Study Of High Sensitivity C-Reactive Protein In Acute Myocardial Infarction

by

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LIST OF ABBREVIATIONS USED

CRP	**-**	**C-reactive protein**
ATP	**-**	**Adults treatment panel -111**
TG	**-**	**Triglycerides**
MAC	**-**	**Membrane attack complex**
Mpc-1	**-**	**Monocytic chemotactic protein-1**
NF-kb	**-**	**Nuclear factor Kappa beta**
PCRP	**-**	**Peripheral CRP**
MCRP	**-**	**Monomeric CRP**
CFHR4	**-**	**Complement factor H receptor**
TNF	**-**	**Tumuor necrosis factor**
MMP	**-**	**Metalloprotienase**
NO	**-**	**Nitric oxide**
IL	**-**	**Interleukin**
LDL	**-**	**Low density lipoprotein**
HDL	**-**	**High density lipoprotein**
VLDL	**-**	**Very low density lipoprotein**
LAD	**-**	**left anterior descending artery**
RAD	**-**	**right anterior descending artery**
LCx	**-**	**Left circumflex artery.**
MI	**-**	**Myocardial infarction.**
AHA	**-**	**American Heart association**
ACC	**-**	**American College of cardiology**

ECHO	**-**	**Echocardiogram**
ECG	**-**	**Electrocardiography**
EF	**-**	**Ejection Fraction**
NSTEMI	**-**	**Non – ST elevation myocardial infarction**
CVD	**-**	**Cardiovascular disease**
CV	**-**	**Cardiovascular**
CHF	**-**	**Congestive Heart failure**
CHD	**-**	**Coronary heart disease.**
IHD	**-**	**Ischemic heart disease**

ABSTRACT

Background:

Inflammatory marker, such as high sensitivity c-reactive protein is a very sensitive acute phase reactant of inflammation. Acute myocardial infarction (MI) triggers an acute phase response which is induced by inflammatory cytokines, which stimulates the liver to synthesize C-reactive protein.

Objective

The present study is to elucidate that a relationship exists between hs- CRP and coronary artery disease and evaluate the correlation of hs-CRP with cardiac markers such toponin I and CPK-MB.

Methodology:

The information for the study was collected from 50 Myocardial infarction patients and 50 patients without myocardial infarction patients who are admitted to BLDE (DEEMED TO BE UNIVERSITY) Shri B.M Patil Medical college Hospital and Research center ,Vijayapura from November 2017 to June 2019.Information was collected through prepared proforma from each patient. All patients were interviewed as per the prepared proforma and then complete clinical examination was done.

- **Inclusion Criteria[100]**

Detection of a rise and/or fall of troponin values with atleast 1 value above the 99th percentile URL and with atleast 1 of the following.

- Patients with Symptoms of acute myocardial ischemia.
- New ischemic ECG changes.
- Development of pathological Q waves.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.

AND

- **Age and sex matched non AMI patients / individuals.**

Exclusion criteria

1. OLD Ischemic heart disease, pericarditis, aortic dissection.
2. Hematological malignancy.
3. Hypothyroidism.
4. Chronic Alcoholics.
5. Chronic Kidney Diseases.
6. Chemotherapy
7. Muscular dystrophy

Results: Mean age group of patients was 57.9. Males out number females **.**In our study hs-CRP was raised in 98% of patients along with troponin I and CPK-MB but there was no linear correlation between them.. Diagnostic criteria of hs-CRP is established by ROC curves and it is increased after 6hrs of infarction.. As hs-CRP increases LVEF is reduced.

Conclusion: There is a significant role of hs-CRP in predicting Acute myocardial infarction and the prediction value is more predominant after 6hours. Thus hs-CRP can play a role in early indentification of MI and can also be used as a confirmatory indicator in MI patients as compared to troponin I and CPK-MB. Higher the serum hs-CRP levels at the time of admission in patients with AMI, greater the patients prone to develop a complication during their hospital stay.

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INTRODUCTION

Acute myocardial infarction (AMI)is a major public Health problem in the developed and developing countries like India, despite progressive research in diagnosis and management over last three decades. During the last few years, major improvements have been achieved in diagnosis and treatment of patients with AMI but inspite of these developments, it remains an important event from clinical point of view.[1, 4, 5]

Large number of asymptomatic individuals are at serious risk of developing a first heart attack because of their genetic predisposition, smoking , unhealthy dietary habits or physical inactivity[2] Evidence is emerging that medical practice does not adequately implement preventive actions in asymptomatic high risk individuals and patients with established coronary disease and thus they remain at substantial risk (recurrent) of disease and death.[3,5] About one-third of patients with evolving MI die before they reach hospital to receive any effective treatment.

It's becoming increasingly clear that inflammation is an important factor for AMI. Inherent to the inflammatory process is the occurrence of an acute phase response. This response is induced by pro-inflammatory cytokines, which are released from the inflamed tissue by inflammatory and parenchyma cells and stimulates the liver to synthesize a number of acute phase proteins. High sensitivity C-reactive protein (hs-CRP) is the classical acute phase reactant, the serum level of which has long been known to increase in AMI[2, 4]

hs-CRP, is a classical acute-phase protein , is an ideal sensitive inflammatory marker, marker of infection and tissue injury and is involved indirectly in the coagulation process . In contrast to all other major acute phase reactants and coagulation proteins, the plasma half-life (19h) is rapid and identical under all

conditions, so the synthesis rate of hs-CRP is the sole determinant of its plasma concentration.

In World Health Organization (WHO) excellent standards for hs-CRP measurement in plasma/serum and anti-CRP antibodies are available which are well-established and are precise, sensitive and robust essays. hs-CRP measurement thus has many advantages in the detection and monitoring of the acute phase response in general and the in relation to atheroma and its complications.

Serum hs-CRP was measured in 936 initially in healthy men taken from a random population to know the association between hs-CRP levels and coronary heart disease in large populations who took part in the first MONICA Augsburg survey. After 8-year follow up, study reported the significance of hs-CRP values in knowing about the prognosis and the occurrence of a first major coronary event.

In clinical studies, circulation levels of hs-CRP were found to correlate with total infarct size and it is an indicator of underlying coronary inflammation as well as the extent of myocardial necrosis.

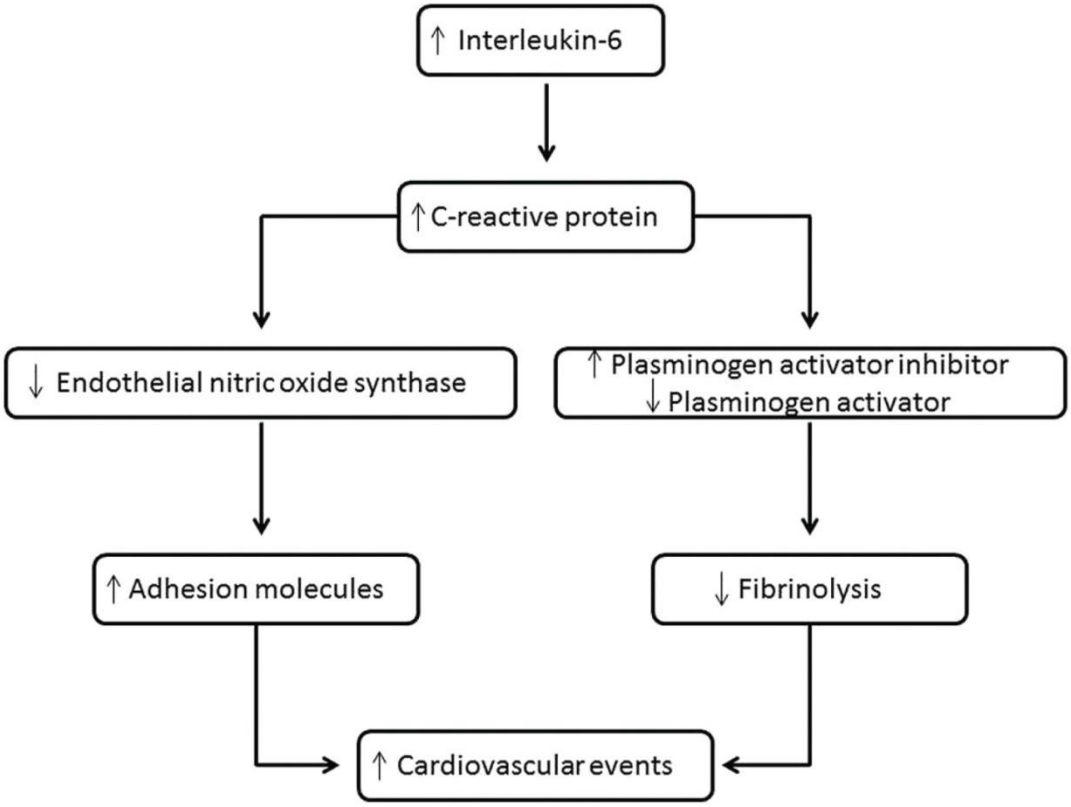
In view of the above context, the present study was done to know the serum concentration of hs-CRP in patients of AMI.

AIMS AND OBJECTIVES

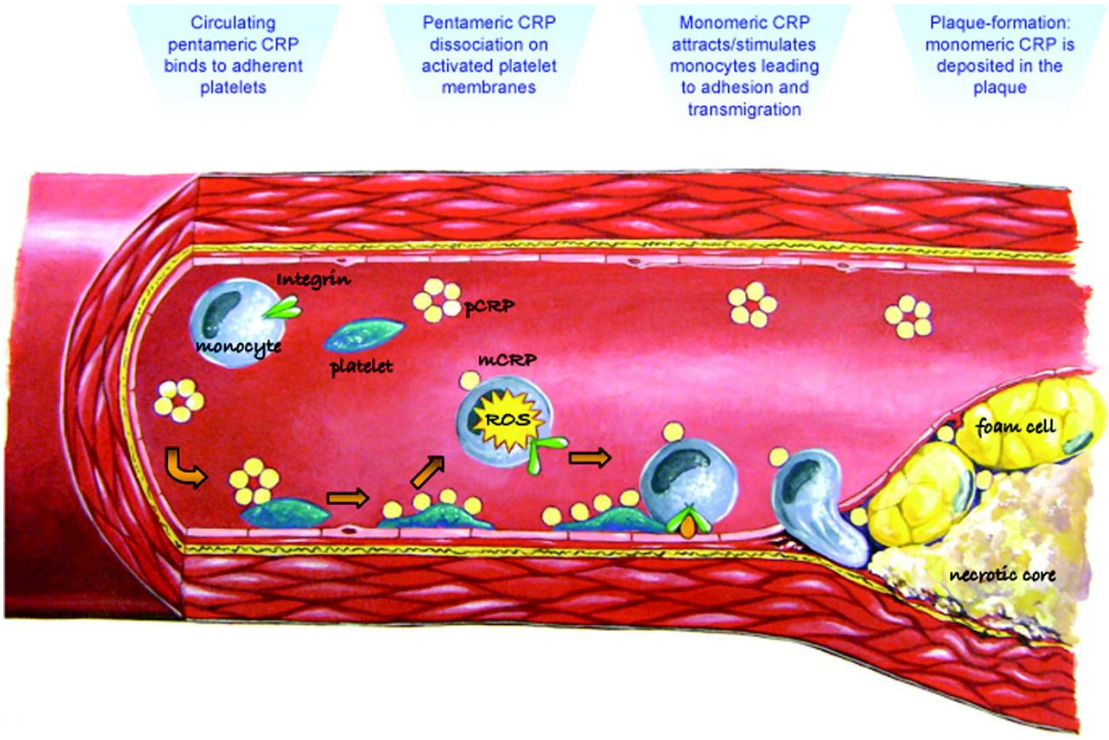
1. To estimate the levels of hs-CRP in clinically diagnosed patients with myocardial infarction.
2. To assess whether the parameters can be alternative markers to troponin I and CPKMB.

REVIEW OF LITERATURE

The leading cause of morbidity and mortality worldwide is cardiovascular disease with the main pathophysiological component being atherosclerosis. Atherosclerosis possesses an essential inflammatory aspect, and the involvement of various inflammatory molecules has been studied, particularly C-reactive protein (CRP).



CRP is a plasma protein, synthesized by liver under the influence of cytokines i.e. IL-6, TNF-alpha. It is resistant to proteolysis with strong phylogenic conservation. Atherosclerosis may be intervened by CRP by directly stimulating the complement system and promoting lipid accumulation, apoptosis, monocyte activation, vascular cell activation and thrombus are among other actions.



The monomeric form is formed from pentameric form after its dissociation in peripheral tissue including atherosclerotic plaques or can be produced de novo in extra hepatic locations. There are different changes in the process of atherosclerosis, as each form exhibits specific affinities for ligands and receptors. Measurement of levels of hs-CRP is selected as a tool for assessing the cardiovascular risk in the view of epidemiological evidence associating high CRP levels with cardiovascular risk.

Cardiovascular disease (CVD) is recognized major cause of morbidity and mortality in worldwide by the "world health organization (WHO)" and responsible for 16million deaths in 2008. 49% of the global mortality with estimated projection of around23 million yearly by 2030[5]

In an approach for prevention of cardiovascular diseases ,knowing about the risk factor and onset, progression has become the topic of interest.

"Cardiovascular risk factors such as (a) modifiable , including dyslipidemia, smoking, diabetes mellitus, hypertension, and (b) non-modifiable such as age, ethnicity and gender (c) triacylglycerides[6], homocysteine[7] ,and various inflammatory

markers are categorized as emerging risk factors by The report of the Expert panel on detection , evaluation and treatment of high blood cholesterol in Adults(ATP 3)"[8].

Evidence suggests that CRP does not participate in the buildup of atheromas per se[9] but only potentiates vulnerability of atheromatous plaque, focusing the need for further studies on CRP. The mechanisms for the involvement of CRP in development and progression of atherosclerosis and the molecular basis are presented here.

"Centre's of Disease control and Prevention and the American heart association gave us a conclusion that it is better to measure C-reactive protein, a sensitive marker of inflammation in order to assess the risk of coronary heart disease".[10]

The "MRFIT (Multiple Risk Factor Intervention Trial) was the first of many primary prevention, prospective epidemiological studies to show a strong relationship between levels of hs-CRP and mortality in CHD".[11]

"Coronary heart disease or Atherosclerosis coronary artery disease is the No.1 killer worldwide."[12]

hs-CRP role in atherosclerosis is proven in many studies. Atherosclerosis is an inflammatory process. Markers are hs-CRP, amyloid A, SICAM -1, homocysteine, IL-6, apolipoprotein B-100, HDL-cholesterol, Total cholesterol l,LDL- cholesterol and ratio of total cholesterol to HDL cholesterol. "hs CRP was the strongest univariate predictor of the risk of cardiovascular events of the 12 markers measured".[13]

C-REACTIVE PROTEIN

C-reactive protein is the first protein to be identified which behaves as an acute phase reactant. It has been labeled for its calcium-dependent interaction with the somatic C-polysaccharide of the pneumococci.

After the discovery of CRP in 1930 by Tilet and Francis. They have found that after serological reactions in pneumonia with the extracts of pneumococci they have noticed that fraction C which is non type specific somatic polysaccharide, was precipitated by the sera of a patient who is acutely ill. The C-reactive material was not found in the sera from normal healthy individuals after the crises and the capacity of patients sera to precipitate C-polysaccharide rapidly dissappeared[14]

Avery OT and his collaborators (1941) characterized the C-reactive material and coined the term "acute phase" which refers to serum from patients acutely ill with infection and containing the CRP which required calcium for its reaction.[15, 16]

Lofstrom G (1944) independently described that the substance responsible was C-reactive protein[17]after noticing capsular swelling reaction of some strains of pneumococci when mixed with acute phase sera. He noticed C-reactive protein in acute phase reaction , non-infectious as well as infectious conditions , in which the concentration of certain plasma proteins increase, due to general and non specific response to most forms of infective and non-infective inflammatory processes, cellular and/or tissue necrosis and malignant neoplasia.

Lofstrum (1994) described the appearance of C reactive protein by the technique of pneumococcal capsular swelling in patient's serum following myocardial infarction[18].C-reactive protein levels rise following myocardial infarction which was shown in subsequent studies[19].

Komodo et al.(2000)[20], Suleiman et al.(2003) ,Kinjo et al(2003) in their studies in the patients with acute MI , have proved that baseline C-reactive protein levels can predict both the short-term and long –term prognosis in such patients.

Rider et al(1997) [21,22]Harris et al.(1999) ,Koenig et al.(1999), Danish et al.(2000), ridker et al.(2000) ,ridker et al(2002) danesh et al(2004) in their studies by measuring

high sensitivity C-reactive protein levels at baseline in apparently healthy men and women including elderly have shown that , CRP levels which were considered in upper level of normal range independently predict the occurrence of major vascular events ,like myocardial infarction ,stroke and deaths.

Studies by Fichtlscherer et al[23], Verma et al., observed that at C-reactive protein levels is a powerful risk factor and predicted future cardiovascular events, also functioned as a proatherosclerotic factor.

"CDC/AHA workshop on inflammatory markers and cardiovascular diseases in Atlanta applications to clinical and public health practice was convened and they came up with guidelines which highlightened the role of C-reactive protein".

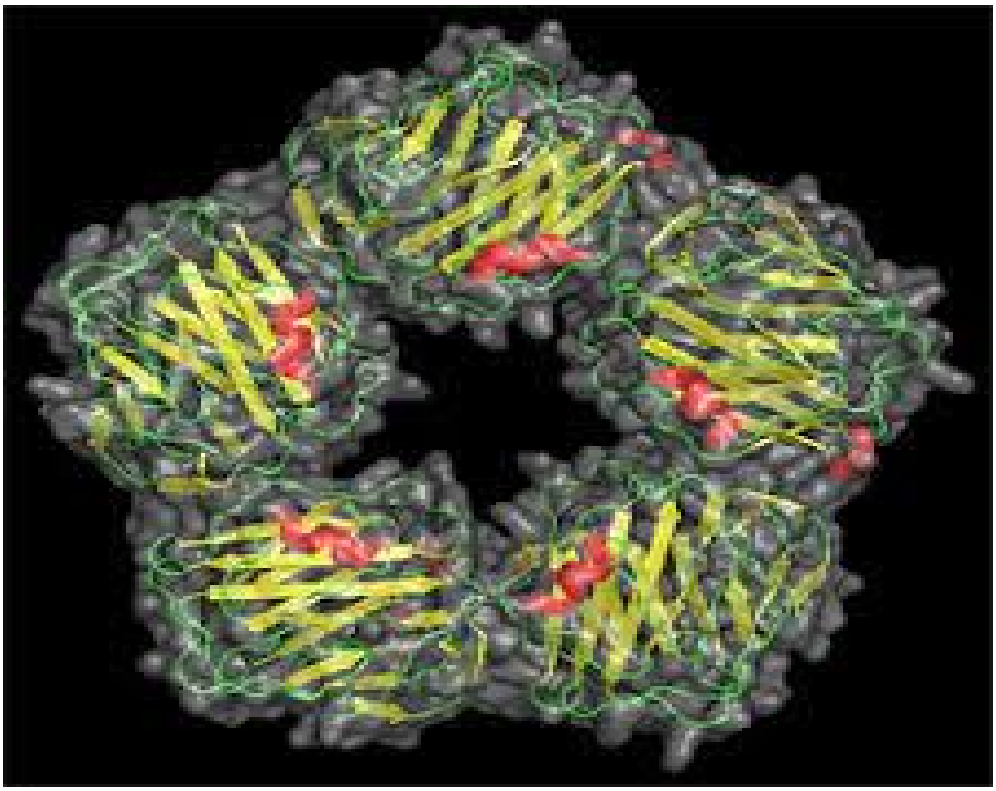
Lee H-J et al. study showed high has-CRP level may be strong predictor for atherosclerotic progression of the coronary arteries suggesting early detection is important[24].

A large study has shown that elevated hs-CRP levels are an independent risk factor for death from CHD.

STRUCTURE OF C-REACTIVE PROTEIN[25]

C - reactive protein belongs to pentraxin family of calcium dependent legend binding plasma proteins. The human C-reactive protein molecule (molecular weight1, 05,500 Da) composed of five identical non glycosylated polypeptide subunit (each of mass 23027 Da) with each subunit containing 206 amino acid residues. The promoters have cyclic pentameric symmetry with annular configuration .Each promoter is composed of a 2 layered beta sheet with flattened jelly roll topography with a 'lectin fold'. The ligand binding site, composed of loops with two calcium ions bound on the concave side with 4 A apart by protein side chains . The other face carriers a single

alpha helix. Only other proteins with a very similar molecular structure are distinct but closely related plasma proteins, serum amyloid-P component.

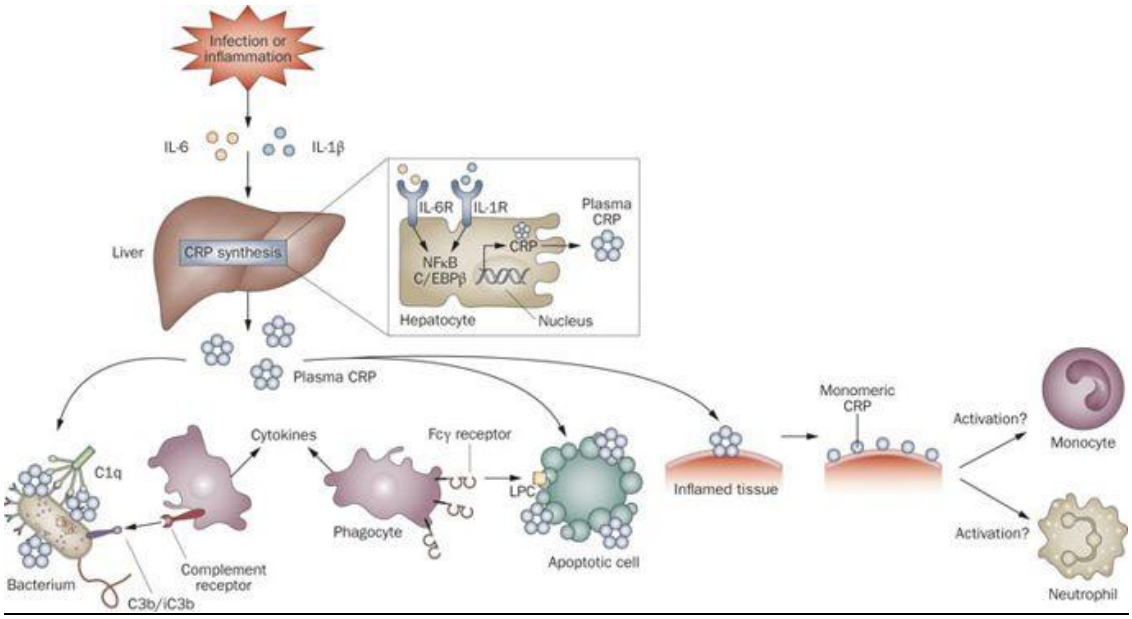


Functional properties

Ligand bound CRP activates the classical complement pathway via C1 and can trigger the inflammatory, opsonising and complex solubilizing activities of the complement system [26.] An important biological function of C-reactive protein may thus be recognized and 'scavenge' cellular debris, making its safe clearance and sustain tolerance to potential auto antigens. C-reactive protein may also protect against infection with pneumococci and hemophilus influenza organisms that can express phosphocholine and may thus contribute to innate immunity.

C-reactive protein can also have tissue damaging effects, complement activation by C-reactive protein exacerbates ischemic injury, and the pro-inflammatory actions of CRP and its binding to phospholipids and lipoproteins may

proatherogenic. Also its capacity to stimulate tissue factor production by macrophages may be proatherogenic.



C-reactive protein synthesis and its serum concentration[27]

Plasma C-reactive protein is produced by hepatocytes, under transcriptional control by the cytokine IL 6 [28, 29]

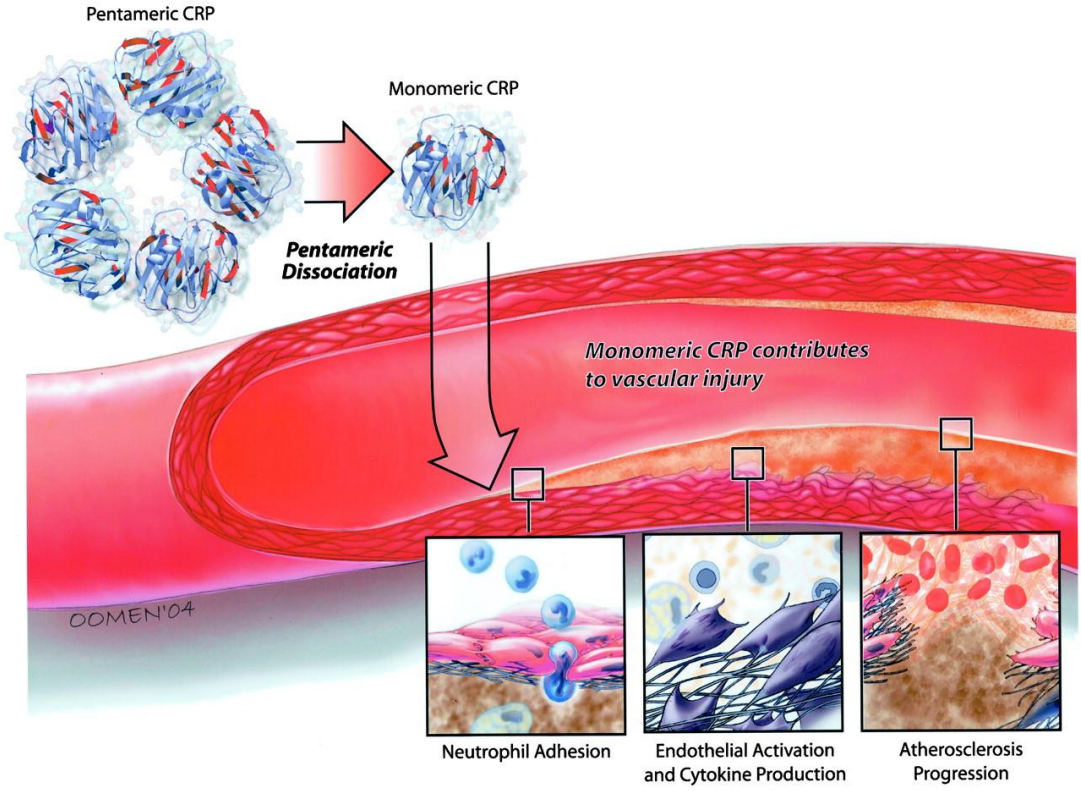
In overtly normal, healthy individuals, CRP is a trace protein, 0.8mg/l being the median value, with arrange of 0.3 to 1.7mg/l. 90%of healthy subjects have levels of less than 3mg/l and 99 percent less than 10mg/l .The values increase with age, with median CRP level is approximately increased twice with age, from approx 1mg/L in the youngest decade to 2mg in the oldest and tend to be higher in females [30] serum levels are lower in healthy newborns, but reaches adult levels within few days.

C-reactive protein values can increase from < 50micro/l to > 500mg/l i.e.10,000-fold after acute phase stimulus. After a single stimulus hepatic synthesis of CRP can occur very rapidly with concentrations rising above 5mg/l by about 6hours and peaks around 48hrs[31]. CRP is stable and not affected with food or time so there is

no need of measuring fasting sample. Hepatocellular impairment interferes with the capacity to interpret CRP levels as it is synthesized exclusively in liver.

Other factors known to influence CRP values

Genetic polymorphisms in IL-1 and IL6 is linked with CRP production and has been implied a polymorphic Guanidine thymidine repeat in the intron of the CRP gene is reportedly associated with differences in base-line CRP concentrations in normal individuals[32.] Interleukin-6 is the major up-regulator of CRP gene expression. Obesity is associated with increase in CRP as adipose tissue synthesizes IL-6.[33]Pentameric and monomeric CRP



Smoking presumably through its anti-inflammatory and tissue damaging effects is known to raise CRP concentrations [34]

Non-drinkers and heavy drinkers had higher CRP concentrations then moderate drinkers as shown by imhof et al in 2001 CRP levels were increased in

women taking oral contraceptives aspirin and statin therapy[35] is known to reduce CRP levels in the serum probably explaining their direct anti-inflammatory effects.

C-reactive protein response in diseases[36, 37]

Malignancy: sarcoma, lymphoma and carcinoma.

Major CRP acute phase Response.

Trauma: Surgery, burns, fractures.

Infections: Viral, Bacterial, severe/systemic fungal, mycobacterium.

Necrosis: Acute Pancreatitis, myocardial infarction, tumor embolization.

Allergic complications of infection: Erythema nodosum, Rheumatic fever.

Inflammatory disease: familial Mediterranean fever, psoriatic arthritis, Rheumatoid arthritis, polymyalgia rheumatic, juvenile chronic arthritis, systemic vacuities, reiters syndrome, chron'sdisease , ankylosing spondylitis.

Routine clinical uses of CRP measurement[37]

Screening test for organic disease

Vasculitides – Polymyalgia rheumatic

behcet's syndrome

Polyarteritis nodosa

Wegner's granulomatosis

Psoriatic arthropathy

Ankylosing spondylitis.

Assessment of disease activity in inflammatory conditions.

Juvenile chronic(rheumatoid) arthritis

Reiter's disease

Rheumatoid arthritis.

Rheumatic fever

Post-operative complications including infection and thromboembolism.

Familial Mediterranean fever

Intercurrent infection in leukemia and its treatment

Acute pancreatitis

Diagnosis and management of infections

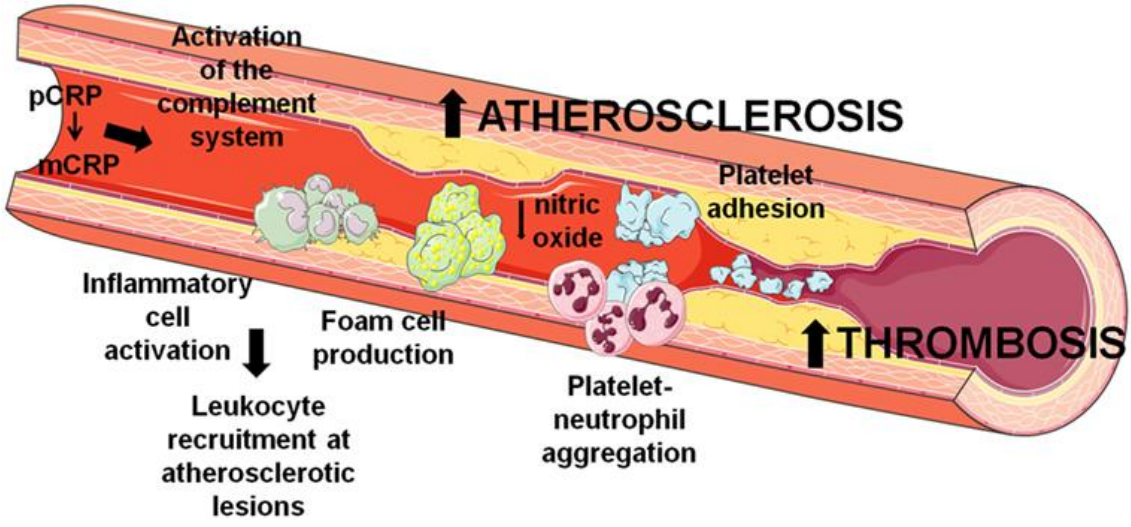
Intercurrent infection in systemic lupus erythematosis

Bacterial endocarditis

Neonatal septicemia and meningitis

C- reactive protein and pathogenesis of atherosclerosis[37]

Plasma lipoproteins binds to CRP and that is well known. It also binds to lipids especially lecithin(phosphatidylcholine). First approach of a possible relationship to atherosclerosis came when it was established that aggregated, but not the original, non-aggregated CRP preferably bound to LDL and some VLDL[38, 39].



However, native CRP binds to oxidized LDL and to incompletely degraded LDL, as found in athermanous plaque and stimulates compliment. Complement plays a role in atherogenisis. CRP promotes compliment activation and thus inflammation in the plaques.

In cell culture foam cells are formed by addition of CRP to LDL, which is typical feature of atherosclerotic plaques .Also elevated CRP levels are associated with blunted systemic endothelial vasodilator function.

"Role of C-reactive protein as predictor of future events in healthy individuals"[40]

Several studies have shown that the increased baseline CRP levels in apparently healthy men(ridker et al ,1997; Ridker et al.,1998; Ridker et al.,2000 ;Ridker et al 2002) including elderly (Harris et al.,1999) is independently correlated with future association of coronary artery disease, myocardial infarction, death due to cardiovascular cause and stroke.[21]

High sensitivity C-reactive protein (hs-CRP) [38]

It is no way different from conventional CRP and hence is not a different analyte. The high sensitivity refers to the lower detection limit of the assay procedures being used. The actual CRP analyte, the plasma protein which is being measured , is the same regardless of the assay limits .Hence by applying these ,CRP levels are detected even in the normal range with individuals in the upper level of the normal(ULN) having adverse future cardiovascular events being healthy prior to that.

Estimation of hs-CRP levels

Various immunological assays are available for detection of hs-CRP levels. The most widely accepted method is dade Behring BN 11 N high sensitivity CRP assay. The various methods used are

1. Immunonephelometric assay.
2. Immuneturbidmetricassays.
3. Immunoluminometricassays.

"Vast majority of hs-CRP immunoassays are calibrated to either the WHO 1st international reference preparation for C-reactive protein. Immunoassay (85/506), introduced in 1986 or CRM 470, introduced in 1993"[41]

Competitive ELISA

This method uses polyclonal anti-CRP antibody coated wells and definite load of biotimylated CRP is added to it and incubated it overnight and peroxidase –labelled ,avidin-biotin complex is added to the wells to generate a colour reaction.hs-CRP concentration is inversely proportional to the colour generated.[42]

Nephelometry

It uses particle-enhanced technology, Monoclonal anti-CRP antibodies are used. These specific antibodies are used. These specific antibodies coated to polymerase particles form complexes with CRP present in sample. The magnitude of scattered light is directly proportional to the amount of antigen –antibody complex and reflects the hs-CRP levels in the sample.[42]

CRP and coronary artery disease.

CRP has emerged as the important marker of inflammation[43.] It is a reliable predictor of cardiovascular risk and he was been evaluated in many phases or coronary disease, it has an array of proinflammatory properties that potentially contribute to the pathogenesis, progress and complications of atheroma.

"Centre for disease control and prevention/American heart association (CDC/AHA) recommendation for the use of hs-CRP in clinical and public health practice"[39]

1. Population science

The whole adult population should not be screened for hs-CRP for purpose of cardiovascular risk assessment (class 3, level of evidence C)

2. Clinical practice

1. hs-CRP can be used for primary prevention of CVD as it helps in risk assessment and can be used for further evaluation and therapy It is an independent marker of risk assessment.
2. hs-CRP is a marker of risk. In adult patient without a known CVD, hs-CRP can be used a part of global risk assessment at the discretion of the physician. The benefits of this strategy remain uncertain
3. hs-CRP levels may be useful in motivating patients to improve lifestyle behaviors. The benefit of this strategy remains uncertain.
4. elevation of hs-CRP (>10mg/dl) after repeated testing should be evaluated for non cardiovascular etiologies.

Among the current inflammatory markers, hs-CRP has the assay characteristics most conclusive to use in practice.

2. “hs-CRP levels, is categorized as follows:

Risk category hs-CRP levels

Low : <1mg/l

Average: 1.0 to 3mg/l

High:>3mg/l

3. “hs-CRP results should be expressed as mg/l only”

MYOCARDIAL INFARCTION

CORONARY CIRCULATION[44]

Blood supply to and from the heart muscle is by the blood vessels from the coronary circulation. Although blood fills the chamber of the heart, the muscle tissue of the heart or myocardium is so thick that it requires coronary blood vessels to deliver blood deep into it. Coronary arteries supply oxygen rich blood to the myocardium. Cardiac vein removes deoxygenated blood from the heart muscle[44]

On the surface of the heart epicardial coronary arteries are present. Epicardial coronary arteries maintain coronary blood flow by auto regulation at levels appropriate to the needs of the heart muscle. Angina or myocardial infarction is caused when these narrow blood vessels are affected by atherosclerosis and gets blocked. Subendocardial vessels run deep into the myocardium

The heart occupies central left part of thorax (lying on the diaphragm). The apex is directed forwards, downwards and leftward and is oriented anteriorly. RCA, LAD, LCX perfuses the myocardium

"Left anterior descending coronary artery" (LAD)

The LAD is divided into two large branches: the LAD and LCx coronary arteries. The LAD courses towards the apex through the anterior interventricular groove and supplies the anterior wall of LV. The artery may continue to the inferoapical wall by wrapping around the apex of LV.

First branch:

"The first branch of the LAD is the first diagonal artery. This branch runs parallel to the LCx artery and supplies the basal anteriolateral wall of LV. If the 1st diagonal is a large branch, complete occlusion of this artery causes ST elevation in

leads me and aVL with reciprocal ST depression in l11 and aVF. These ECG changes may be indistinguishable from that due to occlusion of small LCx coronary artery"[44]

Second branch: The second branch of the LAD is the first septal. This artery may be the first instead of the second branch. This artery penetrates the ventricular septum perpendicularly and supplies the basal septum including the proximal conduction system. Involvement of the first sepal perforator will cause ST elevation in V1. It may also involve the conduction system causing new onset right bundle branch block

Right coronary artery

The right ventricle, the inferior region of the septum is perused by RCA. (Part of segments 3 and9). Sometimes Segment 14 is shared by both arteries but mostly by LAD. The inferior wall can be perfused by RCA instead of LCX, if this artery is dominant type (seen in 10%) if the LAD is long it can perfuse segment 15. Parts of segments 5, 11 and 16 are perused by RCA via the posterolateral branch, if it is very dominant. Lastly, if the LAD is very short, RCA septal branch peruses segment 17. A branch of the posterior descending i.e. AV nodal artery peruses AV node[44]

"Left circumflex coronary artery"

The LCx coronary artery circles the left atrioventricular (AV) groove laterally between the left atrium and LV and gives branches that supply the anteriolateral and posterolateral wall of LV. The artery may be small and may terminate very early. In 10% to 15% of cases, the LCx continues posteriorly towards the crux of the heart and down the posterior interventricular groove as the posterior descending coronary artery. When this occurs, the LCx is the dominant artery. When this occurs, the LCx is the dominant artery and supplies the wall of the LV but also gives rise to the artery to the AV node

"The definition of acute myocardial infarction".[45]

"Myocardial infarction can be defined from a different perspectives related to clinical, electrocardiographic (ECG), biochemical and pathologic characteristics. It is accepted that the term myocardial infarction reflects death of cardiac myocytes caused by prolonged ischemia, initial diagnosis of acute infarction".

History of chest pain/discomfort

ST- segment elevations or (presumed) new left bundle branch block on admission ECG, repeated ECG recordings often needed.

Elevated markers of myocardial necrosis (CK-MB, troponins) [45]

Pathogenesis – Current concepts on the scientific basis of inflammation in atherogensis[46, 47, 48]

Lipid accumulation in the arterial wall along with signs of inflammation occurs in hand in hand in animal models of atherosclerosis. In human and animal models, inflammation is evidenced by leucocyte mediated defense and inflammation in earliest lesions. In atheroma, vascular cell adhesion molecule (VCAM) binds to leucocytes of different types. Interestingly, in the sites prone to develop atheroma there is foci of increased adhesion molecule which overlap. Atheroprotective mechanism is less at branch points in arteries, where there is decreased blood blow to endothelium. For example, local production of endothelium derived nitric oxide is less where the shear stress is absent.

The expression of VCAM-1 is altered in the presence of endogenous vasodilator which has anti-inflammatory properties. Disturbed blood flow can alter the production of certain leukocyte adhesion molecules ICAM-1. Disturbed blood flow can augment the production of certain leukocyte adhesion molecules such as ICAM-1 and inhibit natural protective mechanism. If there is increased wall stress, it

promotes production of arterial smooth muscle cells of proteoglycans which binds and retains lipoprotein particles, and helps in oxidative modification and thus promoting an inflammatory response at the site of lesion formation. Once adherent to endothelium, leucocytes migrate to intima.

Recent research proves that transmigration occurs via chemo attractant molecules. For example, at the site of lesion formation transmigration of monocytes occurs via monocyte chemoattractant protein 1(MCP-1) into the intima.

The local inflammatory response is extended once inflammatory cells enter the arterial wall. Foam cells are formed when the lipoproteins are modified with the help of scavenger receptors expressed by macrophages and permitting them to ingest lipid. Macrophages as well as vascular endothelial cells and SMC's are stimulated by cytokines like TNF-B, gamma interferon which are expressed by the T - cells.

There is elaboration of more advanced atherosclerotic lesion as the inflammation continues with the help of activated leucocytes and intrinsic arterial cells by the release of fibrogenic mediators like the peptide growth factors that help in replication of SMC's. Along with the initiation and evolution of atheroma, inflammatory process contributes in precipitating complications of atheroma. Physical disruption the atherosclerotic plaque causes fatal acute myocardial infarction.

Activated Macrophages which are abundant in atheroma are capable of producing proteolytic enzymes that degrade the collagen and decreases the strength fibrous cap that protects the plaque and makes it vulnerable to rupture.

There is evidence that a link exists between arterial inflammation and thrombosis when the tissue factor which is major procoagulant is produced by the macrophages in the presence of inflammation.

PATHOPHYSIOLOGY: ROLE OF ACUTE PLAQUE RUPTURE[49, 50]

Acute MI usually occurs when coronary blood flow reduces abruptly after occlusion of a coronary artery by thrombosis. The artery previously affected by atherosclerosis and slowly developing, high grade coronary artery stenosis will not typically trigger acute MI because development of rich collateral network overtime.

When there is plaque ruptures and the conditions favor thrombogensis resulting in decreased blood blow, acute MI occurs.

The involved coronary artery gets occluded when the plaque ruptures and mural thrombus forms at that site. Evidence suggests that those with a rich lipid core and thin fibrous cap are more prone to disruption. At the site of disrupted plaque initial monolayer is formed and various agonists (collagen, ADP, epinephrine, serotonin) promote platelet activation.

Thromboxane A2 (a potent local vasoconstrictor) is released after the platelets are stimulated by agonist, further platelet activation occurs, and potential resistance to fibrinolysis develop. Fibrinogen will attach to two platelets and results in cross linking of platelets and aggregation as it is a multivalent molecule.

The thrombus that contains platelet aggregates and fibrin strands occludes the involved coronary artery eventually. In some cases rarely acute MI may be due to coronary artery occlusion caused by coronary emboli, congenital abnormalities, spasm of the coronary artery and wide variety of systemic inflammatory conditions. The amount of myocardial damage caused by coronary occlusion depends on

1. factors that can produce early spontaneously lysis of the occlusive thrombus.
2. Affected vessel which supplies the territory.
3. Oxygen demand of the myocardium whose blood supply has been suddenly limited.

4. Whether the vessel becomes totally occluded or not
5. Time Duration of coronary occlusion.
6. The blood supply to the tissues by the collaterals.
7. Myocardial oxygen demand whose blood supply has been suddenly limited

DIAGNOSTIC PATHWAY IN EMERGENCY DEPARTMENT[51]

"The current ED guidelines for assessing and managing patients who may have ACS rely on 4 main diagnostic tools: clinical history, ECG, levels of cardiac markers, and results of stress testing".

Patients are assigned to one of four categories:

A non cardiac diagnosis, chronic stable angina, possible ACS, or definite ACS. Patients with definite ACS is admitted to the hospital for further treatment. If there is evidence of active, ongoing ischemia or injury or of hemodynamic or electric instability patients are admitted in ICU, otherwise, placing patients in step down unit is reasonable. Need for reperfusion should be thought of in persistent ST elevation.

Relief of ischemia should be done immediately in patients with UA/STEMI by treating them with anti-ischemic, antiplatelet and anticoagulant agents and this becomes essential in achieving the goal and to prevent the recurrence of adverse ischemic events.

Non pharmacological

Absolute Bed rest

Continuous ECG monitoring for patients with on going chest pain at rest.

Supplemental oxygen for patients with cyanosis or patients with respiratory distress or cyanosis

Pharmacological care

Nitroglycerin, sublingual tablet

Morphine sulphate IV for patients whose symptoms are not relieved by nitroglycerin, severe agitation and pulmonary congestion.

Beta blockers, ACE inhibitors with LV dysfunction and with diabetes.

Antithrombotic therapy

Antiplatelet therapy

ASPIRIN[52, 53]

Thromboxane A2 is blocked by aspirin which irreversibly inhibits cycloxygenase 1, thereby diminishing platelet aggregation.

"The ACC/AHA guidelines" recommend an initial daily dose of 325mg followed by daily dose of 75mg to 162mg for long term secondary prevention.

Contraindication for aspirin therapy is include aspirin allergy (asthma or anaphylaxis), active bleeding and platelet disorders.

CLOPIDOGREL[54]

Clopidogrel decreases platelet activation and aggreggion .It blocks theP2Y12 ADP receptor on the surface of platelets. It also increases bleeding time, and reduces blood viscosity, treatment with clopidogrel and aspirin is recommended for essentially all patients with UA/STEMI.

Newer P2Y12 ADP inhibitors

Ticagrelol is a reversible oral P2Y12 receptor antagonist with half life of around 12hrs. Loading dose of 180mg followed by 90mg twice daily.

Prasugrel is an irreversible P2Y12 ADP receptor antagonist that is given 60mg loading dose and 10mg daily maintenance dose.

GP2B/3A inhibitors[55]

These are specific and potent inhibitors of platelet aggregation. These interrupt the final common pathway of fibrinogen mediated cross- linkage of platelets. IVeptifibatide or tirofiban is the preferred choice.

Abiciximab is indicated only if angiography is appreciably delayed and PCI is likely to be performed; otherwise, IV eptifibatide or tirofiban is the preferred choice.

The benefit of this inhibition appears to be greatest for the patients at a risk of complications i.e. those with a TIMI risk score 4 or higher, ST segment changes, recurrent angina, elevated troponin concentrations and diabetes.

ANTICOGULANGT THERAPY

The guideline recommends 4 agents as options -unfractionated heparin (UFH), enoxaparin, fondaparinoux, and bivalrudin.

LIPID LOWERING THERAPY

This should be initiated for all patients in the absence of complications with UA/STEMI irrespective of LDL cholesterol levels.

STEMI management[56]

Reperfusion

General concepts

All patients with STEMI should be evaluated for reperfusion therapy and have a method implemented promptly after contact with the medical system.

The main aim is to recognize and treat the patients with STEMI so that door to balloon time for PCI to be kept as 90min and door to needle time for starting fibrinolytic therapy within 30min.

The severity of MI, the outcome and the size of MI depends on the duration between the onset of symptoms to the initiation of fibrinolytic therapy. As the time passes by the capacity of the fibrinolytic agents to lyse the clot reduces. If the fibrinolytic therapy is administered with 2 hrs of symptoms MI can be aborted. The effectiveness of fibrinolytic agents in dissolving the thrombus diminish with the passage of time. Fibrinolytic therapy administered within the 1st 2hrs (especially the first hour) can occasionally abort MI and dramatically decrease the mortality.

FIBRINOLYIS

In the absence of contraindications, fibrinolysis should be started within 30min of presentation (i.e. door to needle time<30min)

Restoration of coronary artery patency is the principal goal of treatment. Fibrinolytic agents include streptokinase, tenectaplase (TNK) and reteplase (rPA), tissue plasminogen activator (TPA), which are approved.

Thrombolysis in myocardial infarction (TIMI) grading system described angiographically is as follows:

"Grade 0 indicates complete occlusion of the involved artery.

Grade 1 penetration of obstruction by contrast but no distal perfusion.

Grade 2 Perfusion of entire infarct vessel into the distal bed but with flow that is delayed compared with that of normal artery

Grade 3 indicates normal flow with full perfusion of the infarct vessel".

CONTRAINDICATION FOR FIBRINOLYSIS

Absolute contraindications.

Prior ICH

Patients with structural cerebral vascular lesion

Malignant intracranial neoplasm

Ischemic stroke within 3months EXCEPT acute ischemic stroke within 3hours

Active bleeding or bleeding diathesis(excluding menses)

Significant closed head or facial trauma within 3months.

Relative contraindication

History of poorly controlled hypertension.

Uncontrolled hypertension on presentation (>180/110)

History of prior ischemic stroke more than 3months, dementia, or known intracranial pathology not covered in contra-indications.

Recent internal bleeding (within 2 to 4 weeks)

Non compressible punctures of the vasculature

Pregnancy

Active peptic ulcer

Use of anticoagulants currently, the higher INR, the higher the risk of bleeding.

PERCUTANEOUS CORONARY INTERVENTION[56, 57]

INDICATIONS

The fundamental indication of PCI is the presence of one or more coronary stenosis thought to be responsible for a clinical syndrome, that warrant revascularization, is approachable by catheter based techniques, with risk and benefit compare favorably with those of bypass surgery. In patient with multivessel coronary CAD, particularly those with reduced left ventricular function or diabetes, there may also be survival advantage to surgical revascularization. Trials randomizing patient with multivessel disease in whom either balloon angioplasty or bypass surgery is possible have suggested that the two procedures have essentially equivalent in hospital and 3 to 5year mortality rates.

In patient with acute coronary syndromes, the benefits of PCI include reduced death and MI. In unstable angina and NSTEMI, recent studies employing platelet 2b/3a receptor blockers and coronary stenting have shown >20% reduction in death or MI at 6months with a parallel reduction in hospital readmission, compared to a conservative strategy in which PCI was reserved for strongly positive exercise.

In patients who present within 12 hours on onset of symptoms, the current PCI guidelines recommend that primary PCI should be performed. It performed in a

timely fashion by persons skilled in procedure, working in an appropriate laboratory environment.

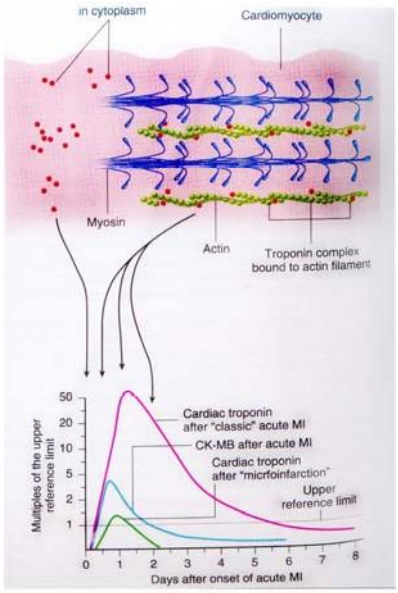
Largely through the introduction of newer interventional devices, PCI has advanced well beyond the treatment of proximal, discrete, subtotal, concentric, non calcified lesion. Even chronically totally occluded coronary arteries can be crossed and dilated effectively and when treatment with drug-eluting stents, have a 90% long term patency rate. In addition to lesion in the native coronary tree, obstructions in the saphneous vein bypass grafts can also be dilated successfully to treat recurrent post-bypass angina, making use of distal embolic protection devices to reduce the incidence of peri-procedural MI caused by the tendency of atheroembolic debris to be liberated during stenting of such lesions.

CARDIAC BIOMARKERS:

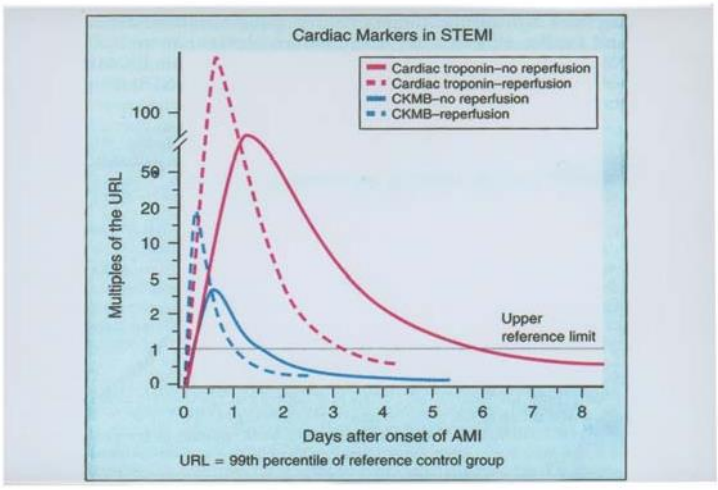
This is the main diagnostic criteria for detection of injury to myocardium. The markers of myocardial injury include CK, CK-MB, aspartate amino transferase, and lactate dehydrogenase and have limitations.

There is lack of specificity, limited sensitivity and short diagnostic window as they are expressed in skeletal muscles too. Due to these limitations and the presence unique amino acid sequence of myofibrillar cardiac troponin-I, monoclonal antibodies were developed for detection of cardiac troponin (I) throughimmunoassay[58]

Figure-1: Cardiomyocyte in the process of Releasing Biomarkers Figure-2: Cardiac Markers in STEMI



CARDIOMYOCYTE IN THE PROCESS OF RELEASING BIOMARKERS



CARDIAC MARKERS IN STEMI

Cardiac troponin-I has very specific amino acid sequence on the N terminus of 31-amino acid which is different from that of the skeletal troponins[59].

Adams et al observed that cardiac troponin-I was not expressed in regenerating human skeletal muscle[59] and was not found in the serum of patients who

had acute or chronic skeletal muscle damage unless concurrent heart muscle injury was is present.

Cardiac troponin-I, which becomes detectable in the serum within 4 hours after infarction, peaks at 14-18 hours, and remains elevated for 5 to 7 days[60] and has sensitivity of 96.6% and specificity of 94.9%.

As a result of the special amino acid sequence, high concentration intracellularly , and release from damaged myocardium, assays for detection of myofibrillar cardiac troponin-I are the most sensitive and specific serum markers of myocardial injury.

Troponin-I is now considered essential to the emergency management of ACS. It has been proved valuable and sensitive in the diagnosis of myocardial necrosis[61]
In a study by KliemanSetal[62] 30% of the patients who had elevated troponin -I had normal CKMB

Initially there was an abnormal cTnI and normal CKMB in 46% of patients with confirmed MI in a study done by Zurish SW et al[63]

These studies tell us that determination of initial cTnI is more powerful diagnostic tool for diagnosis of MI than serial measurement of CPKMB.

The cardiac Tin has been found to have excellent sensitivity and is superior to CKMB as indicator of myocardial necrosis[64].

The Troponins:

Biochemical Make-up:

In cardiac and skeletal muscle the troponins which have three definite proteins(T,C and I) are expressed which are encoded by different types of genes . These molecules form a complex that regulates the calcium-dependent interaction of myosin with actin. The troponin-C is expressed in skeletal and cardiac muscle which

makes its use limited. In contrast to this, troponin I and T in skeletal and cardiac tissues consists of different amino acid sequence and can be differentiated by immunological techniques.

Monoclonal antibodies to cardiac troponins-I and T which have been recently developed have no cross reactivity with their skeletal muscle forms. Currently an enzyme linked immunosorbent assay is being used for clinical use[65].

Cardiac troponin-I is the preffered marker for myocardial injury[66,67]. When there was combined skeletal and cardiac injury observations showed that specificity of troponins is more than CK-MB so measurement of troponin reduces the false positive results and maintains highsensitivity[66,67].

The reason for its sensitivity is that CK-MB is always released in constant amount in low levels so there is always a background low level but this is not seen in a case of troponin I. Hence, it is very sensitive. In many patients where unstable angina was diagnosed after excluding MI by measuring CKMB showed that they had increased levels of cTnI. Follow-up studies had shown that there was high risk of readmission for MI, death or readmission for unstable angina than the patients with fewer levels of cTn[69]values.

Thus improved specificity is coupled with improved sensitivity[66,67]"This fact along with the prolonged time window[70] during which troponin markers are elevated, allow for the detection of a large number of patients at risk for subsequent adverse cardiac event"[71]

Laboratory tests (assays) for Cardiac Troponin-I:

Quantitative Assays:

Food and Drug Administration has approved many quantitative assays for detection of catnip for clinical use[72]

Different studies have shown the usefulness of these new assays for detection of injury of to myocardium, and measuring troponin I has become the centre of a new diagnostic criteria for STEMI[73]

Qualitative Assays:

For diagnosing MI[74]rapid bed side assays for catnip are available and approved.

Interpretation of the Results of Assays:

Majority of catnip which is released, in patients with ST elevated MI is complexes with cTnC[75]. As there is difference in specificities of the antibodies used for detecting free and complexed cTnI[75]there is variations in the cutoff values of cTnI used in the particular laboratory[76] Thus, For cTnI, the definition of an abnormally increased level exceeding that of 99% of a reference control group[73] is used.

Standardization of Assays:

There was substantial confusion in different assays and much of diversity. This can be solved by standardization of assays by the manufacturers with appropriate calibration materials

Recently standardization for CKMB is done by American Assocciation of clinical chemistry.

Normal and Abnormal Values of cTnI:

Normal value in people without heart damage is less than 0.5ng/ml.

Levels between 0.5 ng and 2.0 ng/ ml indicate a diagnosis of unstable angina, other heart disorders, or chronic kidney failure.

Levels more than 2.0 ng/ml indicates that there is significant myocardial injury, such as an infarction, and is at an increased risk for future serious heartevents[77].

Disadvantages of cTnI:

There is very low levels in initial phase of MI (< 6 hrs after symptom onset) so repeat measurements is requires at 8-12 hrs, if negative.

Limited ability to detect early reinfarction.

Failure to show a rise in cTnI does not exclude the diagnosis of ischemic heart disease.

Elevations of cTnI can occur as a result of causes other than MI as mentioned already[78]

Creatine Kinase-MB (CK-MB):

CKMB is one of the three isoenzymes of creatinine kinase (CK)

In cardiac muscle both MM and MB isoenzymes are used. The CKMB can also be present in small quantities in the small intestine , prostate, uterus,tongue and diaphragm. Elevation is CPKMB is considered as the result of MI for practical purposes inspite of small elevations in tissues other than heart.

Strenuous exercise, particularly in professional athletes or runners, can cause elevation of both CK and CK-MB[115]. Despite the small quantities of CKMB can be detected in healthy subjects, the cutoff value for abnormal elevation of CK-MB is usually set a few units above the upper reference limit for a givenlaboratory[79]

Laboratory Tests:

By specific and sensitive immunoassays which use monoclonal antibodies against CK-MB 70, CK-MB is analyzed accurately. Mass assays report result in ng/ml rather than units/ ml and have been confirmed to be accurate than CK-MB activity assays, especially in patients presenting within 4 hours of the onset of STEMI.

Skeletal damage and cardiac muscle damage is distinguished by catnip which is elevated in MI.Other causes for CKMB elevation are myocarditis, trauma, cardiac catheterization, shock and cardiac surgery.

CK-MB Versus cTnI:

The detection of cTnI is earlier after the onset of chest pain (4.5±2.3 hrs) than that of CKMB activity (6.3±3.6 hours). The peak value occurs at 12.2±4.6 hours for cTnI whereas for CKMB at 15.8±9.0 hours after the onset of pain. The cTnI disappears from the plasma between 5 and 9 days after the onset of pain, later then CKMB activity, which disappears between 2nd and 3rdday[80].

The cTnI was positive in elderly patients with myocardial injury and low CK and normal CKMBvalues[81].

Tucker JF et al in their study have found that testing of cTnI is of benefit in identifying AMI □6 hours after presentation with chest pain with a higher sensitivity compared toCK-MB[82].

<u>According to Mario De'Costaet al[81]</u>

The maximum values for cTnI were obtained at sampling times of 6 hours or more, peaking within 12-24 hours and remaining elevated for 5-7 days thereafter.

80% of patients were admitted to the emergency department within 12hours.

The cTnI was abnormal in 49 patients (79% sensitivity) compared with 27 (44% sensitivity) who had abnormal CKMB out of 62patients with AMI- detected in the first specimen obtained at admission.

The overall peak performance of cTnI testing in samples received within 24 hours of admission indicated high sensitivity(97%)

Limitation in Conventional Enzymatic Diagnosis of MI:

Release of plasma CK-MB after irreversible myocardial injury occurs probably within 40 to 60 minutes of sustained coronary occlusion, but the extent and rate of release is minimal such that the plasma CK-MB levels often remains within the normal range up to 13 IU/l for the first 8 to 10 hours.

Most sensitive and reliable quantitative assays such as radioimmunoassay have shown that plasma levels of CKMB can reliably exclude MI only after a minimum of 6 to 10 hours have passed after the onset of chest pain. To this interval must be added the time required for the assay to be performed.

CK-MB Isoforms:

In myocardial tissue CK-MB exists in only 1 form (CK-MB2) but in different isoforms (or sub forms) in plasma (CK-MB1).Compared To conventional assays for CPKMB the use of an absolute level of CK-MB2 of more than 1U/L and a ratio of CK-MB2 to CK-MB1 of greater than 1.5 has increased sensitivity for the diagnosing MI within 6hrs but lacks cardiac specificity as that of CKMB itself and this assay is not widely available[78].

Test Performance of Single Assays:

Although high sensitivities and specificities for diagnosis of myocardial injury can be achieved for several assays through serial sampling, the diagnostic performance of a single value of any of these tests is not nearly as good. A single CKMB value in emergency department patients with h/o chest pain has a sensitivity for detecting AMI is of 34%[83] a single value of cTnI has a sensitivity of about 40%

The diagnostic performance of single values of these tests is influenced considerably by the time elapsed since the onset of symptoms. For example, a single CKMB or troponin drawn within 4 hours of the onset of symptoms has a sensitivity of

less than 25%[83]. However, single values of CKMB and troponins that are drawn more than 12 hours after the onset of symptoms have sensitivities for myocardial infarction in the range of70-90%[83].

Tucker et al[82] used a comprehensive marker strategy including CKMB and cTnI in emergency department for patients who come after 24 hours .Within the first two hours of presentation, CKMB maintained better sensitivity. The troponinisusefulonlywhenmeasured6ormorehoursafterarrival.Sensitivityof 82% for troponin-I is obtained. In patients presenting greater than 24 hours of symptoms onset, troponin-I has a sensitivity of 100% compared with 56.5% for CKMB.

Testing Strategies:

Guidelines from the American College of Cardiology/American Heart Association recommend measurement of biomarkers and cardiac injury in patients with symptoms that are consistent with acute coronary syndromes[84]. Implicit is this recommendation is recognition that patients with very less probability of acute coronary syndrome should not undergo measurement of biomarkers, because of the possibility that false positive results will lead to unnecessary hospitalization, tests, procedures and their complications. Because single values of these assays have limited sensitivity for detecting myocardial injury, a single negative biomarker does not really "rule out" myocardial injury for these low risk patients.

The American College of Cardiology/ American Heart Association guidelines recommend that cTnI or cTnT are the preferred first line markers but note that CKMB (by mass assay) is an acceptable alternative. The preference for cardiac troponins reflects the greater specificity of these markers compared with CKMB and the prognostic value of troponin elevations in the presence of normal CKMB levels. If the initial markers are negative in patients who have presented within the 6 hours of the

onset of pain, the guidelines recommend that another sample should be drawn in the 6 to 12 hours after arrival in the emergency unit[85,86]. The diagnostic work up has been shortened with the help of troponins.

A prospective study tells us that an interval of 6hrs is needed to identify high risk patients using troponin-I. By combining CKMB, troponin-I and myoglobin measurements and use of point-of-care test system (POCT) McCord et al further reduced the time to 90min to exclude MI.

Use of Multiple Cardiac Biomarkers:

For immediate diagnosis, the use of marker which raises first CKMB isoform and a marker that rises later (cTnI) is advocated[87].

Consider all causes of Cardiac Injury:

Detectable Elevation in biomarkers does not always indicate ischemic mechanism of injury but it indicates injury to myocardium. Therefore, increases do not now and did not in the past mandate a diagnosis of myocardialinfarction[88].

If clinically an ischemic mechanism is unlikely, other causes for cardiac injury should be thought of.

<u>They are as follows[89]</u>

Congestive heart failure

Right ventricular injury in people with PE

Direct trauma to the heart .

Septic shock

Mechanical injury such as ablation.

ICD discharges.

Cardioversion

The use of early and reliable marker is recommended in diagnosing MI by the "The National Academy of Clinical Biochemistry"[70]. "The gold standard for detecting myocardial necrosis is troponin and it has to be measured. Qualitative and quantitative point-of-care test devices for troponin-I have been shown to deliver reliableresults"[68, 74]

Point-of-Care Testing:

"The National Academy of Clinical Biochemistry" advises the implementation of point-of-care test system which combines CKMB, troponin-I measurement if the hospital cannot deliver cardiac marker results within 1 hour[70].

Elevation of cardiac enzymes (troponin and CPKMB) in the blood not only tells us about myocardial necrosis but also about the presence of intracoronary thrombus distal embolization of platelet microaggregates[91]. The elevated levels of cardiac troponin-I and CPK-MB are used in targeting potent antithrombin and antiplatelettherapy[91].

Time Window for Reperfusion Therapy:

While the time window for limiting infarct size and preserving ventricular function is 4-6 hours, there are now data to indicate that reperfusion confers a beneficial effect on mortality even when administered as many as 12 hours from the onset of symptoms[92]Fibrinolytics are not indicated in patients without ST elevation.[93].

Comparison of Diagnostic Sensitivities of Different Biomarkers:

Janice Zimmerman et al in their study found that CKMB activity and troponin-T were virtually identical as diagnostic standards. CKMB subforms and troponin-I were also similar in the diagnostic sensitivity.[94]

Serum or Plasma for the Measurement of Cardiac Troponin:

Serum is used for the measuring cardiac troponin-I as heparin interferes with the findings of cardiac troponin I assays.[95,96]

Guidelines for the Sampling Intervals:

The following guidelines are suggested:

Preferably, the diagnosis is made on the basis of no fewer than 2 samples in a 24-h period, separated by at least 4hours.

The diagnosis must be made on the basis of an elevation above normal by at least2-fold If only one sample is available.

In patients admitted beyond 72 hrs from the onset of infarction, cTnI is preferred, since MB-CK levels mayhavereturnedtonormal[97]

Cardiac Markers in Reinfarction:

CPK –MB subform is increased within 4 to 6 hours of infarction and reaches maximum within 12 to 24 hours and returns to normal after 2 to 3days. Early reinfarction is best detected by the CK-MB subforms whereas cTnI is elevated for7 days[94].

International Survey on the Use of Cardiac Markers:

"As of January 1, 1995, no cardiac troponin assays were present. "Food and Drug Administration" approved for use in the US. Worldwide between 1955 and 1999, the use of cTnI assays increased. 12 different troponin assays by seven different manufacturers were used. The assays were used in 24 countries, with the largest number of responses from Denmark (n=19), Canada (n=17) and China (n=10)"

This survey demonstrates that in the clinical laboratory testing of cardiac troponin -I has increased, supporting its role as the new international standard biomarker for the diagnosis of MI and risk stratification in ACS patients[90, 98]

The recent recommendations by both the laboratory medicine and cardiology communities favors cardiac troponin testing as the primary biomarkers of choice[96]. The use of several assays like LDH, LDH isoenzymes and AST is detection of AMI has declined[99]. The increased use of CKMB mass and myoglobin suggests an influence of the new recommendations, which favor use of CKMB mass when troponin is not available.

MATERIALS AND METHODS

SOURCE OF DATA

After getting ethical clearance, eligible patients satisfying the inclusion and exclusion criteria of patients with AMI admitted to BLDE'S Shri B M Patil medical college Hospital and Research centre,Vijayapura between November 2017 to June 2019 are the source of study.

METHOD OF COLLECTION OF DATA:

Information was collected through prepared proforma from each patient. All patients were interviewed as per the prepared proforma and then complete clinical examination was done.

INCLUSION CRITERIA[100]

Detection of a rise and/or fall of troponin values with at least 1 value above the 99th percentile URL and with at least 1 of the following.

- Patients with Symptoms of acute myocardial ischemia.
- New ischemic ECG changes.
- Development of pathological Q waves.
- Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality in a pattern consistent with an ischemic etiology.

EXCLUSION CRITERIA

Old Ischemic heart disease, pericarditis, aortic dissection.

Hematological malignancy

Hypothyroidism

Chronic alcoholics

Chronic kidney disease

Chemotherapy

Muscular dystrophy.

3. Type of study

Prospective, randomized, comparative study.

4. Sample size

Sample size calculation

With Anticipated Mean Difference of mean hs-CRP level between the two study groups as 4.0 and Anticipated SD as 5.6, the minimum sample size per group is 51 with 90% power and 5% level of significance.

By using the formula:

$$n = \frac{(z_\alpha + z_\beta)^2 2\ SD^2}{MD^2}$$

Where Z= Z statistic at a level of significance

MD= Anticipated mean difference

SD= Anticipated Standard deviation

Statistical analysis

Data will be represented using Mean ±SD, and analyzed by Chi square test for association, comparison of means using t test, ANOVA and diagrammatic presentation. ROC analysis for Sensitivity- specificity.

ESTIMATION OF hs-CRP

5ml of venous blood is taken in a plain vacutainer at 6hrs , 24hrs and 48hrs and serum is separated , kept At 2-8degrees until analyses is carried by turbidimetric immunoassay method.

INVESTIGATIONS

- Complete Blood Count with Differential Counts
- Urine routine
- ECG
- Serum CK-MB and Troponin-I, hs-CRP
- Echocardiography
- Blood sugar level
- Lipid profile
- Serum creatinine
- T3,T4,TSH where ever necessary

RESULTS

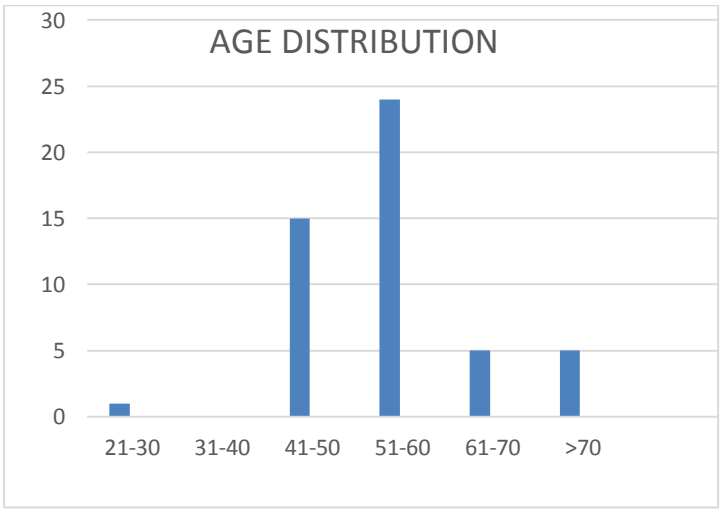
The present study on hs-CRP , troponin I and CPKMB in acute myocardial infarction was carried out in Shree B M Patil medical college and hospital..

The observations noted in the present study are as follows.

TABLE 1: DISTRIBUTION OF PATIENTS ACCORDING TO AGE.

AGE (YRS)	NUMBER	%
21-30	1	2
31-40	0	0
41-50	15	30
51-60	17	34
61-70	12	24
>70	5	10
TOTAL	50	100

FIGURE 1 : DISTRIBUTION OF PATIENTS ACCORDING TO AGE.



In our study , most of the cases were between 40-60 years with mean age of 57.92 years.

TABLE 2: DISTRIBUTION OF CASES ACCORDING TO SEX.

SEX	No.	%
MALE	**39**	**78**
FEMALE	**11**	**22**
TOTAL	**50**	**100**

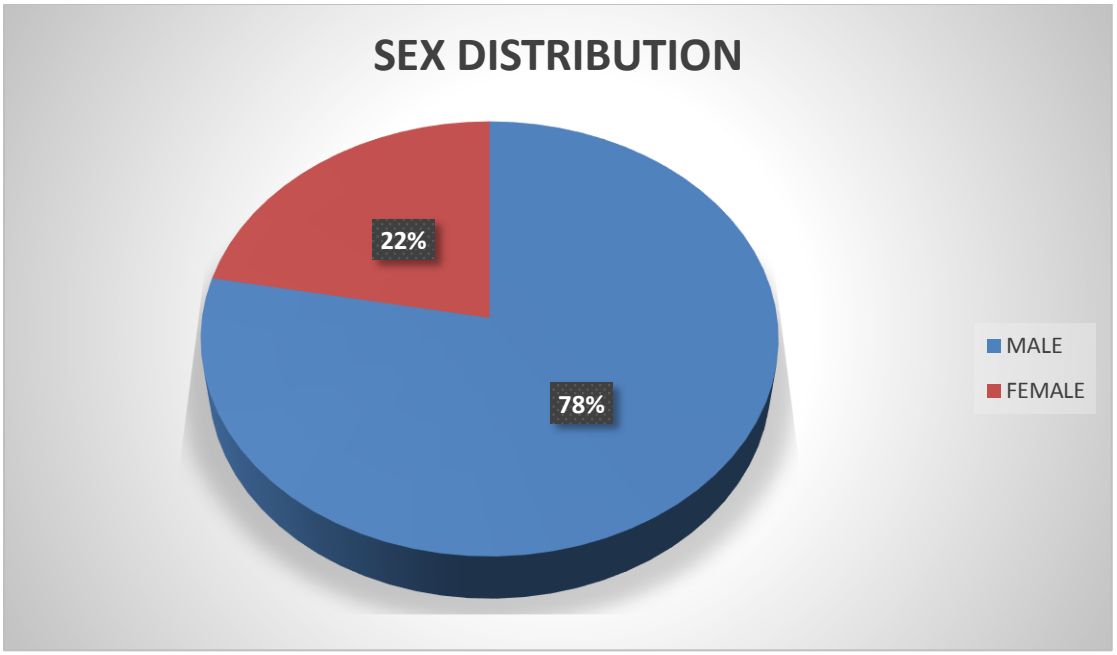


TABLE-3: DISTRIBUTION OF CASES ACCORDING TO OCCUPATION

OCCUPATION	N	%
BUSINESS	4	8
FARMER	15	30
GOVT JOB (2ND DIVISION CLERK)	1	2
HOMEMAKER	11	22
LABOURER	6	12
MEDICAL STUDENT	1	2
SKILLED/SEMISKILLED WORKER (MECHANIC, CARPENTER, LABORER)	12	24
Total	50	100

FIGURE-3: DISTRIBUTION OF CASES ACCORDING TO OCCUPATION

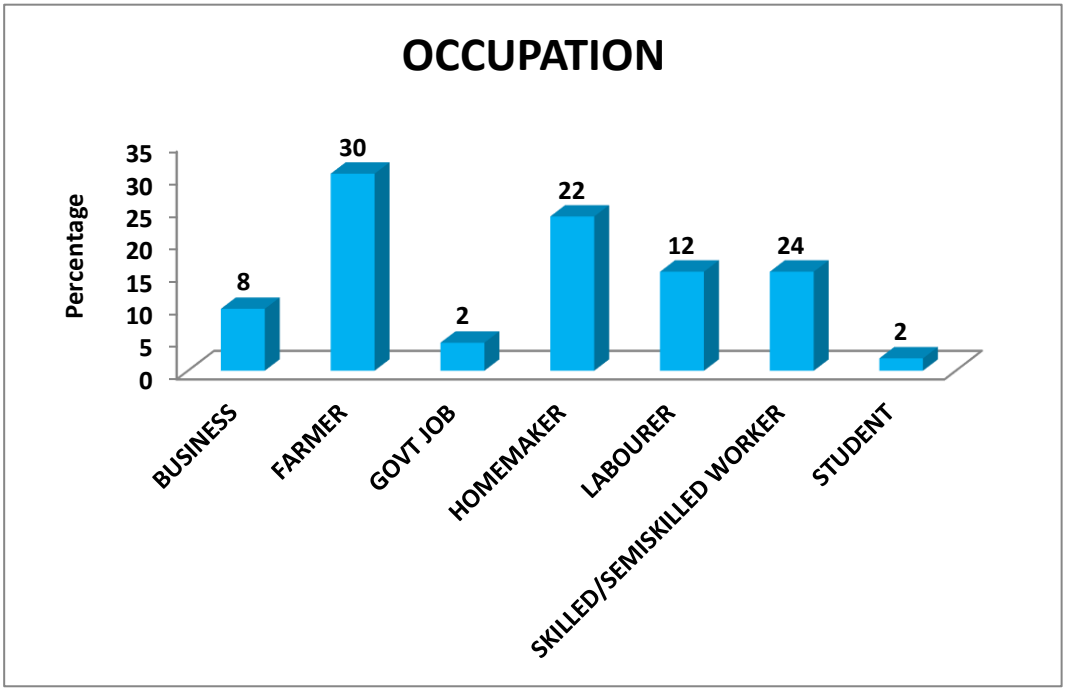
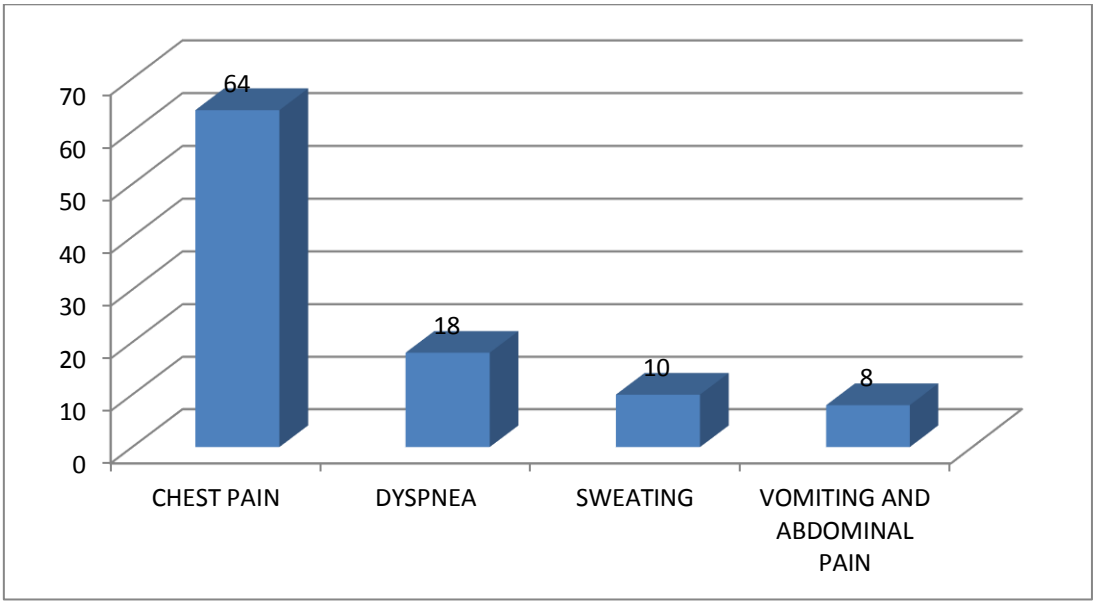


TABLE-4: DISTRIBUTION OF CASES ACCORDING TO CLINICAL FEATURES

CLINICAL FEATURE	N	%
CHEST PAIN	32	64
DYSPNEA	9	18
SWEATING	5	10
VOMITING AND ABDOMINAL PAIN	4	8

FIGURE-4: DISTRIBUTION OF CASES ACCORDING TO CLINICAL FEATURES

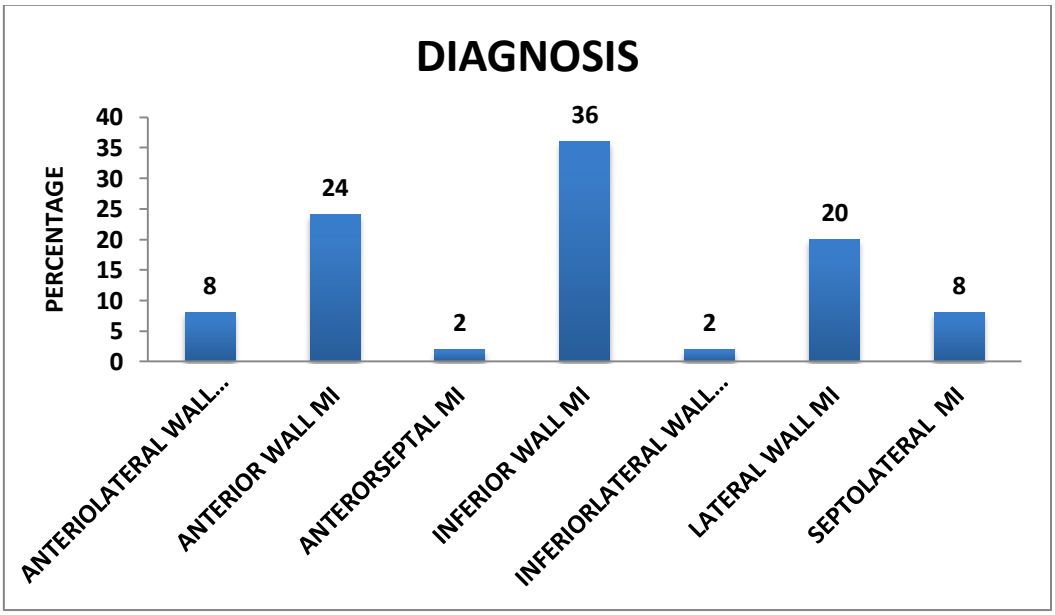


Among the patients with MI , chest pain is predominant symptom in 64% patients followed by dyspnea in 18% and sweating in 10% and abdominal pain and vomiting in 8% of people this study.

TABLE 5: DISTRIBUTION OF DIAGNOSIS

DIAGNOSIS	N	%
ANTERIOLATERAL WALL MI	4	8
ANTERIOR WALL MI	12	24
ANTERORSEPTAL MI	1	2
INFERIOR WALL MI	18	36
INFERIORLATERAL WALL MI	1	2
LATERAL WALL MI	10	20
SEPTOLATERAL MI	4	8
Total	50	100

FIGURE 5: DISTRIBUTION OF DIAGNOSIS



Most of the patients had inferior wall MI (36%) followed by anterior wall MI(24%) and lateral wall MI(20%).

TABLE 6 : RISK FACTOR DISTRIBUTION

RISK FACTOR	NO. OF PATIENTS
HYPERTENSION	29
LDL>100	26
HDL<50	25
TGL>150	20
SMOKER	20
NO RISK FACTOR	15

FIGURE 6 : RISK FACTOR DISTRIBUTION

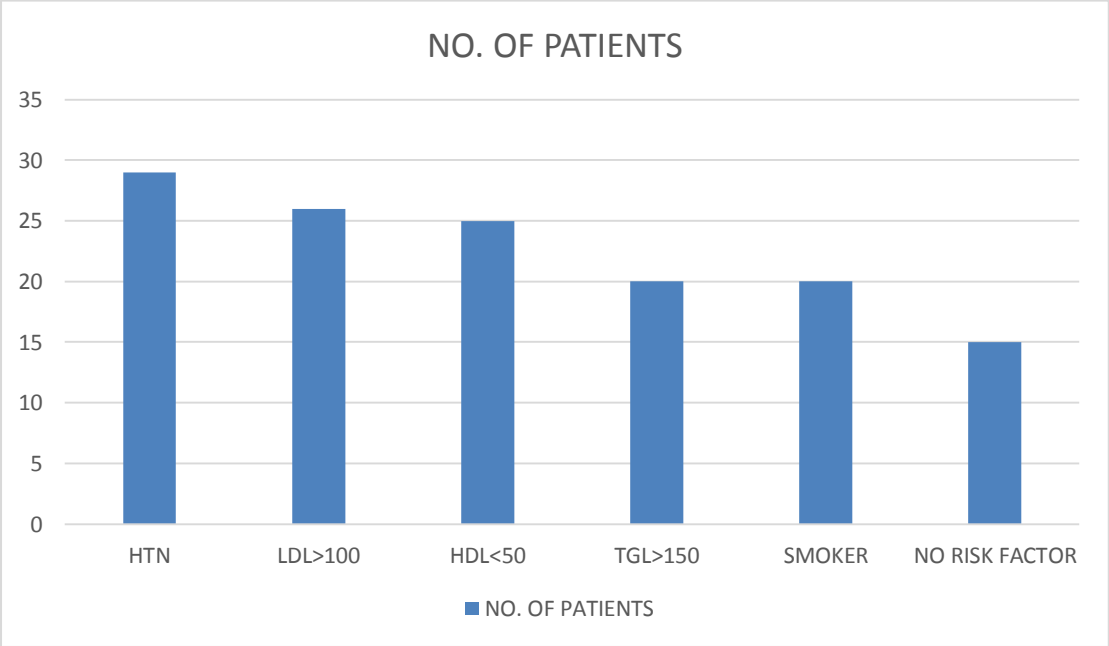
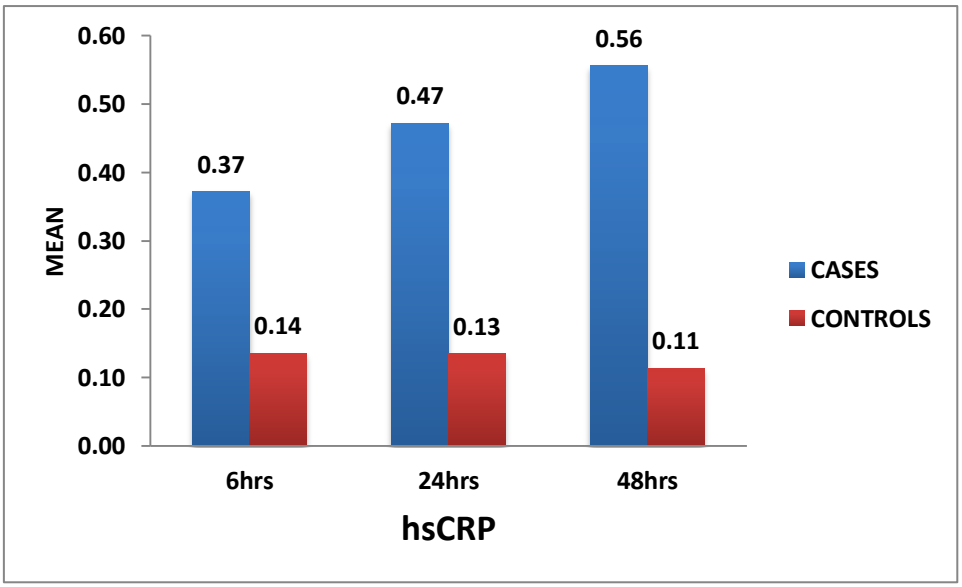


TABLE 7: MEAN hs-CRP LEVEL BETWEEN CASES AND CONTROL

hs-CRP	CASES		CONTROLS		p value
	Mean	SD	Mean	SD	
6hrs	0.37	0.22	0.14	0.10	<0.001*
24hrs	0.47	0.19	0.13	0.13	<0.001*
48hrs	0.56	0.22	0.11	0.09	<0.001*

FIGURE 7: MEAN hs-CRP LEVEL BETWEEN CASES AND CONTROL



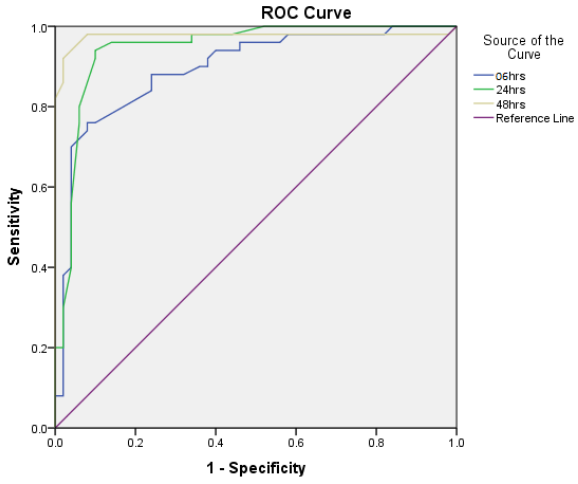
The mean hs-CRP of cases at 6hrs, 24hrs and 48hrs is 0.37, 0.47 and 0.56 respectively and in controls 0.14, 0.13, 0.11 respectively. In all patients with AMI hs-CRP is raised significantly.

TABLE 8: ROC ANALYSIS OF hs-CRP

hsCRP	Area Under the Curve	Std. Error	p value	95% Confidence Interval	
				Lower Bound	Upper Bound
6hrs	0.895	0.033	<0.001*	0.83	0.959
24hrs	0.946	0.024	<0.001*	0.899	0.993
48hrs	0.976	0.02	<0.001*	0.937	1

	Positive if Greater Than or Equal To	Sensitivity	Specificity
TROPONIN I	8.89	90%	94%
CPK- MB	35	90%	88%
hs-CRP at 6hrs	0.199	84.0%	76.0%
24hrs	0.290	92.0%	90.0%
48hrs	0.250	98.0%	92.0%

FIGURE 8: ROC CURVE



The figure above states that with time, after infarction the hs-CRP values are raising. The mean values showed significant difference between the time frames with Wilks lambda showing an F value which is statistically highly significant. The AUC clearly states that hs-CRP values have a raising trend.

Sensitivity and specificity of troponin I and CPK-MB is more than hs-CRP

FIGURE 9a: PEARSON CORRELATION BETWEEN hsCRP AND TROPONIN I

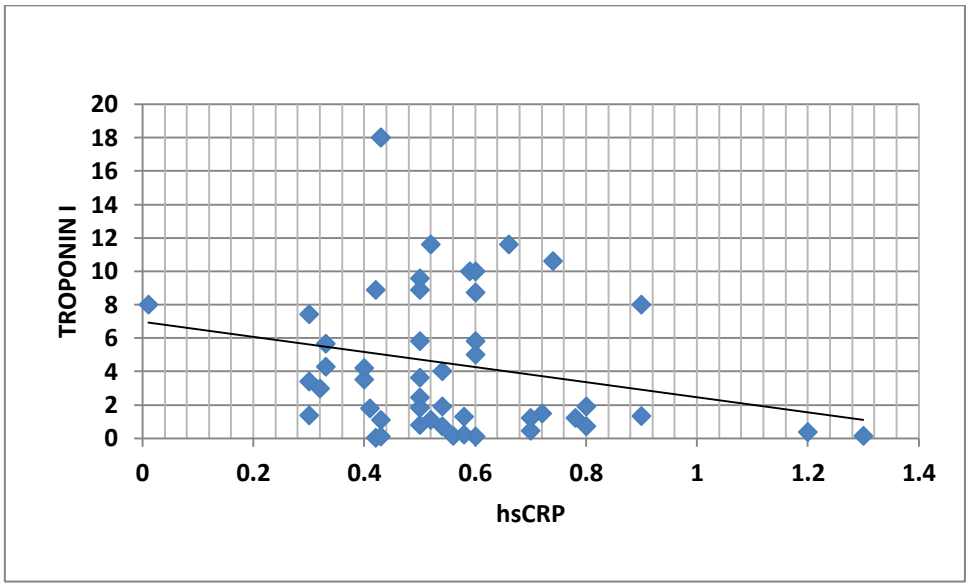


FIGURE 9b: PEARSON CORRELATION BETWEEN hsCRP AND CPKMB

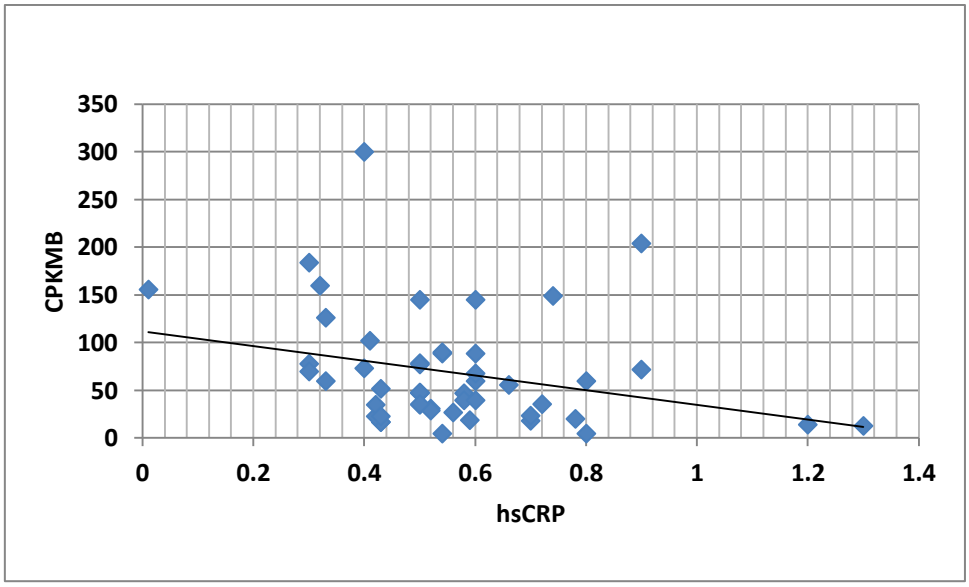


TABLE 9: PEARSON CORRELATION BETWEEN hsCRP AND OTHER PARAMETERS AMONG CASES

CORRELATION BETWEEN hsCRP AND	r value	p value
TROPONIN I	-0.343	0.015*
CPKMB	-0.285	0.045*

TABLE 10: RELATIONSHIP BETWEEN hsCRP, TROPONIN I AND CPKMB BETWEEN CASES AND CONTROLS

PARAMETERS	CASES		CONTROLS		p value
	Mean	SD	Mean	SD	
hs-CRP	0.37	0.22	0.14	0.10	<0.001*
TROPONIN I	7.54	11.74	0.17	0.38	<0.001*
CPKMB	68.82	59.16	27.94	11.96	<0.001*

The hsCRP, troponin I and CPKMB values in cases are more than the controls and is statistically significant but there is no linear correlation between them.

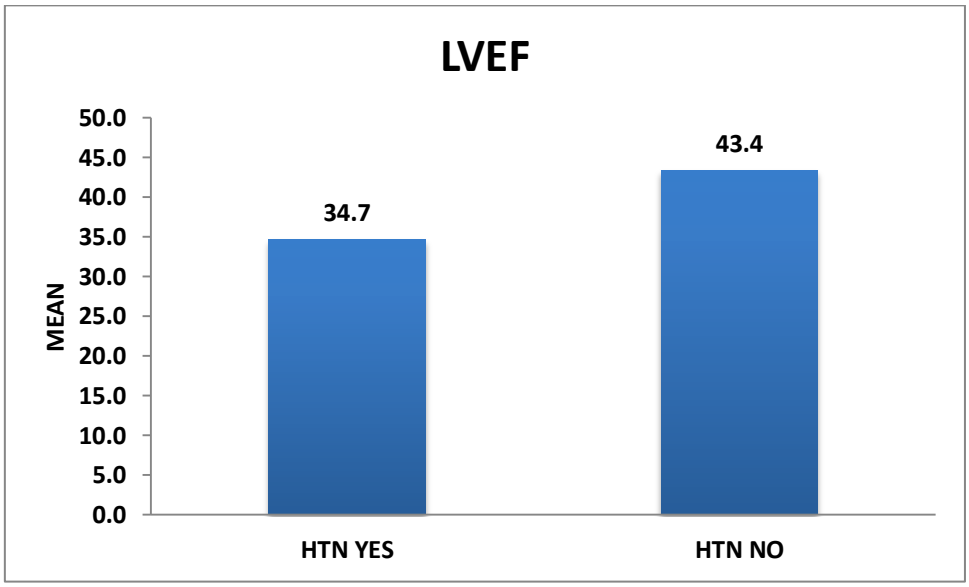
TABLE 10: MEAN LVEF BETWEEN CASES WITH HYPERTENSION AND WITHOUT HYPERTENSION

Out of 50 patients, 20 patients had hypertension.

LVEF	HTN YES		HTN NO		p value
	Mean	SD	Mean	SD	
	34.7	7.7	43.4	8.0	<0.001*

Note: * significant at 5% level of significance (p<0.05)

FIGURE 10 :MEAN LVEF BETWEEN CASES WITH HYPERTENSION AND WITHOUT HYPERTENSION

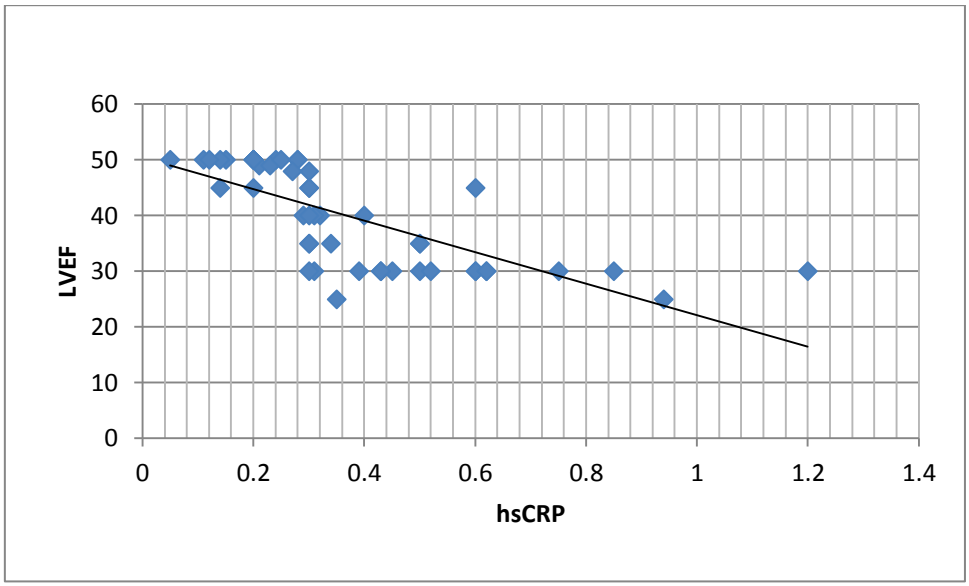


The mean LVEF in patients with MI with HTN is 34.7 and in patients without HTN is 43.4 and is statistically significant.

TABLE 11: PEARSON CORRELATION BETWEEN LVEF AND hsCRP

CORRELATION BETWEEN	r value	p value
LVEF & hs-CRP	-0.716	<0.001*

FIGURE 11: PEARSON CORRELATION BETWEEN LVEF AND hsCRP

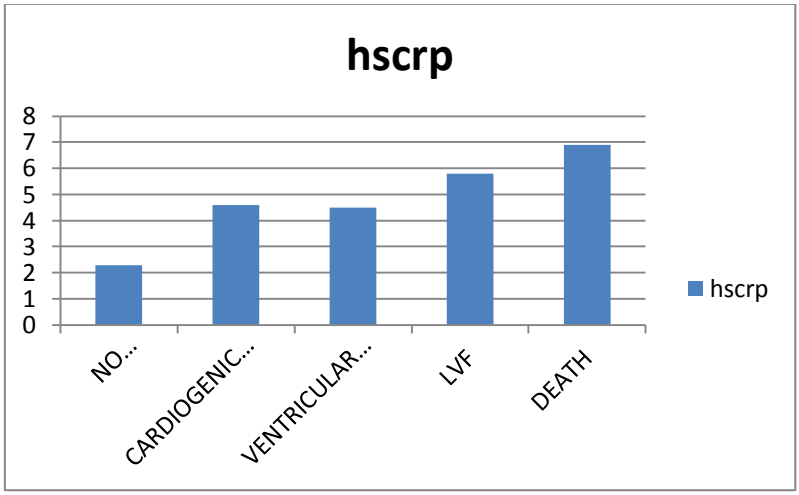


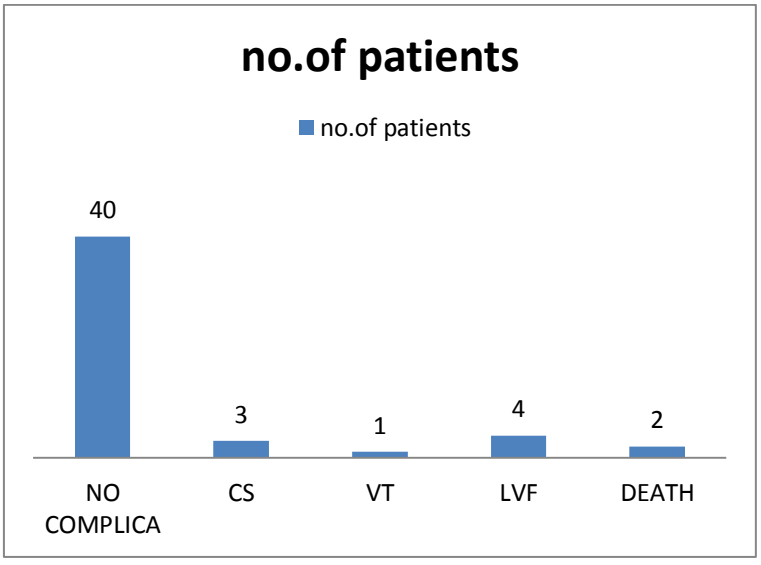
There is negative correlation between hsCRP and LVEF. As the hsCRP values increase LVEF reduces and is statistically significant.

Table 12: AMI COMPLICATIONS AND ITS CORRELATION WITH hs-CRP

COMPICATIONS	No. of patients	Mean hs-CRP
Ventricular Tachycardia(VT)	1	4.5mg/dl
Cardiogenic shock (CS)	3	4.6mg/dl
Left ventricular failure (LVF)	4	5.8mg/dl
DEATH	2	6.9mg/dl
No complications	40	2.28mg/dl

Figure: AMI COMPLICATIONS AND ITS CORRELATION WITH hs-CRP





The mean hs-CRP levels in patients with complications was >4 mg/dL, whereas among those without complication the hs-CRP levels were 2.28 ± 0.379 mg/dL. Higher the hs-CRP more the complications.

DISCUSSION

C-reactive protein is an acute phase reactant indicating the presence of infections or non-infective inflammation, as well as the risk of vascular events. It has been suggested that the relationship between increased serum CRP levels and vascular risk is because of the inflammation seen in atherosclerosis.

CRP, one of the acute phase reactants, is an indicator of a novel plasma marker of atherothrombotic disease. Furthermore, elevated plasma levels of CRP are not disease-specific, but are sensitive markers produced in response to tissue injury, infectious agents, immunological stimuli, and inflammation.

CRP is a nonspecific protein produced in the liver, and its serum levels increase in cases of infection, tissue damage, and inflammation. hs-CRP is a new method which determines lower levels of hs-CRP of < 10mg/l. We used the hs-CRP method in our study and showed significant differences in the hs-CRP level between patients and controls. We determined the serum levels of hs-CRP and found that it is significantly higher in patients with MI than in patients without MI.

Recent available data suggest that MI triggers an acute phase response, results in an increased level of circulating CRP, as well as other inflammatory molecules, such as IL-6 and fibrinogen. However, the degree of inflammatory response is variable

The fact that there are reliable, widely available assays to determine serum concentration of hsCRP, and that this concentration is essentially entirely dependent on the rate of primary production, renders hsCRP a particularly attractive candidate serum marker for this purpose. With a view toward widespread clinical applicability, the assay used for this protocol is highly sensitive, fully automated, commercially available assay.

C-reactive protein has been accepted as a sensitive indicator of atherothrombosis in MI, and CRP levels have been found to be higher in MI patients compared to the healthy population.

Arenillas et al concluded that C-reactive protein predicted further ischemic events.

In our study, most of the cases were between age 40 to 60 years, we found that mean age of cases is 57.92 years.

	Suleiman et al[101]	Ryu S Y et al	Present Study
Mean Age	59+_12	64+_9.9	57_+10

Mean age of the present study with acute MI was 57.92 years is compared to Suleiman et al. (59_+12 years) , but in studies and Ryu S Y et al (64_+9.9 years) are higher than our study group. This indicates that acute MI is more common in the age group of 50-60 years.

Sex incidence of acute MI Patients

Studies	MALE	FEMALE
Tenzin et al	80%	20%
Ryu S Y et al	37.2%	62%
Present study	78%	22%

In our study there is Male predominance and sex wise distribution male 39(78%) and female 11 (22%). This shows that males are at more risk of MI than females. The current view to explain the lower incidence in pre-menopausal women is that they are protected by the sex hormones (estrogen) and also women are at relatively lower rates of exposure to certain risk factors like smoking.

In our study 35(70%) cases have underlying risk factors. 15(30%) Patients do not have risk factors. 20(40%) smokers, 29(58%) cases have hypertension,

25(50%) cases have LDL>100, 20(40%) cases have HDL <50 in females <40 in males, 20(40%) have TGL>150, and by above statistics in our study.

In our study there is elevated level of hsCRP seen in 46 cases and normal level in 4 cases.

In our study, the average elevated hs-CRP is more for cases with risk factors than without risk factors; elevation of hs-CRP is parallel to risk factors present.

In our study, 50 cases are taken, among them 18(36%) were inferior wall MI, 12(24%) Anterior wall MI, 10(20%) lateral wall MI, 4(8%) Septolateral wall MI, 4(8%) Anteriolateral wall MI.

IwonaSwiatkiewiczetal[102] in their study on usefulness of C-reactive protein as a marker of early post-infarct left ventricular systolic dysfunction concluded that measurement of CRP plasma concentration levels may be useful as a marker of LVSD in patients after first STEMI.

Badiger RH[103] et al showed that the raised hs-CRP level in the majority of patients with AMI suggests involvement of inflammation in the etiopathogenisis of MI and has prognostic utility in AMI. Higher the serum hs-CRP levels on admission in patients of AMI the more the patient is prone for developing complications during their hospital stay.

A meta-analysis by Danesh et al[104]showed that the baseline values of four acute phase reactants, hs-CRP, serum amyloid protein, leukocyte count and albumin are associated with one another as well as with the future risk of coronary heart disease. These data support the idea that there are some underlying process related to inflammation that are relevant to CAD.

Volgari et al. measured hs-CRP in 17 patients with MI and were elevated in all patients. A raised serum hs-CRP levels was found on admission in four patients

before a rise in creatinine kinase MB isoenzyme. They found that serial monitoring of serum hs-CRP in parallel with cardiac proteins of short and long half-life provides information for diagnosis and for detecting post infarct complications.

A study by Berk et al.found that hs-CRP level is significantly elevated in MI as compared to the control group with no ischemia. Another study by Abelmouttaleb et al in 142 patients with coronary disease (GROUP1), 37 patients with normal angiograms (GROUP2) and 37 control healthy subjects (GROUP 3) found higher levels of hs-CRP in patients with MI than in patients with stable symptoms and GROUP 2 and GROUP 3.

On admission, the mean hs-CRP levels in patients with complications was >4 mg/dL, whereas among those without complication the hs-CRP levels were 2.28 ± 0.379 mg/dL.

When compared to other studies, present study also found similar results indicating that higher serum hs-CRP levels on admission in patients with AMI are prone for developing complications during their hospital stay. Zairis et al. studied serum hs-CRP levels on admission in 319 patients of AMI and concluded that these levels predict reperfusion failure and short and long-term prognosis after ST elevation in AMI. Mishra et al. studied 50 cases of AMI and observed that serum hs-CRP concentration on admission was significant prognostic indicator of their in hospital stay.

In our prospective observational study, marker of inflammation – hsCRP was found to be significant predictor of acute cardiovascular event. These results of the current study have several important implications. First the findings confirm that markers of inflammation are important predictors of acute cardiovascular events and support the hypothesis that atherosclerosis is, in part, an inflammatory disease.

Second, because we used a commercially available assay to measure plasma hsCRP[22], our results provide clinically relevant confirmation findings. The commercial assay is inexpensive and can be used with standard hospital and outpatient laboratory equipment thus, screening for this predictor of cardiovascular risk would be practical in many clinical settings.

And third, we have correlated the hs-CRP values with cardiac markers i.e. troponin I and CPKMB which is statistically significant.

LIMITATIONS OF HSCRP

Several limitations of hsCRP evaluations require consideration. In case of acute infection or trauma there is non specific increase in inflammatory markers. In patients with known systemic inflammatory conditions hs- CRP measurement should be avoided and at the time of infection or trauma as it may have limited clinical utility. However, these effects have tended to lead to underestimation of true predictive value of hsCRP in epidemiological studies. Across different ethnic groups utility of testing hsCRP is also uncertain. After acute ischemia, levels of hsCRP can rise substantially such that determining an individual's basal levels is difficult, an effect that may result in misclassification.

SCOPE OF FUTURE STUDIES

Although hsCRP is by far the best characterized and most reliable inflammatory biomarker for clinical use, several other markers of inflammation have shown promise in terms of predicting vascular risk. These include cytokines such as interleukin-6, soluble forms of certain cell adhesion molecules such an interleukin adhesion molecule (SICAM), P-selectin, or the mediator CD40 ligand, as well as markers of leukocyte activation such as myeloperoxidase.

Other inflammatory markers associated with lipid oxidation such as lipoprotein- associated phospholipase A2 and pregnancy associated plasma protein A have also shown promise. However, each of these biomarkers has analytic issues that need careful evaluation before routine clinical use. For example, some have too short half-life for clinical diagnostic testing. Whereas the ability of others to predict the risk in settings of broad populations have proved marginal thus for nonetheless, several of these inflammatory biomarkers can shed critical pathophysiological light on the atherothrombotic process, particularly at the time of plaque rupture. For example soluble CD40 ligand (probable released from activated platelets) may provide insight into the efficacy of specific antithrombotic agents independently of CRP.

Similarly myeloperoxidase may provide prognostic information in cases of acute ischemia over and above that associated with troponin and CRP. Thus, continued evaluation of other inflammatory markers may well provide targets for monitors of therapy, particularly in the setting of acute ischemia.

CONCLUSION

The present study aimed at studying hs-CRP in acute myocardial infarction compared to controls and correlating with Troponin I and CPK-MB. A total of 50 cases of myocardial infarction and 50 age and sex matched controls were taken. Mean age of patients was 61±5.5 years.

There were 39 male patients and 11 female patients in the study group. The predominant type of MI is inferior wall MI followed by anterior wall MI and lateral wall MI.

hs-CRP values are more in cases compared to controls and there is a significant role of hs-CRP in diagnosing AMI .

hs-CRP is an acute phase reactant and there is rise in hs-CRP in patients with acute MI along with CPK-MB and troponin I and the results were statistically significant.

The sensitivity and specificity of hs-CRP is less than troponin -I and CPK-MB so, hs-CRP it is considered inferior compared to troponin I and CPK-MB in detecting AMI.

Patients with high hs-CRP showed reduced Left ventricular ejection fraction. The measurement of hs-CRP can be useful as marker of LVSD in patients with AMI.

The raised hs-CRP level in the majority of patients with AMI suggests involvement of inflammation in the etiopathogenesis of MI and has prognostic utility in AMI. Serum hs-CRP levels are potent predictors of prognosis in patients with AMI and elevated levels of hs-CRP at the time of admission indicates a poor prognosis in patients with AMI. Hence the present study concluded that, higher the serum hs-CRP levels on admission in patients of AMI the more the patient is prone for developing complications during their hospital stay.

SUMMARY

A hospital based prospective, randomized, comparative study was conducted from November 2017 to June 2019. A total of 100 cases were included in the study. 50 controls and 50 AMI patients.

- Among AMI patients Males were predominant in our study.
- Male to female ratio was 3.5 :1
- Most patients belonged to a age group of 51-70 with a mean age of 61 ± 5.5 years.
- Chest pain, dyspnea and sweating were the most common presenting symptoms.
- Inferior wall MI is seen in 36% followed by anterior wall MI (24%) and lateral wall MI (10%)
- hs-crp was raised in 98% of patients with AMI.
- Troponin I, CPKMB and hs-CRP was significantly raised in patients with AMI.
- The values of hs-CRP showed a significant difference between the time frames of 6hrs, 24hrs and 48hrs and the difference is increased with the normal as the time progresses.
- Patients with high hs-CRP had low Left ventricular ejection fraction than patients with low hs-CRP.
- Higher the hs-CRP levels on admission in patients with MI, more the risk of complications.

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ANNEXURE-II

INFORMED CONSENT FORM

BLDEU'S SHRI B. M. PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, VIJAYAPUR- 586103

TITLE OF THE PROJECT - STUDY OF hs-CRP in ACUTE MYOCARDIAL INFARCTION.

.I) **INFORMED PART**

1) PURPOSE OF RESEARCH:

I have been informed about this study. I have also been given a free choice of participation in this study.

2) PROCEDURE:

I am aware that in addition to routine care received I will be asked series of questions by the investigator. I have been asked to undergo the necessary investigations and treatment, which will help the investigator in this study

3) RISK AND DISCOMFORTS:

I understand that I may experience some pain and discomfort during the examination or during my treatment. This is mainly the result of my condition and the procedure of this study is not expected to exaggerate these feelings that are associated with the usual course of treatment.

4) BENEFITS:

I understand that my participation in this study will help to patient's survival and better outcome.

5) CONFIDENTIALITY:

I understand that the medical information produced by this study will become a part of Hospital records and will be subject to the confidentiality and privacy regulation. Information of a sensitive personal nature will not be a part of the medical records, but will be stored in the investigator's research file and identified only by a code number. The code-key connecting name to numbers will be kept in a separate location.

If the data are used for publication in the medical literature or for teaching purpose, no name will be used and other identifiers such as photographs and audio or videotapes will be used only with my special written permission. I understand that I may see the photographs and videotapes and hear the audiotapes before giving this permission.

6) REQUEST FOR MORE INFORMATION:

I understand that I may ask more questions about the study at anytime doctor is available to answer my questions or concerns. I understand that I will be informed of any significant new findings discovered during the course of the study, which might influence my continued participation.

If during the study, or later, I wish to discuss my participation in or concerns regarding this study with a person not directly involved, I am aware that the social worker of the hospital is available to talk with me. A copy of this consent form will be given to me to keep for careful reading.

7) REFUSAL OR WITHDRAWAL OF PARTICIPATION:

I understand that my participation is voluntary and that I may refuse to participate or may withdraw consent and discontinue participation in the study at any

time without prejudice to my present or future care at this hospital. I also understand that doctor may terminate my participation in the study after she has explained the reasons for doing so and has helped arrange for my continued care by my own physician or physical therapist, if this is appropriate.

8) INJURY STATEMENT:

I understand that in the unlikely event of injury to me resulting directly from my participation in this study, if such injury were reported promptly, the appropriate treatment would be available to me, but no further compensation would be provided. I understand that by my agreement to participate in this study I am not waiving any of my legal rights.

I have explained to _____the purpose of the research, the procedures required and the possible risks and benefits to the best of my ability in patient's own language.

_____ _____

Date

(Investigator)

II) **STUDY SUBJECT CONSENT STATEMENT:**

I confirm that **doctor** has explained to me the purpose of research, the study procedures that I will undergo, and the possible risks and discomforts as well as benefits that I may experience in my own language. I have read and I understand this consent form. Therefore, I agree to give consent to participate as a subject in this research project.

_____ _____

Participant / Guardian Date

_____ _____

Witness to signature Date

ANNEXURE-III

PROFORMA

Name: **CASE NO:**

Age: **IP NO:**

Sex: **DOA:**

Religion: **DOD:**

Past Occupation:

Present Occupation:

Residence:

Chief complaints:

History of present illness:

Past History:

History of IHD

History of tuberculosis

History of diabetes mellitus

History of Hepatic or Renal diseases

Personal History:

Diet/appetite:

Sleep:

Bladder and bowel habits:

Smoking

Tobacco chewing/Snuff Inhalation

Alcohol:

Family History:

TB: Asthma: Malignancy: DM: HTN:

General Physical Examination

Height :

Weight:

Body Mass Index :

Vitals

Pulse rate:

Blood pressure:

Respiratory rate:

Temp:

Head to toe examination:

SYSTEMIC EXAMINATION.

•Respiratory System

• Cardiovascular System

•Central Nervous System

• Per abdomen

INVESTIGATIONS

HAEMATOLOGY –

Haemoglobin	gm %
Total WBC counts	Cells/mm^3
Differential counts -	
Neutrophils	%
Lymphocytes	%
Eosinophils	%
Monocytes	%
Basophils	%
ESR	mm after 1 hour

ECG:

URINE EXAMINATION -

Albumin	
Sugar	
Microscopy	

BIOCHEMISTRY

❖ Cardiac Markers • CK-MB • Troponin-I • hs CRP	
❖ LIPID PROFILE • Triglycerides • Total Cholesterol • HDL-Cholesterol • LDL-Cholesterol • VLDL-Cholesterol	
❖ Serum creatinine	
❖ Blood urea	
❖ Blood Sugar Levels ▪ RBS ▪ FBS ▪ PPBS ▪ Hba1c	

2D ECHO

TREATMENT

OUTCOME

KEY TO MASTER CHART

hs-CRP	High sensitivity C- reactive protein
TG	Triglycerides
HDL	High density lipoprotein
LDL	Low density lipoprotein
VLDL	Very low density lipoprotein
LVEF	Left ventricular ejection fraction
HTN	Hypertension
T.choles	Total cholesterol
RBS	Random blood sugar

MASTER CHART

					6hrs	24hrs	48hrs											
SL NO	**patients name**	**IP NO**	**AGE**	**SEX**	**hscrp**	**hscrp**	**hscrp**	**TG**	**HDL**	**LDL**	**VLDL**	**T.CHOLES**	**TROPONIN I**	**CPKMB**	**RBS**	**DIAGNOSIS**	**LVEF**	**HTN**
1	SOMANING BHIMARAYA	42208	60	M	0.112	0.168	0.583	85	48	94	40	159	1.3	47	100	INFERIOR WALL MI	50	no
2	GIRIJA BAI	42210	58	F	0.195	0.412	0.413	161	44	76	32	153	1.8	102	101	ANTERIORWALL MI	50	no
3	SUDHA	18246	65	F	0.289	0.661	0.8	80	40	60	40	60	1.9	60	115	LATERAL WALL MI	40	no
4	SURESH	44755	50	M	1.2	0.4	1.2	100	60	62	80	40	0.36	14	200	ANTERIOR WALL MI	30	no
5	MAHADEV JADHAV	13399	52	M	0.14	0.32	0.3	74	36	133	35	185	7.41	78	130	ANTERIOR WALL MI	45	no
6	GM ROJARI	18776	50	M	0.05	0.12	0.3	75	45	103	25	162	3.4	184	126	INFERIOR WALL MI	50	no
7	GURAPPA SIDDAPPA	20449	63	M	0.6	0.8	0.9	88	39	124	38	181	80	204	180	ANTERIOLATERAL WALL	30	yes
8	SHIVAMMA SIDDAPPA	25640	69	F	0.34	0.6	0.8	90	66	100	30	180	0.71	5	110	ANTERIOR WALL MI	35	yes
9	SULTHAN LADLESAB	24130	50	M	0.452	0.5	0.54	92	68	102	34	189	0.71	5	167	LATERAL WALL MI	30	Yes
10	BHIMANAGOUDA	24054	47	M	0.347	0.46	0.6	79	34	107	16	157	8.74	89	90	ANTERIOLATERAL WALL MI	25	No
11	YALLAPPA	17976	50	M	0.2	0.33	0.32	80	40	60	20	110	30	160	160	ANTERORSEPTAL MI	45	No
12	HANAMANT	18795	72	M	0.6	0.7	0.72	84	33	94	17	144	1.5	36	158	INFERIORWALL MI	30	Yes
13	NINGAPPA	19095	45	M	0.32	0.4	0.43	162	43	100	32	110	1.1	52	140	SEPTOLATERAL MI	40	No
14	SIDRAM SIDDAPPA	17045	45	M	0.313	0.4	0.5	171	39	100	34	174	5.8	145	140	INFERIOR WALL MI	40	No
15	AJAY	18662	30	M	0.39	0.48	0.52	153	47	130	31	209	1.1	31	149	ANTERIOLATERAL WALL MI	30	Yes
16	NARASAPPA	21956	70	M	0.3	0.45	0.33	79	42	58	16	116	42.7	126	182	INFERIORWALL MI	45	No
17	SUKADEV SHEKAR	9477	48	M	0.6	0.7	0.6	169	33	58	33	125	0.16	13	130	INFERIORWALL MI	45	Yes
18	SAVALAGAYYA	9185	55	M	0.75	0.5	0.5	68	34	107	136	155	3.63	47	148	INFERIOR WALL MI	30	Yes
19	SUNANDHA	9249	48	F	0.15	0.26	0.56	128	41	95	26	161	0.14	27	120	ANTERIOROLATERAL WALL MI	50	No
20	SAHEBGOUDA	19845	62	M	0.4	0.6	0.7	130	40	80	110	110	1.2	18	202	ANTERIOR WALL MI	40	Yes
21	VITTAL	15565	70	M	0.2	0.3	0.5	169	55	118	34	206	1.82	48	110	INFERIORLATERAL WALL MI	50	Yes
22	ANASUYA	12521	67	F	0.3	0.4	0.43	200	35	52	42	130	180	17	132	INFERIOR WALL MI	40	No

23	RAMACHANDRA	26569	50	M	0.2	0.4	0.6	100	40	100	40	60	0.12	60	115	LATERAL WALL MI	50	Yes
24	MAYAWWA	9099	60	F	0.5	0.56	0.58	101	45	102	35	120	0.22	40	130	LATERAL WALL MI	30	Yes
25	PARASHURAM	13197	75	M	0.3	0.4	0.43	212	35	52	42	130	18	17	132	INFERIORWALL MI	45	No
26	REVANASIDDAPPA	16632	72	M	0.94	0.7	0.78	100	40	120	90	120	1.2	20	152	INFERIORWALL MI	25	Yes
27	SUBHAS	43608	45	M	0.137	0.5	0.59	200	40	100	81	110	10	19	126	INFERIORWALL MI	50	No
28	GURURAJ CHANAPPAB	43562	56	M	0.432	0.475	0.5	201	48	130	130	200	0.8	79	120	ANTERIORWALL MI	30	Yes
29	SHAMRAYA SHIVAPPA	42349	55	M	0.426	0.5	0.54	155	56	119	40	201	1.9	89	130	INFERIORWALL MI	30	No
30	SIDRAM NINGAPPA	8302	56	M	0.313	0.467	0.6	171	39	100	34	174	5.81	145	121	LATERAL WALL MI	30	No
31	KALLAWWA CHANNAPPA	6927	60	F	0.197	0.476	0.5	153	35	91	30	157	2.43	77	130	ANTERIORWALL MI	50	No
32	RAMACHANDRA PANDURANG	26569	50	M	0.3	0.4	0.5	70	47	39	14	100	8.89	35	100	ANTERIORWALL MI	48	No
33	SHARADA MAHADEVAPPAGOUDA	26785	58	F	0.279	0.515	0.6	201	45	103	39	108	5	40	120	LATERAL WALL MI	50	No
34	SHIVASANGAPPA IRASANGAPPA	4642	55	M	0.5	0.507		143	33	103	28	165	80	156	120	INFERIORWALL MI	35	Yes
35	SUDHA MURALIDHAR KULKARNI	1824	65	F	0.28	0.471	0.66	144	49	130	67	208	11.6	56	130	LATERAL WALL MI	50	No
36	BHIMANAGOUDA PATIL	3761	70	M	0.848	0.98	0.9	114	29	40	23	115	1.32	72	321	SEPTOLATERAL MI	30	Yes
37	CHANNAPPA SATHLINGAPPA	12823	65	M	0.304	0.4	0.42	97	36	111	19	167	0.035	23	132	ANTERIORWALL MI	30	No
38	LAXMIBAI	4110	60	F	0.616	0.62	0.7	130	40	120	50	130	0.44	24	169	INFERIORWALL MI	30	yes
39	MALLIKARJUN VEERAPPA	10015	76	M	0.209	0.3	0.33	134	25	92	27	144	565	60	99	SEPTOLATERAL MI	49	no
40	MOUSUMBEE SHANUSHA	27873	70	F	0.238	0.3	0.4	94	61	105	18	185	3.52	73	120	LATERAL WALL MI	50	no
41	BRIJMOHAN	43996	45	M	0.523	0.54	0.54	100	46	100	40	200	4	90	130	LATERAL WALL MI	30	yes
42	RAMACHANDRA PANDURANG	34232	42	M	0.3	0.4	0.42	70	47	39	14	100	8.89	35	100	ANTERIORWALL MI	35	no
43	NINGAPPA RAMANINGAPPA LONI	9047	50	M	0.62	0.5	0.52	170	28	121	34	183	11.6	29	150	INFERIOR WALL MI	30	yes
44	VITTAL BHIMAPPA CHIURI	15565	60	M	0.266	0.3	0.5	132	197	52	45	160	1.82	48	94	INFERIOR WALL MI	48	yes
45	MALLAPPA	5334	54	M	0.3	0.4	0.43	50	48	87	10	145	0.117	23	94	ANTERIOWALL MI	35	no
46	IRAPPA BALLAPA	3599	58	M	0.2	0.3	0.5	127	49	110	25	185	9.56	36	81	LATERAL WALL MI	50	no
47	SITARAMCHAJU	3065	60	M	0.5	0.55	0.6	130	50	120	40		10	68	310	SEPTOLATERAL MI	35	yes
48	MOINASAB	8947	55	M	0.122	0.6	0.74	189	43	84	37	165	10.6	149	147	INFERIORWALL MI	50	no
49	GIRIMALLAYYA	18330	78	M	0.23	0.3	0.4	73	31	92	15	138	42	300	117	ANTERIOR WALL MI	49	no
50	RUDRAGOUDA	28835	70	M	0.245	0.28	0.3	87	45	98	40	120	1.39	70	137	INFERIORWALL MI	50	no

CONTROLS

1	RAMMANA	16635	65	M	0.012	0.2	0.11	160	23	94	32	150	1.19	10	124	FEVER
2	SHIVABASAMMA	17573	78	F	0.1	0.2	0.02	110	40	120	70	140	0.012	40	120	LRTI
3	SHAFGUFTA	15207	40	F	0.014	0.02	0.11	140	56	130	100	200	0.012	20	140	Fever
4	NINGANNA	15560	42	M	0.05	0.3	0.02	100	40	110	80	120	0.012	13	133	headache
5	SHANTHABAI	17554	54	F	0.2	0.3	0.2	150	56	116	30	190	0.012	8	161	NON CARDIAC CHEST PAIN
6	JAYADEEP	20238	45	M	0.03	0.03	0.05	222	52	157	44	253	0.184	19	140	TRAUMA
7	JANKIBAI	253	58	F	0.143	0.161	0.11	95	56	120	28	190	0.0189	8	120	UTI
8	CHANDRABAGA	15050	78	F	0.041	0.04	0.04	89	38	77	18	133	0.054	10	179	DIARRHOEA
9	RAMMANA MALLEPA UPPAR	16635	63	M	0.012	0.013	0.012	80	27	96	16	140	1.19	24	152	UTI
10	MAMTAJBEE DAVALSAB	14422	40	F	0.131	0.012	0.11	100	58	122	29	130	0.012	28	150	FEVER
11	MEENAKSHI SRIMANTH KATTIMANI	13599	75	F	0.117	0.12	0.13	98	58	87	50	120	0.013	37	156	URTI
12	SAROJINI CHANDRAMGOUDA	908	68	F	0.11	0.12	0.15	138	43	73	27	142	0.012	28	112	RTA
13	UTTAM	18525	28	M	0.12	0.14	0.13	103	50	120	30	140	0.015	23	130	FEVER
14	ANSABAI KEMU RATHOD	6036	40	F	0.13	0.15	0.18	108	67	99	20	130	0.012	21	128	FEVER
15	REVANASIDDAPPA SHANMUKAPPA	16632	72	M	0.13	0.12	0.12	110	68	88	30	120	0.013	30	120	UTI
16	CHANDU CHAJU RATHOD	8070	60	M	0.15	0.13	0.12	108	68	98	45	130	0.012	34	114	URTI
17	SAVITHA VASANT	7674	28	F	0.012	0.014	0.013	109	50	73	52	120	0.013	30	120	FEVER
18	APPASAB SHIVANAGOUDA PATIL	7892	52	M	0.013	0.013	0.2	110	53	120	54	130	0.012	34	120	DIARRHOEA
19	MAHADEV NAGAPPA	13399	50	M	0.112	0.587	0.03	112	54	120	56	140	0.012	38	130	UTI
20	SHIVAMMA SHANKREPPA KALE	25640	69	F	0.087	0.2	0.03	113	60	105	23	187	0.118	28	140	LRTI
21	SUSHILA BALU	25408	60	F	0.1	0.22	0.12	168	68	140	48	230	0.013	39	150	DIARRHOEA
22	ARVIND VISHWANANTH	135	55	M	0.187	0.23	0.2	91	40	108	18	76	0.056	19	130	DIARRHOEA
23	KALLAWWA CHINNAPPA	6927	50	F	0.2	0.12	0.3	120	15	68	24	107	0.024	7	108	URTI
24	NOORJAHAN	17480	50	M	0.12	0.03	0.13	130	40	120	56	140	0.012	30	110	FEVER
25	TUKARAM SOMANNA NAVI	2243	65	M	0.1	0.22	0.14	70	44	140	14	198	1.2	28	117	LRTI
26	PARASHRAM DURGAPPA	13197	50	M	0.2	0.13	0.11	114	61	106	24	189	0.64	27	147	FEVER
27	SHANTAWWA	13412	45	F	0.2	0.26	0.12	294	43	103	59	206	0.08	75	103	UTI
28	REVANASIDDAPPA	8339	60	M	0.1	0.4	0.4	73	28	92	14	135	0.12	30	148	DIARRHOEA

29	GANGABAI YAMANAPPA	27632	90	F	0.167	0.02	0.12	90	45	110	20	200	0.11	34	130	FEVER
30	PADDU PRADHANI CHAVAN	18994	65	M	0.23	0.1	0.11	78	45	100	40	110	0.027	25	76	LRTI
31	MUKTABAI SRIMANTH KATTIMANI	13599	60	F	0.117	0.02	0.11	130	40	120	56	110	0.012	17	110	LRTI
32	GURUPADAYYA NINGAYYA	14419	75	M	0.203	0.02	0.05	110	68	130	49	180	0.012	30	130	ANEMIA
33	MOUSUMBEE SHANUSHA	27873	70	F	0.238	0.03	0.02	110	67	120	48	140	0.013	32	120	UTI
34	KALLAWWA GURULINGAYYA	17714	50	F	0.12	0.03	0.01	101	44	93	20	101	0.012	36	130	DIARRHOEA
35	GAMANABAI RATHOD	5955	60	F	0.0396	0.01	0.02	120	47	98	40	112	0.013	38	120	UTRI
36	GANGABAI YAMANAPPA	34232	90	F	0.167	0.02	0.03	120	49	96	47	110	0.014	39	130	FEVER
37	BALU RAM	25270	70	M	0.1	0.2	0.1	218	41	133	44	217	0.012	15	110	UTI
38	SIDDAPPA PUNDALINGAPPA	369	65	M	0.34	0.2	0.1	49	45	63	10	118	0.25	12	170	FEVER
39	HANAMANTH	23321	66	M	0.1	0.02	0.04	46	89	56	67	110	0.02	10	120	SINUSITIS
40	MALLAPPA	11022	63	M	0.07	0.05	0.06	110	90	58	68	112	0.03	34	130	URTI
41	JAYABUN MOHAMADSAB	1167	52	F	0.103	0.05	0.3	112	98	120	23	120	0.012	30	120	RTA
42	NINGAWWA SIDDAPPA	12370	35	F	0.662	0.05	0.02	110	98	130	32	130	0.013	40	112	FEVER
43	UMESH	29188	51	M	0.06	0.03	0.04	112	99	120	48	120	0.012	40	110	ANEMIA
44	CHANDRASHEKAR MARUTI	556	46	F	0.2	0.05	0.1	100	45	100	40	100	0.012	40	112	LRTI
45	PARAPPA	4476	65	M	0.2	0.1	0.2	72	100	110	14	157	0.011	25	110	FEVER
46	SHIVAMMA SHANKREPPA KALE	25640	69	F	0.087	0.2	0.2	113	60	105	23	187	1.8	32	69	ANEMIA
47	SUBHAS HANAMATH	43608	45	M	0.137	0.5	0.3	113	70	58	68	110	0.012	34	110	UTI
48	RATNABAI VASU CHAVAN	5241	45	F	0.18	0.2	0.11	136	65	101	27	194	0.641	35	110	URTI
49	SUNANDA	9249	48	F	0.15	0.26	0.12	128	41	95	26	161	0.14	27	120	FEVER
50	SHARANU	26426	44	M	0.2	0.1	0.12	110	42	98	38	180	0.018	34	120	LRTI