Dissertation on

"CYSTATIN C LEVELS IN CORONARY ARTERY DISEASE AND ITS CORRELATION WITH CORONARY ANGIOGRAM"

Submitted in Partial Fulfillment for the Degree of

M.D GENERAL MEDICINE

BRANCH –I

INSTITUTE OF INTERNAL MEDICINE

MADRAS MEDICAL COLLEGE

THE TAMIL NADU DR.MGR MEDICAL UNIVERSITY

CHENNAI-600 003

MAY - 2020

CERTIFICATE

This is to certify that the dissertation entitled "**CYSTATIN C LEVELS IN CORONARY ARTERY DISEASE AND ITS CORRELATION WITH CORONARY ANGIOGRAM**" is a bonafide original work done by **Dr.THENMOZHI.T**, in partial fulfillment of the requirements for M.D GENERAL MEDICINE BRANCH- I Examination of the Tamil Nadu Dr.MGR Medical University to be held in APRIL 2020, under my guidance and supervision in 2019

Prof. Dr. M. Anusuya, M.D.,
Guide and Research Supervisor
Institute of Internal Medicine
Madras Medical College
Rajiv Gandhi Govt. General Hospital
Chennai-600 003

Prof. Dr. S. Raghunanthanan,M.D.,
Director and Professor
Institute of Internal Medicine
Madras Medical College
Rajiv Gandhi Govt. General Hospital
Chennai-600 003

Prof.Dr.R.Jayanthi, M.D.,FRCP(Glasg)
DEAN
Madras Medical College &
Rajiv Gandhi Government General Hospital
Chennai-600 003

DECLARATION BY THE CANDIDATE

I **Dr.THENMOZHI. T**, **Registration Number:201711022** hereby solemnly declare that the dissertation entitled "**CYSTATIN C LEVELS IN CORONARY ARTERY DISEASE AND ITS CORRELATION WITH CORONARY ANGIOGRAM"** is done by me at the Institute of Internal Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai during 2019 under the guidance and supervision of **Prof. Dr. M. ANUSUYA M.D** .This dissertation is submitted to the Tamil Nadu Dr.MGR Medical University, Chennai towards the fulfillment of requirements for the award of M.D Degree in General Medicine (Branch -I)

Dr. THENMOZHI.T
Post Graduate Student
M.D. General Medicine
Place: Institute of Internal Medicine
Date: Madras Medical College, Chennai-600 003

ACKNOWLEDGEMENT

I express my heartful gratitude to the **Dean, Prof. Dr. R. JAYANTHI M.D., FRCP (Glasg)** Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai-3 for permitting me to do this Study.

I am very grateful to **Prof. Dr. M. ANUSUYA M.D.**, Professor of Medicine, Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai-3 who guided my work throughout the period of my study and for her constant support and encouragement.

I am very grateful to **Prof. Dr.G.PRATHAP KUMAR , M.D.,DNB D.M, FACC, CARDIOLOGY,** Senior Assistant Professor of Cardiology, Institute of Cardiology, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai-3 who guided my work throughout the period of my study and for his constant support for my thesis.

I am very much thankful for the help rendered by my Assistant Professors **Dr.P.Balamanikandan M.D., and Dr.Mohammed Hassan Maricar M.D.,** for their constant help and encouragement.

I am extremely thankful to all the members of the **Institutional Ethical Committee** for giving approval for my study

LIST OF ABBREVATIONS

CAD	-	coronary artery disease
CVD	-	cardiovascular disease
CKD	-	chronic kidney disease
MI	-	myocardial infarction
STEMI	-	ST elevation myocardial infarction
NSTE-ACS	-	non ST elevation acute coronary syndrome
NSTEMI	-	non ST elevation myocardial infarction
LBBB	-	left bundle branch block
PCI	-	percutaneous coronary intervention
CABG	-	coronary artery bypass graft
AWMI	-	anterior wall myocardial infarction
IWMI	-	inferior wall myocardial infarction
PWMI	-	posterior wall myocardial infarction
ALWMI	-	anterolateral wall myocardial infarction
PLWMI	-	posterolateral wall myocardial infarction
RHD	-	rheumatic heart disease
LDL	-	low density lipoprotein
HDL	-	high density lipoprotein
TGL	-	triglycerides
CK	-	creatinine kinase
TIMI	-	thrombolysis in myocardial infarction
UFH	-	unfractionated heparin
VEGF	-	vascular endothelial growth factor
TGF-B	-	transforming growth factor -beta
ADP	-	adenosine di -phosphate
HsTn	-	high sensitivity cardiac troponin
MRI	-	magnetic resonance imaging
NPO	-	nil per oral
ECG	-	electrocardiogram

CONTENTS

INTRODUCTION

Cardiovascular diseases are the leading cause of mortality and morbidity throughout the world. Its estimated to cause 17.9 million deaths throughout the world [1]. Of this, coronary artery disease accounts for 8 million deaths. Its common cause is atherosclerotic disease of the coronary arteries. Smoking, diabetes, hypertension, dyslipidemia are the major risk factors to develop coronary artery disease. Electrocardiogram, echocardiogram, cardiac biomarkers and coronary angiogram aid in diagnosis and management of coronary artery disease.

A number of markers are available to identify myocyte necrosis. A newer marker cystatin c is found to be associated with coronary artery disease and also predicting the severity of the disease in patients with normal renal function. This study aims to analyse serum cysatin c levels in coronary artery disease patients and its correlation with coronary angiogram.

AIMS AND OBJECTIVES

To analyse cystatin C levels in unstable angina ,STEMI and NSTEMI patients and its coronary angiographic correlation

SECONDARY OBJECTIVES

1. In STEMI/NSTEMI patients , to analyse if cystatin C levels correlate with the severity of the disease
2. In unstable angina patients ,to analyse if cystatin levels can help in early risk stratification, which in turn aid in early intervention
3. To analyse if cystatin C can be used as a cardiac biomarker.

REVIEW OF LITERATURE

EPIDEMIOLOGY

The increasing incidence of cardiovascular diseases is due to the epidemiologic transition. There are four stages in epidemiologic transition [2]. First is Pestilence and famine stage. Infections like tuberculosis, typhoid and cholera are the major cause of death in these countries. Second stage is Receding pandemics where mortality due to infections is declining and major cardiovascular deaths are attributable to rheumatic heart disease. Third stage is Degenerative and manmade diseases where the predominant cardiovascular disease type is coronary heart disease and stroke. Delayed and degenerative disease stage is the fourth stage in which CAD, stroke and congestive heart failure are the predominant CVD types [3]. Recently, age of inactivity and obesity related diseases is on the rise. Most of the developed countries are in the fourth stage while the developing countries are in second and third stages.

In India, coronary heart disease is becoming the predominant form of cardiovascular disease [4]. This is attributable to the changing life style patterns where physical inactivity is increasing along with increasing intake of total calories from animal fat. Due to these factors, cardiovascular diseases especially coronary artery disease incidence is increasing in India.

RISK FACTORS

SMOKING-

Smoking is said to cause 32% of coronary artery disease deaths globally. It's an avoidable cause of cardiovascular disease. Passive smoking is also a risk factor [5]. It is related to myocardial infarction, strokes, recurrent MI, aortic aneurysm, peripheral vascular diseases and sudden cardiac death[6]. It accelerates atherosclerotic disease by causing endothelial dysfunction. Smoking cessation reduces the risk of an adverse coronary event by 50 % in the first two years of quitting. The risk is similar to non smokers after 3-5 years of quitting.

HYPERTENSION-

Until 45 years of age, higher percentage of hypertension is in men. Between 45 and 64, both sexes have similar percentage. Beyond 65 years of age women have higher percentage of hypertension. Both systolic and diastolic blood pressure carries similar risk for cardiovascular mortality. Pulse pressure is also a predictor of cardiovascular events. Ambulatory BP monitoring is better predictor. Magnitude of BP reduction is important in reducing cardiovascular risk than choice of drugs [7].

DYSLIPIDEMIA -

LOW DENSITY LIPOPROTEIN CHOLESTEROL (LDL)-

High LDL levels is an independent risk factor of acute coronary events .Familial hypercholesterolemia lead to accelerated atherosclerosis and cardiovascular events early in life. Genetic mutations affecting LDL metabolism like PCSK9-propertin convertase subtilisin/kexin type9 result in lifelong reduction in LDL cholesterol levels and reduced risk. Statin therapy is used for reducing LDL levels .Its found that for every1 mmol/L reduction in LDL levels there is 22% reduction decrease in CAD risk. Recently monoclonal antibodies inhibiting PCSK9 binding is developed, which prolong the t1/2 of LDL receptors and thereby minimizing the LDL levels.[8]

HIGH DENSITY LIPOPROTEIN CHOLESTEROL (HDL)-

There is an inverse relationship between HDL levels and cardiovascular risk. Its found to have a protective role in atherosclerosis. However raising HDL cholesterol levels have shown no beneficial effects in reducing the coronary events.

TRIGLYCERIDES-

Increased triglyceride levels are associated with increased cardiovascular risk. Weight reduction, exercise,dietary control have beneficial effect in reducing triglycerides level. Omega 3 fatty acid is FDA approved drug for hypertriglyceridemia.

DIABETES:

Diabetes related cardiovascular risk develops even before hyperglycemia is established. The risk of cardiovascular death is twofold in diabetic men and fourfold in diabetic women compared to non diabetics. Silent ischemia and atypical presentations are very common in diabetic patients [9].

DIET:

Low intake of fruits, vegetables,nuts, omega 3 fatty acids are associated with increased CAD risk. Processed red meat is associated with high risk of cardiovascular disease [10].

CORONARY ARTERY DISEASE

CAD includes acute coronary syndrome ,sudden cardiac death ,recurrent myocardial infarction, congestive cardiac failure, etc. Acute coronary syndrome includes – ST segment elevation myocardial infarction (STEMI) , non ST elevation myocardial infarction (NSTEMI) and unstable angina[11]. One of the following criteria must be present in the appropriate clinical setting to diagnose myocardial infarction [12].

- Increase or decrease in the cardiac biomarker along with,
    1. Ischemic symptoms
    2. ECG changes
    3. New pathologic Q waves
    4. Echocardiogram showing regional wall motion abnormality

- Sudden cardiac death with ECG changes or coronary thrombus found at autopsy before rise in cardiac biomarkers could be detected.
- PCI associated MI if biomarker level rises 5 times > the 99 th percentile upper reference limit
- Coronary artery bypass graft (CABG) related MI
- Histopathological proof of MI

GLOBAL TASK FORCE CLINICAL CLASSIFICATION OF MYOCARDIAL INFARCTION

- TYPE 1 MI- due to plaque rupture
- TYPE2 MI- secondary to ischemia .eg. anemia, coronary artery spasm
- TYPE 3 MI- in setting of sudden cardiac arrest
- TYPE4 MI-PCI associated MI
- TYPE5 MI-CABG associated MI

ST SEGMENT ELEVATION MYOCARDIAL INFARCTION (STEMI)

Abrupt complete thrombotic occlusion of a coronary artery in a previously atherosclerosed vessel produces STEMI[13].

PATHOPHYSIOLOGY-

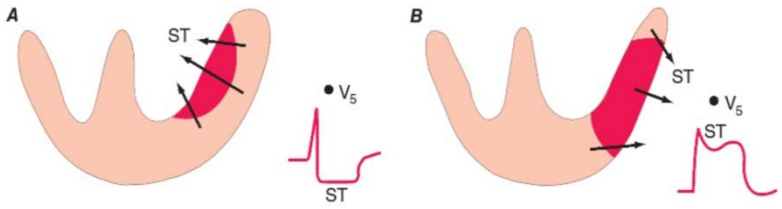
STEMI occurs when a mural thrombus rapidly develops at the site of vascular injury. This injury can be precipitated by factors like smoking, dyslipidemia, stress, etc. Disruption of an atherosclerotic plaque exposes its contents to the blood favouring thrombogenesis completely occluding the coronary artery. Atherosclerotic plaques with rich lipid core and thin fibrous

cap are prone for disruption [14]. After an injury, a monolayer of platelet is formed at the disruption site followed by platelet activation. Following this, thromboxane A2 is released further activatating platelets. This results in conformational change in glycoprotein 11b/111a receptor with high affinity for fibrinogen. Fibrinogen produces platelet cross linking. Further, activation of coagulation cascade produces thrombin resulting in complete occlusion of coronary artery [15].

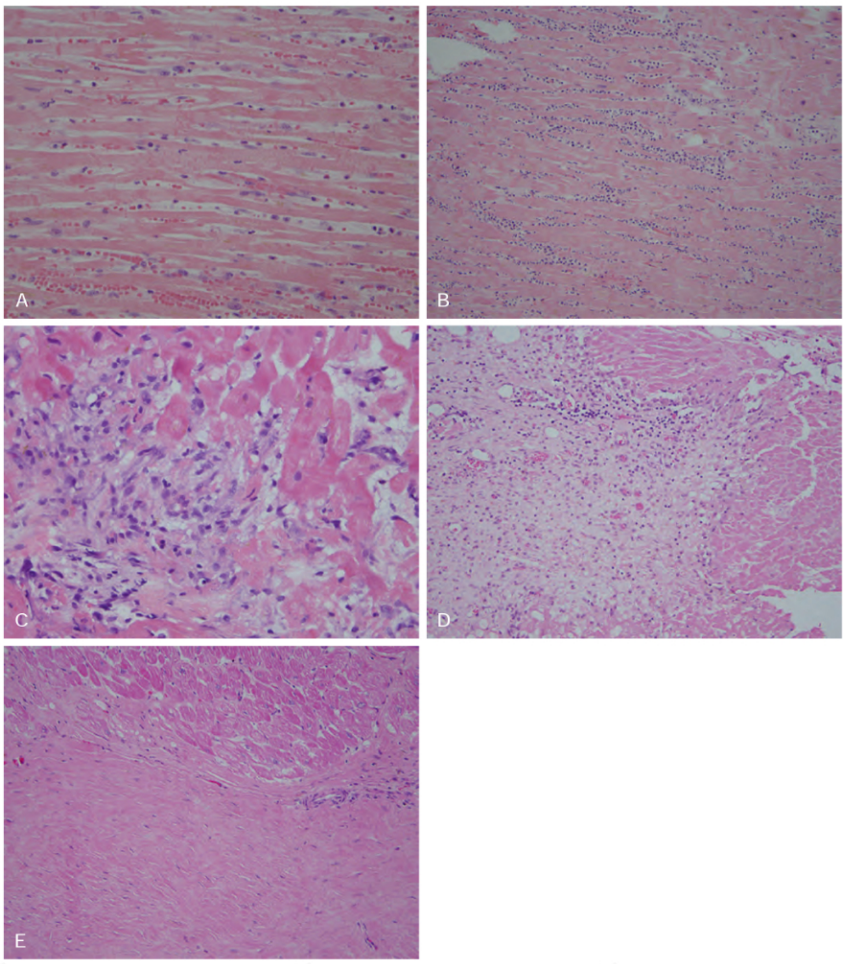
HEART MUSCLE-

The cellular effects of myocardial ischemia can be seen within seconds of hypoxia. Irreversible injury occurs in 20 minutes and complete within 6 hours if not timely reperfused. [16]

Grossly myocardial infarction is 2 types – transmural infarct and subendocardial infarct. In Transmural infarct, full thickness of the ventricular wall is necrosed whereas in subendocardial infarct only the subendocardium or intramural myocardium or both but never upto epicardium. However these gross changes identified only after at least 6 hours when necrosis has occurred.[17]



Histologic changes can be seen in 2-3 hours. Within hours of death , slices of myocardium immersed in triphenyl tetrazolium chloride stains the non infarcted myocardium brickred and the infarcted area unstained. Within 20 minutes of coronary artery occlusion there will be a reduction in the glycogen granules, cellular swelling and distortion of sarcoplasmic reticulum. These changes are reversible if timely reperfused. If not,disruption of mitochondria occurs with amorphous aggregation and margination of nuclear chromatin and myofibril relaxation occurs which are all irreversible changes[18][19].



PATTERNS OF MYOCARDIAL NECROSIS

Coagulation necrosis occurs in the centre of an infarct following ischemia. There will be stretched myofibrils, with pyknotic nuclei and phagocytosed myocardial cells. Mitochondrial damage with flocculent amorphous densities without calcification is seen.

Contraction band necrosis occurs following establishment of reflow . The myofibrils are hypercontracted with contraction bands. mitochondrial damage with calcification is seen mostly in non transmural infarcts[20].

Myocytolysis is myocyte vacuolization following prolonged ischemia without necrosis and its potentially reversible.

Myocardial cells undergoing apoptosis show shrinkage, DNA fragmentation and phagocytosis without inflammatory infiltrates. Its seen in the stage of ventricular remodeling[21] .

CURRENT CONCEPTS OF CELLULAR EVENTS

Day 1 to day 3 after occlusion of coronary artery is called the first wave. monocytes ,so called the demolition crew , will be present and releases proinflammatory cytokines[22][23]. On Day 3 to Day 7, “repair” monocytes producing vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-B)predominates, leading to scar formation and ventricular remodeling[24][25].

NON –ST Elevation ACUTE CORONARY SYNDROMES

It includes Non ST elevation Myocardial Infarction (NSTEMI) and unstable angina. NSTEMI present with typical symptoms and without persistent ST elevation in 2 contiguous leads with elevated cardiac biomarkers more than 99 percentile of normal. Unstable angina patients present with typical or atypical symptoms with negative biomarkers[26].

Its pathogenesis involves any of the following process.

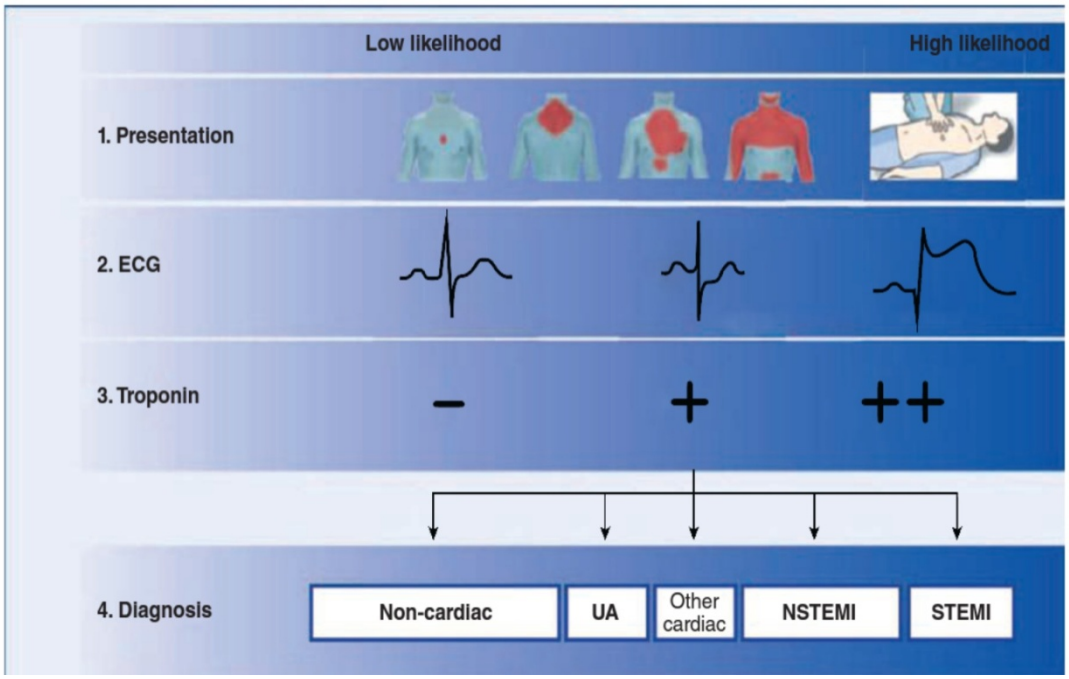
- Disruption of an atheromatous plaque
- Vasoconstriction
- Intraluminal narrowing of coronary artery.
- Imbalance in oxygen demand and supply.

CLINICAL MANIFESTATION

Triggers like heavy exercise, acute illness,emotional stress can precipitate STEMI. Many cases are reported in the early morning hours [27]. Pain is the most common symptom and described as crushing and constricting type of pain lasting for >30 minutes. Pain radiates retrosternally and to the ulnar aspect of left arm mostly. Sometimes pain maybe in the epigastric region leading. It arises from the injured nerve endings and not the necrosed myocardium. Thus pain means ischemia and not infarction and needs immediate reperfusion of the occluded vessel. Once blood flow is restored, pain disappears [28]. Other symptoms include diaphoresis, palpitations

,giddiness ,nausea ,vomiting etc. atypical presentations are seen in diabetics and women[29].

Physical findings include tachycardia and hypertension / hypotension. S3 , S4 may be heard, soft S1 and paradoxical S2 split. A midsystolic or late systolic murmur might be heard in mitral area. Pericardial friction rub can be heard in transmural MI.



LABORATORY INVESTIGATIONS

There are 3 temporal phases of STEMI .

- Acute - few hours to 7 days
- Healing -7 to 28 days
- Healed - >=29 days

ELECTROCARDIOGRAPHY-

It's the most easily available and an important diagnostic test in evaluation of myocardial infarction. A person coming with chest pain must have an ECG interpreted in 10 minutes because STEMI needs immediate reperfusion therapy. It helps in early identification of the types of acute coronary syndromes[30].

ECG manifestations in Acute Myocardial Infarction(absence of LBBB)

STEMI-

New ST elevation at the J point in 2 contiguous leads

- More than or equal to 0.1 mV in leads excluding V2 and V 3
- In leads V2 and V3 ,
    - >= 0.2 mV >= 40 year men
    - >=0.25 mV <40 years men
    - >=0.15 mV in women

NSTEMI and UNSTABLE ANGINA-

- Two contiguous leads with new ST depression >= 0.05 mV
- Two contiguous leads with T inversion >=0.1mV with a prominent R wave / R/S ratio>1

ECG manifestations in Acute Myocardial Infarction with LBBB

- ST elevation >= 1 mm & concordant with QRS -5 points
- ST downslope >=1mm in V1 ,V2 / V 3- 3 points

- ST elevation >=5 mm discordant with QRS – 2 points

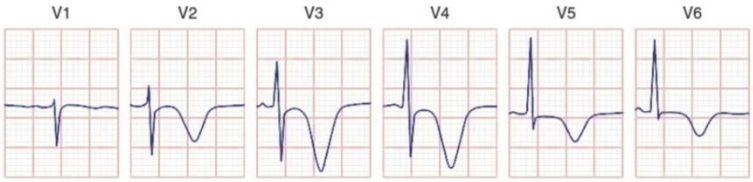
A score of 3 or more is in favour of Acute myocardial infarction

ECG changes associated with previous myocardial infarction (absence of LBBB & LVH)

- Any Q in V 2 ,V3 >= 0.02 seconds or a QS in V2 ,V3
- Leads 1, 11 , aVL, aVF - QS complex or in V4 –V6 any 2 contiguous leads (1, Avl; V1-V6; 11,111, aVF) or Q wave >=0.03 second and >= 0.1 mV
- V1 , V2 - R wave >= 0.04 seconds & R/S >=1 ,concordant T wave without conduction defects.

ECG CHANGES IN NON ST Elevation ACUTE CORONARY SYNDROME

ST depression and T wave inversions are the abnormalities in NSTE-ACS. Comparison of the current ECG with previous ECG is necessary to find ST depressions as little as 0.05 mV. Transient ST elevation is suggestive of unstable angina . A completely normal ECG in a patient with chest discomfort does not rule out acute coronary syndrome [31]. The patient can have ischemia in a area not well represented in 12 lead ECG. Thus serial ECG must be done once in every 30 minutes until pain is relieved or MI is diagnosed. In ischemia involving acute marginal branch of right coronary artery or left circumflex artery, ECG will be non diagnostic. Coronary angiography finds out such culprit vessel.



LOCALISATION OF SITE OF MYOCARDIAL INFARCTION FROM ECG

Anterior wall myocardial infarction can be identified by ST –T changes in the precordial leads V1-V6. Lateral wall ischemia seen in leads V5,V6,1,aVL. Inferior wall ischemic changes seen in leads 11,111 and aVF. Posterior wall ischemia can be identified with the reciprocal ST depressions in lead V1 - V3. Right ventricular myocardial infarction identified with ST –T changes in right sided chest leads –V1 , aVR

Deep T wave inversions in multiple precordial leads might be suggestive of severe left anterior descending coronary artery obstruction . Necrosis of the myocardial tissue produces decreased R wave amplitude or abnormal Q waves.

ECHOCARDIOGRAPHY

It uses high frequency ultrasound waves penetrating the body but reflecting only from relevant structures to generate an image. Earlier M mode echocardiogram was used with only a one ultrasound beam. Modern echocardiograms uses phased array transducers emitting ultrasound waves in sequence which are reflected and sensed by receiving elements. Then image is generated by scan converter. Recently stress echocardiogram assess cardiac function during exercise . Whenever electrocardiogram is non diagnostic ,

echocardiogram can identify regional wall motion abnormalities . It also assess the left ventricular function following a MI. Acute dangerous complications of myocardial infarction like mitral regurgitation ,ventricular wall ruptures can be detected early[32] .

RADIONUCLEOTIDE IMAGING:

Radio nucleotide imaging studies are also used for evaluation of patients with coronary artery disease , both for diagnosis and prognostication. High resolution cardiac MRI detects myocardial infarction by late enhancement technique. MRI after gadolinium administration shows bright areas of infarction in between dark areas of normal myocardium[33]. Myocardial perfusion imaging studies with thallium and technetium can detect a transmural infarct but it cannot differentiate acute infarct from chronic one.

CORONARY ANGIOGRAPHY

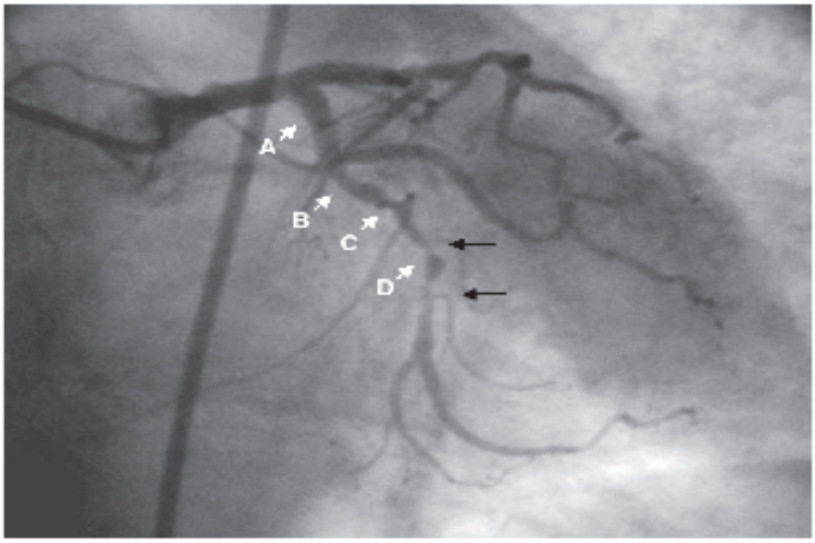
It's the standard invasive imaging technique to view the lumen of the coronary arteries. There are 3 major coronary arteries- right coronary artery , left anterior descending and left circumflex artery. 85 % individuals have right dominant system, ie- right coronary artery is the origin of atrioventricular nodal branch .5% people have left dominant system normally ie, these branches arise from the left coronary artery. 10% population will have codominant system [34].

Coronary angiogram showing luminal narrowings is expressed as percent stenosis by comparing the diseased segment with proximal normal

segment. A stenosis of more than 50% is significant . Its utmost usefulness is in NSTE-ACS. Its found that 85% of NSTE-ACS patients had more than 50 % stenosis of the major coronary arteries. 20% had single vessel disease , 20 % had double vessel disease and 35% had triple vessel disease. Angiographic picture of disrupted atherosclerotic plaque shows eccentric stenosis, overhanging edges and a narrow neck and a thrombus in coronaries might look like a hazy polypoidal intraluminal mass .

Indications for coronary angiography

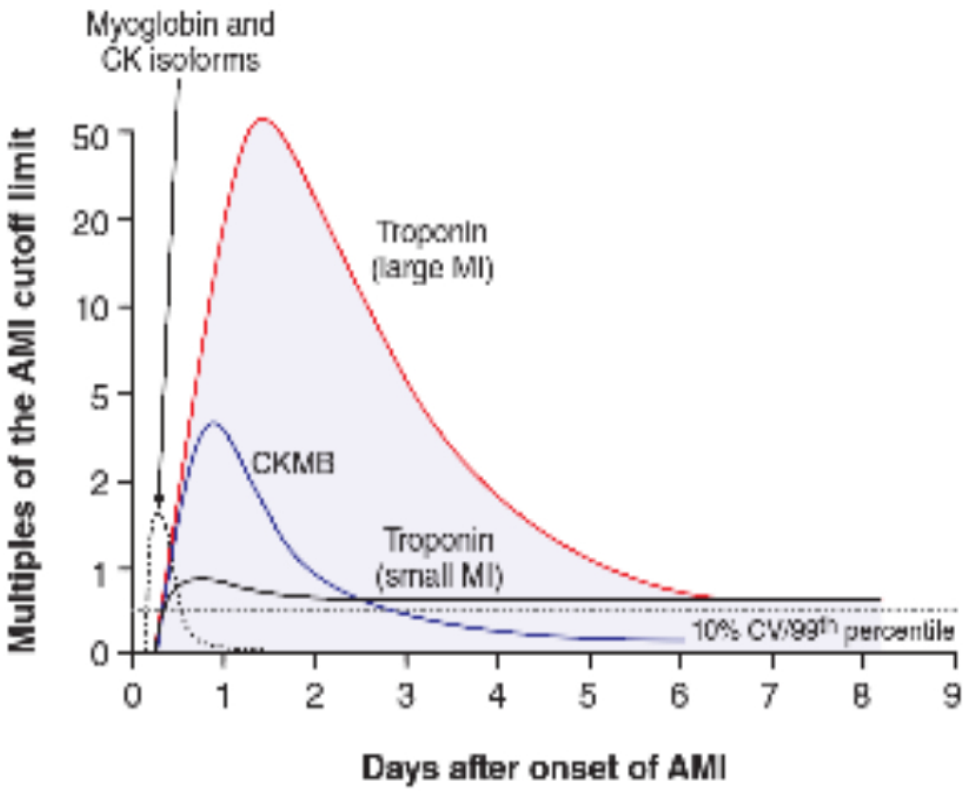
- Chest pain of unknown etiology and equivocal non invasive test results.
- Acute coronary syndrome
- Stable angina class 11,111,1V on conservative treatment
- Following primary PCI in STEMI patient to assess the reperfusion
- If a STEMI patient is having persistent / recurrent ischemia
- STEMI patient with pulmonary edema /reduced ejection fraction, cardiogenic shock, for risk stratification



CARDIAC BIOMARKERS

Injured myocardial cells release proteins. Myocardial cell injury can occur in many conditions other than myocardial infarction like myocarditis due to infections, toxins,etc. Also initiation of treatment for a MI patient should not be delayed awaiting the cardiac biomarker results. A rapid clinical judgement and ECG is sufficient to start treatment.

The integrity of sarcolemmal membrane is disrupted after necrosis. The intracellular macromolecules leak into the cardiac interstitium and then into the lymphatics around the infarct. The rate of appearance of these proteins in the peripheral blood depends on their intracellular location, molecular weight, local blood and lymphatic supply and their rate of elimination .



CARDIAC SPECIFIC TROPONINS

It mediates the contractile process of cardiac striated muscle. It has 3 subunits- troponin C, troponin I ,troponin T. Troponin C binds to calcium ions . Troponin I binds to actin and inhibits the actin myosin interactions. Troponin I is found in the cytoplasm also. Troponin T binds to tropomyosin. Some of the TnT is dissolved in cytoplasm. Following myocardial cell injury, cytosolic troponin T and troponin I are first released . Different genes code for cardiac and skeletal troponin T and troponin I. Thus cardiac troponin specific antibodies enable their detection. Any rise or fall in the cTnT or c TnI,in appropriate clinical setting aids in the diagnosis of myocardial infarction.

Conventional assays detect cardiac specific troponins cTnT and cTnI in 3 hours after onset of chest discomfort. Troponin I remain elevated for 7 to 10 days while cardiac specific troponin T remains elevated for upto 14 days. Thus they help in diagnosing patients with late presentation. They are also released following successful recanalisation [35] .

HIGH SENSITIVITY CARDIAC TROPONIN hsTn

Assays detecting cardiac troponin in more than 50% of apparently healthy people is called high sensitivity cardiac troponin. it has greater sensitivity but diminished specificity for myocardial infarction as it detects myocardial injury in settings other than myocardial infarction. These high sensitive troponin assays detect troponin release earlier than previous generation assays thus improving the diagnostic accuracy [36]. hsTn assays help distinguishing acute myocardial infarction from underlying structural cardiac disease[37]. Such “delta” criteria help improve the specificity of this test[38] . Its possible to classify patients with suspected acute coronary syndrome as “very low risk for myocardial infarction or death in next 30 days if hsTn value is <= 5 ng/L(negative predictive value NPV,99.6%). hsTn levels more than 9.2 ng/L favour acute coronary syndrome[39].

CREATINE KINASE MB ISOENZYME

Creatine kinase has two isoforms CK-MM and CKMB. CK MM isoform is present in all skeletal muscles. CK-MB isoform is mostly concentrated in cardiac tissue and is considered more cardiac specific than CK-

MM. Thus a relative ratio of CK-MB mass to CK activity calculated and a value >= 2.5 is suggestive of but not diagnostic of myocardial injury. It rises within 4-8 hours of insult and normalizes in 2 -3 days. An advantage of using CK MB as cardiac biomarker is its short t1/2. This helps in estimating the timing of myocardial infarction(eg. Normal CK-MB and elevated troponin suggest an myocardial infarction that occurred several days ago) and also in diagnosing reinfarction in a patient with myocardial infarction recently like in last week.

OTHER CARDIAC BIOMARKERS

Copeptin is found to be secreted by the pituitary gland at the earliest in MI. It's the C- terminal part of vasopressin prohormone [40]. In CHOPIN study, sensitive troponin and negative copeptin within 6 hours of onset of symptoms had a negative predictive value of 99.2%. However another study showed no benefit in NPV for myocardial infarction with one hour copeptin test with hsTn assay.

Inflammatory biomarkers are increased during episodes of acute coronary syndrome [41].

B type natriuretic peptide levels provide information regarding the ventricular wall stress. The magnitude of their rise in myocardial ischemia is related to the prognosis [42][43] .

Following are new novel biomarkers in acute coronary syndrome :

Markers Predicting Death & Or Ischemia:-

- Chemokine ligand-5 & ligand 8 = mediate monocyte recruitment following ischemia.
- Interleukin -6 =stimulates synthesis of C-reactive protein
- Interleukin -17 = it has a role in vulnerable plaque development
- Secretory phospholipase A2= favours atherosclerosis by hydrolyzing phospholipids to lysophospholipids and fatty acids
- Pregnancy- associated plasma protein A= it's a zinc binding metaloproteinase destabilizing the vulnerable plaques
- Pentraxin 3= associated with thin caps in the vulnerable plaques
- Placental growth factor=it's a primary inflammatory instigator of instability in an atherosclerotic plaque
- Hearty –type fatty acid –binding protein=its involved in the fatty acid metabolism in the myocardium
- Growth differentiation factor 15= It belongs to the transforming growth factor beta family
- Myeloperoxidase - released during monocyte degranulation
- Membrane attack complex

MARKERS PREDICTING HEART FAILURE

- Osteoprotegerin
- Mid regional proadrenomedullin
- Mid regional proatrial natriuretic peptide
- Neopterin
- Copeptin

CYSTATIN C – A POTENTIAL MARKER OF CAD

Cystatin is a lysosomal proteinase inhibitor and cysteine protease inhibitor [44]. Its present in all tissues and body fluids. Recently its role in predicting onset and severity of cardiovascular disease is being studied. Its an established biomarker of kidney function.

A study has been done to evaluate the role of serum cystatin C in asymptomatic coronary artery disease with metabolic syndrome with normal renal function. The result of the study showed that serum cysytatin C has significant association with CAD [45].

Another study done in Indian patients , revealed higher plasma cystatin C levels are associated with severe CAD, proved angiographically , even in patients with normal renal function[46]. Also found that serum cystatin C can be used as a marker to predict the severity of atherosclerosis in suspected CAD patients[47].

MANAGEMENT OF ACUTE CORONARY SYNDROME

PRE HOSPITAL CARE

Educating the public regarding seeking early medical attention for chest discomfort is of utmost importance [48]. Prehospital care includes

- ✓ Early , prompt seeking of medical attention
- ✓ Emergency medical team
- ✓ Quick transport of the patient to a hospital
- ✓ Early initiation of treatment

MANAGEMENT IN THE EMERGENCY DEPARTMENT

- Control of chest pain
- Triaging and identification of high risk patients needing urgent reperfusion .

The overall goal is initiation of percutaneous coronary intervention within 90 minutes of first medical contact[49][50].

Aspirin , a cyclooxygenase 1 inhibitor in platelets ,at dose of 160-325 mg should be administered in emergency department.

Airway, breathing and circulation must be secured.

CONTROL OF DISCOMFORT

Sublingual nitroglycerin upto 3 doses of 0.4 mg given reduces the chest discomfort, by both decreasing the myocardial oxygen demand and increasing the oxygen supply. It should be avoided in patients with hypotension.

Morphine at repetitive small doses of 2 -4 mg is an effective analgesic

Oral beta blocker therapy must be initiated in the first 24 hours in patients without any of the following:

- Heart failure
- Low cardiac output
- Cardiogenic shock
- Contraindications to beta blockers.

MANAGEMENT STRATEGIES

Reperfusion therapy planned when ST segment elevation of 2mm in two contiguous precordial leads and 1mm in limb leads is present. It can be done with primary percutaneous coronary intervention or fibrinolysis. Main aim is timely restoration of coronary perfusion . Though 1/3 STEMI patients undergo spontaneous reperfusion, therapy accelerates the opening of the occluded vessel.

PRIMARY PERCUTANEOUS CORONARY INTERVENTION

PCI with angioplasty / stenting without prior fibrinolysis is called primary PCI. Its preferred when diagnosis is in doubt, cardiogenic shock, bleeding risk ,mature clot and when the patient has contraindication for fibrinolysis therapy [51].

FIBRINOLYSIS

In the absence of contraindication, fibrinolysis must be initiated within 30 minutes of presentation.[52] Its done with tissue plasminogen activator,

streptokinase, tenecteplase and reteplase. It augments the conversion of plasminogen to plasmin which lyses the fibrin thrombi. The main goal is to achieve TIMI grade 3 coronary flow. Tenecteplase and reteplase are bolus fibrinolytics[53]. Contraindications to fibrinolysis treatment is hemorrhagic cerebrovascular accident anytime in the past, a non hemorrhagic stroke within the past one year , marked hypertension SBP >=180 mm/hg and DBP >= 110 mm/hg, aortic dissection suspect and any active internal bleeding.

INTEGRATED REPERFUSION STRATEGY

Coronary angiogram done following fibrinolysis and if there is evidence of either

- Failure of perfusion –a rescue PCI must be done or
- Reocclusion of coronary artery , urgent PCI must be done

HOSPITAL PHASE MANAGEMENT

- Adequately equipped coronary care units with defibrillator
- Physical activity – bed rest -first 6-12 hours, upright posture within 24 hours, in the absence of complications ambulate within their room in day 2, by day 3 ambulation upto 185 m, atleast 3 times/day.
- Diet –first 4-12 hours, either NPO or liquids only, <= 30% fat and cholesterol <=300 mg/day and 50-55% carbohydrates.
- Bowel management – stool softeners like dioctyl sodium sulfosuccinate
- Sedation with diazepam, lorazepam and oxazepam.

PHARMACOTHERAPY

ANTITHROMBOTIC AGENTS

Aspirin, a cyclooxygenase 1 inhibitor is the standard antiplatelet .

P2Y12 ADP inhibitors –clopidogrel, prasugrel, ticagrelor. They along with aspirin prevent the complication [54].

Unfractionated heparin is the standard anticoagulant in use ,at loading dose of 60 U/kg followed by maintenance dose of 12 U/kg/hr infusion.

Alternatives to UFH are low molecular weight heparin, fondaparinux, direct thrombin inhibitor bivalirudin[55].

BETABLOCKERS

RENIN ANGIOTENSIN ALDOSTERONE SYSTEM INHIBITORS

COMPLICATIONS OF ACUTE CORONARY SYNDROME

- Ventricular dysfunction
- Congestive cardiac failure
- Cardiogenic shock
- Arrhythmias
- Pericarditis
- Thromboembolism
- Left ventricular aneurysm

MATERIALS AND METHODS

STUDY DESIGN -

Prospective cohort study

SOURCE OF DATA –

Patients who were diagnosed as acute coronary syndrome and coronary artery disease at Rajiv Gandhi Government General Hospital, Chennai and who underwent coronary angiogram during their course of treatment , were included in this study ,provided they fulfilled the inclusion and exclusion criteria.

SAMPLE SIZE –

Total number of CAD patients- 50

Control -10 non coronary artery disease patients undergoing coronary angiogram.

STUDY DURATION- 1 year (June 2018 to May 2019)

INCLUSION CRITERIA

- ✓ Age - >18 years
- ✓ Renal function tests - normal
- ✓ Clinical features -chest pain, discomfort at rest ,with exertion , palpitations ,sweating ,radiating pain
- ✓ ECG changes - ST elevation, ST depression , T wave inversion , LBBB
- ✓ Echocardiographic features suggestive of acute coronary syndrome

EXCLUSION CRITERIA

- Not satisfying the inclusion criteria
- Lack of written informed consent
- Patient refusal
- K/C/O chronic kidney disease
- K/C/O heart failure/ liver failure
- Major surgery, trauma in the previous month

METHODOLOGY

Patients aged more than 18 years ,presenting with complaints of chest pain , associated with sweating ,palpitatins, radiation of pain to left arm , dyspnoea were first taken a 12 Lead ECG . If the ECG showed

New ST elevations at J point in two contiguous leads along with following cut off

- >=0.1mV in all the leads except V2 & V3
- V2 & v3 showing ,
  - In male >= 40 yrs ,>=0.2 mV
  - In male <40 yrs, >= 0.25 mV
  - In female ,>=0.15 mV

Or new ST depression >= 0.05 mV in two contiguous leads or T wave inversion of more than or equal to 0.1 mV in two contiguous leads with R/S >1 or prominent R wave or new onset left bundle branch block.

A diagnosis of acute coronary syndrome was made and echocardiogram was done to detect any regional wall motion abnormalities consistent with myocardial ischemia and infarction. Cardiac specific troponin T was tested by rapid card method in these patients. Later their renal function tests done . Those patients whose renal function tests were normal and satisfying the inclusion criteria , were included in the study. After obtaining their consent , 4 ml venous blood was drawn from them and tested for serum Cystatin C levels.

They were also simultaneously tested for serum lipid levels , serum CK and serum CK-MB levels. Then they underwent treatment with either percutaneous coronary intervention, fibrinolysis ,anticoagulation and/or pharmacotherapy. Later coronary angiography was performed in these patients.

As control , 10 non CAD patients like RHD patients with valvuar leshions , congenital heart disease patients planned for surgery were tested for serum cystatin C levels before being subjected to pre operative coronary angiogram.

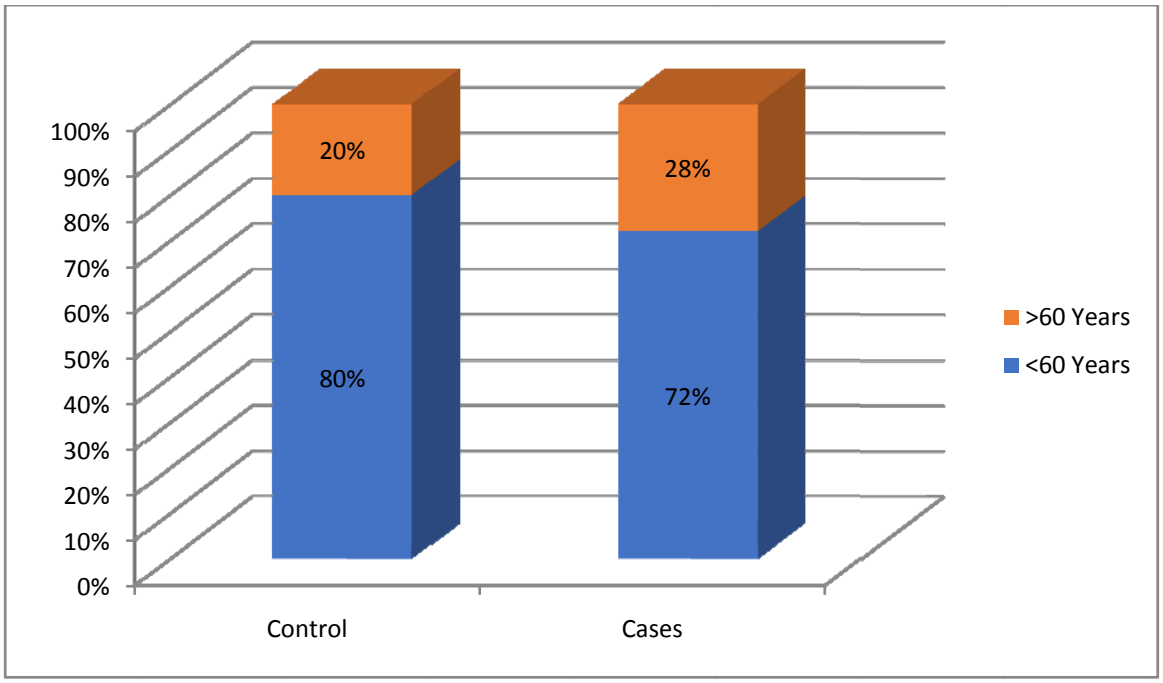
The serum cystatin C level in these patients and their coronary angiographic reports were analysed.

OBSERVATION AND RESULTS

TABLE 1: AGE DISTRIBUTION

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
AGE GROUP	<60 Years	Count	14	22	36
		% within CYSTATIN_GROUP	58.3%	84.6%	72.0%
	>=60 Years	Count	10	4	14
		% within CYSTATIN_GROUP	41.7%	15.4%	28.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=0.273 P=0.602



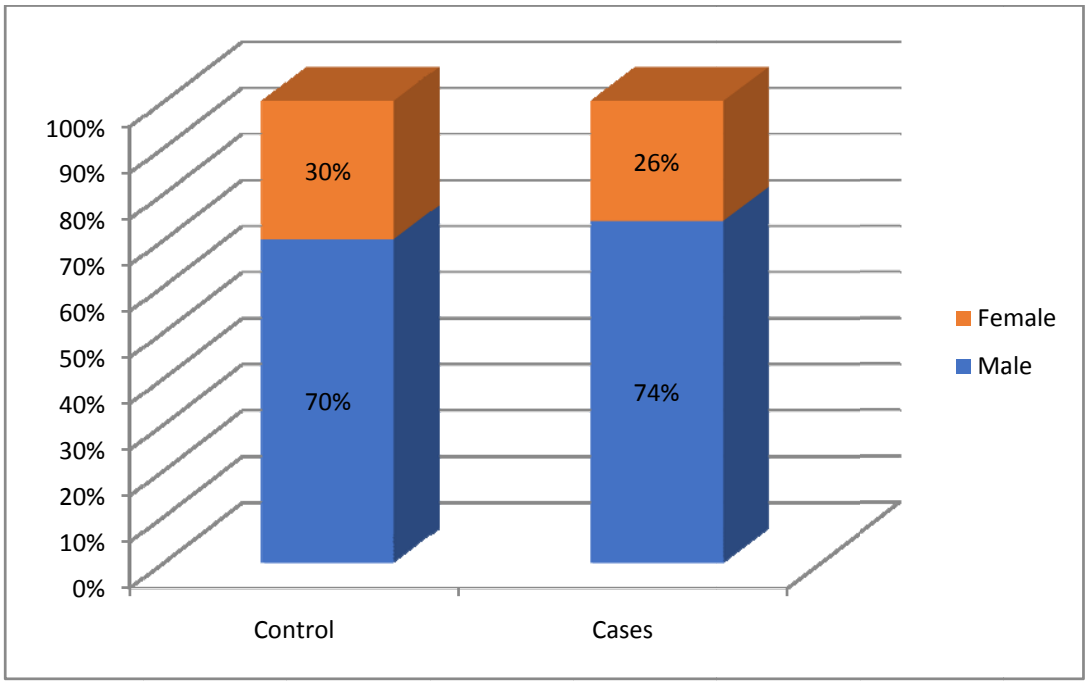
Among the CAD cases, 72% of them were <= 60 years of age & 28% more than 60 years of age

Among the control,80 % of them were <= 60 years of age & 20 % were more than 60 years of age

TABLE 2: SEX DISTRIBUTION

			group		Total
			Control	Cases	
sex	Male	Count	7	37	44
		% within group	70.0%	74.0%	73.3%
	Female	Count	3	13	16
		% within group	30.0%	26.0%	26.7%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=0.068 P=0.794



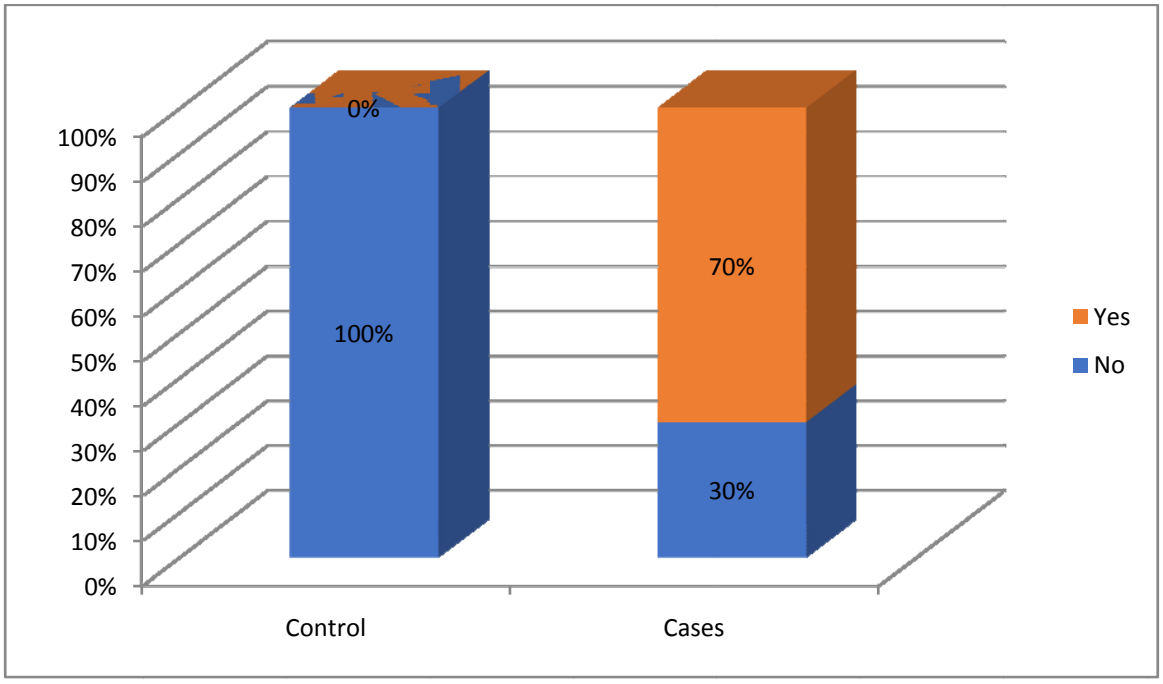
Among the CAD cases, 74% were male and 26% were female

Among the control, 70 % were male & 30 % were female

TABLE 3:STEMI DISTRIBUTION

		group		Total
		Control	Cases	
stemi	No Count	10	15	25
	No % within group	100.0%	30.0%	41.7%
	Yes Count	0	35	35
	Yes % within group	0.0%	70.0%	58.3%
Total	Count	10	50	60
	% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=16.8* P=0.001



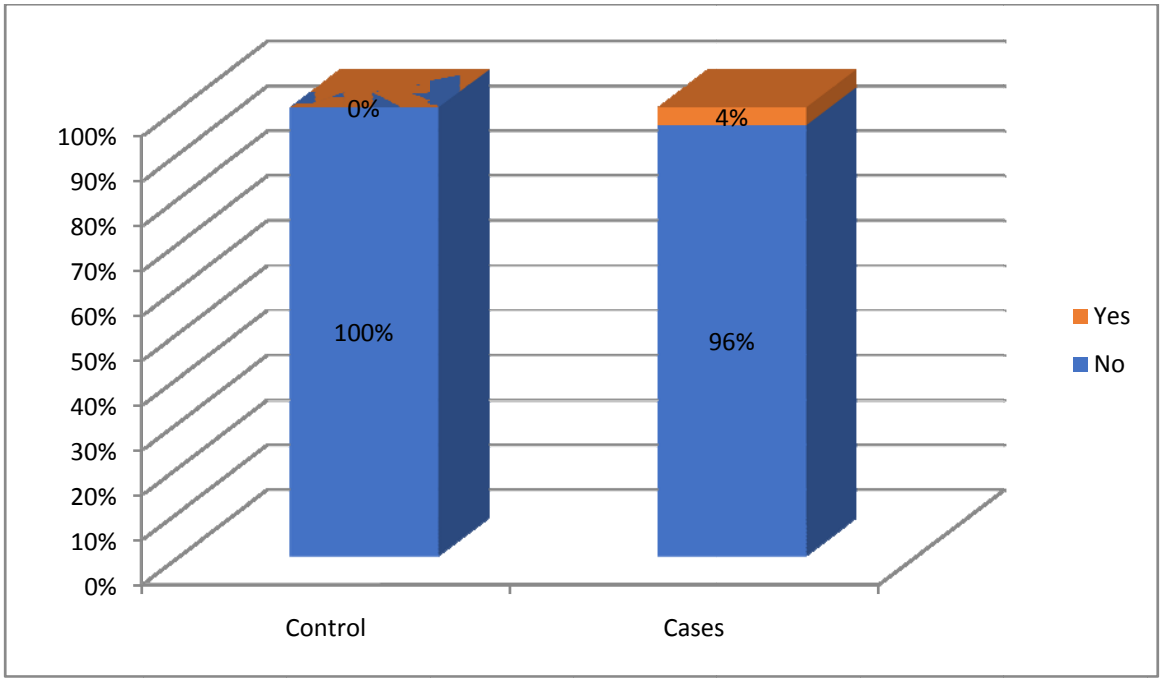
Among the CAD cases, 70 % had STEMI while 30 % didn't have.

Among the control,no one had MI

TABLE 4: NSTEMI DISTRIBUTION

			group		Total
			Control	Cases	
nstemi	No	Count	10	48	58
		% within group	100.0%	96.0%	96.7%
	Yes	Count	0	2	2
		% within group	0.0%	4.0%	3.3%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=0.414 P=0.520



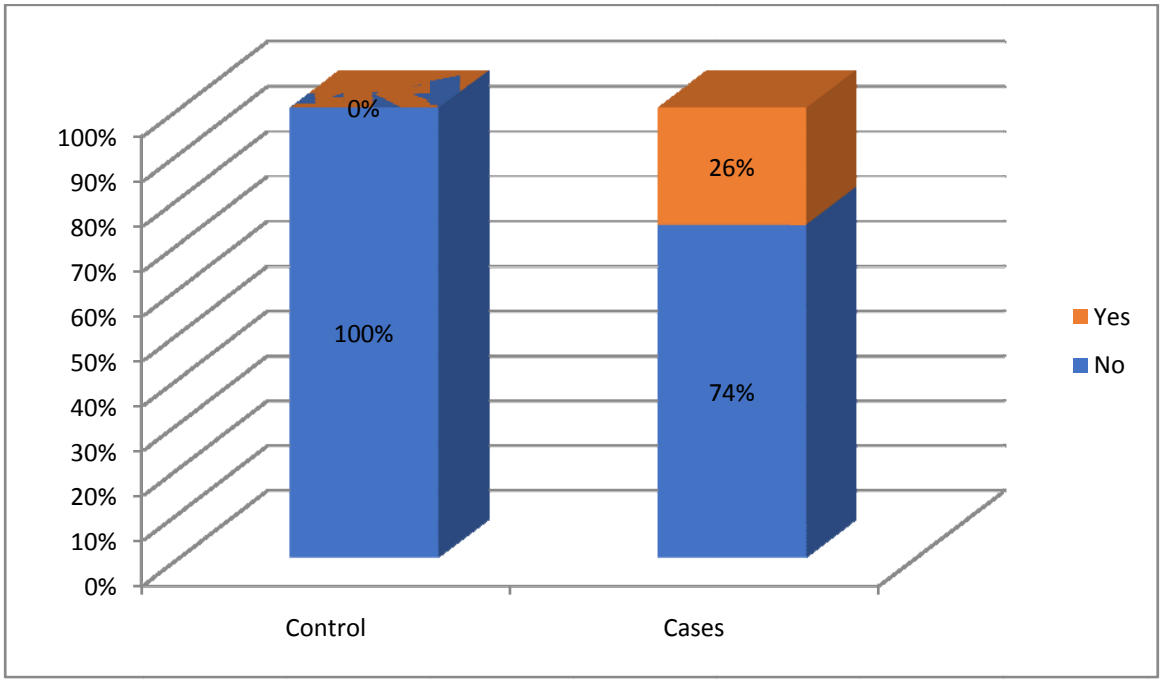
Among the CAD cases, only 4% of them had NSTEMI

While the control group did not have NSTEMI

TABLE 5: UNSTABLE ANGINA DISTRIBUTION

			group		Total
			Control	Cases	
angina	No	Count	10	37	47
		% within group	100.0%	74.0%	78.3%
	Yes	Count	0	13	13
		% within group	0.0%	26.0%	21.7%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=3.319 P=0.068



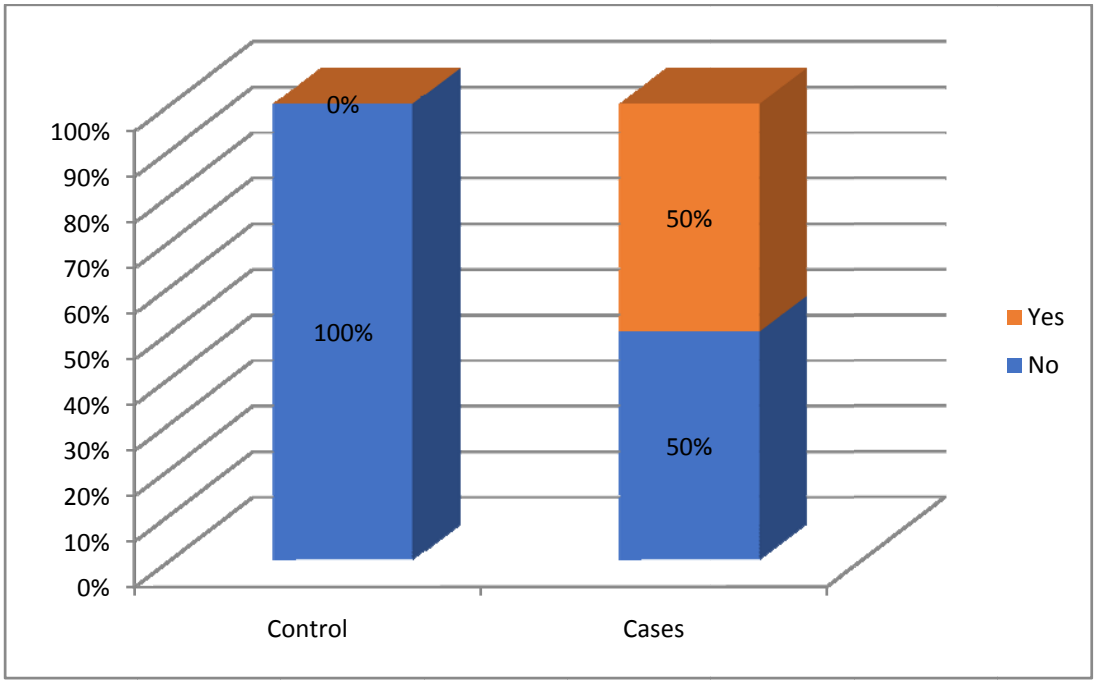
Among the CAD cases,26% of them had unstable angina

While none in the control group had MI

TABLE 6: AWMI DISTRIBUTION

			group		Total
			Control	Cases	
awmi	No	Count	10	25	35
		% within group	100.0%	50.0%	58.3%
	Yes	Count	0	25	25
		% within group	0.0%	50.0%	41.7%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=8.571* P=0.003

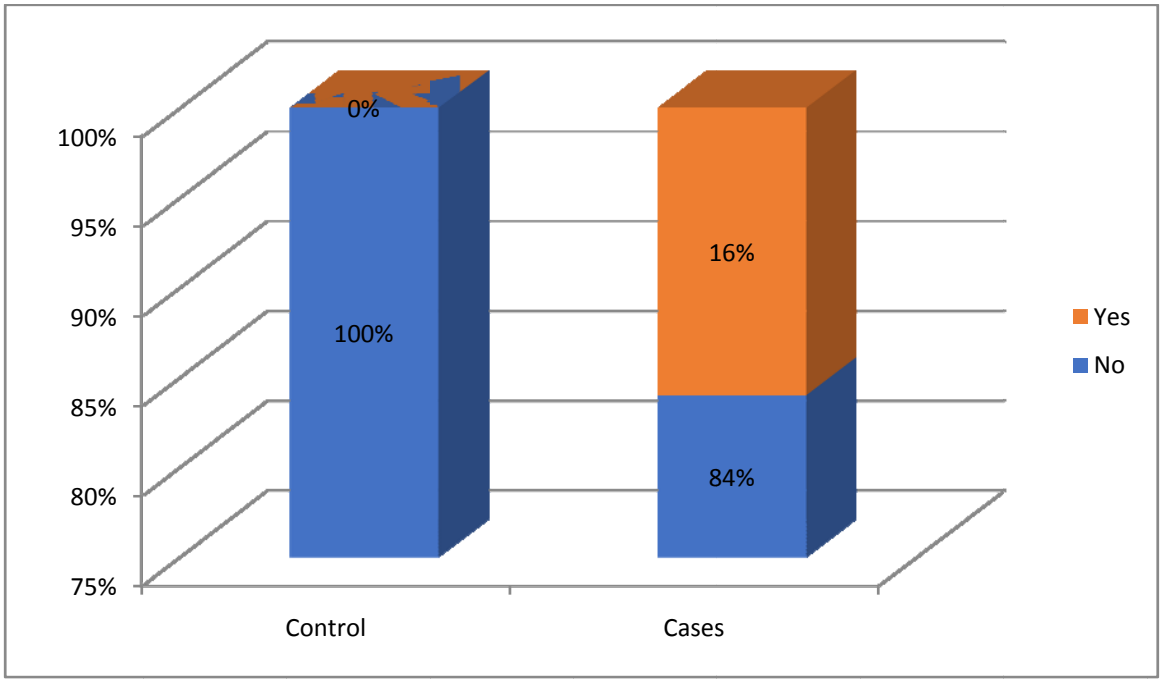


Among the CAD cases,50 % had AWMI.

TABLE 7: IWMI DISTRIBUTION

			group		Total
			Control	Cases	
iwmi	No	Count	10	42	52
		% within group	100.0%	84.0%	86.7%
	Yes	Count	0	8	8
		% within group	0.0%	16.0%	13.3%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=1.846 P=0.174

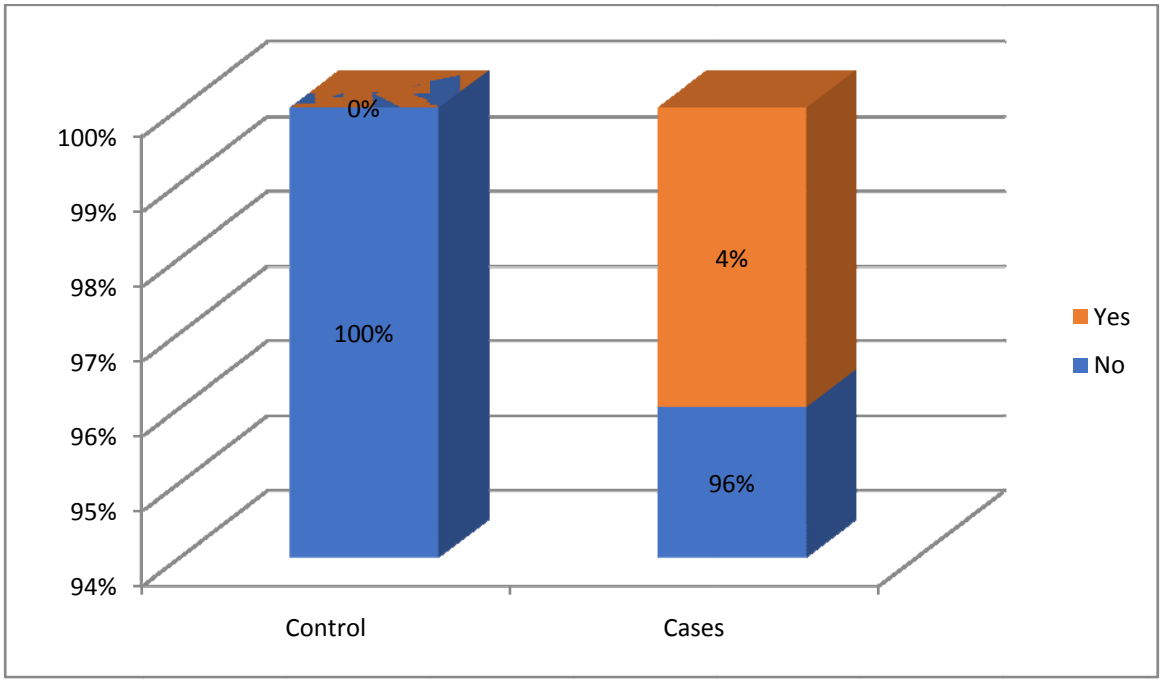


Among the CAD cases, 16 % had IWMI

TABLE 8 : PWMI DISTRIBUTION

			group		Total
			Control	Cases	
pwmi	No	Count	10	48	58
		% within group	100.0%	96.0%	96.7%
	Yes	Count	0	2	2
		% within group	0.0%	4.0%	3.3%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=0.414 P=0.520

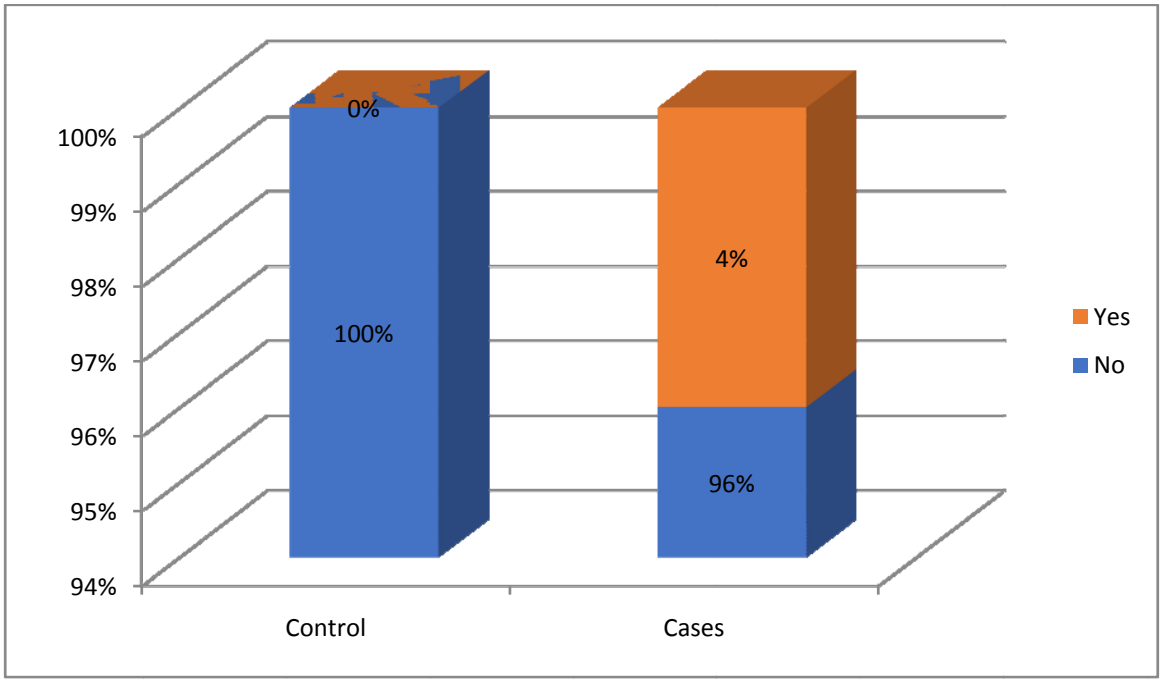


Amon g the CAD cases, only 4 % had PWMI

TABLE 9: ALWMI DISTRIBUTION

			group		Total
			Control	Cases	
alwmi	No	Count	10	48	58
		% within group	100.0%	96.0%	96.7%
	Yes	Count	0	2	2
		% within group	0.0%	4.0%	3.3%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=0.414 P=0.520

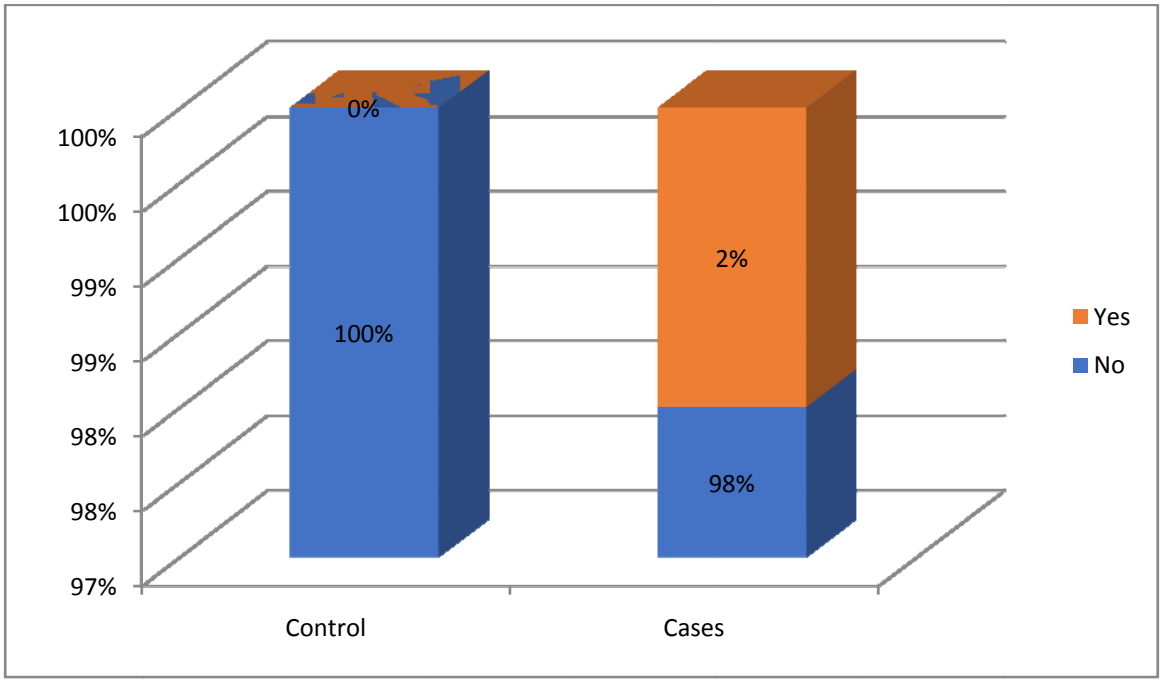


Among the CAD cases, 4 % had ALWMI

TABLE 10: PLWMI DISTRIBUTION

			group		Total
			Control	Cases	
plwmi	No	Count	10	49	59
		% within group	100.0%	98.0%	98.3%
	Yes	Count	0	1	1
		% within group	0.0%	2.0%	1.7%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=0.203 P=0.652

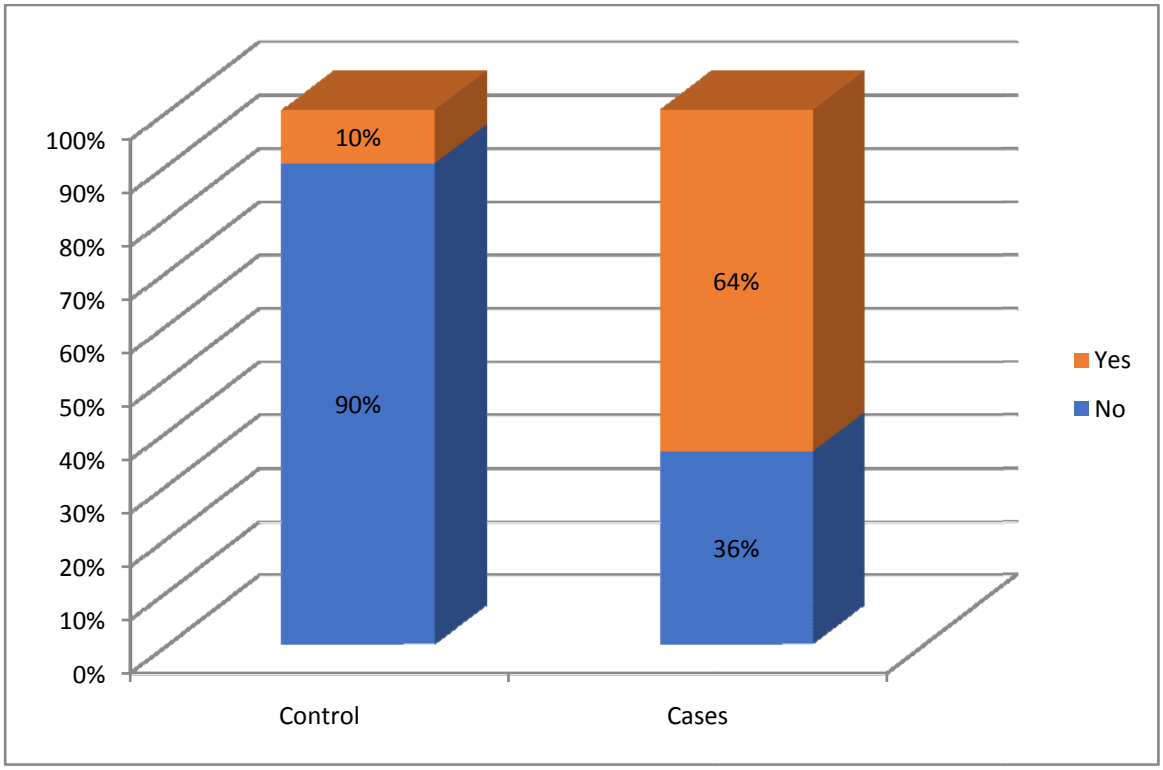


Among the CAD cases,2% had PLWMI

TABLE 11– DIABETIC DISTRIBUTION

		group		Total
		Control	Cases	
dm No	Count	9	18	27
	% within group	90.0%	36.0%	45.0%
dm Yes	Count	1	32	33
	% within group	10.0%	64.0%	55.0%
dm Total	Count	10	50	60
	% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=9.818* P=0.002



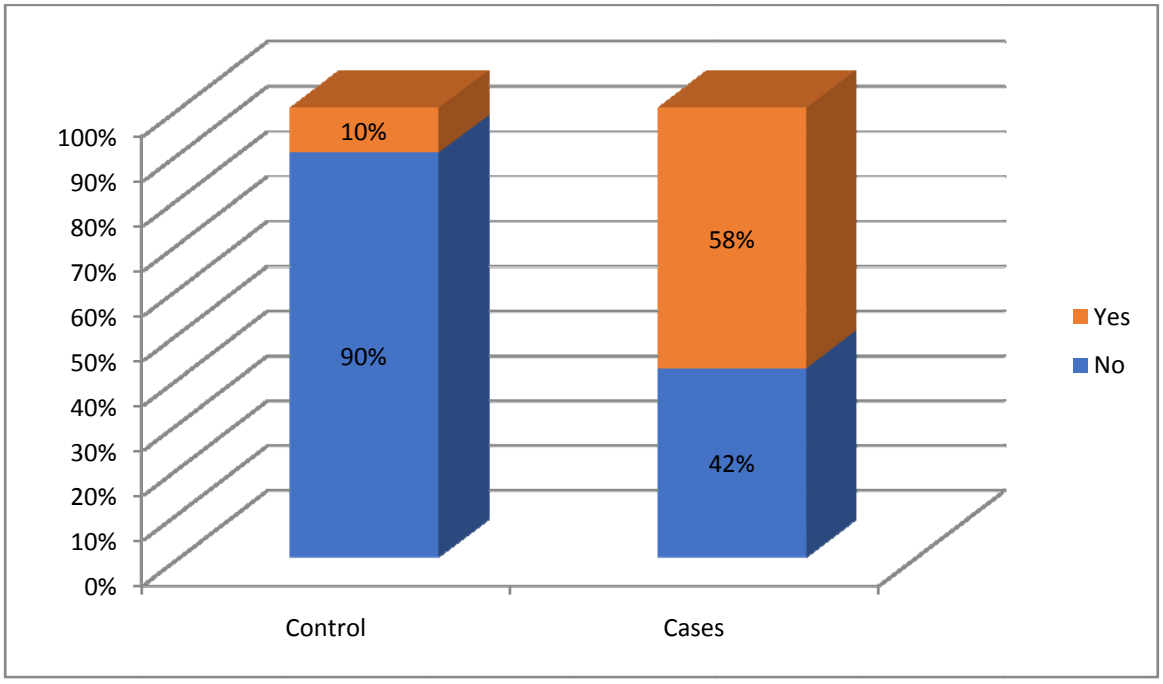
Among the CAD cases, 64 % of them were diabetics

Among the control group,10 % were diabetics

TABLE 12: HYPERTENSION DISTRIBUTION

		group		Total
		Control	Cases	
htn	No	Count	9	21	30
		% within group	90.0%	42.0%	50.0%
	Yes	Count	1	29	30
		% within group	10.0%	58.0%	50.0%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=7.680* P=0.006

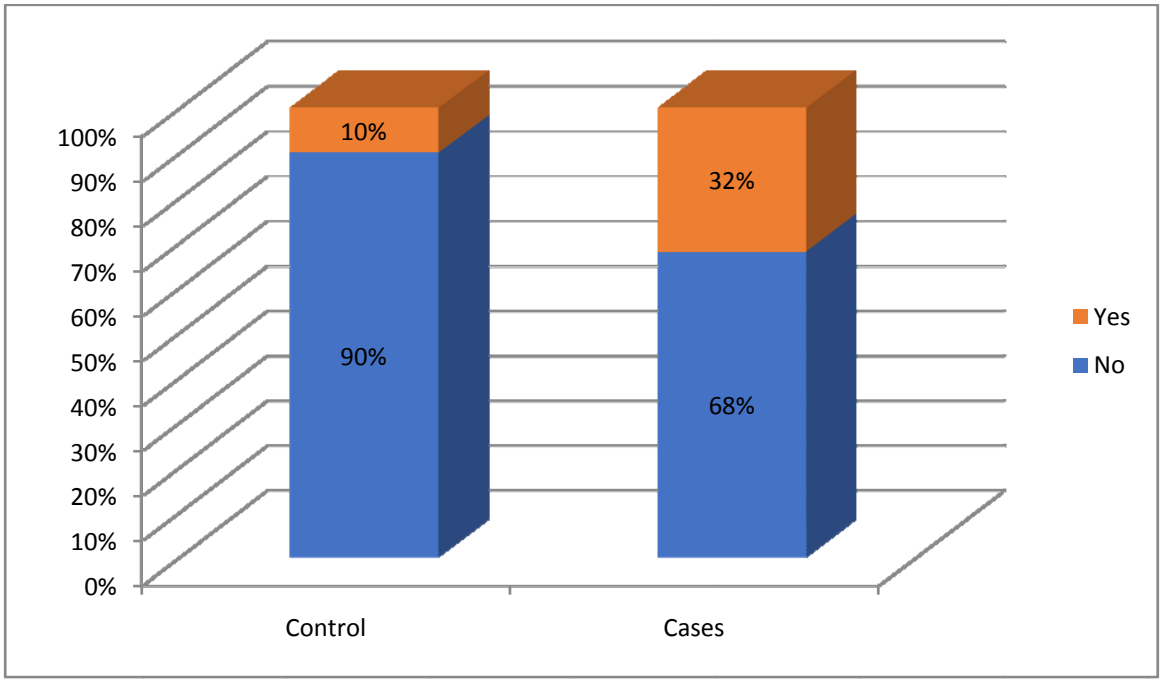


Among the CAD cases,58% were hypertensives while only 10 % of the control group were hypertensives

TABLE 13: ALCOHOLIC DISTRIBUTION

			group		Total
			Control	Cases	
alcoholic	No	Count	9	34	43
		% within group	90.0%	68.0%	71.7%
	Yes	Count	1	16	17
		% within group	10.0%	32.0%	28.3%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=1.986 P=0.159

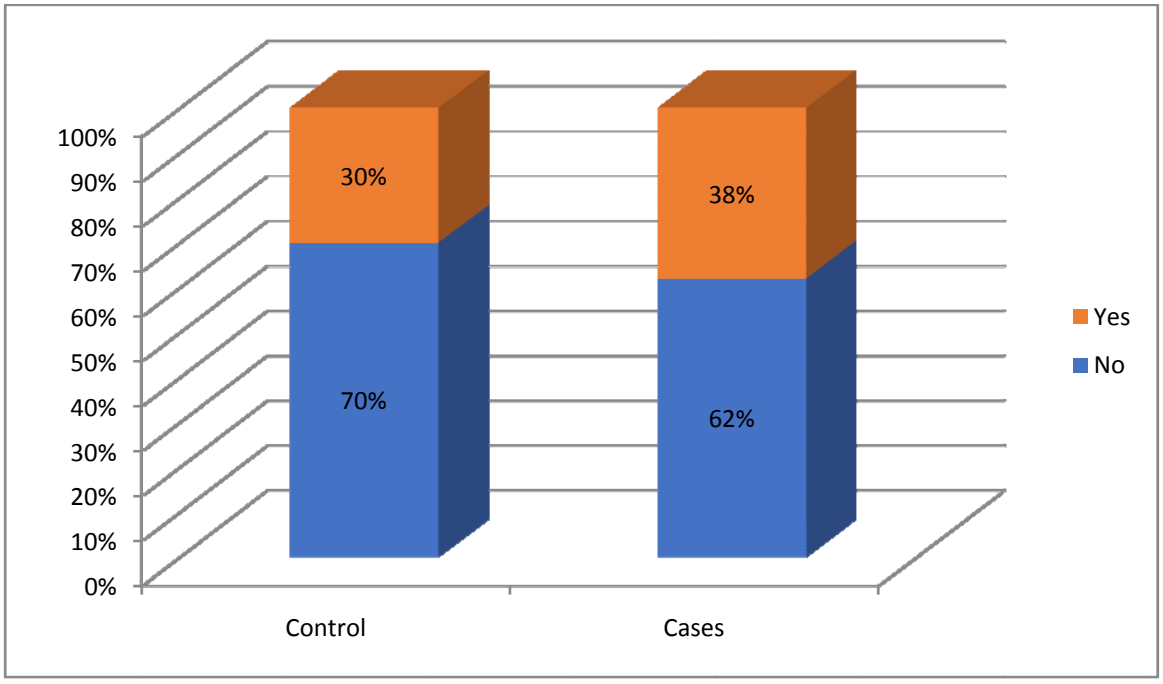


Among the cases, 32 % were alcoholics while in control group,10 % were alcoholics

TABLE 14: SMOKER DISTRIBUTION

			group		Total
			Control	Cases	
smoker	No	Count	7	31	38
		% within group	70.0%	62.0%	63.3%
	Yes	Count	3	19	22
		% within group	30.0%	38.0%	36.7%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=0.230 P=0.632



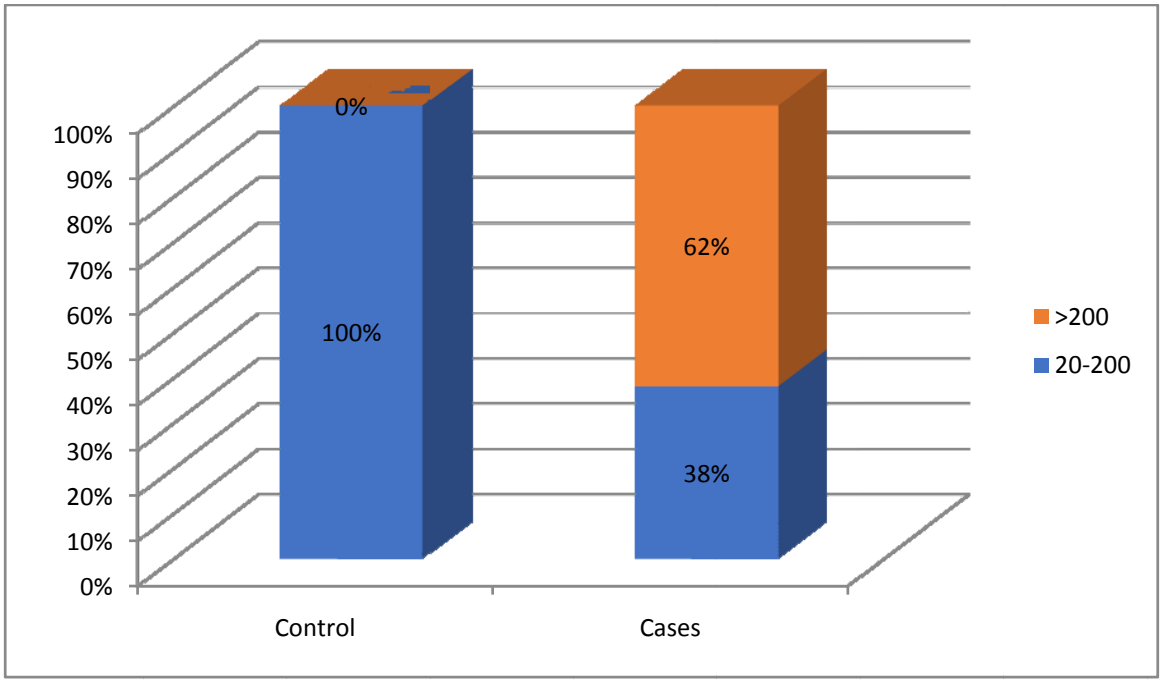
Among the CAD cases,38% were smokers

Among the control,30 % were smokers

TABLE 15: CK DISTRIBUTION

			group		Total
			Control	Cases	
CK_GROUP	20-200	Count	10	19	29
		% within group	100.0%	38.0%	48.3%
	>200	Count	0	31	31
		% within group	0.0%	62.0%	51.7%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=12.828* P=0.001

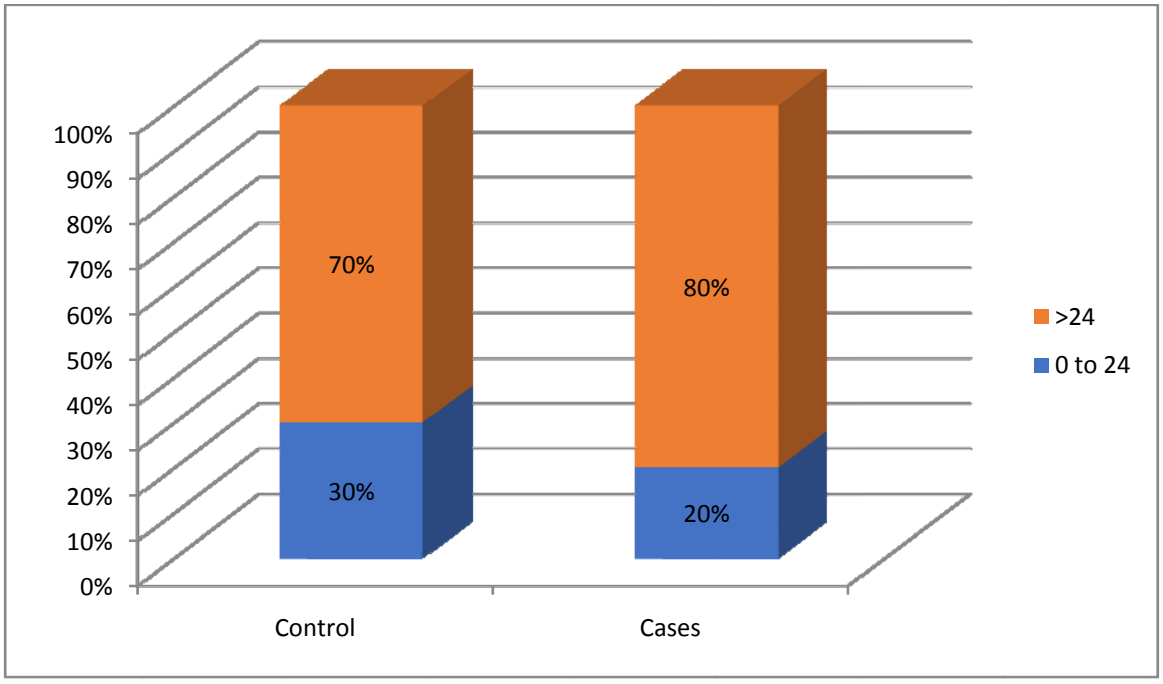


Among the CAD cases,62% had elevated CK while the controls had normal CK

TABLE 16: CK –MB DISTRIBUTION

			group		Total
			Control	Cases	
CK_MBGROUP	0-24	Count	3	10	13
		% within group	30.0%	20.0%	21.7%
	>24	Count	7	40	47
		% within group	70.0%	80.0%	78.3%
	Total	Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=0.491 P=0.483



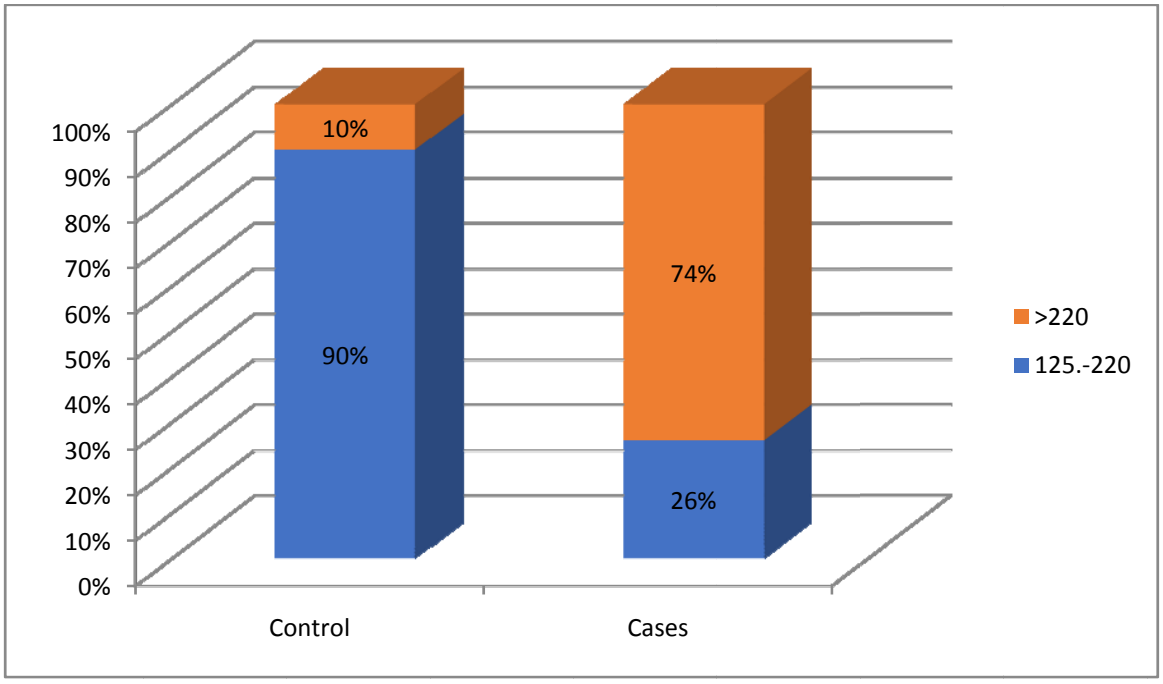
Among the CAD case,80 % had increased CK-MB

Among the controls,70 % had increased CK-MB

TABLE 17 : LDH DISTRIBUTION

			group		Total
			Control	Cases	
IDH_GROUP	125-220	Count	9	13	22
		% within group	90.0%	26.0%	36.7%
	>220	Count	1	37	38
		% within group	10.0%	74.0%	63.3%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=14.699* P=0.001

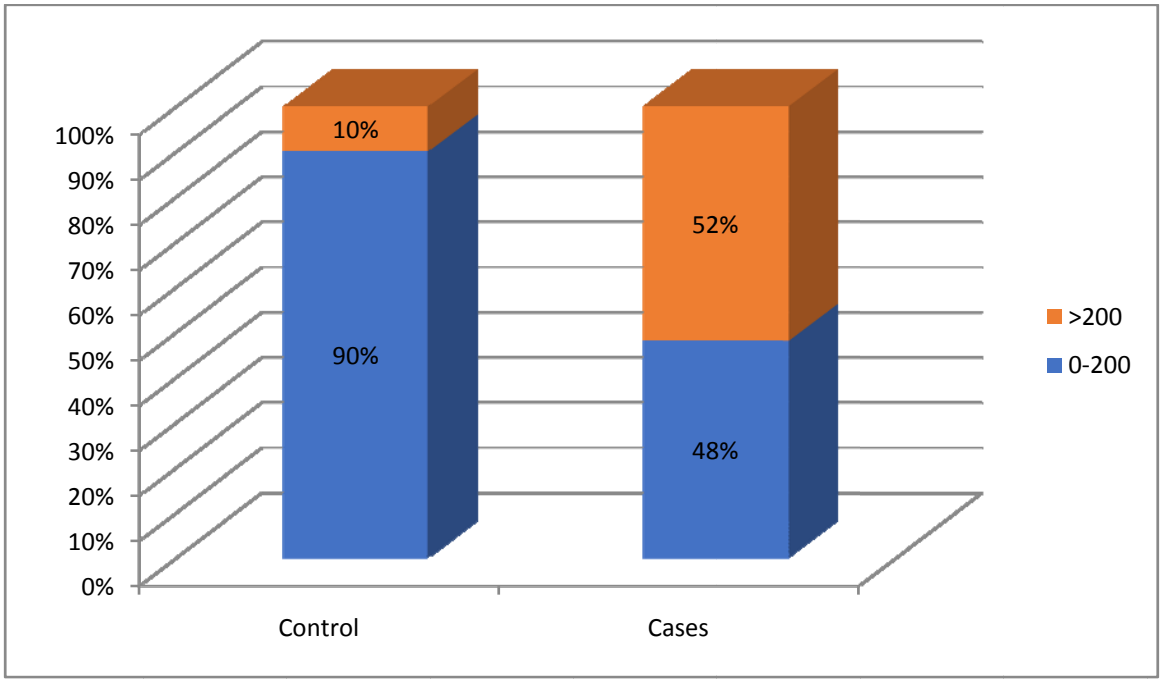


Among the CAD cases,74 % had increased LDH, while 10% of the control group only had increased LDH

TABLE 18: TOTAL CHOLESTEROL DISTRIBUTION

			group		Total
			Control	Cases	
TCHOLESTROL_GROUP	0-200	Count	9	24	33
		% within group	90.0%	48.0%	55.0%
	>200	Count	1	26	27
		% within group	10.0%	52.0%	45.0%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=5.939* P=0.015

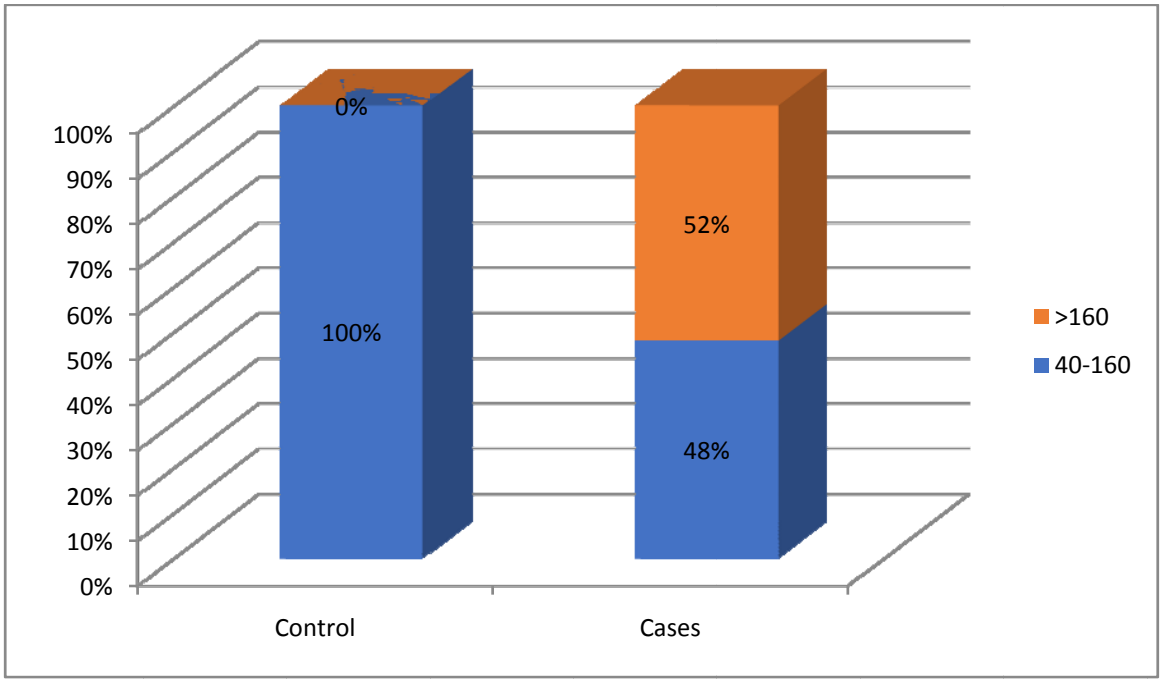


52% of the cases had elevated total cholesterol while only 10 % of control had it.

TABLE 19: TRIGLYCERIDE DISTRIBUTION

			group		Total
			Control	Cases	
TGL_GROUP	40-160	Count	10	24	34
		% within group	100.0%	48.0%	56.7%
	>160	Count	0	26	26
		% within group	0.0%	52.0%	43.3%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=9.176* P=0.002

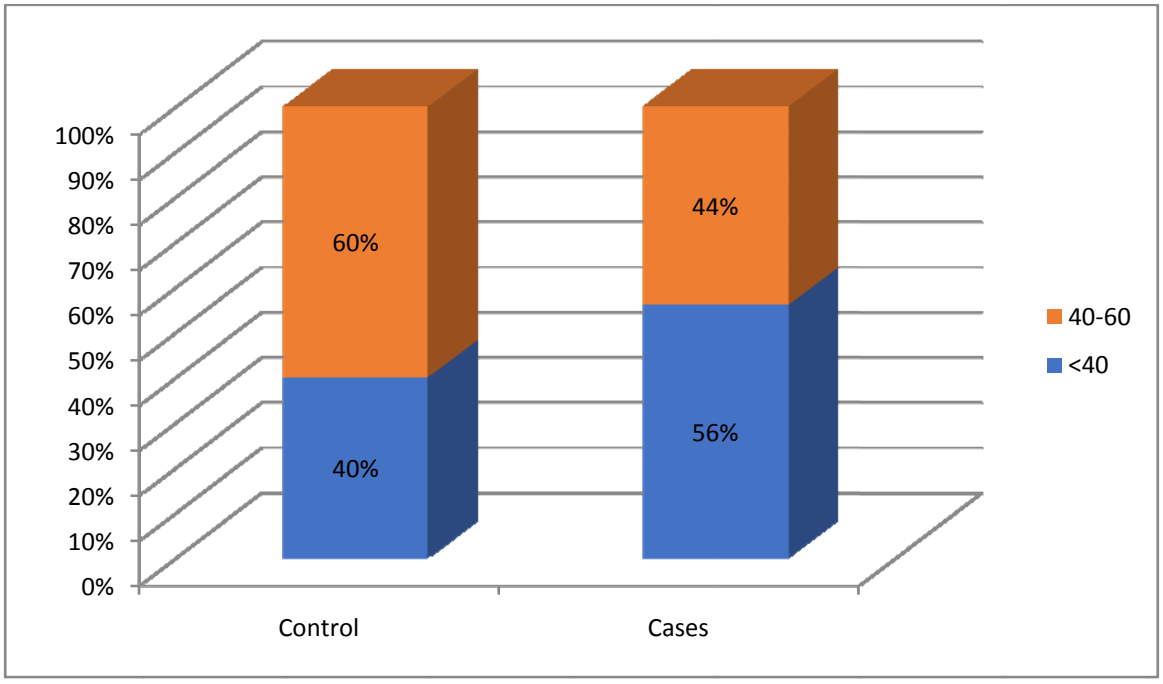


52% of the CAD cases had elevated TGL while it was normal in the control group

TABLE 20: HDL DISTRIBUTION

			group		Total
			Control	Cases	
HDL_GROUP	<40	Count	4	28	32
		% within group	40.0%	56.0%	53.3%
	40-60	Count	6	22	28
		% within group	60.0%	44.0%	46.7%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=0.857 P=0.355



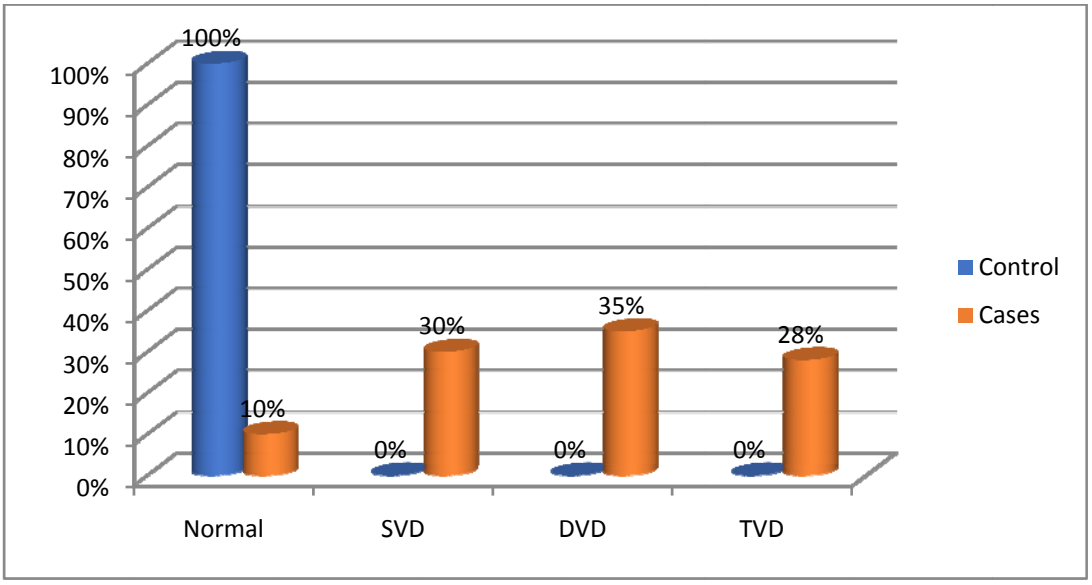
56 % of the CAD cases had decreased HDL

40 % of the control had decreased HDL

TABLE 21 : CORONARY ANGIOGRAM DISTRIBUTION

			group		Total
			Control	Cases	
angio	Normal	Count	10	5	15
		% within group	100.0%	10.0%	25.0%
	SVD	Count	0	15	15
		% within group	0.0%	30.0%	25.0%
	DVD	Count	0	16	16
		% within group	0.0%	32.0%	26.7%
	TVD	Count	0	14	14
		% within group	0.0%	28.0%	23.3%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=36.00* P=0.001



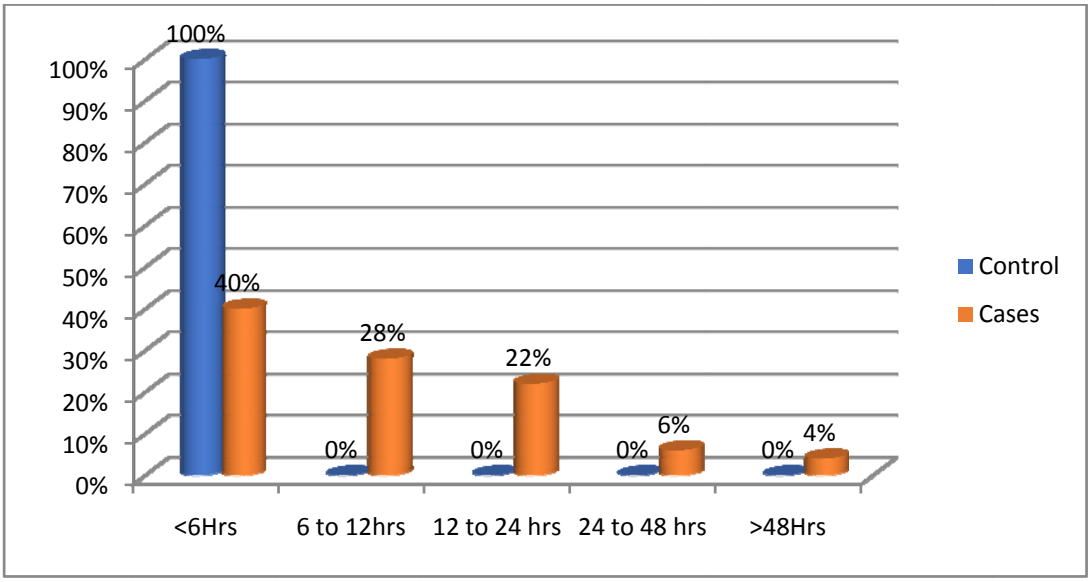
Among the CAD cases who underwent coronary angiogram, 28% had TVD,35% had DVD,30% had SVD & 10%of them had normal coronaries

All the controls had normal coronary angiographic report.

TABLE 22: TIME DISTRIBUTION

			group		Total
			Control	Cases	
time_group	<6 HRS	Count	10	20	30
		% within group	100.0%	40.0%	50.0%
	6 -12 HRS	Count	0	14	14
		% within group	0.0%	28.0%	23.3%
	12 -24Hrs	Count	0	11	11
		% within group	0.0%	22.0%	18.3%
	24-48 Hrs	Count	0	3	3
		% within group	0.0%	6.0%	5.0%
	>48Hrs	Count	0	2	2
		% within group	0.0%	4.0%	3.3%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=12.00* P=0.017



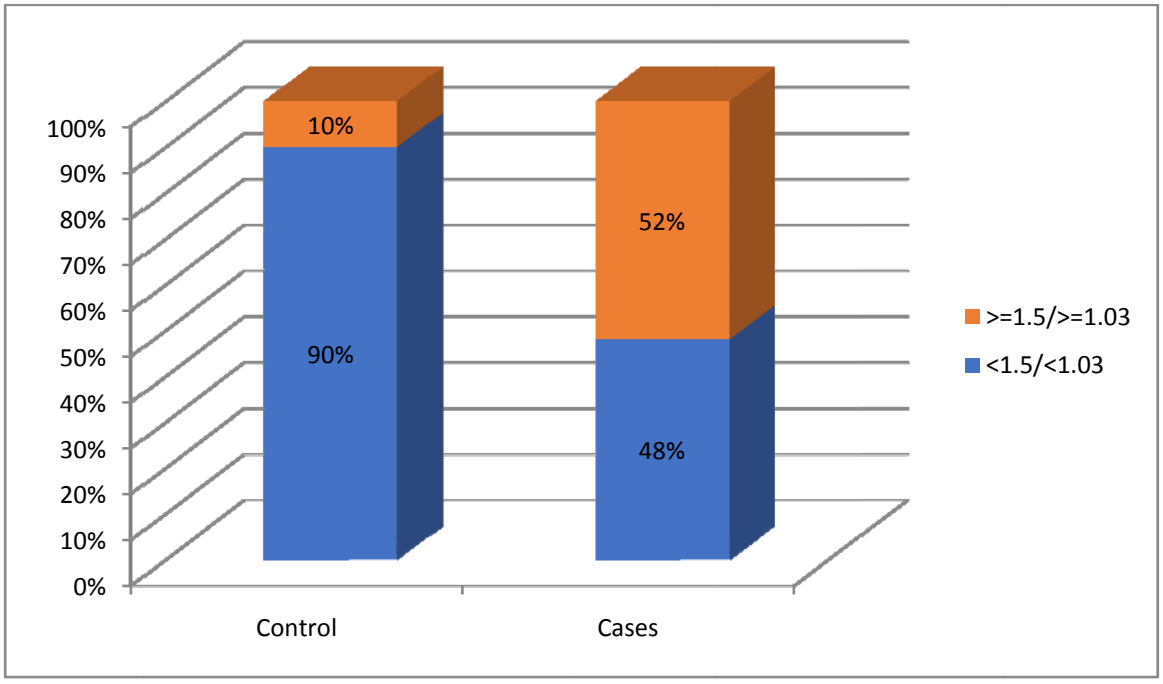
Among the CAD cases, 40 % presented within 6 hours of symptom onset, 28% within 6-12 hours, 22% within 12 to 24 hours , 6 % within 24 to 48 hours and 4 % after 48 hours

The control group had elective admission for coronary angiogram as per their individual disease profile and it was done within 6 hours of admission and they all had normal coronaries.

TABLE 23: CYSTATIN C DISTRIBUTION

			group		Total
			Control	Cases	
CYSTATIN_GROUP	<1.5/<1.03	Count	9	24	33
		% within group	90.0%	48.0%	55.0%
	>=1.5/>=1.03	Count	1	26	27
		% within group	10.0%	52.0%	45.0%
Total		Count	10	50	60
		% within group	100.0%	100.0%	100.0%

Pearson Chi-Square=5.939* P=0.015



Among the CAD cases, 52% of them had elevated cystatin C levels

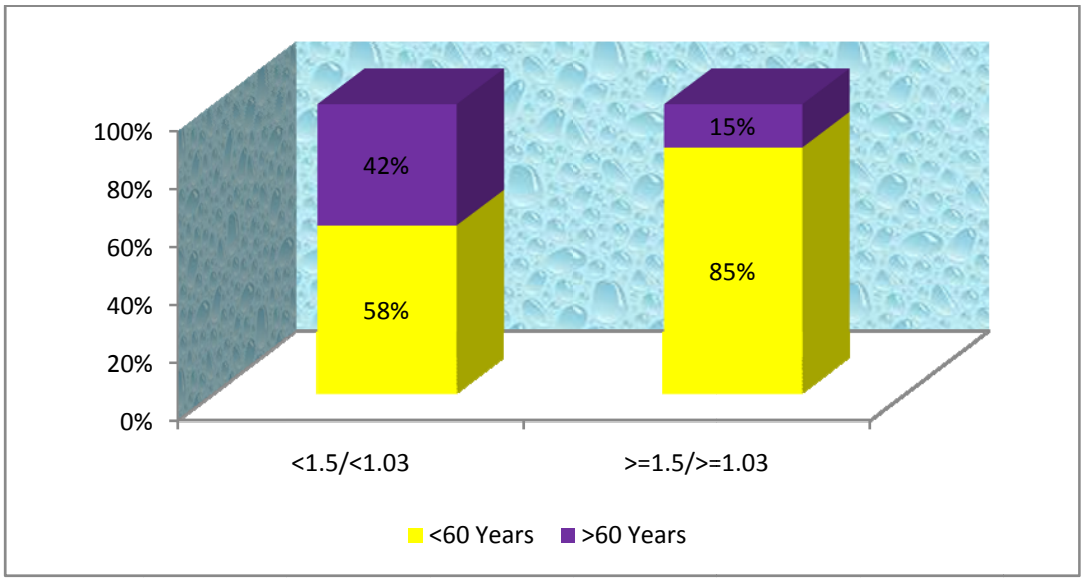
While only 10 % of the control had elevated cystatin C levels.

TABLE 24: CYSTATIN C LEVELS –AGEWISE DISTRIBUTION AMONG CAD

Crosstab

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
AGE GROUP	<60 Years	Count	14	22	36
		% within CYSTATIN_GROUP	58.3%	84.6%	72.0%
	>=60 Years	Count	10	4	14
		% within CYSTATIN_GROUP	41.7%	15.4%	28.0%
	Total	Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=4.276* P=0.039

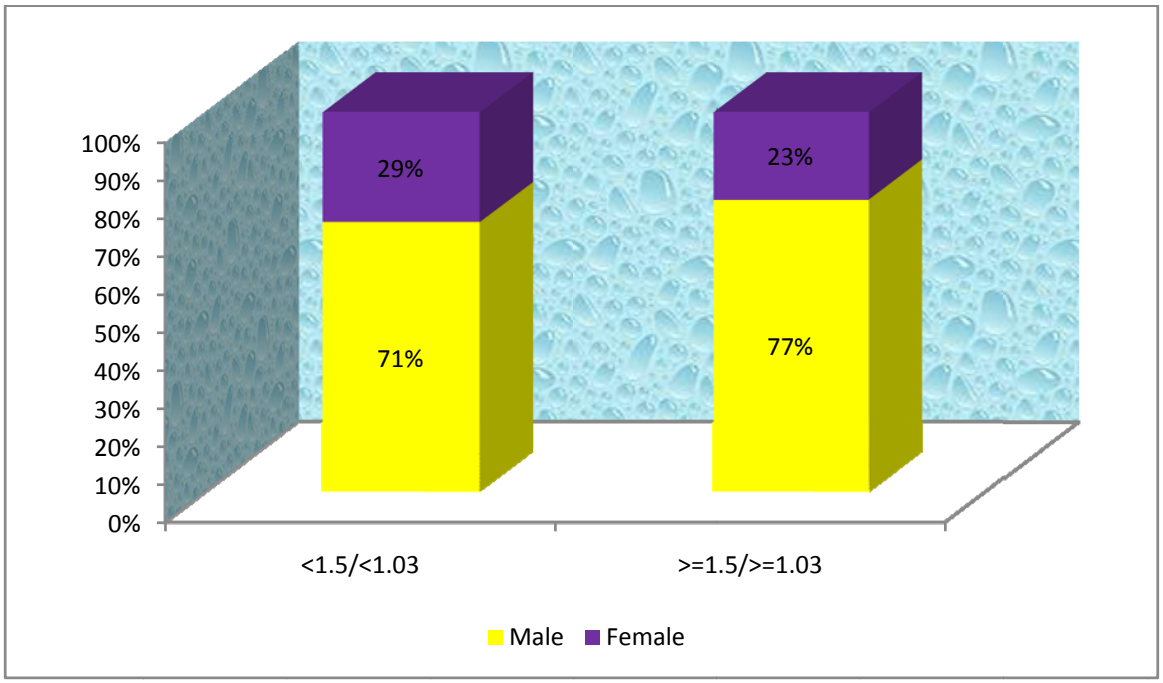


Among the CAD cases, 85% of the people less than 60 years of age had elevated cystatin C levels .

TABLE 25: CYSTATIN C LEVELS SEX WISE DISTRIBUTION AMONG CAD

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
sex	Male	Count	17	20	37
		% within CYSTATIN_GROUP	70.8%	76.9%	74.0%
	Female	Count	7	6	13
		% within CYSTATIN_GROUP	29.2%	23.1%	26.0%
	Total	Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=0.241 P=0.624

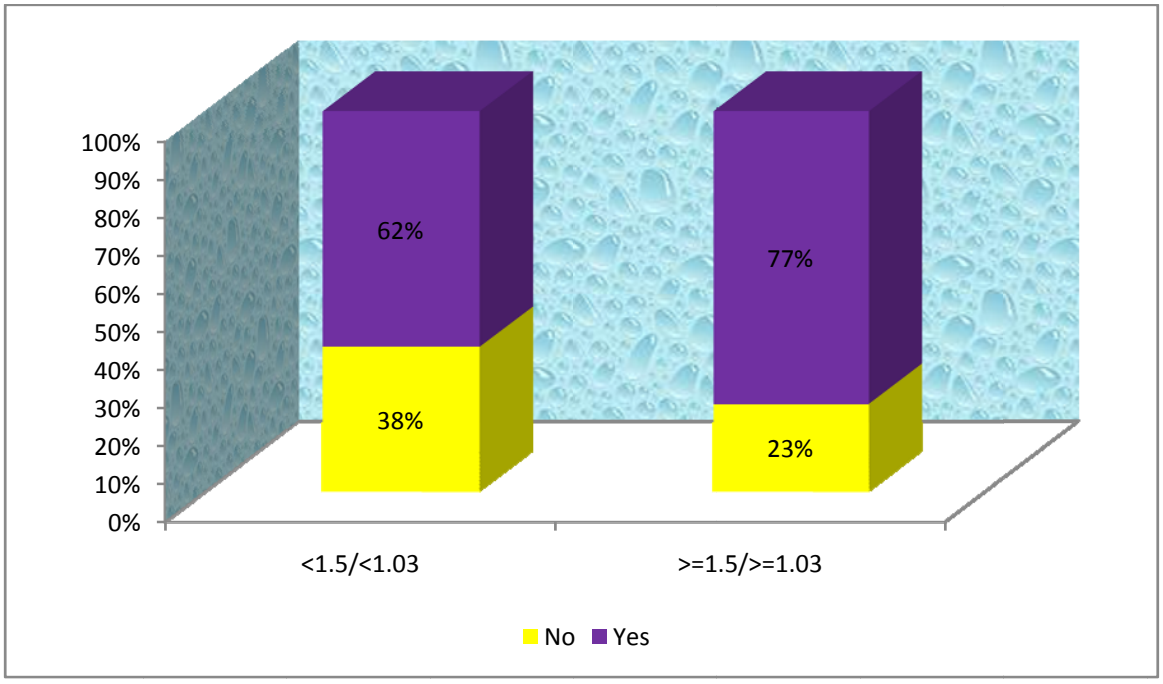


Among the CAD cases, 77% of them with increased cystatin C levels were male.

TABLE 26: CYSTATIN C LEVELS IN STEMI

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
stemi	No	Count	9	6	15
		% within CYSTATIN_GROUP	37.5%	23.1%	30.0%
	Yes	Count	15	20	35
		% within CYSTATIN_GROUP	62.5%	76.9%	70.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=1.236 P=0.266

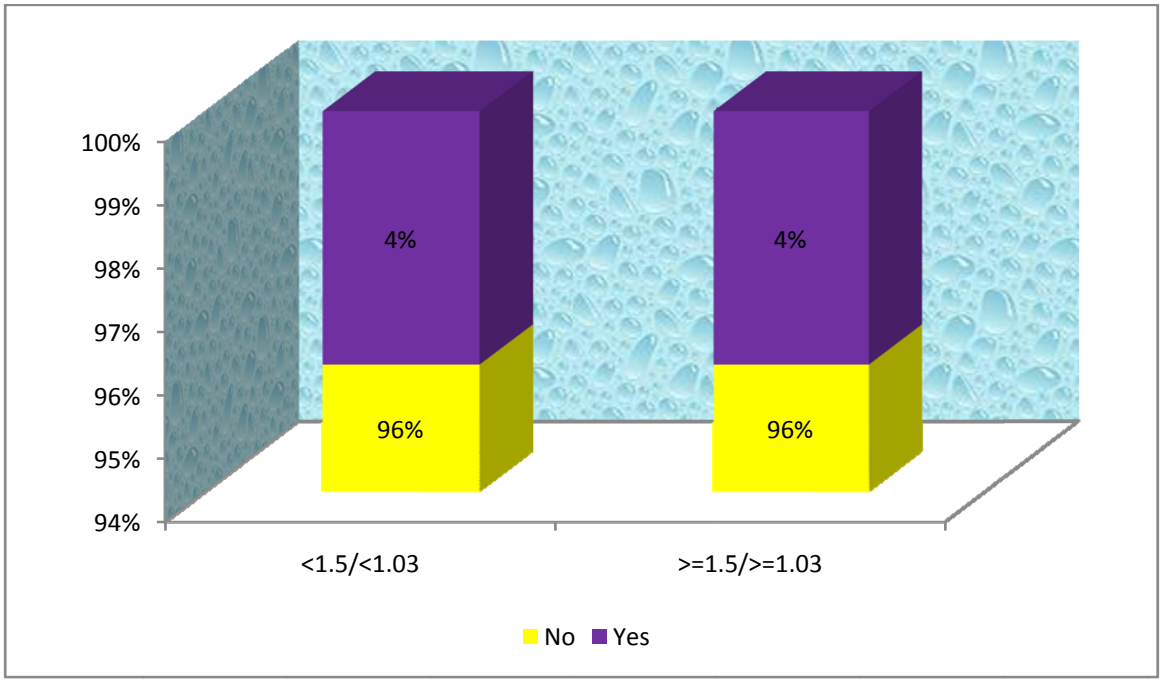


Among the cystatin C positive CAD cases, 77 % had STEMI

TABLE 27: CYSTATIN C LEVELS IN NSTEMI

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
nstemi	No	Count	23	25	48
		% within CYSTATIN_GROUP	95.8%	96.2%	96.0%
	Yes	Count	1	1	2
		% within CYSTATIN_GROUP	4.2%	3.8%	4.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=0.003 P=0.954

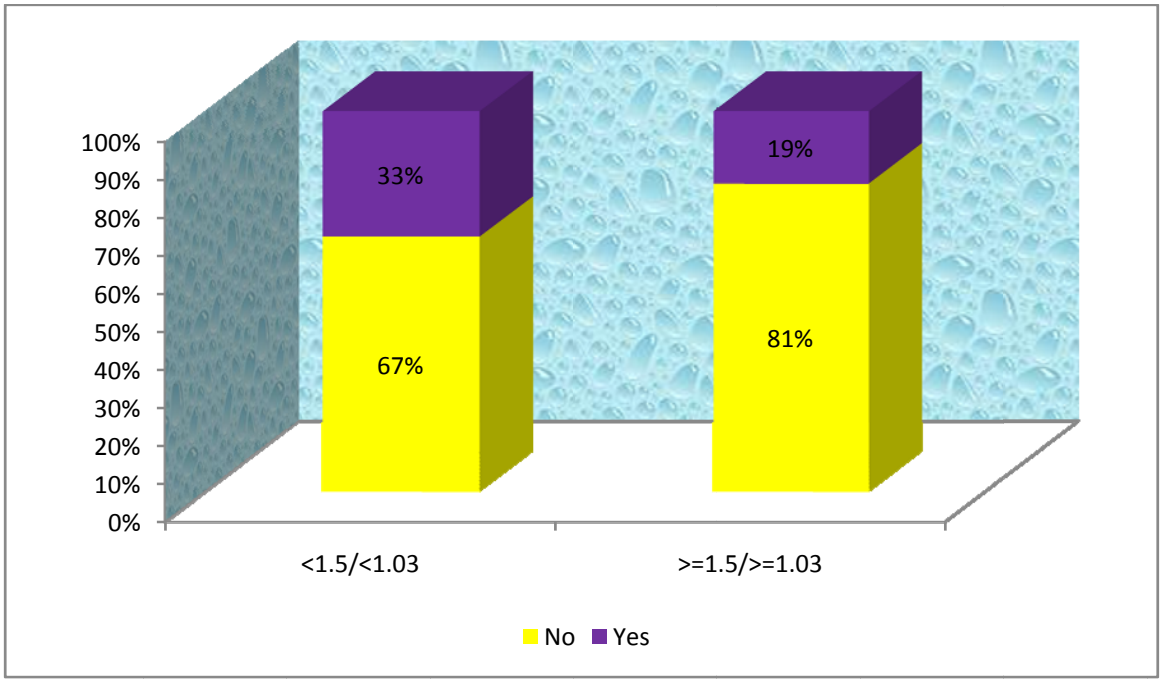


Among the cystatin C positive CAD cases, 4% had NSTEMI

TABLE 28: CYSTATIN C LEVELS IN UNSTABLE ANGINA

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
angina	No	Count	16	21	37
		% within CYSTATIN_GROUP	66.7%	80.8%	74.0%
	Yes	Count	8	5	13
		% within CYSTATIN_GROUP	33.3%	19.2%	26.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=1.290 P=0.256

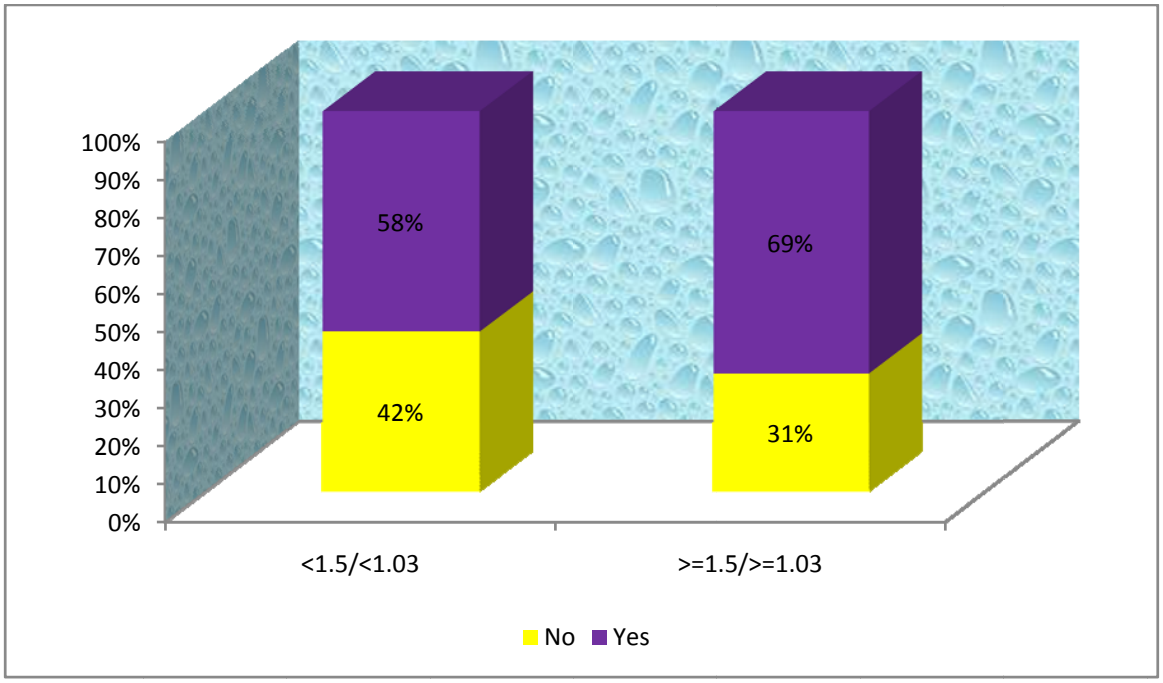


Among the cystatin C positive CAD cases, 19% Had unstable angina

TABLE 29: CYSTATIN C LEVELS IN DIABETIC CAD

		CYSTATIN_GROUP		Total
		<1.5/<1.03	>=1.5/>=1.03	
dm No	Count	10	8	18
	% within CYSTATIN_GROUP	41.7%	30.8%	36.0%
dm Yes	Count	14	18	32
	% within CYSTATIN_GROUP	58.3%	69.2%	64.0%
Total	Count	24	26	50
	% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=0.643 P=0.423

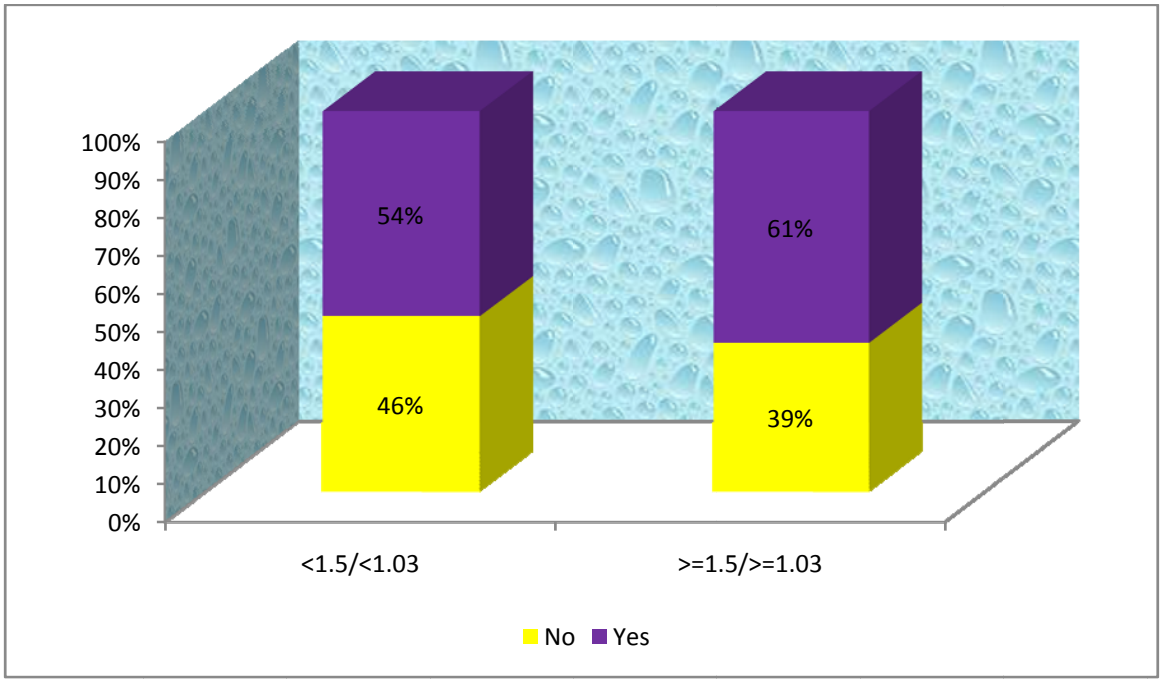


Among the cystatin C positive CAD cases, 69% were diabetics

TABLE 30: CYSTATIN C LEVELS IN HYPERTENSIVE CAD

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
htn	No	Count	11	10	21
		% within CYSTATIN_GROUP	45.8%	38.5%	42.0%
	Yes	Count	13	16	29
		% within CYSTATIN_GROUP	54.2%	61.5%	58.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=0.278 P=0.598

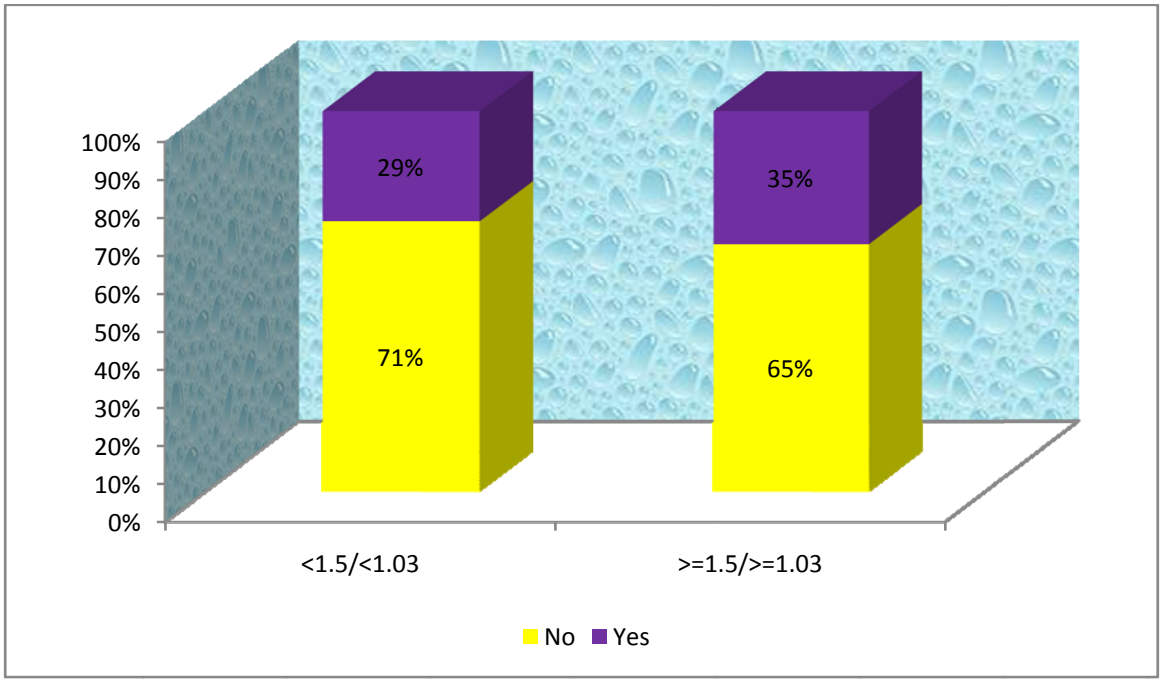


Among the cystatin C positive CAD cases, 61 % of them were hypertensives

TABLE 31 : CYSTATIN C LEVELS IN ALCOHOLIC CAD

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
alcoholic	No	Count	17	17	34
		% within CYSTATIN_GROUP	70.8%	65.4%	68.0%
	Yes	Count	7	9	16
		% within CYSTATIN_GROUP	29.2%	34.6%	32.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=0.170 P=0.680

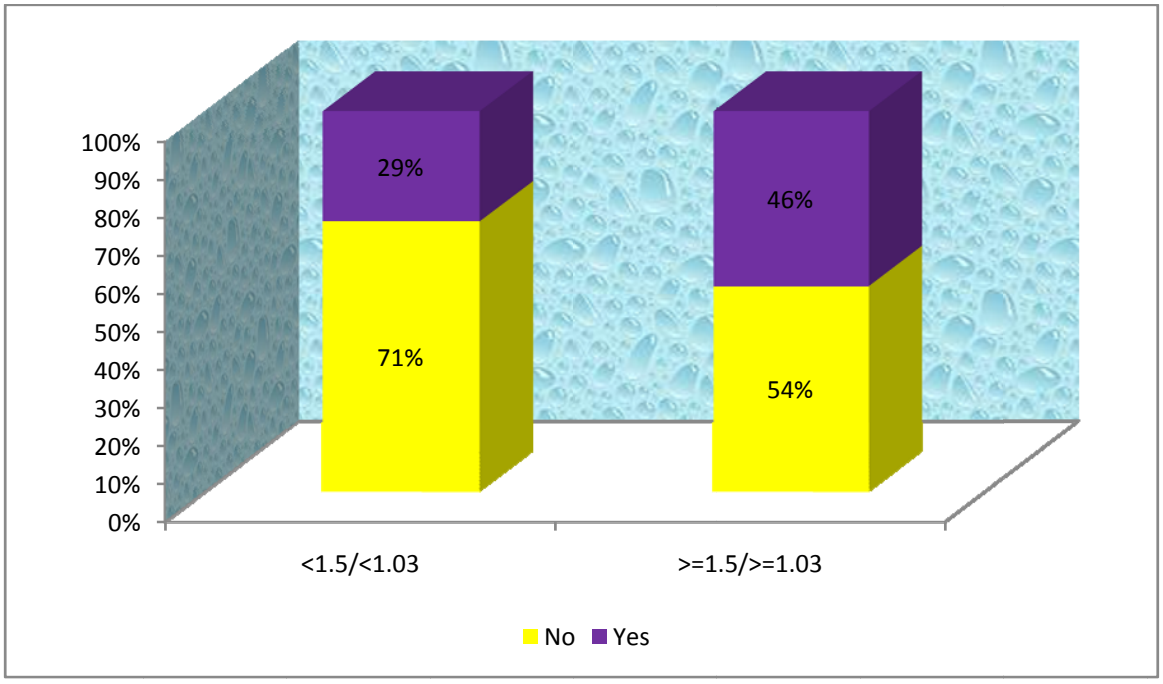


Among the cystatin c positive CAD cases, 35 % of them were alcoholics

TABLE 32; CYSTATIN C LEVELS IN SMOKER CAD

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
smoker	No	Count	17	14	31
		% within CYSTATIN_GROUP	70.8%	53.8%	62.0%
	Yes	Count	7	12	19
		% within CYSTATIN_GROUP	29.2%	46.2%	38.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=1.529 P=0.216

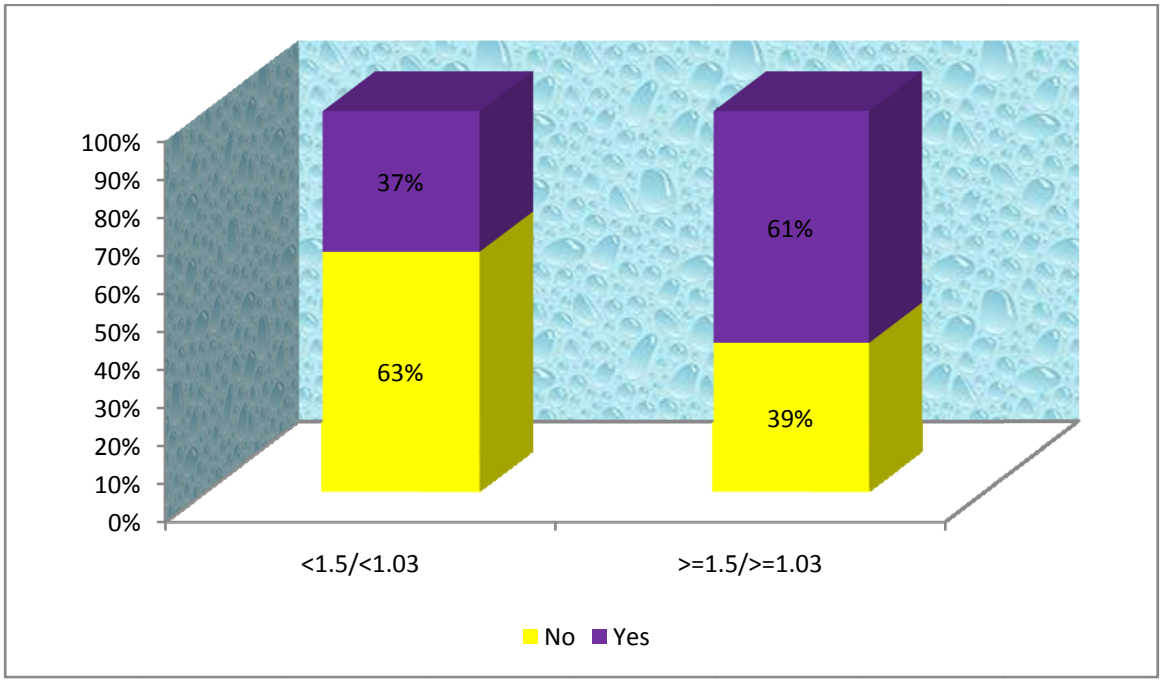


Among the cystatin c positive CAD cases, 46% were smokers

TABLE 33: CYSTATIN C LEVELS IN AWMI

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
awmi	No	Count	15	10	25
		% within CYSTATIN_GROUP	62.5%	38.5%	50.0%
	Yes	Count	9	16	25
		% within CYSTATIN_GROUP	37.5%	61.5%	50.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=2.885 P=0.089

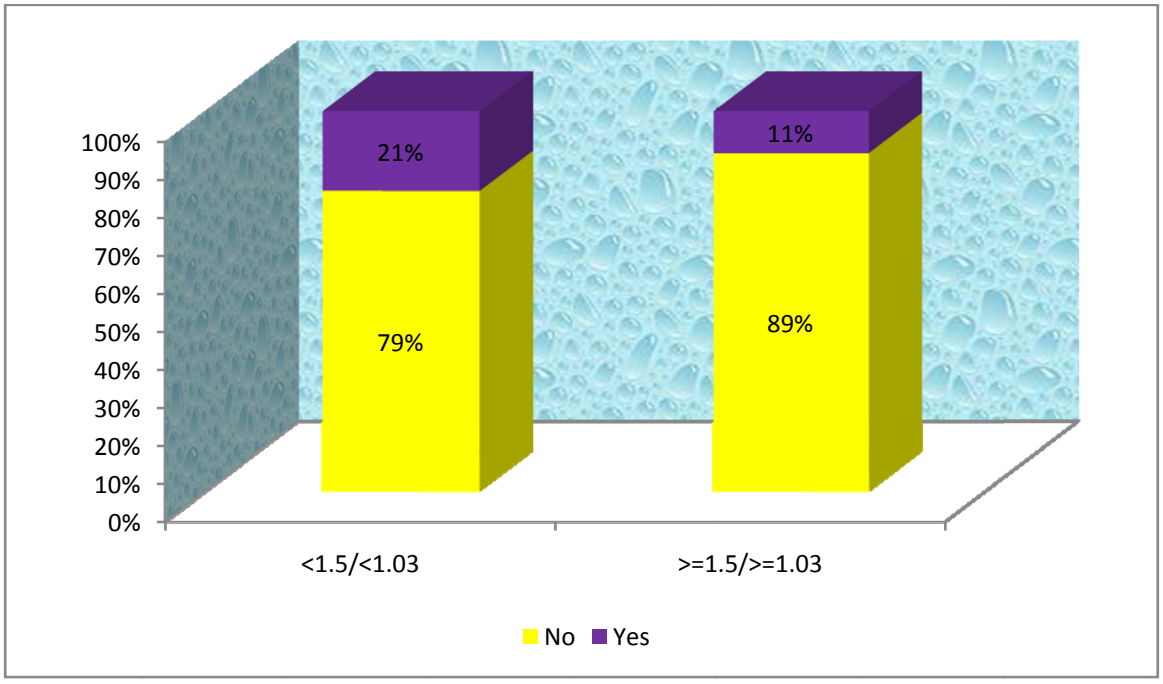


Among the cystatin c positive CAD cases, 61 % had AWMI

TABLE 34: CYSTATIN C LEVELS IN IWMI

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
iwmi	No	Count	19	23	42
		% within CYSTATIN_GROUP	79.2%	88.5%	84.0%
	Yes	Count	5	3	8
		% within CYSTATIN_GROUP	20.8%	11.5%	16.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=0.802 P=0.370

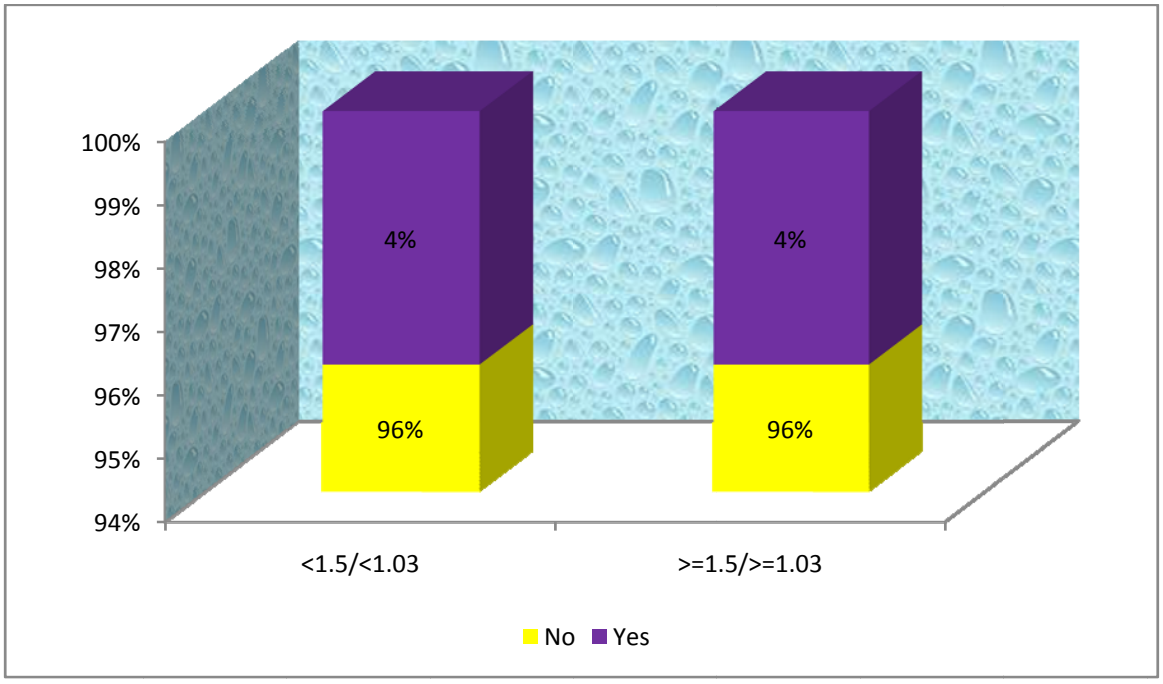


Among the cystatin c positive CAD cases, 11% had IWMI

TABLE 35:: CYSTATIN LEVELS IN PWMI

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
pwmi	No	Count	23	25	48
		% within CYSTATIN_GROUP	95.8%	96.2%	96.0%
	Yes	Count	1	1	2
		% within CYSTATIN_GROUP	4.2%	3.8%	4.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=0.003 P=0.954

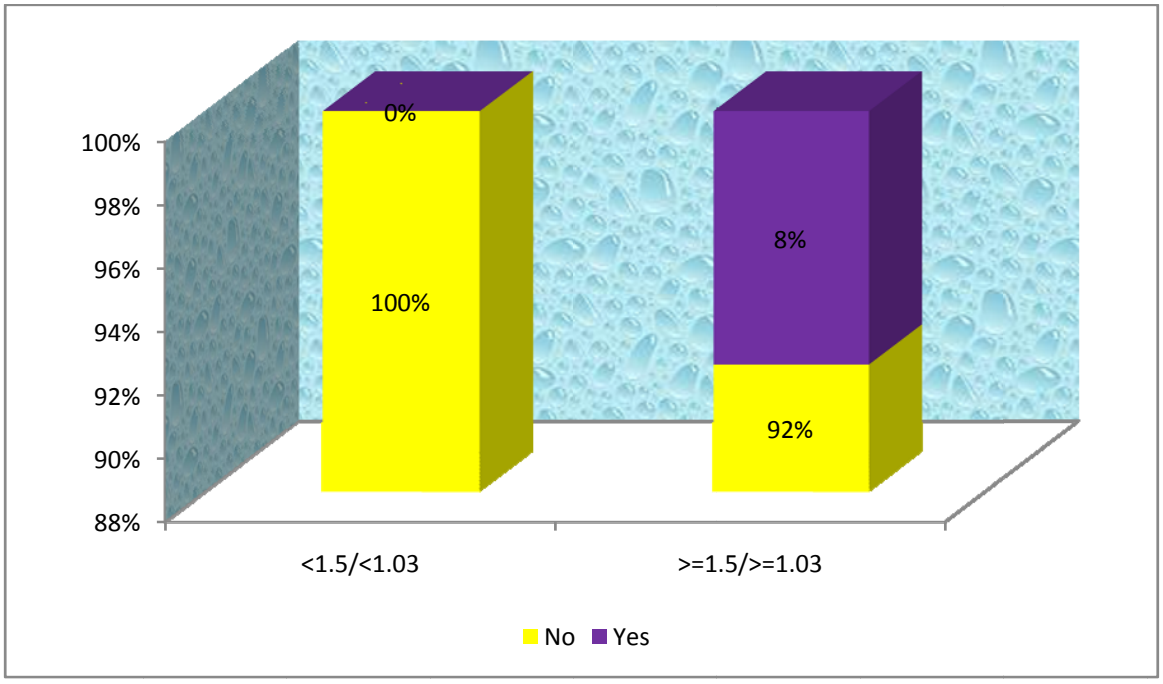


Among the cystatin C positive CAD cases, 4% had PWMI

TABLE 36: CYSTATIN C LEVELS IN ALWMI

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
alwmi	No	Count	24	24	48
		% within CYSTATIN_GROUP	100.0%	92.3%	96.0%
	Yes	Count	0	2	2
		% within CYSTATIN_GROUP	0.0%	7.7%	4.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=1.923 P=0.166

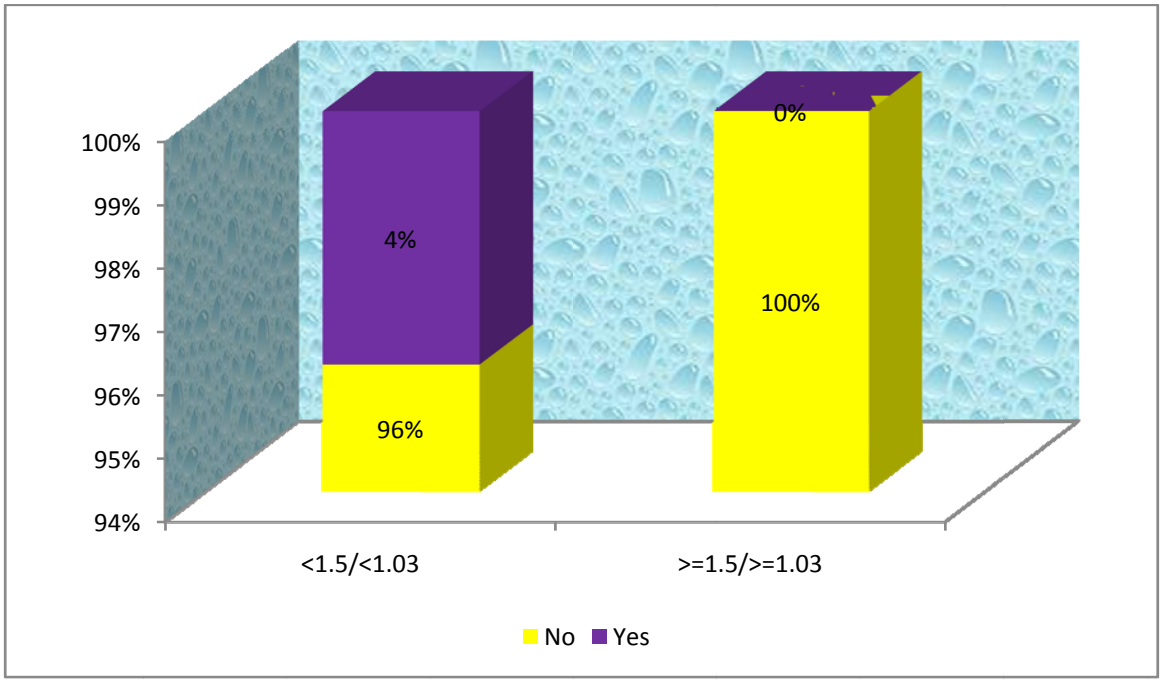


Among the cystatin C positive CAD cases, 8% had ALWMI

TABLE 37: CYSTATIN C LEVELS IN PLWMI

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
plwmi	No	Count	23	26	49
		% within CYSTATIN_GROUP	95.8%	100.0%	98.0%
	Yes	Count	1	0	1
		% within CYSTATIN_GROUP	4.2%	0.0%	2.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=1.105 P=0.293

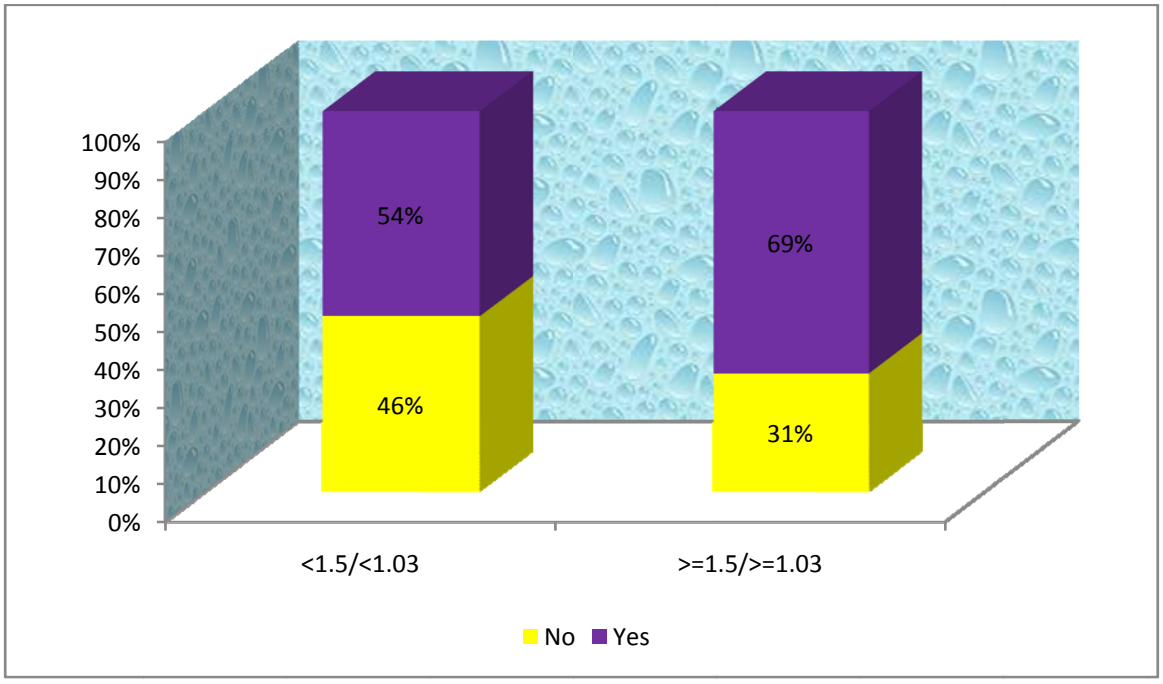


Among the cystatin C positive CAD cases, none had PLWMI

TABLE 38: CYSTATIN C LEVELS VS CK

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
CK_GROUP	20-200	Count	11	8	19
		% within CYSTATIN_GROUP	45.8%	30.8%	38.0%
	>200	Count	13	18	31
		% within CYSTATIN_GROUP	54.2%	69.2%	62.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=1.202 P=0.273

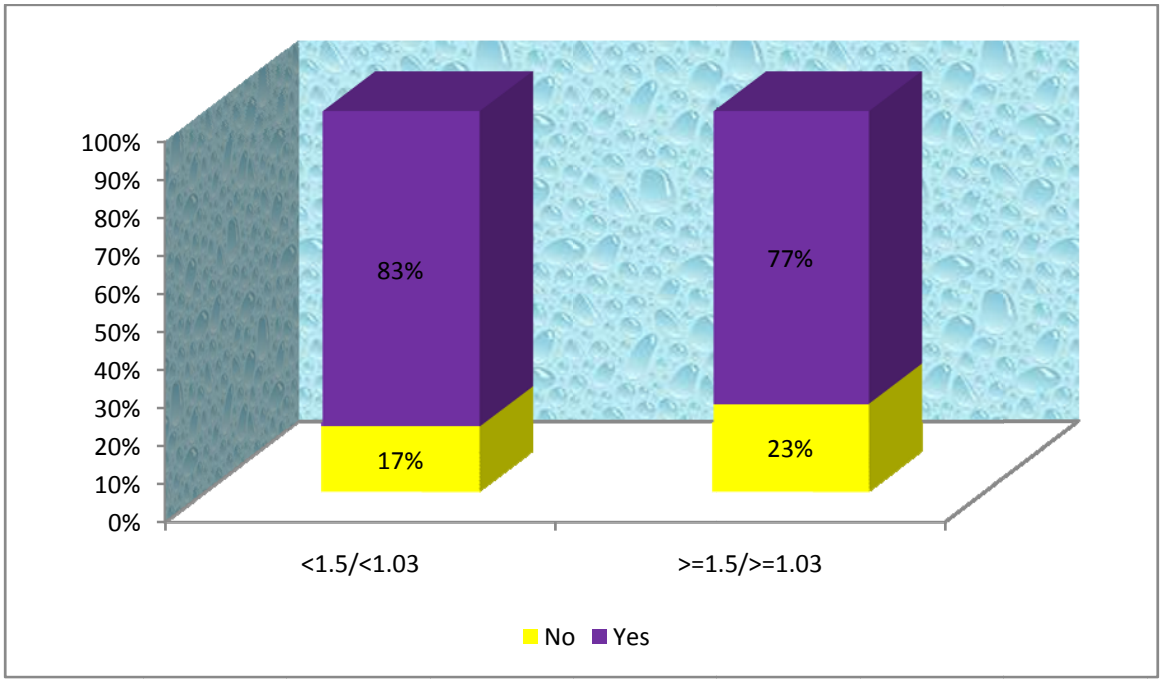


69 % of cystatin C positive CAD cases had elevated CK levels

TABLE 39: CYSTATIN C LEVELS VS CK-MB

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
CK_MB GROUP	0-24	Count	4	6	10
		% within CYSTATIN_GROUP	16.7%	23.1%	20.0%
	>24	Count	20	20	40
		% within CYSTATIN_GROUP	83.3%	76.9%	80.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=0.321 P=0.571

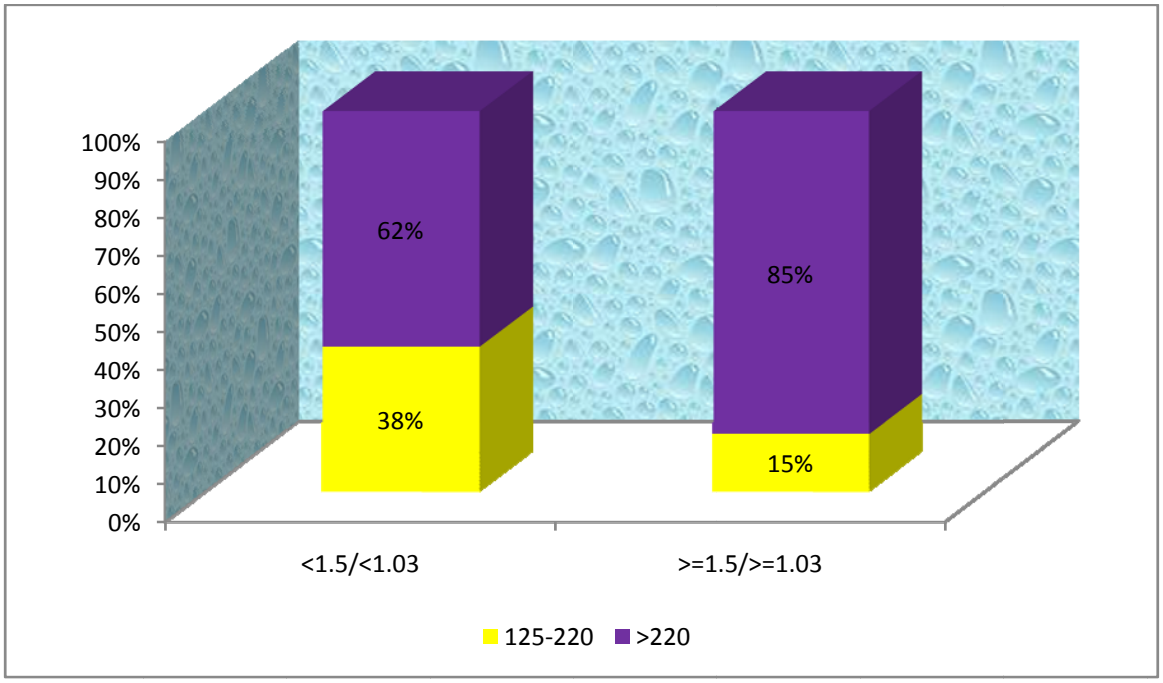


77 % of the cystatin c positive CAD cases had elevated CK-MB levels

TABLE 40: CYSTATIN C LEVELS VS LDH

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
IDH_ GROUP	125-220	Count	9	4	13
		% within CYSTATIN_GROUP	37.5%	15.4%	26.0%
	>220	Count	15	22	37
		% within CYSTATIN_GROUP	62.5%	84.6%	74.0%
	Total	Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=3.172 P=0.075

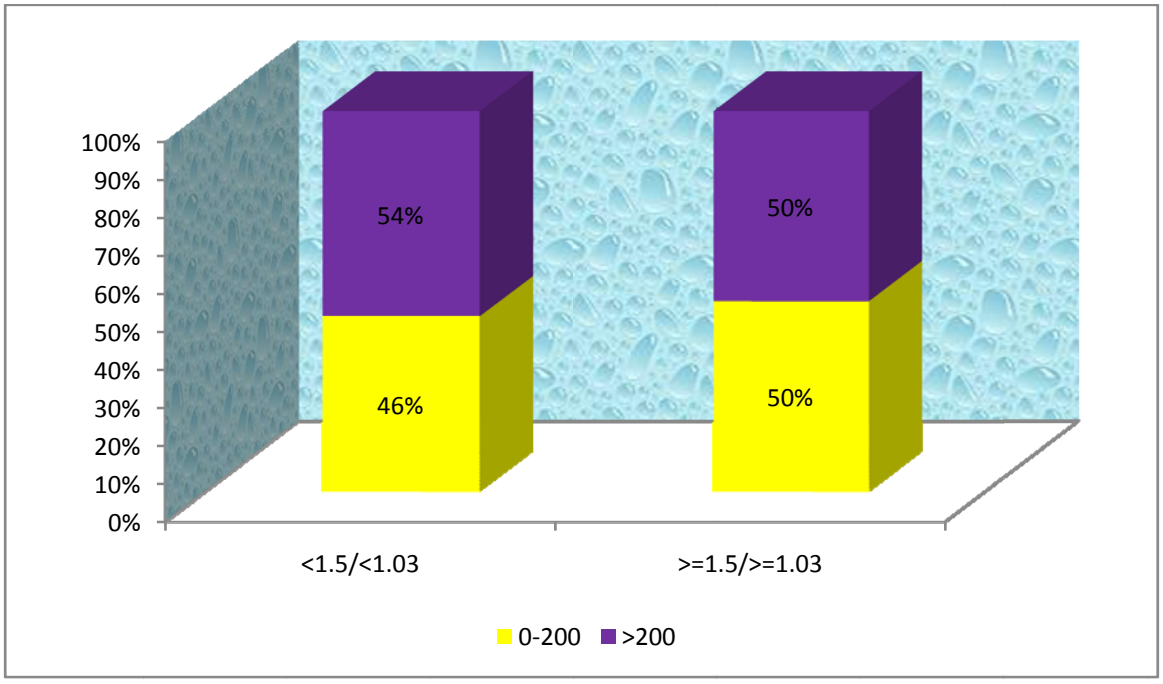


85% of the cystatin C positive CAD cases had elevated LDH levels

TABLE 41: CYSTATIN C LEVELS VS TOTAL CHOLESTEROL

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
TCHOLESTROL _ GROUP	0-200	Count	11	13	24
		% within CYSTATIN_GROUP	45.8%	50.0%	48.0%
	>200	Count	13	13	26
		% within CYSTATIN_GROUP	54.2%	50.0%	52.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=0.087 P=0.768

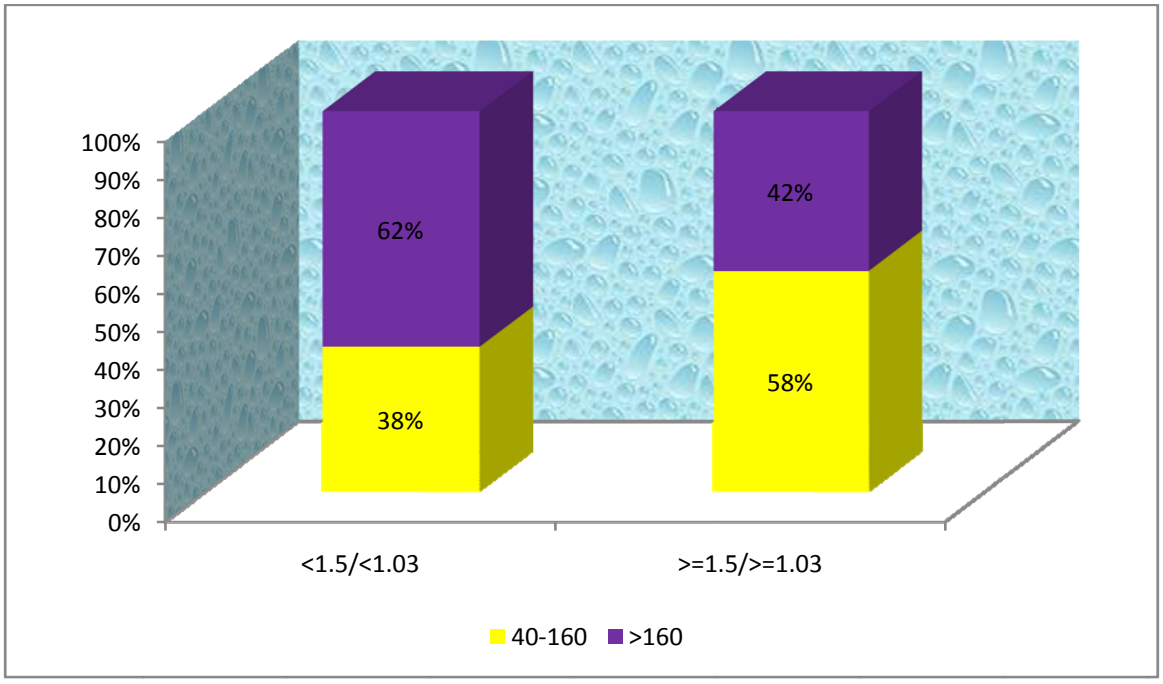


50% of the cystatin c positive CAD cases had increased total cholesterol levels

TABLE 42: CYSTATIN C LEVELS VS TRIGLYCERIDES

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
TGL_GROUP	40-160	Count	9	15	24
		% within CYSTATIN_GROUP	37.5%	57.7%	48.0%
	>160	Count	15	11	26
		% within CYSTATIN_GROUP	62.5%	42.3%	52.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=2.039 P=0.153

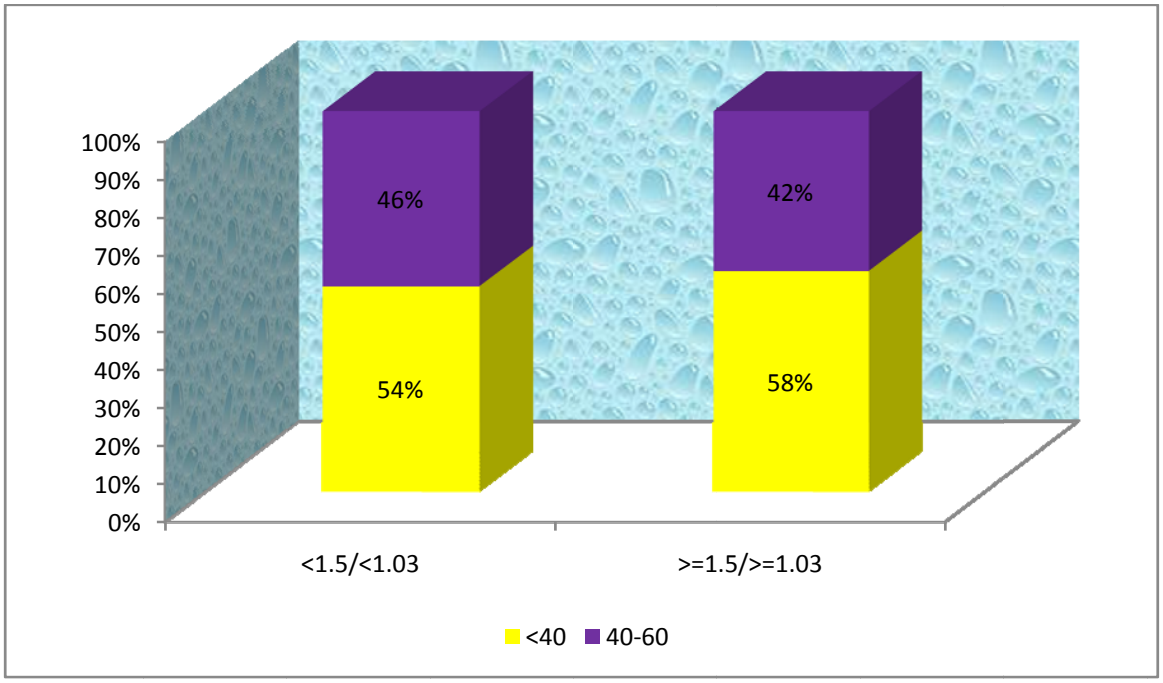


42% of the cystatin C positive CAD cases had increased TGL

TABLE 43: CYSTATIN C LEVELS VS HDL

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
HDL_GROUP	<40	Count	13	15	28
		% within CYSTATIN_GROUP	54.2%	57.7%	56.0%
	40-60	Count	11	11	22
		% within CYSTATIN_GROUP	45.8%	42.3%	44.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=0.063 P=0.802

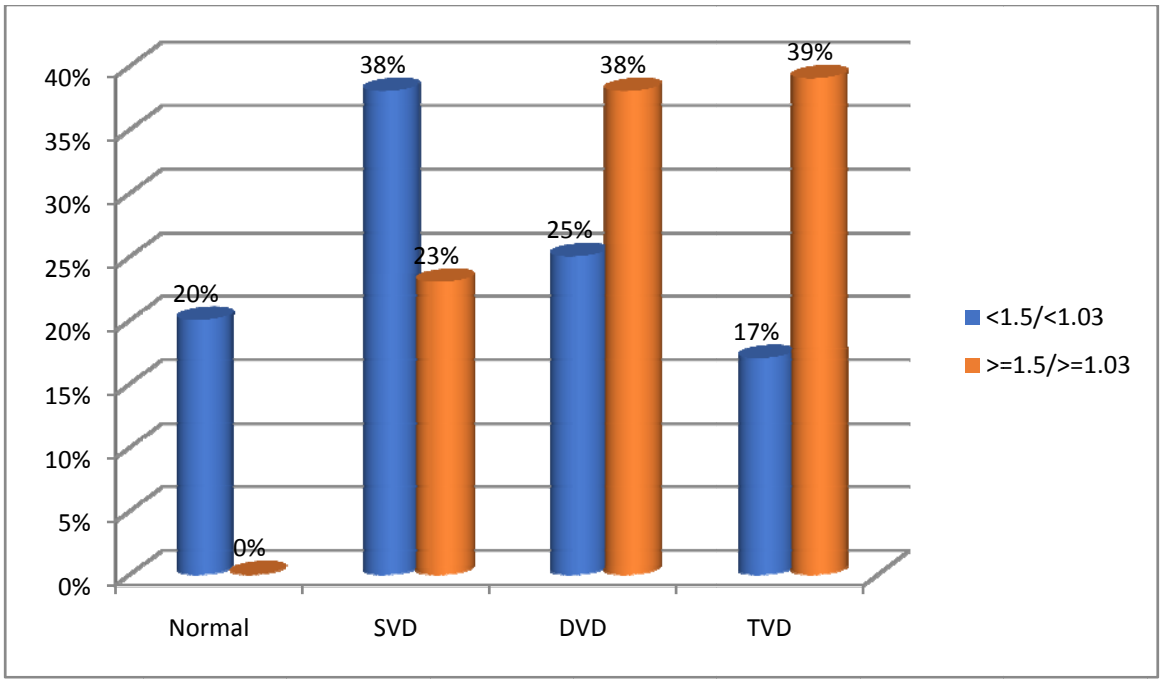


58% of the cystatin c positive CAD cases had decreased HDL levels

TABLE 44: CYSTATIN C LEVELS VS CORONARY ANGIOGRAM

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
angio	Normal	Count	5	0	5
		% within CYSTATIN_GROUP	20.8%	0.0%	10.0%
	SVD	Count	9	6	15
		% within CYSTATIN_GROUP	37.5%	23.1%	30.0%
	DVD	Count	6	10	16
		% within CYSTATIN_GROUP	25.0%	38.5%	32.0%
	TVD	Count	4	10	14
		% within CYSTATIN_GROUP	16.7%	38.5%	28.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=9.106* P=0.028

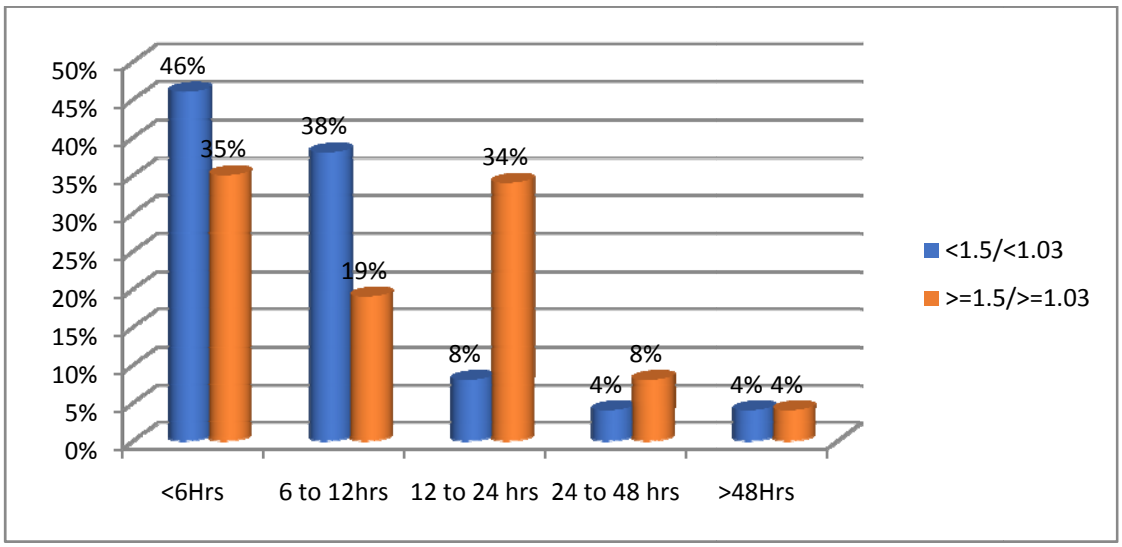


Among the cystatin c positive CAD cases who underwent coronary angiogram, 39% had TVD, 38% had DVD and 23 % had SVD. Applying the pearson chi square analysis , p value calculated as 0.028 ,which is significant. That is as cystatin C level increases , the incidence of DVD and TVD increases. Thus cystatin C correlates with the severity of the CAD.

TABLE 45:CYSTATIN C LEVEL VS TIME DISTRIBUTION

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
time_group	<6 HRS	Count	11	9	20
		% within CYSTATIN_GROUP	45.8%	34.6%	40.0%
	6 -12 HRS	Count	9	5	14
		% within CYSTATIN_GROUP	37.5%	19.2%	28.0%
	12 -24Hrs	Count	2	9	11
		% within CYSTATIN_GROUP	8.3%	34.6%	22.0%
	24-48 Hrs	Count	1	2	3
		% within CYSTATIN_GROUP	4.2%	7.7%	6.0%
	>48Hrs	Count	1	1	2
		% within CYSTATIN_GROUP	4.2%	3.8%	4.0%
Total		Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=6.060 P=0.195



As per this chart, no significant relationship could be established between cystatin c levels and the time of onset of symptoms, among the cystatin c positive CAD cases

TABLE 46:TROPONIN DISTRIBUTION AMONG CASES

			group		Total
			Control	Cases	
troponin	Positive	Count	0	29	29
		% within group	0.0%	58.0%	48.3%
	Negative	Count	10	21	31
		% within group	100.0%	42.0%	51.7%
	Total	Count	10	50	60
		% within group	100.0%	100.0%	100.0%

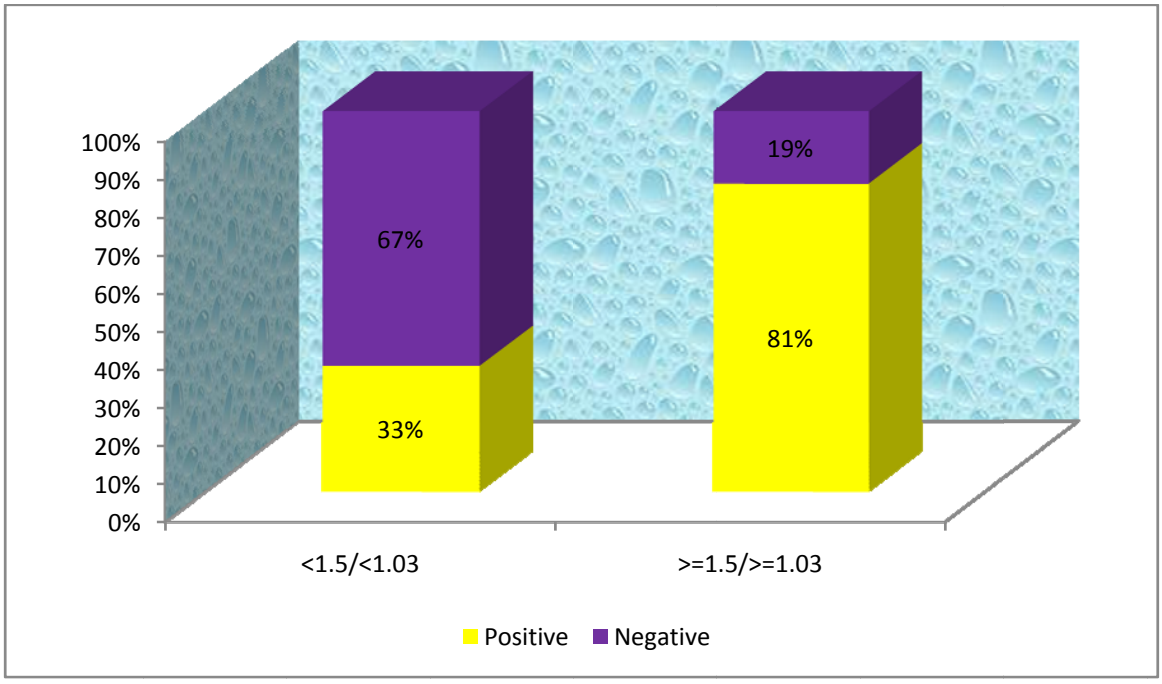
Pearson Chi-Square=11.226** p=0.001

Among the CAD cases, 58 % of them had positive tropoin,while control group had normal troponin levels.

TABLE 47: CYSTATIN C LEVEL VS TROPONIN

			CYSTATIN_GROUP		Total
			<1.5/<1.03	>=1.5/>=1.03	
Troponin	Positive	Count	8	21	29
		% within CYSTATIN_GROUP	33.3%	80.8%	58.0%
	Negative	Count	16	5	21
		% within CYSTATIN_GROUP	66.7%	19.2%	42.0%
	Total	Count	24	26	50
		% within CYSTATIN_GROUP	100.0%	100.0%	100.0%

Pearson Chi-Square=11.528** p=0.001



Among the cystatin c positive CAD cases, 81% had elevated troponin levels.

DISCUSSION

Cystatin C is a potent cysteine proteinase inhibitor. Owing to its low molecular weight, its freely filtered and reabsorbed at the proximal renal tubules but not secreted. Its been established as the reliable marker of renal function than creatinine. Recent studies have found significant relation between higher serum cystatin c levels and increased cardiovascular disease risk even in patients without renal disease. Its also found that serum serum cystatin levels independently predict the coronary atherosclerotic burden.

A prospective cohort study on serum cystatin C levels in coronary artery disease patients with normal renal function and its correlation with coronary angiogram was conducted at our Institute of Internal Medicine , Madras medical college and Rajiv Gandhi Government General Hospital for a period of 1 year from June2018 to May 2019 . 50 patients who were diagnosed to have coronary artery disease and who fulfilled the inclusion and exclusion criteria were included in the study after obtaining their consent. 10 non coronary artery disease patients like Rheumatic heart disease patients, ASD, etc undergoing pre operative coronary angiogram were taken as control.

In this study comprising 50 coronary artery disease patients , 72% of the CAD patients were less than 60 years of age and 28 % were more than 60 years of age. Among the 10 non CAD control patients, 80% were less than 60 years of age and 20% were more than 60 years of age. Of the 50 CAD cases, 84.6% of them with increased serum cystatin C levels were less than 60 years

of age and 15.4 % of them were more than 60 years of age. Pearson chi square result for this data is 4.276 and p value is 0.039, which is significant. That is there is a significant relationship between age group and cystatin C levels. As per this data younger CAD patients (< =60 years) tend to have raised serum cystatin C levels than the elderly.

Among cases, 74% were male and 26 % were female while among the control group, 70% were male and 30 % were female. Of the cases, 76.9% of the male CAD had elevated serum cystatin C levels while 23.1% of female CAD patients had elevated cystatin C levels. Pearson chi square result is 0.241 and the p value is 0.624. Its not significant. That is there is no significant relationship between serum cystatin levels and male/female sex.

Among the coronary artery disease cases, 52 % of them had elevated cystatin C levels while only 10 % of the control had increased cystatin C levels. Pearson chi square analysis done for this data and the result is 5.939 .p value is calculated to be 0.015 which is significant. It means cystatin C levels have significant relationship with coronary artery disease.

As per a study by Azza Dandana et al, on clinical utility of serum cystatin C predicting CAD in patients without CKD, it was concluded that serum cystatin C levels can be useful biochemical marker, predicting CAD and its severity.

According to a study by Urbonaviciene et al, higher serum cystatin C levels were found to be independent predictor of 5 year cardiovascular mortality in patients with normal renal function and peripheral arterial disease.

Among the CAD cases, 70% of them had STEMI, 4% of them had NSTEMI and 26 % had unstable angina. The control group patients did not have coronary artery disease. They had cardiovascular diseases like rheumatic valvular heart disease, atrial septal defect, ventricular septal defect,etc,.

Of the 35 STEMI cases, 20 of them had elevated serum cystatin C levels while 15 of them had normal cystatin C levels.. Pearson chi square for this data is 1.236 and p value is 0.266, which is not significant. That is there is no significant relationship between STEMI and cystatin C levels. Of the 2 NSTEMI patients, only one of them had elevated cystatin C levels. P value for this data is 0.954 which is not significant. Hence there is no correlation between cystatin C levels and NSTEMI. Similarly of the 13 unstable angina patients , 5 of them had increased cystatin C levels and the p value for this data is 0.256, which is not significant. That is there is no significant relationship between cystatin C levels and unstable angina.

Regarding the co-morbidities, among the CAD cases, 64 % of them had diabetes mellitus and in the control group ,10% had diabetes. Of the 32 diabetic CAD patients, 18 of them had elevated serum cystatin C levels. Pearson chi square result of this data is 0.643 and p value is 0.423 which is not significant. Thus no significant relation exists between diabetics and cystatin C levels.

While 58% of the CAD cases were hypertensives, only 10 % of the control group had hypertension. Of the 29 hypertensive CAD patients, 16 of them had elevated serum cystatin C levels. Pearson chi square result for this data is 0.278 and p value is 0.598(insignificant). Hence there is no significant relationship between hypertension and cystatin C levels.

32% of CAD patients were alcoholics while 10 % of the control group were alcoholic. Of the 16 alcoholic CAD cases, 9 had elevated cystatin C levels p. pearson chi square result for this data is 0.170 and p value is 0.680(insignificant) .hence no significant relation between alcoholic and cystatin C levels.

Regarding smoking, 38% of the cases were smokers. Of the 19 smoker CAD, 12 had raised serum cystatin c levels . pearson chi square analysis result is 1.529 and p value is 0.216(insignificant) . Hence no significant relation can be established between smoking and cystatin C levels.

Among the cases , 50 % of them had anterior wall myocardial infarction, 16% had inferior wall myocardial infarction , 4% had posterior wall myocardial infarction , 4 % had anterolateral wall myocardial infarction , 2% had posterolateral wall myocardial infarction. Among the 25 AWMI cases,16 had elevated serum cystatin C levels. After applying pearson chi square analysis for this data, p value is calculated to be 0.089(insignificant). No significant relation could be established between cystatin C levels and AWMI. Similarly no significant relation could be demonstrated between serum cystatin C levels and IWMI,PWMI,ALWMI and PLWMI.

Among the cases ,52% had elevated creatine kinase levels , 80% had elevated CK-MB levels , 74 % of them had elevated lactate dehydrogenase levels. Of the 31 creatinine kinase positive CAD, 18 had elevated serum cystatin C levels. After applying the pearson chi square tests for the following data, p value was 0.273(insignificant). Of the 40 CK-MB positive CAD cases, 20 had raised serum cystatin C levels . pearson chi square analysis of this data is 0.321 and p value is 0.571(insignificant). Thus there is no significant relation between CK, CK-MB and serum cystatin C levels. Also of 37 lactate dehydrogenase positive CAD patients , 22 had elevated serum cystatin C levels. Pearson chi square result and p value were insignificant showing that no significant relation existed between LDH and serum cystatin C levels.

Of the CAD patients , 58 % were troponin positive. Pearson chi square chart for this data was 11.226 and p value is SIGNIFICANT (0.001). Thus CAD patients will have significant troponin elevation. Of the troponin positive CAD cases, 80.8% of them had elevated cystatin C levels. Pearson chi square analysis for this data is 11.528 and p value is 0.001 ,which is very much significant. Thus troponin levels have relation with serum cystatin C levels.

Regarding the lipid profile, 52 % of the cases and 10 % of the control had increased total cholesterol levels . 52 % of cases had elevated triglyceride levels. While 56 % of the cases had decreased HDL levels , only 40% of the control group had decreased HDL levels. Of the 26CAD patients with high total cholesterol, 13 had raised serum cystatin C levels. Of 26 CAD cases with high triglyceride levels, 11 had elevated cystatin C levels. Of the 28 CAD

patients with decreased HDL levels, 15 had raised serum cystatin C levels. On applying pearson chi square test for the following data, p value is found to be insignificant ,thereby establishing that no significant relation exists between serum cystatin C levels and lipid levels.

Among the 50 CAD cases who underwent coronary angiogram, 30 % had single vessel disease , 32 % had double vessel disease , 28 % had triple vessel disease while 10 % of them had normal coronary angiogram. All the control group patients had a normal coronary angiogram. Of the 26 cystatin positive CAD cases who underwent coronary angiogram,6 of them had single vessel disease , 10 had double vessel disease and 10 had triple vessel disease. On applying pearson chi square test for this data ,result was 9.1026 and p value is 0.028 which is SIGNIFICANT. Thus as serum cystatin level increases ,the severity of coronary artery disease also increases .

According to a study conducted by Batra et al, among 150 Indian patients who underwent coronary angiography, higher plasma cystatin C levels were associated with diffuse CAD and increased incidence of triple vessel disease even in patients with normal renal function.

As per a study conducted by Niccoli et al, the significant association between serum cystatin C levels and cardiovascular events is due to increased coronary atherosclerotic burden, and its independent of renal function.

Among the coronary artery disease cases, 40% of them presented to hospital within 6 hours of symptom onset , 28% of them within 6 to 12 hours ,

22% of them within 12 to 24 hours , 6 % of them within 24 to 48 hours and 4% of them presented after more than 48 hours. Of the 26 cystatin C positive CAD cases, 9 presented <= 6 hours, 5 within 6 to 12 hours ,9 within 12 to 24 hours ,2 of them beween 24 to 48 hours and one person presented after more than 48 hours. Pearson chi square test applied to this data and p value calculated and is 0.195 (insignificant). Thus no significance is there in onset of coronary event and the serum cystatin C levels.

CONCLUSION

- Coronary artery disease is the leading cause of morbidity and mortality throughout the world
- Cardiac specific biomarkers like troponin T ,troponin I ,creatinine kinase –MB ,helps in definitive diagnosis of an acute coronary event.
- Markers to predict CAD earlier, its severity and prognosis is being studied .
- Recently serum cystatin C levels and its association with coronary artery disease in patients with normal renal function is being studied .
- Increased serum cystatin C levels are found to be associated with higher risk of fatal as well as non fatal cardiovascular events independent of the renal function
- It is also found to correlate with early stage of coronary atherosclerotic plaques burden
- A study on Indian population also revealed the association of higher serum serum cystatin c levels and increased incidence of triple vessel disease proved angiographically.
- Our study “serum cystatin C levels in CAD and its coronary angiographic correlation ’’done in RGGGH explains the following points

- ✓ Cystatin C levels is found to be significantly elevated in coronary artery disease patients with normal renal function.
- ✓ Increased serum cystatin C levels is found to be significantly associated with younger CAD patients (<= 60 years of age)
- ✓ Serum cystatin C levels correlate with serum troponin levels
- ✓ Serum cystatin C levels is found to be significantly associated with severity of CAD as proved by coronary angiography. That's as serum cystatin level rises , the incidence of double vessel and triple vessel disease increases.
- ✓ Thus serum cystatin C is a predictor of coronary artery atherosclerotic burden.
- ✓ Thus it can used as an early marker of CAD incidence ,to identify the high risk individuals and aid in early treatment ,intervention if needed.
- ✓ Cystatin C level in CAD patients has no significant variation between males and females.
- ✓ Its also not found to have significant association with co morbidities like diabetes and hypertension, among the CAD patients
- ✓ Its insignificantly associated with smoking and alcohol in CAD patients
- ✓ Its not significantly associated with the lipid levels in the CAD patients.
- ✓ Serum cystatin C levels also has no significant association with the time of onset of an acute coronary event.
- ✓ It does not have any causal relationship with CAD.

LIMITATIONS

- Sample size of this study is small
- Atherosclerotic burden is measured only in coronary arteries via angiography. It needs to be also assessed with many factors like carotid intimal thickness, stroke occurrence, peripheral arterial diseases or any other vascular events.

BIBLIOGRAPHY

1. Thomas A .Gaziano, J.Michael Gaziano, Epidemiology of Cardiovascular Disease, Harrison's Principles of internal medicine,20 th edition.
2. Data from AR Omran: The epidemiologic transition : Atheory of the epidemiology of population change. Milbank Mem Fund Q 49:509,1971; and SJ Olshansky, AB Ault:
3. The fourth stage of epidemiologic transition: The age of delayed degenerative diseases. Milbank Q64:355, 1986.
4. ROTH G et al: Global and regional patterns in cardiovascular mortality from 1990 to 2013. Circulation 132 :1667,2015.
5. Oberg M ,Jaakkola MS,Woodward A,et al. worldwide burden of disease from exposure to second hand smoke: a retrospective analysis of data from 192 countries. Lancet.2011;377(9760):139-146
6. Piano MR, Benowitz NL , Fitzerald GA,et al. Impact of smokeless tobacco products on cardiovascular disease: implications for policy, prevention, and treatment: a policy statement from the American Heart Association. Circulation.2010;122(15):1520-1544
7. Danaei G , Finucane MM, Lu Y, et al. National,regional and Global trends in systolic blood pressure since 1980:systematic analysis of health examination surveys and epidemiological studies with 786 coun try –years and 5.4 million participants. Lancet 2011;377(9765):568-577

8. Farzadfar F , Finucane MM, Danaei G ,et al. National ,regional and global trends in serum total cholesterol since 1980: systematic analysis of health examination surveys and epidemiological studies with 321 country –years and 3 million participant Lancet .2011;377(9765):578-586.
9. Whiting DR, Guariguata L,Weil C,Shaw J.IDF diabetes atlas: global estimates of the prevalence of diabetes foe 2011 and 2030. Diabetes Res Clin Pract. 2011;94(3):311-321
10. Popkin BM , Adair LS ,Ng SW Global nutrition transition and the pandemic of obesity in developing countries.Nutr Rev.2012;70(1):3-21
11. Bertoni AG, bonds DE, Thom T , Chen GJ, Goff DC Jr.Acute coronary syndrome national statistics: challenges in definitions. Am Heart J. 2005;149:1055-1061
12. Thygesen K, Alpert JS, Jaffe AS ,et al. Third Universal Definition of myocardial infarction. Eur Heart J.2012;33:2551-2567
13. Madias JE, Chintalapaly G ,Choudry M ,et al. Correlates and in-hospital outcome of painless presentation of acute myocardial infarction : a prospective study of a consecutive series of patients admitted to the coronary care unit. J Investig Med.1995;43:567-574.
14. Motoyama S , Ito H , Sarai M ,et al. Plaque characterization by coronary computed tomography angiography and the likelihood of acute coronary events in mid –term follow up.J Am Coll Cardiol.2015;66:337-346

15. Crea F , Liuzzo G.Pathogenesis of acute coronary syndromes. J Am Coll Cardiol.2013;61;1-11.
16. Libby P Nahrendorf M ,Swirski FK. Leukocytes link local and systemic inflammation in ischemic cardiovascular disease: an expanded "cardiovascular continuum. J Am Coll Cardiol.2016;67:1091-1103
17. Montecucco F et al; Pathophysiology of ST segment elevation myocardial infarction: Novel mechanisms and treatments. Eur Heart J 37:1268,2016
18. Dong Y,Undyala VV, Gottlieb RA, Mentzer RM Jr ,Przyklenk K. Autophagy;definition ,molecular machinery , and potential role in myocardial ischemia –reperfusion injury. J Cardiovasc Pharmacol Ther.2010:15:220-230
19. Weiss JN, Korge P, Honda HM, Ping P.Role of the mitochondrial permeability transition in myocardial disease.Circ Res.2003;93:292-301
20. Jennings RB . Historical perspective on the pathology of myocardial ischemia / reperfusion injury.Circ Res .1976;38:I80-I91
21. Zhang JH, Xu M. DNA fragmentation in apoptosis. Cell Res.2000;10:205-211.
22. Reimer K A, Jennings RB .The 'wavefront phenomenon" of myocardial ischemic cell death.II.Transmural progression of necrosis within the framework of ischemic bed size(myocardium at risk)and collateral flow.Lab Invest.1979;40:633-644

23. Reimer KA ,Lowe JE, Rasmussen MM, Jennings RB.The wavefront phenomenon of ischemic cell death.1.Myocardial infarct size vs duration of coronary occlusion in dogs.Circulation.1977;56:786-794
24. Frangogiannis NG .The inflammatory response in myocardial injury,repair and remodeling.Nat Rev Cardiol.2014;11:255-265
25. Prabhu SD,Frangogiannis NG.The biological basis for cardiac repair after myocardial infarction from inflammation to fibrosis.Circ Res .2016;119:91-112
26. Amsterdam EA ,Wenger NK,Brindis RG,et al.2014 AHA/ACC guideline for the management of patients with non st –elavation acute coronary syndromes:a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol.2014;64:e139-e228
27. Sharkey SW ,Lesser JR,Garberich RF,et al.Comparison of circardian rhythm patterns in takotsubo cardiomyopathy versus ST- segment elevation myocardial infarction.Am J Cardiol.2012 110 795-799
28. Kreatsoulas C ,Shannon HS,Giacomini M ,et al Reconstructing angina:cardiac symptoms are the same in women and men.JAMA Intern Med.2013;173:829-831
29. Scirica BM .Prevalence, incidence ,and implications of silent myocardial infarctions in patients with diabetes mellitus.Circulation.2013;127:965-967

30. Goldberger's clinical Electrocardiography: Simplified approach,9 th ed.Philadelphia,Elsevier,2017
31. Electrocardiography ,in Braunwauld's Heart Disease: A Textbook of Cardiovascular Medicine,11th ed ,JL Jameson et al(eds). Philadelphia, Elsevier, 2017
32. SOLOMON SD et al: Essential Echocardiography , a companion to Braunwauld's Heart Disease,Elsevier,2018
33. DI CARLI MF et al : The future of cardiovascular imaging. Circulation 133:2640,2016
34. MOSCUCCI M(ed): Grossman & Baim's Cardiac Catheterization, Angiography, and Intervention, 8 th ed. Philadelphia, Lippincott William's & Wilkin's.2014
35. Reiter M ,Twerenbond R ,Reichlin T,et al. Early diagnosis of acute myocardial infarction in patients with pre existing coronary artery disease using more sensitive cardiac troponin assays.Eur Heart J.2012;33:988-997
36. Morrow DA .Evidence –based algorithms using high sensitivity cardiac troponin in the emergency department JAMA Cardiol.2016;1:379-381
37. Carlton E,Greenslade J ,Cullen L,et al. Evaluation of high sensitivity cardiac troponin I levels in patients with suspected acute coronary syndrome .JAMA Cardiol.2016;1:405-412

38. Morrow D.Bonaca M.Real world application of ‘delta” troponin: diagnostic and prognostic implications. J Am Coll Cardiol.2013; 62:1239-1244
39. Pickering JW, Greenshade JH,Cullen L,et al.Assessment of the European Society of Cardiology 0-hour/ 1-hour algorithm to rule –out and rule-in acute myocardial infarction.Circulation 2016;134:1532-1541
40. Sukul D, Bonaca MP, Ruff CT ,et al. diagnostic performance of copeptin in patients with acute non traumatic chest pain :BWH-TIMI ED Chest Pain Study. Clin Cardiol.2014;37:227-232
41. Krintus M, Kozinski M,KUBICA J, Sypniewska G.C ritical appraisal of inflammatory markers in cardiovascular risk stratification. Crit Rev Clin Lab Sci.2014;51:263-279
42. Nadir MA,Witham MD, Szwejkowski BR, Struthers AD. Meta-analysis of B-type natriuretic peptide’s ability to identify stress induced myocardial ischemia. Am J Cardiol.2011;107:662-667
43. Scirica BM ,Sabatine MS ,Jarolim P,et al. Assessment of multiple cardiac biomarkers in non –ST-segment elevation acute coronary syndromes: observations from the MERLIN-TIMI 36 trial. Eur Heart J. 2011;32:697-705
44. Azza Dandana ,et al – Clinical utility of serum cystatin C in Predicting coronary artery disease in patients without chronic kidney disease,29 January 2014,Journal of Clinical Laboratory Analysis

45. Xie Qing ,et al-Cystatin C and asymptomatic coronary artery disease in patients with metabolic syndrome and normal glomerular filtration rate,14 th September 2012,Cardiovasc Diabetol.2012;11:108
46. Batra A, et al-Association pf plasma cystatin C levels with angiographically documented coronary artery disease in patients of Indian origin.
47. Joao Victor Salgado,et al –How to understand the association between cystatin C levels and cardiovascular disease: imbalance ,counterbalance ,or consequence?, Journal of Cardiology, volume 62, Issue 6,December 2013, Pages 331 -335
48. O'Gara PT,Kushner FG, Ascheim DD, et al.2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation / American Heart Association Task Force on Practice Guidelines. Circulation .2013;127:e362
49. Levine GN ,Bates ER ,Blankenship JC et al.2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention:executive summary . A report of the A merican College of Cardiology Foundation/ American Heart Association Task Force on PracticE Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation. 2011;124:2574

50. Hollander JE et al: State-of-the-art evaluation of emergency department patients presenting with potential acute coronary syndromes. Circulation 134:547,2016

51. Grines CL. Brown KF , Marco J,et al. A comparison of immediate angioplasty with thrombolytic therapy for acute myocardial infarction. N Engl J Med.1993;328:673-679

52. Armstrong PW, Collen D. Fibrinolysis for acute myocardial infarction;current status and new horizons for pharmacological reperfusion, part 2. Circulation.2001;103(24):2987-2992

53. Llevadot J, Giugliano RP, Antman EM.BOLUS fibrinolytic therapy in acute myocardial infarction.JAMA.2001;286(4):442-449

54. Yusuf S, Zhao F,Mehta SR,et al.Effects of clopidogral in addition to aspirin in patients with acute coronarysyndromes without ST-segment elevation.N Engl J Med.2001;345(7):494-502

55. Antman em ,Morrow DA, McC abe CH,et al.Enoxaparin versus unfractionated heparin with fibrinolysis for ST elevation myocardial infarction.N Eng J Med.2006;354(14):1477-1488

PROFORMA

NAME -

AGE -

SEX -

SYMPTOMS -

DURATION OF SYMPTOMS -

PAST HISTORY -

CKD/SURGERY/TRAUMA/DM/ HTN/ DYSLIPIDEMIA

EXAMINATION FINDINGS:

GENERAL EXAMINATION:

BP -

PR -

CVS-

RS -

ECG -

ECHOCARDIOGRAPHY -

ROUTINE LAB INVESTIGATION -

CYSTATIN C LEVEL -

CORONARY ANGIOGRAM -

STUDY ANALYSIS -

STUDY OUTCOME MEASURES -

In STEMI/NSTe-acs patients ,does cystatin C level correlate with the coronary angiographic disease severity

In unstable angina patients, can cystatin C levels help in early risk stratification,which in turn can aid in early intervention

To analyse if cystatin C can be used as cardiac biomarker

COMPLICATIONS, IF ANY DURING THE STUDY :-

INFORMATION SHEET

We are conducting a study on "**CYSTATIN C LEVELS IN CORONARY ARTERY DISEASE AND ITS CORRELATION WITH CORONARY ANGIOGRAM**" among patients attending Rajiv Gandhi Government General Hospital, Chennai and for this study your clinical and investigation details may be valuable to us.

The purpose of this study is to assess the serum cystatin C levels in coronary artery disease patients and to find its correlation with coronary angiogram.

We are selecting certain patients and if your are found eligible, you might need to undergo a coronary angiogram, which is a invasive investigation.

The privacy of the patients included in the study will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information would be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitiled.

The results of the study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator Signature of Participant

Date:

Place:

PATIENT CONSENT FORM

Study Detail : **CYSTATIN C LEVELS IN CORONARY ARTERY DISEASE AND ITS CORRELATION WITH CORONARY ANGIOGRAM**

Study Centre : Rajiv Gandhi Government General Hospital, Chennai.

Patient's Name :

Patient's Age :

Identification Number :

Patient may check (√) these boxes

1. I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask questions and all my questions and doubts have been answered to my complete satisfaction.
2. I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected.
3. I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study.
4. I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms.
5. I hereby consent to participate in this study.
6. I hereby give permission to undergo detailed clinical examination and investigations as required.

Signature of Investigator Signature/thumb impression of participant

Study investigator name: DR.THENMOZHI.T

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

EC Reg.No.ECR/270/Inst./TN/2013
Telephone No.044 25305301
Fax: 011 25363970

CERTIFICATE OF APPROVAL

To
Dr. T.Thenmozhi
I Year PG in M.D. General Medicine
Institute of Internal Medicine
Madras Medical College
Chennai

Dear Dr.T.Thenmozhi,

The Institutional Ethics Committee has considered your request and approved your study titled **"CYSTATIN C LEVELS IN CORONARY ARTERY DISEASE AND ITS CORRELATION WITH CORONARY ANGIOGRAM " - NO.21042018**

The following members of Ethics Committee were present in the meeting held on **03.04.2018** conducted at Madras Medical College, Chennai 3

1. Prof.P.V.Jayashankar	:Chairperson
2. Prof.R.Jayanthi,MD.,FRCP(Glasg) Dean,MMC,Ch-3	: Deputy Chairperson
3. Prof.Sudha Seshayyan,MD., Vice Principal,MMC,Ch-3	: Member Secretary
4. Prof.N.Gopalakrishnan,MD,Director,Inst.of Nephrology,MMC,Ch	: Member
5. Prof.S.Mayilvahanan,MD,Director,Inst. of Int.Med,MMC, Ch-3	: Member
6. Prof.A.Pandiya Raj,Director, Inst. of Gen.Surgery,MMC	: Member
7. Prof.Shanthy Gunasingh, Director, Inst.of Social Obstetrics,KGH	: Member
8. Prof.Rema Chandramohan,Prof.of Paediatrics,ICH,Chennai	: Member
9. Prof. Susila, Director, Inst. of Pharmacology,MMC,Ch-3	: Member
10.Prof.K.Ramadevi,MD., Director, Inst. of Bio-Chemistry,MMC,Ch-3	: Member
11.Prof.Bharathi Vidya Jayanthi,Director, Inst. of Pathology,MMC,Ch-3	: Member
12.Thiru S.Govindasamy, BA.,BL,High Court,Chennai	: Lawyer
13.Tmt.Arnold Saulina, MA.,MSW.,	:Social Scientist
14.Thiru K.Ranjith, Ch- 91	: Lay Person

We approve the proposal to be conducted in its presented form.

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

10/4/18

Member Secretary – Ethics Committee

URKUND

Urkund Analysis Result

Analysed Document: plag2.docx (D58022126)
Submitted: 31/10/2019 22:28:00
Submitted By: thenmozhiryzentronz@gmail.com
Significance: 1 %

Sources included in the report:

suren thesis final.docx (D57129573)
PLIAGARISM FINAL THESIS.docx (D57343330)
THESIS CONTENET 75 PAGES.docx (D31209418)
for plagiarism.docx (D56591712)
https://www.researchgate.net/publication/221767756_Association_of_plasma_cystatin_C_levels_with_angiographically_documented_coronary_artery_disease_in_patients_of_Indian_origin
https://thoracickey.com/st-segment-elevation-myocardial-infarction-415/

Instances where selected sources appear:

8

CERTIFICATE - II

This is to certify that this dissertation work titled **"CYSTATIN C LEVELS IN CORONARY ARTERY DISEASE AND ITS CORRELATION WITH CORONARY ANGIOGRAM"** of the candidate **Dr.THENMOZHI.T** with **Registration Number 201711022** for the award of M.D. Degree in the branch of BRANCH-1 GENERAL MEDICINE. I personally verified the urkund.com website for the purpose of plagiarism check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **1%** of plagiarism in the dissertation.

Guide & supervisor sign

with seal

நோயாளி தகவல் தாள்

மாரடைப்பு நோயாளிகளில் சிஸ்டாடின் சி அளவை கண்டறிதல், சிஸ்டாடின் சி அளவு மற்றும் இந்நோயாளிகளின் கரோனரி ஆன்ஜியோகிராமிற்கும் இடையே உள்ள தொடர்பை ஆய்வு செய்தல்.

CYSTATIN C LEVELS IN ACUTE CORONARY SYNDROME AND ITS CORRELATION WITH CORONARY ANGIOGRAM

நோயாளிகளுக்கான தகவல்:

உங்களை இந்த ஆராய்ச்சியில் பங்கு கொள்ள அழைக்கிறோம். நாங்கள் உங்களுக்கு கொடுக்கும் இந்த படிவத்தில் உள்ள விவரங்களைக் கொண்டு நீங்கள் இந்த ஆராய்ச்சிக்கு உட்படலாமா அல்லது நிராகரிக்கலாமா என்பதை நீங்களே முடிவு செய்யலாம். மேலும் உங்களின் சந்தேகங்களையும் எங்களிடம் கேட்கலாம். நீங்கள் எங்கள் ஆராய்ச்சிக்கு தகுதி உள்ளவராகும் பட்சத்தில். சென்னை. இராசீவ் காந்தி அரசு பொது மருத்துவமனையில் நடைபெறும் இந்த ஆராய்ச்சியில் உங்களை பங்கெடுத்துக்கொள்ள செய்வோம்.

ஆராய்ச்சியின் நோக்கம் :

இதய மின் அலைவரைவில் (ECG), STEMI/NSTEMI வகை மாரடைப்பு நோயாளிகளில் சிஸ்டாடின் சி அளவிற்கும், அந்நோயாளிகளுக்கு செய்யப்பட்ட கரோனரி ஆன்ஜியோகிராமிற்கும் இடையே உள்ள தொடர்பை ஆராய்தல்.

இதய மின் அலைவரைவில் (ECG), Unstable Angina மாரடைப்பு நோயாளிகளிலும் மேற்கண்ட தொடர்பை ஆராய்ந்து இந்நோயாளிகளில் எவருக்கு விரைவான தற்காப்பு சிகிச்சை தேவை என்பதை கண்டறிதல்.

சிஸ்டாடின் சி யை மாரடைப்பு குறிக்கும் குறியீடாக பயன்படுத்த இயலுமா என ஆய்வு செய்தல்.

சுய ஒப்புதல் படிவம்

ஆயவு நடத்தபடும இடம :இராசீவ காந்தி அரசு பொது மருத்துவமனை,
சென்னை மருத்துவக் கலலூரி, சென்னை.

பங்குபெறுபவரின பெயர் : பங்குபெறுபவரின வயது :

பங்குபெறுபவரின எண :

இந்த ஆயவில்குறிப்பிட்டுள்ள மருத்துவஆயவின விவரங்கள் எனக்கு விளக்கபபட்டது. நான இவவாய்வில தனனிசசையாக பங்கேறகிறேன். எந்த காரணத்தினாலும்எந்த சட்ட சிக்கலுக்கும உட்படாமல் நான் இவவாய்வில இருந்து விலகிக்கொள்ளலாம் எனறும அறிந்து கொணடேன.

இநத ஆயவு சமபநதமாகவோ அதை சாரந்த மேலும் ஆயவு மேறகொள்ளும்போதும இந்த ஆயவில பங்கு பெறும மருத்துவர் என்னுடைய மருத்துவ அறிக்கையை பார்ப்பதற்கு என அனுமதி தேவையில்லை எனபதை அறிந்து கொள்கிறேன். இந்த ஆய்வின் மூலம் கிடைக்கும முடிவை பயனபடுத்திக்கொள்ள மறுக்கமாட்டேன.

இந்த ஆய்வில் பங்குகொள்ள ஒப்புக்கொள்கிறேன். இந்த ஆய்வை மேறகொள்ளும மருத்துவ அணிக்கு உணமையுடன் இருப்பேன் என்று உறுதியளிக்கிறேன்.

பங்கேறபவரின் கையொப்பம் சாட்சிகளின் கையொப்பம்

இடம : இடம :

தேதி : தேதி :

பங்கேறபவரின்பெயர் மறறும் விலாசம :

ஆய்வாளரின கையொப்பம்

MASTER CHART

S.No	age	sex	cystatin c	stemi	nstemi	angina	echo	dm	htn	alcoholic	smoker	timewind	awmi	iwmi	pwmi	alwmi	plwmi	creatinine	ck	ck-mb	troponin	ldh	t.cholest	tgl	hdl	angio
1	60	female	1.59	yes	x	x	rwma+/ef-49	yes	yes	x	x	48 hrs	yes	x	x	x	x	0.8	121	20	positive	267	221	320	46	svd
2	57	male	2.13	yes	x	x	rwma+/ef-50	yes	yes	yes	yes	16hrs	yes	x	x	x	x	0.6	582	204	positive	446	274	204	32	dvd
3	48	male	1.48	yes	x	x	rwma+/ef-48	x	yes	yes	yes	14hrs	yes	x	x	x	x	0.8	642	96	positive	524	266	186	36	dvd
4	65	female	1.21	x	x	yes	rwma+/ef-44	x	yes	x	x	6hrs	x	x	x	x	x	0.8	53	8	negative	156	160	103	39	dvd
5	45	male	0.76	yes	x	x	rwma+/ef-55	x	x	yes	yes	8hrs	yes	x	x	x	x	0.9	278	89	negative	221	180	236	38	svd
6	60	male	0.96	yes	x	x	rwma+/ef-46	x	x	yes	yes	24 hrs	x	x	x	x	yes	0.7	268	80	positive	456	246	184	40	dvd
7	62	male	0.95	yes	x	x	rwma+/ef39			yes	yes	4 hrs	yes	x	x	x	x	0.7	2020	100	negative	1456	129	68	41	dvd
8	63	male	0.93	x	yes	x	rwma+/ef-38	yes	x	x	x	7hrs	x	yes	x	x	x	0.8	407	64	negative	879	110	170	19	tvd
9	46	male	0.86	x	x	yes	no rwma/ef-60	x	yes	yes	x	8hrs	x	x	x	x	x	0.9	182	42	negative	202	184	130	44	normal
10	61	male	1	yes	x	x	rwma+/ef-34	yes	yes	yes	yes	48 hrs	yes	x	x	x	x	0.8	610	56	positive	408	276	190	30	dvd
11	39	male	0.91	yes	x	x	rwma+/ef-52	x	x	x	x	1hr	yes	x	x	x	x	0.8	1957	256	negative	751	186	148	47	tvd
12	47	female	0.99	yes	x	x	no rwma	yes	yes	x	x	1 week	x	yes	x	x	x	0.6	576	146	positive	438	150	198	30	svd
13	48	female	0.72	yes	x	x	rwma+/ef-55	yes	no	x	x	7hrs	x	yes	x	x	x	0.4	101	14	negative	177	243	292	49	svd
14	73	male	1.1	yes	x	x	rwma+/ef-40	yes	yes	x	yes	4hrs	yes	x	x	x	x	0.9	302	40	negative	240	232	158	38	svd
15	70	male	0.78	yes	x	x	rwma+/ef-45	x	x	x	x	5hrs	yes	x	x	x	x	0.6	177	26	negative	245	163	175	43	dvd
16	30	female	0.88	x	x	yes	no rwma/ef-55	yes	x	x	x	4hrs	x	x	x	x	x	0.8	184	34	negative	180	198	146	32	normal
17	63	male	1.21	yes	x	x	rwma+/ef-48	yes	yes	x	x	10hrs	yes	x	x	x	x	0.9	484	156	positive	558	276	184	28	tvd
18	68	male	1.51	yes	x	x	rwma+/ef-32	yes	x	yes	yes	8hrs	yes	x	x	x	x	0.7	1202	204	positive	648	195	140	38	tvd
19	78	male	1.22	x	x	yes	no rwma/ef-51	yes	yes	x	x	4hrs	x	x	x	x	x	1	156	42	negative	186	242	186	40	svd
20	50	male	0.87	x	x	yes	no rwma/ef-60	x	yes	x	x	6hrs	x	x	x	x	x	0.6	134	36	negative	148	264	180	30	normal
21	52	male	1.11	yes	x	x	rwma+/ef-51	yes	yes	yes	yes	16hrs	yes	x	x	x	x	0.9	562	210	positive	550	220	134	42	dvd
22	60	male	1.22	x	x	yes	global hypo/ef-25	yes	yes	x	x	14hrs	x	x	x	x	x	0.8	179	25	positive	289	225	160	57	tvd
23	37	male	1.19	x	x	yes	no rwma/ef-55	x	yes	x	x	3hrs	x	x	x	x	x	0.9	150	45	negative	207	176	184	42	svd
24	43	male	2.52	yes	x	x	no rwma/ef-60	x	x	yes	yes	48 hrs	x	x	x	yes	x	1	223	10	positive	464	112	132	31	tvd
25	60	male	0.92	x	x	yes	no rwma/ef-55	x	yes	x	x	7hrs	x	x	x	x	x	0.6	180	22	negative	182	188	124	36	normal
26	55	female	2.47	yes	x	x	no rwma/ef-60	yes	yes	x	x	3hrs	x	yes	x	x	x	0.9	25	15	negative	209	214	178	41	dvd
27	57	male	1.19	yes	x	x	rwma+/ef-52	yes	x	x	x	4hrs	yes	x	x	x	x	0.8	436	108	positive	280	192	80	29	tvd
28	55	male	1.64	yes	x	x	rwma+/ef-46	yes	yes	yes	yes	22hrs	x	yes	x	x	x	0.7	709	188	positive	368	289	180	36	tvd
29	55	female	1.09	x	x	yes	no rwma/ef-60	yes	yes	x	x	5hrs	x	x	x	x	x	0.6	76	18	negative	282	175	68	29	svd
30	49	male	1.26	yes	x	x	rwma+/ef-44	yes	yes	yes	yes	4hrs	yes	x	x	x	x	0.8	326	78	positive	526	242	168	26	dvd
31	58	male	1.04	yes	x	x	rwma+/ef-50	yes	yes	yes	yes	7hrs	yes	x	x	x	x	0.9	446	174	positive	642	286	180	28	tvd
32	56	male	1.08	x	x	yes	no rwma/ef-62	x	yes	x	yes	9hrs	x	x	x	x	x	0.7	170	32	negative	169	195	89	32	svd
33	40	male	1.13	x	yes	x	rwma+/ef-52	x	x	x	yes	6hrs	x	x	x	yes	x	1	405	17	positive	182	179	170	38	dvd
34	49	male	1.36	yes	x	x	rwma=/EF-41	yes	x	x	x	13 hrs	yes	x	x	x	x	0.9	505	128	positive	506	266	186	43	tvd
35	55	male	1.1	yes	x	x	rwma+/ef-30	yes	x	x	x	4 hrs	yes	x	x	x	x	0.9	808	49	positive	321	156	57	46	dvd
36	80	male	1.56	yes	x	x	rwma+/ef-44	x	x	x	x	72 hrs	yes	x	x	x	x	0.9	497	94	positive	386	182	134	36	tvd
37	61	female	1.66	yes	x	x	rwma+/ef-55	yes	yes	x	x	3hrs	x	yes	yes	x	x	0.9	257	42	positive	358	187	149	56	dvd
38	50	female	2.02	x	x	yes	global hypo/ef-27	yes	yes	x	x	10 hrs	x	x	x	x	x	1	55	29	negative	256	284	160	47	tvd
39	52	male	1.14	yes	x	x	rwma+/ef-58	yes	x	x	x	18hrs	yes	x	x	x	x	0.8	160	18	positive	272	190	143	42	svd
40	43	female	1.4	yes	x	x	rwma+/ef-38	x	x	x	x	15 hrs	yes	x	x	x	x	0.8	530	92	positive	1222	188	127	54	svd
41	45	male	0.96	yes	x	x	rwma+/ef-56	yes	yes	yes	yes	3 hrs	x	x	yes	x	x	0.8	167	18	negative	400	225	230	40	svd
42	54	female	0.99	yes	x	x	rwma+/ef-40	yes	x	x	x	10 hrd	yes	x	x	x	x	0.7	468	74	positive	490	294	182	30	dvd
43	48	male	0.93	x	x	yes	no rwma/ef-58	x	x	x	x	6hrs	x	x	x	x	x	0.9	178	82	negative	212	175	94	55	normal
44	46	female	0.57	yes	x	x	no rwma/ef-60	yes	x	x	x	7 hrs	x	yes	x	x	x	0.7	284	68	positive	328	250	164	42	svd
45	74	female	0.96	x	x	yes	rwma+/ef-46	yes	yes	x	x	4hrs	x	x	x	x	x	1	176	32	negative	186	234	190	34	tvd
46	50	male	0.75	yes	x	x	rwma+/ef-52	yes	yes	yes	yes	14hrs	yes	x	x	x	x	0.6	220	40	positive	286	250	132	46	svd
47	75	male	1.43	yes	x	x	rwma+/ef-48	yes	yes	x	x	10hrs	x	yes	x	x	x	0.8	398	180	positive	674	264	190	38	svd
48	62	male	1.58	yes	x	x	rwma+/ef-50	yes	yes	x	x	8hrs	yes	x	x	x	x	0.6	508	102	positive	465	279	186	32	dvd
49	58	male	1.6	yes	x	x	rwma+/ef-42	x	x	x	yes	6hrs	yes	x	x	x	x	0.9	478	160	positive	368	188	79	38	dvd
50	52	male	1.88	yes	x	x	rwma+/ef-52	yes	yes	yes	yes	18hrs	yes	x	x	x	x	0.7	590	158	positive	458	254	124	34	tvd

CONTROL

1	45	male	0.82	x	x	x	rhd/ms/mr	x	x	x	yes	preop	x	x	x	x	x	0.9	124	24	negative	168	156	78	40	normal
2	58	male	0.6	x	x	x	rhd/severe ms	yes	x	x	yes	preop	x	x	x	x	x	0.71	98	33	negative	212	160	68	22	normal
3	62	female	0.9	x	x	x	rhd/as/ar	x	x	x	x	preop	x	x	x	x	x	0.93	145	20	negative	180	144	40	42	normal
4	65	male	1.1	x	x	x	rhd/as	x	yes	x	yes	preop	x	x	x	x	x	0.82	162	28	negative	168	200	52	48	normal
5	46	male	0.5	x	x	x	rhd/mr	x	x	x	x	preop	x	x	x	x	x	0.7	189	44	negative	156	176	84	37	normal
6	46	male	1	x	x	x	rhd/severe mr	x	x	yes	x	preop	x	x	x	x	x	0.5	90	20	negative	148	152	60	56	normal
7	60	female	0.9	x	x	x	asd	x	x	x	x	preop	x	x	x	x	x	1	88	32	negative	98	190	92	40	normal
8	40	male	0.7	x	x	x	vsd	x	x	x	x	preop	x	x	x	x	x	0.98	142	38	negative	187	260	54	36	normal
9	30	male	1.2	x	x	x	rhd/ms/mr	x	x	x	x	preop	x	x	x	x	x	0.73	182	36	negative	221	196	40	28	normal
10	36	female	0.87	x	x	x	rhd/severe mr	x	x	x	x	preop	x	x	x	x	x	0.89	176	40	negative	166	170	58	46	normal

units	
cystatin C	mg/L
creatinine	mg/dL
T. cholesterol	mg/dL
HDL	mg/dL
triglycerides	mg/dL
CK	IU/L
CK-MB	IU/L
LDH	IU/L