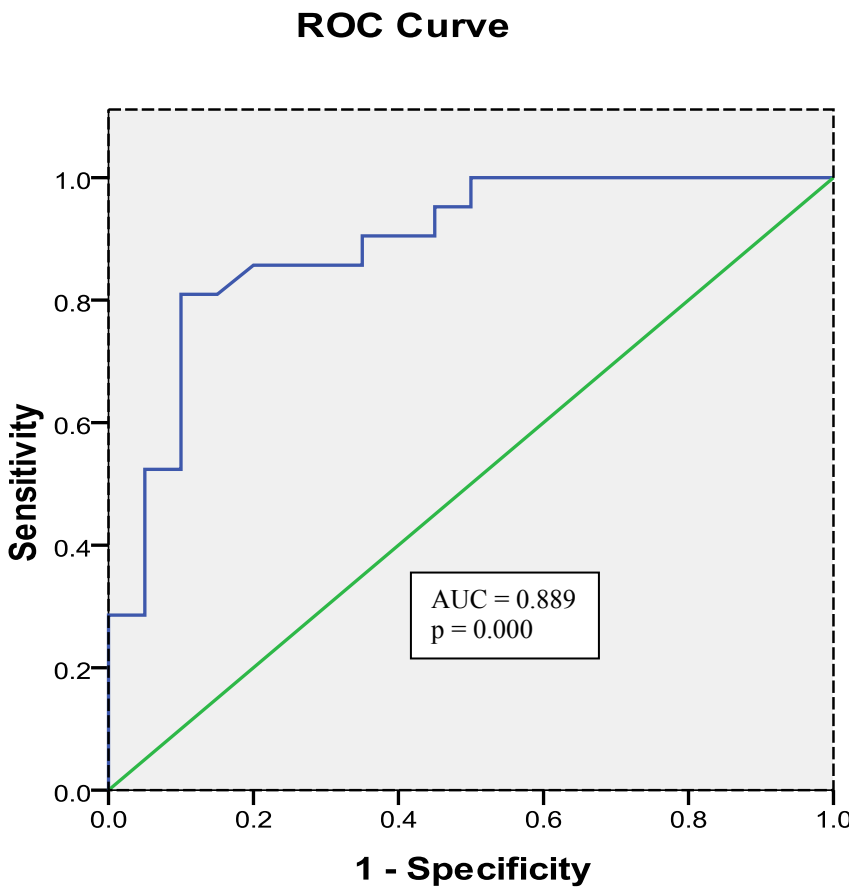
ROC curve was generated to assess the best cut off point of CIMT that yields the best sensitivity & specificity to detect active disease. This was done using both NIH & ITAS as the gold standard.

Table 13. With NIH as gold standard:



A mean CIMT of ≥ 0.82mm yields a sensitivity of 87% & a specificity of 65% and a mean CIMT ≥ 0.85mm yields a sensitivity of 80% & a specificity of 73%.

Table14. With ITAS as the gold standard:



By this, CIMT ≥ 0.82mm yield a sensitivity of 86% & a specificity of 80% and mean CIMT ≥ 0.85mm yield a sensitivity of 81% & a specificity of 90%.

Table 15. Using ROC data, best cut off points derived for CIMT were as below: -

Gold Std	CIMT measure	Sensitivity	Specificity	LR (+)	LR (-)
ITAS	CIMT ≥ 0.82mm	86%	80%	4.3	0.5
	CIMT ≥ 0.85mm	81%	90%	8.1	0.21
NIH	CIMT ≥ 0.82mm	87%	65%	2.5	0.002
	CIMT ≥ 0.85mm	80%	73%	2.96	0.27

This would mean that if ITAS is used as the gold standard to detect active TA, a CIMT ≥ 0.85mm adds approximately 40% to the pretest probability of an active disease.

DISCUSSION

Assessment of disease activity in TA is currently suboptimal. The currently accepted method is NIH criteria. This however has many limitations - the nonvalidated status[40] of the score, the low sensitivity[31]& the need for an invasive angiographic study. Many serum markers of disease activity have been suggested by various clinical studies. Apart from the acute phase reactants which has a low specificity for TA, the others suggested include MMP-3/TIMP-1 ratio (Matrix MetaloProteinase – 3 / Tissue Inhibitor of MetalloProteinase – 1, ratio), Interleukin-18 levels, etc. newer imaging techniques like MRI, F-18 FDG PET scans & F-18 FDG PET-CT scans are promising in the diagnosis & assessment of disease activity in patients with TA. However these tests are expensive & not easily available. It was in this setting that the ITAS scoring was proposed & subsequently validated in 1 study. The ITAS, a more sensitive assessment tool for TA than the BVAS scoring, involves 59 items in 11 organ-based scoring systems with emphasis on the cardiovascular system (19 items). By this scoring the disease is considered to be active if the score exceeds 2 and each item is scored only if the abnormality is new or worse, within the past 3 months. Hence at 1st visit or presentation this scoring suggests disease extent rather than disease activity.

High resolution B-mode ultrasonography is an inexpensive, easily available & sensitive tool. Studies have shown an increase in CIMT in many inflammatory conditions such as RA, psoriatic arthritis[48, 49] Behcet's disease and Takayasu's arteritis[50, 51]. The arch vessels are commonly involved in patients with TA - in 62.85% of the cases in this study. Hence

an ultrasonographic evaluation & CIMT assessment may be helpful in evaluating the disease activity in patients with TA.

Seth et al from their study in 37 patients of Takayasu arteritis concluded that increased CCA–IMT is a reliable marker of active disease, especially in the absence of angiographically visible carotid disease [55]. Studies assessing CIMT in Takayasu arteritis are limited.

Studies with Carotid ultrasound in TA with / without correlation with activity

Study	No. of patients in the study	CIMT (mm) in Takayasu Arteritis		
		Active	Inactive	Control
Raninen et al[57]	16	1.75 ±0.86	0.74 ±0.11	
Seth et al[55]	37	1.5 ± 0.16	0.9 ± 0.19	0.6 ± 0.13
Park et al[44]	10	3.3 ±0.8	1.6 ± 0.4	n/a
Zielenski et al[54]	18	1.1 ± 0.1		0.6 ±0.01
c-CAT study (Present study)	41	1.05 ± 0.33	0.73±.20	0.50 ± 0.06

In our study, we found that the mean CIMT was significantly higher in patients with TA than in controls. Among the patients with TA, mean CIMT was higher in active disease than in inactive disease. Moreover there was a moderate, statistically significant correlation between CIMT and the currently used NIH score & even the validated ITAS score. This suggests that CIMT can be used to reliably assess disease activity in patients

with TA. We demonstrated a significant association of CIMT ≥ 0.80mm with NIH ≥ 2, ITAS ≥ 3 & ESR ≥ 40mm in 1hour. There was no significant association with CRP. Even among patients with angiographic arch vessel involvement, the correlations of CIMT ≥ 0.80mm were similar. A similar lack of CRP correlation was also seen in one of the previous studies. Noris et al[37] in their study of cytokines in TA, demonstrated that cytokines correlated with the ESR but not with CRP values. This lack of CRP correlation however was not adequately explained.

By NIH criteria, only 36.6% had active disease; whereas by ITAS scoring, 51.2% had active disease. This demonstrates the problem of a low sensitivity with NIH scoring which is well known. Our institution being a referral centre, many of the TA patients were already on treatment with steroids. This may also contribute to the relatively lower percentage of patients with active disease in this study.

In our study, the arch vessels and the infra-diaphragmatic abdominal aorta were most commonly involved segments, in 62.85% & 51.21% respectively. This is in keeping with the previous studies. Most of the patients were of the angiographic type V. This suggests a more extensive disease pattern seen in our patients. This may also be so since most of our patients are referrals from elsewhere.

By this c-CATstudy, abnormal CIMT (≥ 0.80mm) had a sensitivity of 86% & a specificity of 61% to detect an active disease, when NIH was used as the gold standard for detecting active disease. But when ITAS was used as the gold standard, a CIMT ≥ 0.80mm had a sensitivity of 86% & a specificity of 75%.

ROC curve analysis demonstrated that the best likelihood ratios were for a CIMT ≥ 0.85mm & when the gold standard is ITAS. Thus using ITAS as the gold standard & CIMT ≥ 0.85mm yield a positive likelihood ratio of 8.10, suggesting a moderate likelihood & hence may be better parameters to assess disease activity. It adds approximately 40% to the pretest probability of an active disease.

LIMITATIONS:

1. Though a prospective study, it is at best a descriptive single centre, nonrandomized study.
2. Doppler US is operator-dependent although studies have consistently shown that when done by trained personnel, CIMT measurement is highly reproducible. However much of the limitation can be overcome by using a semi-automated border detection program which is available in the newer high end ultrasonographic machines.

CONCLUSIONS

1. Abnormal CIMT (CIMT ≥ 0.80mm) is an easily available & economical tool that can be used to reliably assess disease activity in patients with TA.

2. Using the NIH criteria, CIMT ≥ 0.80mm has a sensitivity of 86% and a specificity of 61% to detect active TA.

3. A likelihood ratio of 2.2 for a CIMT ≥ 0.80mm to detect active TA increases to 8.1 when ITAS is used as the gold standard and the cut-off for an abnormal test is a CIMT ≥ 0.85mm. However larger studies need to be done before these changes can be incorporated into routine clinical practice.

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APPENDIX - 1

PROFORMA

Correlation of CIMT with disease Activity in Takayasu's Arteritis (c-CAT Study)

Patient Details:

Name of the patient: Hospital No.:

Age/Sex:

Address & Telephone No.:

History:

H/o Smoking: Y / N duration: H/o Diabetes: Y / N duration:

H/o CVA/ TIA: Y / N duration: H/o IHD: Y / N duration:

H/o Renal failure: Y /N duration:

Laboratory Data: (Date of enrolment:)

ESR: CRP:

Examination findings at 1st visit:

Site	Side	Pulses	Blood Pressure	Bruit
Carotids	Right			
	Left			
Subclavian	Right			
	Left			
Brachial	Right			
	Left			
Radial	Right			
	Left			
Femoral	Right			
	Left			
Popliteal	Right			
	Left			
D. Pedis	Right			
	Left			
P. Tibial	Right			
	Left			

CIMT:		Right	Left
	Proximal CCA		
	Mid CCA		
	Bulb		
	Mean		
FIMT			

Activity at enrolment: Active / In-Active.

NIH criteria:

ITAS score:

Angiographic Data at baseline.

		Right	Left
CCA	Ostial		
	Proximal		
	Mid		
	Distal		

APPENDIX - 2

ITAS – Indian Takayasu Activity Score	
Tick Box only if abnormality is present (new or worse) within past 3 months. Tick box only if abnormality is ascribed to current, active vasculitis.	Visit Date : Patient ID

1. SYSTEMIC

None ☐

Malaise/Wt. Loss>2Kg ○

Myalgia/Arthralgia/Arthritis. ○

Headache ○

Fever ○

2. MUCOUS MEMBRANES

None ☐

Present ○

3. EYES

None ☐

Blurred Vision ○

Sudden Vision Loss ○

Other ○

4. CHEST

None ☐

Persistent Cough ○

Dyspnea/Wheeze ○

Hemoptysis/Hemorrhage ○

Massive Hemoptysis ○

Respiratory Failure ○

5. ABDOMEN

None ☐

Severe Abdominal Pain ○

Bloody Diarrhea ○

Gut Perforation/Infarct ○

6. RENAL ☐

None

Hypertension (Diastole >90) ○

"" Systolic >140 ○

Proteinuria (>1+/0.2g/24H) ○

Hematuria (>1+/10RBC/ml) ○

Creatinine (1.4-2.73 mg/dl) ○

Creatinine (2.75-5.5mg/dl) ○

Creatinine (>5.5 mg/dl) ○

Rise in creatinine >30% or
> 25% fall in creatinine clearance. ○

7. Nervous System

None ☐
Organic Confusion/Dementia ○
Seizures (not hypertensive) ○
Stroke ○
Syncope ○
Cord Lesion ○

8. Genitourinary System

None ☐
Sexual Impotence ○
Abortions ○

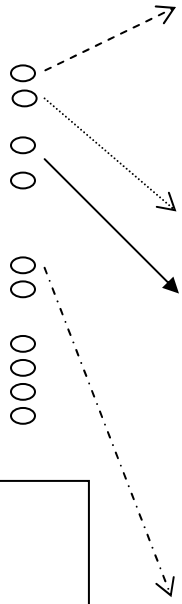
9. CARDIOVASCULAR SYSTEM

None ☐
Bruits (see 9a) ○
Pulse Inequality (See 9b) ○

New Loss of Pulses (See 9c) ○
New Loss of pulses with threatened loss of limb. ○

Claudication (See9d) ○
Carotidodynia ○

Aortic Incompetence ○
Pericardial Pain/Rub ○
Ischemic Cardiac Pain ○
Congestive Cardiac Failure ○



9a. Bruits	**R**		**L**
Carotid	○		○
Vertebral	○		○
Subclavian	○		○
Renal	○		○
Abdominal		○	
Inguinal	○		○

9b. Pulse and BP Inequality

Present		○	

9c. Pulse Loss

Carotid	○		○
Subclavian	○		○
Brachial	○		○
Radial	○		○
Femoral	○		○
Popliteal	○		○
Posterior Tibial	○		○
Dorsalis Pedis	○		○

9d. Claudication

Arm		○	
Leg		○	

Cardiology Opinion/Tests

No Active Vasculitis ○
Pericarditis ○
Myocardial Infarct/Angina ○
Cardiomyopathy ○

10. Other Vasc items:

11. Physician Global Opinion (Active / Grumbling or persistent / Inactive):

12. ESR :

CRP:

S.No	Name & Hospital Number	Age	Sex	(Mean of CCA) CIMT		Pulse		Diagnosis & Echo
				Right	Left	Right	Left	
1	Kumaravel 607801d	23	M	0.47mm	0.48mm	2+	2+	Normal
2	Karthick 609969D	20	M	0.40mm	0.47mm	2+	2+	Normal
3	K Sen 612422D	10	M	0.53mm	0.55mm	2+	2+	Normal
4	Prita, 613773D	14	F	0.55mm	0.48mm	2+	2+	Normal
5	Harka k,252034d	41	F	0.52mm	0.47mm	2+	2+	Normal
6	Karthiyani, 865044c	25	F	0.45mm	0.52mm	2+	2+	Normal
7	Revathi, 700825c	36	F	0.54mm	0.53mm	2+	2+	Normal
8	Sandiya, 346244C	23	F	0.48mm	0.45mm	2+	2+	Normal
9	Saranya, 566412D	20	F	0.55mm	0.50mm	2+	2+	Normal
10	Sanoj Roy 463731D	30	M	0.53mm	0.53mm	2+	2+	HOCM
11	Brijesh, 261886D	32	M	0.50mm	0.50mm	2+	2+	Normal
12	John, 395410B	30	M	0.47mm	0.50mm	2+	2+	Normal
13	sridevi, 176176d	22	F	0.64mm	0.62mm	2+	2+	CRF
14	Julius,	30	M	0.53mm	0.54mm	2+	2+	Normal
15	Reena K, 531977D	19	F	0.51mm	0.53mm	2+	2+	ASD
16	Sanju , 609694D	18	F	0.43mm	0.42mm	2+	2+	syncope
17	Ankita das, 291990d	13	F	0.50mm	0.43mm	2+	2+	Normal
18	Govindammal, 262348D	24	F	0.42mm	0.40mm	2+	2+	?Hemic murmur
19	Sandhya, 610175D	25	F	0.53mm	0.50mm	2+	2+	Normal
20	Kalpana, 244640D	26	F	0.57mm	0.53mm	2+	2+	VSD, AR
21	Shobha, 486950D	26	F	0.43mm	0.50mm	2+	2+	MR
22	Bilashi, 579275D	36	F	0.44mm	0.47mm	2+	2+	post MVR
23	Phurpa, 626709d	32	F	0.54mm	0.56mm	2+	2+	ILD
24	shreya, 621486c	22	F	0.47mm	0.47mm	2+	2+	Normal
25	Priyanka, 628009D	23	F	0.40mm	0.40mm	2+	2+	Normal
26	Varsha, 629416d	23	F	0.48mm	0.53mm	2+	2+	RSOV to RA
27	Poongodi,072856d	23	F	0.53mm	0.48mm	2+	2+	ASD
28	Shobha, 486950d	27	F	0.56mm	0.63mm	2+	2+	Post MVR
29	Soumitra, 937260A	42	F	0.63mm	0.60mm	2+	2+	ASD
30	Sivagami,580169d	23	F	0.60mm	0.53mm	2+	2+	Mild MR

Master Sheet - Control Data

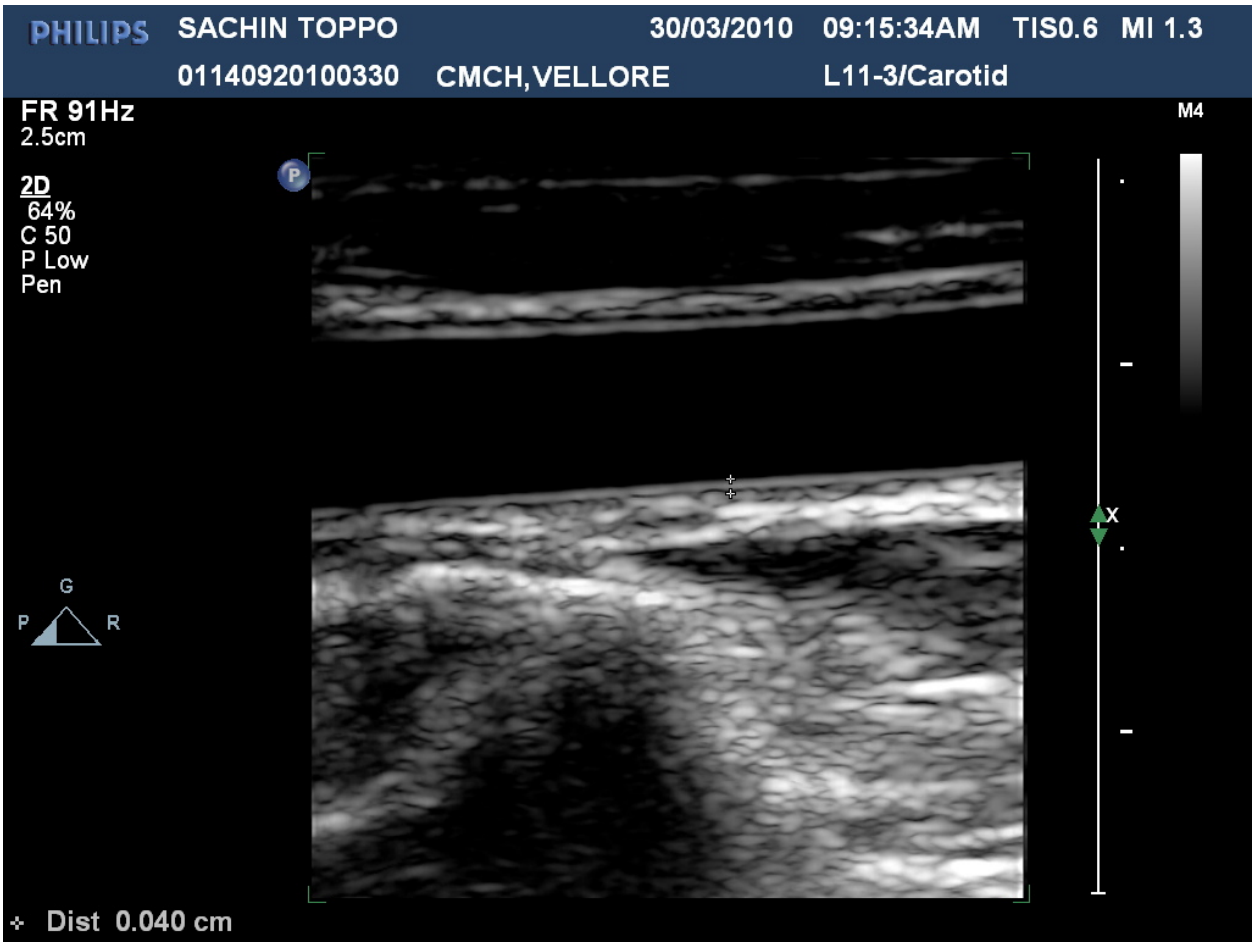


Figure1 – CIMT measured in the study

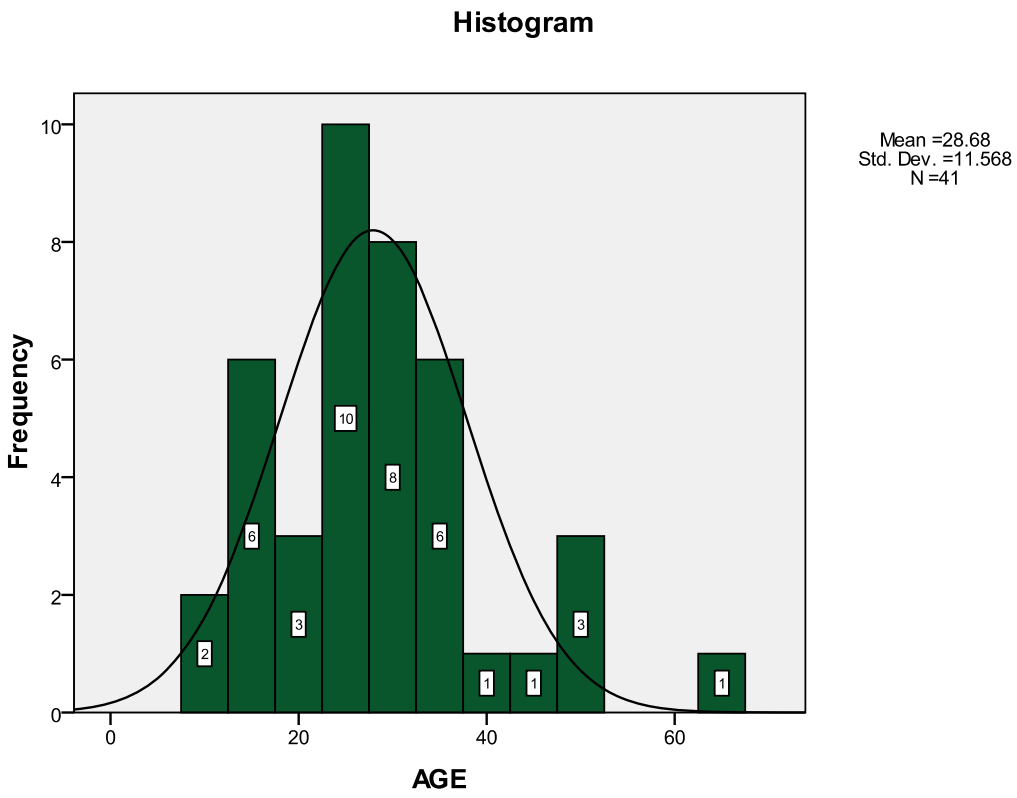


Figure 2. Age distribution of the patients

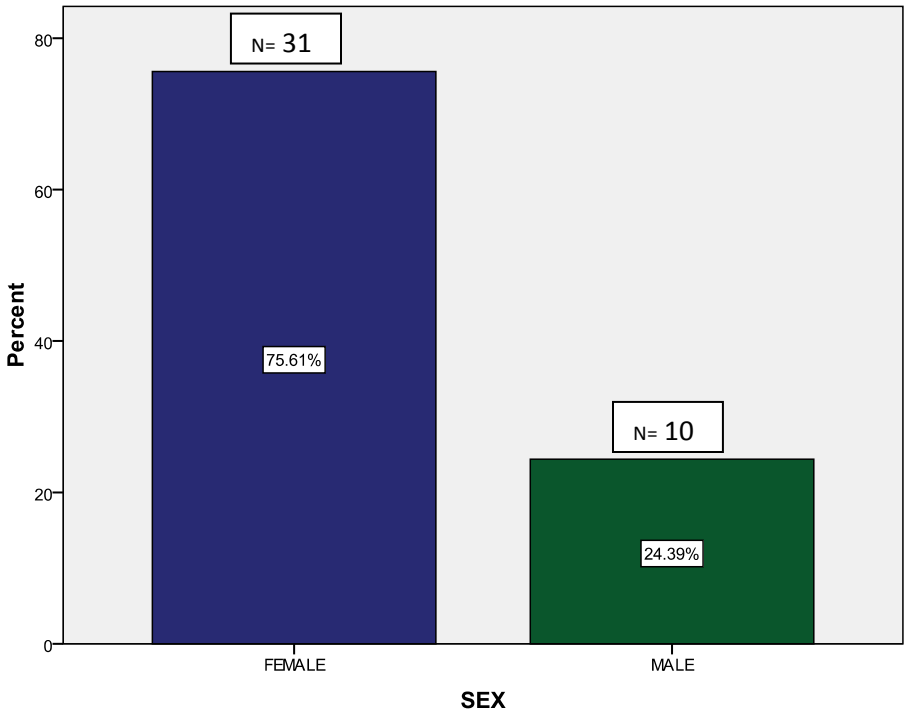


Figure 3. Sex distribution of the patients

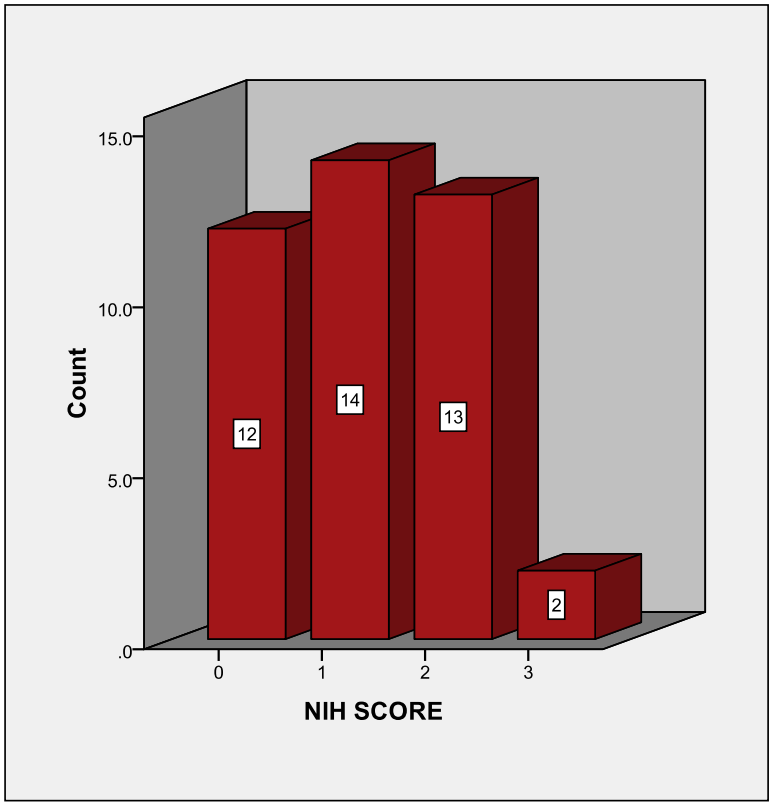


Figure 4. **Distribution of NIH scores in the study population**

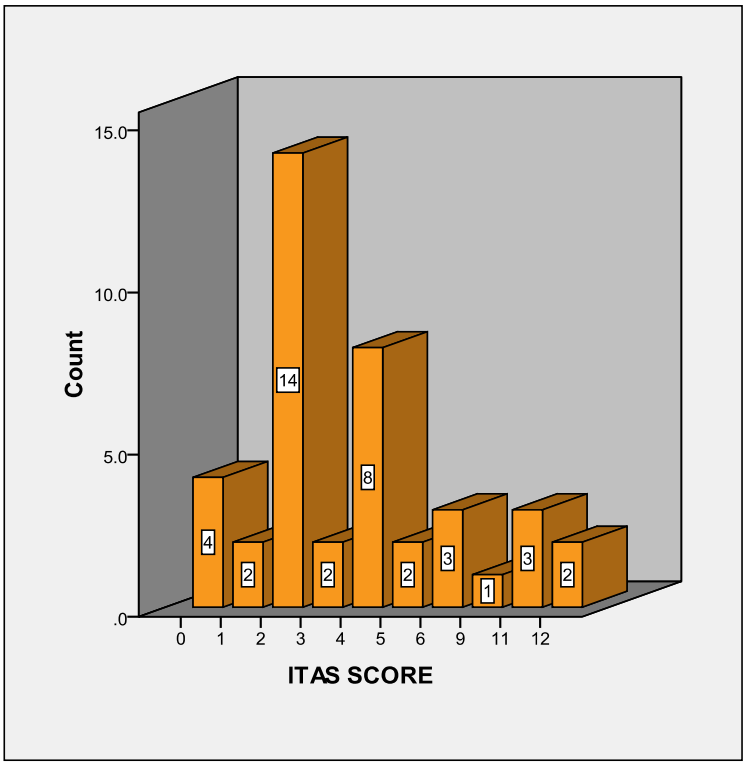


Figure 5. **Distribution of ITAS scores in the study population**

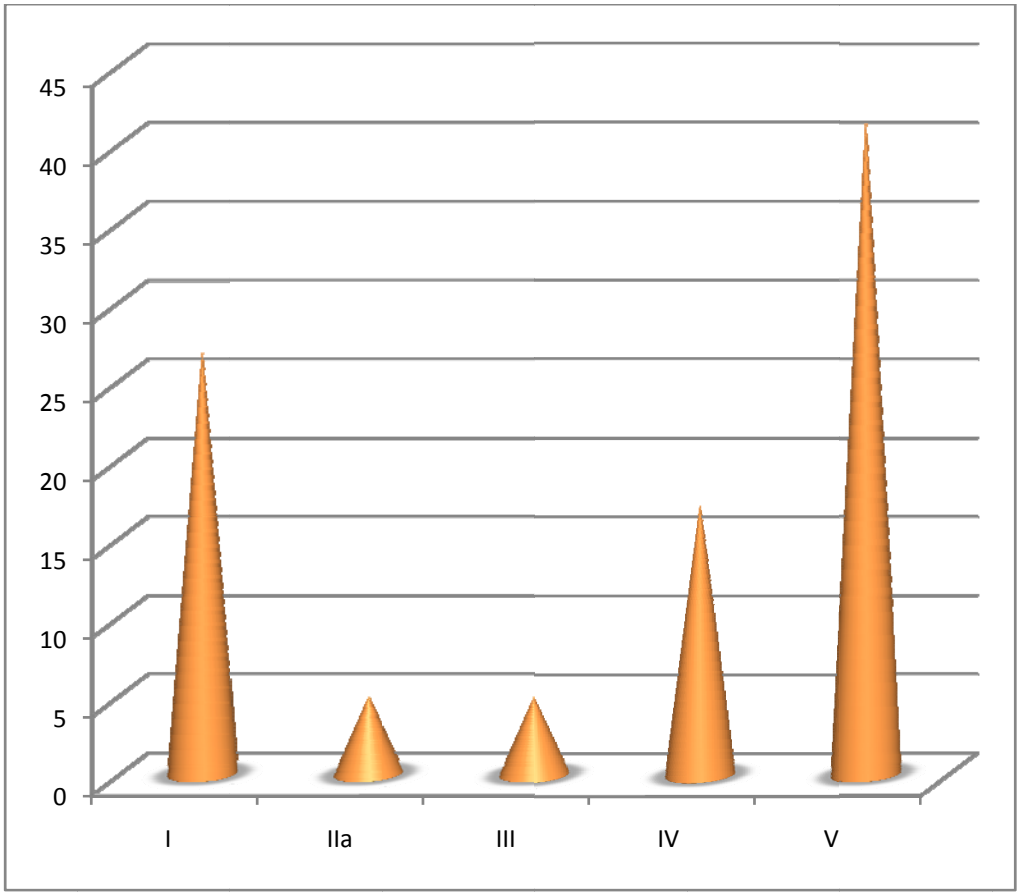


Figure 6. **Distribution of angiographic types in the study population**

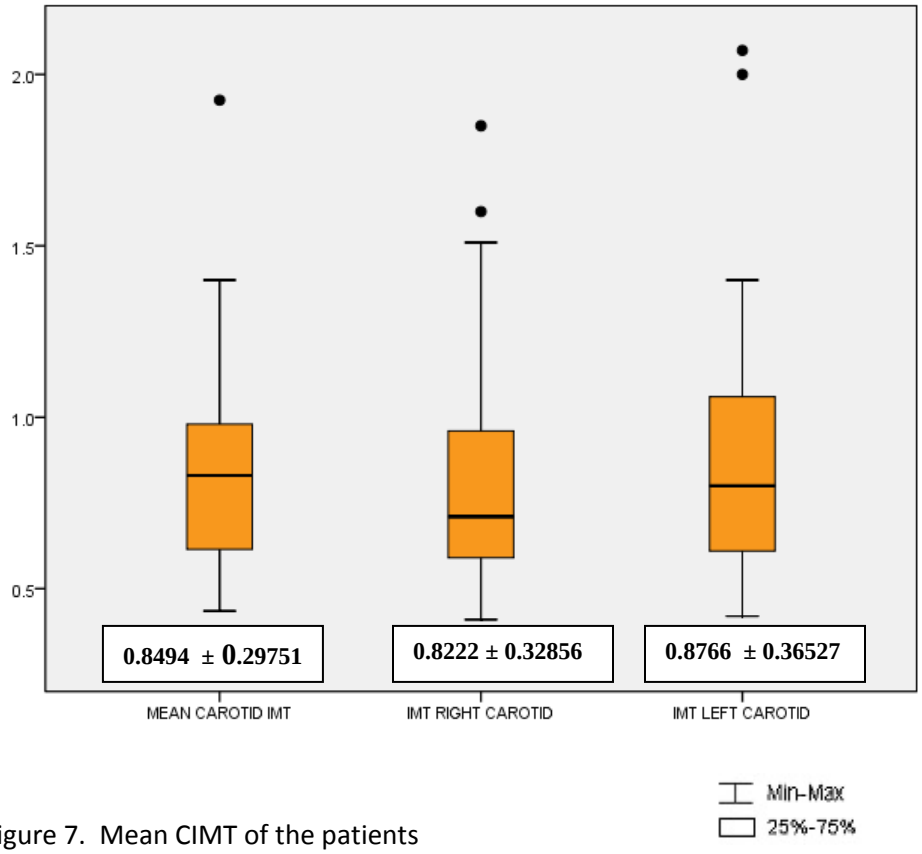


Figure 7. Mean CIMT of the patients

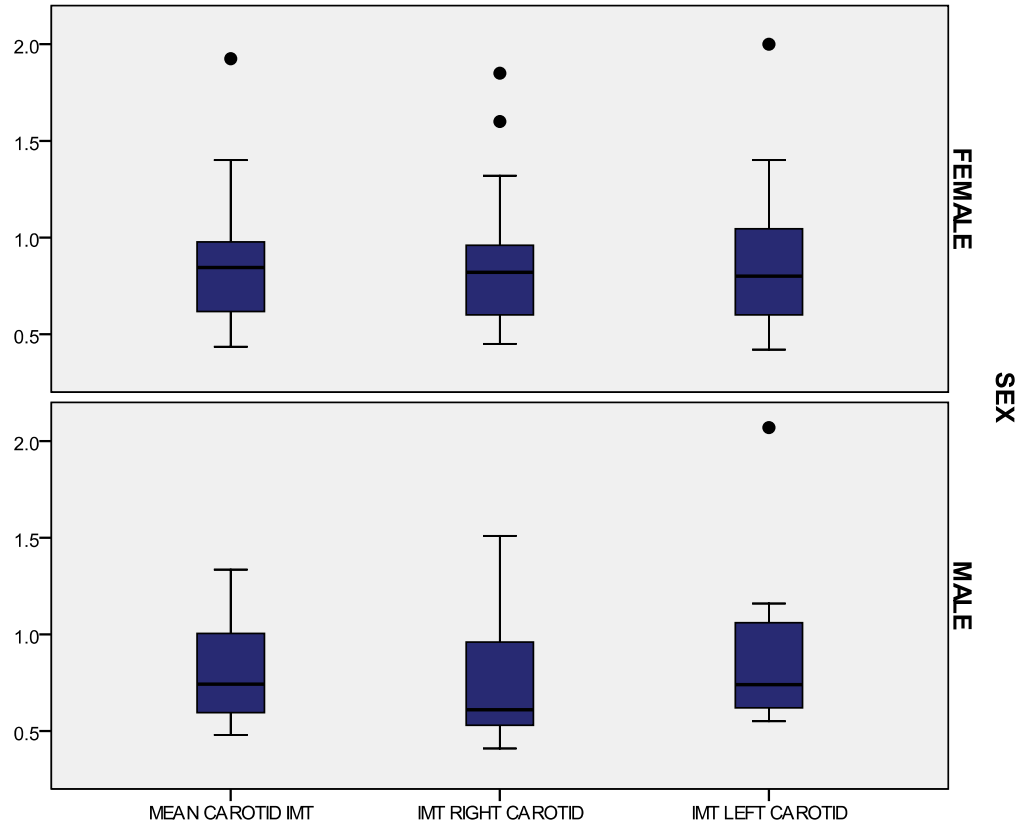


Figure 8. Mean CIMT of the patients by sex distribution

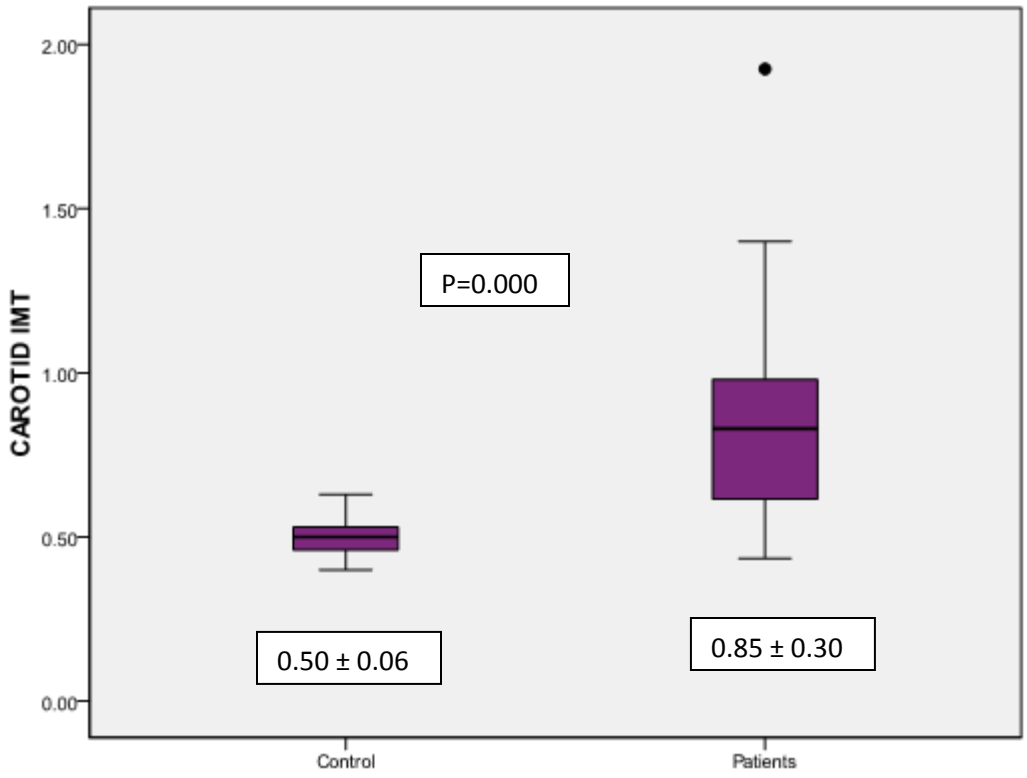


Figure 9. Mean CIMT among controls and patients

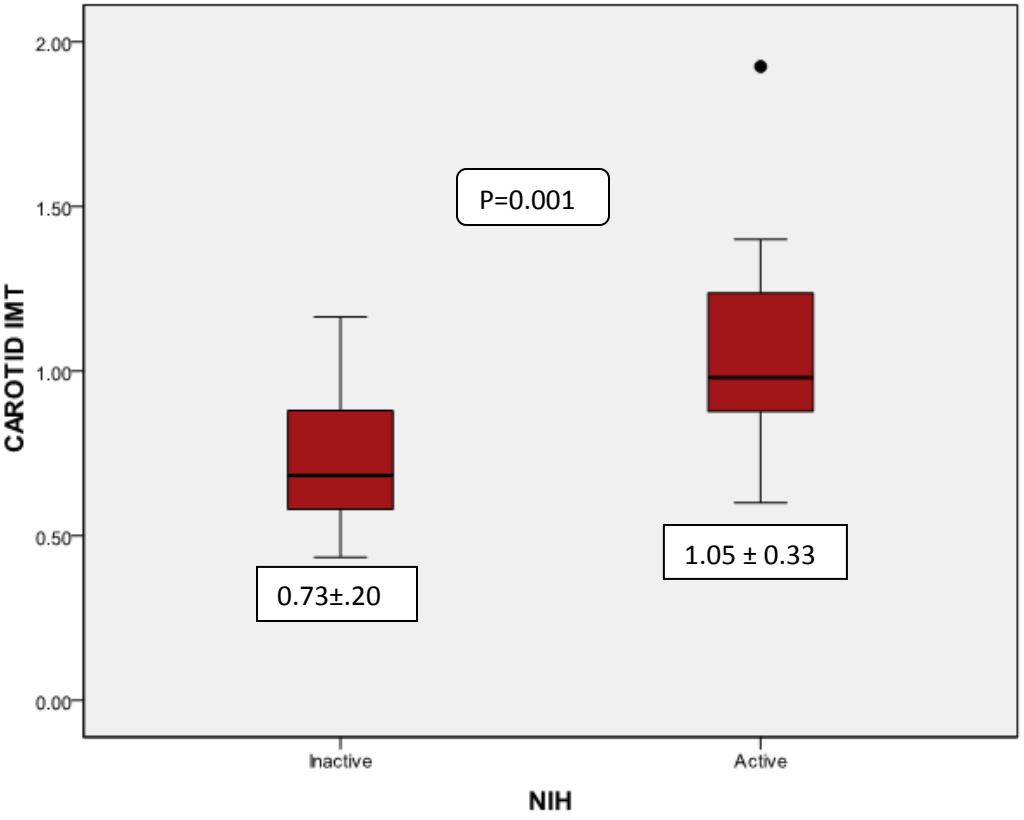


Figure 10. CIMT among patients with active/inactive disease

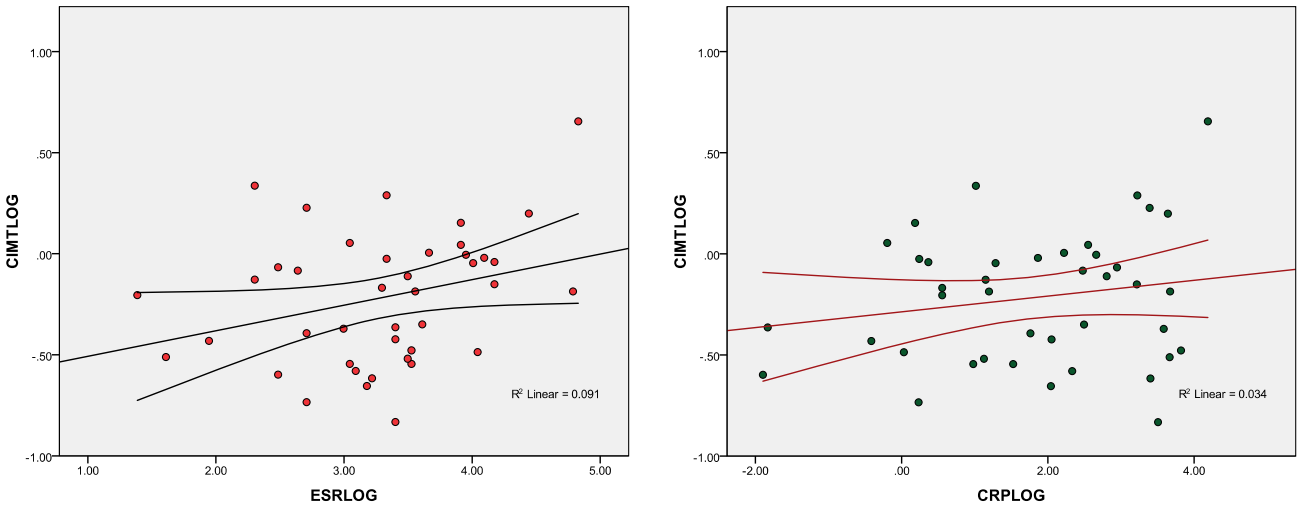


Figure 11. Scatter plot showing the correlation of CIMT with ESR & CRP

Master sheet - Patient data

No.	Name & Hospital Number	Age	Sex	Activity				CIMT (Mean)		Pulse		CCA angio		BP	angio type	aneur
				ESR	CRP	NIH	ITAS	Right	Left	Right	Left	Right	Left			
1	Jerusha Lepcha, 394788-D	14	F	55	3.61	2	11	1.00mm	0.91mm	1+	2+	O	O	139/75(100)	I	
2	Dorji, 411886-D	33	F	27	1.74	0	2	0.91mm	0.78mm	2+	2+	N	N	144/72[100]	V	
3	Sarbani, 373121-D	51	F	60	6.44	2	11	1.00mm	0.96mm	2+	2+	N	N	148/58(88)	V	
4	Baby, 341126-D	37	F	4	1.74	0	0	0.83mm	0.80mm	3+	3+	N	N	150/80(107)	IV	
5	Jabarani, 333204-D	32	F	34	45.6	2	2	0.65mm	0.59mm	2+	2+	N	N	158/83(105)	IV	
6	Rohina, 331725-D	32	F	65	1.44	1	1	1.26mm	0.66mm	2+	2+	N	N	160/94/91	I	
7	Elcy, 283746-D	34	F	65	24.9	2	3	0.96mm	0.76mm	2+	2+	N	N	184/87(128)	I	
8	Rani, 013100-C	33	F	14	11.9	2	4	0.71mm	1.13mm	2+	1+	N	O	170/65(104)	V	
9	Bibekanda, 167351-B	51	M	34	4.59	0	2	0.57mm	0.59mm	2+	2+	N	N	110/80	V	
10	Janaki.C., 005493-D	31	F	5	39	2	2	0.53mm	0.67mm	2+	2+	N	N	144/76[101]	III	
11	Yuvaraj, 456622-D	18	M	15	29.7	2	5	0.44mm	2.07mm	2+	1+	N	N	106/81 (94)	IIa	+
12	Gayathri, 417815-D	25	F	25	30	1	0	0.53mm	0.55mm	2+	2+	N	A	190/110 (140)	V	+
13	Suparna, 534311-D	13	F	20	36	1	6	0.54mm	0.84mm	2+	1+	N	A	135/72 (98)	V	
14	Tamilselvi, 346764-D	24	F	30	33.3	1	2	0.45mm	0.42mm	2+	2+	N	N	130/80	V	
15	Vidyapraveena, 366826-D	29	F	15	5.82	0	2	0.62mm	0.73mm	2+	2+	N	N	142/95(117)	I	
16	Padmini, 438036-D	27	F	125	65.9	3	12	1.85mm	2.00mm	2+	2+	N	A	108/61 (86)	I	
17	Prateek, 534438-D	10	M	30	7.76	1	2	0.69mm	0.62mm	2+	2+	N	N	96/70	IV	
18	Rochana, 517508-D	15	F	24	7.69	1	2	0.49mm	0.55mm	2+	2+	N	N	180/89	V	
19	Manpi, 196066-d	12	F	35	3.3	0	2	0.86mm	0.80mm	2+	2+	N	N	143/72/101	IV	
20	Nandita, 041168-D	24	F	12	0.154	0	1	0.61mm	0.49mm	2+	2+	N	N	134/83(109)	I	
21	Pinki Das, 309437-D	26	F	28	1.27	0	6	0.59mm	1.36mm	2+	1+	N	A	140/50	V	
22	Manjunath, 586990-D	32	M	15	1.26	0	2	0.41mm	0.55mm	3+	1+	A	O	170/80	I	
23	Tushara, 380493-B	27	F	21	0.821	0	0	0.85mm	1.26cm	2+	0	A	A	114/50(80)	I	
24	Ashok, 621740-C	25	M	120	39.3	2	4	0.60mm	1.06mm	2+	1+	N	O	170/100	V	+
25	Santhosh,930583-C	16	M	33	3.08	0	2	0.53mm	0.66mm	2+	2+	N	N	140/77(106)	IV	

Master sheet - Patient data

No.	Name & Hospital Number	Age	Sex	Activity				CIMT (Mean)		Pulse		CCA angio		BP	angio type	aneur
				ESR	CRP	NIH	ITAS	Right	Left	Right	Left	Right	Left			
26	Anju, 977967-C	25	F	85	38.1	3	6	1.32mm	1.12mm	1+	2+	A	N	142/71(102)	I	
27	Sabika, 539802-C	22	F	21	2.66	1	2	0.59mm	0.57mm	2+	2+	N	N	150/90	IV	
28	Eldrick, 475512b,	63	M	39	9.2	1	9	1.17mm	0.84mm	2+	1+	N	O	220/100	V	
29	Chinni, 384603D,	16	M	28	25.1	2	4	1.51mm	1.16mm	2+	2+	A	A	113/66(85)	IIa	+
30	Laltu, 498217D	25	M	7	0.66	0	11	0.62mm	0.68mm	3+	3+	N	N	146/72(101)	III	
31	Malna, 435520C	30	F	52	14.3	2	4	1.07mm	0.92mm	1+	2+	N	N	153/78(98)	I	
32	Sumita, 431470D,	30	F	33	16.5	2	12	0.82mm	0.97mm	2+	0	N	A	175/101 (127)	V	
33	Krishnaveni, 058242C	48	F	10	2.76	2	4	1.60mm	1.20mm	2+	2+	A	N	130/70	V	
34	Biplobi Barua, 323132D,	35	F	50	1.2	1	4	0.93mm	1.40mm	2+	1+	N	N	120/80	I	
35	Chitra Maya, 269071D	16	F	50	12.8	2	4	0.96mm	1.13mm	2+	2+	A	N	147/85 (111)	V	
36	Phub Wagmo, 558209C	22	F	12	19	1	3	0.94mm	0.93mm	2+	2+	N	N	121/57(75)	V	+
37	Jasmin Begum, 174566D,	35	F	37	12.1	1	2	0.68mm	0.73mm	2+	2+	N	N	104/70	V	
38	Sashukumari, 716696C	28	F	22	10.3	1	2	0.57mm	0.55mm	2+	2+	N	N	100/70	V	
39	G. Jaya, 517647D	45	F	30	0.16	0	0	0.78mm	0.61mm	2+	2+	N	N	170/90	IV	+
40	Neera Jakshi, 423840D	23	F	57	1.03	1	5	0.71mm	0.52mm	2+	2+	N/A	N/A	140/90	N/A	
41	Patel Kishore, 308484D	42	M	10	3.15	1	4	0.96mm	0.80mm	2+	2+	N/A	N/A	130/90	N/A	