“ROLE OF NOVEL BIOMARKER HEART TYPE FATTY ACID BINDING PROTEIN IN DIAGNOSING ACUTE CORONARY SYNDROME IN COMPARISON WITH TROPONIN I AND CK-MB – A ONE YEAR CROSS SECTIONAL STUDY IN KLES DR PRABHAKAR KORE HOSPITAL AND MRC, BELGAUM”

REG NO. BG0112005

Dissertation

Submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
of the requirements for the degree of

M. D.
in
GENERAL MEDICINE

DEPARTMENT OF MEDICINE,
JAWAHARLAL NEHRU MEDICAL COLLEGE,
BELGAUM, KARNATAKA

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ENDORSEMENT

This is to certify that the dissertation entitled **"ROLE OF NOVEL BIOMARKER HEART TYPE FATTY ACID BINDING PROTEIN IN DIAGNOSING ACUTE CORONARY SYNDROME IN COMPARISON WITH TROPONIN I AND CK-MB – A ONE YEAR CROSS SECTIONAL STUDY IN KLES DR PRABHAKAR KORE HOSPITAL AND MRC, BELGAUM"** is a bonafide research work done by **CANDIDATE REG NO. BG0112005**

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LIST OF ABBREVIATIONS USED

µg/L	-	Micro gram per liter
^{0}C	-	Degree centigrade
ACB	-	Albumin cobalt binding
ACS	-	Acute coronary syndromes
AHA	-	American Heart Association
ALMI	-	Anterolateral wall myocardial infarction
AMI	-	Acute myocardial infarction
ASMI	-	Anteroseptal myocardial infarction
AWMI	-	Anterior wall myocardial infarction
B-FABP	-	Brain-type fatty acid protein
BNP	-	Brain natriuretic peptide
BP	-	Blood pressure
CAD	-	Coronary Artery Disease
CHD	-	Coronary heart disease
CHF	-	Congestive heart failure
CK-MB	-	Creatine kinase-MB
CRP	-	C-reactive protein
CTEPH	-	Chronic thromboembolic pulmonary hypertension
cTn	-	Cardiac troponin
cTnI	-	Cardiac troponin I
cTnT	-	Cardiac troponin T
CVD	-	Cardiovascular disease
DTN	-	Door-to needle
e.g.	-	For example

ECG	-	Electrocardiogram
ED	-	Early diagnosis
ED	-	Emergency department
EIA	-	Enzyme immunoassay
ELISA	-	Enzyme linked immunosorbent assay
ESRD	-	End stage renal disease
FDA	-	Food and Drug Administration
GRACE	-	Global Registry of Acute Coronary Events
h	-	Hour
HDL	-	High density lipoprotein
HF	-	Heart failure
H-FABP	-	Heart-type fatty acid-binding protein
HsCRP	-	High-sensitive C-reactive protein
I-FABP	-	Intestine-type fatty acid protein
IMA	-	Ischaemia-modified albumin
IWMI	-	Inferior wall myocardial infarction
JVP	-	Juvenile venous pressure
LBBB	-	Left Bundle Branch Block
LDL	-	Low density lipoprotein
LR	-	Likelihood ratio
Mb	-	Myoglobin
MI	-	Myocardial infarction
min	-	Minute
mm Hg	-	Millimeters of mercury
MPO	-	Myeloperoxidase

n	-	Total number
NPVs	-	Negative predictive values
NSTEMI	-	Non ST elevation myocardial infarction
NT-ProBNP	-	N-terminal fragment of the prohormone BNP
PAPP-A	-	Pregnancy-associated plasma protein-A
PE	-	Pulmonary Embolism
PIGF	-	Placental growth factor
PIGF	-	Placental growth factor
PPVs	-	Positive predictive values
PTX3Q	-	Pentraxin 3
RBBB	-	Right Bundle Branch Block
SaO2	-	Oxygen saturation
sCD40L	-	Soluble CD40 ligand
SD	-	Standard deviation
STEMI	-	ST elevation myocardial infarction
TNB	-	Tetramethylbenzidine
UA	-	Unstable angina
UAP	-	Unstable Angina Pectoris
US	-	United States

ABSTRACT

Background and objectives

Recent studies suggest that human heart type fatty acid binding protein (H-FABP) may be a potential marker for early diagnosis of ACS. This study was aimed to assess the utility of H-FABP as an early biomarker in patients with acute coronary syndrome in comparison with troponin I.

Methodology

The present one year cross-sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013. A total of 61 patients who presented with acute coronary syndrome were studied. Estimation of H-FABP was done using H-FABP, Human, ELISA kit.

Results

Males constituted 68.85% of the study population and 31.15% were females. The commonest age group was between 61 to 70 year (34.43%) and the mean age was noted as 59.75 ± 11.34 years. Majority of the patients (98.36%) presented with chest pain. History of hypertension and diabetes was present in 47.5% and 36.07% of the patients respectively. Personal history of alcohol consumption and smoking was noted in 26.23% of the patients each and tobacco chewing was noted in 22.95%. On examination, 21.31% of the patients presented with pallor. On ECG, the commonest diagnosis was ASMI (36.07%) followed by IWMI (26.23%). Majority (90.16%) of the patients had raised troponin I (>0.04) levels and H-FABP was raised in 98.36% of the patients. Of the 57 patients with

raised H-FABP levels, 54 had raised troponin I levels and 3 had normal troponin I yielding to a sensitivity of 98.18% and specificity of 50%. The strength of agreement in predicting the diagnosis of ACS was 'moderate (Kappa=0.566; SE of kappa = 0.193; 95% CI: From 0.187 to 0.944). The sensitivity and specificity of H-FABP considering CK-MB as reference standard was 92.59% and 25% respectively.

Conclusion and interpretation

Raised serum H-FABP, plays an important role in the early diagnosis of acute coronary syndromes.

Keywords

Acute coronary syndrome; Cardiac biomarkers; Creatinine kinase MB; Heart type fatty acid binding protein; Troponin I;

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INTRODUCTION

Coronary heart disease (CHD) is the leading cause of death in India and the leading cause of death worldwide. Previously thought to affect primarily high-income countries, CHD now leads to more death and disability in low- and middle-income countries, such as India, with rates that are increasing disproportionately compared to high-income countries. CHD affects people at younger ages in low- and middle-income countries, compared to high-income countries, thereby having a greater economic impact on low- and middle-income countries.[1]

Coronary Artery Disease (CAD) is the leading causes of heart failure and death worldwide. Acute cardiac events that may lead to acute myocardial infarction (AMI) and sudden cardiac death are unpredictable. Conduction disturbances, like Right Bundle Branch Block (RBBB) or Left Bundle Branch Block (LBBB) may be considered as a predictor of severity of CAD and coronary events. Previous studies revealed the impact of intra-ventricular conduction disturbances on survival of patients with AMI and patients with chronic CAD.[2]

Coronary heart disease (CHD) occurs when the arteries of the heart that normally provide blood and oxygen to the heart are narrowed or even completely blocked. Angina is exertional chest pain, pressure, or discomfort caused by such narrowings or blockages in the heart arteries, which reduce the flow of blood.[3]

Acute coronary syndromes (ACS), otherwise known as heart attacks, occur when a blockage occurs suddenly. Acute cardiac events that may lead to acute myocardial infarction (AMI) and sudden cardiac death are unpredictable.[2]

Symptoms of a heart attack include: pain or discomfort in the middle of the chest, arms/shoulders/elbows (classically on the left side), jaw, or back. In addition the person may feel shortness of breath, nausea/vomiting, light-headedness/faint/pale, or may break into a cold sweat. Women are more likely to have shortness of breath, nausea, vomiting, and back or jaw pain.[3]

Acute coronary syndrome (ACS) is an umbrella term for a wide spectrum of clinical sign and symptoms suggestive of myocardial ischaemia. The ultimate clinical implication of ACS may therefore vary from assuredly benign to potentially fatal. Thus further risk stratification of this syndrome complex is imperative. It has been seen that 50% of patients hospitalized for suspected ACS ultimately leave the hospital with other diagnoses.[4] Further management of ACS is resource-intensive and thus proper risk stratification is mandatory to avoid needless hospitalizations and interventional procedures. The traditional clinical tools for risk stratification such as history, physical examination, and ECG though undoubtedly important may prove to be inadequate in the majority of cases. This has led to the search for circulating markers that better establish diagnosis and thus aid in appropriate and rapid patient triage.[5]

The cardiac necrosis markers creatine phosphokinase and its isoenzymes and especially troponin have come to the forefront in the past decade to better identify high-risk individuals suitable for the most resource-intensive treatment. This is reflected in the various management guidelines of ACS where cardiac enzymes are the cornerstone in decision making. In addition, the success and usefulness of these biomarkers has led to intense research in this field resulting in several newer biomarkers emerging on the horizon of clinical use in ACS.[5]

Diagnosis of acute coronary syndrome (ACS) encompasses a wide spectrum of myocardial ischaemia varying from assuredly benign to potentially fatal. Cardiac biomarkers have had a major impact on the management of this disease and are now the cornerstone in its diagnosis and prognosis.[5]

Recent studies in laboratories and the emergency department have shown that heart-type fatty acid-binding protein (H-FABP), a more recently developed cardiac biomarker, is able to detect myocardial damage as soon as one hour after onset of ischemia and, therefore, is regarded the earliest plasma marker available.[6-9] A bedside test for H-FABP, providing results within 15 minutes,[10] could potentially reduce diagnostic uncertainty for patients suspected of ACS in primary care. This prompted us to assess and compare the utility of H-FABP in comparison with troponin I and CK-MB as an early biomarker in patients with acute coronary syndrome.

OBJECTIVES

The objective of the present study was to assess and compare the utility of H-FABP in comparison with troponin I and CK-MB as an early biomarker in patients with acute coronary syndrome.

REVIEW OF LITERATURE

Heart disease is the major cause of death in the united states.[11] Many Americans with heart disease will present at the hospital with an acute coronary syndrome (ACS) that will put them at significant risk of morbidity and death.[12]

Although timely and appropriate treatment reduces the risk of an immediate or subsequent poor outcome, the high prevalence of risk factors for coronary artery disease (CAD) ensures that the development of future ACS will also be high. Unfortunately, the prevalence of risk factors is stratified by economics, education level, and cultural differences, among other factors, which puts patients who may be least likely or the least able to seek skilled care at the most risk for poor outcomes.[12]

The presence of multiple risk factors increases the risk of developing CAD. However, theories of athero- sclerotic plaque formation have changed such that cholesterol is no longer the lone culprit in CAD. Cellular signaling associated with inflammation is increasingly implicated in the initiation and progression of atherosclerotic plaques. Plaques have been shown to develop early in life and remain subclinical for years or decades, depending on the accelerating effects that risk factors and genetic predisposition to CAD will have on disease progression.[12]

Epidemiology

STEMI is a major health problem of the world. In 2001, 7.1 million deaths were attributed to ischemic heart disease worldwide, 1 80% of which were in low-income countries.[13,14] Half a million people suffer a STEMI in the US each year.[15] The prevalence of CAD is increasing in South Asians.[16] Coronary risk factors are

more common in south Asians as compared to the rest of the world and CAD manifests at a younger age.[13,14]

According to the American Heart Association (AHA), 71.3 million Americans had some form of cardiovascular disease (CVD) in 2003. CVD was responsible for nearly 1 million deaths in 2003. Among Americans with CVD, 13.2 million are estimated to have CAD. ACS is a manifestation of CAD that encompasses acute myocardial infarction (AMI) and unstable angina (UA), which is the dangerous middle ground between stable angina and myocardial infarction. Although the death rate from CAD has been declining since 1950, approximately 40% of Americans who experience a coronary event this year will die as a result. For those who experience a recurrent coronary event, the risk of death is 4 to 6 times that of the general population.[11]

Mortality

Mortality in patients with AMI has been observed to increase for each 30 minutes that passes before appropriate intervention. Timely treatment upon presentation contributed to the reduced in-hospital mortality (11.2% to 9.4%) observed in the 1990s and "median door-to-drug time" was reduced by nearly 50% for patients requiring thrombolytic therapy.[17]

Despite efforts to improve patient management, there is no evidence suggesting that the risk of developing CAD is declining. The INTERHEART study, for example, found that 9 modifiable risk factors accounted for 90% of first AMIs.[18]

A 2003 Centers for Disease Control and Prevention study of adults showed that the prevalence of respondents with 2 or more CVD risk factors correlated with increased age, lower levels of education, and lower levels of income.[19]

Prevalence also varied according to psychosocial factors, race, and state of residence. African Americans and Native Americans had the highest prevalence of multiple risk factors with greater than 46%, whereas Asian Americans had the lowest prevalence with less than 26%. Approximately 26% of college graduates had multiple risk factors, whereas more than 50% of those who did not complete high school had multiple risk factors. Respondents with a household income of $50 000 or greater had a 29% prevalence of multiple risk factors, whereas more than 50% of respondents with a household income of $10 000 or less had multiple risk factors. Disabled respondents reported approximately a 70% prevalence of multiple risk factors compared with only 34% of those who were homemakers or employed.[12]

Winkleby et al[20] reported health profiles among young adults who were 18 to 24 years old that were particularly alarming. Between 1990 and 2000, this group showed large increases in the prevalence of smoking and obesity with corresponding low rates of physical activity and fruit and vegetable intake.

The high prevalence of major modifiable CVD risk factors among young Americans is expected to exacerbate the healthcare crisis anticipated to follow the aging of the baby boomers. Coupled with the increased prevalence of obesity and diabetes across age groups, the aging population and poor health profiles among young adults are driving an increase in CVD and the most potent risk factors for poor cardiovascular outcomes, such as hypertension and dyslipidemia.[12]

Natural history of acute coronary syndromes in India[15]

- Patients are younger at presentation (mean age 57.5 years)
- Lower socioeconomic groups are substantially affected (75%)
- STEMI is more common in Indians as compared to the West
- Medical attention is received late (median 6 hr after onset of symptoms)
- Majority of patients receive thrombolysis (80%)
- Median door-to needle time (DTN) is 50 min
- Standard of care medications are received less often
- 30-day mortality is higher as compared to the west
- Most patients reach hospital by private/public transport
- Most patients pay directly for their own treatment

The scenario of acute coronary syndromes in India calls for a lot of improvement. The lower rate of education and awareness in the lower socioeconomic strata, infrastructural problems, financial difficulties, lack of ambulance services, suboptimal DTN, and lack of widespread primary PCI programs make pre-hospital thrombolysis a potentially important option here.[15]

Risk factors

Nonmodifiable factors that influence risk for coronary artery disease include age, sex, family history, and ethnicity or race. Men have a higher risk than women. Men older than age 45, women older than age 55, and anyone with a first-degree male or female relative who developed coronary artery disease before age 55 or 65, respectively, are also at increased risk. Modifiable risk factors include elevated levels of serum cholesterol, low-density lipoprotein cholesterol, and triglycerides;

lower levels of high-density lipoprotein cholesterol; and the presence of type 2 diabetes, cigarette smoking, obesity, a sedentary lifestyle, hypertension, and stress.[21]

Pathophysiology

Plaque formation

The accumulation of atherosclerotic plaques is no longer considered to be the simple result of cholesterol storage. Inflammation is increasingly implicated in plaque formation. At the cellular level, plaque accumulates in response to many signals that cause blood cells, such as monocytes, to adhere to the endothelium of the arterial lumen. Inflammatory responses to insults such as bacterial toxins, in addition to traditional risk factors, such as dyslipidemia, hypertension, hyperglycemia, and obesity, can initiate monocyte adherence.[22]

Once adhered to the endothelium, monocytes migrate into the vascular wall to the arterial intima, the muscular layer closest to the vessel lumen. At this point, they transform into macrophages and begin to ingest the modified lipoprotein particles, which accumulate in the intima naturally and at an accelerated rate in people with hyperlipidemia. These lipid- filled macrophages are also known as foam cells, which are the hallmarks of atherosclerotic plaques. Foam cells typically come together to form a plaque within the intima. Many foam cells die by apoptosis, disintegrate with debris becoming membrane-bound, and then are eliminated by phagocytosis or by shedding. The original modified lipoproteins, macrophages, foam cells, and apoptotic debris, in addition to other important factors, such as collagen and von Willebrand factor, form the core of the plaque.[23]

Plaque progression

Ultrasound studies have shown that atherosclerotic plaques are widely distributed in the coronary arteries and that these plaques begin to form early in life.[24,25]

Therefore, atherosclerotic plaques only become clinically evident when they gain enough bulk to obstruct coronary circulation, often resulting in stable angina, or they become physically disrupted and form an acute clot at the site, resulting in UA or AMI. Studies using serial observations by angiography have suggested that plaque progression is not a linear process and more likely occurs as the result of physical disruption of plaques.[12]

Many patients who present with ACS will have more than one disrupted plaque that may have become symptomatic through several mechanisms.[26]

First, erosion of the epithelial monolayer, separating the intima from the vessel blood flow, can produce a thrombus by exposing collagen and von Willebrand factor factors that promote platelet aggregation (one of the first steps in thrombus formation).[27]

Endothelial monolayer erosion can be initiated by cell death or subendothelial basement membrane (a supportive layer that exists in between the endothelium and elastic lamina in the intima) degradation. Inflammatory activation of T cells subjects the endothelial cells to attack in addition to local signaling that may increase apoptosis.[28]

Secondly, plaque growth also results from intraplaque hemorrhages. Inflammatory cells within the plaque promote angiogenesis (the creation of new blood vessels that will deliver nutrients to the plaque) by secreting mediators.[29]

These small, fragile new vessels are prone to rupture. Thrombin production upon rupture stimulates the release of platelet-derived growth factor and transforming growth factor beta, which are potent stimulants for smooth muscle growth, further increasing plaque bulk.[30]

A third mechanism of plaque growth occurs when a plaque's fibrous cap tears, permitting contact between the plaque core and circulating coagulation factors in the blood. Inflammatory mediators, such as interferon-gamma, inhibit new collagen production necessary to maintain cap integrity, weakening the cap.[23]

In addition to the decreased collagen production, existing collagen is usually weakened because collagenases are over expressed in plaque tissue.[31]

These mechanisms leave the fibrous cap of many plaques vulnerable to physical insult. If this vulnerability results in a microtear, a small subclinical thrombus may be formed, reabsorbed into the plaque, and then covered by additional fibrous tissue that is stimulated to grow by the release of platelet-derived growth factor and transforming growth factor beta. This process results in a bulky, fibrous plaque instead of a fatty plaque.[23]

If the tear exposes a substantial amount of the plaque's prothrombotic core, a large, fatal acute thrombus may result.

Thrombus formation

Disrupted plaques allow contact between the blood and collagen, which activates platelets. The tissue growth factors produced by macrophages and smooth muscle cells also initiate coagulation.[32]

Platelet activation results in the transformation of the glycoprotein IIb/IIIa receptors on the platelets. These receptors are vital to thrombus formation because they are the sites where fibrinogen connects, enabling a "mesh" or "aggregation" of platelets to grow, and initiating thrombus formation.[33]

These mechanisms work in conjunction to produce the interlinked, aggregated platelets that are the hallmarks of the coronary thrombus. Clot formation is augmented in the presence of factors that inhibit natural fibrinolytic action. Plasminogen-activating inhibitor-1 levels are increased in patients with conditions that predispose them to CAD, such as diabetes and hypertension.18 This fibrinolytic inhibitor weakens the body's natural defense against clot formation and increases the potential for thrombi to form larger, more damaging occlusions.[12]

ACS begins when a disrupted atherosclerotic plaque in a coronary artery stimulates platelet aggregation and thrombus formation. It’s the thrombus occluding the vessel that prevents myocardial perfusion. In the past, researchers supposed that the narrowing of the coronary artery in response to thickening plaque was primarily responsible for the decreased blood flow that leads to ischemia, but more recent data suggest that it’s the rupture of an unstable, vulnerable plaque with its associated inflammatory changes or as Hansson puts it in a review article in the New England

Journal of Medicine, “most cases of infarction are due to the formation of an occluding thrombus on the surface of the plaque.”[34]

Myocardial cells require oxygen and adenosine 5b-triphosphate (ATP) to maintain the contractility and electrical stability needed for normal conduction. As myocardial cells are deprived of oxygen and anaerobic metabolism of glycogen takes over, less ATP is produced, leading to failure of the sodium–potassium and calcium pumps and an accumulation of hydrogen ions and lactate, resulting in acidosis. At this point, infarction—cell death—will occur unless interventions are begun that limit or reverse the ischemia and injury. During the ischemic phase, cells exhibit both aerobic and anaerobic metabolism.[21]

If myocardial perfusion continues to decrease, aerobic metabolism ceases and eventually anaerobic metabolism will be significantly reduced. This period is known as the injury phase. If perfusion is not restored within about 20 minutes, myocardial necrosis results and the damage is irreversible. Impaired myocardial contractility, the result of scar tissue replacing healthy tissue in the damaged area, decreases cardiac output, limiting perfusion to vital organs and peripheral tissue and ultimately contributing to signs and symptoms of shock. Clinical manifestations include changes in level of consciousness; cyanosis; cool, clammy skin; hypotension; tachycardia; and decreased urine output.[35]

Patients who have experienced an MI are therefore at risk for developing cardiogenic shock. In an attempt to support vital functions, the sympathetic nervous system responds to ischemic changes in the myocardium. Initially, both cardiac output and blood pressure decrease, stimulating the release of the hormones

epinephrine and norepinephrine, which in the body's attempt to compensate increase the heart rate, blood pressure, and afterload, ultimately increasing myocardial demand for oxygen. As oxygen demand increases at the same time that its supply to the heart muscle decreases, ischemic tissue can become necrotic.[23]

Low cardiac output also leads to decreased renal perfusion, which in turn stimulates the release of renin and angiotensin, resulting in further vasoconstriction. Additionally, the release of aldosterone and antidiuretic hormone promotes sodium and water reabsorption, increasing preload and ultimately the workload of the myocardium.[36]

Signs and symptoms

The degree to which a coronary artery is occluded typically correlates with presenting symptoms and with variations in cardiac markers and electrocardiographic findings. Angina, or chest pain, continues to be recognized as the classic symptom of ACS. In unstable angina, chest pain normally occurs either at rest or with exertion and results in limited activity. Chest pain associated with NSTEMI is normally longer in duration and more severe than chest pain associated with unstable angina. In both conditions, the frequency and intensity of pain can increase if not resolved with rest, nitroglycerin, or both and may last longer than 15 minutes. Pain may occur with or without radiation to the arm, neck, back, or epigastric area. In addition to angina, patients with ACS also present with shortness of breath, diaphoresis, nausea, and lightheadedness. Changes in vital signs, such as tachycardia, tachypnea, hypertension, or hypotension, and decreased oxygen saturation (SaO2) or cardiac rhythm abnormalities may also be present.[38]

Atypical ACS symptoms

Many women present with atypical symptoms, resulting in delayed diagnosis and treatment.[39]

Women frequently experience shortness of breath, fatigue, lethargy, indigestion, and anxiety prior to an acute MI and may not attribute those symptoms to heart disease.[40]

It's also important for clinicians to realize that women tend to experience pain in the back rather than substernally or in the left side of the chest and do not characterize it as pain, but may instead report a numb, tingling, burning, or stabbing sensation;[41] in fact, a recent study found that, when compared with men, women diagnosed with ACS more often reported indigestion, palpitations, nausea, numbness in the hands, and atypical fatigue than chest pain.[42]

Silent ischemia

Ischemia can also occur without any obvious signs or symptoms. The classic Framingham Heart Study was initiated in 1948 to explore contributing factors for cardiovascular disease and has provided the scientific community with much of what is known today about heart disease. Findings from this longitudinal study of 5,209 participants found that 50% of patients diagnosed with an MI experienced silent ischemia and did not exhibit any of the classic symptoms of ACS.[43]

Populations more likely to experience a silent MI include people with diabetes, women, older adults, and those with a history of heart failure.[43] As the prevalence of diabetes rises, silent ischemia may also become more common.[21]

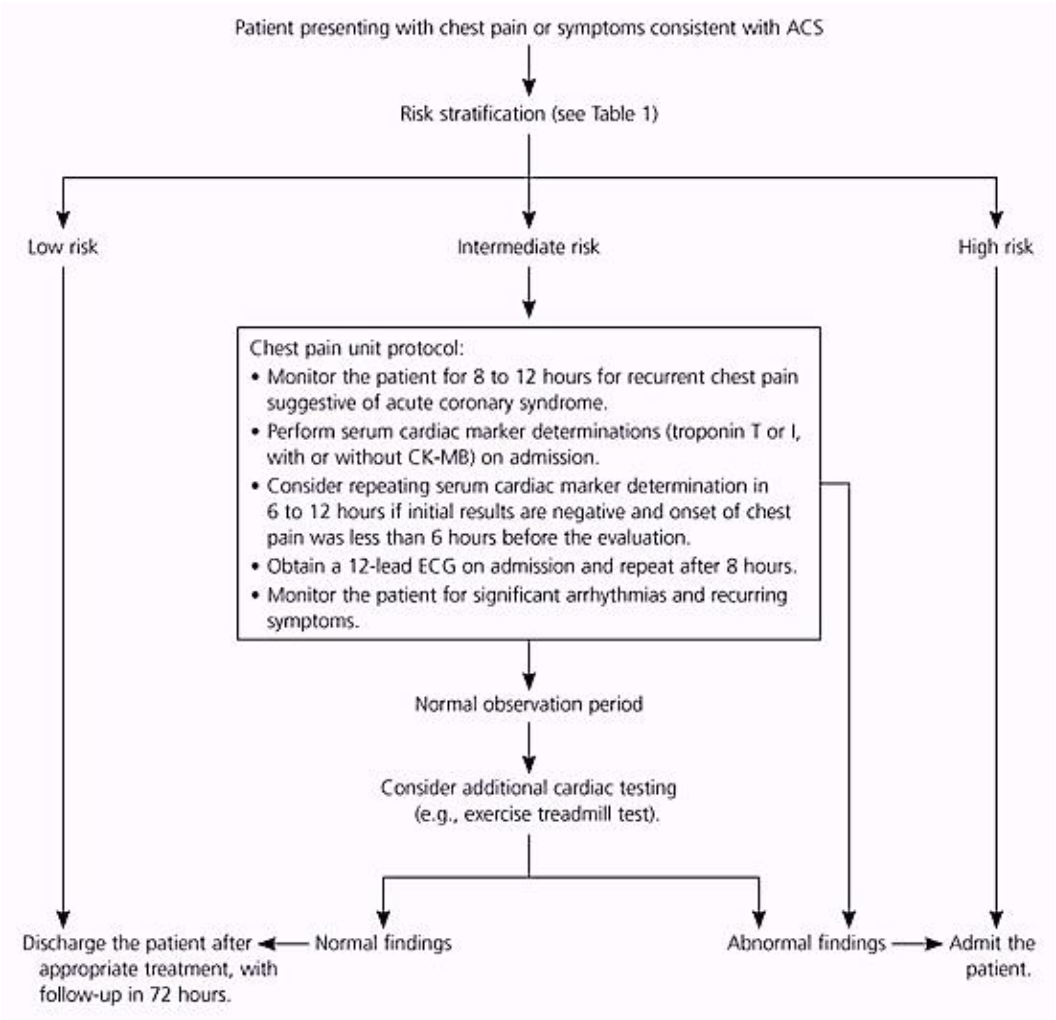
Symptoms of acute coronary syndrome include chest pain, referred pain, nausea, vomiting, dyspnea, diaphoresis, and light-headedness.[44] Some patients may present without chest pain; in one review,[45] sudden dyspnea was the sole presenting feature in 4 to 14% of patients with acute myocardial infarction. Pain may be referred to either arm, the jaw, the neck, the back, or even the abdomen. Pain radiating to the shoulder, left arm, or both arms somewhat increases the likelihood of acute coronary syndrome (likelihood ratio [LR]: 1.6).[44]

Typical angina is described as pain that is substernal, occurs on exertion, and is relieved with rest. Patients with all three of these features have a greater likelihood of having acute coronary syndrome than patients with none, one, or even two of these features. Chest pain that occurs suddenly at rest or in a young patient may suggest acute coronary vasospasm, which occurs in Prinzmetal's angina or with the use of cocaine or methamphetamine. Only about 2% of patients with cocaine-associated chest pain have acute coronary syndrome.[46]

Atypical symptoms do not necessarily rule out acute coronary syndrome. One study[47] found the syndrome in 22% of 596 patients who presented to emergency departments with sharp or stabbing pain. However, a combination of atypical symptoms improves identification of low-risk patients. The same study[47] demonstrated that patients presenting with sharp or stabbing pain, pleuritic pain, and positional chest pain had only a 3% likelihood of having acute coronary syndrome.

The physical examination in patients with acute coronary syndrome frequently is normal. Ominous physical findings include a new mitral regurgitation murmur, hypotension, pulmonary rales, a new third heart sound (S_3 gallop), and new

jugular venous distention. Chest-wall tenderness reduces the likelihood of acute coronary syndrome (-LR: 0.2).[48]



Evaluation of Patients with Chest Pain or Symptoms Suggesting ACS

The likelihood of silent ischemia traditionally has been thought to be greater in patients with diabetes. The "silent myocardial infarction" hypothesis is based on the relatively high incidence of ischemic changes noted on screening ECGs in patients with diabetes.[44]

However, in a prospective observational study[49] of 528 patients with symptoms suggestive of coronary artery disease on presentation to the emergency

department of a cardiac referral center, symptoms did not differ significantly in patients with and without diabetes. The increased frequency of ischemic changes noted on screening ECGs in patients with diabetes simply may reflect their greater baseline risk of coronary artery disease.

Any patient with a history suggestive of acute coronary syndrome should be evaluated in a facility that has ECG and cardiac monitoring equipment. Patients with suspected acute coronary syndrome who have chest pain at rest for more than 20 minutes, syncope/presyncope, or unstable vital signs should be referred to an emergency department immediately. The diagnosis of acute myocardial infarction, which includes both STEMI and NSTEMI, requires at least two of the following: ischemic symptoms, diagnostic ECG changes, and serum cardiac marker elevation.[44]

The likelihood of acute myocardial infarction is extremely low in patients with a normal or nearly normal ECG who are younger than 60 years and do not have pain described as “pressure” or pain radiating to the arm, shoulder, neck, or jaw. The likelihood of acute infarction is 1.1% or less with a normal ECG and 2.6 percent or less with nonspecific ECG changes.[44]

Diagnosis

The patient’s clinical history, presenting symptoms, biomarker levels, and electrocardiographic results are all evaluated.

Cardiac biomarkers

Injured myocardial cells release proteins and enzymes known as cardiac bio-markers into the blood. These markers help practitioners determine whether the

patient is having or has recently had an acute MI (either an NSTEMI or a STEMI). The utility of various biomarkers is determined by the timing and duration of their elevation as well as by the extent of their cardiac specificity. The cardiac troponins, troponin T and troponin I, are the most cardiac-specific biomarkers. These structural proteins are not normally found in serum; therefore elevated serum levels may predict the degree of thrombus formation and microvascular embolization associated with coronary lesions. Levels of troponins I and T increase within four to six hours of myocardial injury; troponin I levels remain elevated for four to seven days, and troponin T levels remain elevated for 10 to 14 days. Normal reference ranges for cardiac biomarkers vary among laboratories; in order to diagnose myocardial necrosis a single troponin elevation greater than the 99th percentile of an agreed-upon reference control group is required.[50]

Cardiac troponins are the preferred biomarkers for diagnosing acute MI because elevated levels correlate with a more accurate diagnosis, predict a high risk of future cardiac events even when levels of the myocardium-specific biomarker creatine kinase-MB (CK-MB) are normal or only mildly elevated, and elicit fewer false positives when concurrent skeletal muscle injury is present (after trauma or surgery, for example). But if a laboratory is unable to process troponins, CK-MB is considered a reasonable alternative. CK-MB is a cardiac-specific enzyme that's released within four to six hours of injury and remains elevated for 48 to 72 hours after injury. Two consecutive levels of CK-MB greater than the 99th percentile of a reference control group contribute to the diagnosis of acute MI.[50]

Myoglobin, a heme protein, is not cardiac specific, yet it's still considered a valuable biomarker because it's the first to rise after myocardial damage. If a patient

presents with ACS symptoms that started less than three hours earlier, CK-MB and troponin levels may not yet be elevated. In such a case, myoglobin can rule out or lead to an early diagnosis of acute MI and prompt decisive therapy.[50]

Electrocardiographic findings

The AHA and the ACC recommend that a 12-lead electrocardiogram (ECG) be performed in patients with symptoms consistent with ACS and interpreted by an experienced physician within 10 minutes of ED arrival.2 Findings on a 12-lead ECG help the practitioner to differentiate between myocardial ischemia, injury, and infarction; locate the affected area; and assess related conduction abnormalities. Electrocardiographic findings reflective of unstable angina or NSTEMI include ST-segment depression and inverted T waves. ST depression will normally resolve when the ischemia or pain has resolved, although T-wave inversion may persist. Providers should review electrocardiographic findings as well as levels of cardiac biomarkers to distinguish between unstable angina and NSTEMI.[21]

On the other hand, ST elevation on a 12-lead ECG in two contiguous leads is diagnostic of STEMI. With STEMI, T-wave inversion may also be present. These changes normally subside within hours of an MI. Abnormal Q waves appear on an ECG in the presence of an MI as a result of alterations in electrical conductivity of the infarcted myocardial cells. Once an abnormal Q wave has developed it usually remains permanently on the ECG. Therefore, an abnormal Q wave on an ECG does not necessarily signal a current acute MI, but could indicate an old MI.[51]

Role of biomarkers in risk stratification of acute coronary syndrome

Biomarkers in acute coronary syndrome[5]

Established biomarkers	Emerging biomarkers
Troponin I	Myeloperoxidase
Troponin T	Metalloproteinase
Brain natriuretic peptide (BNP)	Soluble CD40 ligand
NT-Pro BNP	Ischemia modified albumin
C-reactive protein (CRP)	Pregnancy associated plasma protein A
	Cystatin C
	Fatty acid binding protein
	Placental growth factor (PIGF)

Various biomarkers underscoring different facets of the pathophysiology and outcomes of ACS[5]

Inflammation

- C-reactive protein
- Myeloperoxidase
- Matrix metalloproteinase
- Soluble CD40 ligand

Platelet activation

- Soluble CD40 ligand

Vulnerable plaque

- Pregnancy-associated plasma protein-A
- Myeloperoxidase
- Placental growth factor
- Matrix metalloproteinase

Myocardial necrosis

- Creatine phophokinase and isoenzymes
- Troponin I and T
- Fatty acid binding protein

Ischaemia

- Ischaemia modified albumin

Pump failure

- Brain natriuretic peptide
- NT-pro brain natriuretic peptide

Diagnosis of acute coronary syndrome (ACS) encompasses a wide spectrum of myocardial ischaemia varying from assuredly benign to potentially fatal. Cardiac biomarkers have had a major impact on the management of this disease and are now the cornerstone in its diagnosis and prognosis. In this review we discuss both the established and the newer emerging biomarkers in ACS and their role in highlighting not only myocardial necrosis but also different facets of the pathophysiology of ACS. The future of cardiac biomarker testing may be in multimarker testing to better characterize each patient of ACS and thus tailor both short-term and long-term therapy accordingly. This novel concept, however, needs to be tested in clinical trials for its incremental value and cost-effectiveness.[5]

The traditional clinical tools for risk stratification such as history, physical examination, and ECG though undoubtedly important may prove to be inadequate in the majority of cases. This has led to the search for circulating markers that better establish diagnosis and thus aid in appropriate and rapid patient triage. The cardiac necrosis markers creatine phosphokinase and its isoenzymes and especially troponin have come to the forefront in the past decade to better identify high-risk individuals suitable for the most resource-intensive treatment. This is reflected in the various management guidelines of ACS where cardiac enzymes are the cornerstone in decision making. In addition, the success and usefulness of these biomarkers has led to intense research in this field resulting in several newer biomarkers emerging on the horizon of clinical use in ACS.[5]

Established biomarkers

Cardiac troponin (cTn)

Cardiac troponin is a well established biomarker for diagnosis and prognosis of ACS. The data for troponins in ACS is robust even at minimally elevated levels. Measurement of cTnT and cTnI is now the crucial step in new diagnostic criteria for MI. With current high quality analytic methods, cardiac troponin measurements are highly sensitive and specific for myocardial injury. In the appropriate clinical setting (high certainty that the troponin is due to acute coronary syndrome) even minor elevations of troponin identify high risk underlying coronary morphology like patients with plaque rupture, large thrombus burden and distal embolisation. These patients clearly benefit from aggressive anti-platelet, anti-thrombotic and revascularization therapy.[5]

cTn typically increases more than 20 times above the upper limit of the reference range in myocardial infarction as compared to creatine kinase-myocardial band (CK-MB) which usually increases 10 times above the reference range. This provides an improved signal - to - noise ratio, enabling the detection of even minor degree of necrosis with troponin. The cTn begins to elevate 3 h from the onset of chest pain in MI. Because of the continuous release, cTn elevation persists for days (cTnI: 7-10 days, cTnT: 10-14 days). This prolonged course of release with troponin is advantageous for the late diagnosis of MI, however, it limits the diagnosis of early reinfarction.[5]

The cardiac troponin especially cTnT pose diagnostic challenges in patients of chronic renal failure. Frequent cTnT elevations (30 to 70% of end stage renal disease (ESRD) patients compared with <5% in similar patients of cTnI) are seen in patients of renal failure in the absence of clinical suspicion of ACS.[52]

The putative mechanisms for chronic elevation of troponin in chronic renal disease patients include endothelial dysfunction, acute cardiac stretch, microinfarction and left ventricular hypertrophy.[53]

However, it is important to understand that in the setting of acute coronary syndrome these patients should be treated as if renal failure were not present as the short term prognostic value of troponin T for cardiovascular event is similar in patients with and without renal failure. Data comparing the two cTn suggest that cTnI may be slightly more sensitive. However, this may be due to different release kinetics of the two biomarkers and to different limits of detection of the currently available assays.[54]

The other advantage of cTnI may be its greater specificity in patients of ESRD. However, the important advantage of cTnT is that due to international patent restrictions there is only one assay for its measurement, thus cTnT demonstrates a high degree of precision at the low end of measurement range and a relatively uniform cut-off concentration. In contrast, at least 18 different commercial assays for cTnI are available leading to considerable variation in the cut-off concentrations in the definition of a myocardial infarction by cTnI values.[55] Thus, a clinician should be aware of the cTnI cut-off values specifically associated with the particular assay used by the laboratory.[5]

Brain natriuretic peptide (BNP)

Brain natriuretic peptide is a neurohormone synthesized in ventricular myocardium and released in response to cardiac stretch. NT-ProBNP is the N-terminal fragment of the prohormone BNP. These natriuretic peptides have prognostic value across the full spectrum of acute coronary syndrome patients. Patients with elevated BNP or NT-proBNP are at significantly increased risk for subsequently developing heart failure and death both in the short- and long-term. This is seen regardless of their troponin levels and even when there is no clinical evidence of heart failure.[56]

The prognostic value of these peptides is over and above the conventional risk factors like age, Killip class and left ventricular ejection fraction. Studies have shown that BNP predicts high risk features in ACS, such as more severe underlying atherosclerosis, left ventricular dysfunction, left ventricular hypertrophy, and the burden of the ischaemic insult.[57]

Thus it may be prudent to conclude that in patients with ACS, the higher the BNP, the more severe the haemodynamic insult due to ischaemia and the worse the prognosis.[5]

C-reactive protein (CRP)

C-reactive protein is a nonspecific inflammatory marker that is released by the liver in response to the acute phase injury. CRP can be measured by multiple assays in acceptable precisions down to or below 0.3 mg/l and most give comparable results (designated as high-sensitive CRP or hsCRP). CRP in addition to BNP and troponin does appear to provide some additional value in the prognostication of ACS;[58]

However, the incremental value is modest. In terms of the association of CRP and ACS it is important to distinguish cases without (unstable angina) and with necrosis (acute MI). In cases of AMI, CRP release is triggered as an acute phase reactant secondary to necrosis and levels of CRP are much higher and these have been correlated with infarct size. Though infarct size is the major determinant of long term prognosis after AMI; mortality has been shown to be related to CRP levels independent of left ventricular systolic function.[59]

In the absence of infarction, CRP levels correlate to the extent of atherosclerosis and some studies have shown that it predicts coronary events in patients of unstable angina independent of troponin levels.[5]

However, a more recent large prospective study showed only a weak association of CRP levels and future coronary events in patients of ACS and even

this disappeared once adjusted for other common clinical variables. This study included about two-thirds of AMI patients and one-third unstable angina patients.[60]

Another interesting implication of CRP in ACS has been in terms of treatment: in a study of ACS patients, those with low CRP levels after statin therapy had better clinical outcomes than those with higher CRP levels, regardless of the resultant level of LDL cholesterol. Thus implying that statin therapy in these high risk patients of ACS should be driven not only by the target lipid levels but also the CRP levels achieved.[61]

These data suggest that CRP levels in ACS may be of prognostic significance but their incremental value over conventional factors and biomarkers may be modest.

Emerging biomarkers

Myeloperoxidase (MPO)

Myeloperoxidase is a haemoprotein and lysosomal enzyme released from neutrophilic granules and monocytes.[62]

MPO is released into the extracellular fluid and general circulation during inflammatory conditions. This enzyme has been associated with oxidation of lipids contained within LDL, dysfunctional HDL and consumption of nitric oxide thus rendering the normally anti-thrombotic endothelial surface thrombogenic via expression of various pro-thrombotic and anti-fibrinolytic factors.[63]

MPO elevation has been associated with adverse ventricular modeling after MI and with progression to heart failure.[64]

MPO is responsible for fibrous cap disintegration making it a marker of plaque instability and inflammation.[5]

A recent study revealed that elevated MPO levels were marker of cardiac death independent of troponins, CRP in patients of ACS thus highlighting its utility in these patients.[65]

However, increased MPO is not likely to be specific to cardiac diseases, as activation of neutrophil and macrophages can occur in any infectious, inflammatory or infiltrative disease process.[5]

Soluble CD40 ligand

Soluble CD40 ligand (sCD40L) is expressed on platelets and released from them on activation. It has biological activity that can trigger an inflammatory reaction in vascular endothelial cells by the secretion of cytokines and chemokines.[66]

Membrane bound CD40L and sCD40L forms interact with the CD40 receptor molecule, which is present not only on B cells but also on monocytes, macrophages, and endothelial and smooth muscle cells in atheroma, leading to release of matrix MMPs and subsequent destabilization of the plaque. Thus upregulation of the CD40L system may play a pathogenic role also in triggering ACS.[5]

Increased sCD40L concentrations have been demonstrated in other inflammatory disorders, e.g., autoimmune diseases, multiple sclerosis, and inflammatory bowel disease, as well as in stroke, hypercholesterolaemia, and diabetes.[67]

In OPUS-TIMI16 trial increased sCD40L was associated with a higher risk for future death and recurrent myocardial infarction independent of other variables including cTnI and CRP. Importantly in combination with cardiac troponin I it significantly improved risk prediction for future death and MI.[68]

Similarly in the CAPTURE study of ACS, increased sCD40L concentrations were associated with a higher risk of death and non-fatal MI. Notably elevation of soluble CD40 ligand identified the subgroup of patients likely to benefit from anti-platelet treatment with abciximab.[69]

Therapeutic benefits of sCD40L were also seen in MIRACL Study wherein patients with acute coronary syndromes and high sCD40L had a significant reduction in the risk of recurrent cardiovascular events with early statin therapy.[70]

However, recent studies have flagged doubts on the influence of pre-analytical and analytical conditions on measurement of sCD40L and thus additional studies are warranted before implementing wider clinical use.[71]

Ischaemia modified albumin

Ischaemia induces a conformational change in albumin, so that it can no longer bind to transitional metals such as cobalt or copper. Using the albumin cobalt binding (ACB) test, the quantum of ischaemia modified albumin can be estimated and this serves as an index of ischaemia.[5]

Ischaemia-modified albumin (IMA) has been shown to be an independent predictor of short- and long-term adverse outcomes over and above conventional known risk in patients with ACS.[72]

Increased IMA values may be found in patients with cancer, infections, end-stage renal disease, liver disease, and brain ischaemia also. The commercially available IMA test appears to be relatively sensitive for identifying unstable angina. However, the test's specificity is relatively poor and the assay is cumbersome to use. With greater refinement it may be a useful test in the emergency department (ED) to rule out ischaemia which is more important at that stage.[5]

Pregnancy-associated plasma protein-A

Pregnancy-associated plasma protein-A (PAPP-A) is a large, zinc binding proteinase produced by different cell types, including fibroblasts, vascular smooth muscle cells, male and female reproductive tissues and belongs to the insulin-like growth factor family. It is thought to be released when neovascularization occurs and thus may be a marker of incipient plaque rupture. Its level has been shown to be elevated in unstable plaques and in circulation in patients of ACS.[73]

In study of patients with angiographically confirmed acute coronary syndrome, elevated serum PAPP-A was a strong independent predictor of death or recurrent MI, even in patients with normal serum troponin T.[74]

Thus preliminary data suggest a possible novel role of PAPP-A in identifying vulnerable plaques, however, additional studies are needed. Moreover, standardized assays for PAPP-A are not available.[5]

Cystatin C

Cystatin C is a low molecular weight basic protein that is freely filtered and metabolized after tubular reabsorption. There is a U.S. Food and Drug

Administration-(FDA) cleared assay that is analytically robust. Some studies have revealed the usefulness of the cystatin C as a prognostic marker in heart failure and acute coronary syndrome. This protein is less influenced by age, gender, and muscle mass than serum creatinine and thus may be better indicator of cardiovascular risk than serum creatinine especially in elderly.[5]

Fatty acid binding protein

It is one of the proteins which is rapidly released after myocardial infarction and is considered as alternative to myoglobin. It is an extremely valuable marker of myocardial necrosis in the early hours of ACS and more sensitive than CK-MB, CK-MB mass and cTn.[75]

Placental growth factor (PlGF)

It is one of the families of platelet-derived proteins that function as potent chemoattractants for monocytes and are involved in the regulation of vascular endothelial growth. It has a high homology with vascular endothelial growth factor. Plasma PlGF measurements have been shown to be an independent biomarker of adverse outcome in patients with suspected ACS. Plasma PlGF appears to extend the predictive and prognostic information gained from traditional biomarkers of necrosis, platelet activation, and systemic inflammation, and has great potential as an independent biomarker for plaque disruption, ischaemia, and thrombosis.[5]

Multiple biomarker testing

The emergence of different biomarkers in ACS provides insight into the varied pathophysiology of this disease. The future of ACS management would

probably shift from single to multimarker testing leading to better characterization of each individual case and thus aid to singularize the stratagem of management of each case in the short- and long-term.[5]

In a study to assess the role of multi-marker testing cTnI, CRP and BNP were measured in 450 patients of ACS.[58] It was seen that the mortality was independently related to each biomarker tested and there was a near doubling of mortality rate for each additional biomarker that was positive. Similarly the short term and intermediate cardiac event rates were also strongly related to the number of biomarker positive at admission.

The role of the multiple testing of emerging biomarkers over and above that of the currently established ones needs to be tested in a study and more importantly the impact of a biomarker highlighting a specific pathophysiologic mechanism of ACS in tailoring therapy for an individual patient needs to be established. Although there is still a long way till we reach this destination, it is a noble goal, and the desired direction for the future of cardiac medicine.[5]

Importance of biomarkers, both in diagnosis and prognosis, of ACS is now well established. Biomarkers like troponin, BNP and CRP are in wide clinical use and substantial evidence of their utility in ACS is present. In addition, several newer biomarkers have recently emerged and may soon be in clinical use as these exemplify different facets of the pathophysiology of ACS and thus may have important therapeutic and prognostic implication over and above that of the established biomarkers.

The early detection and diagnosis of fatal diseases has been a highly controversial subject in the Emergency Department (ED). Investigations on more sensitive and specific markers still continue. One of the promising plasma markers for the detection of tissue injury is a low molecular weight cytoplasmic protein, the heart-type fatty acid binding protein (H-FABP).[76]

The FABP Family

The FABP family is a superfamily of intracellular lipid-binding proteins that have roles in the transport and storage of lipids. Its functions are facilitation of intracellular long-chain fatty acid transport, regulation of gene transport and protection of cardiac myocytes against detergent-like effects of long-chain fatty acids, especially during ischaemia. As a member of this family, H-FABP is a low molecular weight protein (15-20 kDa) that is abundant in the cytoplasm of myocardial cells with its special tissue distribution. H-FABP is known to be released from injured myocardium. It is abundantly expressed in cardiomyocytes, but also in skeletal muscle, distal tubular cells of the kidney, specific parts of the brain, lactating mammary gland, and placenta. Liver-type fatty acid binding protein (L-FABP) is mainly present in hepatocytes, but can also be found in ileal and jejunal enterocytes, colonocytes and proximal tubular cells of the kidney. In the brain and intestine, brain-type fatty acid protein (B-FABP) and intestine-type fatty acid protein (I-FABP) are tissue-specific, but H-FABP and L-FABP are co-expressed.[76,77]

H-FABP

Like other members of the FABP family, H-FABP is a protein with low molecular weight. It is found at high concentrations in the cytoplasm of cardiac

myocytes (4-8%). It is rapidly released in to the circulation following myocardial damage. It can be detected within 20 minutes (min) of cardiac damage. It reaches peak levels at 3-4 hours and returns to normal range in 24 h.[76]

H-FABP can be detected by enzyme linked immunosorbent assay (ELISA), enzyme immunoassay (EIA), microparticle enhanced immunoassay, fully automated latex-agglutination assay, and qualitative lateral-flow assay.[77]

There are authors that independently propose an upper reference limit of 6µg/L for H-FABP. Its early elevation and rapid clearance by the kidneys make it a candidate for becoming a useful tool in the early detection of cardiac damage.[76]

H-FABP and Cardiovascular Diseases

With a wide variation from acute myocardial ischaemia to peripheral venous occlusion, cardiovascular diseases represent a large group of diseases with high mortality and morbidity. In the literature, there are many studies that have investigated possible biochemical markers for earlier detection of heart tissue damage.

Unstable Angina Pectoris (UAP) and H-FABP

The phrase "unstable angina pectoris" (UAP) refers to chest pain with no ST elevation on electrocardiogram (ECG) and negative serum biomarkers after the onset of chest pain (cardiac troponin T (cTnT) level <0.03 µg/L 12h after admission). According to the characteristics of the pain, angina is divided into three groups: Rest, new-onset and increasing. In patients with UAP, elevated plasma levels of cTnT and

cardiac Troponin I (cTnI) are the indicators of minor myocardial injury due to ischaemia.[76,77]

Kathrukha et al.[78] proved in their study that H-FABP levels elevate earlier than cTnI levels in patients with UAP.

Another study, reported that H-FABP levels elevate in the pericardial fluid in UAP patients.[79]

Nagahara et al.[80] revealed that, among the biomarkers (creatine kinase MB isoenzyme (CK-MB), myoglobin (Mb), cTnT, and H-FABP), H-FABP had better overall diagnostic value for the detection of myocardial injury in patients who presented with chest pain. They also found that H-FABP had high positive predictive values (PPVs) (84-91%), high sensitivities (75-77%) and better negative predictive values (NPVs) (nearly 40%).

A prospective study, reported that H-FABP assessed within 4h of symptoms was superior to cTnT for the detection of acute myocardial infarction (MI). It was, thus, concluded that measuring H-FABP in addition to cTnT at the time of admission with chest pain would assist in the early diagnosis of acute MI.[81]

Current data suggest that H-FABP may be an early biochemical marker to indicate minor myocardial damage in patients with UAP.

Acute Myocardial Infarction and H-FABP

Early diagnosis of acute MI is crucial, as this allows earlier initiation of appropriate treatment and improves patient outcome. Although ECG remains the best test to detect acute MI in the ED, it has relatively low sensitivity. Generally, ST

segment elevations in a standard 12-lead ECG suggest transmural injury, while ST segment depressions suggest subendocardial ischaemia. However, in the initial ECG, 50% of patients will not have diagnostic ST segment elevations.[82]

Cardiac markers are also useful tools in the diagnosis of acute MI. Cardiac troponins are the preferred markers. However, their delayed appearance in serum (rise to a peak level in 12h following an acute MI with a prolonged elevation for 7-10 days before returning to baseline), gives rise to the need for an earlier biochemical marker.[76]

Nakata et al.[83] reported that, among the other biochemical markers, H-FABP had the highest sensitivity in the evaluation of hospitalisation, angiography and interventional therapy requirement.

In 2004, Chan et al.[84] claimed that two samples of H-FABP (one at admission, the other 1h after admission) could reliably diagnose acute MI, and 100% of non-acute MI patients could be excluded with no false negative results.

O'Donoghue et al.[85] reported that among 2287 patients with acute coronary syndromes (ACS), those who had high levels of H-FABP had increased risk of recurrent MI, heart failure (HF), death or the composite of these endpoints. They demonstrated that H-FABP is an independent and strong predictor of adverse cardiac events in ACS.

Ishii et al.[86] reported that H-FABP is an independent predictor of cardiac events within six months of patient admission (with a median value of 9.8µg/L as the cut-off for predicting cardiac events). It was also reported that H-FABP might provide prognostic information superior to cTnI in the early hours of ACS.

Liyan et al.[87] reported that in patients presenting to the ED with chest pain without elevation in cTnT levels and ST segment elevation on ECG, the combination of ischaemia-modified albumin and H-FABP levels is an independent sensitive method for the identification of ACS.

In another study, H-FABP was found to be inadequate to diagnose acute MI by itself (the sensitivity and specificity at presentation were 83.3% and 30.0%, respectively). It was also found that when positive, it was faster than cTnI. It was suggested to evaluate H-FABP in combination with other markers.[88]

H-FABP is a promising biomarker for the early exclusion of acute MI in the ED, but cannot be used alone to rule out the diagnosis.[76]

In a review and meta-analysis,[89] it was concluded that H-FABP did not fulfil the diagnostic requirements needed for a safe and early diagnosis of MI when applied as a stand-alone diagnostic test. It was also concluded that sound diagnostic studies examining the additional role of H-FABP combined with clinical findings and other diagnostic tests are needed to further clarify a potential future role for this cardiac biomarker.[76]

Heart Failure and H-FABP

Sugiura et al.[90] investigated the utility of myosin light chain-I, cTnT, H-FABP, and CK-MB in the prediction of prognosis of patients with congestive heart failure (CHF). They demonstrated that these proteins are related to increased risk of future acute deterioration of CHF.

Ishino et al.[91] reported that when combined measurement of B-type natriuretic peptide (BNP), H-FABP, and pentraxin 3 (PTX3) is elevated in CHF, patients are at greater risk of adverse cardiac events than patients with a lower number of elevated biomarkers.

In a study by Niizeki et al,[92] it was reported that combined measurement of BNP and H-FABP at admission might be useful in risk stratification for future cardiac events in patients with CHF. Their results suggested that the H-FABP and BNP concentrations at admission are associated with both cardiac death and nonfatal cardiac events in patients hospitalised for CHF.

Niizeki et al.[93] reported in another study that serial measurement of H-FABP levels (at both admission and discharge) provides additional prognostic information in CHF. They found that the group with high levels of H-FABP both at admission and discharge had the highest risk of cardiac events (death from worsening CHF, sudden cardiac death and worsening CHF requiring re-admission).

These data suggests that H-FABP may be a useful tool for detection of myocardial injury and risk assessment of patients with CHF.

Cardiomyopathies, Myocarditis and Pericardial Diseases and H-FABP

In a study, Komamura et al.[94] showed that a serum concentration of H-FABP before discharge independently predicted the long-term risk of critical cardiac events with a power comparable to that of BNP in non-cardiac cardiomyopathy.

Likewise, it was shown that increased serum H-FABP levels indicate ongoing myocardial damage in patients with HCM. When the extent of thallium 201

perfusion defects and serum H-FABP levels were compared in patients with HCM and HF, a relationship was demonstrated.[95]

Tambara et al.[79] reported that pericardial fluid level of H-FABP is an indicator of myocardial ischaemia occurring within 24h of their measurement. H-FABP may be secreted into the interstitial space by increased permeability of the myocardial cell membrane associated with severe myocardial ischaemia. The authors concluded that pericardial fluid reflects pathophysiological conditions of cardiomyocytes more sensitively than circulating blood. Further investigations are needed to demonstrate the utility of H-FABP in cardiomyopathies, myocarditis and pericardial diseases.

Pulmonary Embolism (PE) and H-FABP

Kaczynska et al.[96] determined the serum concentrations of Mb, cTnT and N-terminal fragment of proBNP (NT-proBNP) as well as H-FABP in 77 patients with acute PE. They reported that measured H-FABP level on admission is a useful tool for short-term risk stratification. Increased level of H-FABP was found to be superior to Mb, cTnT and proBNP.

Boscheri et al.[97] reported that H-FABP significantly predicted mortality in patients with pulmonary embolism at intermediate risk. They also reported that it was significantly associated with impaired right ventricular function and showed better correlation with mortality than troponin I. They concluded that it might be a novel prognostic parameter enabling the optimization of management strategy in the very difficult population of pulmonary embolism at intermediate risk.

Lankeit et al.[98] also reported that in the population with chronic thromboembolic pulmonary hypertension (CTEPH), baseline H-FABP levels were significantly higher in patients with an adverse outcome during the follow-up period compared with those with a favourable course. The results of their study indicated that H-FABP could be a reliable novel predictor of outcome in patients with CTEPH.

H-FABP is a valuable early marker of cardiac injury in acute coronary syndromes and minor myocardial injury in heart failure. Its utility increases when evaluated in combination with other biochemical markers. Nevertheless, investigations to expose an excellent marker that has cardiospecificity and a prolonged detectability in plasma are required. Recent researches seem to suggest a role of H-FABP in the management of other diseases seen frequently in the ED.

Overall, advances in methodologies for protein identification and a greater understanding of the inflammatory pathophysiology of atherothrombosis have contributed to a proliferation of candidate biomarkers in ACS over the past several years. Many of these novel markers reflect pathways that are distinct from myocardial necrosis, because it is largely believed that high-quality troponin assays allow little room for other markers of necrosis. Recent guidelines, in fact, recommend that troponins are the only necrosis markers that should be measured routinely for diagnosis and risk stratification in ACS.[50]

However, despite a robust evidence base supporting their routine measurement in ACS, troponins have several important limitations. In particular, because of troponins' relative large size and location bound within the contractile apparatus of the cardiomyocyte, troponin release is typically delayed for several

hours after the onset of ischemic injury. Thus, blood must be sampled at least 6 h after the onset of ischemic discomfort in order to achieve adequate sensitivity. As such, for a large number of patients without classic symptomatology or electrocardiographic changes, significant irreversible myocardial injury might occur before a definitive therapeutic plan is implemented. In addition, troponin levels might remain elevated for 7 to 14 days after the initial ischemic insult, thereby limiting sensitivity for detecting recurrent myocardial injury. Importantly, because current troponin assays are unable to detect ischemia in the absence of necrosis, troponins are unable to identify patients with unstable angina who are at increased risk of adverse outcomes and who might benefit from specific treatment strategies. Finally, it is increasingly recognized that, among hospitalized patients, a substantial proportion of elevated troponin levels are caused by conditions other than ACS.[99]

Troponins, although specific for myocardial necrosis, are by no means specific for acute plaque rupture leading to ischemic injury. Kilcullen et al.[100] reported on the prognostic utility of heart-type fatty acidbinding protein (H-FABP) in patients with ACS. Heart type fatty acid-binding protein is a biomarker of myocardial necrosis and injury that offers several theoretical advantages over troponin. Heart-type fatty acid-binding protein is smaller in size (14 to 15 kDa) than troponin I or T (21 to 37 kDa) and is concentrated in the cytoplasm of cardiomyocytes. Owing to its small size, H-FABP is released quickly into the circulation when membrane integrity is compromised in response to myocardial injury. Levels of H-FABP are detectable as early as 2 to 3 h and typically return to baseline levels within 12 to 24 h of the initial insult. Consistent with these findings, a growing number of studies have shown that H-FABP is a sensitive marker for the

diagnosis of myocardial infarction (MI) (and might be more sensitive than older-generation troponin assays when measured in the early hours after symptom onset. Moreover, because of its rapid release kinetics, H-FABP might be useful for the detection of reperfusion after ST-segment elevation MI.[101] These properties theoretically make H-FABP an attractive marker both for the detection of myocardial ischemia in the absence of necrosis and possibly for the early detection of recurrent myocardial injury. To date, however, there is no definitive evidence to show that ischemic injury below the threshold for necrosis can lead to H-FABP release.

It is reported that elevated levels of H-FABP measured in the first few days after an ACS event were associated with an increased risk of death, heart failure, and early recurrent ischemic events. Moreover, H-FABP seemed to provide incremental information for risk stratification that was independent of established risk factors and biomarkers, including troponin I, B-type natriuretic peptide, and myoglobin. Because H-FABP is released and cleared rapidly from the circulation, we hypothesized that elevation in serum H-FABP at this later time point (41-20 h) might help to identify patients with either ongoing or recurrent myocardial injury who are at particular risk of adverse outcomes.[85] However an important limitation to this report was the use of an older generation troponin assay, which precluded definitive evaluation of the incremental utility of H-FABP beyond that which is provided by newer high-sensitivity troponin assays.[102]

Kilcullen et al.[100] evaluated the prognostic utility of H-FABP in a registry of 1,448 patients with ACS from West Yorkshire, United Kingdom. Hearttype fatty acid-binding protein was powerfully and independently associated with the risk of

death when measured within 12 to 24 h of symptom onset after ACS. Moreover, H-FABP identified subjects at increased risk of death even when troponin levels were normal. This study provides important confirmatory information to substantiate the prognostic utility of this emerging marker and addresses the most important limitations of prior study.[85] In particular, the current analysis employed the use of higher-sensitivity assays for the assessment of both troponin and H-FABP. In the presence of a negative troponin I, an elevation in H-FABP was associated with a significant increase in the risk of death after adjusting for variables in the GRACE (Global Registry of Acute Coronary Events) prediction model and for levels of C-reactive protein.

Perhaps the most intriguing question that remains is why H-FABP might provide prognostic information for death and heart failure that is independent of and superior to troponin. The answer to this question may reveal more about troponin as it does about H-FABP. It is of interest that the association of H-FABP (as well as myoglobin and creatine kinase-myocardial band) with infarct size seems to follow a straightforward single compartmental model, whereas the association between troponin and infarct size is considerably more complex.[102]

Although it is tempting to speculate that H-FABP elevation might identify ischemic injury below the threshold of detection with troponin, mortality was considerably higher among patients in this subgroup in the present study than one would expect for patients with ACS who have normal troponin levels. Future studies correlating H-FABP levels with necropsy findings among patients with normal troponin levels would be particularly helpful for characterizing the mechanistic links between H-FABP elevation and mortality. Alternatively, delayed-enhancement

magnetic resonance imaging studies might allow delineation of differences in the relationships between various biomarkers of necrosis and myocardial injury. At present, it seems the most plausible hypothesis is that elevated levels of H-FABP at later time points might identify patients with either ongoing or recurrent myocardial injury who are at increased risk of death.[102]

Although much further investigation will be required before the clinical use of H-FABP can be considered, literature provides early confirmatory evidence to suggest that this biomarker might help to identify high-risk patients who are troponin negative. Even though troponins remain the benchmark for ACS biomarkers, they have important limitations, and investigators should continue to evaluate other biomarkers in the necrosis class, provided their incremental utility relative to state-of-the-art troponin assays can be definitively established.

METHODOLOGY

This one year cross-sectional study was performed at the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013.

Study design and duration

The study design was a one year cross-sectional study.

Study period

This study was carried out from January 2013 to December 2013.

Source of Data

Patients presenting with signs and symptoms of acute coronary syndrome at Emergency out patient and in patient departments of KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum were enrolled.

Sample size

A total of 60 patients presenting with signs and symptoms of acute coronary syndrome were studied.

Sampling method

Due to the scarcity of data in the literature regarding the accuracy of H-FABP a minimum sample of 60 patients fulfilling selection criteria was planned. However 61 patients fulfilled the selection criteria hence were included in the study.

Selection criteria

Inclusion Criteria

- Patients presenting with manifestations suggestive of acute myocardial ischemia such as;
    - Chest pain with or without radiation
    - Palpitations
    - Shortness of breath
    - Lower jaw pain
    - Left arm pain
    - Epigastric pain
    - Hypotension
    - New or increasing lower extremity edema
    - Other symptoms suggestive of ischaemia

Exclusion Criteria

- Chest pain of more than 24 hours duration.
- Patients having liver and kidney disorders.
- Patients with brain ischaemia.
- Patients with tumors.

Ethical clearance

Prior to the commencement, the study was approved by the Ethical and Research Committee of Jawaharlal Nehru Medical College, Belgaum.

Informed consent

The eligible patients were informed about the nature of study and enrolled after obtaining a written informed consent (Annexure–I).

Data collection

Patients were interviewed and demographic data, history of other comorbid conditions and personal history were noted. Further these patients underwent clinical examination followed by systemic examination. These findings were noted on a predesigned and pretested proforma (Annexure-II).

Investigations

The patients underwent following investigations

- Electrocardiography
- CK MB
- Troponin I
- H-FABP
- Chest X-ray
- 2D echocardiography
- Lipid profile
- Renal function tests
- Liver function tests

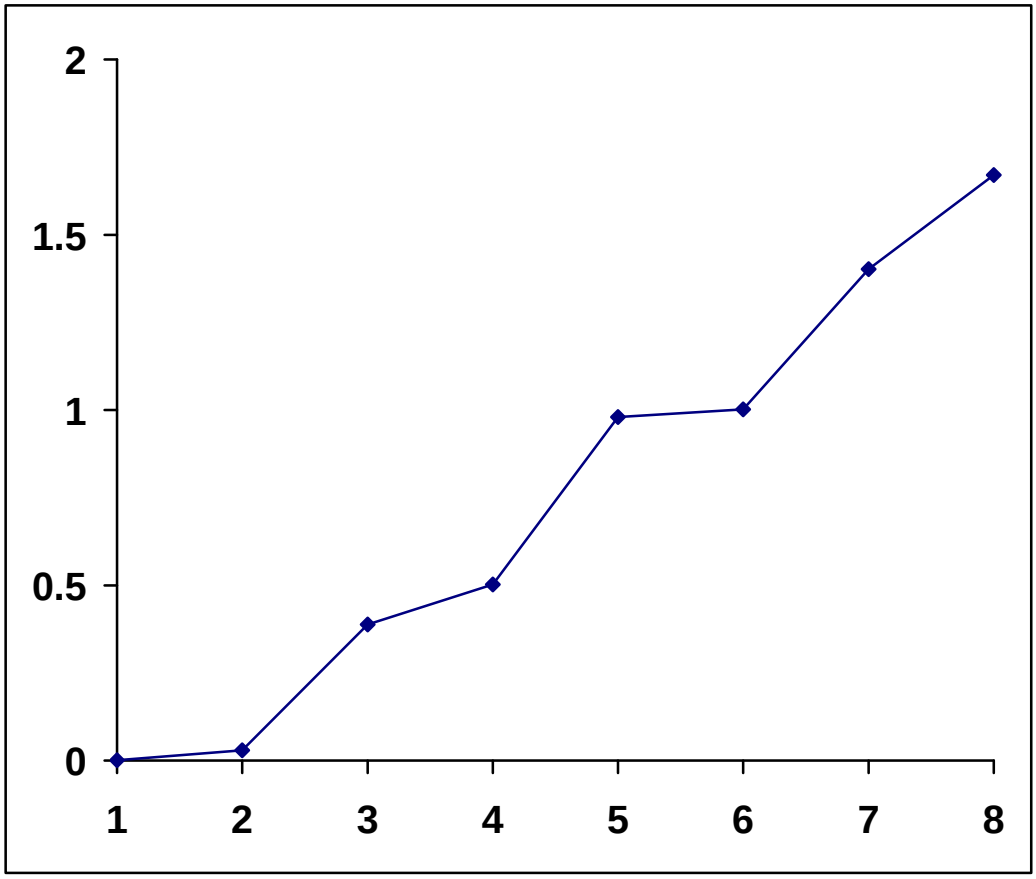
Estimation of H-FABP

Under aseptic precaution, blood sample were collected. The collected samples were centrifuged for the separation of sera for a period of 15 minutes before being tested for H-FABP. Estimation of H-FABP was done using H-FABP, Human, ELISA kit manufactured by Hycult Biotech, Netherlands.

Human, ELISA kit

The human H-FABP ELISA is a ready-to-use solid-phase enzyme-linked immunosorbent assay based on the sandwich principle with a working time of 1½ hours (normal format) or 50 minutes (rapid format). The efficient format of 1 plate with twelve disposable 8-well strips allows free choice of batch size for the assay. Samples and standards are captured by a solid bound specific antibody. Biotinylated tracer antibody will bind to captured human H-FABP. Streptavidin-peroxidase conjugate will bind to the biotinylated tracer antibody. Streptavidin-peroxidase conjugate will react with the substrate, tetramethylbenzidine (TMB). The enzyme reaction is stopped by the addition of citric acid. The absorbance at 450 nm is

measured with a spectrophotometer. A standard curve is obtained by plotting the absorbance (linear) versus the corresponding concentrations of the human H-FABP standards (log). The human H-FABP concentration of samples, which are run concurrently with the standards, can be determined from the standard curve.



Statistical methods

The data obtained was coded and entered into the Microsoft Excel Spreadsheet (Annexure III). The categorical data was expressed in terms of rates, ratios and percentages and continuous data was expressed as mean ± standard deviation. The utility of H-FABP in comparison with troponin I as an early biomarker in patients with acute coronary syndrome was determined by calculating

sensitivity, specificity, positive predictive value and negative predictive value. Kappa statistics was used to determine the strength of agreement.

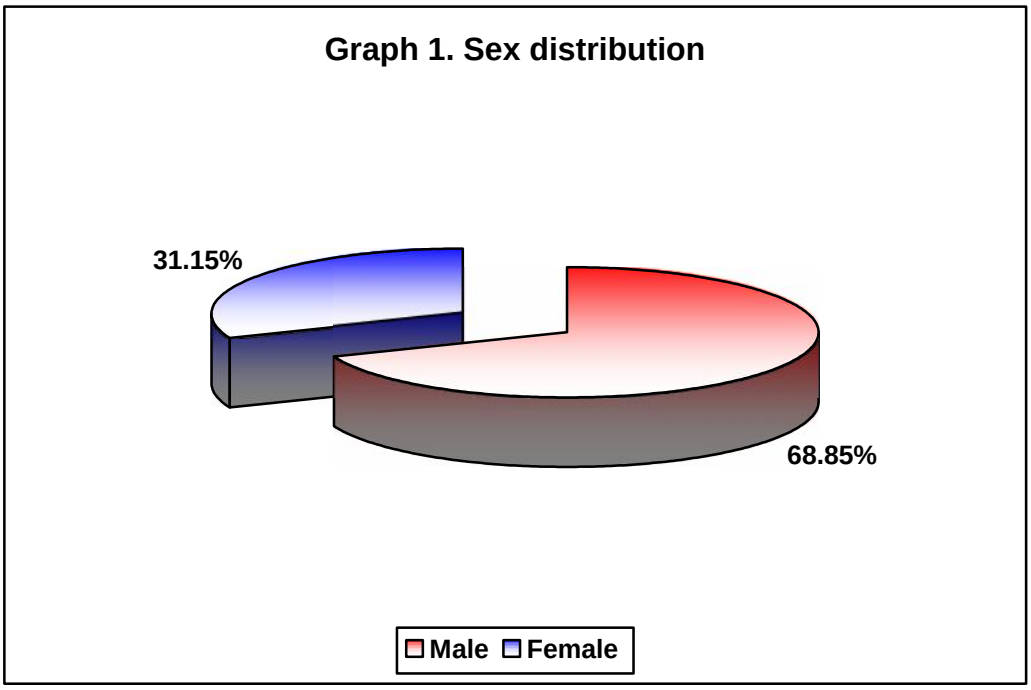
RESULTS

This one year cross-sectional study was carried out in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum. A total of 61 patients who presented with acute coronary syndrome from January 2013 to December 2013 were studied.

The data obtained was analysed and the final results and observations were tabulated as below.

Table 1. Sex distribution

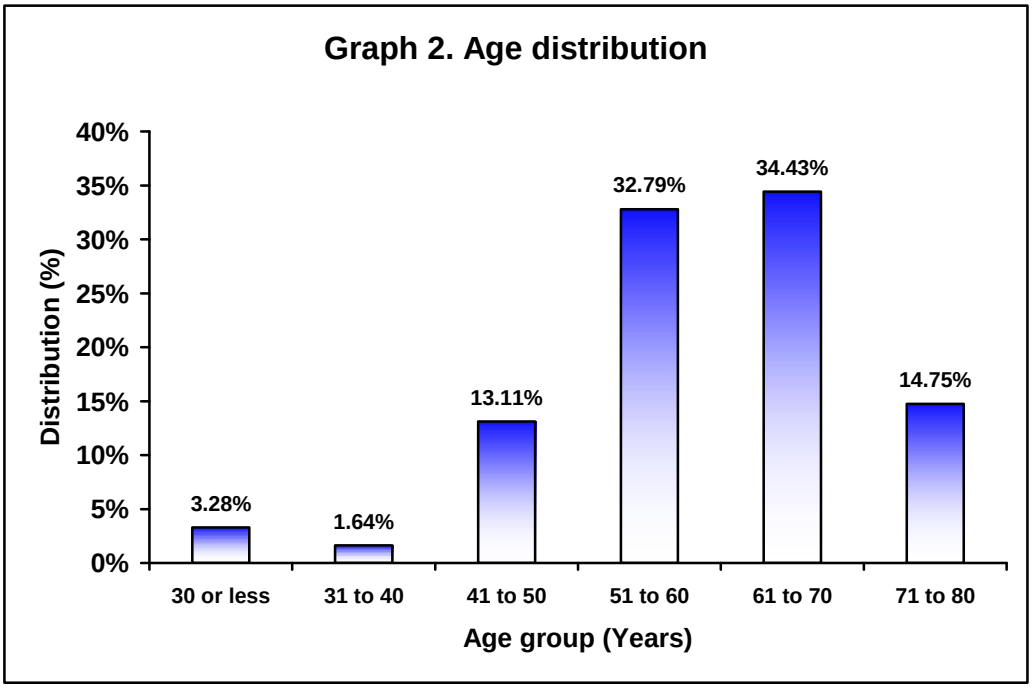
Sex	Distribution (n=61)	
	Number	**Percentage**
Male	42	68.85
Female	19	31.15
Total	**61**	**100.00**



In the present study 68.85% of the patients were males and 31.15% were females. The male to female ratio was found to be 2.21:1.

Table 2. Age distribution

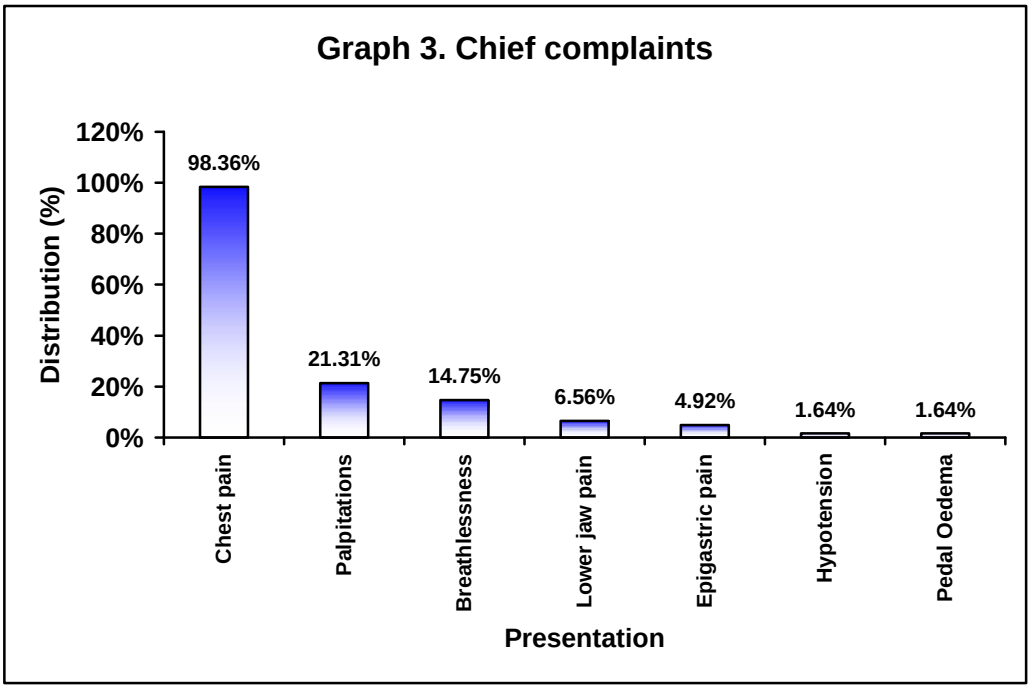
Age group (Years)	Distribution (n=61)	
	Number	**Percentage**
30 or less	2	3.28
31 to 40	1	1.64
41 to 50	8	13.11
51 to 60	20	32.79
61 to 70	21	34.43
71 to 80	9	14.75
Total	**61**	**100.00**



In this study 34.43% of the patients were aged from 61 to 70 years. The mean age was noted as 59.75 ± 11.34 years.

Table 3. Chief complaints

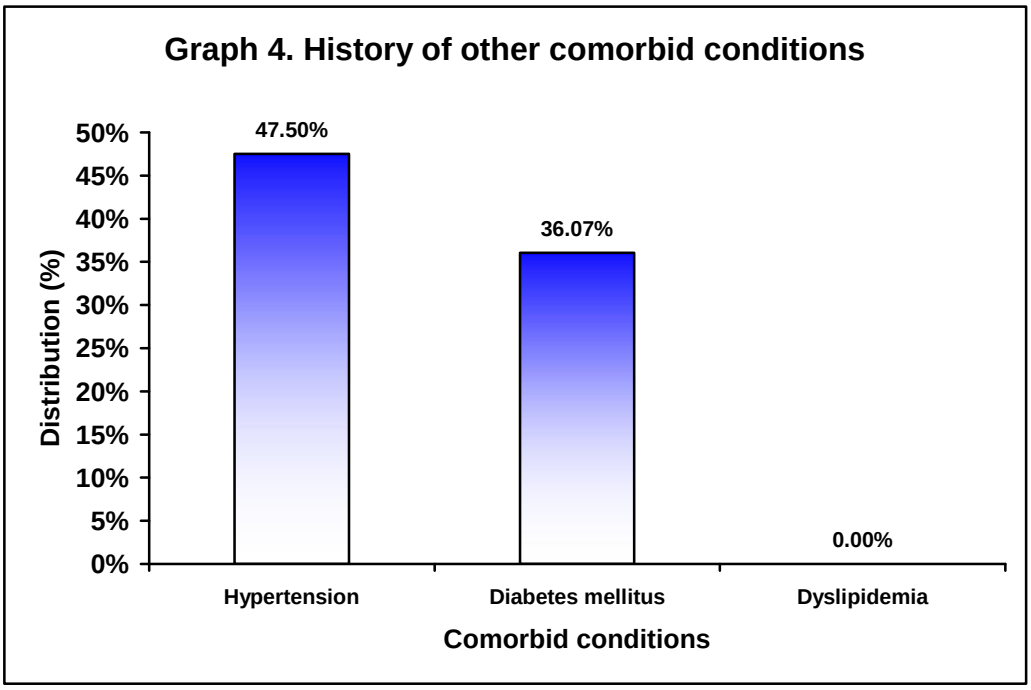
Presentation	Distribution (n=61)	
	Number	Percentage
Chest Pain	60	98.36
Palpitations	13	21.31
Breathlessnes	9	14.75
Lower jaw pain	4	6.56
Epigastric pain	3	4.92
Hypotension	1	1.64
Pedal Oedema	1	1.64



In the present study 98.36% of the patients presented with chest pain. The other complaints were palpitations (21.31%), breathlessness (14.75%), lower jaw pain (6.56%), epigastric pain (4.92%), hypotension (1.64%) and pedal oedema (1.64%).

Table 4. History of other comorbid conditions

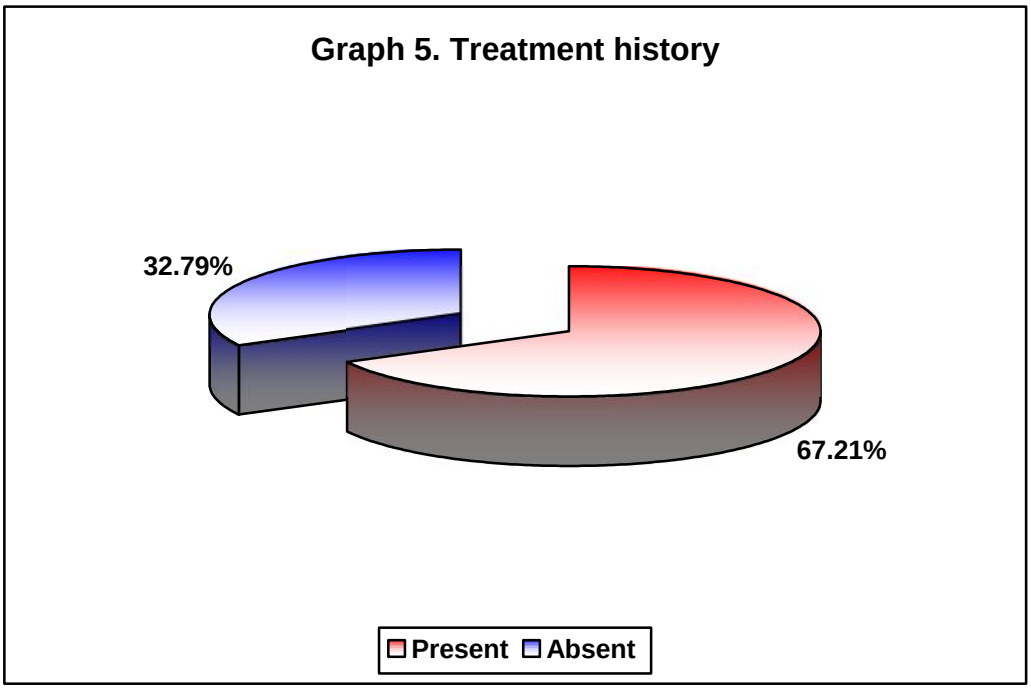
Comorbid conditions	Distribution (n=61)	
	Number	Percentage
Hypertension	29	47.54
Diabetes mellitus	22	36.07
Dyslipidemia	0	0.00



In this study 47.5% of the patients reported history of hypertension while diabetes was noted among 36.07%.

Table 5. Treatment history

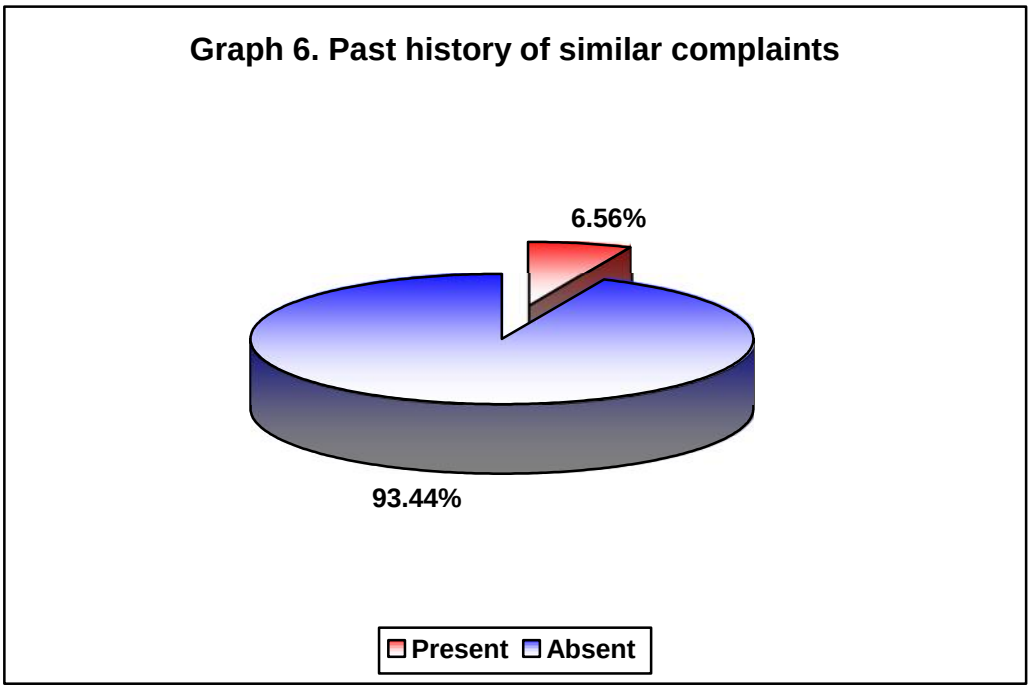
History	Distribution (n=61)	
	Number	**Percentage**
Present	41	67.21
Absent	20	32.79
Total	**61**	**100.00**



In the present study 67.21% of the patients reported treatment history.

Table 6. Past history of similar complaints

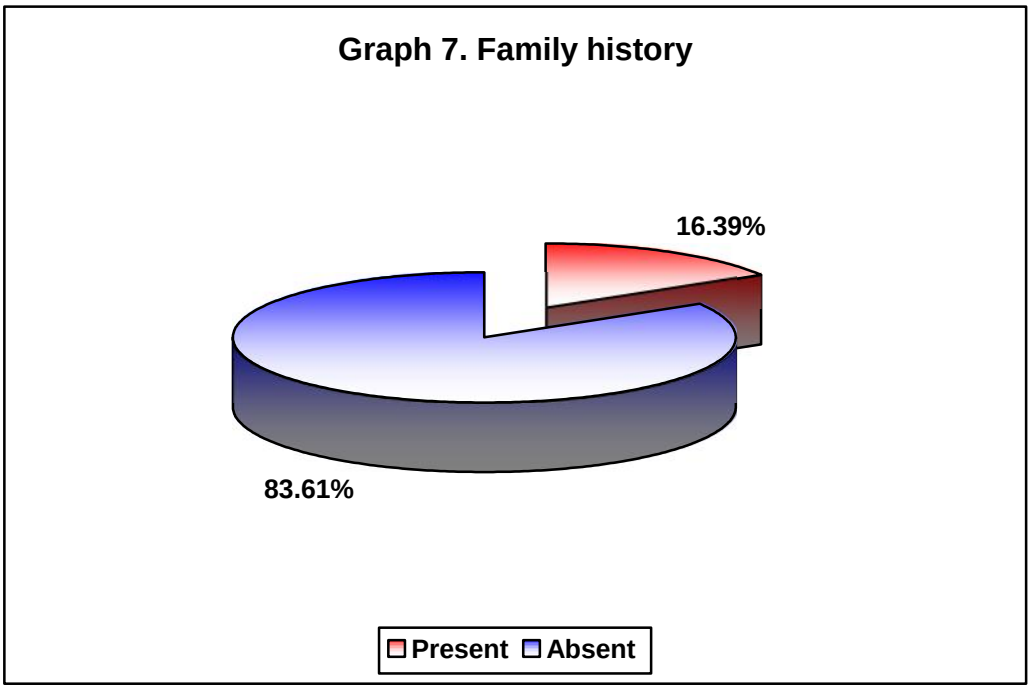
History	Distribution (n=61)	
	Number	**Percentage**
Present	4	6.56
Absent	57	93.44
Total	**61**	**100.00**



In this study 6.56% of the patients reported past history of similar complaints.

Table 7. Family history

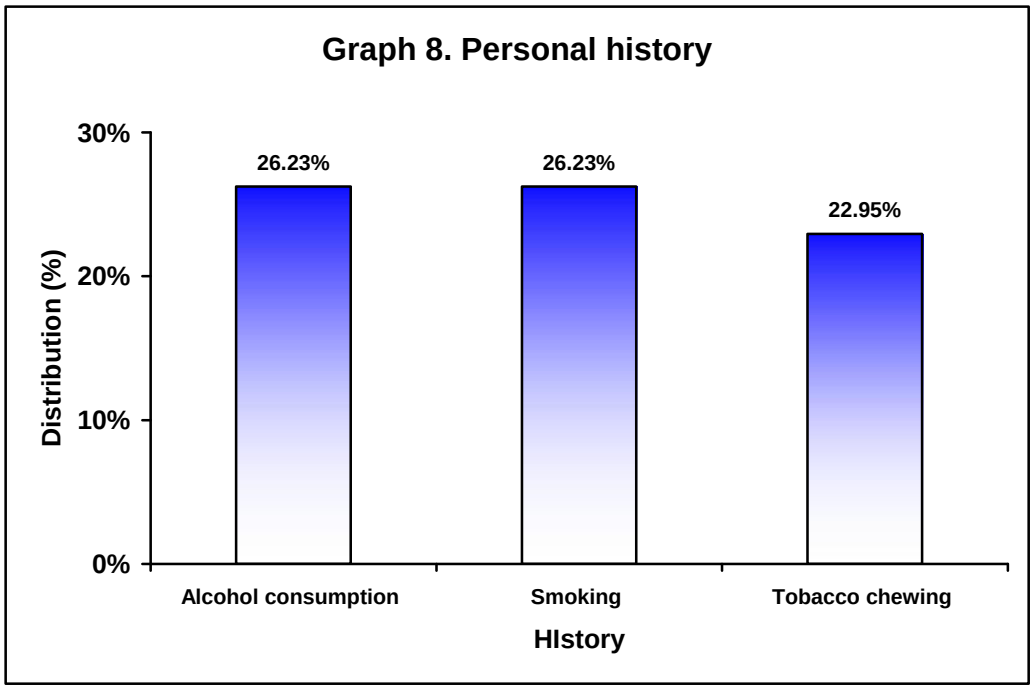
History	Distribution (n=61)	
	Number	**Percentage**
Present	10	16.39
Absent	51	83.61
Total	**61**	**100.00**



In the present study 16.39% of the patients had family history of acute coronary syndrome.

Table 8. Personal history

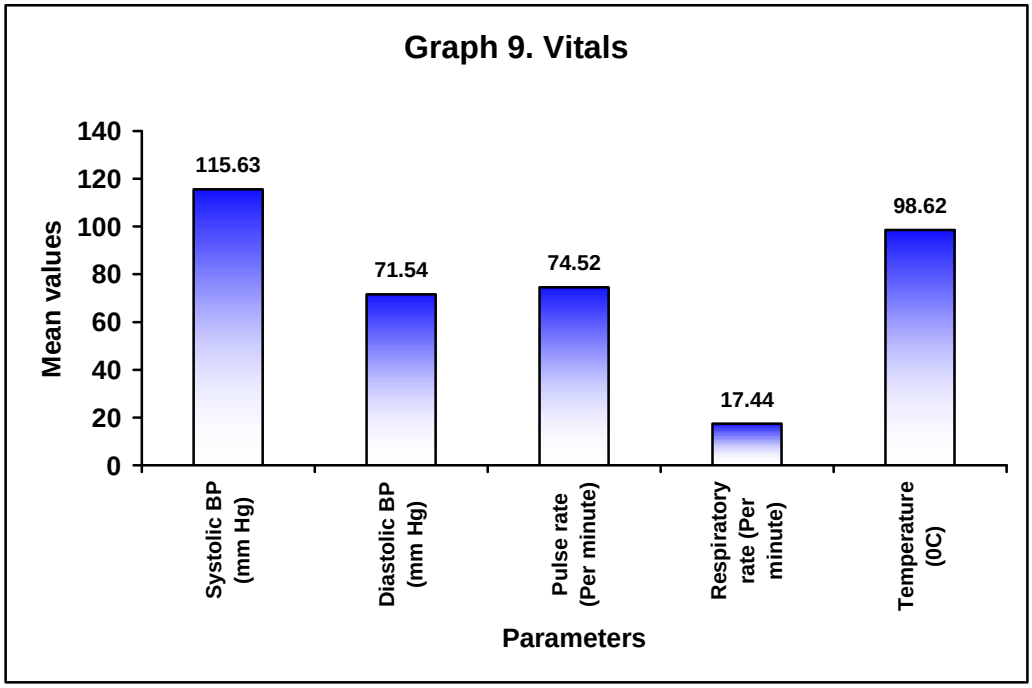
History	Distribution (n=61)	
	Number	Percentage
Alcohol consumption	16	26.23
Smoking	16	26.23
Tobacco chewing	14	22.95



In this study 26.23% of the patients each reported personal history of alcohol consumption and smoking while tobacco chewing was noted in 22.95%.

Table 9. Vitals

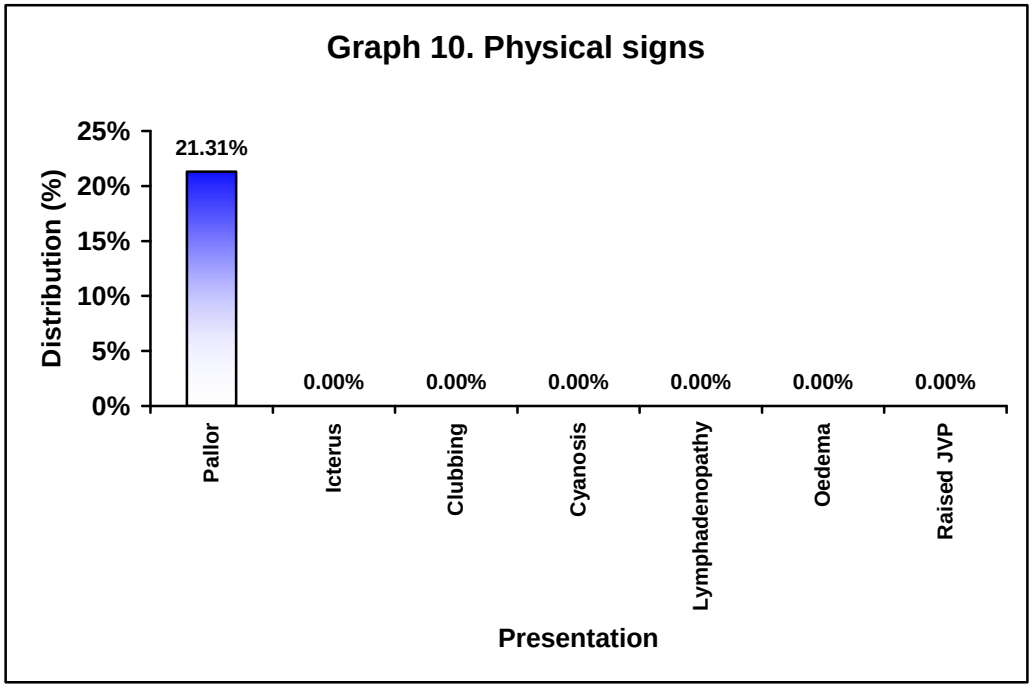
Parameters	Distribution (n=61)	
	Mean	**SD**
Systolic BP (mm Hg)	115.63	23.07
Diastolic BP (mm Hg)	71.54	11.40
Pulse rate (Per minute)	74.52	23.20
Respiratory rate (Per minute)	17.44	3.96
Temperature (^{0}C)	98.62	0.10



The mean systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate and temperature are as shown in table 9.

Table 10. Physical signs

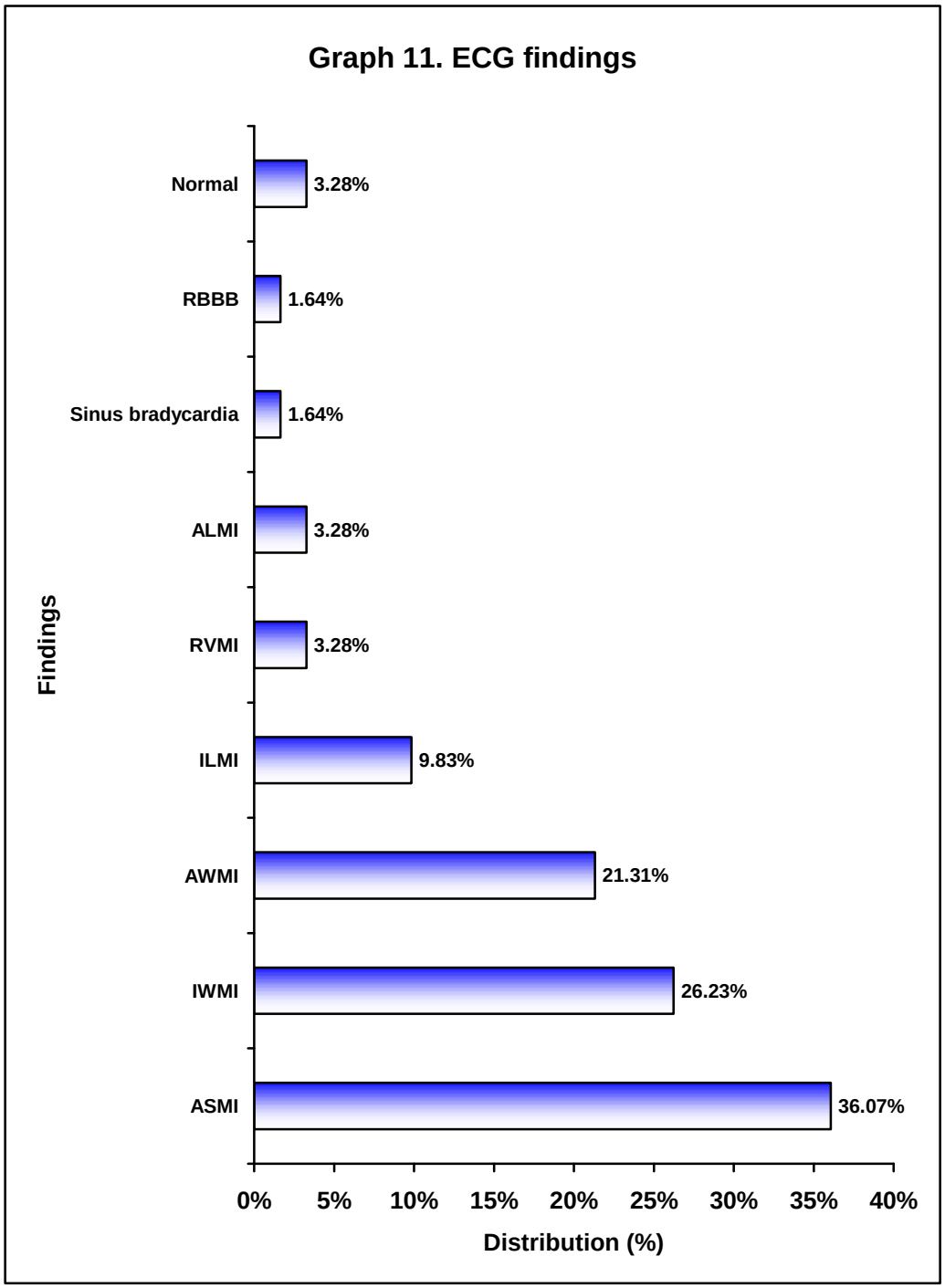
Presentation	Distribution (n=61)	
	Number	Percentage
Pallor	13	21.31
Icterus	0	0.00
Clubbing	0	0.00
Cyanosis	0	0.00
Lymphadenopathy	0	0.00
Oedema	0	0.00
Raised JVP	0	0.00



In this study 21.31% of the patients presented with pallor.

Table 11. ECG findings

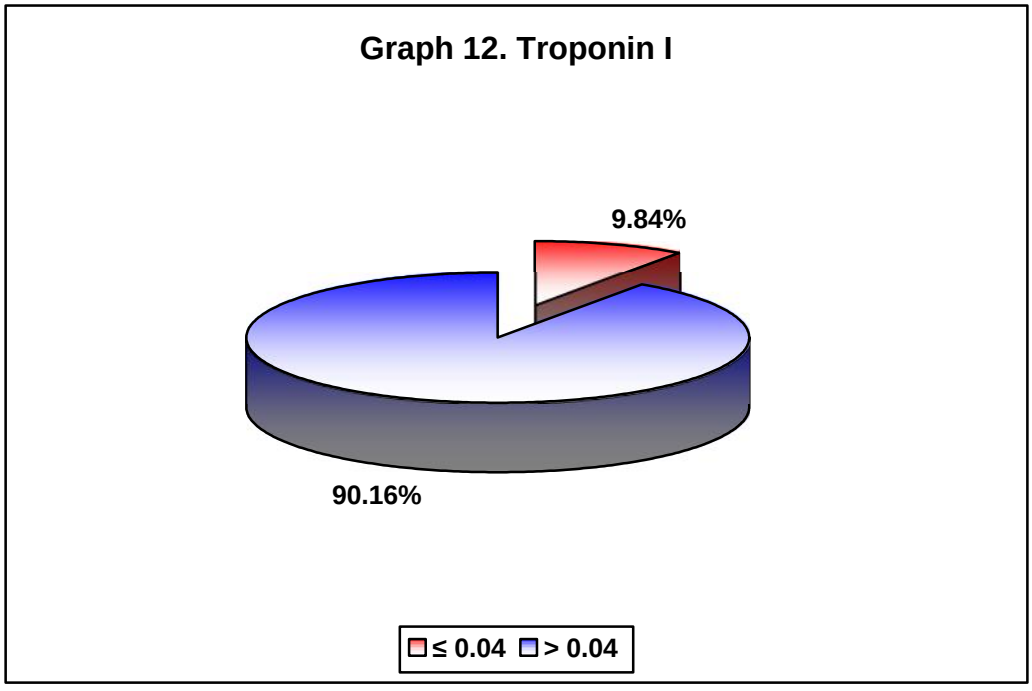
Findings	Distribution (n=61)	
	Number	**Percentage**
ASMI	22	36.07
IWMI	16	26.23
AWMI	13	21.31
ILMI	6	9.83
RVMI	2	3.28
ALMI	2	3.28
Sinus bradycardia	1	1.64
RBBB	1	1.64
Normal	2	3.28



In this study on ECG, most of the patients had ASMI (36.07%) followed by IWMI (26.23%), AWMI (21.31%) and ILMI (9.83%).

Table 12. Troponin I

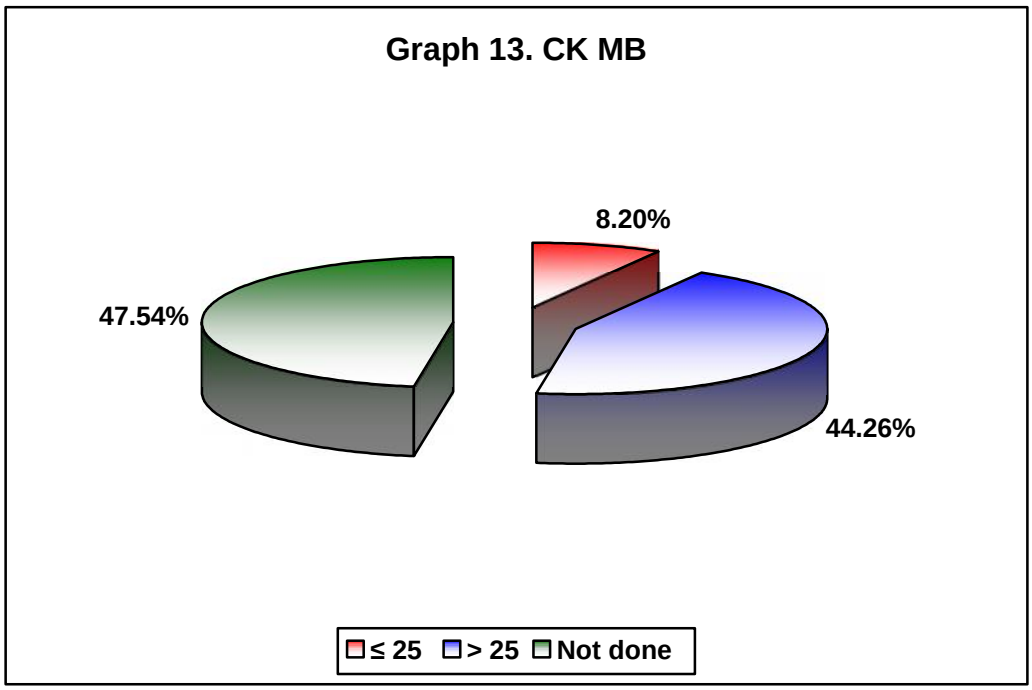
Troponin I	Distribution (n=61)	
	Number	**Percentage**
≤ 0.04	6	9.84
> 0.04	55	90.16
Total	**61**	**100.00**
Mean ± SD	**11.52 ± 17.18**	



In the present study majority (90.16%) of the patients had raised troponin I (>0.04) levels.

Table 13. CK MB

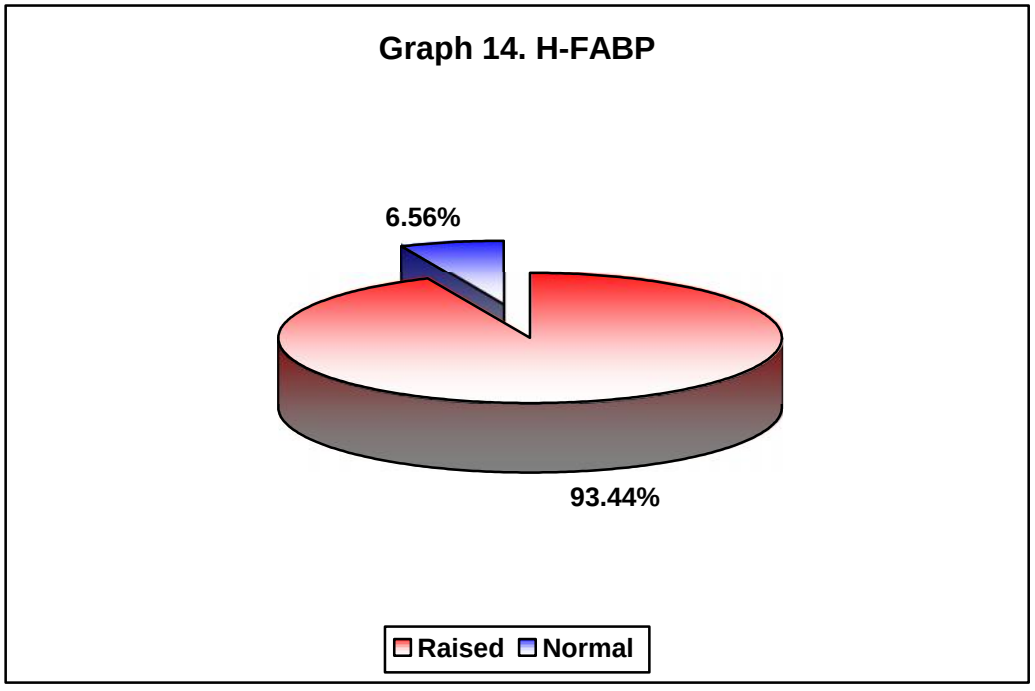
CK MB	Distribution (n=61)	
	Number	**Percentage**
≤ 25	5	8.20
> 25	27	44.26
Not done	29	47.54
Total	**61**	**100.00**
Mean ± SD	**107.32 ± 93.09**	



In the present study CK MB was done in 32 patients and of these 27 (44.26%) had raised CK MB levels.

Table 14. H-FABP

H-FABP	Distribution (n=61)	
	Number	**Percentage**
Raised	57	93.44
Normal	4	6.56
Total	**61**	**100.00**
Mean ± SD	**0.40 ± 0.78**	



In this study H-FABP was raised in 93.44% of the patients.

Table 15. Accuracy of H-FABP in predicting acute coronary syndrome considering troponin I as reference standard

H-FABP	Troponin I		Total
	Raised	Normal	
Raised	54	3	57
Normal	1	3	4
Total	55	6	61

Sensitivity	Specificity	PPV	NPV
98.18	**50.00**	**94.74**	**75.00**

p < 0.001

Kappa= 0.566; SE of kappa = 0.193; 95% CI: From 0.187 to 0.944

In this study 57 patients had raised H-FABP levels. Among them, 54 had raised troponin I levels and 3 had normal troponin I yielding to a sensitivity of 98.18% and specificity of 50%. The strength of agreement in predicting the diagnosis of acute coronary syndrome was 'moderate (Kappa=0.566; SE of kappa = 0.193; 95% CI: From 0.187 to 0.944).

Table 16. Accuracy of H-FABP in predicting acute coronary syndrome considering CK-MB as reference standard

H-FABP	CK-MB		Total
	Raised	Normal	
Raised	25	3	28
Normal	2	1	3
Total	27	4	31

Sensitivity	Specificity	PPV	NPV
92.59	**25.00**	**89.29**	**33.33**

p < 0.001

Kappa= 0.197; SE of kappa = 0.240; 95% CI: From -0.274 to 0.667

In this study CK-MB was done in 31 patients and 27 patients had raised CK-MB levels. Among them, 25 had raised H-FABP levels and 2 had normal H-FABP levels. The sensitivity of H-FABP considering CK-MB as reference standard was 92.59% and specificity was 25%. The strength of agreement in predicting the diagnosis of acute coronary syndrome was poor (Kappa=0.197; SE of kappa = 0.240; 95% CI: From -0.274 to 0.667).

DISCUSSION

Diagnosing and excluding ACS (which includes myocardial infarction (MI) and unstable angina (UA)) often pose a diagnostic challenge to the clinicians. Missing an ACS may lead to excess morbidity and mortality which could have been prevented with optimal treatment. Cardiac biomarkers play an important role in the diagnosis of acute coronary syndrome. An ideal marker which can predict the onset of the disease, could aid in reducing the deaths due to ACS. Cardiac troponins have been the preferred biomarker but due to its delayed appearance in the serum, there is a still a need for reliable biomarker.[104]

Recent studies suggest that human heart type fatty acid binding protein (H-FABP) may be a potential marker for early diagnosis of ACS. Fatty acid-binding proteins (FABPs) are relatively small cytoplasmic proteins (12–15 KDa) that are abundant in tissues with active fatty acid metabolism, including the heart. In fact, heart-type FABP (H-FABP) is particularly important for myocardial homoeostasis, since 50–80% of the heart's energy is provided by lipid oxidation and H-FABP ensures intracellular transport of insoluble fatty acids. Following myocardial cell damage, this small protein diffuses much more rapidly than troponins through the interstitial space and appears in the circulation as early as 90 min after the onset of the symptoms, reaching its peak within six hours. These features make H-FABP an excellent candidate marker of myocardial injury and very recent data suggest that it may indeed provide prognostic information superior to that of cardiac troponins in the early hours of acute coronary syndrome.[104] The present study was an attempt to

assess and compare the utility of H-FABP in comparison with troponin I and CK-MB as an early biomarker in patients with acute coronary syndrome.

Nonmodifiable factors that influence risk for coronary artery disease include age and sex. Men have a higher risk than women.[21] The same was true in the present study. In this study male preponderance was noted with males forming 68.85% of the study population and the male to female ratio was found to be 2.21:1. The commonest age group was between 61 to 70 years comprised of 34.43% of the patients whereas 14.75% of the patients were aged between 71 to 80 years. The mean age was found to 59.75±11.34 years suggesting higher incidence of ACS among elderly population. These findings were consistent with a reported by Mansoor AH, et al[15] who reported higher risk of acute coronary syndrome in average age group of 57.5 years among Indians.

Nearly all the patients (98.36%) presented with complaints of chest pain and next common complaint was palpitations (21.31%) followed by breathlessness (14.75%), lower jaw pain (6.56%), epigastric pain (4.92%), hypotension (1.64%) and pedal oedema (1.64%).

Hypertension was present in nearly half of the study population (47.5%) and 36.07% of the patients gave history of diabetes mellitus. Further personal history of alcohol consumption and smoking was present in 26.23%, of the patients each and tobacco chewing was present in 22.95%.

Based on ECG findings, 36.07% of the patients had ASMI, 26.23% had IWMI, 21.31% had AWMI and 9.83% had ILMI.

In the present study cardiac enzymes including troponin I were elevated in 90.16% of the patients while CK MB was done in 32 patients of which 27 (44.26%) had raised CK MB levels. Maximum number of patients that is, 98.36% of the patients had raised H-FABP levels. Of the 57 patients with raised H-FABP levels, 54 had raised troponin I levels and 3 had normal troponin I indicating that the overall sensitivity of H-FABP in the diagnosis of ACS was 98.18% while the specificity of 50%. The strength of agreement between F-HABP and troponin I in predicting the diagnosis of acute coronary syndrome was 'moderate (Kappa=0.566; SE of kappa = 0.193; 95% CI: From 0.187 to 0.944). Further CK-MB was done in 31 patients and 27 patients had raised CK-MB levels. Of these, 25 had raised H-FABP levels and 2 had normal H-FABP levels. The sensitivity and specificity of H-FABP considering CK-MB as reference standard was 92.59% and 25% respectively. However, the strength of agreement in predicting the diagnosis of acute coronary syndrome was poor (Kappa=0.197; SE of kappa = 0.240; 95% CI: From -0.274 to 0.667).

Following myocardial injury, H-FABP is released into the blood stream by damaged myocytes and is rapidly cleared from the blood by renal filtration.[105] It is also reported that urinary levels of H-FABP correlate with the severity of the myocardial injury. Hayashida et al.[106] have demonstrated urinary and plasma H-FABP levels may be an early and sensitive biochemical marker for the diagnosis of myocardial injury in patients undergoing cardiac surgery. Prior reports have shown >80% sensitivity of H-FABP within the period of 30–210 min for diagnosis of AMI.[107] Due to the similar release kinetics of H-FABP and myoglobin, several studies have focused on comparison of H-FABP and myoglobin levels at

presentation. All these studies have shown the area under the curve for H-FABP to be significantly higher than myoglobin.[108-111]

One study by Glatz et al.[109] has further demonstrated increased area under the ROC for H-FABP (0.945) than myoglobin (0.892) in patients admitted 3–6 h after symptom onset. A study by Ruzgar et al.[112] showed 38% sensitivity on troponin, 76% sensitivity on CK-MB and 95% sensitivity on H-FABP in patients admitted within six hours of chest pain onset. Within 6–24 hours, sensitivity of troponin and CK-MB increased to 100 and 90% respectively, while that of H-FABP was 91%. After 24 hours, the sensitivity of H-FABP drastically decreased to 27.3% while that of troponin and CK-MB remained the same.

Another study[113] observed 89% sensitivity of H-FABP within two hours of chest pain where troponin had a sensitivity of 22%. Our study focused on H-FABP levels at admission rather than kinetic studies of the marker.

Our results were in complete agreement with the above studies demonstrating 98.18% sensitivity and 50% specificity. These results indicate the fact that H-FABP is well suited for early detection of ACS.

This study mainly deals with elevated H-FABP levels at admission to exclude patients with non-cardiac chest pain. These results show that troponin levels rise more than six hours after symptom onset because of a timelag in its release, whereas H-FABP is usually positive in patients within first four hours of a acute myocardial infarction. Although, a relatively small number of clinical studies have been performed, all of these studies have shown better or similar performance of H-FABP, and its utility to rule out MI in patients with ACS, is promising.

CONCLUSION

Overall, raised serum H-FABP, plays an important role in the early diagnosis of acute coronary syndromes. A single measure of H-FABP was highly sensitive and may enable faster triaging of emergency patients, earlier discharge of patients with non-cardiac chest pain.

SUMMARY

Recent studies suggest that human heart type fatty acid binding protein (H-FABP) may be a potential marker for early diagnosis of ACS. This study was aimed to assess the utility of H-FABP as an early biomarker in patients with acute coronary syndrome in comparison with troponin I and CK-MB.

The present one year cross-sectional study was done in the Department of Medicine, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum from January 2013 to December 2013. A total of 61 patients who presented with acute coronary syndrome were studied. Estimation of H-FABP was done using H-FABP, Human, ELISA kit.

Males constituted 68.85% of the study population and 31.15% were females. The commonest age group was between 61 to 70 year (34.43%) and the mean age was noted as 59.75 ± 11.34 years. Majority of the patients (98.36%) presented with chest pain. History of hypertension and diabetes was present in 47.5% and 36.07% of the patients respectively. Personal history of alcohol consumption and smoking was noted in 26.23% of the patients each and tobacco chewing was noted in 22.95%. On examination, 21.31% of the patients presented with pallor. On ECG, the commonest diagnosis was ASMI (36.07%) followed by IWMI (26.23%). Majority (90.16%) of the patients had raised troponin I (>0.04) levels and H-FABP was raised in 93.44% of the patients. Of the 57 patients with raised H-FABP levels, 54 had raised troponin I levels and 3 had normal troponin I yielding to a sensitivity of 98.18% and specificity of 50%. The strength of agreement in predicting the diagnosis of ACS was 'moderate (Kappa=0.566; SE of kappa = 0.193; 95% CI:

From 0.187 to 0.944). The sensitivity and specificity of H-FABP considering CK-MB as reference standard was 92.59% and 25% respectively. However, the strength of agreement in predicting the diagnosis of acute coronary syndrome was poor (Kappa=0.197; SE of kappa = 0.240; 95% CI: From -0.274 to 0.667).

Raised serum H-FABP, plays an important role in the early diagnosis of acute coronary syndromes.

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ANNEXURE I – CONSENT FORM

"ROLE OF NOVEL BIOMARKER HEART TYPE FATTY ACID BINDING PROTEIN IN DIAGNOSING ACUTE CORONARY SYNDROME IN COMPARISON WITH TROPONIN I AND CK-MB – A ONE YEAR CROSS SECTIONAL STUDY IN KLES DR PRABHAKAR KORE HOSPITAL AND MRC, BELGAUM"

Objective and purpose of the study:

This research is intended to to assess the utility of H-FABP as an early biomarker in patients with acute coronary syndrome in comparison with troponin I. The Principal investigator of the study is Dr. *** ****** under the guidance of Dr. ***** ******.

Procedure:

If you agree to be part of the research study you will be asked the relevant history and will be subjected to relevant clinical examination and investigations.

Alternatives

Taking part in this study is voluntary. You may choose not to take part in this study, or if you decide to take part now, you can later change your mind and withdraw from the study. Your decision will not change the present or future health care or other services that you receive. The study doctor or sponsor may stop your participation in this study at any time. If you choose not to take part in the study you will receive the standard treatment for patients with your condition.

Voluntary participation / withdrawal

Your participation in this study is entirely voluntary and you may withdraw from the study at any time.

Privacy and Confidentiality

All information collected about you during the course of this study will be kept confidential to the extent permitted by law. The code numbers will identify you in this research record. Information from this study may be published but your identity will be confidential in any publication.

Institution / Sponsor's policy

Does not apply to this research

Financial incentives for participation

You will not be paid / offered any gifts /incentives for participating in the study.

Authorization to publish the results

The results of the study would be forwarded to the KLE University, Belgaum as part of requirement towards the completion of MD degree, review and publishing.

If you have any questions about your right as a participant you may call

Dr. **** *****,
Investigator,
PG in General Medicine,
Jawaharlal Nehru Medical College,
Belgaum
Contact No: **** ******

Dr. ****** ******,
Professor,
Department of Medicine,
Jawaharlal Nehru Medical College,
Belgaum
Contact No: **** ******

Dr. **** ******,
Chairman, Ethical Committee for
Human Research,
Jawaharlal Nehru Medical College,
Belgaum
Contact No: ***** ***** Ext: ****

Consent Statement

I voluntarily agree to take part in this study by signing below. I may withdraw at any time. I am not giving up any of my legal rights by signing this form. My signature below indicates that I have read, or it has been read to me, and has been explained to me in my vernacular language and had had all my questions answered. I will be given a copy of this consent form.

Signature / Left thumb print of the participant or legally authorized representative

Name of the Participant: _____

Signature / Thumb print _____

Impression of the participant

Name of the legally _____

Authorized representative / guardian

Signature / Thumb print _____

Name of the witness _____

Signature / Thumb print _____

Investigators name _____

and signature

Date: Place:

Dr. ***** *****,
Investigator,
PG in General Medicine,
Jawaharlal Nehru Medical College,
Belgaum
Contact No: ***** ******

Dr. ***** ******,
Professor,
Department of Medicine,
Jawaharlal Nehru Medical College,
Belgaum
Contact No: ***** *****

ANNEXURE II – PROFORMA

1. Sl. No. :

2. Name :

3. Age :

4. Sex :

5. Occupation :

6. Religion :

7. Ip No./Op No. :

8. Address :

9a. Date of Admission: 9b. Date of Discharge:

10. Chief complaints:

11. History of present illness:

12 Treatment history

13 Past History

14. Family history

15. Personal history

General physical examination

Blood pressure: Pulse:

Respiratory rate: Temperature:

Pallor:

Icterus:

Clubbing:

Cyanosis:

Lymphadenopathy:

Edema:

JVP:

Systemic examination

Cardiovascular system:

a. Peripheral

b. Central

Respiratory system:

Central nervous system:

Per abdomen:

Investigations

ECG:

TROPONIN I: CK MB:

H-FABP-ELISA KIT:

Serum creatinine:

Lipid profile

2D Echocardiography:

Chest X-ray

ANNEXURE III – KEY TO MASTER CHART

-	-	Absent
+	-	Present
ALMI	-	Anterior lateral myocardial infarction
ASMI	-	Anteroseptal myocardial infarction
AWMI	-	Anterior wall myocardial infarction
BP	-	Blood pressure
CK-MB	-	Creatinine kinase MB
CVS	-	Cardiovascular system
F	-	Female
H-FABP	-	Heart type fatty acid binding protein
ILMI	-	Inferolateral myocardial infarction
IU/L	-	International units per litre
LBBB	-	Left bundle branch block
M	-	Male
mg/dL	-	Milligrams per deciliter
mm Hg	-	Millimeters of mercury
N	-	Normal
RVMI	-	Right ventricular myocardial infarction
SINUSBRADY	-	Sinus bradycardia
Syst.	-	Systemic

ANNEXURE III - MASTER CHART

Serial Number	In patient number	Age (Years)	Sex	Duration (hours)	Presenting complaints							Other			Treatment history	Past history	Family history	Habits			General physical examination											Syst. Examination						Investigations										
																					BP											CVS						Cardiac enzymes				Liver Profile				
					Chest Pain	Breathlessnes	Palpitations	Lower jaw pain	Epigastric pain	Hypotension	Pedal Oedema	Hypertension	Diabetes mellitus	Dyslipidemia				Alcohol consumption	Smoking	Tobacco chewing	Systolic (mm Hg)	Diastolic (mm Hg)	Pulse rate (/minute)	Respiratory rate (/Minute)	Temperature	Pallor	Icterus	Clubbing	Cyanosis	Lymphadenopathy	Oedema	JVP	Peripheral	Central	Respiratory system	Central nervous system	Per abdomen	Electrocardiogram	Troponin I	CK-MB	H-FABP	2D echocardiography	Serum creatinine (mg/dL)	Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)	SGOT (IU/L)	SGPT (IU/L)	Chest X-ray
1	606663	65	M	2.0	+	+	-	-	-	-	-	-	-	-	+	+	-	-	-	+	90	60	110	16	98.6	+	-	-	-	-	-	N	N	N	N	N	N	AWMI	0.77	-	0.183	+	1.45	N	N	N	N	N
2	608659	70	M	3.5	+	-	-	-	-	-	-	+	-	-	+	-	+	-	-	-	100	60	96	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	AWMI	0.05	-	0.383	+	1.02	N	N	N	N	N
3	600931	75	F	11.0	+	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	80	40	140	40	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ILMI	28	-	0.39	+	0.9	N	N	N	N	N
4	575083	68	M	7.0	+	-	-	-	-	-	-	+	+	-	+	-	-	-	-	+	110	60	84	17	98.6	+	-	-	-	-	-	N	N	N	N	N	N	ASMI	15.61	-	0.388	+	1.2	N	N	N	N	N
5	584926	65	M	5.0	+	-	-	-	-	-	-	-	-	-	-	-	-	-	+	-	170	90	80	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	5.28	-	0.448	+	0.9	N	N	N	N	N
6	609390	45	F	4.0	+	-	-	-	-	-	-	-	-	-	+	-	-	-	-	-	110	70	76	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	IWMI	0.4	-	0.25	+	0.46	N	N	N	N	N
7	608391	68	F	13.0	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	100	60	32	18	98.6	-	-	-	-	-	-	N	N	N	N	N	N	IWMI	0.8	-	0.49	+	0.46	N	N	N	N	N
8	566837	78	M	13.5	+	-	-	-	-	-	-	-	+	-	+	-	-	-	-	-	100	70	60	18	98.6	-	-	-	-	-	-	N	N	N	N	N	N	IWMI	50	242	1.67	+	0.55	N	N	N	N	N
9	597190	52	M	8.0	+	-	-	-	-	-	-	+	-	-	+	-	-	-	-	+	140	90	64	18	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	0.62	35	6.035	+	1.4	N	N	N	N	N
10	603341	55	M	4.0	+	-	+	-	-	-	-	+	-	-	+	+	+	-	+	-	70	-	46	30	99	+	-	-	-	-	-	N	N	N	N	N	N	LBBB, ILMI	0.4	-	0.368	+	0.82	N	N	N	N	N
11	600587	60	M	6.5	+	-	-	-	-	-	-	-	-	-	+	+	-	+	-	+	130	80	30	14	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI,ILMI	6.13	146	0.229	+	0.96	N	N	N	N	N
12	600636	64	M	12.5	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100	-	110	30	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ILMI, RVMI	12	-	0.49	+	1.4	N	N	N	N	N
13	603491	49	M	3.0	+	-	-	-	-	-	-	-	-	-	+	-	+	-	-	-	140	90	150	18	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	1.1	99	0.316	+	0.9	N	N	N	N	N
14	564216	55	M	6.0	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	100	70	84	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	1.2	-	0.108	+	0.5	N	N	N	N	-
15	564006	73	M	3.0	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	140	90	84	16	98.6	+	-	-	-	-	-	N	N	N	N	N	N	LATMI	2.34	74	0.001	+	1.17	N	N	N	N	N
16	564002	64	M	4.5	+	-	-	-	-	-	-	-	-	-	+	-	+	-	-	-	100	60	52	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	SINUSBRADY	0	99	0.98	+	1.4	N	N	N	N	N
17	588175	75	F	7.5	+	+	-	-	-	-	-	-	+	-	+	-	-	-	-	-	110	60	54	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	IWMI	0.8	-	0.274	+	0.7	N	N	N	N	N
18	604219	62	M	0.5	-	+	-	-	-	-	-	-	-	-	-	-	-	+	+	-	100	60	84	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	0.16	-	0.199	+	0.6	N	N	N	N	N
19	598798	68	F	5.0	+	-	-	-	-	-	-	-	+	-	+	-	-	-	-	-	160	60	32	16	98.6	-	-	-	-	-	-	N	AN	N	N	N	N	ALMI	0.22	-	0.281	+	1.4	N	N	N	N	N
20	604217	68	M	0.5	+	+	-	-	-	-	-	-	-	-	+	-	-	+	+	-	110	70	82	16	98.6	+	-	-	-	-	-	N	N	N	N	N	N	ASMI	0.04	-	0.199	+	1.23	N	N	N	N	N
21	599799	55	M	7.5	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	140	80	64	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ILMI	1.36	1	0.304	+	1.01	N	N	N	N	N
22	619654	65	M	2.0	+	-	-	-	-	-	-	+	+	-	+	-	-	-	-	-	140	90	104	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	AWMI	0.77	-	0.9	+	1.3	N	N	N	N	N
23	619650	73	F	5.5	+	-	-	-	-	-	-	+	-	-	+	-	-	-	+	-	160	70	130	18	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	0.48	-	0.118	+	1.2	N	N	N	N	N
24	569831	35	F	10.0	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	110	70	82	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	0.47	-	0.023	+	0.83	N	N	N	N	N
25	619473	65	M	9.0	+	-	-	-	-	-	-	-	+	-	+	-	-	-	-	-	130	80	84	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	IWMI	19.81	337	0.353	+	0.82	N	N	N	N	N
26	570247	60	F	15.5	+	+	-	-	-	-	-	-	+	-	+	-	-	-	-	-	120	70	64	16	98.6	+	-	-	-	-	-	N	N	N	N	N	N	ASMI	50	-	0.58	+	0.8	N	N	N	N	N
27	568712	50	F	17.7	+	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-	100	60	62	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	AWMI	50	-	0.186	+	0.95	N	N	N	N	N
28	575083	60	M	8.0	+	-	+	-	-	-	-	+	+	-	+	-	-	+	+	-	140	90	70	16	99	-	-	-	-	-	-	N	N	N	N	N	N	IWMI	15.61	120	0.118	+	120	N	N	N	N	N
29	569321	72	M	9.5	+	-	-	-	-	-	-	+	+	-	+	-	-	+	+	+	130	70	64	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	15.2	114	0.107	+	0.9	N	N	N	N	N
30	574101	55	M	16.0	+	+	+	-	-	-	-	-	-	-	-	-	+	+	-	-	100	70	84	16	99	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	0	17	0.063	+	0.76	N	N	N	N	N
31	574019	62	M	9.0	+	-	+	-	-	-	-	+	-	-	+	-	-	-	+	+	120	80	72	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	IWMI	7.6	31	0.022	+	0.7	N	N	N	N	N

ANNEXURE III - MASTER CHART

Serial Number	In patient number	Age (Years)	Sex	Duration (hours)	Presenting complaints							Other			Treatment history	Past history	Family history	Habits			General physical examination												Syst. Examination						Investigations										
																					BP												CVS						Cardiac enzymes					Liver Profile				
					Chest Pain	Breathlessnes	Palpitations	Lower jaw pain	Epigastric pain	Hypotension	Pedal Oedema	Hypertension	Diabetes mellitus	Dyslipidemia				Alcohol consumption	Smoking	Tobacco chewing	Systolic (mm Hg)	Diastolic (mm Hg)	Pulse rate (/minute)	Respiratory rate (/Minute)	Temperature	Pallor	Icterus	Clubbing	Cyanosis	Lymphadenopathy	Oedema	JVP	Peripheral	Central	Respiratory system	Central nervous system	Per abdomen	Electrocardiogram	Troponin I	CK-MB	H-FABP	2D echocardiography	Serum creatinine (mg/dL)	Total bilirubin (mg/dL)	Direct bilirubin (mg/dL)	SGOT (IU/L)	SGPT (IU/L)	Chest X-ray
32	569897	45	M	4.0	+	-	-	-	-	-	-	+	+	-	+	-	-	+	+	-	110	70	64	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	AWMI	0.02	33	0.011	+	7.23	N	N	N	N	N
33	563933	55	F	4.5	+	-	+	+	+	+	+	+	+	-	+	-	+	-	-	-	130	90	82	14	99	+	-	-	-	-	-	N	N	N	N	N	N	ILMI,RVMI	0.4	24	0.124	+	1.29	N	N	N	N	N
34	589284	75	F	12.0	+	-	-	-	-	-	-	+	+	-	+	-	-	-	-	-	160	70	74	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	0.08	-	0.839	+	1.2	N	N	N	N	N
35	568750	68	M	14.0	+	-	-	-	-	-	-	+	+	-	+	-	-	-	-	-	120	70	82	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	IWMI	0.31	174	0.156	+	1.4	N	N	N	N	N
36	589203	58	M	18.0	+	-	+	-	-	-	-	+	+	-	+	-	-	-	+	+	100	72	74	17	98.6	+	-	-	-	-	-	N	N	N	N	N	N	IWMI	50	324	0.3	+	1.2	N	N	N	N	N
37	613034	45	F	10.0	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	110	70	72	16	98.6	+	-	-	-	-	-	N	N	N	N	N	N	ASMI	12	120	0.487	+	0.8	N	N	N	N	N
38	578638	65	M	17.0	+	-	-	-	-	-	-	-	-	-	-	-	-	+	-	-	120	80	70	18	98.6	-	-	-	-	-	-	N	N	N	N	N	N	IWMI	0.2	100	0.68	+	0.77	N	N	N	N	N
39	617890	42	F	10.0	+	-	-	-	-	-	-	+	+	-	+	-	+	-	-	-	130	78	62	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	AWMI	0.16	44	0.322	+	0.82	N	N	N	N	N
40	623728	60	F	15.5	+	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	120	60	64	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	AWMI	0.08	60	0.183	+	0.9	N	N	N	N	N
41	578627	65	F	5.7	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	110	70	66	17	98.6	+	-	-	-	-	-	N	N	N	N	N	N	ASMI	4.12	95	0.197	+	0.9	N	N	N	N	N
42	595803	57	M	18.5	+	-	+	-	-	-	-	+	+	-	+	-	+	+	-	+	100	60	72	18	98.6	-	-	-	-	-	-	N	N	N	N	N	N	IWMI	13.7		0.254	+	0.94	N	N	N	N	N
43	603464	58	F	17.0	+	-	-	+	-	-	-	+	-	-	+	-	-	-	-	-	120	80	98	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	50	-	0.242	+	1.2	N	N	N	N	N
44	597190	52	M	3.0	+	-	-	-	-	-	-	+	-	-	+	-	-	-	-	+	140	90	64	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	IWMI	0.62	35	0.235	+	1.5	N	N	N	N	N
45	601100	25	M	13.5	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	+	130	80	84	17	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	21.8	-	0.246	+	0.9	N	N	N	N	N
46	598312	56	M	7.0	+	-	-	-	-	-	-	+	-	-	+	-	-	-	-	-	100	70	34	18	98.6	-	-	-	-	-	-	N	N	N	N	N	N	AWMI	1	36	0.215	+	1.4	N	N	N	N	N
47	589203	80	M	12.5	+	-	-	-	-	-	-	-	+	-	-	-	-	-	-	-	110	60	80	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	AWMI	50	324	0.03	+	1.5	N	N	N	N	N
48	597813	68	M	3.0	+	-	-	+	-	-	-	+	-	-	+	-	-	-	+	-	110	70	68	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	N	0.12	-	0.45	+	1.4	N	N	N	N	N
49	584926	65	M	4.0	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	170	90	80	17	98.6	-	-	-	-	-	-	N	N	N	N	N	N	AWMI	5.28	78	0.258	+	0.4	N	N	N	N	N
50	602969	49	M	5.0	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	140	90	100	18	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	1.1	22	0.199	+	0.9	N	N	N	N	N
51	603349	55	M	5.0	+	-	+	-	-	-	-	+	-	-	+	-	+	-	+	-	70	-	48	21	98.6	-	-	-	-	-	-	N	N	N	N	N	N	IWMI	0.04	-	0.368	+	1.23	N	N	N	N	N
52	617050	26	M	3.0	+	-	-	+	-	-	-	+	-	-	-	-	-	+	+	-	100	60	82	17	98.6	-	-	-	-	-	-	N	N	N	N	N	N	N	0.1	-	0.29	+	0.46	N	N	N	N	N
53	598907	65	M	15.0	+	-	-	-	-	-	-	-	+	-	-	-	-	+	+	-	110	68	64	18	98.6	+	-	-	-	-	-	N	N	N	N	N	N	IWMI	50	205	0.278	+	0.82	N	N	N	N	N
54	585811	47	M	12.0	+	-	+	-	+	-	-	+	+	-	+	-	-	+	-	+	100	60	80	18	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	6.95	145	0.246	+	0.77	N	N	N	N	N
55	598124	55	F	7.5	+	-	-	-	+	-	-	+	-	-	+	-	-	-	-	-	60	-	34	19	98.6	+	-	-	-	-	-	N	N	N	N	N	N	IWMI	-	48	0.137	+	0.64	N	N	N	N	N
56	600382	65	M	5.5	+	-	+	-	-	-	-	-	-	-	-	-	-	+	-	-	98	64	62	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	0.62	35	0.243	+	0.9	N	N	N	N	N
57	604431	68	F	6.0	+	+	-	-	-	-	-	+	+	-	+	+	-	-	-	-	102	64	74	18	98.6	-	-	-	-	-	-	N	N	N	N	N	N	AWMI	3.5	110	0.339	+	1.9	N	N	N	N	N
58	598120	56	M	4.0	+	-	-	-	-	-	-	+	-	-	+	-	-	+	+	-	120	80	70	16	98.6	+	-	-	-	-	-	N	N	N	N	N	N	IWMI	50	-	0.412	+	0.9	N	N	N	N	N
59	598908	72	M	12.0	+	-	-	-	-	-	-	+	-	-	+	-	-	+	+	+	110	60	72	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	AWMI	25.78	-	0.242	+	0.8	N	N	N	N	N
60	598131	57	F	10.0	+	+	-	-	-	-	-	-	+	-	+	-	-	-	-	-	94	62	68	16	98.6	-	-	-	-	-	-	N	N	N	N	N	N	ASMI	23.15	-	0.029	+	0.7	N	N	N	N	N
61	598906	60	M	11.0	+	-	-	-	-	-	-	+	-	-	+	-	+	+	-	+	110	70	72	18	98.6	-	-	-	-	-	-	N	N	N	N	N	N	AWMI	33	-	0.184	+	0.6	N	N	N	N	N