TO ASSESS PERICORONARY ADIPOSE TISSUE THICKNESS AND PERICORONARY FAT ATTENUATION AS PREDICTORS FOR SIGNIFICANT CORONARY ARTERY DISEASE

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DM CARDIOVASCULAR IMAGING AND

VASCULAR INTERVENTIONALRADIOLOGY

(2021-2023)

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

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A THESIS SUBMITTED BY

DR. BASAVARAJ N BIRADAR

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

DM CARDIOVASCULAR IMAGING AND VASCULAR INTERVENTIONAL RADIOLOGY

(2021-2023)

DECLARATION BY THE STUDENT

CERTIFICATE

I, Dr. Basavaraj N Biradar hereby certify that I had personally carried out the work depicted in the thesis titled**, "TO ASSESS PERICORONARY ADIPOSE TISSUE THICKNESS AND PERICORONARY FAT ATTENUATION AS PREDICTORS FOR SIGNIFICANT CORONARY ARTERY DISEASE."**

No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

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Date: 29-8-2023

(* If external help was sought, declare and acknowledge)

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*Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

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Submitted by

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for the degree of

DM

CARDIOVASCULAR IMAGING AND VASCULAR INTERVENTIONAL RADIOLOGY

of **SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM**

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ACKNOWLEDGEMENTS

- I hereby express my sincere gratitude to all my teachers & guides especially Dr. Jineesh Valakkada (Associate Professor), Dr. Anoop Ayyappan (Associate Professor) Department of Imaging Sciences and Interventional Radiology, Dr. Bijulal S. (Professor), Department of cardiology for their constant unwavering support, insightful criticism, expert supervision and immense patience throughout this study.
- I would specially like to acknowledge my gratitude to my past and present colleagues and the technologists of the Department of IS and IR and the advanced radiology technology trainees of the department for their valuable assistance at all times during this study.
- I express my deep gratitude to all the participants of the study without whom this research was not possible.
- I would also like to extend my heartfelt gratitude to my family for being immensely supportive all through my endeavours. I could not have achieved what I have without their prayers, love and support.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVIATIONS (Optional)

S No	Abbreviation	Full Form
1	IHD	Ischemic Heart disease
2	CVD	Cardio vascular disease
3	PAT	Pericardial adipose tissue
4	EAT	Epicardial adipose tissue
5	PCAT	Pericoronary adipose tissue
6	CCTA	Coronary computed tomography angiography
7	CAD	Coronary artery disease
8	ACE	Acute coronary events
9	FAI	Fat Attenuation Index
10	CCS	Coronary calcium score
11	AHA	American Heart association
12	RCA	Right coronary artery
13	LAD	Left anterior descending
14	EMR	Electronic medical record
15	CADRADS	Coronary Artery Disease Reporting And Data System
16	NSTEMI	Non- ST elevation myocardial infarction
17	STEMI	ST elevation myocardial infarction

SYNOPSIS

TO ASSESS PERICORONARY ADIPOSE TISSUE THICKNESS AND PERICORONARY FAT ATTENUATION AS PREDICTORS FOR SIGNIFICANT CORONARY ARTERY DISEASE.

SYNOPSIS BY

DR. BASAVARAJ N BIRADAR

for

DM CARDIOVASCULAR IMAGING AND VASCULAR INTERVENTIONAL RADIOLOGY

of

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

SYNOPSIS

TITLE: To assess pericoronary adipose tissue thickness and pericoronary fat attenuation as predictors for significant coronary artery disease

AIMS AND OBJECTIVES:

1. To determine the association between pericoronary adipose tissue thickness and non-obstructive coronary artery stenosis
2. To study the association between pericoronary adipose tissue thickness and vulnerable plaque characteristics.
3. To find the association between pericoronary adipose tissue attenuation (FAI) changes and acute coronary events in the study population during clinical follow-up.

MATERIALS AND METHODS:

This was a single-centre prospective observational study. All the consecutive patients between January 2014 to July 2021 who presented with complaints of atypical chest pain and underwent Coronary Computed Tomography Angiography study in the Department of Imaging Sciences and Interventional Radiology, SCTIMST Thiruvananthapuram fulfilling the inclusion and exclusion criteria were selected. In patients with CADRADS 1 to 3 non-obstructive CAD, the pericoronary adipose tissue thickness, plaque characteristics, coronary stenosis and pericoronary FAI were measured around the proximal RCA and coronary artery segment with plaque showing maximum stenosis or vulnerable plaque features using a semi-automated

post-processing software – Syngovia Frontier Coronary Plaque Analysis (Siemens Healthineers, Germany). All the patients were then followed up for development of acute coronary events including unstable angina, NSTEMI or STEMI. The statistical analysis was done using Statistical Package for Social Sciences (SPSS) software, version 25.0.

RESULTS:

1360 patients underwent coronary CT angiography between July 2014 and July 2020. Based on exclusion criteria, 1240 studies were excluded and the remaining 120 patients with non-significant coronary artery stenosis in coronary CT angiography were included in the study. During the median follow up period was of 60 months, 21 patients developed acute coronary events which included 13 unstable angina and 8 NSTEMI cases. Cox multivariate regression analysis showed that age, sex, hypertension, Dyslipidemia, Hypothyroidism, and family history of CAD were not significantly associated with the development of ACE. The presence of Diabetes mellitus showed a significant association with the development of ACE. The mean PCAT thickness in our study was 8.52 ± 2.5mm. Mild positive correlation existed between PCAT thickness and coronary artery stenosis (Pearson correlation coefficient of 0.117, p=0.204). The PCAT thickness was higher in the $\geq$ 50% stenosis group (8.73 ± 2.65mm) compared to the <50% stenosis group (8.37 ± 2.4mm), but the difference was not statistically significant (p value=0.446). The mean PCAT thickness in patients with vulnerable plaque features was higher (8.8 ± 2.48mm) than those without high-risk (8.46 ± 2.52mm), but the difference between the two groups was not statistically significant (p value=0.575). The median plaque burden of study

was 110 (58.25-201.5). The median plaque burden in patients with ACE (225(147-298)) was significantly higher as compared to patients without events (90(48-174)) (Mann Whitney test, p-value <.0001). Our study's mean value of RCA- FAI was -80.07 ± 5.93 HU. The RCA-FAI of patients with ACE (-73.18 ± 3.48 HU) was significantly higher as compared to patients without events (-81.53 ± 5.28) (p-value <.0001). The mean value of Lesion FAI in our study was -79.23 ± 7.16 HU. The Lesion- FAI in patients with ACE was -74.31 ± 5.65 HU, which was also significantly higher as compared to patients without events (-80.27 ± 7.03 HU) (p value=0.0004). Using ROC curve analysis, RCA- FAI was the best predictor of ACE at a cut-off point of > -77.3 HU (with AUC of 0.915) compared to lesion-FAI. At a cut-off FAI of -77.3, RCA-FAI showed high sensitivity (95.24%), specificity (83.84%), and negative predictive value (98.80%) for correctly predicting ACE. There was significant positive correlation between RCA-FAI and Lesion-FAI [Pearson correlation coefficient of 0.56 (p-value <0.0001)]. The analysis of risk factors for ACE showed degree of stenosis, RCA-FAI, Lesion-FAI, diabetes mellitus, stenosis $\geq$50 % as significant risk factors for development of ACE with hazard ratio of 1.051(1.011 to 1.092), 1.164(1.078 to 1.257), 1.059(1.005 to 1.116), 3.193(1.318 to 7.732) and 3.401(1.31 to 8.825) respectively on univariate analysis. On multivariate regression analysis, RCA-FAI, diabetes mellitus, and stenosis $\geq$50% were independent risk factors of ACE after adjusting for confounding factors with a hazard ratio of 1.236 (1.098 to 1.39), 3.976(1.533 to 10.308) and 4.181(1.489 to 11.74) respectively.

CONCLUSION:

In our study PCAT thickness showed mild positive correlation with degree of coronary stenosis. PCAT thickness was higher in the> 50% stenosis group and compared to the <50% stenosis group. PCAT thickness was also higher in group with vulnerable plaque features compared to group without vulnerable plaque features. Our study results showed that pericoronary adipose tissue FAI measurement around proximal RCA (RCA-FAI) can predict ACE in non-obstructive coronary artery disease patients. Detection of high RCA FAI of > -77.3 HU on Coronary CT angiogram can help to identify high-risk patients in this group of non-obstructive CAD patients who might need regular follow-up and early initiation of interventions to prevent ACE. However, studies with larger sample sizes and longer follow-up duration are needed.

INTRODUCTION

Ischemic heart disease remains the leading cause of death in upper-middle and high-income economies (1). Ischemic heart disease (IHD) and stroke constitute the majority of Cardiovascular disease (CVD) mortality in India (83%)(2). The Global Burden of Diseases, Injuries, and Risk Factors (GBD) study has reported that deaths and disability from coronary heart disease have more than doubled in India in the last 30 years (3). Vascular inflammation has been considered to be a central driver of atherogenesis resulting in IHD (4). Currently, very few methods are readily available for the early detection of vascular inflammation in coronary arteries. Such a method would enable the timely deployment of measures to prevent disease progression and future cardiovascular events. Despite the well-established role of inflammation in vascular disease pathogenesis, it is still unclear how to select patients with high levels of vascular inflammation who would benefit most by targeting inflammation. Circulating biomarkers like hsCRP or IL6 are excellent in detecting systemic inflammation that usually co-exists with coronary inflammation. However, they are often driven by other systemic or local inflammatory conditions like arthritis, infections and other conditions (5). Thus there is a need for a better biomarker of early atherosclerosis to prevent the progression of atherosclerosis.

Pericardial adipose tissue (PAT) is the total visceral fat depot surrounding the heart. Epicardial adipose tissue (EAT) is the fat between the myocardium and visceral pericardium. In contrast, pericoronary adipose tissue (PCAT) is a part of epicardial adipose tissue that directly surrounds the coronary arteries (6). The

association between increased epicardial adipose tissue and coronary atherosclerosis is well established (7) (8) (9). However, few studies have examined the association between PCAT and atherosclerosis in the underlying coronary arteries. A recent study revealed that the PCAT has very different morphological and functional characteristics compared to the rest of EAT depot (10). Given its proximity to the vascular wall, PCAT interacts directly with it bidirectionally. PCAT secretes pro-inflammatory cytokines and other bioactive mediators, which diffuse into the adjacent vascular wall, promoting atherogenesis in a paracrine manner ('outside-in signalling) (11) (12). Reverse signalling from the vessel wall to the surrounding fat also takes place in a paracrine way (via 'inside-out' signalling). Studies have demonstrated that inflammatory molecules (e.g. TNF-a, interleukin-6) released from the inflamed arterial wall diffuse into the perivascular space inducing lipolysis and suppressing adipogenesis (10). This response reduces adipocyte size and leads to a gradient of the lipophilic phase of PVAT around the vascular wall (10). Therefore, reported differences in epicardial fat biology could be the cause of vascular disease rather than the result of vascular inflammation.

A recent study demonstrated PCAT changes as a novel marker of the development of atherosclerosis (10). It is suggested that adipocytokines produced by PCAT might amplify vascular inflammation through paracrine effects, leading to local atherogenesis, plaque instability, and neovascularisation (13). However, it is a challenge to evaluate pericoronary fat by non-invasive techniques. Coronary computed tomography angiography (CCTA) is a sensitive and widely used imaging modality for diagnosing coronary artery disease (14) (15). CCTA enables non-invasive visualisation and quantification of pericoronary adipose tissue and the

characterisation of vulnerable plaques (16) (17). Its widely accepted as a first-line investigational tool for the detection of CAD by the National Institute for Health and Care Excellence and European Society of Cardiology guidelines (18) (19). The change in the composition of perivascular fat around inflamed arteries leads to shifting its attenuation on CCTA from the lipid (more negative Hounsfield unit [HU] values [e.g., closer to –190 HU]) to the aqueous phase (less negative HU values [e.g., closer to –30 HU]). A novel imaging biomarker, the perivascular "fat attenuation index (FAI)", captures these inflammation-induced changes in pericoronary fat attenuation, enabling early detection of coronary inflammation using routine coronary CTA (10).

We postulate that by quantifying pericoronary fat using CT, future inflammation can be predicted, which could indirectly predict future adverse coronary events independent of the degree of coronary stenosis. Thus, it helps in risk stratification by identifying high-risk patients who benefit from more intensive therapeutic strategies.

AIMS AND OBJECTIVES

1. To determine the association between pericoronary adipose tissue thickness and non-obstructive coronary artery stenosis
2. To study the association between pericoronary adipose tissue thickness and vulnerable plaque characteristics.
3. To find the association between pericoronary adipose tissue attenuation (FAI) changes and acute coronary events in the study population during clinical follow-up.

Clinical question: Can pericoronary FAI predict acute coronary events (ACE) in patients with non-significant coronary artery disease (CADRADS 1 and 2 and CADRADS 3 (with negative stress test –TMT or CAG FFR)?

Null Hypothesis:

There is no significant association between pericoronary FAI changes and the occurrence of ACE in patients with non-significant coronary artery disease.

Alternate Hypothesis

There is a significant association between pericoronary FAI changes and the occurrence of ACE in patients with non-significant coronary artery disease.

LITERATURE REVIEW

Coronary artery disease (CAD) as a precursor of myocardial infarction (MI) has a significant impact on survival and quality of life. It is further associated with a significant health-related economic burden (18). Previous studies have demonstrated an association between EAT and the presence and extent of coronary artery disease (20). Recently, studies have implicated vessel wall inflammation in initiating and progressing the atherosclerosis disease process. Hence there has been increased interest in the assessment of PCAT changes as a non-invasive marker of coronary inflammation. Coronary computed tomography angiography (CCTA) is a widely used imaging modality for diagnosing coronary artery disease as it allows non-invasive visualisation and quantification of pericoronary adipose tissue in addition to characterisation of vulnerable plaques. CCTA-derived pericoronary fat attenuation index (FAI) is considered a novel imaging biomarker of coronary inflammation. The following literature review focuses on this non-invasive assessment of PCAT to identify coronary inflammation and its implications on risk stratification and prognosis of patients with CAD.

PARADIGM SHIFT FROM EAT TO PCAT EVALUATION: ROLE IN CORONARY INFLAMMATION

Epicardial adipose tissue (EAT) is the visceral adipose tissue fat depot located between the myocardium and the visceral layer of the pericardium and covers 80% of the cardiac surface (21). Due to contact with the myocardium, factors released from EAT have a direct paracrine effect on cardiomyocytes and a potential

role in the development of CAD (22). Pathological conditions, such as obesity and diabetes, and genetic and environmental factors may drive the shift towards dysfunctional EAT characterised by a pro-inflammatory and pro-atherosclerotic phenotype.(23) The role of vascular inflammation in the development of coronary atherosclerosis and rupture of vulnerable plaques, resulting in acute coronary syndrome (ACS), has long been postulated.(24)

Currently, there are yet-to-be-published recommendations for the standardisation of EAT measurements.(25) EAT 3D volume quantification on cardiac CT is considered the most accurate measurement, with the most literature describing its value.(25) Nevertheless, EAT volume as a measure of coronary inflammation has some significant limitations. Systemic influences, such as obesity and diabetes, as well as medications, can affect EAT and EAT volume.(26) These systemic influences may cause differences between populations or reflect temporary systemic variations instead of coronary inflammation. The need for a more specific imaging marker related to coronary inflammation has recently turned attention to PCAT.

PCAT is defined as the adipose tissue within the EAT depot that surrounds the coronary arteries (27) and has, therefore, the closest interaction with the adjacent coronary arteries.(28) Although PCAT is included in the EAT depot, they have different pathophysiological effects and clinical significance. Recent studies have shown a bidirectional, biochemical communication between the coronary arterial wall and PCAT.(10) When PCAT becomes dysfunctional, it can produce biologically active factors that induce endothelial dysfunction and inflammation, leading to the

progression of atherosclerosis. (5)Vice versa, signals originating from the coronary wall can affect PCAT in a paracrine manner and lead to decreased perivascular lipid accumulation, with decreased lipophilic content and smaller, undifferentiated, lipid-poor adipocytes.(5) These factors result in volume and attenuation differences of the PCAT depot, which can be evaluated using coronary CT angiography. (10)

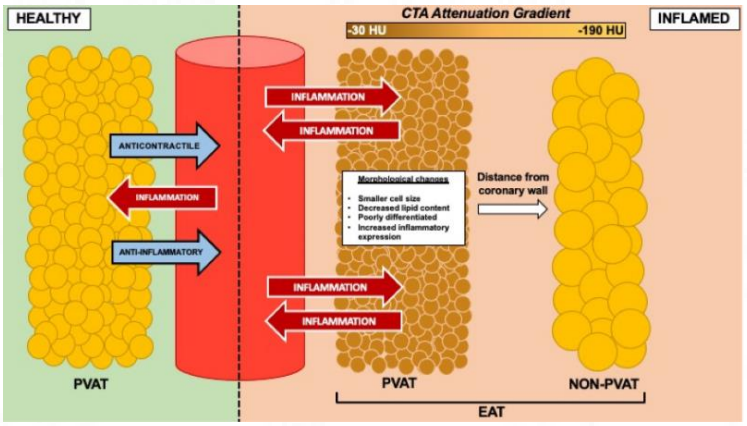


Figure 1: Depicting bidirectional cross-talk between PCAT and coronary artery wall.

PCAT MEASUREMENT METHODOLOGIES:

Several measurement methods for CT evaluation of PCAT have been reported in the literature: thickness, volume and attenuation, the last being the most commonly used.(29) There are different approaches to defining the length and location of PCAT measurements.

PCAT THICKNESS:

It is measured as the thickness of the adipose tissue around the coronary artery. The most common way to measure PCAT thickness is by calculating the maximum EAT width around the proximal coronary artery in cross-sectional CT images. CCTA studies on PCAT thickness on axial views or multiplanar reformats showed good

reproducibility and reported improved metabolic syndrome and atherosclerosis diagnosis in CAD patients. (5,10)

PCAT thickness measurement is a simple and fast approach. However, PCAT thickness contains less information than other PCAT variables, and sometimes it is difficult to visually identify and distinguish PCAT and EAT thickness.

PCAT VOLUME:

PCAT volume is rarely used and is subject to controversy since it is hard to define the measurement range of PCAT volume. There are several ways to calculate PCAT volume. One way is by using the PCAT segmentation method, so the PCAT volume is 3mm around the coronary arteries in CCTA.(30) Another way is manually tracing the region containing PCAT in axial images perpendicular to the centre line of the coronary artery and subsequently summing every slice to create one volumetric measurement in CCTA.(31) A third way is to manually define a region of interest (ROI) according to coronary segments and use the 3D reconstructions to calculate PCAT volume in non-contrast cardiac CT.(32)

PCAT volume provides additional 3D information on PCAT compared to thickness. However, PCAT volume measurements have yet to be standardised, and differences in measurement approaches, as described above, could lead to different results. There is controversy about the association of PCAT volume with CAD, and the outcomes of the few available studies show conflicting results.(10,32)

PCAT FAT ATTENUATION INDEX (FAI):

PCAT FAI is considered the recent 'imaging biomarker' of coronary inflammation. Here, the HU values of voxels in pericoronary adipose tissue (defined as −190 to

−30HU) perpendicular to the centre line of the coronary artery in 3D reconstruction are averaged.(10) It indirectly measures adipocyte size and lipid content, reflecting inflammation status. In contrast to PCAT volume, the role of PCAT FAI in coronary inflammation has been proven in pathophysiological studies with histological samples.(10) PCAT FAI measurements have a higher inter- and intra-reader agreement compared to PCAT thickness or volume.(30,33,34) However, one study showed that variation in contrast intensity of CCTA images affects PCAT FAI assessment and that lumen-normalisation might be required for accurate PCAT FAI measurements. (35)

PATIENT-BASED PCAT-FAI MEASUREMENTS:

Most recent studies have focused on PCAT FAI of the right coronary artery (RCA) as a patient-based biomarker. Patient-based PCAT FAI measurement has a preference for the evaluation of patient-based prognostic purposes.

In the landmark study by Antonopoulos et al., RCA-based PCAT FAI was measured.(10) The origin point of the measurement was located 10 mm from the ostium of the RCA. A study by Kanaji et al. used the average PCAT FAI of all three main coronary arteries with 40 mm measured length and width equivalent to the vessel diameter as a patient-based measure instead of the RCA only.(36)

VESSEL-BASED PCAT-FAI MEASUREMENTS:

Although patient-based measurements are helpful in identifying patient-level disease status and overall risk prediction, many CAD parameters, such as stenosis degree and plaque burden, are vessel-based. In addition, invasive coronary interventions are

vessel-specific. Finally, because of the different anatomy of coronary arteries, it is essential to define and standardise the measurement's anatomical start and end points per coronary artery.

Ma et al. proposed a 10mm length and 1mm width, using the original RCA measurement starting point to avoid interference from the myocardium and veins, and is applicable for all three coronaries.(34) A study by Balcer et al. used an even shorter measurement length of 5 mm in order to measure PCAT FAI on a per-segment level.(32) For RCA measurements, the most common approach starts 10 mm from the ostium, while for LAD and LCX, most studies set the starting point at the bifurcation point of the left coronary artery.

LESION-BASED PCAT FAI MEASUREMENTS:

Some studies used lesion-specific methods to investigate features such as high-risk plaque (HRP) features, plaque composition and hemodynamic significance. Lesion-based measurements can be performed in different ways. The most common approach is to take a PCAT measurement length equivalent to the length of the lesion. Another approach is to use a standard measurement length of 10 mm that covers the lesion.(37) This method uses a uniform measurement length; however, in longer lesions, information may be incomplete.

EFFECT OF SCAN PARAMETERS ON PCAT FAI MEASUREMENT:

The proof-of-concept studies of PCAT FAI were performed on 120 kVp CCTA scans.(10) Ma et al., investigating the effect of kVp levels on PCAT FAI in patients without CAD, showed that PCAT FAI is significantly lower at lower kVp levels (70

kVp: −95.6 HU ± 9.6 vs 120 kVp: −79.3 HU ± 6.8).(34) Two other studies confirmed these results, using dual-layer spectral CT systems that enable image reconstruction at different keV levels. They showed that PCAT FAI measurements at 120 kVp were higher than in 40 keV images in patients with and without CAD.(38) (39)

All of these results indicate that for evaluating PCAT FAI, the kVp level and scan parameters should be considered, especially when quantitative comparisons are made between different scans or using thresholds.

PCAT FAI AS A BIOMARKER OF CAD:

Earlier Coronary CTA studies have demonstrated the incremental diagnostic and prognostic value of evaluating plaque features and composition over stenosis severity alone.(40,41) In recent studies, PCAT FAI measurement has also shown an association with these features of coronary atherosclerosis.

PCAT FAI and coronary stenosis:

Ma et al. investigated lesion-specific PCAT FAI in 165 patients and showed a minimal but significant difference between lesions with a minimal (<25%) and severe stenosis (>70%) (−98.3 HU vs −96.2 HU, p = 0.037).(37)

PCAT FAI and plaque burden:

In 2018, Goeller et al. analysed PCAT FAI around every coronary lesion in matched ACS (n = 19) and stable CAD (n = 16) patients.(42) They showed that PCAT FAI was increased around high-plaque burden lesions compared to low-burden ones,

within the same patient, both in the ACS group (−69.1 HU vs −74.8 HU; p = 0.01) and stable CAD group (−69.1 HU vs −76.4 HU, p = 0.01).

Multiple studies have demonstrated that CCTA is able to detect plaque features associated with ACS risk.(43,44)

PCAT FAI and high-risk plaque (HRP) features:

Yuvaraj et al. matched 41 patients with stable CAD presenting with HRP on CCTA to 41 patients without HRP. They found that RCA-based PCAT FAI was higher in patients with HRP than in patients without (−80.7HU ± 6.50 vs −84.2HU ± 8.09 p = 0.03). (45) PCAT FAI was also higher in patients with subsequent ACS compared to those without in the whole population (−78.0 HU ± 7.3 vs −83.3 HU ± 7.3, p = 0.02) and in patients with HRP only (−76.8 HU ± 5.7 vs −82.0 HU ± 6.3, p = 0.03).

PCAT FAI AS A TOOL FOR CAD RISK STRATIFICATION AND PROGNOSTICATION:

Current cardiac risk stratification relies on traditional clinical risk factors such as age, sex, race, body mass index, hyperlipidaemia, hypertension (46) and imaging biomarkers such as the coronary calcium score (CCS) measured using CT.(47) Coronary calcification represents a non-reversible process that does not regress in response to appropriate medical treatment, limiting its value in secondary prevention.(48) On the other hand, inflammation has a vital role in both atherogenesis and atherosclerotic plaque rupture leading to ACS. (24,49) Therefore, detection of the coronary inflammation risk using PCAT FAI could guide more

timely preventive measures in patient care and serve as an early-stage prognosticative marker.

Oikonomou et al. in the 'CRISP CT study' - investigated patient-based PCAT FAI and its correlation to clinical outcomes in 3912 patients. They showed that high PCAT FAI (≥ −70.1 HU) could predict all-cause and cardiac mortality better than clinical risk factors and state-of-the-art interpretation of CCTA (HR 9.04, 95% CI: 3.35–24.40, $p < 0.0001$ for cardiac mortality; 2.55, 1.65–3.92, $p < 0.0001$ for all-cause mortality). (50)

In a study by Hoshino et al. including 220 consecutive patients with intermediate stenosis, the authors showed that a PCAT FAI ≥ −73.1 HU was related to an increased risk of major adverse cardiac events (MACE) (multivariate HR 3.11, 95%CI:1.40–6.94, $p = 0.005$). Goeller et al. defined a similar cut-off value of −73.5 HU for PCAT FAI as an independent predictor of MACE (HR 2.01, $p = 0.044$).(51)

Some studies have also focused on the relationship between PCAT FAI and outcomes in specific high-risk subgroups. Ichikawa et al. analysed 333 patients with Type 2 diabetes and showed that high LAD-derived PCAT FAI predicted MACE.(52)

SUMMARY OF REVIEW OF LITERATURE WITH LACUNAE IN LITERATURE:

PCAT FAI is considered the novel biomarker of CAD. Coronary inflammation is implicated in the initiation and progression of atherosclerosis. Due to its proximity to the coronary artery, the signals originating from the coronary wall affect PCAT in a paracrine manner and lead to the gradient of decreased perivascular lipid

accumulation with smaller, undifferentiated, lipid-poor adipocytes. These spatial changes in PCAT attenuation can be captured using coronary CT angiography in the form of FAI. High PCAT FAI is an independent predictor of MACE and can predict all-cause and cardiac mortality better than traditional clinical risk factors and calcium scores.

However, most studies assessing PCAT in the literature included patients with various grades of coronary stenosis from CADRADS 1 TO 5. The risk of occurrence of ACE is high in CADRDAS 4 and 5 group patients compared to CADRADS 1 to 3. Also, many of these studies are retrospective, and PCAT was analysed after an ACE event or after revascularisation. None of the studies have focused exclusively on non-obstructive coronary stenosis involving only CADRADS 1 to 3 patients. Most of these patients with non-obstructive CAD are kept on clinical follow-up. However, if at-risk patients in this cohort can be identified early using PCAT FAI measurement from CCTA, primary prevention can be initiated to prevent MACE in these patients.

Hence there is a need for a prospective study involving CADRADS 1 to CADRADS 3 non-obstructive coronary artery disease patients to assess whether PCAT FAI can predict acute coronary events in this group of patients.

MATERIALS AND METHODS

Study type:

This was a single-centre prospective observational study. All the consecutive patients between January 2014 to July 2021 who presented with complaints of atypical chest pain and underwent a Coronary Computed Tomography Angiography study in the Department of Imaging Sciences and Interventional Radiology, SCTIMST Thiruvananthapuram fulfilling the inclusion and exclusion criteria were selected. The study was performed after obtaining institutional ethics committee approval (IEC No: SCT/IEC/1807/JANUARY/2022).

Typical angina chest pain was defined as “dull, heavy, tight or crushing pain in the center of the chest radiating to neck, lower jaw or left arm, worsening with exertion or stress and relieved with rest or nitroglycerin. Atypical chest pain was defined as epigastric or back pain, described as burning or stabbing in nature, non-radiating and not relieved by rest or nitroglycerin.

Inclusion criteria:

1. All patients with atypical chest pain underwent Coronary Computed Tomography Angiography studies between January 2014 to July 2021 in the Department of ISIR SCTIMST.
2. Patients with non-obstructive coronary artery disease i.e. CADRADS 1, CADRADS 2 and CADRADS 3 (with negative results after stress test-TMT or CAG with FFR)
3. Follow-up data for ten years available in EMR

Exclusion criteria:

1. Patients with post coronary artery bypass graft status.
2. Patients with post coronary artery stenting status.
3. Studies with normal coronary arteries (CADRADS 0).
4. Studies with coronary artery stenosis $\geq$ 70 % (CADRADS 4 and 5).
5. Studies with inadequate image quality.

STUDY DESIGN:

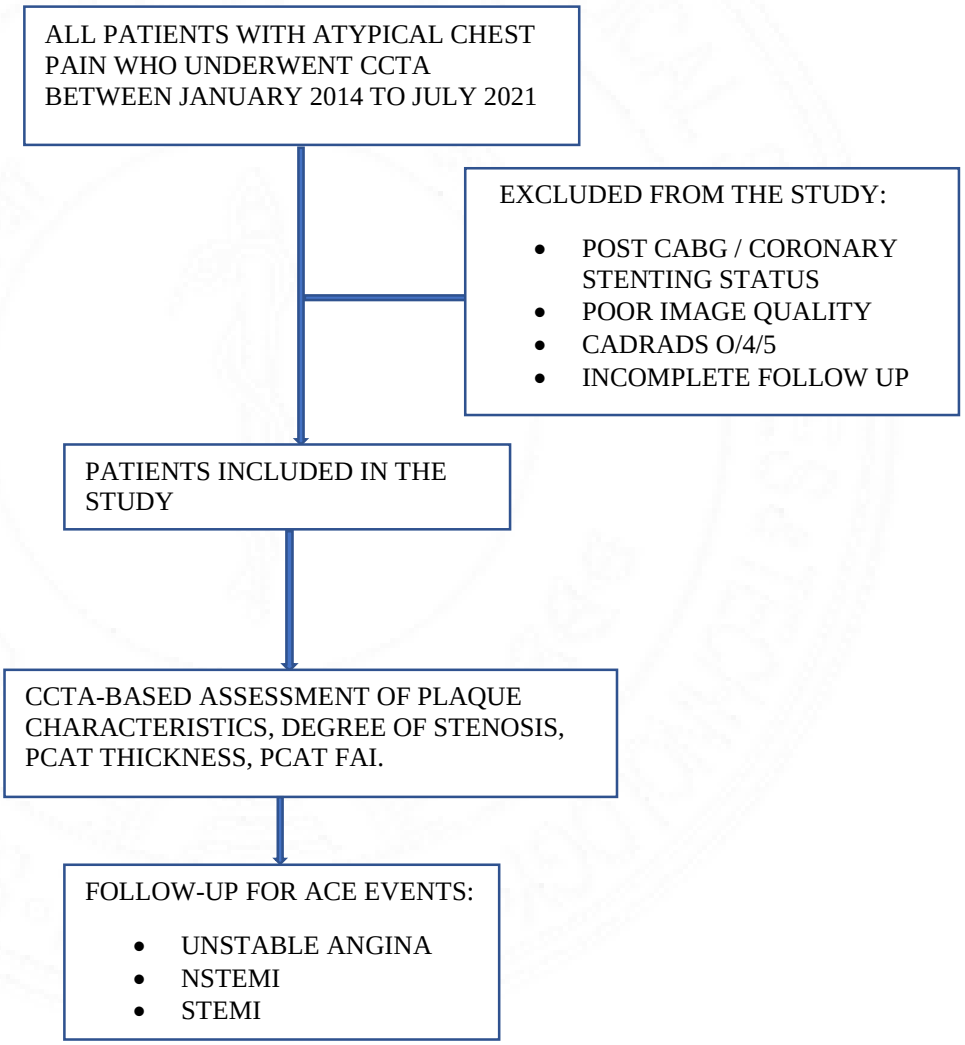


Figure 2: Flow chart showing study design

For analysis, the CCTA images were retrieved from the PACS, anonymised and stored separately in numbered folders. These images were post-processed and analysed by a reader with three years of experience interpreting CCTA studies. Demographic characteristics, presenting symptoms (Atypical chest pain, Dyspnoea on exertion, palpitation), co-morbidities and risk factors of the enrolled patients were recorded from the electronic medical records (EMR). These patients were then followed up for the development of acute coronary events, including unstable angina, NSTEMI and STEMI. Total follow-up duration and time to development of acute coronary event were recorded from the EMR.

CORONARY CT ANGIOGRAPHY PROTOCOL:

Coronary CT angiography was performed in 256 slices Philips Brilliant CT scanner. The standard protocol established in the Department for the last 10 years was followed for all the patients in the study.

In patients with high heart rate (> 70 bpm), oral Tab. Metoprolol 25 mg was given for control of heart rate. All patients received sublingual nitroglycerin (10 mg) 5 minutes before the scan. Angiogram was obtained after injecting an iodinated contrast agent (2 ml/kg body weight) at a rate of 5-6 ml/sec through the right antecubital vein through an 18 Gauge cannula followed by 30 ml saline injection at the same rate.

The contrast agent used was Omnipaque (Iohexol) with an iodine concentration of 350 mg/ml. Scanning was performed from the level of the tracheal bifurcation up to the diaphragm to image the entire heart. The enhancement scan was controlled using bolus tracking. The trigger threshold, located in the ascending aorta, was set at 100

HU. The kVp was set at 120. Data acquisition was performed using retrospective ECG gating (Prospective ECG gating from 60 to 85% of the R–R interval was used when the heart rate did not exceed 70 beats per minute).

CT IMAGE ANALYSIS:

Coronary artery Segments were categorised according to the modified American Heart Association classification (16 segments). Coronary artery segments with a diameter of >2 mm were evaluated for the presence of plaques, type of plaque (calcified, non-calcified or mixed), vulnerable plaque characteristics and degree of stenosis at the plaque level. The images were evaluated on axial, coronal, sagittal and curved multiplanar reformation (CPR) planes.

I. PCAT THICKNESS MEASUREMENT:

Short-axis CPR images were used to measure pericoronary adipose tissue thickness. It was measured as the sum of the perpendicular thickness of the fat between the coronary artery and the pericardium and the coronary artery and myocardium. The fat thickness was measured at the site of maximum stenosis.

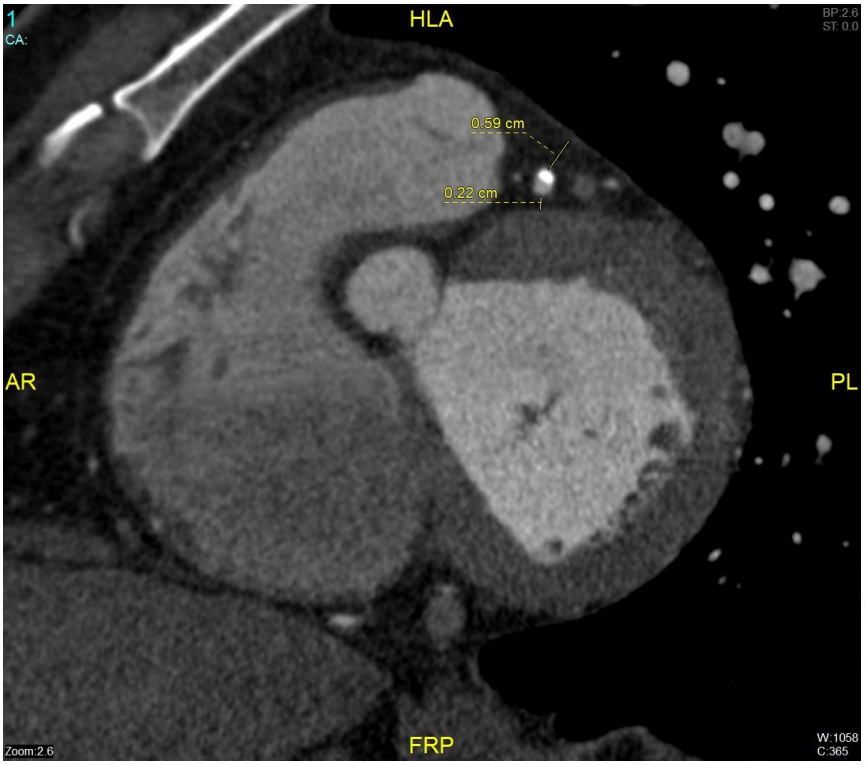


Figure 3: showing PCAT thickness measurement technique on CCTA image

II. CORONARY PLAQUE ANALYSIS WORKFLOW:

Coronary plaque analysis was done using semi-automated post-processing software – Syngovia Frontier Coronary Plaque Analysis (Siemens Healthineers, Germany), a research tool. The following steps were followed.

1. Coronary CT angiogram data was retrieved from PACS and loaded to plaque analysis software.
2. Coronary artery segmentation was done according to the American Heart Association (AHA) convention -16 segment model.
3. Proximal coronary artery segment of diameter >2mm containing plaque was selected.

4. The proximal and distal markers are placed at the margins of the coronary segment containing plaque. The outer and inner boundaries of the vessel wall are manually adjusted if required.

Figure 4: showing CCTA based coronary artery segmentation and plaque analysis

5. The software then automatically analyses and displays the total plaque burden, maximum stenosis grade, remodelling index and plaque composition. Based on HU values, plaque composition is displayed as a histogram showing calcified, lipid-rich and fibrotic components of plaque. Vulnerable plaques were defined as those displaying at least two of the following features: Positive remodelling, Low attenuation plaque, Spotty calcification or Napkin ring sign.

Plaque Volume (in mm3) is a measured plaque parameter and plaque burden is normalised to patient's individual coronary vessel volume. Plaque burden calculated from the measured plaque volume using formula, 100 X (plaque volume/vessel volume).

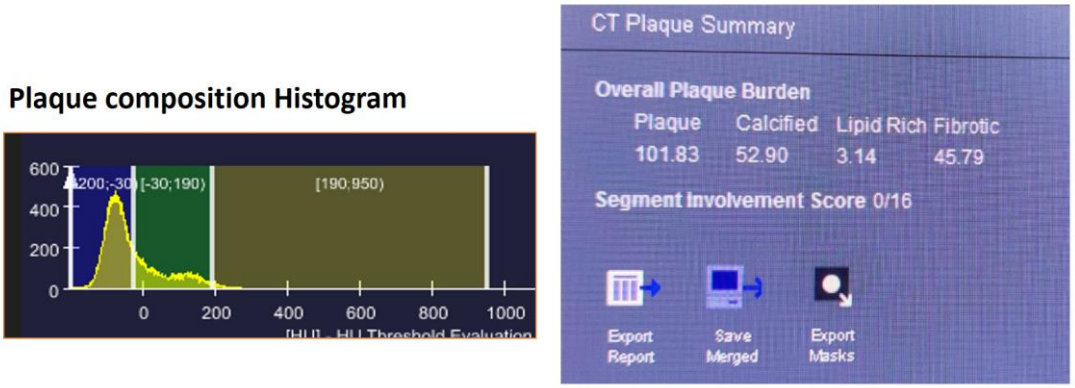


Figure 5: showing Plaque composition and plaque burden analysis

6. Degree of maximal coronary artery stenosis reported according to Coronary Artery Disease Reporting And Data System (CADRADS) from CADRADS 0 (no plaque/stenosis) to CADRADS 5 (total occlusion).

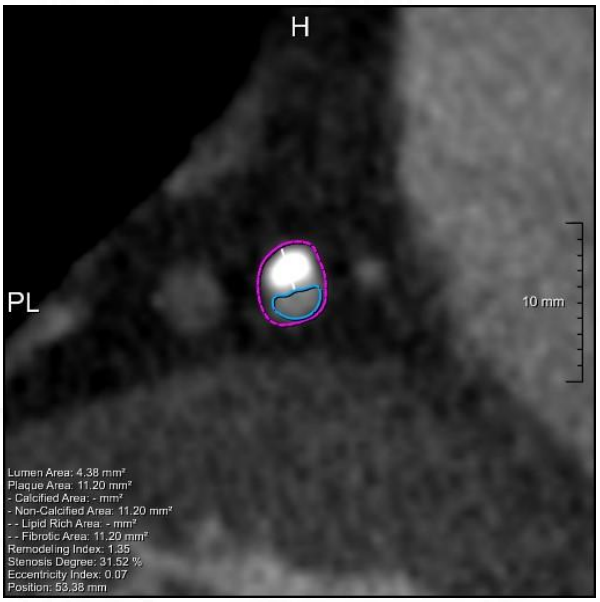


Figure 6: showing coronary artery stenosis assessment

III. PCAT FAI MEASUREMENT:

1. Pericoronary Fat Attenuation Index (FAI) was measured using semi-automated post-processing software – Syngovia Frontier Coronary Plaque Analysis (Siemens Healthineers, Germany), a research tool.
2. Perivascular adipose tissue is defined by selecting the volume of fat around the coronary artery segment at a radial distance equal to the diameter of the underlying coronary artery segment.
3. Using the "FAI"- preset, the thresholds for fatty tissue is set between -200 and -30.

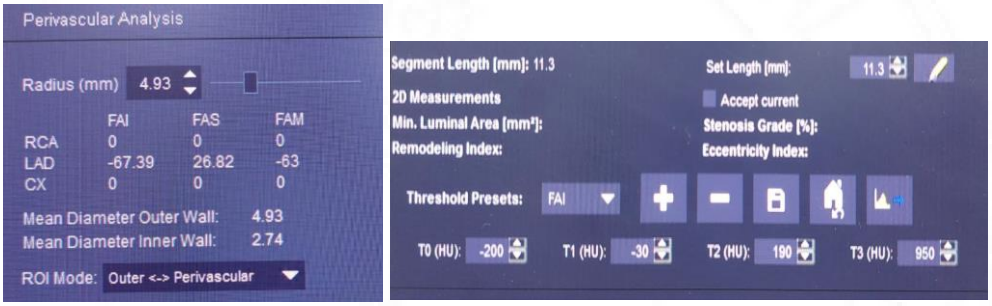


Figure 7: showing selection of perivascular adipose tissue and FAI preset

4. <u>LESION (PLAQUE) PCAT FAI MEASUREMENT</u>:

   The lesion PCAT FAI was measured around coronary artery segment containing plaque (in RCA, LAD or LCX). The plaque causing maximum stenosis or displaying vulnerable plaque features was selected for analysis in cases with multiple plaques. The length of pericoronary adipose tissue selected for lesion FAI measurement was equal to the length of the plaque.

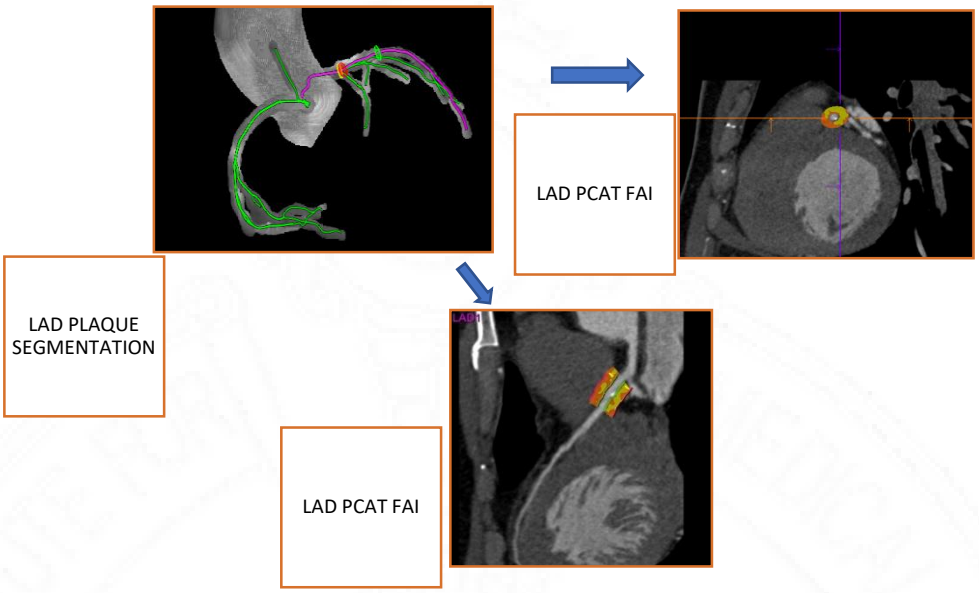
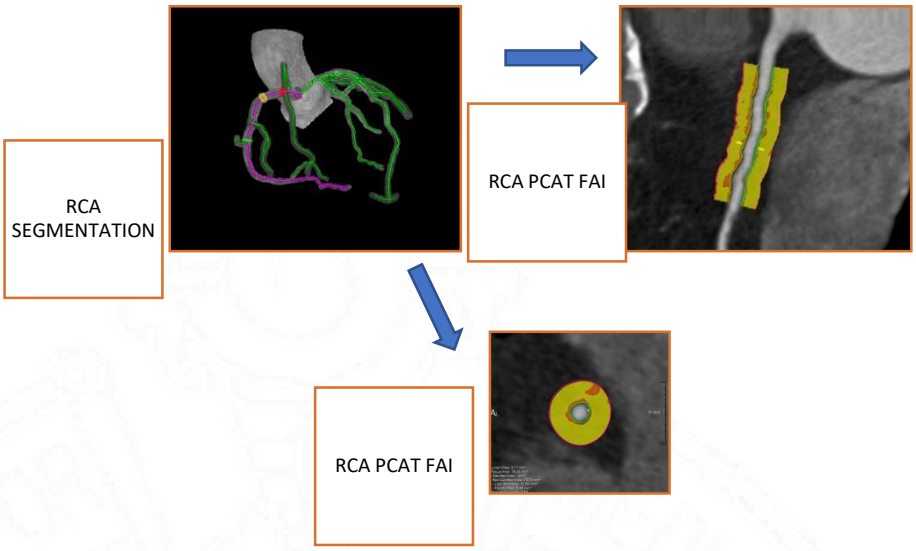


Figure 8: showing lesion FAI measurement

5. RCA PCAT FAI MEASUREMENT:

In all patients, right coronary artery PCAT FAI was measured around the proximal 4cm (from 11 mm to 50mm) of the right coronary artery. The first 10mm of RCA was not included in the FAI measurement to avoid the effects of the aortic wall.



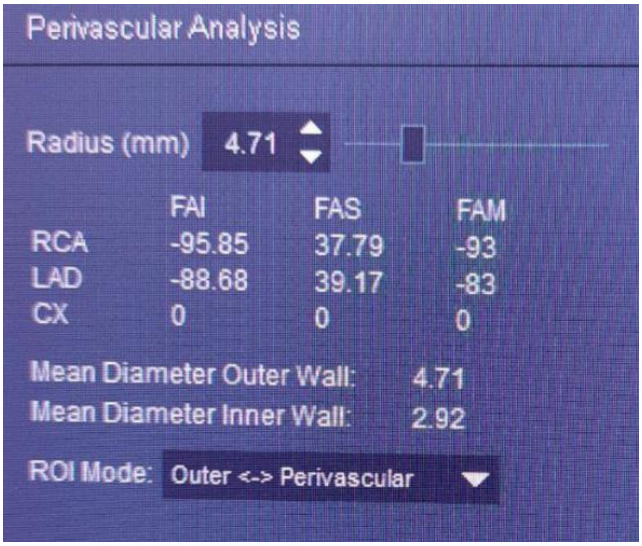


Figure 9: showing RCA FAI measurement

FOLLOW-UP OF PATIENTS:

All the patients were followed up for development of any acute coronary events. Acute coronary event (ACE) was defined as a composite of Unstable angina,

NSTEMI, or STEMI. The total duration of follow-up and time to occurrence of ACE was recorded in months.

Unstable angina was defined as 'myocardial ischaemia at rest or on minimal exertion in the absence of acute cardiomyocyte injury, characterised by prolonged (>20 minutes) angina at rest; new onset of severe angina; angina that is increasing in frequency, longer in duration, or lower in threshold'. The cardiac biomarker (Troponin I) was within normal limits. ECG may be normal or show ST depression, transient ST-elevation, or prominent T-wave inversions.

Non-ST elevation myocardial infarction (NSTEMI) was defined as 'myocardial ischaemia with acute cardiomyocyte injury/necrosis, characterised by symptoms similar to unstable angina with elevated cardiac biomarker (Troponin I - above the 99th percentile upper reference limit). ECG may show ST depression, transient ST elevation, and/or prominent T-wave inversions.

STEMI was defined as 'myocardial ischaemia with acute cardiomyocyte necrosis, characterised by persistent chest discomfort or other symptoms suggestive of ischaemia with an elevated cardiac biomarker (Troponin I) and ECG showing ST-segment elevation in at least two contiguous leads (≥0.25 mV in men below the age of 40 years, ≥0.2 mV in men over the age of 40 years, or ≥0.15 mV in women in leads V2 –V3 or≥0.1 mV in other leads (in the absence of left ventricular hypertrophy or left bundle branch block (LBBB).

STATISTICAL ANALYSIS

The Categorical variables were presented in the form of numbers and percentages (%). On the other hand, the quantitative data were presented as the means ± SD and median with 25th and 75th percentiles (interquartile range). The data normality was checked by using the Kolmogorov-Smirnov test. In the cases in which the data was not standard(Gaussian), we used non-parametric tests. The following statistical tests were applied to the results:

1. The comparison of the quantitative and not normally distributed variables was analysed using Mann-Whitney Test, and variables which were quantitative and normally distributed in nature were analysed using the Independent t-test.

2. The comparison of the variables, which were qualitative, were analysed using the Chi-Square test. Fisher's exact test was used if any cell had an expected value of less than 5.

3. Kaplan Meier survival analysis curve to assess event-free survival and log-rank test was used for comparison.

4. Pearson correlation coefficient was used for the correlation of RCA-Fat Attenuation Index with the Lesion-Fat Attenuation Index, pericoronary adipose tissue thickness(mm) with a degree of stenosis(percentages) and correlation of RCA-Fat and Lesion-Fat Attenuation Index with age. The Spearman rank correlation coefficient was used to correlate RCA-FAI and Lesion-FAI with plaque burden.

4. Receiver operating characteristic curve was used to find cut-off point, sensitivity, specificity, positive predictive value and negative predictive value of the RCA-Fat Attenuation Index and Lesion-Fat Attenuation Index for predicting ACE.

5. Univariate and multivariate Cox proportional hazard regression was used to find out significant risk factors of ACE.

The data entry was done in the Microsoft EXCEL spreadsheet, and the final analysis was done using Statistical Package for Social Sciences (SPSS) software, IBM manufacturer, Chicago, USA, version 25.0. For statistical significance, p-value of less than 0.05 was considered statistically significant.

RESULTS

1360 patients underwent coronary CT angiography between July 2014 and July 2020. Based on exclusion criteria, 1240 studies were excluded from the study. The remaining 120 patients were included in the study.

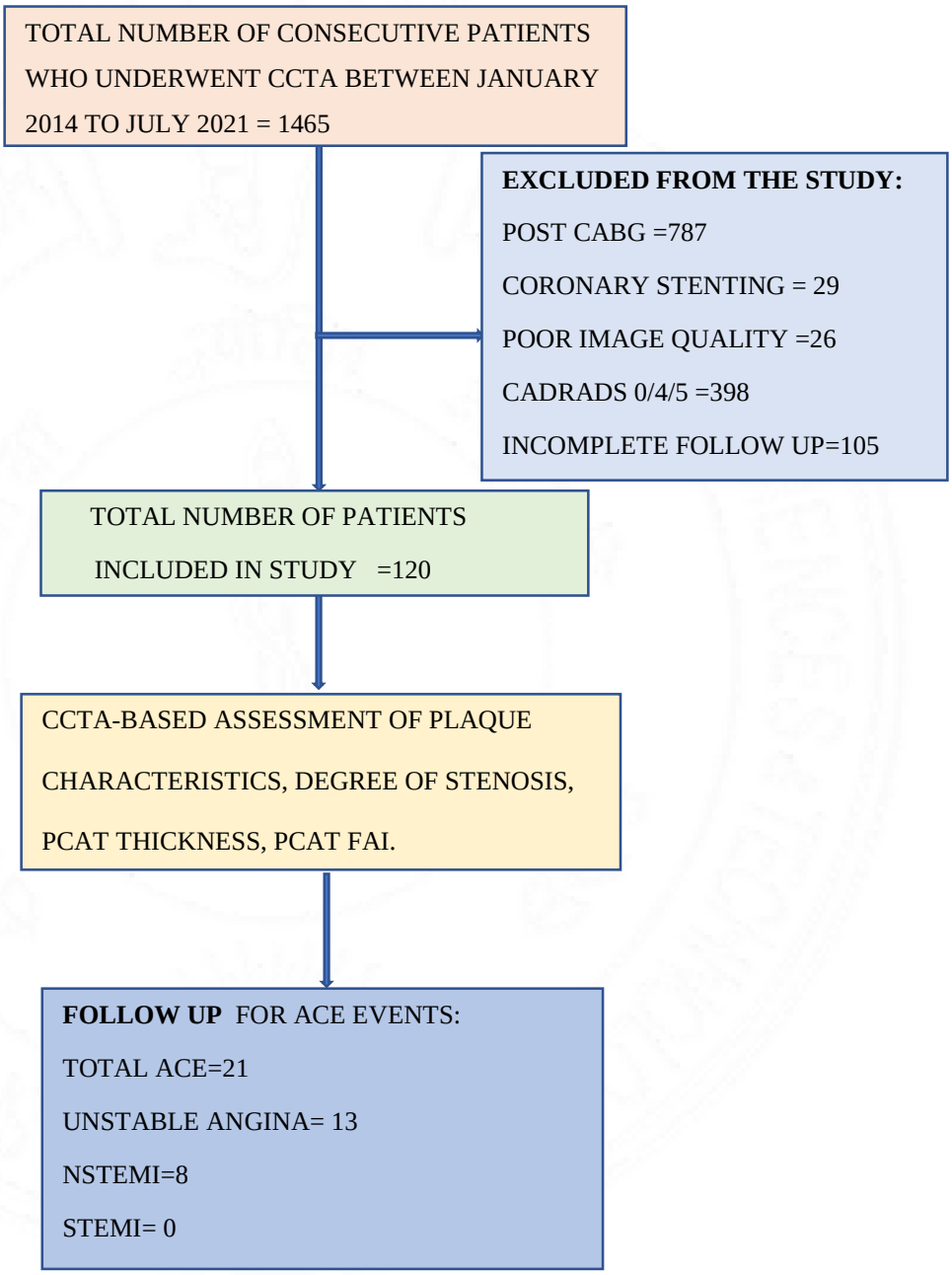


Figure 10: Flow chart showing study design and results

120 Coronary Computed Tomography Angiographies were analysed during the study period fulfilling the inclusion and exclusion criteria. The patient demographics, coronary plaque characteristics, coronary artery stenosis, Pericoronary adipose tissue thickness, pericoronary adipose tissue FAI and acute coronary events were studied, and the results are as follows.

1. **Patient characteristics and demographics:**

Variable	**Value (in percentage)**
Total no of patients	120
Age (Mean ± SD) in years	59.23 ± 10.8
Male Sex	71 (59.17%)
Atypical Chest Pain	103 (85.83%)
Dyspnea	28 (23.33%)
Palpitation	11 (9.17%)
Diabetes mellitus	45 (37.50%)
Hypertension	80 (66.67%)
Dyslipidemia	53 (44.17%)
Smoking	10 (8.33%)
Hypothyroidism	9 (7.50%)
Family history of CAD	12 (10.00%)
Follow-up duration (Mean ± SD) in months	56.88 ± 10.93

Table 1: showing patient characteristics and demographics

Of the 120 patients in our study, 71(59.17%) were males, and 49(40.83%) were females. The mean age of study subjects was 59.23 ± 10.8 years (ranging from 28 to 83 years). Among co-morbidities, 80(66.67%) cases had hypertension, 53(44.17%) had dyslipidaemia, and 45(37.50%) had diabetes mellitus, followed by a family history of CAD in 10%, history of present smoking in 8.33% and hypothyroidism in 7.5% cases. The most common presenting complaint was atypical chest pain in 85.83% of cases, followed by dyspnoea in 23.3% and palpitation in 9.1% of cases.

2. CADRADS distribution:

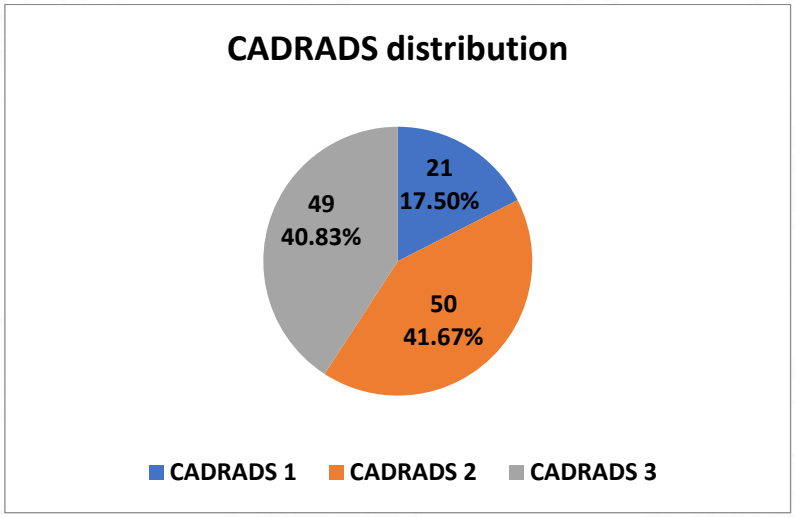


Figure 11: Pie chart showing CADRADS distribution in the study

In our study, CADRADS 2 and non-obstructive CADRADS 3 (negative results after stress test- TMT or CAG with FFR) cases were almost equal, followed by 21(17.50%) cases of CADRADS 1 CAD. The mean value of coronary artery stenosis in the study was 40.38 ± 14.55 %.

3. Coronary Plaque Analysis:

3a. Plaque Type distribution :

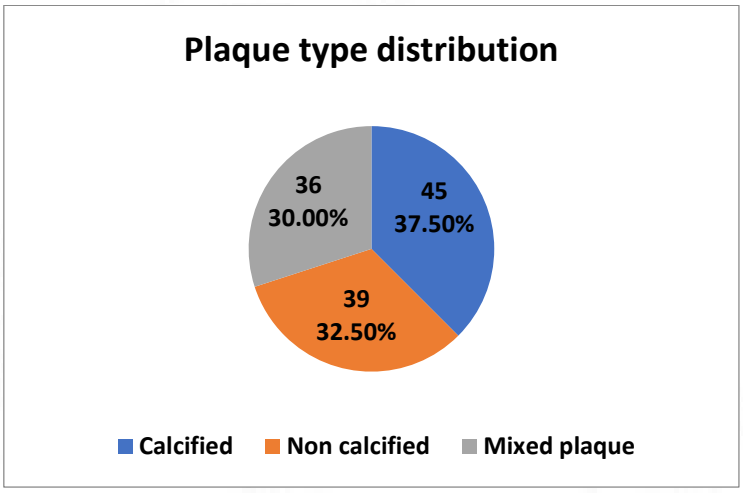


Figure 12: Pie chart showing plaque type distribution in the study

Based on plaque composition, 45(37.50%) patients had calcified plaques, 39(32.50%) had non calcified plaques and 36(30.00%) had mixed plaques.

Of 120 patients, 21(17.50%) cases showed vulnerable plaque features.

3b. Plaque burden:

The plaque burden in the study ranged from 10 to 730. Mean plaque burden was 153.41 ± 138.43 with median (25th-75th percentile) of 110(58.25-201.5).

4. Acute coronary events (ACE) distribution:

During the follow-up period, 21(17.50%) cases developed acute coronary events. Of these, 13 cases had Unstable angina, and 8 had NSTEMI. The diagnosis of ACE was made on the basis of ECG findings and blood Troponin-T levels.

5. Follow-up duration:

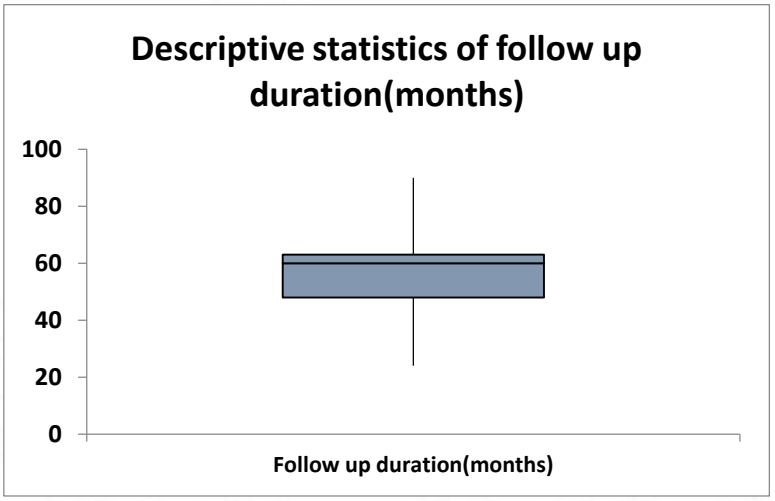


Figure:13 Box and Whisker Plot showing follow-up duration of study subjects

The follow-up duration in the study ranged from 24 months to 84 months. Mean follow up duration was 56.88 ± 10.93 months with median (25th-75th percentile) of 60(48-63) months.

6. PERICORONARY ADIPOSE TISSUE THICKNESS ASSESSMENT:

6a. Association of PCAT thickness with Coronary artery stenosis:

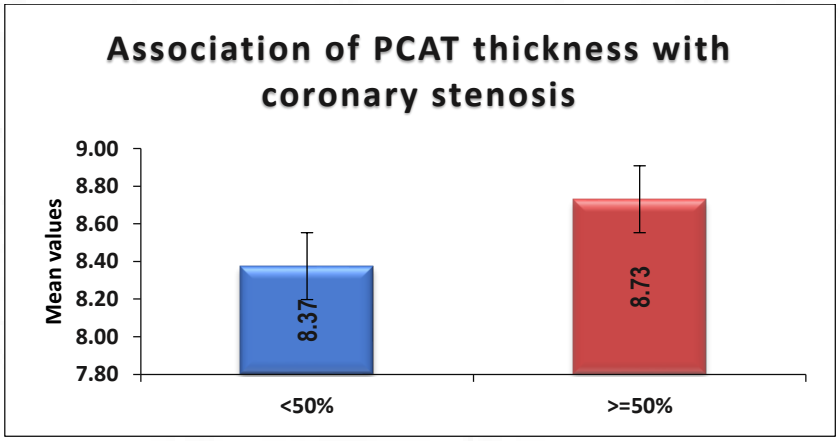


Figure 14 : showing the association of pericoronary adipose tissue thickness with stenosis

Our study showed a mean pericoronary adipose tissue thickness of 8.52 ± 2.5mm. The ≥ 50% stenosis group had higher PCAT thickness (8.73 ± 2.65mm) compared to the <50% stenosis group (8.37 ± 2.4mm). However, the difference was insignificant (Independent T-test, p value=0.446).

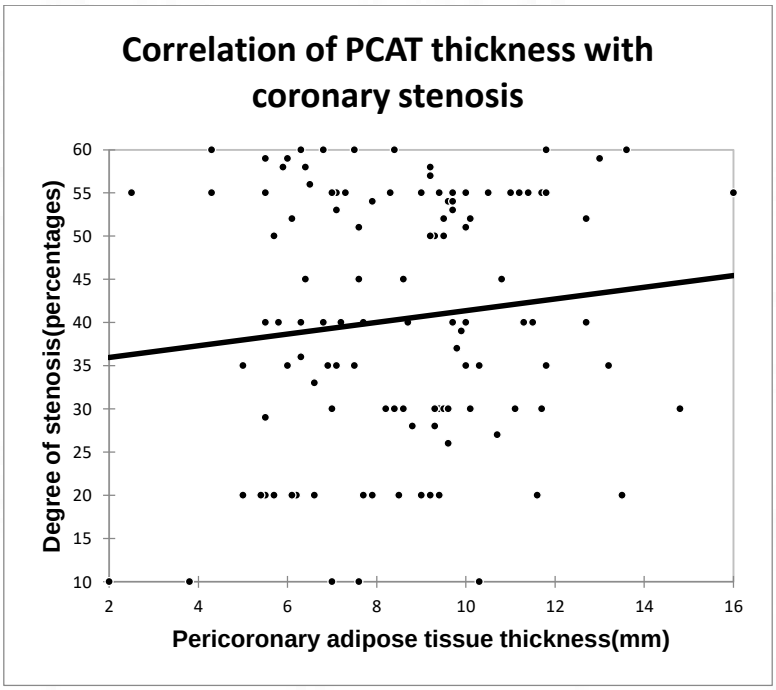


Figure 15 : showing correlation of PCAT thickness with degree of coronary stenosis

Our study showed a non-significant mild positive correlation between pericoronary adipose tissue thickness and degree of stenosis with a Pearson correlation coefficient of 0.117 (p value= 0.204).

6b. Association of PCAT thickness with Vulnerable plaque:

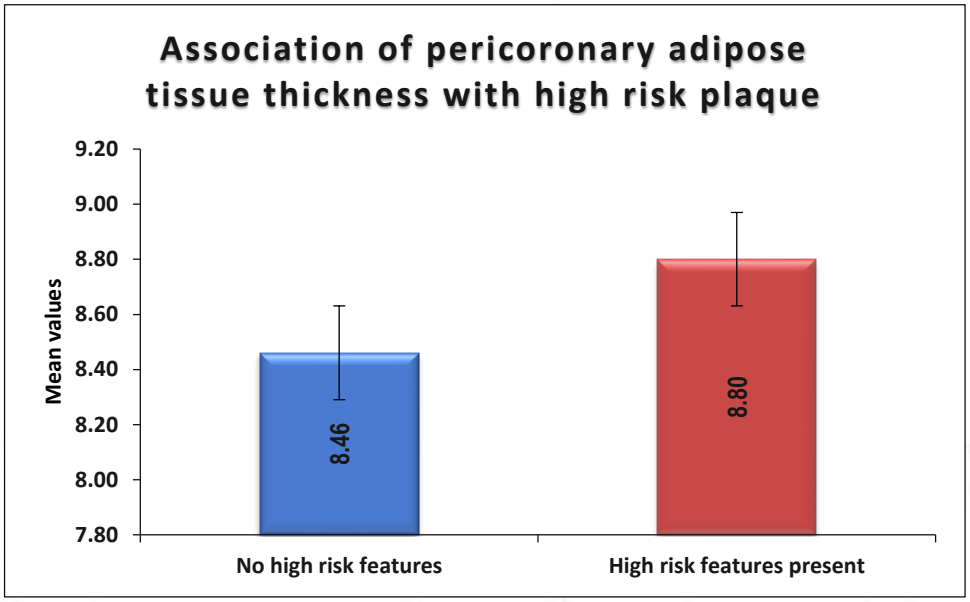


Figure 16: showing the association of PCAT thickness with high-risk plaque features

In the present study, the mean PCAT thickness was higher in patients with vulnerable plaques (8.8 ± 2.48 mm) compared to patients without vulnerable plaques (8.46 ± 2.52mm). However, the difference between the two groups was not significant (Independent t-Test, p value=0.575).

6c. Association of PCAT thickness with ACE:

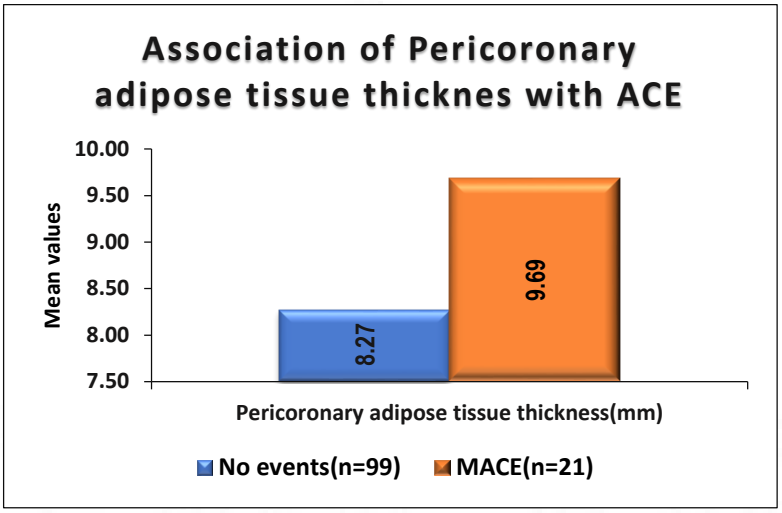


Figure 17: showing the association of PCAT thickness with ACE

In our study, the mean PCAT thickness in patients with ACE (9.69 ± 2.79mm) was significantly higher as compared to patients without ACE (8.27 ± 2.38mm) (p value=0.017).

7. Association of CADRADS with ACE:

CADRADS	No events(n=99)	ACE(n=21)	Total	P value
CADRADS 1	20 (20.20%)	1 (4.76%)	21 (17.50%)	0.007*
CADRADS 2	45 (45.45%)	5 (23.81%)	50 (41.67%)	
CADRADS 3	34 (34.34%)	15 (71.43%)	49 (40.83%)	
Total	99 (100%)	21 (100%)	120 (100%)	

* **Fisher's exact test**

Table 2: showing the association of CADRADS with ACE

Of the total 21 acute coronary events in our study, there was one acute coronary event in CADRADS 1 group, 5 events in CADRADS 2 and 15 events in CADRADS 3(with negative results after stress test- TMT or CAG with FFR). There was a significant difference between the three groups in terms of occurrence of ACE events. (Fisher's Exact Test, p value=0.007)

7a. CADRADS 1and 2 versus CADRADS 3 group:

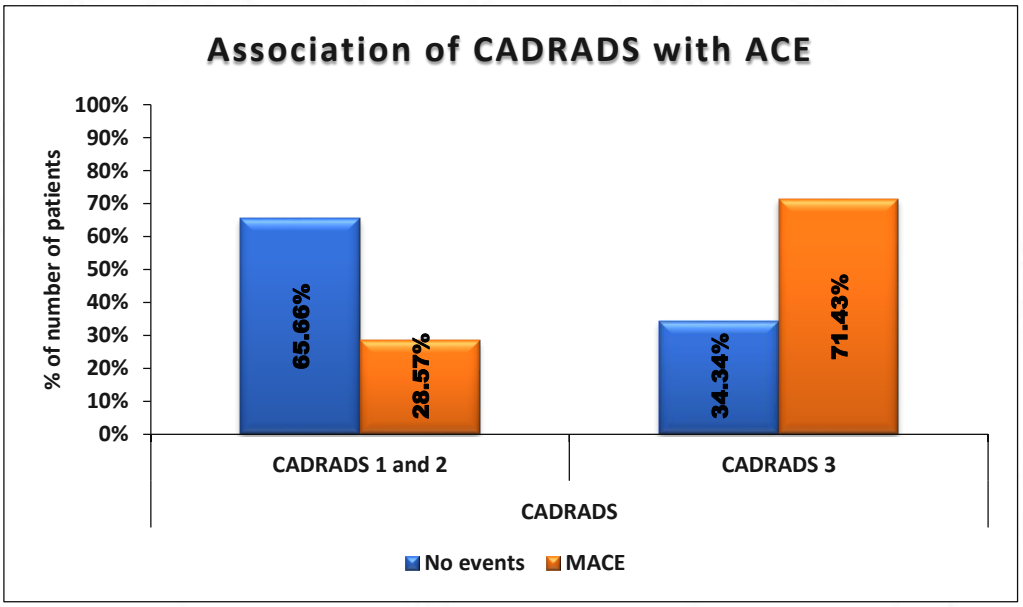


Figure 18: showing the association of CADRADS with ACE

In the subgroup analysis, the number of ACE events in CADRADS 3 (with negative results after stress test- TMT or CAG with FFR) group (15 events) was significantly higher when compared with combined total CADRADS 1 and 2 groups ACE events (6 events) (p = 0.002).

8. Association of plaque burden with ACE:

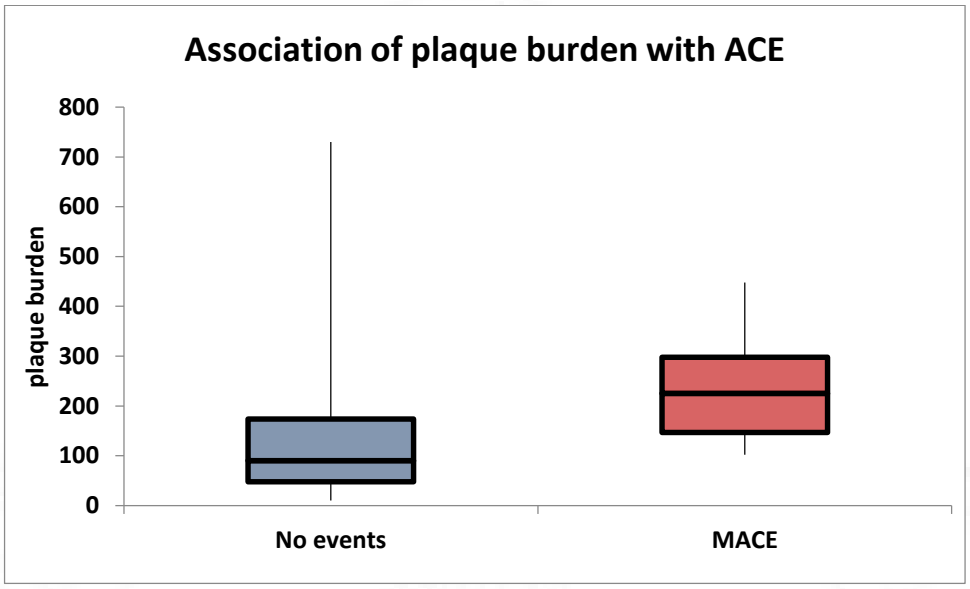


Figure 19 - Box-whisker plot showing the association of plaque burden with ACE.

In our study, the mean value of plaque burden was 153.41 ± 138.43 with a median (25th-75th percentile) of 110 (58.25-201.5). The median plaque burden in patients with ACE (225(147-298)) was significantly higher as compared to patients without events (90(48-174)) (Mann Whitney test, p-value <.0001).

9. PERICORONARY ADIPOSE TISSUE FAI (PCAT FAI) ANALYSIS:

8a. RCA FAI :

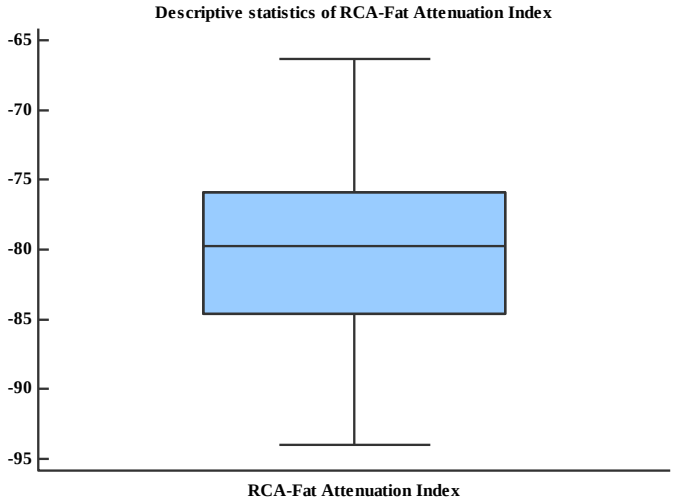


Figure 20:- Box and Whisker Plot showing descriptive statistics of RCA-FAI.

In our study, the mean value of RCA-FAI was -80.07 ± 5.93 HU with a median (25th-75th percentile) of -79.74(-84.448--75.863) HU.

8b. Association of RCA-Fat Attenuation Index with ACE:

RCA-Fat Attenuation Index	No events(n=99)	ACE(n=21)	Total	P value
Mean ± SD	-81.53 ± 5.28	-73.18 ± 3.48	-80.07 ± 5.93	<.0001‡
Median(25th-75th percentile)	-80.22 (-85.6--78.6)	-73.5 (-74.6--71.6)	-79.74 (-84.448--75.863)	
Range	-94--67.9	-82--66.3	-94--66.3	

‡ **Independent t-test**

Table 3 : showing association of RCA-FAI with ACE

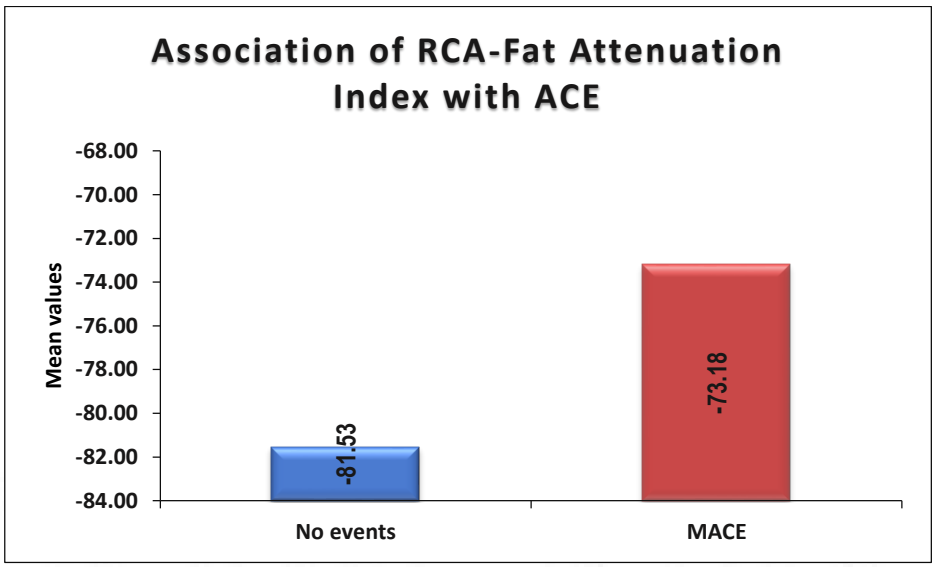


Figure 21: showing the association of RCA FAI with ACE

In our study, mean RCA-FAI in patients with ACE (-73.18 ± 3.48HU) was significantly higher as compared to patients without events (-81.53 ± 5.28HU) (Independent T-test, p-value <.0001)

8c. LESION FAI :

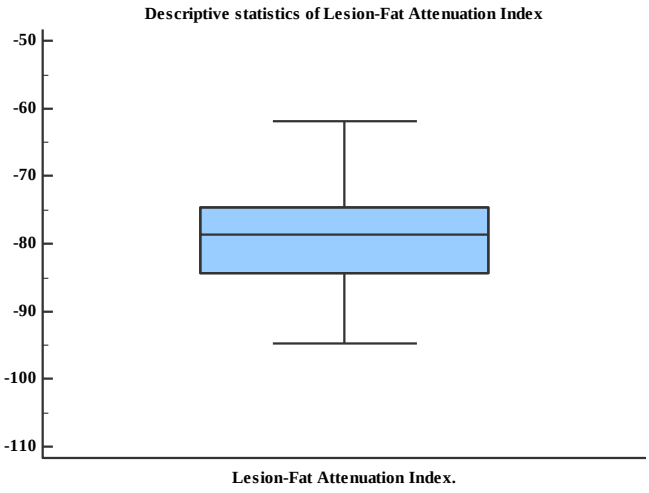


Figure 22:- Box and Whisker Plot showing descriptive statistics of Lesion FAI

The mean Lesion-Fat Attenuation Index in the present study was -79.23 ± 7.16 HU with median(25th-75th percentile) of -78.58(-84.325--74.718) HU.

8c. Association of Lesion-Fat Attenuation Index with ACE :

Lesion-Fat Attenuation Index	No events(n=99)	ACE(n=21)	Total	P value
Mean ± SD	-80.27 ± 7.03	-74.31 ± 5.65	-79.23 ± 7.16	0.0004‡
Median(25th-75th percentile)	-80.39 (-85.67--75.595)	-75.5 (-77.69--72.3)	-78.58 (-84.325--74.718)	
Range	-105.1--58	-86.2--61.97	-105.1--58	

‡ **Independent t-test**

Table 4: showing association of Lesion-FAI with ACE

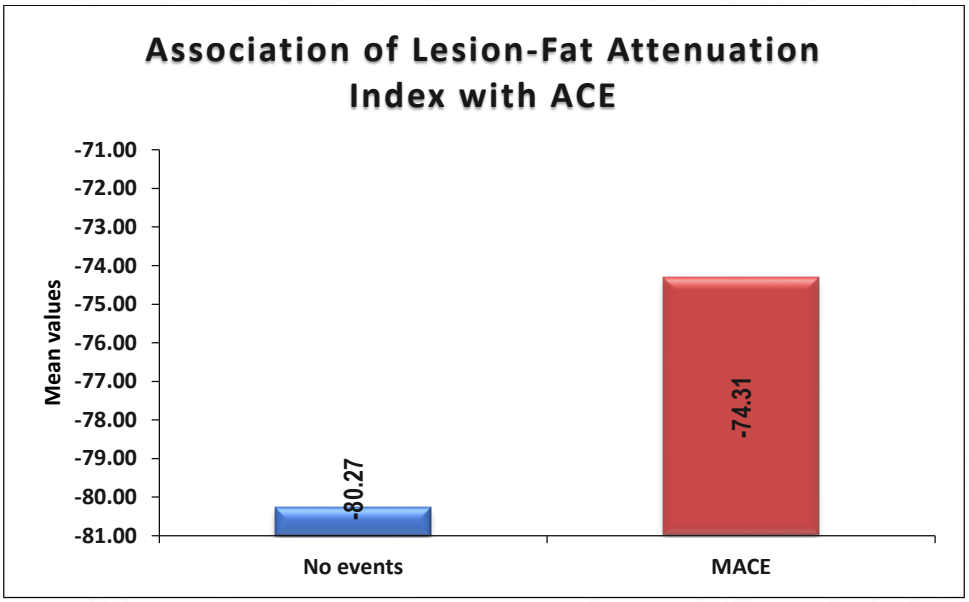


Figure 23: showing the association of Lesion FAI with ACE

In our study, mean Lesion- FAI in patients with ACE (-74.31 ± 5.65 HU) was significantly higher as compared to patients without events (-80.27 ± 7.03 HU) (Independent t-test, p value=0.0004).

8d. Correlation of RCA-FAI with Lesion-FAI in total study group:

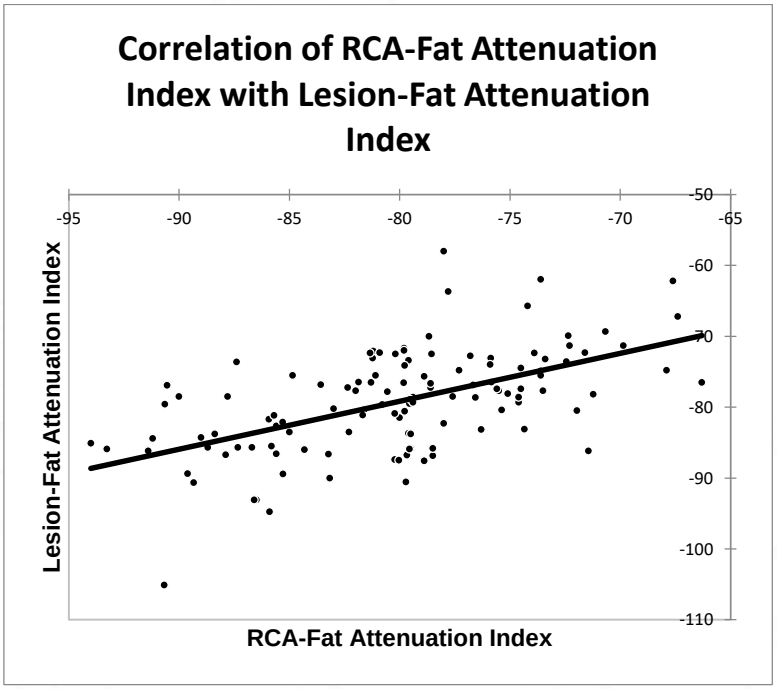
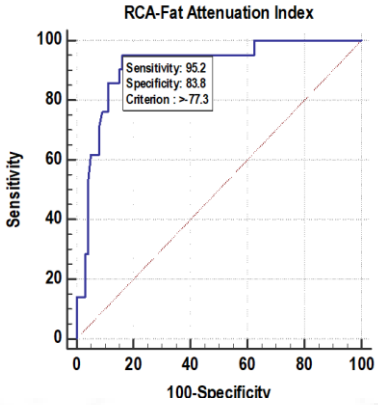


Figure 24: Correlation of RCA-FAI with Lesion-FAI in the total study group.

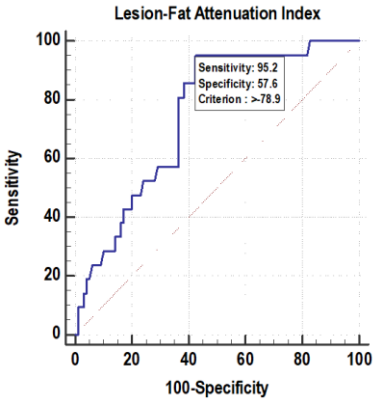
In the present study, a significant positive correlation was seen between RCA-FAI and Lesion-FAI with a Pearson correlation coefficient of 0.56 (p-value <0.0001)

8e. Receiver operating characteristic curve of RCA-FAI and Lesion FAI for predicting ACE:

ROC curve of RCA- FAI for predicting ACE



ROC curve of Lesion- FAI for predicting ACE



Figures 25 and 26 :- showing ROC curve of RCA-FAI and Lesion-FAI for predicting ACE.

In our study, RCA FAI and Lesion FAI both showed significant discriminatory power to predict ACE. Interpretation of the area under the ROC curve showed that the performance of RCA-FAI (AUC 0.915; 95% CI: 0.850 to 0.958) was outstanding. Discriminatory power of Lesion-FAI (AUC 0.747; 95% CI: 0.659 to 0.822) was acceptable. Among both parameters, RCA-FAI was the best predictor of future ACE at a cut-off point of > -77.3 HU with Sensitivity of 95.24%, Specificity of 83.84%, Positive predictive value of 55.6%, Negative predictive value of 98.8% and diagnostic accuracy of 85.83%.

9. Kaplan Meier survival analysis curve to assess event-free survival:

Variable			Value
Total N			120
N of Events			21
Censored		N	99
		Percent	82.50%
EFS at the end of 3 years			100.00%
EFS at the end of 5 years			86.02%
Mean	Estimate		75.5649
	Standard Error		2.56429
	95% Confidence Interval	Lower Bound	70.5389
		Upper Bound	80.5909
Median	Estimate		72
	Standard Error		3.38
	95% Confidence Interval	Lower Bound	65.3752
		Upper Bound	78.6248

Table 5: showing Kaplan Meier survival analysis to assess event-free survival

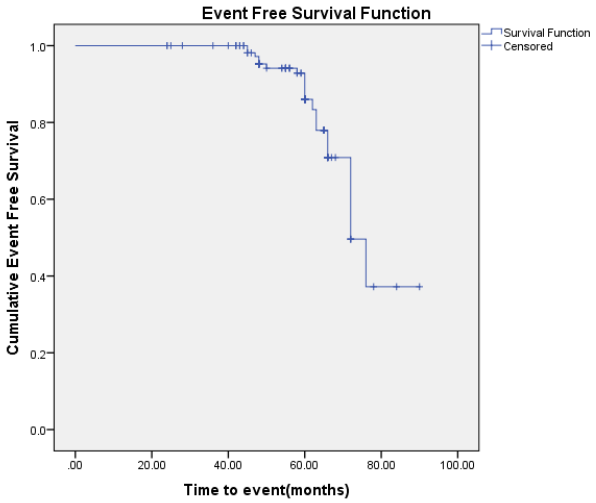
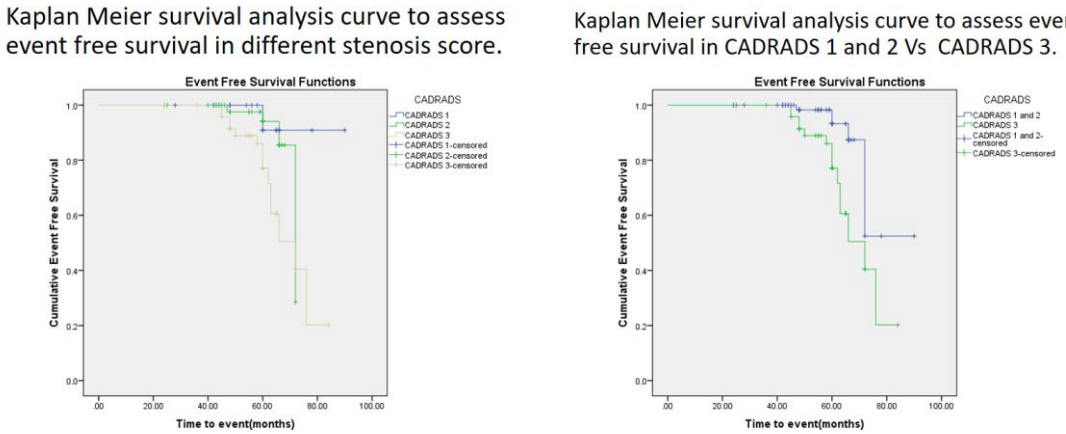


Figure 27 :- showing Kaplan Meier survival analysis curve to assess event-free survival in total study subjects.

In our study, on Kaplan Meier analysis, the actuarial event-free survival rate at the end of 3 years was 100% and at the end of 5 years was

86.02%. Median event-free survival time was 72 months (65.37 to 78.62 months).

9a. Kaplan Meier survival analysis curve to assess event-free survival in different CADRADS categories:



Figures 28 and 29:- showing KM survival analysis curve to assess event-free survival in different CADRADS categories.

The Kaplan-Meier analysis showed a significant difference in event-free survival between the three CADRADS groups. The mean event-free survival time was 87± 2 months in CADRADS 1 group, 70± 0.9 months in CADRADS 2 group and 68± 2 months in CADRADS 3 group. The event free survival rate at the end of 5 years was significantly higher in CADRADS 1(90.91%) and CADRADS 2 (94.08%) groups compared to CADRADS 3 (77.15%) group. (Log Rank Test, p=0.018).

In the subgroup analysis, the Kaplan Meier analysis of CADRADS 1 and 2 as a group assessed against CADRADS 3(non-obstructive CAD) showed a significant difference in event-free survival between the two groups. The mean event-free survival time was 80± 3 months in CADRADS 1 and 2 groups, while it was 68± 2

months in CADRADS 3 group. At the end of 5 years, the event-free survival rate was significantly higher in the CADRADS 1 and 2 group (93.24%) as compared to patients in the CADRADS 3 group (77.15%) (Log Rank Test, p=0.006).

10. **Univariate Cox proportional hazard regression to find out significant risk factors of ACE:**

On performing univariate regression analysis, the degree of stenosis, RCA-FAI, Lesion-FAI, diabetes mellitus, and stenosis $\geq$ 50% were significant risk factors of ACE. With the increase in RCA-FAI, Lesion-FAI and degree of stenosis (percentages), the risk of ACE significantly increases with hazard ratio of 1.164(1.078 to 1.257), 1.059(1.005 to 1.116), 1.051(1.011 to 1.092) respectively. Patients with diabetes mellitus, and stenosis $\geq$ 50% had a significantly high risk of ACE with a hazard ratio of 3.193(1.318 to 7.732), and 3.401(1.31 to 8.825), respectively.

Variables	Beta coefficient	Standard Error	P value	Hazards ratio	95.0% CI for hazards ratio	
					Lower	Upper
Age(years)	-.013	.021	.539	.987	.946	1.029
Degree of stenosis(percentages)	.050	.020	.011	1.051	1.011	1.092
Plaque burden	.002	.001	.067	1.002	1.000	1.005
Pericoronary adipose tissue thickness(mm)	.097	.079	.220	1.102	.943	1.288
RCA-Fat Attenuation Index	.152	.039	.0001	1.164	1.078	1.257
Lesion-Fat Attenuation Index	.057	.027	.031	1.059	1.005	1.116
Gender						
Female				1.000		

Male	.247	.465	.595	1.280	.515	3.185
Atypical chest pain	.528	.746	.479	1.695	.393	7.323
Dyspnoea	-.105	.486	.829	.900	.347	2.334
Palpitation	-.860	.759	.257	.423	.096	1.872
Diabetes mellitus	1.161	.451	.010	3.193	1.318	7.732
Hypertension	-.278	.465	.550	.757	.304	1.885
Dyslipidemia	.325	.453	.474	1.383	.569	3.365
Smoking	.328	.570	.565	1.388	.454	4.240
Hypothyroidism	.766	.763	.316	2.151	.482	9.604
Family history of CAD	.349	.759	.645	1.418	.321	6.274
Calcium score						
0				1.000		
1 to 100	.611	.788	.438	1.843	.394	8.629
101 to 400	.921	.799	.249	2.511	.524	12.022
>400	-.048	1.236	.969	.953	.084	10.755
CADRADS						
CADRADS1				1.000		
CADRADS2	.985	1.104	.372	2.678	.308	23.297
CADRADS3	1.959	1.036	.059	7.095	.931	54.082
Stenosis						
<50%				1.000		
≥ 50%	1.224	.487	.012	3.401	1.310	8.825
Plaque type						
Calcified				1.000		
Non calcified	.186	.507	.714	1.204	.446	3.252
Mixed plaque	-.127	.574	.825	.881	.286	2.712
High-risk plaque						
No high-risk features				1.000		
High-risk features present	.773	.499	.122	2.165	.814	5.761

Table 6: showing Univariate Cox proportional hazard regression analysis to find out significant risk factors of ACE

11. Multivariate Cox proportional hazard regression to find out significant independent risk factors of ACE:

On multivariate regression analysis in our study, the RCA-FAI, diabetes mellitus, and stenosis ≥ 50% were significant independent risk factors of ACE after adjusting for confounding factors. Patients with diabetes mellitus and stenosis ≥ 50% had a significantly high risk of ACE with a hazard ratio of 3.976(1.533 to 10.308) and 4.181(1.489 to 11.74), respectively. With the increase in RCA-FAI, the risk of ACE significantly increases with a hazard ratio of 1.236(1.098 to 1.39). Lesion FAI was not a significant independent risk factor for ACE on multivariate analysis.

Variables	Beta coefficient	Standard Error	P value	Hazards ratio	95.0% CI for hazards ratio	
					Lower	Upper
RCA-Fat Attenuation Index	.212	.060	.0004	1.236	1.098	1.390
Lesion-Fat Attenuation Index	-.044	.039	.259	0.957	0.887	1.033
Diabetes mellitus	1.380	.486	.005	3.976	1.533	10.308
Stenosis						
<50%				1.000		
≥50%	1.431	0.527	.007	4.181	1.489	11.74

Table 7 : showing Multivariate Cox proportional hazard regression analysis to find out significant risk factors of ACE

12. Kaplan Meier survival analysis curve to assess event-free survival in non-diabetics and diabetics.

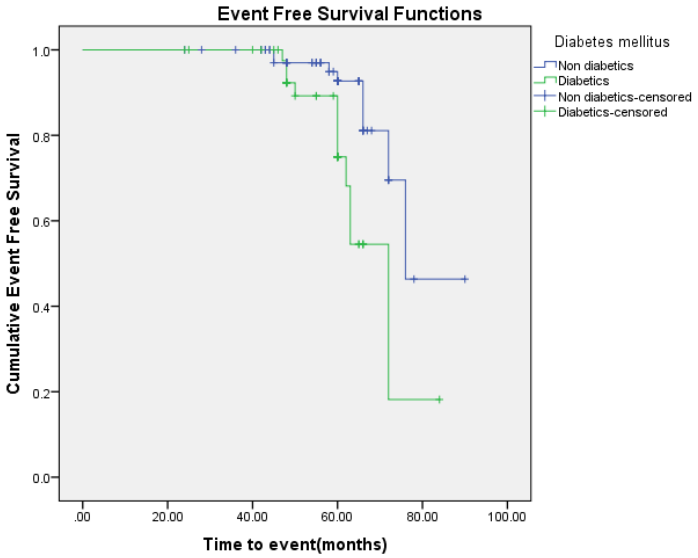
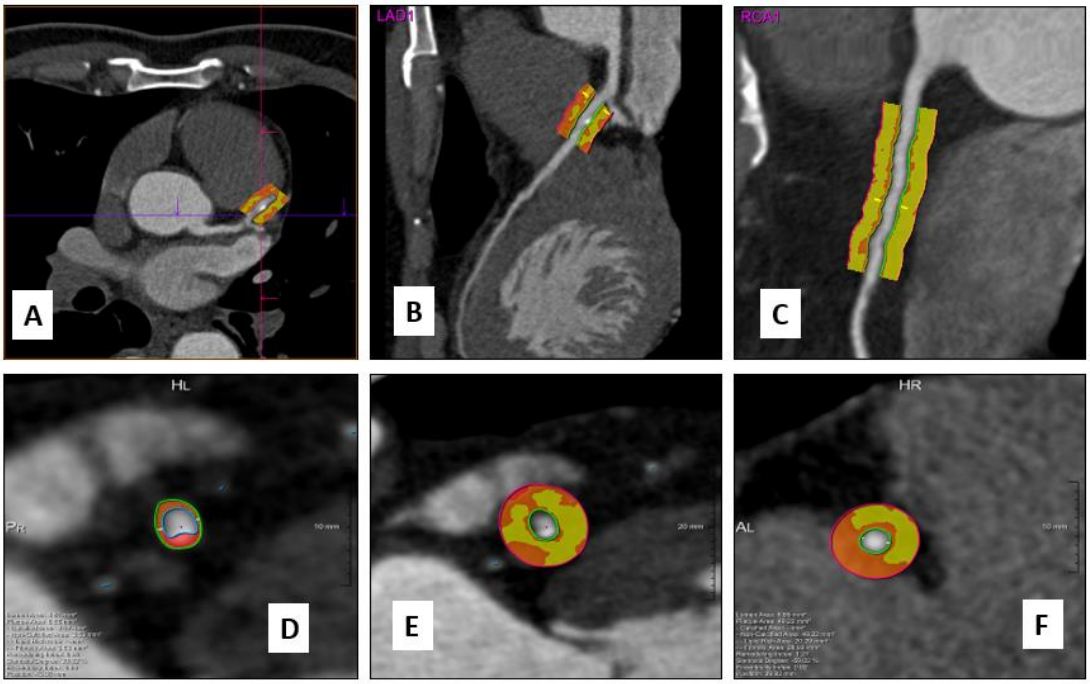


Figure 30:- showing K-M survival analysis curve to assess event-free survival in diabetics and non-diabetics.

On subgroup analysis, the Kaplan Meier survival analysis of diabetics and non-diabetics showed a significant difference in event-free survival between the two groups, with a mean survival time of 79±3 months in non-diabetics and 68±2 months in diabetics. Event free survival rate at the end of 5 years was significantly higher in non-diabetics (92.70%) as compared to diabetics (74.95%) (Log Rank test, p value=0.005)

REPRESENTATIVE CASES:

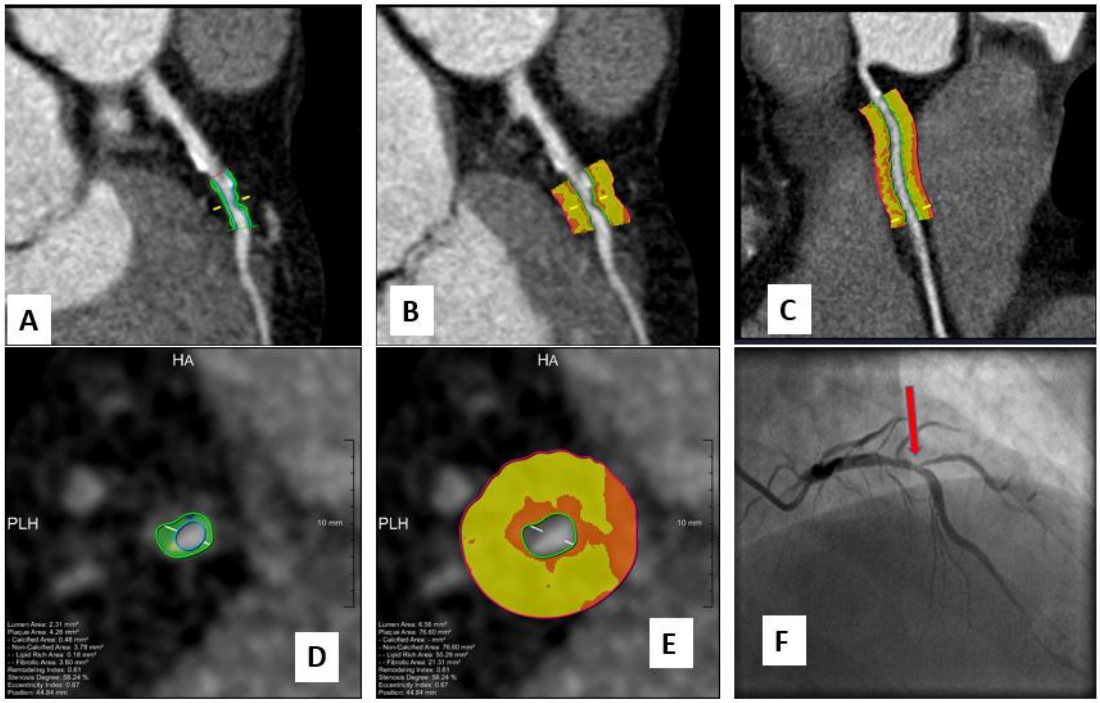
CASE 1: A 58 year male with atypical chest pain.



LAD Segment 6
PCAT Thickness= 7.3mm
Plaque burden = 68
Stenosis=22%
RCA FAI= -88.2 HU
LESION FAI=-84.6 HU
Follow up period = 90 months
No ACE events

Fig 31. Images A and D show a mixed plaque in segment 6 of LAD with 22% stenosis. PCAT thickness was 7.3mm and plaque burden of 68. Images B and E show Lesion FAI measurement with value of -84.6 HU. Images C and F show RCA FAI measurement with value of -88.2 HU. Both RCA and lesion FAI were well above the cut off FAI of -77.3 HU. The patient had no ACE on follow up.

CASE 2 : A 62 year male with atypical chest pain. Known DM and hypertension.

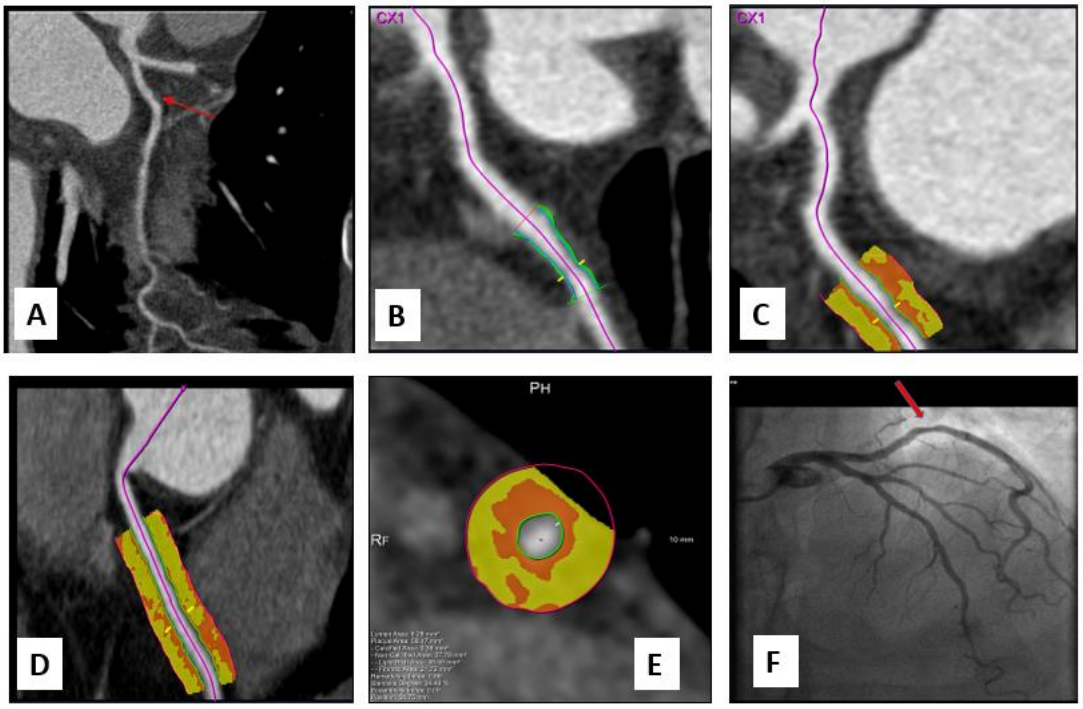


LAD Segment 6
Plaque burden =102
Stenosis=56%
RCA FAI= -75.6 HU
LESION FAI=-77.4 HU
Developed UA after follow up period of=45 months
Troponin T <0.010 ng/mL
Underwent PCI to LAD

Fig 32. Images A and D show a mixed plaque in segment 6 of LAD with 56% stenosis. PCAT thickness was 13.6 mm and plaque burden of 102. Images B and E show Lesion FAI measurement with value of -75.6 HU. Images C show RCA FAI measurement with value of -77.4 HU. The RCA FAI was high in this patient and lesion FAI was just below the cut off FAI of -77.3 HU. The patient developed NSTEMI after 45 months with elevated Troponin-T levels of 0.071 ng/Ml. Figure F

shows coronary angiogram with 70% stenosis in proximal LAD. Patient underwent PCI to LAD.

CASE 3 : A76 year male with atypical chest pain and dyspnea on exertion. Known DM, hypertension and dyslipidemia.

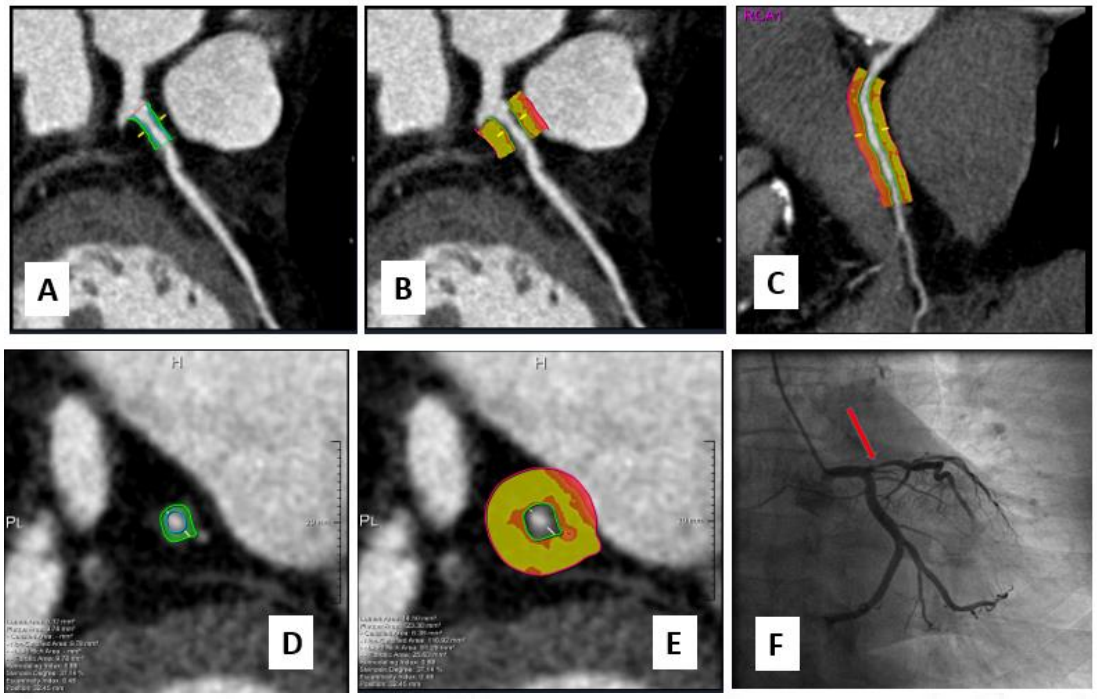


LCX Segment 11
PCAT Thickness= 7.5mm
Plaque burden = 201
Positive Remodeling present
Stenosis=35%
RCA FAI= -73.6 HU
LESION FAI=-75.5 HU
Developed Unstable angina after follow up period of 60 months.
Troponin T <0.010

Fig 33. Images A and B show a non-calcified plaque in segment 11 of LCX with 35% stenosis. PCAT thickness was 13.6 mm and plaque burden of 102. Images C and E show Lesion FAI measurement with value of -75.5 HU. Images D shows RCA

FAI measurement with value of -73.6 HU. Both the RCA FAI and lesion FAI were high in this patient with values above the cut off FAI of -77.3 HU. During follow up the patient developed unstable angina after 60 months. Figure F shows coronary angiogram with 50% stenosis in proximal LCX.

CASE 4 : A 56 year male with atypical chest pain. Known DM and dyslipidemia.



LAD Segment 6
PCAT Thickness= 10.3mm
Plaque burden = 322
Stenosis=37%
RCA FAI= -74.6 HU
LESION FAI=-78.6HU
Developed Unstable angina after
Follow up period of 47 months
Troponin T <0.010

Fig 34. Images A and D show a non-calcified plaque in segment 6 of LAD with 37% stenosis. PCAT thickness was 10.3 mm and plaque burden was 322. Images B and E show Lesion FAI measurement with value of -78.6 HU. Images C shows RCA FAI

measurement with value of -74.6 HU. The RCA FAI was high in this patient, however the Lesion FAI was below the cut off FAI of -77.3 HU. On follow up the patient developed unstable angina after 47 months. Figure F shows coronary angiogram with60% stenosis in proximal LAD. Patient underwent PCI to LAD.

DISCUSSION

Of 120 patients with non-significant coronary artery stenosis in coronary CT angiography who were followed for median of 60 months, 21 developed acute coronary events. Cox multivariate regression analysis showed that age, sex, hypertension, Dyslipidemia, Hypothyroidism, and family history of CAD were not significantly associated with the development of ACE. The presence of Diabetes mellitus showed a significant association with the development of ACE. PCAT thickness and high plaque burden showed significant association with development of ACE. Both RCA FAI and lesion FAI showed significant discriminatory power to predict ACE. However, among both parameters, RCA- FAI was the best predictor of ACE (cut-off point of > -77.3 HU). The multivariate Cox proportional hazard regression analysis showed that RCA-FAI, diabetes mellitus and stenosis >50% were significant independent risk factors of ACE after adjusting for confounding factors. The increase in RCA-FAI increased the future risk of ACE [hazard ratio of 1.236 (1.098 to 1.39].

Association between PCAT Thickness and coronary stenosis:

Our study showed a mean PCAT thickness of 8.52 ± 2.5mm. A non-significant mild positive correlation existed between PCAT thickness and coronary artery stenosis (Pearson correlation coefficient of 0.117, p=0.204). In the subgroup analysis, the PCAT thickness was higher in the > 50% stenosis group (8.73 ± 2.65mm) compared to the <50% stenosis group (8.37 ± 2.4mm), but the difference

was not statistically significant (p value=0.446). In a study by Petra MG et al., which included 128 patients, the mean PCAT thickness in patients with <50% stenosis was 10.1 ± 0.5mm and in > 50% stenosis group it was 10.4 ± 0.3mm. They also found no significant difference in PCAT thickness between the two groups. (53) In another study by Demircelik MB et al., the mean PCAT thickness was 13.2 ± 2.1mm, and their study showed a significant difference in PCAT thickness between the <50% stenosis (12.4 ± 1.5mm) group and > 50% stenosis group (16.3 ± 2.1mm). (20) However, the higher values of mean PCAT thickness in this study could be due to different methods used for PCAT thickness measurement, where the coronary artery diameter was also included in the total PCAT thickness. In addition, the measurements were done on axial views, which could have led to overestimation due to obliquity. Our study measured PCAT thickness in short-axis CPR images and did not include coronary artery diameter which is a better measurement of the fat thickness.

Association between PCAT Thickness and vulnerable plaque characteristics:

In our study, 21 patients had coronary plaques with vulnerable plaque features. The mean PCAT thickness in patients with vulnerable plaque features was higher (8.8 ± 2.48mm) than those without high-risk (8.46 ± 2.52mm). However, the difference between the two groups was not statistically significant (p value=0.575).

To the best of our knowledge we could not find studies in literature correlating PCAT thickness with vulnerable plaque features. However, a study correlating PCAT volume with plaque composition was noted. In this study by P.

Maurovich-Horvat et al, comparing PCAT volume to the presence of plaque as well as plaque morphology, they found that PCAT volume was greater in patients with plaque than without plaque ($p < 0.001$). Also PCAT volume was greatest in coronary segments with mixed plaque followed by non-calcified plaque, calcified plaque, and the lowest volume in segments with no plaque ($p < 0.001$), suggesting that while non-calcified plaque is part of the earlier stage of atherosclerosis and calcified plaque is part of the later chronic phase, the most active process is with the development of mixed plaques.(54) Our study also showed higher PCAT thickness in patients with high risk plaque features compared to those without, but the measured parameter PCAT thickness in our study cannot be compared directly with PCAT Volume of the above mentioned study.

Pericoronary FAI and future Acute coronary event: Lesional versus RCA FAI

Our study's mean value of RCA- FAI was -80.07 ± 5.93 HU. The RCA-FAI of patients with ACE was -73.18 ± 3.48 HU, which was significantly higher as compared to patients without events (-81.53 ± 5.28) (p-value <.0001). The mean value of Lesion FAI in our study was -79.23 ± 7.16 HU. The Lesion- FAI in patients with ACE was -74.31 ± 5.65 HU, which was also significantly higher as compared to patients without events (-80.27 ± 7.03 HU) (p value=0.0004).

RCA- FAI was the best predictor of ACE at a cut-off point of > -77.3 HU (with AUC of 0.915) compared to lesion-FAI. At a cut-off FAI of -77.3, RCA-FAI showed high sensitivity (95.24%), specificity (83.84%), and negative predictive value (98.80%) for correctly predicting ACE. Patients with high RCA FAI had

underlying coronary inflammation, which could explain the associated high risk of ACE in this group of patients. The coronary inflammation-induced changes in pericoronary adipose tissue in the form of decreased lipophilic content and smaller, undifferentiated, lipid-poor adipocytes led to an increase in pericoronary FAI measured on CCTA.

The Cardiovascular Risk Prediction using Computed Tomography (CRISP-CT) study by Antonopoulos et al. also aimed to assess the predictive value of the perivascular FAI for of all-cause mortality and cardiac mortality.(50) In their post-hoc analysis of outcome data gathered prospectively from two independent cohorts, the mean PCAT FAI was –75·1 HU $\pm$ 8·6 in the derivation cohort and –77·0 HU $\pm$ 8·5 in the validation cohort. They found a cut-off PCAT FAI of -70.1 HU for correctly predicting acute MI and cardiac mortality. High PCAT FAI values ($\geq$–70·1 HU) were associated with increased risk of acute MI (n=23 reported events; adjusted HR 5·08, 95% CI 1·89–13·61; p=0·0012). Compared to the CRISP-CT study, our study showed lower values of mean PCAT FAI (-80.07 ± 5.93 HU). This could be due to different study populations (Derivation cohort from Germany and validation cohort from the USA) involved the CRISP-CT study compared to Indian population in our study. Another reason for the noted difference in FAI values could be the heterogeneity in CADRADS categories included in the study cohorts. The CRISP-CT study included patients from CADRADS 1 to 5, whereas was our study only included patients with CADRADS 1 to 3 with non-obstructive CAD. The results from the validation cohort of the CRISP-CT study showed that a 'significant positive association of high perivascular FAI values with adverse cardiac events was

consistent across ethnic groups'. The ability of high RCA FAI to predict ACE in our Indian study population further supports this finding of the CRISP-CT study.

In our study, at a cut-off of -77.3, RCA-FAI showed high sensitivity (95.24%), specificity (83.84%), negative predictive value (98.80%) and positive predictive value of 55.60% for correctly predicting ACE. These findings are similar to the CRISP-CT study. In their study, the perivascular FAI cut-off of –70·1 HU at a median follow-up of 72 months in the derivation cohort showed specificity 85·0%, sensitivity 67·7%, negative predictive value 99·5%, positive predictive value 5·9% in predicting all-cause and cardiac mortality. A study by Hoshino et al., which included 220 consecutive patients with intermediate stenosis, showed that a PCAT FAI ≥ −73.1 HU was related to an increased risk of major adverse cardiac events (MACE) (multivariate HR 3.11, 95%CI:1.40–6.94, p = 0.005). (55,56) Another study by Goeller et al. defined a similar cut-off value of −73.5 HU for PCAT FAI as an independent predictor of MACE (HR 2.01, p = 0.044). (51) The findings from our study concur with above-mentioned studies. The lower cut-off PCAT FAI to predict ACE in our study could be due to different study populations and CADRADS categories involved in the study.

Our study showed a significant positive correlation between RCA-FAI and Lesion-FAI [Pearson correlation coefficient of 0.56 (p-value <0.0001)]. The results from the CRISP-CT study also showed similar findings. In their study, high perivascular FAI values around the proximal RCA and LAD artery predicted all-cause and cardiac mortality and correlated strongly. They concluded that the perivascular FAI measured around the RCA could be used as a representative

biomarker of global coronary inflammation (for prediction of cardiac mortality, hazard ratio [HR] 2·15, 95% CI 1·33–3·48; p=0·0017 in the derivation cohort, and 2·06, 1·50–2·83; p<0·0001 in the validation cohort). The analysis of risk factors for ACE in our study showed that degree of stenosis, RCA-FAI, Lesion-FAI, diabetes mellitus, stenosis ≥50 % as significant risk factors for development of ACE with hazard ratio of 1.051(1.011 to 1.092), 1.164(1.078 to 1.257), 1.059(1.005 to 1.116), 3.193(1.318 to 7.732) and 3.401(1.31 to 8.825) respectively on univariate analysis. However on multivariate regression analysis, RCA-FAI, diabetes mellitus, and stenosis ≥50% were independent risk factors of ACE after adjusting for confounding factors with a hazard ratio of 1.236 (1.098 to 1.39), 3.976(1.533 to 10.308) and 4.181(1.489 to 11.74) respectively. This finding is rather interesting in the sense that Lesion -FAI lost its significance in multivariate analysis compared to RCA-FAI. This indicates that lesion FAI is a co-variate of RCA FAI . Also, in cases with multiple plaques, lesion FAI may not be a true representative of the culprit plaque.

In our study Type 2 diabetes mellitus showed significant association with ACE and was independent risk factor ACE with hazard ratio of 3.976(1.533 to 10.308). It is well established in literature from prospective studies like Framingham study that diabetes is an independent risk factor of ACE. (57) Several factors including increased oxidative stress, hypercoagulability, endothelial dysfunction (due to persistent hyperglycemia) have been implicated in pathogenesis of atheroma formation leading to macrovascular complications of DM including ACE. A study by Vesa et al., showed that in patients with DM the absolute risk of MACE remains two times higher compared to patients without DM. (58) Our study shows results similar to above mentioned studies.

In our study smoking was not significantly associated with ACE. This may be due to smaller sample size and lower number of people with smoking in the study.

Our study cohort was non-significant coronary artery disease and results from our study that RCA FAI was able to predict the occurrence of future acute coronary events in this group of patients, throws light on the pathophysiology of FAI. Compared to other studies which found the association of lesion FAI with MACE, our study showed RCA FAI as independent risk factor for ACE. The findings of our study can be explained by the fact that the lesion FAI is dynamic in nature and high lesion FAI values due to inflammatory changes in PCAT are only seen in CCTA scans done during acute coronary events or immediately after revascularization. However, results from our study indicate that RCA FAI is more reliable and consistent parameter than lesion FAI. It can be considered surrogate maker of global coronary vascular inflammation even in non-obstructive CAD patients and can help to predict ACE in this group of patients undergoing CCTA.

Our study is unique because it involves only CADRADS 1 to 3 patients with non-significant obstructive coronary artery disease. In comparison, most of the studies in the literature have included CADRADS 1 to 5 patients. Also, our study involved prospective follow-up of patients to look for the development of acute coronary events, unlike other studies which were retrospective in nature and included patients after the development of ACE or revascularization. Thirdly, in our study, we also measured FAI around individual coronary plaques in addition to RCA FAI. In contrast, very few studies in the literature have done a similar analysis, and most of the studies have measured FAI around proximal coronary arteries only.

Our study has multiple limitations. The sample size is modest, and the study is single institutional. The smaller size is due to the inclusion of only non-obstructive CADRADS 1 to 3 patients. In patients with multiple plaques, we selected the plaque with maximum stenosis or displaying vulnerable plaque features, and FAI was measured around that particular plaque. However, one of the other plaques may have been responsible for the acute coronary event, hence affecting the results of our study. Also longer follow-up period would have been better, as the patients in our study had lower stenosis grades.

To conclude, in our study PCAT thickness showed mild positive correlation with degree of coronary stenosis. PCAT thickness was higher in the> 50% stenosis group and compared to the <50% stenosis group. PCAT thickness was also higher in group with vulnerable plaque features compared to group without vulnerable plaque features. Our study results showed that pericoronary adipose tissue FAI measurement around proximal RCA (RCA-FAI) can predict ACE in non-obstructive coronary artery disease patients. Detection of high RCA FAI of > -77.3 HU on Coronary CT angiogram can help to identify high-risk patients in this group of non-obstructive CAD patients who might need regular follow-up and early initiation of interventions to prevent ACE. However, studies with larger sample sizes and longer follow-up duration are needed.

SUMMARY AND CONCLUSIONS

In this single-center prospective observational study, 120 patients with low to intermediate probability of CAD fulfilling inclusion and exclusion criteria underwent Coronary CT angiogram. In patients with CADRADS 1 to 3 non-obstructive CAD, the pericoronary adipose tissue thickness and FAI were measured around the proximal RCA and coronary segment with a plaque showing maximum stenosis or vulnerable plaque features. In addition to the PCAT assessment, patient demographics and risk factors for acute coronary events were also assessed. Subsequently, these patients were followed up for a mean duration of 56 months for the development of any acute coronary events. During the follow-up period, 21 patients developed acute coronary events, including 13 patients with Unstable angina and 8 patients with NSTEMI. In the PCAT analysis, the RCA and Lesion PCAT FAI were significantly higher in the ACE group compared to patients without ACE. The RCA FAI showed a significant and high positive correlation with Lesion FAI, indicating that RCA PCAT FAI can be used as a surrogate marker of global coronary tree FAI. Our study showed that RCA FAI cut-off value of >- 77.3 HU can predict ACE (area under the curve of 0.915) with high sensitivity, specificity and negative predictive value. A non-significant mild positive correlation was seen between PCAT thickness and the degree of coronary stenosis. Although the PCAT thickness was higher in the> 50% stenosis group and group with vulnerable plaque features compared to the <50% stenosis group and group without vulnerable plaque features, the difference was not statistically significant.

Among other Coronary CT angiography parameters, the CADRADS 3 group with non-obstructive CAD had a significantly higher number of ACE events than combined CADRADS 1 and 2 group events (p-value =0.002). Also, the plaque burden in patients who experienced ACE was significantly higher than those without ACE (p-value <0.001). The Kaplan Meyer event-free survival analysis curves showed significantly higher event-free survival in CADRADS 1 and 2 groups compared to CADRADS 3 non-obstructive CAD group (p value= 0.006). Among demographic and clinical risk factors, the event-free survival in non-diabetics was significantly higher than patients with diabetes mellitus (p value=0.005).

In the multivariate regression analysis of significant risk factors for ACE, the RCA-FAI, diabetes mellitus, and coronary artery stenosis $\geq$ 50% were significant independent risk factors of ACE after adjusting for confounding factors. With the increase in RCA-FAI, the risk of ACE significantly increased with HR of 1.236(95%CI 1.098 to 1.39). Other demographics and risk factors, including age, sex, hypertension, hyperlipidaemia, smoking, hypothyroidism and family history of CAD, did not show a statistically significant association with ACE.

To conclude, in our study PCAT thickness showed mild positive correlation with degree of coronary stenosis. PCAT thickness was higher in the> 50% stenosis group and compared to the <50% stenosis group. PCAT thickness was also higher in group with vulnerable plaque features compared to group without vulnerable plaque features. Our study results showed that pericoronary adipose tissue FAI measurement around proximal RCA (RCA-FAI) can predict ACE in non-obstructive coronary artery disease patients. Detection of high RCA FAI of > -77.3 HU on Coronary CT

angiogram can help to identify high-risk patients in this group of non-obstructive CAD patients who might need regular follow-up and early initiation of interventions to prevent ACE. However, studies with larger sample sizes and longer follow-up duration are needed.

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ANNEXURES

List of publications from thesis – NIL

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Academic Qualifications (Most recent qualification first)

Degree/Certificate	Year	Institution, Country
MD RADIODIAGNOSIS	2013	BJ GOVT MEDICAL COLLEGE PUNE , INDIA
MBBS	2008	JJM MEDICAL COLLEGE DAVANGERE, INDIA

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration

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Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country

JAN 2021	SENIOR RESIDENT	SCTIMST THIRUVANANTHAPURAM, INDIA
APRIL 2016	ASSISTANT PROFESSOR	FMMC, MANGALORE, INDIA
SEPTEMBER 2014	ASSISTANT PROFESSOR	SDMCMSH, DHARWAD, INDIA
JULY 2013	ASSISTANT PROFESSOR	SVMGMC, SOLAPUR , INDIA

Brief summary of relevant research experience:

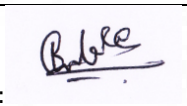
PUBLISHED FEW ORIGINAL RESEARCH ARTICLES –

-PROFILE OF FOCAL LIVER LESIONS BY DIFFUSION WEIGHTED MAGNETIC RESONANCE IMAGING. MEDPULSE-INTERNATIONAL JOURNAL OF RADIOLOGY. 2019

-STUDY OF CORRELATION BETWEEN MAGNETIC RESONANCE SPECTROSCOPY AND GLIOMA GRADING - INTERNATIONAL JOURNAL OF CONTEMPORARY MEDICINE SURGERY AND RADIOLOGY. 2019

-EVALUATION OF AWARENESS OF RADIATION PROTECTION AND HAZARDS AMONG PARAMEDICAL PERSONNEL WORKING IN RADIOLOGY DEPARTMENT OF A TEACHING HOSPITAL. INTERNATIONAL JOURNAL OF CONTEMPORARY MEDICINE SURGERY AND RADIOLOGY. 2017

Current project/s at hand:

Signature: 	Date: 28 -08-2023 Place: THIRUVANANTHAPURAM

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Academic Qualifications (Most recent qualification first) MD RadioDiagnosis, MBBS		
Degree/Certificate	Year	Institution, Country
Fellowship GI intervention radiology	2017	AIIMS – NEWDELHI
MD radiodiagnosis	2013	AIIMS- NEWDELHI
DNB RADIODIAGNOSIS	2014	
Details of professional registration: (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration TCMC- 44903		
Current and previous positions (most recent position first)		
Month and Year	Title	Institution/Company, Country
2018 FEB-present	Assistant professor – IS and IR	SCTIMST- TRIVANDRUM
2014-2017	Senior resident	AIIMS – NEWDELHI

ications:. 1.Valakkada J ,Chandran R, Mishra P, Pawar DK, Maitra S,. Internal jugular vein thrombosis from rhino-cerebral mucormycosis: Be careful before cannulation. Indian J Crit Care Med Peer-Rev Off Publ Indian Soc Crit Care Med. 2014 Aug
2.Kumar V, Karunakaran A, Valakada J. Septo-optic dysplasia. Int Ophthalmol. 2017 Jan 3
3.Jineesh ,Gamanagatti S, Rangarajan K, Kumar A,. Blunt abdominal trauma: imaging and intervention. Curr Probl Diagn Radiol. 2015 Aug;44(4):321–36.
4.Abdominal lymphangiomatosis with intestinal lymphangectasia – MR lymphangiography (CDPR)
5. primary cutaneous histoplasmosis with splenic involvement

Current project/s at hand: IVIM in hepatocellular carcinoma

Signature: 

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Academic Qualifications (Most recent qualification first) PDCC. MD RadioDiagnosis, MBBS

Degree/Certificate	Year	Institution, Country
PDCC in vascular interventions and cardiac imaging	2015	Sree Chitra Tirunal Institute for Medical Sciences & Technology, Trivandrum
MD (Radio-Diagnosis) Doctor of Medicine	2014	**Institute Of Post Graduate Medical Education And Research & SSKM hospital, Kolkata.**
MBBS	2010	Govt . medical college, Kozhikode, Kerala

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration - TCMC no: 42911 of 2011

Current and previous positions (most recent position first)

Month and Year	Title	Institution/Company, Country
July 2017	Assistant Professor, IS & IR	SCTIMST
Jan 2016	Assistant Professor(Ad hoc), IS & IR	SCTIMST

Brief summary of relevant research experience:
Have got intramural and extramural funding for few unique projects and are in the process of completion

Current project/s at hand: 1) Role of non-contrast and post contrast myocardial T1 mapping in hypertrophic and dilated cardiomyopathy-IEC approved no: SCT/ IEC/856/feb2016. 2) Three-dimensional printing in congenital heart disease- Jun2018-jun2021 in SERB, Govt of India. SCT/ IEC/1076/dec2017. 3) assessment of carotid plaque vulnerability using 3T MRI & correlation with carotid endarterectomy- TDF fund approved project, 2-year duration–October 2018-2020. SCT/ IEC/1239/aug2018.	
Signature:	Date: 27-6-19 Place: Thiruvananthapuram

Sasidharan	Bijulal	
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Academic Qualifications (Most recent qualification first)		
Degree/Certificate	Year	Institution, Country
DM Cardiology	2005	SCTIMST, India
MD General Medicine	2002	MG University, India

Details of professional registration : (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration TC MC Reg 26007. Year 1997		
Current and previous positions (most recent position first)		
Month and Year	Title	Institution/Company, Country
Dec 2018	Professor	SCTIMST, India
Dec 2014	Additional Professor	SCTIMST, India
Dec 2011	Associate professor	SCTIMST, India

Brief summary of relevant research experience:

Have been clinical PI in two major funded projects and CoPI in two other funded projects

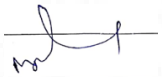
Current project/s at hand:

1. Development of nitinol based occlusion device for non-surgical closure of atrial septal defect.

Principal Investigator. Funding agency- TRC

2. Prospective, Single-arm, Multi-center, Observational Registry to further Validate Safety and Efficacy of the Ultimaster DES in Real-World Patients. Principal Investigator (site). Funding agency- Terumo India Ltd

3. My Val1- A prospective single arm, multicentric, open lable study of My Val TAVR system in the treatment of severe symptomatic native aortic valve stenosis –Co PI (site). Funding agency – Merill Life Sciences Pvt Ltd

Signature :  Date : 2/9/21

APPENDICES :

APPENDIX A - ETHICS COMMITTEE APPROVAL

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
तिरुवनन्तपुरम - ६९५०११, केरल, इंडिया
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM
Thiruvananthapuram - 695 011, Kerala, India
(An Institute of National Importance under Govt. of India)
Grams : Chitramet, Phone : +91-471-2443152, Fax : +91-471-2550728 / 2446433, E-mail : sct@sctimst.ac.in, Website : www.sctimst.ac.in

Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1807/JANUARY/2022 21.02.2022

Dr. Basavaraj N Biradar
Senior Resident
Department of Imaging Sciences and Interventional Radiology
SCTIMST, Thiruvananthapuram

Dear Dr. Basavaraj Biradar,

The Institutional Ethics Committee held on 29th January, 2022, reviewed and discussed your application to conduct the study titled "**TO ASSESS THICKNESS OF PERICORONARY ADIPOSE TISSUE AND PERICORONARY FAT ATTENUATION AS A PREDICTOR FOR SIGNIFICANT CORONARY ARTERY DISEASE** " (IEC/1807).

The following members of the Ethics Sub-committee were present at the meeting held on 29th January, 2022.

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
2.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
3.	Dr. Harikrishna Varma P. R	Ph.D (Materials Sciences)	Male	Medical Technology	Yes
4.	Dr. Manikandan.S	MBBS,MD,PDCC	Male	Clinician	Yes
5.	Dr. Ashalatha R	MBBS, MD,DM	Female	Clinician	Yes
6.	Dr. Biju Soman	MBBS,MD, DPH, MSc, DLSHTM	Male	Basic Medical Scientist	Yes
7.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

Page 1 of 2

The following documents were reviewed:

1. *Checklist Form*
2. *Covering letter addressed to the Chairperson, IEC, SCTIMST dated 31.12.2021*
3. *IEC Application Form*
4. *Project Proposal*
5. *Declaration form*
6. *CV of PI and Co-PIs*
7. *Proforma*
8. *SRC Recommendation*

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,

Dr. G. Srinivas
Member Secretary, IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES & TECHNOLOGY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST
THIRUVANANTHAPURAM

APPENDIX B -SUPPLEMENTARY TABLES:

TITLE OF STUDY: To assess pericoronary adipose tissue thickness and pericoronary fat attenuation as predictors for significant coronary artery disease	
1.1 Hospital ID -	
1.2 Age- Years	
1.3 Sex- Male /Female	
1.4 Date Of CT Coronary Angiography Study	
2.RISK FACTORS	
2.1 Diabetes mellitus	
2.2 Hypertension	
2.3 Hyperlipidemia	
2.4 Smoking	
2.5 Hypothyroidism	
2.6 Family h/o CAD	
3.SYMPTOMS	
3.1 Chest pain	
3.2 Dyspnoea	
3.3 Palpitation	
3.4 Syncope	
3.5 Edema	
5.CORONARY CT ANGIOGRAM 5.1 Calcium score 5.2 Coronary artery stenosis - Segment CADRADS 5.3 Vulnerable plaque characteristics 5.3a. Positive remodelling- 5.3b. Spotty calcification - 5.3c. Napkin ring sign- 5.3d. LAP 5.4 Pericoronary adipose tissue thickness - Segment	

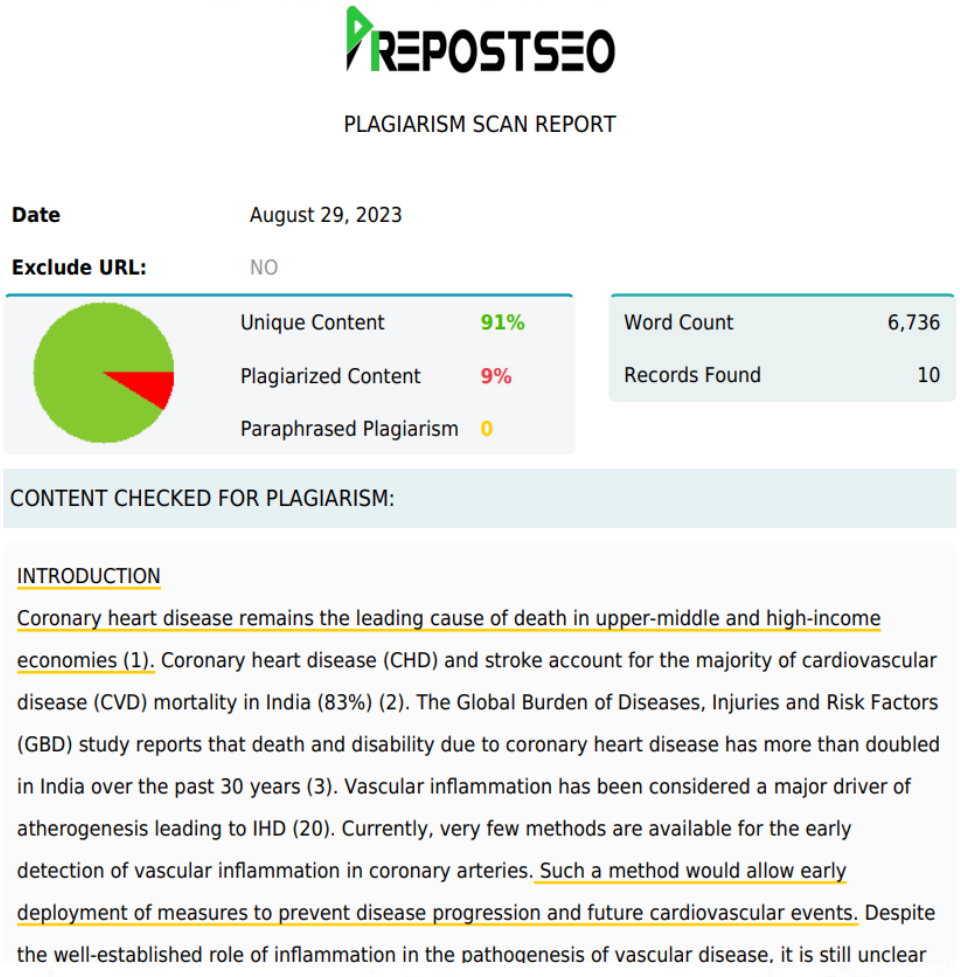
Thickness(mm) 5.5 Fat Attenuation Index - RCA LAD LCX	
6. Follow up-	
6.1. Duration	
6.2 ACS- UA	
STEMI	
NSTEMI	
6.3 Coronary revascularization	
6.4 Hospitalisation for heart failure	
6.5 Death - cause of death –	

APPENDIX - PUBLICATIONS

NIL

Appendix D :

Plagiarism check report



PLAGIARISM SCAN REPORT

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INTRODUCTION

Coronary heart disease remains the leading cause of death in upper-middle and high-income economies (1). Coronary heart disease (CHD) and stroke account for the majority of cardiovascular disease (CVD) mortality in India (83%) (2). The Global Burden of Diseases, Injuries and Risk Factors (GBD) study reports that death and disability due to coronary heart disease has more than doubled in India over the past 30 years (3). Vascular inflammation has been considered a major driver of atherogenesis leading to IHD (20). Currently, very few methods are available for the early detection of vascular inflammation in coronary arteries. Such a method would allow early deployment of measures to prevent disease progression and future cardiovascular events. Despite the well-established role of inflammation in the pathogenesis of vascular disease, it is still unclear