

**METABOLIC FACTORS AND THEIR IMPACT ON PROGNOSIS
AND EARLY COMPLICATIONS OF ACUTE MYOCARDIAL
INFARCTION IN TYPE 2 DIABETES MELLITUS
(SERUM URICACID, BLOOD SUGAR & TOTAL CHOLESTEROL)**



**Dissertation submitted in partial fulfillment of regulation for the award
of M.D. DEGREE IN GENERAL MEDICINE (BRANCH -I)**



**The Tamilnadu
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Chennai**

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CERTIFICATE

This is to certify that dissertation entitled “**METABOLIC FACTORS AND THEIR IMPACT ON PROGNOSIS AND SHORT TERM COMPLICATIONS OF ACUTE MYOCARDIAL INFARCTION IN TYPE 2 DIABETES (URIC ACID, SUGAR, CHOLESTEROL)**”, submitted by Dr. ARUL MURUGAN .C to the faculty of General Medicine, The Tamil Nadu Dr. M.G.R. Medical University, Chennai in the partial fulfillment of the requirement of M.D Degree - Branch I (General Medicine) is a bonafide research work carried out by him under my direct supervision and guidance.

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This is submitted to The **TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY**, Chennai, in partial fulfillment of the requirement for the award of M.D. Degree Examination, Branch-I (General Medicine) to be held in **APRIL 2010**.

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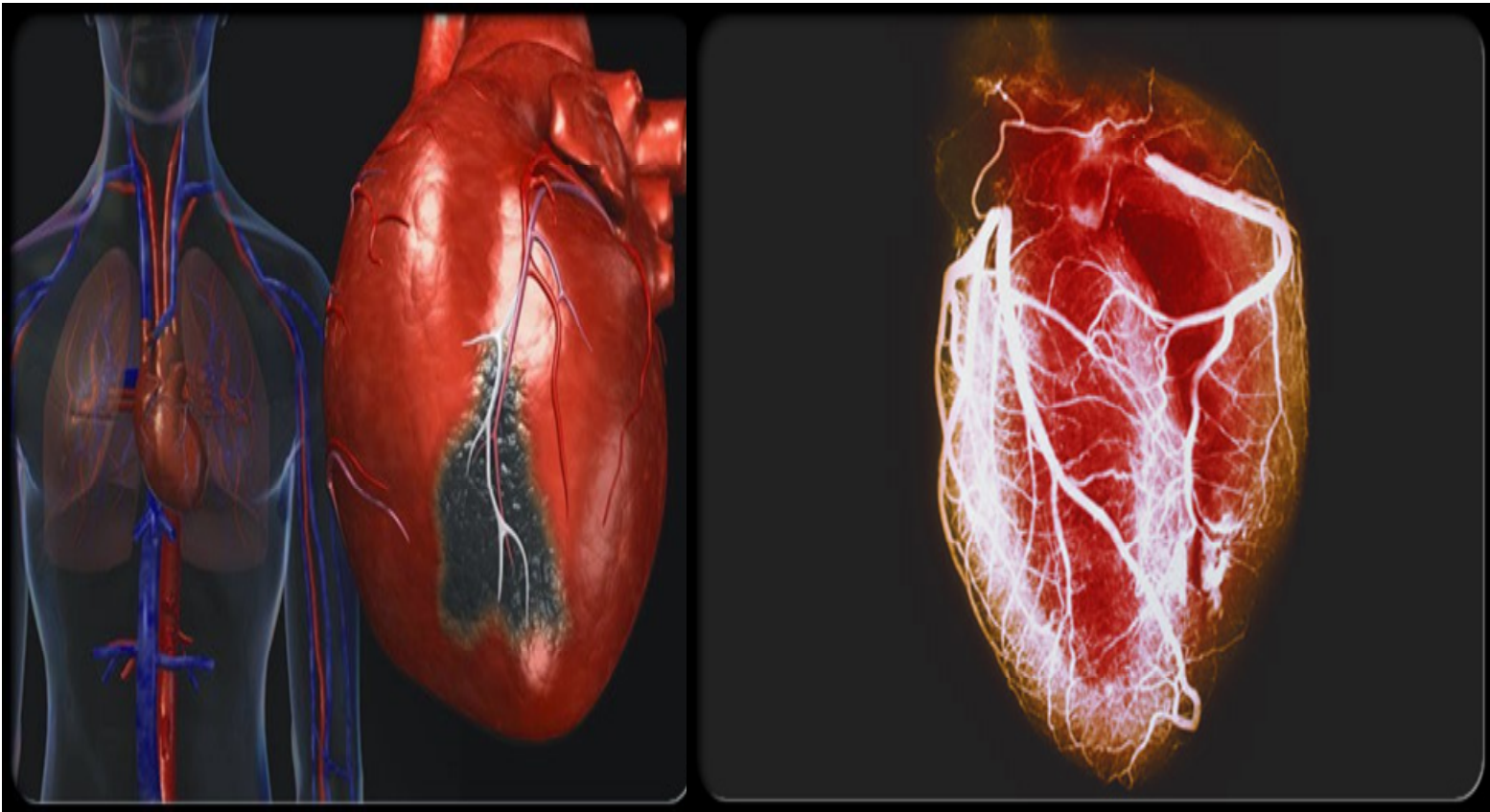
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ACUTE MYOCARDIAL INFARCTION

CORONARY ANGIOGRAPHY



Introduction

INTRODUCTION

Coronary artery disease is the most common cause of mortality in type 2 diabetes mellitus. Type 2 diabetes is also increasing in epidemic proportions in south Indian population. Despite the development of modern coronary care unit, acute myocardial infarction diabetes mellitus is still challenge to physicians because of atypical presentation of AMI in diabetes, too many variables predicting the outcome of treatment.

Acute Myocardial Infarction is the leading cause of mortality in both developed and developing countries (Rogers WJ et.al¹., Kesteloot H et.al²). Factors contributing to death in diabetics following Acute Myocardial Infarction are many.

These factors relate mainly to electrical disturbances in the form of Arrhythmia (Carmeliet E³, Thompson CA⁴) and mechanical disturbances in the form of pump failure (Hochman et. al⁵., Bertrand M et. al⁶.). Most sudden deaths in Acute Myocardial Infarction occur within one hour due to ventricular fibrillation and also due to left ventricular failure when there is an extensive injury (Lewis EF et. Al⁷.) Rest of the deaths following Myocardial Infarction occur within first one week and death cannot be predicted and occurs suddenly. Hence many trials have been conducted to identify markers that would be helpful to predict the risk of such adverse cardiac events.

Many trials have used serum Magnesium level (Milionis HJ et al.⁸), C-Reactive Protein levels (Ridker PM, Morrow DA et al.⁹), Malonyldialdehyde, (Pol Merkurisz Lek¹⁰) white blood cell count (Comparan Nunez. A et. Al¹⁰), as a predictor for mortality and morbidity following Acute Myocardial Infarction and risk of developing adverse cardiac events like sudden cardiac death and congestive heart failure. This Study Is One Of Such Kind In That It Tries To **VALIDATE THE PROGNOSTIC ROLE OF METABOLIC FACTORS (SERUM URIC ACID LEVEL, BLOOD SUGAR , TOTAL CHOLESTEROL LEVELS) FOLLOWING ACUTE MYOCARDIAL INFARCTION IN TYPE 2 DIABETES**(Kojima S., Sakamoto, Am .J Cardiol . 2005 Aug, Sakai H University of Medical Science, Otsu, Japan, Niizeki T., J. Cardiology 2006 May, Joshua M, Circulation 2003: American Heart Association.)

Previous studies have established that serum uric acid levels reflect circulating xanthine oxidase activity and oxidative stress production following Acute Myocardial Infarction. Free radicals produced in large amounts during myocardial ischemia and reperfusion take part in the degradation of cellular and subcellular membrane structures. The source of oxygen radicals in ischemic myocardium are Neutrophils recruited into the necrotic region as well as metabolic transformation of Hypoxanthine and Xanthine to Uric acid (Domonsky L et. al¹⁰)

Thus it is evident that elevated Uric acid levels is a good marker of oxidative stress and useful to assess the prognostic events in AMI. This forms the basis of the study.

Hyperglycemia on admission is a well known predictor of mortality after myocardial infarction even among without known type 2 diabetes mellitus as evidenced by journal of American college of cardiology (J Am Coll Cardiol, 2002; 40:1748-1754).¹⁰ This study is one to validate prognostic role of uric acid along with blood sugar & total cholesterol after myocardial infarction in type 2 diabetes mellitus.

Aims of the Study

IMS OF THE STUDY

1. To know about serum uric acid level and impact on short term mortality
2. On admission glucose and total cholesterol levels and their impact on severity of AMI along with serum uric acid elevation
3. To study the atypical presentations in DM presenting with acute myocardial infarction
4. To assess the prognostic significance of serum Uric acid level in Acute Myocardial Infarction in type 2 diabetics.
5. To evaluate serum Uric acid levels with incidence of cardiac failure in diabetes with AMI.
6. To validate the relation between Quantitative serum Uric acid level on admission and Killip's class status on AMI in type2 DM,
7. To know whether the incidence of Arrhythmias bears a relation with serum Uric acid level in Acute Myocardial Infarction.

Review of Literature

REVIEW OF LITERATURE

Ischemic Heart Disease is the generic designation for a spectrum of disorders resulting from imbalance between the myocardial need for oxygen and the adequacy of blood supply¹¹. In 90- 95% of cases the reduction in the coronary blood flow is related to atherosclerotic narrowing or the subepicardial coronary trunks. Coronary vasospasm alone or superimposed on atherosclerotic narrowing may contribute to the reduction of flow¹².

Depending upon the rate of development of the arterial narrowing and its ultimate severity, four basic clinico pathologic syndromes may result.

They are

1. Angina pectoris.
2. Myocardial Infarction
3. Chronic Ischemic Heart Disease
4. Sudden Cardiac Death – which may be superimposed on any of the three conditions.

MYOCARDIAL INFARCTION :

This is the catastrophic frequently fatal form of Ischemic Heart Disease that usually results from precipitous reduction or arrest of a significant portion of coronary flow. In great majority of cases wide spread

severe coronary atherosclerosis of the coronary arteries underlie Myocardial Infarction. In addition some sudden event such as coronary thrombosis must unfavorably alter the precarious balance. Alternatively the myocardial supply can be suddenly reduced by a superimposed vasospasm. Congenital abnormalities such as anomalous origin of left anterior descending coronary artery from the pulmonary artery may cause myocardial ischemia and infarction. But it is very rare.

Coronary atherosclerosis creates a disparity between myocardial needs and supply. Myocardium extracts a high and virtually fixed fraction of oxygen from the coronary arterial blood. Atherosclerotic arteries can not dilate and so incapable of adjusting to the demands. Transient deficit of oxygen can be compensated by anerobic glycolysis with the production of lactate¹³. If the imbalance is not transient, it passes from the reversible ischemic injury to the irreversible ischemic necrosis. Depending upon the rate of development of the arterial narrowing and its ultimate severity, three basic clinico pathologic syndromes occur namely Angina pectoris, Acute coronary insufficiency & Myocardial Infarction.

Angina pectoris is a clinical syndrome resulting from transient reversible myocardial ischemia and is produced by any effort which increases the metabolic demands of the myocardium beyond the capacity of the coronary circulation. The anginal pain is due to accumulation of certain

metabolites that are formed in ischemic working muscle. It is diagnosed clinically by the typical history of the site, the character and duration of pain, the site of its radiation and by its characteristic precipitating and relieving factors. Here the ECG will be usually normal. Ischemic changes can be demonstrated only by the stress ECG.

Acute Myocardial Infarction is a pathologic process resulting from the reduced perfusion of a segment of the myocardium such that irreversible injury occurs. The infarct may be subendocardial or transmural.

Subendocardial infarct refers to a multifocal, non-confluent areas of ischemic necrosis, often distributed circumferentially. This does not extend beyond. The inner one third to one half of the thickness of the left ventricular wall. The patients with this type of infarction are more prone for cardiac arrhythmias. Coronary thrombosis is not found in more than 10% such cases¹⁴.

Transmural infarct refers to a confluent area of ischemic necrosis extending at some point from the subendocardium to the epicardium . Coronary thrombosis is usually present in 90-95% of these cases.

EPIDEMIOLOGY :

The incidence of fatal Myocardial Infarction progressively rises with age to peak in the 55-65 years old group.

Myocardial Infarction occur in younger individuals, even in the third decade of life, particularly when predispositions to atherosclerosis, Hypertension diabetes, familial hypercholesterolemia & other causes of hyperlipoproteinemia are present.

Virtually throughout life, males are at significantly greater risk than females, the differential progressively declining with advancing age. Except for those having some predisposing atherogenic condition, women are remarkably protected against Myocardial Infarction during reproductive life. Women using oral contraceptives have 3 to 4 fold greater risk than non users and this increased risk does not appear to be related to the duration of use¹⁵.

CIGARETTE SMOKING:

Cigarette smoking particularly in combination with other risk factors has been shown to have a strong and consistent association with increased incidence of atherosclerosis, by increasing catecholamine stimulation which enhances platelet aggregation and peripheral lipid mobilization and decreasing the ratio of HDL to LDL¹⁶.

STRESS AND PERSONALITY :

Stress is associated with increased catecholamine secretion and mental stress may thus be a aggravating factor. Type A individuals who are

anxious, aggressive, impatient, competitive, always in a frustrate mood are more prone for IHD¹⁷.

SEDENTARY LIFE STYLE :

Exercise conditioning when regularly employed, reduces the rate of fatal Heart disease¹⁸. It is proved that HDL level increases with exercise, & also augments fibrinolytic response and there by provide a potential protective mechanism against development of thrombi within coronary arteries¹⁹.

DIABETES MELLITUS :

It has been shown that a diabetic patients serum can cause hyperplasia of smooth muscle cells. Furthermore, high blood sugar is often associated with obesity, hypertension, increased triglycerides, Low HDL, increased LDL and abnormal platelet adhesiveness. Diabetes is said to double the risk of ischemia in men and women 3-4 times. Silent Myocardial Infarction is thought to occur with increased frequency in diabetes and should be suspected whenever symptoms of left ventricular failure appear suddenly²⁰.

CORONARY BLOOD FLOW :

The blood flow in coronary arteries resembles that in other regions in being dependant on the blood pressure and on the vascular resistance of the

arteries and the arterioles. A feature of the coronary circulation is that the arteries are compressed by the contracting myocardium during systole. Consequently coronary blood flow occurs mainly during diastole²¹.

The normal coronary circulation is dominated and controlled by the myocardial requirements for oxygen. This need is met by the heart's ability to vary coronary vascular resistance and therefore blood flow. Considerably while the myocardium extracts a high and relatively fixed percentage of oxygen.

The large epicardial vessels serve as conduits in healthy persons, although they are capable of constriction and relaxation they are referred as the conductance vessels. The intramyocardial vessels normally exhibit striking changes in tone and are therefore referred as resistance vessels.

Hence with exercise and emotional stress, the changing oxygen needs affect coronary vascular resistance and in this manner regulate the supply of blood and oxygen (metabolic regulation). These same vessels adapt to physiologic alterations in blood pressure in order to maintain coronary blood flow at levels appropriate to myocardial needs. (Auto regulation).

The frequencies of the critical narrowing of each of the three main arterial trunks and the associated myocardial lesions are as follows²² :

- a) LEFT ANTERIOR DESCENDING : Anterior wall of left ventricle near
(40-50%) coronary artery apex, anterior 2/3 septum
- b) RIGHT CORONARY ARTERY : Posterior wall of left ventricle
(30-40%) Posterior 1/3 of inter ventricular septum
- c) LEFT CIRCUMFLEX C ARTERY : Lateral wall of left ventricle.
(15-20%)

REVISED DEFINITION OF MYOCARDIAL INFARCTION:²³

Either one of the following criteria satisfies the diagnosis for an acute, evolving or recent MI :

1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK- MB) of biochemical markers of myocardial necrosis with at least one of the following :
 - a. Ischemic symptoms.
 - b. Development of pathologic Q waves on the ECG reading.
 - c. ECG changes indicative of ischemia (ST Elevation or depression)
 - d. Coronary artery intervention (eg : coronary angioplasty)
2. Pathological findings of acute MI .

Criteria for established MI :

Either of the following criteria satisfies the diagnosis for established MI :

1. Development of new pathological Q waves on serial ECG readings. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.
2. Pathological findings of a healed or healing MI.

Several researchers all over the world have been attempting for decades to establish those criteria that best define patients with a poorer prognosis. Taken in toto, the various studies and articles published in the literature may be classified conveniently into two major headings:

1. Criteria obtained at the initial physician contact including patient characteristics (eg : age, gender), details of history, the initial clinical examination findings .
2. The laboratory parameters obtained on admission.

CHEST PAIN :

Despite the recent advances in the laboratory diagnosis of Acute Myocardial Infarction (AMI), the history remains of substantial value in arriving at a diagnosis. A prodrome of chest discomfort can usually be elicited in 20 to 60% of patients with AMI.²⁴

The pain of AMI resembles that of classic Angina pectoris, except that is more severe, occurs at rest or with lesser activity than usual, lasts longer

(more than 30 minutes) is associated with more systemic symptoms (eg : diaphoresis, nausea) and not relieved by rest or nitrates. On occasion it radiates to the arms. Less common sites of radiation include the abdomen back, lower jaw, and neck. The pain may radiate as high as the occipital area but not below the umbilicus.

In an analysis of the atypical presentations of AMI, Bean et.al., lists the following :²⁵

1. Congestive Heart failure.
2. Classic angina pectoris (not severe or prolonged).
3. Atypical locations of the pain.
4. CNS manifestations, from a reduced cardiac output, resembling a stroke.
5. Apprehension and nervousness.
6. Sudden Mania and Psychosis.
7. Syncope, over whelming weakness.
8. Acute indigestion,Peripheral embolism.

To this list must be added those patients with “silent” AMI – who have had no symptoms at onset. Such presentations are commoner in diabetes and hypertensives, and both of these conditions are also associated with an increased mortality.²⁶

PHYSICAL FINDINGS :

Most patients are anxious and restless, attempting unsuccessfully to relieve the pain by moving about in bed, altering their position, and stretching. Pallor associated with perspiration and coolness of the extremities occurs commonly. About one fourth of patients with Anterior Infarction have manifestations of sympathetic nervous system hyperactivity (tachycardia or hypertension) and upto one half with Inferior Infarction show evidence of para sympathetic hyperactivity (bradycardia or hypotension).²⁷

The apical impulse may be difficult to palpate. S3, S4 gallop sounds, decreased intensity of first Heart sound and paradoxical splitting of second Heart sound may be there. A transient mid systolic or late systolic apical systolic murmurs may be heard in mitral area. Pericardial friction rub is heard at some time in the course of disease. The carotid pulse is often decreased in volume, reflecting reduced stroke volume. In most transmural MI patients, systolic pressure declines by approximately 10-15 mmHg from the pre infarction state.

SERUM CARDIAC BIOMARKERS :

These cardiac markers are released into the blood in large quantities from necrotic heart muscle after MI.

Creatinine phosphokinase (CK) rises within 4 to 8 hour and generally returns to normal by 48 to 72 hrs . An important draw back of total CK measurement is its lack of specificity for STEMI (ST Elevation MI), as CK may be elevated with skeletal muscle trauma. Creatinine phosphokinase MB isoenzyme (CK-.MB) has the advantage over total CK that is not present in significant concentrations in extra cardiac tissue and therefore is more specific.

However, cardiac surgery, myocarditis, electrical cardioversion often result in elevated serum levels of CK-MB. A ratio (relative index) of CKMB mass : CK activity > 2.5 suggests but is not diagnostic of a myocardial rather than a skeletal muscle source for the CK – MB elevation.²⁸

Cardiac specific troponin T (cTnT) and cardiac specific troponin I (cTnI) are not normally detectable in the blood of healthy individuals, but may increase after STEMI to levels > 20 times higher than the upper reference limit. They are now the preferred biochemical markers of MI. Levels of cardiac troponins remain elevated for 7 to 10 days after STEMI .

Myoglobin is released into the blood within a few hours of the onset of STEMI. But it lacks cardiac specificity, because it is rapidly excreted in the urine, So blood levels return to the normal range with in 24 hours of the onset of infarction.

Serum lipids are often determined in patients with STEMI. During the first 24 to 48 hours after admission, total Cholesterol and HDL cholesterol remain at or near baseline values, generally fall after 48 hours. The fall in HDL cholesterol after STEMI is greater than total cholesterol. Elevation of white blood cell count (Polymorphonuclear Leukocytosis) appears within a few hours and peaks at 2 to 4 days.

Erythrocyte Sedimentation Rate peaking during the first week and elevated for 1 or 2 weeks. Other markers like C-Reactive Protein, LDH, SGOT also elevated.²⁹

CARDIAC IMAGING :

Two dimensional echocardiography, Doppler echocardiography , myocardial perfusing imaging with Thallium 201 or 99mTc – Sestamibi scan useful in Acute MI. Radio nuclide ventriculography carried out with 99mTc labeled red blood cells frequently demonstrates wall motion disorders and ejection fraction in MI patients.³⁰

HEMODYNAMIC ABNORMALITIES:

In 1976, Swan, Forrester, and their associates measured the cardiac output and wedge pressure simultaneously in a large series of patients with acute Myocardial Infarction and identified four major hemodynamic subsets of patients.³¹

1. Patients with normal perfusion and without pulmonary congestion (normal cardiac output and normal wedge pressure).
2. Patients with normal perfusion and pulmonary congestion. (normal cardiac output and elevated wedge pressure).
3. Patients with decreased perfusion but without pulmonary congestion. (reduced cardiac output and normal wedge pressure).
4. Patients with decreased perfusion and pulmonary congestion. (reduced cardiac output and elevated wedge pressure).

This classification which overlaps with a crude clinical classification proposed earlier by Killip and Kimball, has proved to be quite useful, but it should be noted that patients frequently pass from one category to another with therapy and sometimes even spontaneously.

HEMODYNAMIC CLASSIFICATION OF PATIENTS WITH AMI BY KILLIP CLASSIFICATION :

CLASS	DEFINITION³¹
I	Patients with MI and no evidence of Heart failure.
II	Patients with MI, Early Heart failure as manifested by bibasilar rales, and at times S3 gallop.
III	Patients with MI, features of pulmonary edema (Rales >1/2lung fields)
IV	Patients with MI, cardiogenic shock

HEART FAILURE :

Heart failure is a state when the heart cannot maintain an adequate cardiac output or can do so only at the expense of an elevated filling pressure. Heart failure is frequently due to coronary artery disease, tends to affect elderly people and often leads to prolonged disability. Cardiac output is a function of preload, afterload and myocardial contractility. The primary abnormality in Heart failure is impairment of ventricular function leading to a fall in cardiac output. This activates counter regulatory neurohormonal mechanisms that in normal physiological circumstances would support cardiac function, but in the setting of impaired ventricular function can lead to a deleterious increase in both afterload and preload. A vicious circle may be established because any additional fall in cardiac output will cause further neurohormonal activation and increasing peripheral vascular resistance.³³

Stimulation of the renin-angiotensin-aldosterone system leads to vasoconstriction, salt and water retention and sympathetic activation mediated by angiotensin II, which is a potent constrictor of arterioles both in the kidney and systemic circulation. Salt and water retention is promoted by release of aldosterone, endothelin (a potent vasoconstrictor peptide with marked effects on the renal vasculature) and in severe Heart failure. Anti Diuretic Hormone (ADH), Natriuretic peptides are released from the atria in response to atrial stretch, and act as physiological antagonists to the fluid

conserving effect of aldosterone and extremely useful in diagnosis, prognosis & monitoring therapy.

After Myocardial Infarction, cardiac contractility is impaired and neurohormonal activation may lead to hypertrophy of non-infarcted segments with thinning, dilatation and expansion of the infarcted segment. (remodelling). This may lead to deterioration in ventricular function and worsening of heart failure.

MECHANISMS OF CHRONIC CONGESTIVE HEART FAILURE

DUE TO CORONARY ARTERY DISEASE: ³⁵

(Severely depressed LV function) :

MYOCARDIAL INFARCTION :

1. Large (usually Anterior) transmural infarct with severe depression of LV function (EF<30-35%) due to acute extensive loss of myocardium.
2. Multiple infarcts with extensive myocardial fibrosis (not always clinically recognized) resulting in severe reduction in systolic function (Ischemic cardiomyopathy)
3. Prior myocardial infarction with mitral regurgitation (systolic function mildly to severely decreased).
4. LV aneurysm.
5. Late post MI systolic dysfunction, known as LV remodelling.

MYOCARDIAL ISCHEMIA :

1. Extensive regions of hibernating LV myocardium – viable but ischemic (low coronary blood flow) zones of LV systolic dysfunction often accompanied by reversible and irreversible dysfunction fibrosis or scar.
2. Ischemic papillary muscle dysfunction resulting in mitral regurgitation.

NORMAL OR MILDLY DEPRESSED LV FUNCTION:

1. Diastolic dysfunction related to ischemia and or LV hypertrophy.
2. Severe mitral regurgitation.
3. Ventricular septal defect (rare)

Any of above superimposed on cardiac distress related to other etiologies

1. Valvular heart disease
2. Preexisting non ischemic cardiomyopathy.

MORTALITY :

Studies involving large number of patients have revealed wide variations in the time elapsed between symptom onset and arrival at the hospital. Researchers have investigated for a relationship between this delay and in hospital mortality. However there are certain complexities in their relationship as follows .

Most sudden deaths in AMI occur due to ventricular Arrhythmias and this risk is maximum in the first hour after symptom onset. With each subsequent hour, the risk decreases, giving rise to the paradoxical situation where a patient who presents late to the hospital has a lesser risk of sudden death than one who presents early for treatment. 40-60% of patients have some degree of left ventricular dysfunction at presentation if untreated, this may go on to a cardiogenic shock, the commonest cause of inhospital death in AMI. This implies that the patient who presents sufficiently early for shock to be treated or prevented has a better prognosis .

Established beyond reasonable doubt that the patient who presents early enough for thrombolysis has large benefits from reperfusion, vastly improving the prognosis.

Raitt et.al., have shown that each 30 minute delay is associated with a 1% increase infarct size.³⁶ Julian D.G analyzing the results of five mortality trials, concluded that gaining about one hour prior to thrombolysis decreases mortality by about 17%.³⁷ Even for patients presenting at later than this window period of 6 hours, thrombolysis can be beneficial, compared to those that do not receive such treatment. Yusuf et al., showed a 22% reduction in mortality for those treated at 12-24 hours. The ISIS – 2 trial extended the concept of beneficial late perfusion with its results revealing a significant benefit beyond 6-12 hours, and even 12-24 hours.³⁸ These findings are

confirmed by the ISIS- 3 and EMERAS trials.³⁹ The newer agents such as t-PA, Urokinase or even emergency coronary angioplasty may achieve better late reperfusion than Streptokinase.⁴⁰

GENDER RELATED DIFFERENCES IN PROGNOSIS :

Unlike in previous years, the incidence of AMI in women is increasing. AMI in women has certain peculiarities. Women are mostly older than men at presentation and are more likely to have atypical pain, Hypertension, Diabetes, unstable angina, hyperlipidemia, congestive cardiac failure or silent infarctions are all commoner in women. Women more frequently have non – Q AMI and tend to present later to hospital.⁴¹ Of interest after STEMI, younger women but not older women have higher rates of inhospital mortality than men of the same age.

The pathogenic mechanisms different in women include :⁴²

- A greater incidence of vasospastic and micro circulatory angina.
- Different plaque components (more cellular and fibrous tissue).
- Different endothelial tone due to hormonal influences.
- Different hemostasis (higher fibrinogen and factor VIII levels).

DIABETES AND ITS EFFECTS ON PROGNOSIS :

The early pioneering studies on AMI, especially those by Killip and Norris suggested that the presence of diabetes had a significant effect on the mortality. The famous Framingham Heart study indicated that diabetes increased the risk of death in women, but not men, after a first AMI. They tend to have larger infarcts, and show a greater incidence of shock, cardiac failure and metabolic problems.⁴³

HYPERTENSION AND ITS EFFECT ON PROGNOSIS :

The GISSI – 2 trial one of the largest ever series of AMI patients (11,843 patients, of which 3306 were hypertensive) investigated the prognostic value of hypertension in those receiving thrombolysis. Their results show a significantly higher mortality for hypertensives LV failure and recurrent ischemic events were also more common among hypertensives.⁴⁴

Patients develop cardiogenic shock when more than 40% of the myocardium is destroyed. Beyond the immediate phase, cardiogenic shock is the commonest cause of mortality. The hospital mortality for cardiogenic shock is in the region of 60-80%. The incidence of ventricular arrhythmias and heart block was found to be higher in these patients. (Killip et.al.) By multivariate analysis of their cohort of 845 patients. Hands et.al., found that the predictors of cardiogenic shock included age >65, ejection fraction

<35%, peak CK-MB value more than 160 IU/ L and a history of diabetes or prior infarction⁴⁵

PROGNOSTIC PARAMETERS AT HOSPITAL ADMISSION IN AMI⁴⁶

PARAMETERS	EFFECT ON PROGNOSIS
Age	Prognosis worsens with increasing age
Sex	Women have a worse prognosis than men
Heart Rate	Heart rate >100/mt indicates a poor prognosis
Cardiogenic shock	A very high early mortality
Congestive Heart failure	Indicates a poor prognosis even when treated successfully
ST segment deviation	The more ST segment deviation or Q wave formation, the larger the infarct and the worse prognosis.
Enzymes	Not admission levels, but evolving rise in cardiac enzymes estimate infarct size
Troponin	levels Elevated admission troponin – I or troponin – T indicates a worse prognosis even in the absence of rising CPK or CK MB.

URIC ACID BIOCHEMISTRY

Uric acid is the final breakdown product of Purine metabolism. Most mammals have the ability to catabolize purines to allantoin, a more water soluble end product.

Purines such as adenosine and guanine from the breakdown of ingested nucleic acids or from tissue destruction are converted into uric acid primarily in the liver. Uric acid is transported in the plasma from the liver to the kidney, where it is filtered by the glomerulus. Reabsorption of 98-100% of the uric acid in the glomerular filtrate occurs in the proximal tubules. Small amounts of uric acid are secreted by the distal tubules into the urine. This route accounts for about 70% of the daily uric acid excretion. The remainder is excreted into the GI tract and degraded by bacterial enzymes. Uric acid is produced only in tissues that contain xanthine oxidase, primarily the liver and small intestine.

Nearly all of the uric acid in plasma is present as monosodium urate. At the pH of plasma, Urate is insoluble; at concentrations greater than 6.4 mg/dl the plasma is saturated. As a result, urate crystals may form and precipitate in the tissue. In the urine at $\text{pH} < 5.7$, uric acid crystals may form.

HUMANS CATABOLIZE PURINES TO URIC ACID : ⁴⁷

Humans convert the major purine nucleosides adenosine and guanosine to the excreted end product uric acid via the intermediates and reactions. Adenosine is first deaminated to inosine by adenosine deaminase. Phosphorolysis of the N-glycosidic bonds of inosine and guanosine, catalyzed by purine nucleoside phosphorylase releases ribose 1 – phosphate and a purine base. Hypoxanthine and guanine next form xanthine in reactions catalysed by xanthine to uric acid in a second reaction catalyzed by xanthine oxidase and guanase respectively. Xanthine is then oxidised to uric acid in a second reaction catalyzed by xanthine oxidase. Thus xanthine oxidase provides a potential locus for pharmacologic intervention in patients with hyperuricemia.

Net excretion of total uric acid in normal humans averages 400- 600 mg/24hr. In mammals other than higher primates, the enzyme uricase cleaves uric acid, forming the highly water soluble end product allantoin. However, since humans lack uricase, the end product of purine catabolism in man is uric acid. Amphibians, birds and reptiles also lack uricase and excrete uric acid and guanine as end products of purine catabolism.

Humans catabolize purines to weak uric acid. (pK 5.8) which depending on urinary pH, exists as the relatively insoluble acid (at acidic

pH) or its more soluble sodium urate salt. Urate crystals are diagnostic of gout, a metabolic disorder of purine catabolism. Other disorders include Lesch – Nyhan syndrome, von Gierkes disease and hypouricemias.

HYPERURICEMIA :

It can result from increased production or decreased excretion of uric acid or from a combination of the two processes. Hyperuricemia is defined as a plasma concentration of > 7mg/dl in males and > 6mg/dl in females.

CLASSIFICATION OF HYPERURICEMIA BY PATHOPHYSIOLOGY⁴⁸

URATE OVERPRODUCTION :

- Primary idiopathic HPRT deficiency, PRPP synthetase Over activity
- Hemolytic processes, Lymphoproliferative Diseases
- Myeloproliferative Diseases, Rhabdomyolysis, Exercise
- Alcohol, Obesity, Purine rich diet, Polycythemia vera
- Psoriasis, Pagets disease

DECREASED URIC ACID EXCRETION:

- Lead intoxication, Renal insufficiency, Hyperparathyroidism
- Polycystic kidney disease, Hypothyroidism
- Diabetes insipidus, Toxaemia of pregnancy
- Hypertension, Bartters syndrome

- Acidosis, Down syndrome, Drug ingestion
- Salicylates (>2g/d), Starvation ketosis, Diuretics
- Berylliosis, Alcohol
- Sarcoidosis, Levodopa, Ethambutol, Pyrazinamide, Cyclosporine

COMBINED MECHANISM :

- Glucose - 6 – Phosphatase deficiency
- Fructose – 1 – Phosphate aldolase deficiency
- Alcohol, Shock

Note : HPRT : Hypoxanthine Phospho Ribosyl Transferase

PRPP : Phospho Ribosyl Pyro Phosphate.

Accelerated purine nucleotide degradation can also cause hyperuricemia i.e with conditions of rapid cell turnover, proliferation or cell death, as in Leukemic blast crisis, cytotoxic therapy for malignancy, hemolysis or rhabdomyolysis. Hyperuricemia can result from excessive degradation of muscle ATP after strenuous physical exercise or status epilepticus.

Hyperuricemia of Myocardial Infarction, smoke inhalation and acute respiratory failure may also be related to accelerated breakdown of ATP.

SECONDARY CAUSES OF HYPERURICEMIA⁴⁹

1. Obesity
2. Dyslipidemia (Usually type 4) with raised VLDL and normal cholesterol levels; hypercholesterolemia with increased LDL cholesterol and Low HDL cholesterol.
3. Hypertension
4. Insulin resistance with hyperinsulinemia and impaired glucose tolerance.
5. Ischemic Heart Disease.

OXIDATIVE STRESS :

There is evidence that oxidative stress is increased both systemically and in the myocardium of patients with Heart failure.⁵⁰ Increased oxidative stress may be due to reduced antioxidant capacity of the increased production of reactive oxygen species, which may be a consequences of mechanical strain on the myocardium or stimulation by neuro hormones and inflammatory cytokines. Possible sources of increased production of reactive oxygen species include the mitochondria, xanthine oxidase and NADPH oxidase.⁵¹ Reactive oxygen species can stimulate myocyte hypertrophy, reexpression of fetal gene programs and apoptosis in cardiac myocytes in culture.⁵² There is no evidence that uric acid is toxic to myocardium.

Hyperuricemia may be a marker of coincident cardiac disease, but not a causal risk factor. The increased plasma uric acid concentration observed in patients with ischemic heart disease could arise from upregulated vascular adenosine synthesis associated with ischemia and the subsequent degradation of adenosine to uric acid. The relationship of urate to endothelial function is complex. Plasma uric acid accounts for 60% of the free radical scavenging activity in human plasma. It interacts with peroxynitrite to form a stable Nitric oxide donor, so promoting vasodilation and reducing the potential for peroxynitrite induced oxidative damage. Conversely it could have an adverse effect on endothelial function by promoting leukocyte adhesion to the endothelium.⁵³

URIC ACID PREDICTS CLINICAL OUTCOMES IN HEART FAILURE :

Insights Regarding the Role of Xanthine Oxidase and Uric Acid in Disease Pathophysiology :

In the current issue of circulation, Anker and Colleagues⁵⁴ report that elevated levels of uric acid predict mortality and the need for heart transplantation in patients with congestive heart failure. Serum concentrations of uric acid added important prognostic information alone and when combined with measures of cardiac function (ejection fraction) and patient functional status (maximal oxygen consumption with exercise) and

were independent of renal function, serum sodium, Blood urea, diuretic usage, and patient age.

A consideration of the mechanism of uric acid production and metabolism offers insight into the relationship between uric acid levels and Heart failure outcomes. Moreover, uric acid levels may reflect xanthine oxidase pathway activity, which has the potential to myocardial energetics and myofilament calcium sensitivity.⁵⁵

POTENTIAL MECHANISMS FOR INCREASED URIC ACID IN HEART FAILURE :

Uric acid is a metabolic byproduct of purine metabolism. Serum uric acid may increase in the failing circulation because of increased generation, decreased excretion, or a combination of the 2 factors. There are several possible contributors to increased uric acid production in Heart failure, including increased abundance and activity of xanthine oxidase, increased conversion of xanthine dehydrogenase to xanthine oxidase, or increased xanthine oxidase substrate resulting from enhanced ATP breakdown to adenosine and hypoxanthine. As uric acid is excreted primarily by the kidney, decreased renal perfusion could lead to increased uric acid levels. To the extent that Heart failure leads to tissue ischemia and a rise in serum lactate, renal uric acid excretion can be further impaired as lactate competes with urate via an organic anion exchanger in the proximal tubule.⁵⁶

PATHOPHYSIOLOGICAL ROLE OF THE XANTHINE OXIDASE

PATHWAY IN HEART FAILURE:

The elevation in serum uric acid may reflect increased xanthine oxidase pathway activity and in turn the generation of superoxide and resultant oxidative stress via the xanthine oxidase system.⁵⁷ Xanthine oxidase is upregulated within the heart in both experimental and human heart failure. Much had previously been made of the difficulty in identifying xanthine oxidase within the hearts of certain mammalian species, including humans,⁵⁸ nevertheless, it is clear that xanthine oxidase, which is produced in highest abundance in the liver and gut may circulate in the blood and adhere to endothelium in distant sites.

Moreover, xanthine oxidase is expressed in cardiac myocytes, as shown by immunohistochemistry and may participate in intracrine signaling.

PATHOPHYSIOLOGICAL ROLE OF URIC ACID IN HEART FAILURE :

Beyond xanthine oxidase activity, recent experimental studies suggest that uric acid itself may have a role in cardiovascular and renal pathophysiology. This might seem surprising, as uric acid can function as an antioxidant both by itself and by promoting superoxide dismutase activity,⁵⁹ and might therefore be considered potentially protective. However, uric acid

potently stimulates vascular smooth muscle cell proliferation in vitro, an effect mediated by stimulation of mitogen-activated protein kinases, cyclooxygenase2, and platelet derived growth factor⁶⁰

CLINICAL UTILITY OF URIC ACID MEASUREMENTS :

From a clinical perspective, the current study raises the issue of whether serum uric acid levels should be routinely measured in Heartfailure patients.⁶¹ Indeed this is likely to be a controversial issue, and one which will require evaluation in the context of measurement of brain natriuretic peptide (BNP), a serum marker that also possesses prognostic and diagnostic value in Heart failure patients. Much in the same way as BNP has been evaluated, it will be of great value to assess whether uric acid levels change in response to Heart failure therapy in a manner that predicts clinical outcome.

Whether or not uric acid levels are ready for clinical use, the observation that uric acid levels possess prognostic information adds an extremely intriguing finding to mounting evidence that xanthine oxidase and uric acid play pathophysiological roles in Heart failure and its precursor, hypertension. Indeed, the amassing data have led to the planning of a clinical trial entitled A phase II – III prospective, Randomized, Double – Blind, Placebo – Controlled Efficacy and safety study of Oxypurinol Added to

Standard therapy in patients with NYHA class III- IV Congestive Heart Failure (OPT-CHF) initiated in 2003, which will test clinical outcomes using a composite endpoint comprising measures of heart failure morbidity, exercise capacity, and mortality. The findings of Anker and colleagues, therefore, not only bring to light a potentially new diagnostic test but also provide a novel line of evidence that the xanthine oxidase pathway and / or uric acid itself may be of pathophysiological importance in heart failure progression

Materials and Methods

MATERIALS AND METHODS

The study was conducted at Coimbatore medical college hospital, Coimbatore during the period of AUGUST 2008 – JULY 2010.

100 known type 2 diabetics on treatment who were presenting with AMI were included in the study and serially followed up in the intensive care units. Out of 100 patients 54 were males, 46 were female diabetics.

STUDY DESIGN

This is a prospective study design, This study is aimed to assess the prognostic role of metabolic factors serum uric acid, total cholesterol & blood sugar levels following Acute Myocardial Infarction in type 2 DM & correlating their levels with short term complications.

This study included 100 known type 2 diabetics on medications presented with Acute myocardial infarction. This study included 100 type 2 DM patients of Acute Myocardial Infarction of which patient who had a normal Uric acid level were taken as a control and the rest who had elevated Uric acid level were taken up as study population.

In both groups the complications and short term outcome were compared.

INCLUSION CRITERIA :

Patients with previous history of type 2 diabetes with Acute ST ELEVATION Myocardial Infarction were entered into the study. A definite diagnosis of Acute ST Elevation Myocardial Infarction was made if the patients satisfied the following criteria:

1. A History of typical retrosternal compressive chest pain or atypical presentations in type 2 diabetes lasting for more than 30 minutes, not relieved by rest or nitrates.
2. Atypical symptoms,
3. Typical ECG changes of Acute ST Elevation Myocardial Infarction (ST,T changes in two contiguous leads)

EXCLUSION CRITERIA :

1. Patients with elevated renal parameters.
2. Patients with Gout.
3. Patients with History of chronic alcoholism.
4. Patients with previous History of IHD & on Aspirin therapy.
5. Patients with newly diagnosed Diabetes mellitus.
6. Patients with hypertension and patients on Diuretics therapy.
7. Patients with hematological malignancy, hypothyroidism.

Above patients were excluded because the coexisting disease or drug therapy might itself produce a high Uric acid level.

Only patients known to have type 2 diabetes on any one of three therapies namely diet, OHAs or insulin were included.

VARIABLES RECORDED DURING THE STUDY:

Routine History, physical examination, Routine laboratory investigations were performed in all subjects.

1. Presenting History :

- Duration of chest discomfort
- Associated symptoms like sweating, palpitations, dyspnoea.
- Time of onset of symptoms.
- Atypical symptoms,

2. Killip's classification on admission :

3. Admission Electrocardiogram (ECG) :

- Site of infarction : Anterior, Extensive anterior, Inferior, Right ventricular, multiple wall MI
- No of leads with Q waves or ST Elevation.

4. Laboratory Investigations :

- Full Blood count

- Blood Sugar, Blood Urea, Serum creatinine, Serum
- Electrolytes.
- Serum Uric acid level on admission.
- Urine Albumin, Sugar, Deposits.
- Serum cholesterol on admission

Qualifying patients received thrombolytic therapy with 1.5 million units of Streptokinase followed by Heparin for 5 – 7 days.

Assessment of left ventricular ejection fraction by Echocardiography was performed either on day 4 or 5 of hospitalisation in most patients or earlier if clinically indicated.

Immediately after admission blood samples are sent for estimation of serum uric acid, blood sugar and total cholesterol.

Abnormal values were interpreted as follows :

1. HYPERURICEMIA

Males > 7 mgs %

Females > 6 mgs %

2. HYPERGLYCEMIA : Blood sugar > 200 mgs %

3. DYSLIPIDEMIA : Total cholesterol > 240 mgs %

URIC ACID ESTIMATION :

The method used for analysis is Enzymatic method (Uricase method) by using Auto analyser. In our laboratory, values taken as normal range⁶²

For Males : 3.4 - 7.0 mg/dl

For Females : 2.4 - 6.0 mg/dl

METHODOLOGY:

Methods using URICASE, the enzyme that catalyzes the oxidation of uric acid to allantoin are most specific.⁶³ The simplest of these methods measures the differential absorption of uric acid and allantoin at 293 nm.⁶⁴ The difference in absorbance before and after incubation with URICASE is proportional to the uric acid concentration.

This method has been proposed as candidate reference method.⁶⁵ This method was done in our study. This is the most specific method.

Observations and Results

RESULTS AND OBSERVATIONS

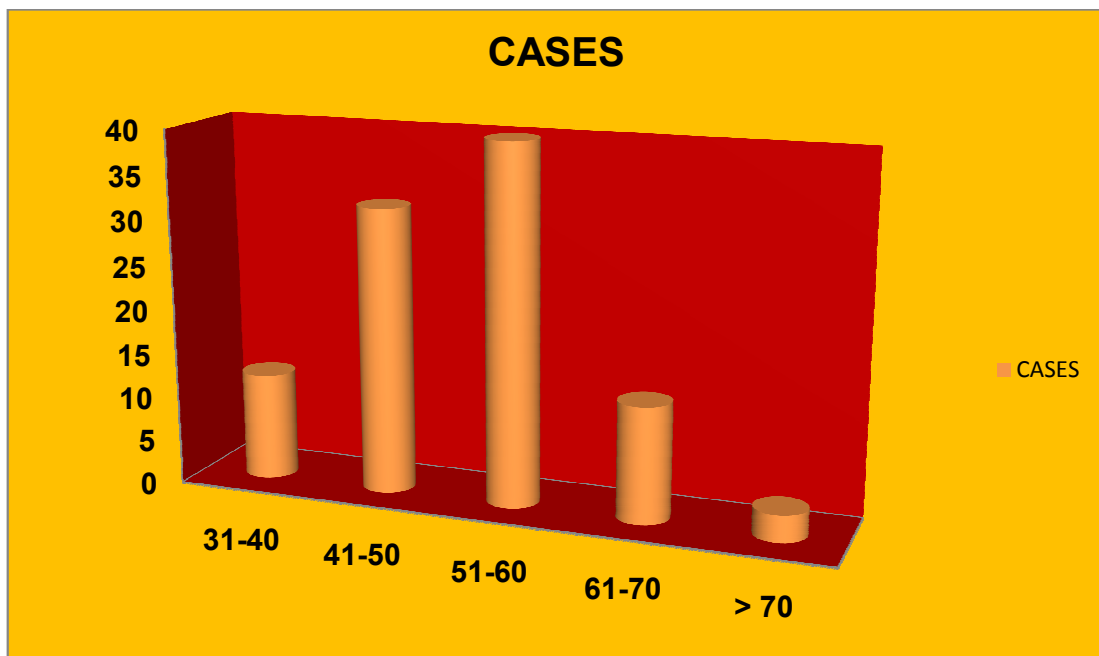
The study population consisted of 100 type 2 diabetic patients with 54 males and 46 females. All patients were admitted in ICCU initially for 5 days cared in adjoining immediate cardiac care ward and discharged after an average period of 10 days provided there were no complications.

The various observations made in this study are depicted below,

AGE INCIDENCE TABLE 1

Age in years	31-40	41-50	51-60	61-70	>70
No of cases	12	32	40	13	3

FIGURE 1

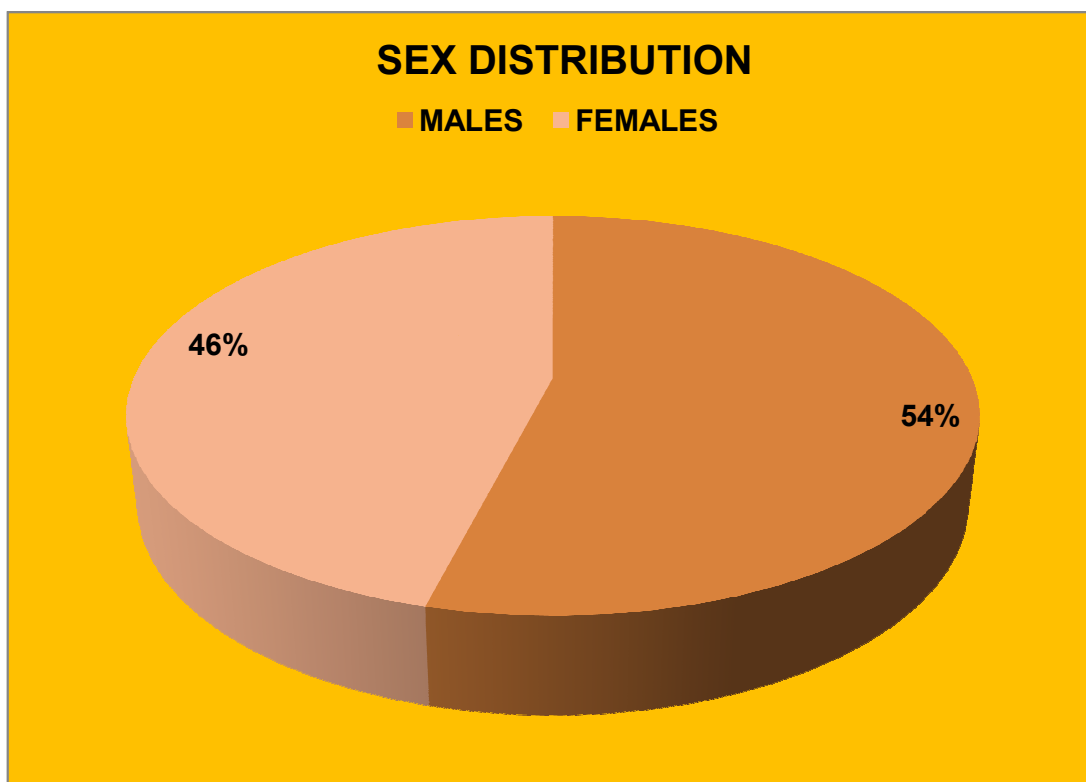


SEX INCIDENCE

TABLE 2

Sex	No of Cases	Percentage
males	54	54
Females	46	46

FIGURE2

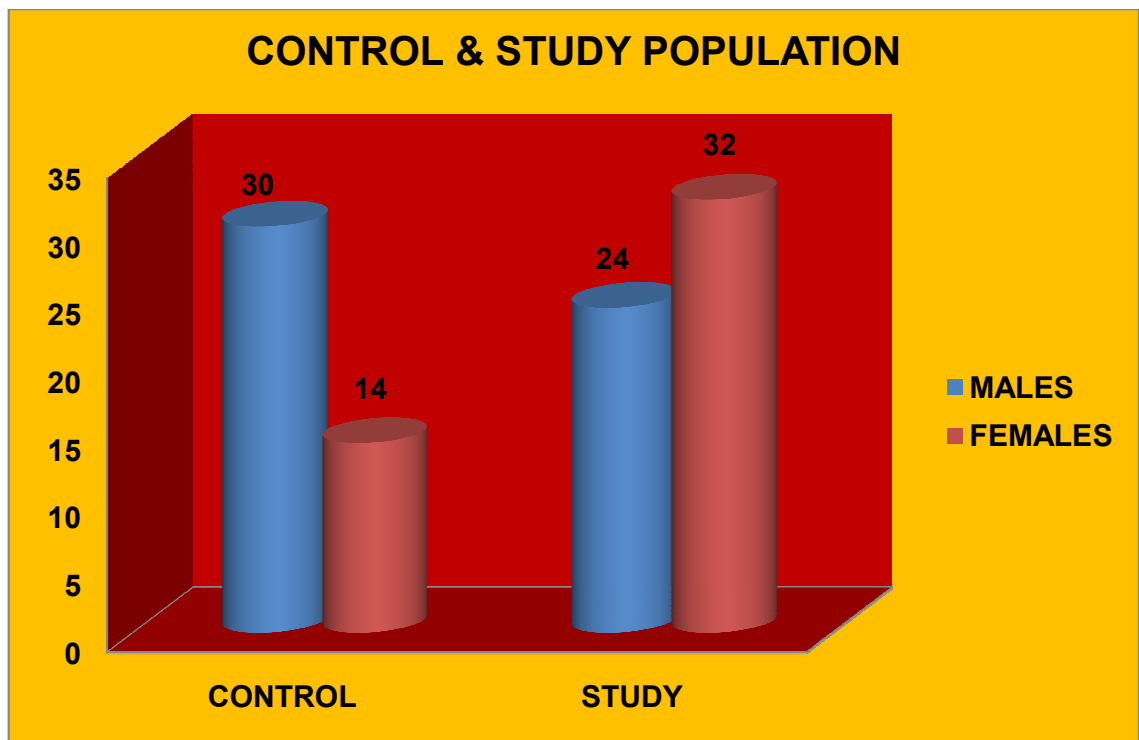


CONTROL AND STUDY POPULATION

TABLE : 3

SEX	CONTROL POPULATION (44)	STUDY POPULATION (56)
MALE	30 (68.2 %)	24 (42.8 %)
FEMALE	14 (31.8 %)	32 (57.2%)

FIGURE 3

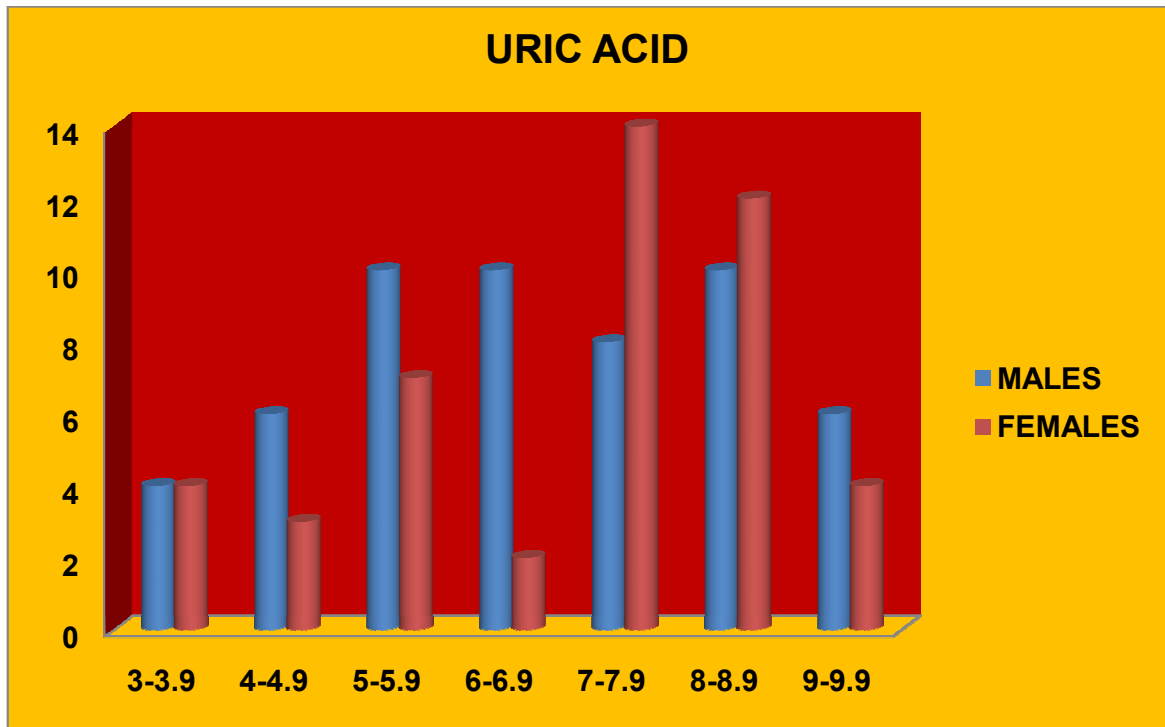


**DISTRIBUTION OF PATIENTS ACCORDING TO URIC ACID
LEVEL & SEX – IN TOTAL POPULATION**

TABLE : 4

Uric acid(mg/dl)	3.0-3.9	4.0-4.9	5.0-5.9	6.0-6.9	7.0-7.9	8.0-8.9	9.0-9.9
Males	4	6	10	10	8	10	6
Females	4	3	7	2	14	12	4

FIGURE 4



STATISTICAL SIGNIFICANCE :

TABLE : 5

URIC ACID VALUES	NO OF CASES	MEAN URIC ACID VALUE	STANDARD DEVIATION	P VALUE (UNPAIRED 't' TEST)
HIGH (STUDY)	56	8.05	0.712	< 0.0001
NORMAL (CONTROL)	44	5.09	1.005	

By using unpaired 't' test, the estimated

't' value = 17.2

Degree of freedom (df) = 98

Standard Error of difference = 0.172

The two-tailed **P VALUE is less than 0.0001**, this difference is considered to be **EXTREMELY STATISTICALLY SIGNIFICANT**.

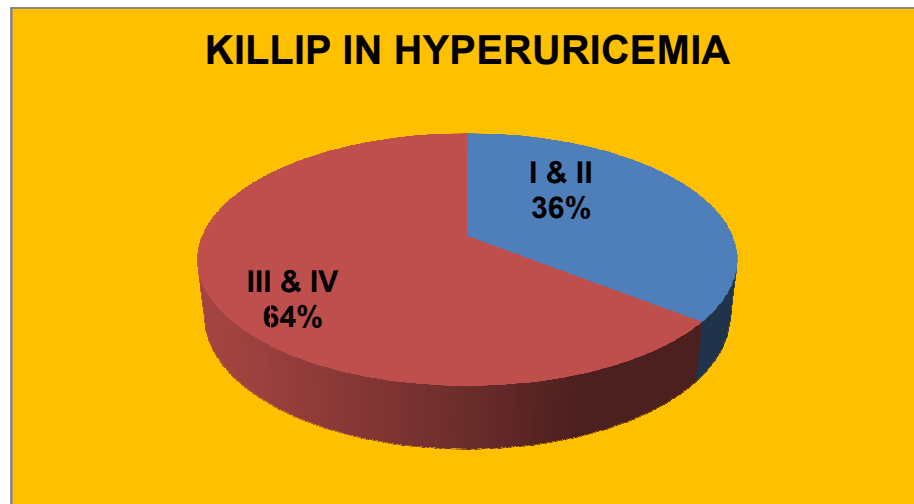
KILLIP CLASS IN HIGH SERUM URIC ACID POPULATION

(STUDY GROUP)

TABLE : 6

Killip Class	I & II	III & IV
No of patients	20	36

FIGURE 5



Percentage of patients with Killip I & II in high serum uric acid population

$$= \frac{20 \times 100}{56} = 35.7\%$$

Percentage of patients with High killip class III & IV in High serum uric acid population

$$= \frac{36 \times 100}{56} = 64.3\%$$

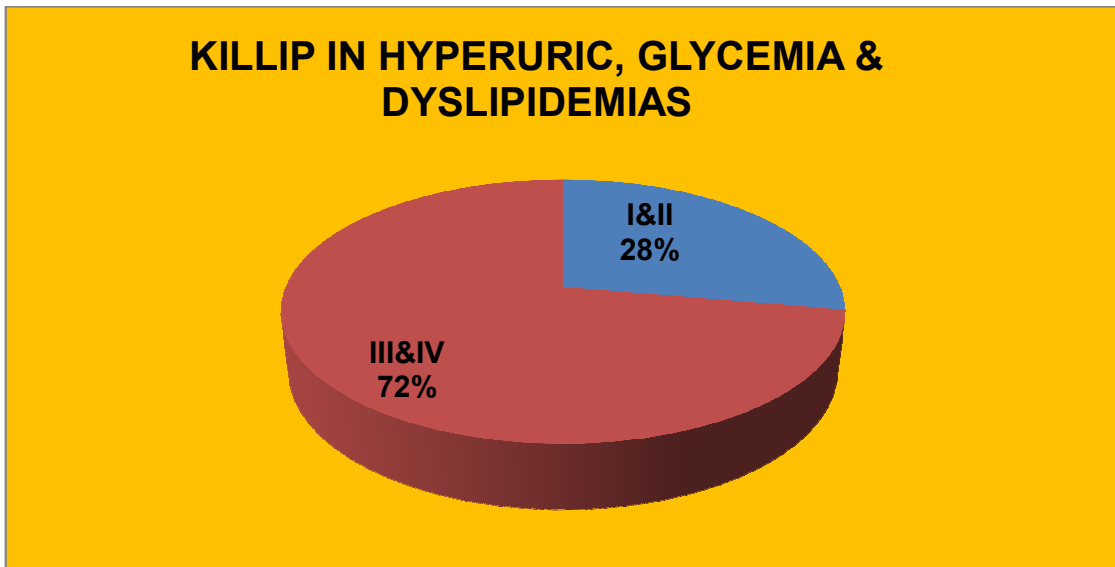
KILLIP CLASS IN CASES WITH CONCURRENT ELEVATION OF URIC ACID, TOTAL CHOLESTEROL AND BLOOD SUGAR.

TOTAL NO OF PATIENTS WITH CONCURRENT HYPERURICEMIA, HYPERGLYCEMIA & DYSLIPIDEMIA IN THIS STUDY : 36

TABLE 7

Killip class	No of Cases
I & II	10
III & IV	26

FIGURE 6



Percentage of patients with Killip I & II in hyperuricemia, hyperglycemia & dyslipidemia

$$= \frac{10 \times 100}{36} = 27.8\%$$

Percentage of patients with killip class III & IV hyperuricemia, hyperglycemia & dyslipidemia

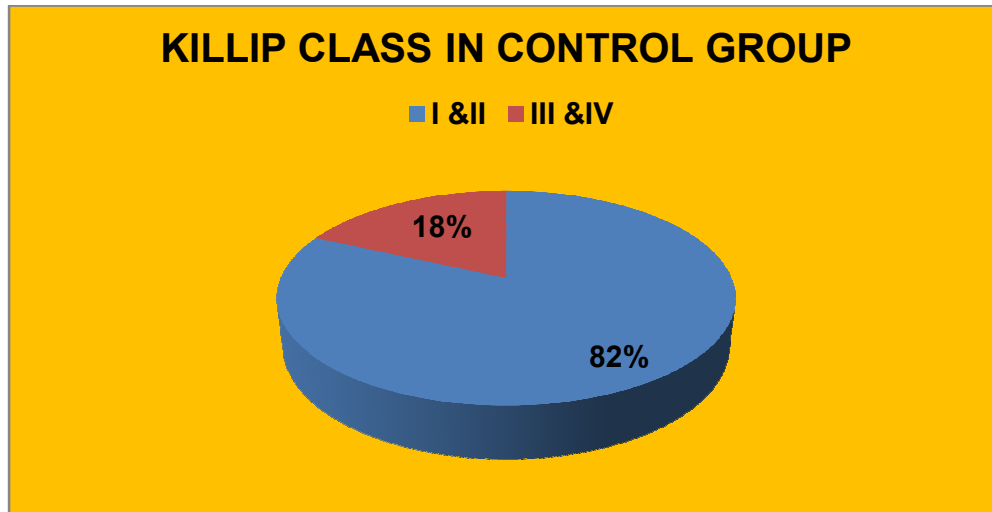
$$= \frac{26 \times 100}{36} = 72.2\%$$

**KILLIP CLASS IN NORMAL SERUM URIC ACID POPULATION
(CONTROL GROUP)**

TABLE : 9

Killip Class	I & II	III & IV
No of Patients	36	8

FIGURE 7



Percentage of patients with Killip I & II in normal uric acid population

$$= \frac{36 \times 100}{44} = 81.8\%$$

Percentage of patients with Killip III & IV in normal uric acid population

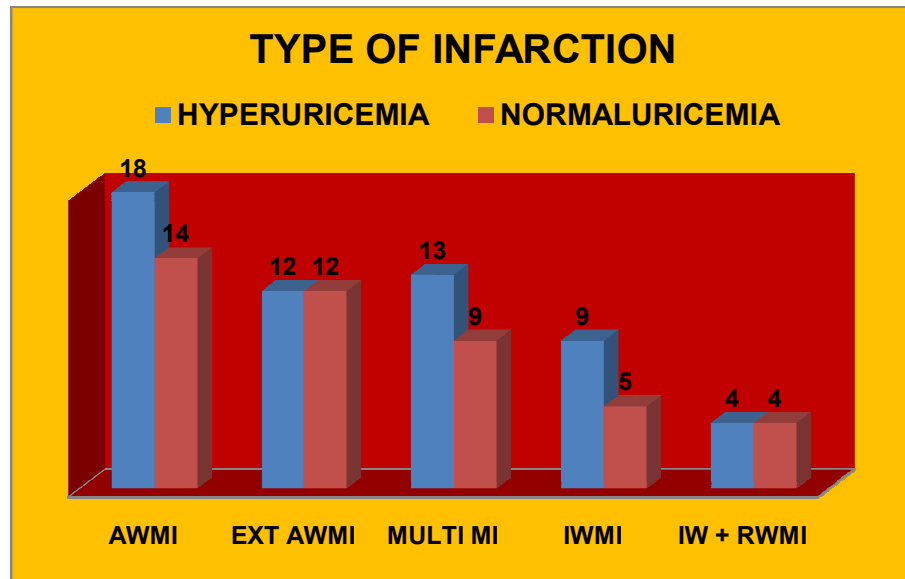
$$= \frac{8 \times 100}{44} = 18.2\%$$

TYPE OF INFARCTION

TABLE : 10

TYPE	IN HIGH SERUM URIC ACID POPULATION	IN NORMAL SERUM URIC ACID POPULATION
AWMI	18	14
EXT AWMI	12	12
MULTI WALL MI	13	9
IWMI	9	5
IWMI + RWMI	4	4
TOTAL	56	44

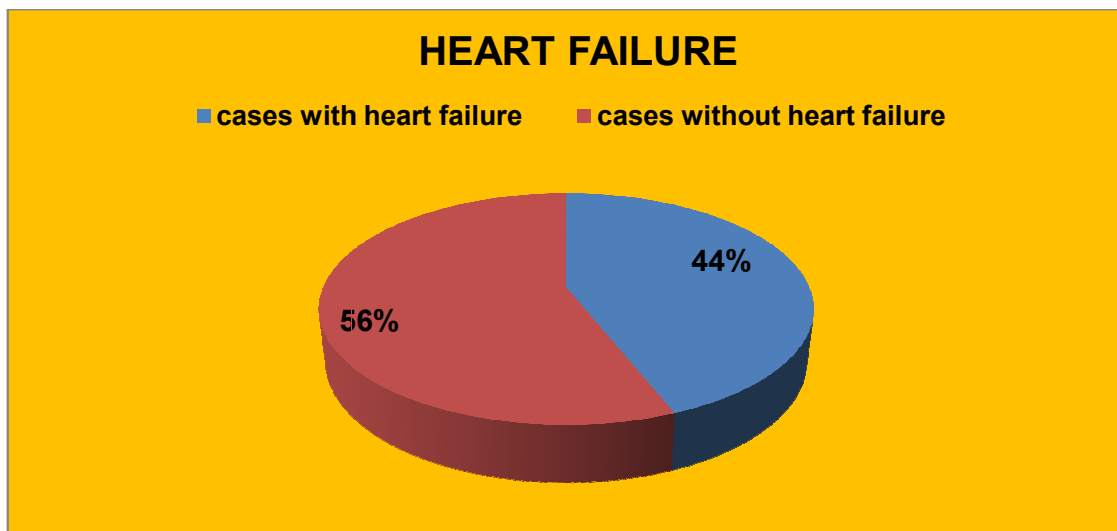
FIGURE 8



**INCIDENCE OF HEART FAILURE IN TOTAL POPULATION
(TABLE : 11 & FIGURE 9)**

Total no of patients studied	No of patients who developed Heart failure
100	44

ie. 44 % of patients in the study developed Heart failure.

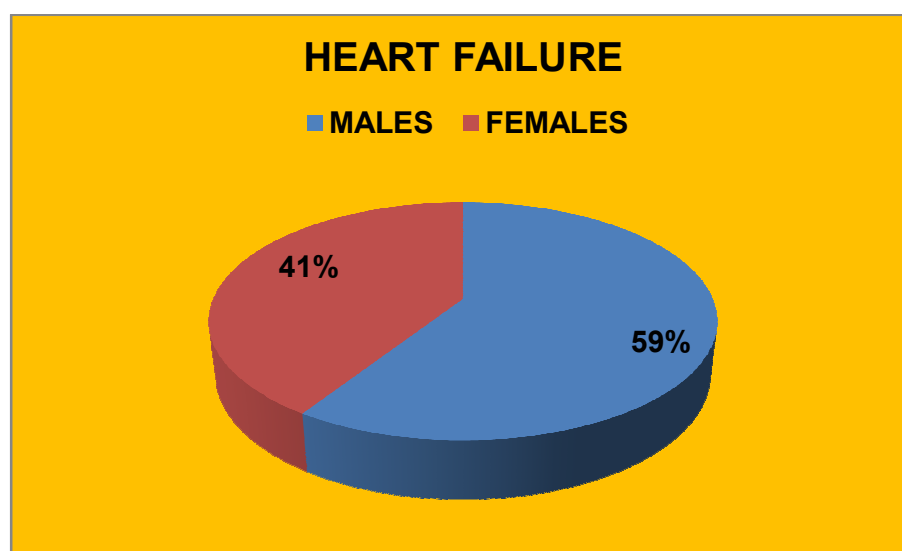


HEART FAILURE ACCORDING TO SEX

(TABLE : 12 & FIGURE 10)

Total no of Heart failure patients	MALES	FEMALES
44	26 (59.09 %)	18 (40.90%)

FIGURE 10

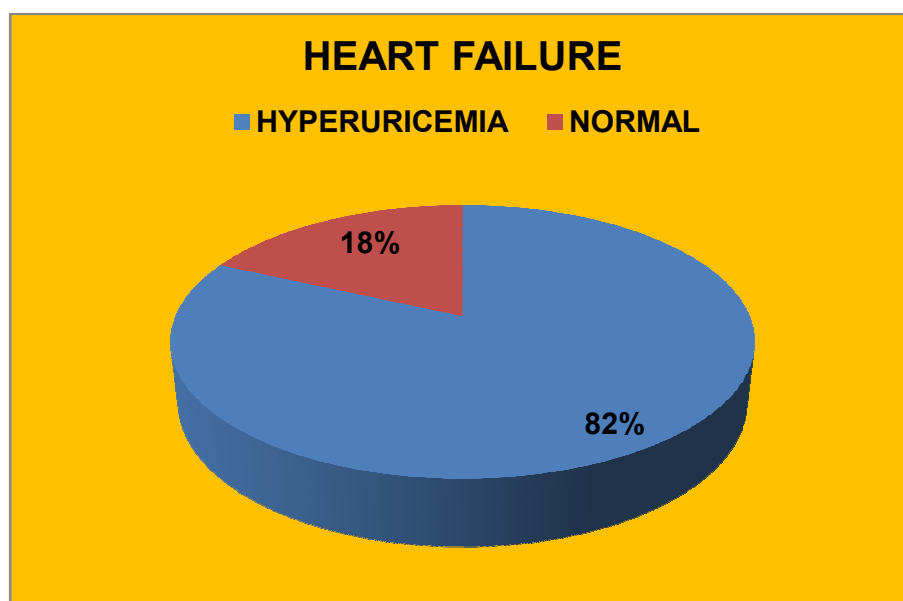


PROPORTION OF HEART FAILURE CONTRIBUTED BY
PATIENTS WITH NORMAL & HIGH SERUM URIC ACID LEVEL

(TABLE : 13 & FIGURE 11)

HEART FAILURE	HYPERURICEMIA	NORMOURICEMIA
44	36	8

FIGURE 11



Contribution of patients with High Serum uric acid level to Heart failure

$$= \frac{36 \times 100}{44} = 82\%$$

Contribution of patients with Normal serum uric acid level to Heart failure

$$= \frac{8 \times 100}{44} = 18\%$$

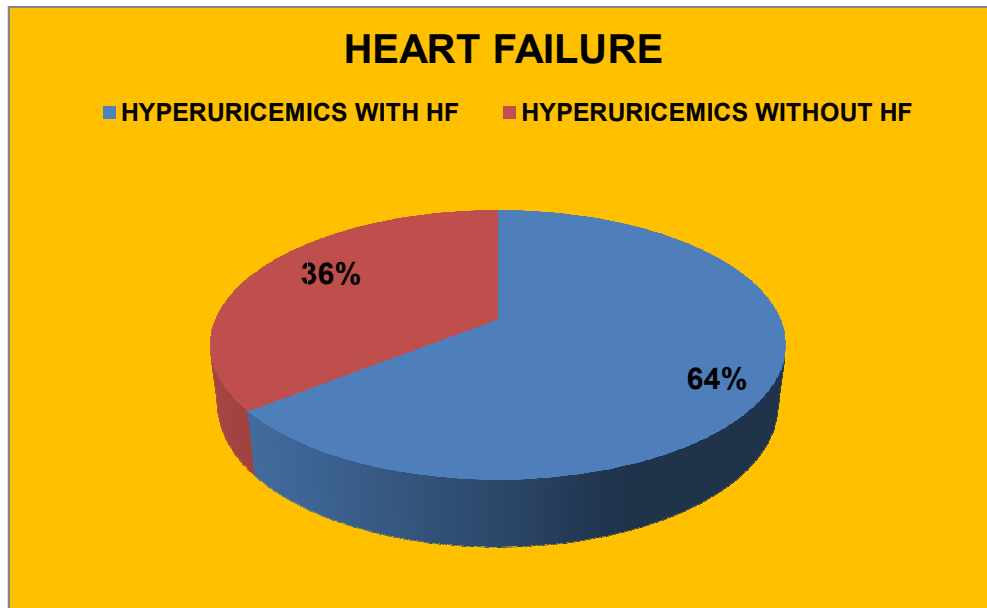
It is observed that patients with high uric acid level contributes 82 % to the total incidence of Heart failure.

**INCIDENCE OF HEART FAILURE IN PATIENTS WITH HIGH
SERUM URIC ACID LEVEL (STUDY GROUP)**

TABLE : 14

No of patients with high serum uric acid level	No of patients with Heart failure
56	36

FIGURE 12



$$Incidence = \frac{36 \times 100}{56} = 64.2\%$$

ie. 64.2% of patients with high uric acid level developed Heart failure. 35.8 % of patients with high uric acid level didn't develop Heart failure.

HEART FAILURE IN HYPERURICEMICS HYPERGLYCEMICS & DYSLIPIDEMICS

TABLE 15

Total no of patients with heart failure	Total no of patients with heart failure hyperurecimia hyperglycemia and dyslipidemia
44	28

$$Incidence = \frac{28 \times 100}{44} = 63.63\%$$

FIGURE 13

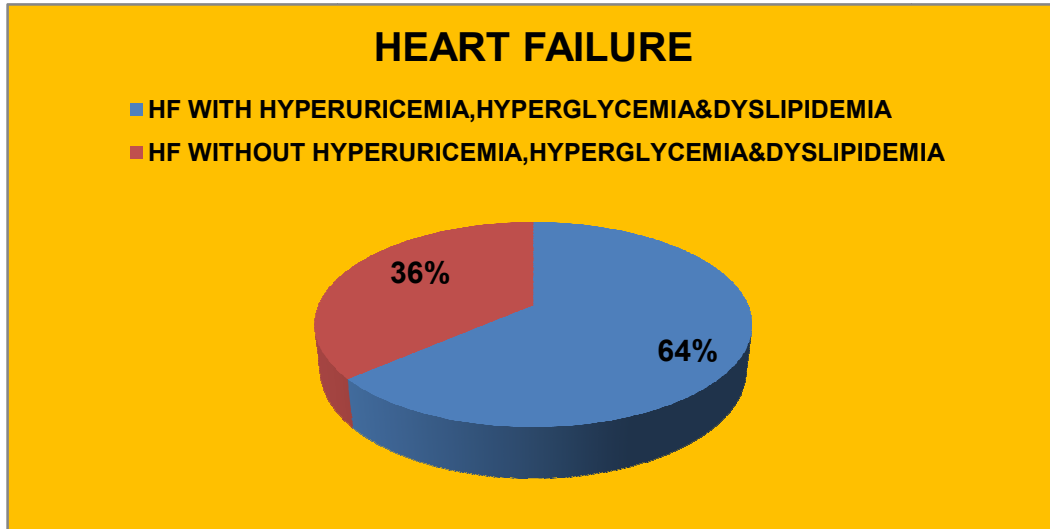
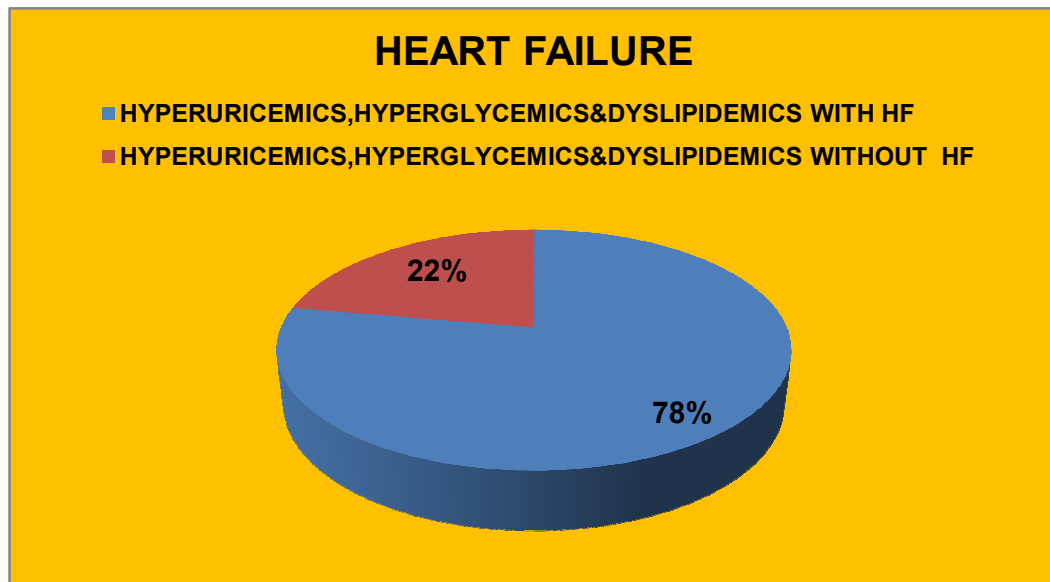


TABLE 16

Total no of patients with hyperuricemia hyperglycemia and dyslipidemia	Total no of patients with heart failure in hyperuricemia, hyperglycemia and dyslipidemia
36	28

FIGURE 14



$$Incidence = \frac{28 \times 100}{36} = 77.8\%$$

**INCIDENCE OF HEART FAILURE IN PATIENTS WITH NORMAL
SERUM URIC ACID LEVEL (CONTROL GROUP)**

TABLE : 17

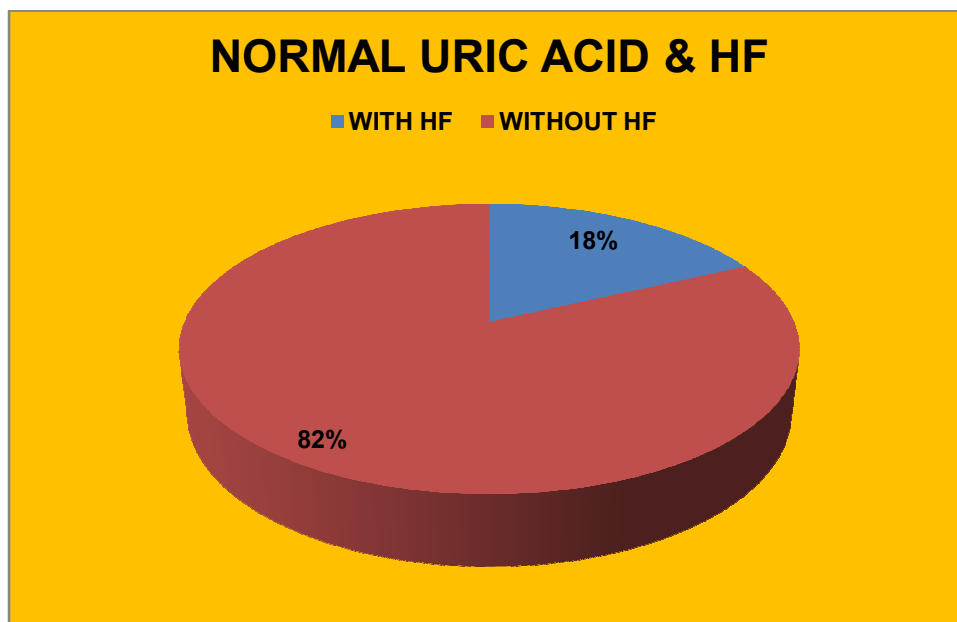
No of patients with normal serum uric acid level	No of patients with Heart failure
44	8

$$Incidence = \frac{8 \times 100}{44} = 18.18\%$$

ie. 18.1% of patients with normal uric acid level developed Heart failure.

Ie. 81.9 % of patients with normal uric acid level didn't develop Heart failure.

FIGURE 15

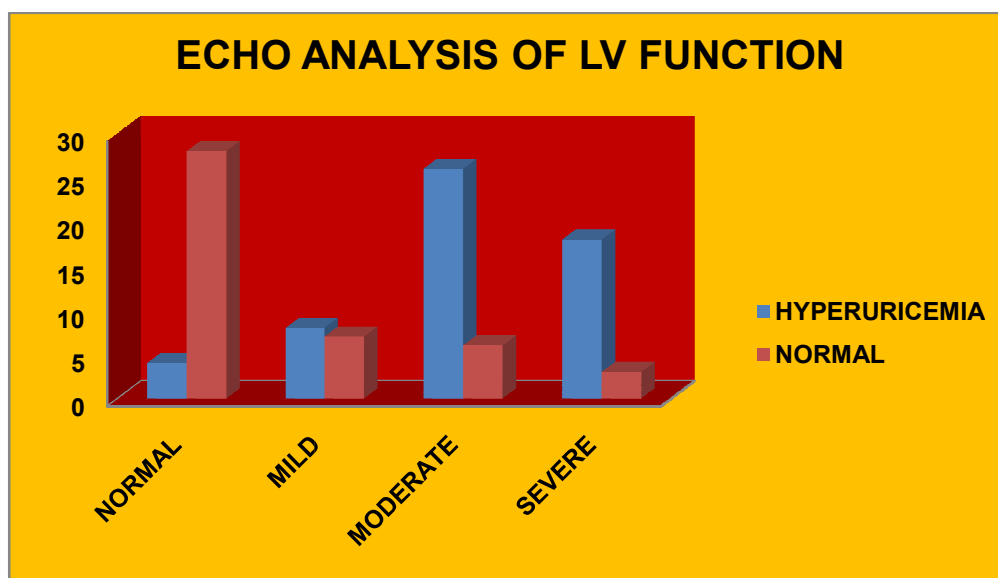


ECHOCARDIOGRAM ANALYSIS

TABLE : 18

Echo findings	In high uric acid Pts (56)	In normal uric acid Pts (44)
Normal LV systolic function	4	28
Mild LV dysfunction	8	7
Moderate LV dysfunction	26	6
Severe LV dysfunction	18	3
Total	56	44

FIGURE 16

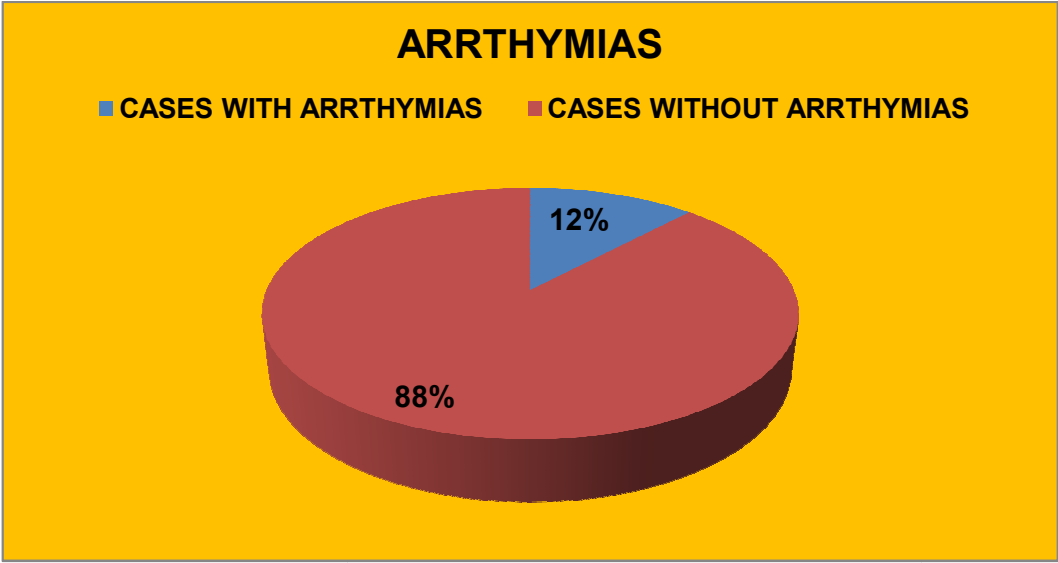


INCIDENCE OF ARRHYTHMIAS (IN TOTAL POPULATION)

TABLE : 19 & FIGURE 17

Total no of patients studied	Cases with Arrhythmias
100	12

ie.12 % of patients in the study developed Arrhythmias.

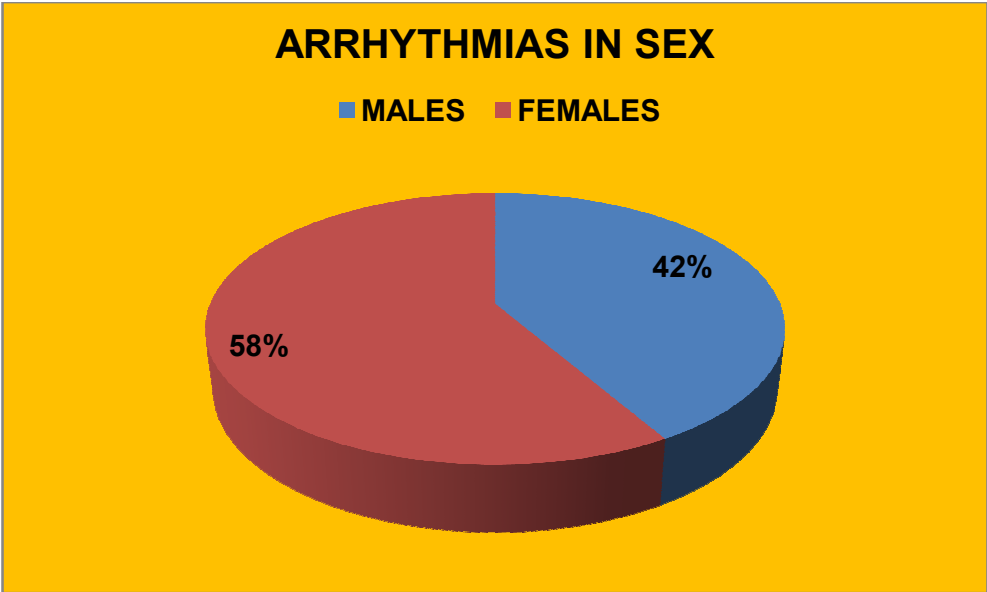


ARRHYTHMIAS ACCORDING TO SEX

TABLE : 20

CASES WITH ARRHYTHMIAS	MALES	FEMALES
12	5(41.7%)	7(58.3%)

FIGURE 18

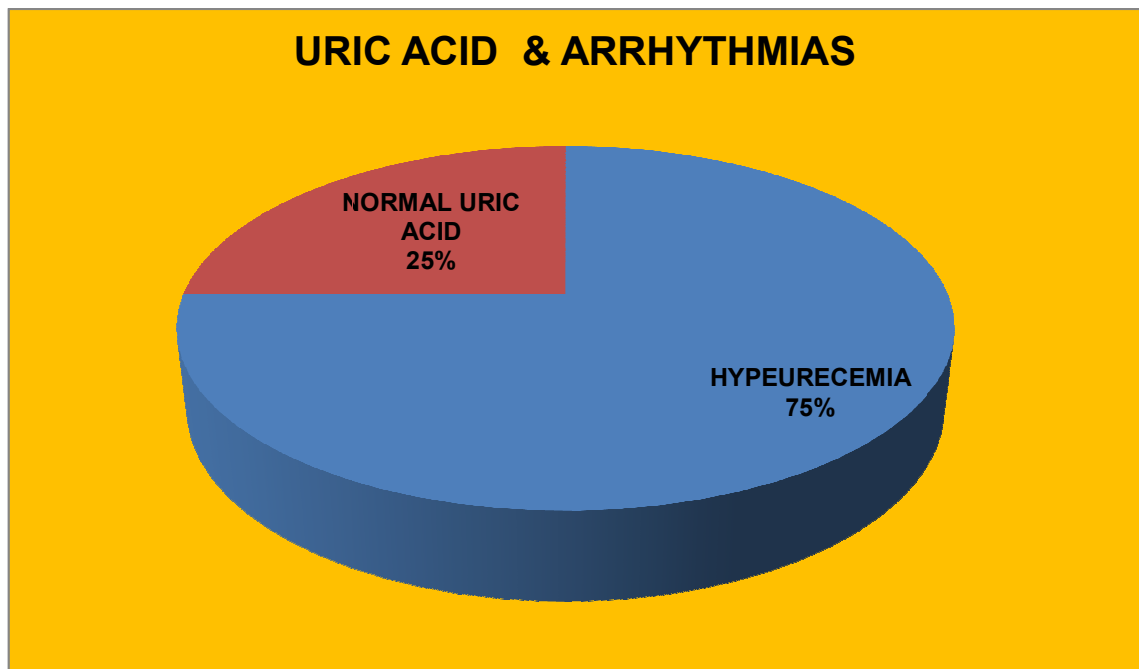


**PROPORTION OF ARRHYTHMIAS CONTRIBUTED BY
PATIENTS WITH NORMAL & HIGH SERUM URIC ACID LEVEL**

TABLE : 21

Total no of patients with Arrhythmias	No of patients with high serum uric acid	No of patients with normal serum uric acid
12	9	3

FIGURE 19



Contribution of patients with High serum uric acid level to Arrhythmias

$$= \frac{9 \times 100}{12} = 75\%$$

Contribution of patients with Normal serum uric acid level to Arrhythmias

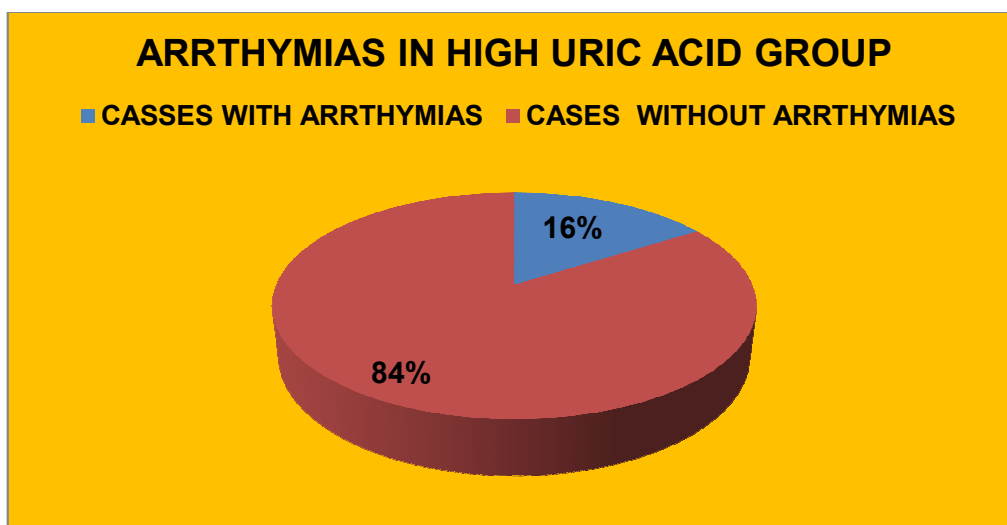
$$= \frac{3 \times 100}{12} = 25\%$$

**INCIDENCE OF ARRHYTHMIAS IN PATIENTS WITH HIGH
SERUM URIC ACID LEVEL (STUDY GROUP)**

TABLE : 22

No of patients with high serum uric acid levels	No of patients with Arrhythmias
56	9

FIGURE 20



$$Incidence = \frac{9 \times 100}{56} = 16\%$$

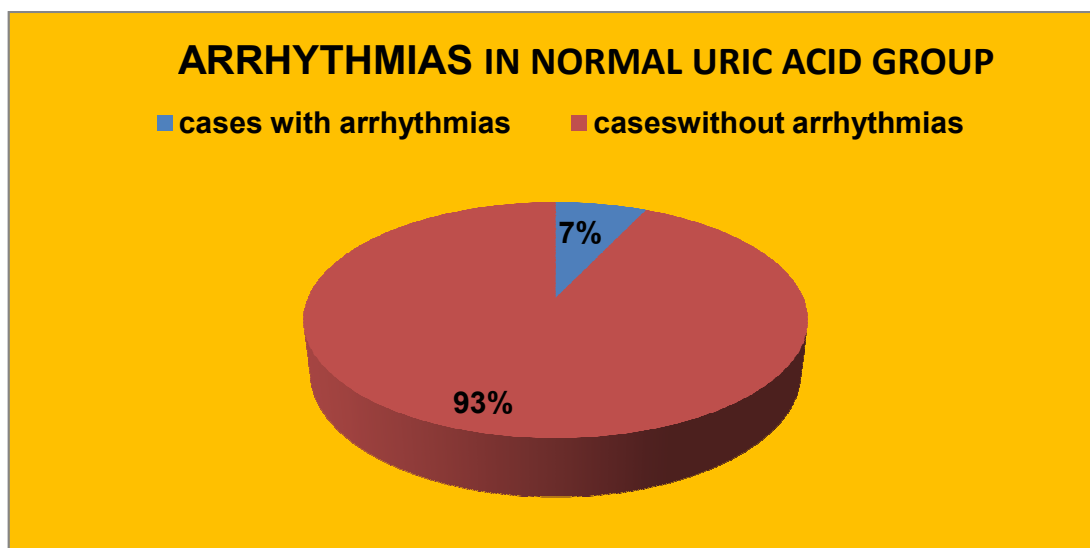
ie. 16 % of patients with high uric acid level developed Arrhythmias.

**INCIDENCE OF ARRHYTHMIAS IN PATIENTS WITH NORMAL
URIC ACID LEVEL (CONTROL GROUP)**

TABLE : 23

No of patients with normal uric acid	No of patients with Arrhythmias
44	3

FIGURE 21



$$Incidence = \frac{3 \times 100}{44} = 6.8\%$$

ie. ONLY 6.8 % of patients with normal uric acid level developed Arrhythmias.

INCIDENCE OF MORTALITY (IN TOTAL POPULATION)

TABLE : 24

Total no of patients studied	No of patients died
100	15

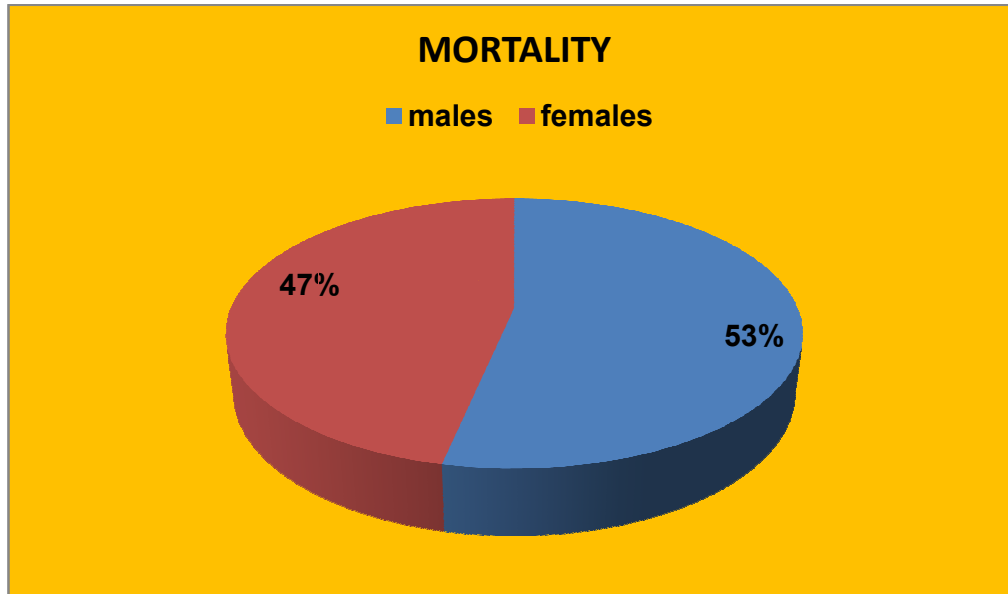
ie, 15 % of patients in the study died

MORTALITY ACCORDING TO SEX

TABLE : 25

Total no of deaths	Male (%)	Female (%)
15	8(53.3%)	7 (46.7%)

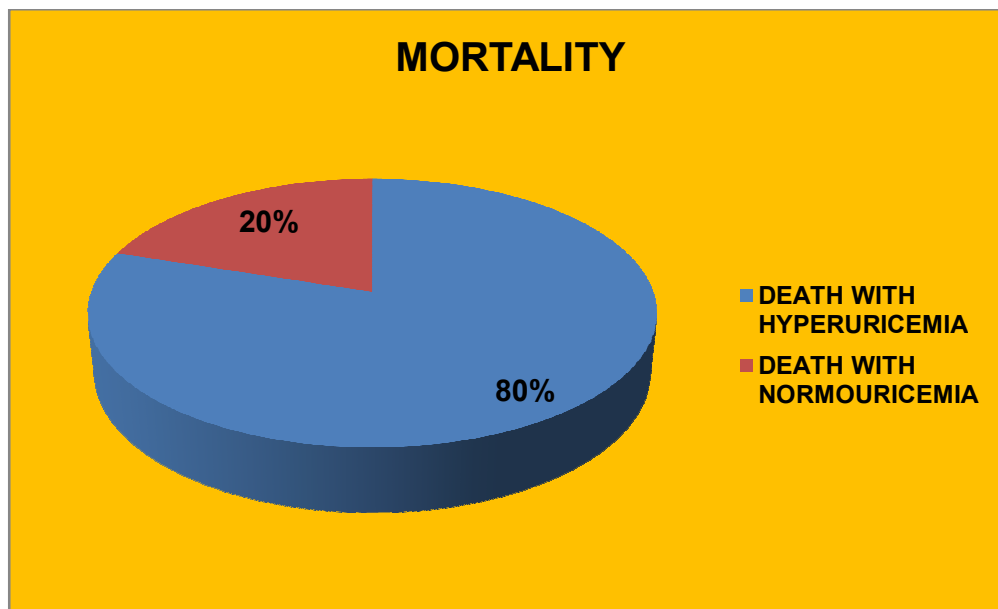
FIGURE 22



PROPORTION OF MORTALITY CONTRIBUTED BY PATIENTS WITH NORMAL & HIGH SERUM URIC ACID LEVEL Table : 26

TOTAL NO OF DEATHS	HYPERURICEMIA	NORMAL
15	12	3

FIGURE 24



Contribution of patients with High serum uric acid level to Mortality

$$= \frac{12 \times 100}{15} = 80\%$$

Contribution of patients with Normal serum uric acid level to Mortality

$$= \frac{3 \times 100}{15} = 20\%$$

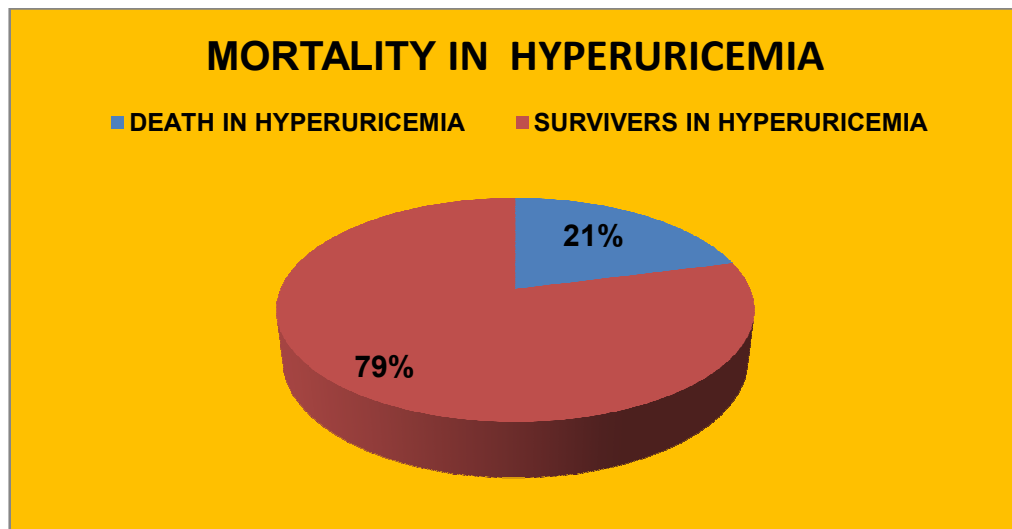
It is observed that patients with high uric acid level contributes 80% to the total incidence of mortality.

INCIDENCE OF MORTALITY IN PATIENTS WITH HIGH SERUM URIC ACID LEVEL (STUDY GROUP)

TABLE : 27

No of patients with high serum uric acid level	No of deaths
56	12

FIGURE 25



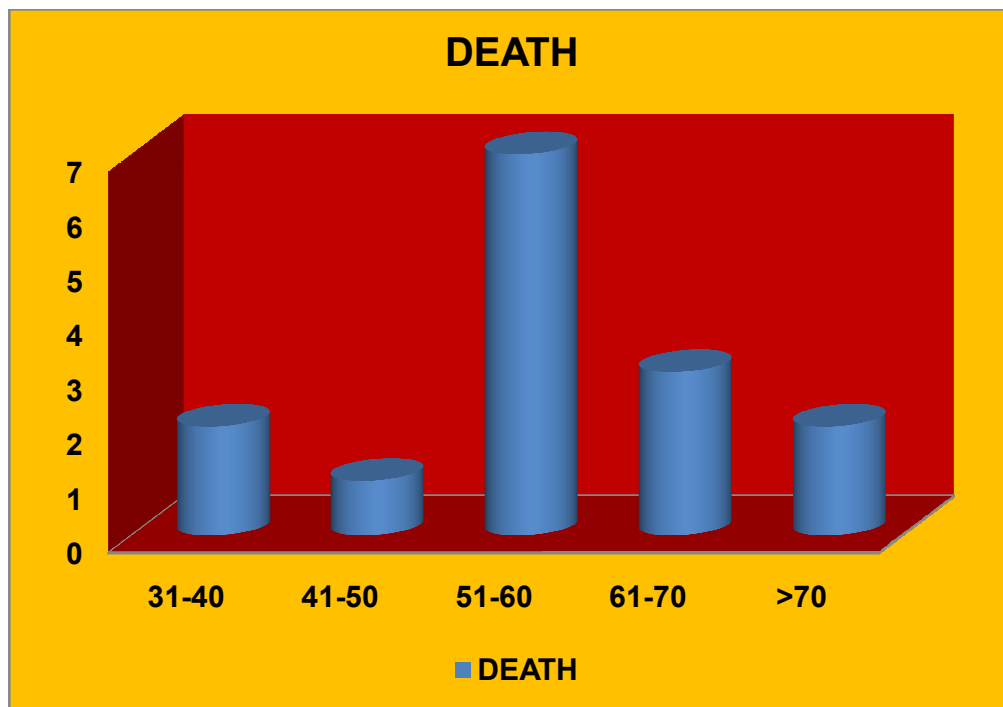
$$Incidence = \frac{12 \times 100}{56} = 21.4\%$$

ie. 21.4 % of patients with high uric acid level died in the study.

MORTALITY IN AGE GROUP TABLE 28

Age	Total No of Patients
31-40	2
41-50	1
51-60	7
61-70	3
>70	2

FIGURE 26

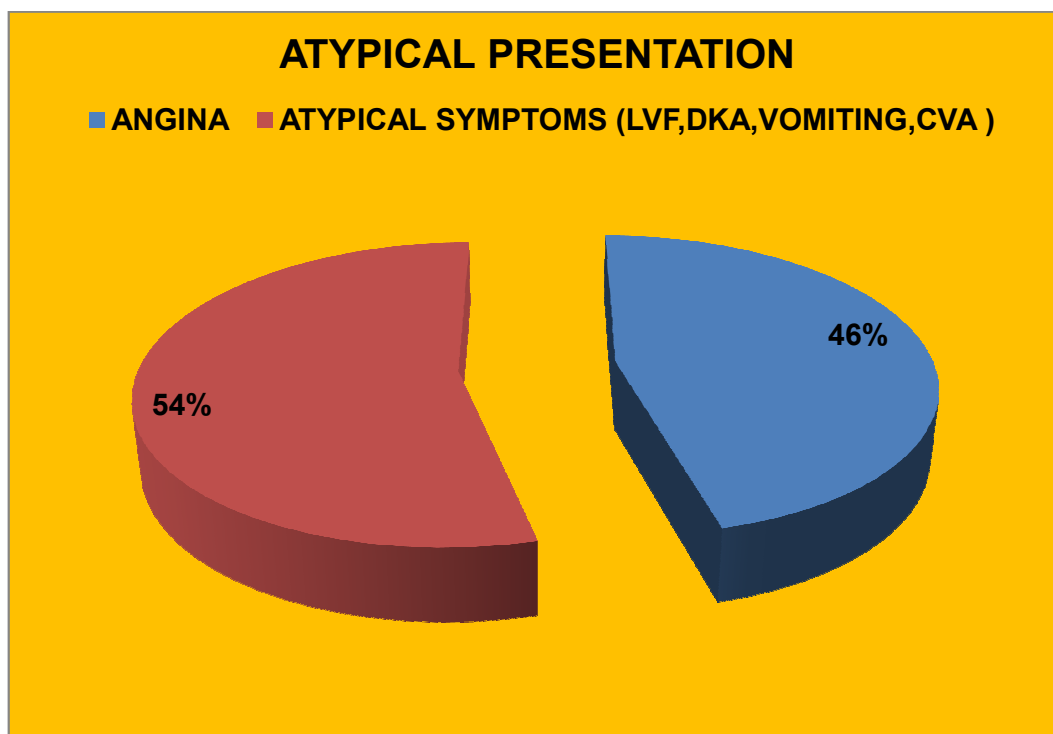


PATIENTS PRESENTATION ON ADMISSION

TABLE 29

SL NO	DISTRIBTION OF SYMPTOMS	NO OF CASES	PERCENTAGE
1	TYPICAL CHEST PAIN	46	46
2	ATYPICAL SYMPTOMS	54	54

FIGURE 27



Discussion

DISCUSSION

Total number of type 2 Diabetic patients included in this study were 100, out of 100 patients 56 cases had elevated uric acid, 36 had concurrent elevation of serum uric acid, blood sugar, and total cholesterol above normal range following myocardial infarction.

AGE :

Of the 100 patients studied 12 patients were in the age group of 21-30 years, 32 patients were in the age group of 41-50 years, 40 patients were in the age group of 51-60 years, 13 patients were in the age group of 61-70 years, 3 patients were more than 70 years of old (Table 1 & figure 1)

SEX :

In this study no of male patients were 54 patients, no of female patients were 46 (table 2 & figure 2)

CONTROL & STUDY POPULATION:

Out of 100 patients studied 44 patients had Normal uric acid level and they were taken up as control. Of which 30 (68.2 %) were males and 14 (31.8%) were females The rest 56 patients had elevated uric acid level and they were taken up as study group. Of which 24 (42.8%) were males and 32 (57.2 %) were females . (Table 3 & Fig : 3). Mean uric acid value & standard

deviation for the study group are 8.1 & 0.56. Mean uric acid value and standard deviation for the control group is 4.8 & 1.03. The estimated P value using unpaired t test is <0.0001 . So this is statistically very significant. Both were compared with various outcomes.

CLINICAL STATUS- KILLIP CLASS & URIC ACID:

In this study 32 patients presented with Killip class I, 24 patients presented with Killip class II, 28 patients presented with Killip class III, 16 patients presented with Killip class IV. Killip class III & IV were taken as high risk category in this study and evaluated whether high uric acid concentration after myocardial infarction correlated with this high risk Killip class.

When clinical status of patients based on Killip class I to IV and uric acid were analysed, the following observations were made. In the control group who had normal serum uric acid level, 81.8 % belonged to I & II Killip class and only 18.2 % belonged to Killip class III & IV as against the study group 35.7 % Killip class I & II and 64.3 % Killip class III & IV which parallelly associates with the elevated uric acid level and the clinical status (Table 6 & 7, fig 5 & 6).

Our study correlates with Kojima S, Sakamoto et al., (American journal of cardiology, 2005 Aug 15) who also showed patients who had high

uric acid level belonged to higher Killip class. Hence uric acid can also be used as an predictor of prognosis, but also a predictor of severity. Moreover incidence of killip class III & IV in cases with concurrent hyperuricemia, hyperglycemia & dyslipidemia is 72.3 % compared with 64.3 % with study group ,so that concurrent elevation of uric acid,sugar & cholesterol significantly increases morbidity.

TYPE OF INFARCTION & URIC ACID :

In this study 32 patients presented with Anterior Wall Myocardial Infarction (AWMI) of which 18 patients had high uric acid level, 22 patients presented with Ext AWMI , of which 12 patients had high uric acid level, 22 presented with multiple wall MI, of which 13 patients had high uric acid level, 14 patients presented with Inferior Wall Myocardial Infarction (IWMI), of which 9 patients had high uric acid level , 8 patients presented with inferior and Right Ventricular Myocardial Infarction (RVMI), of which 4 patients had high uric acid level. When areas of infarction and uric acid levels were observed, an increased level of uric acid in Anterior wall Myocardial Infarction was noted. This cannot be taken into statistical account, because the overall incidence of Anterior Wall Myocardial Infarction itself was high. (Table 10 & FIGURE 8).

HEART FAILURE :

44 out of 100 patients in this study had Heart failure in the post Myocardial Infarction period. So the incidence of heart failure was 44 %. Of which 26 (59 %) were males, 18 (41 %) were females.(Table 11 & 12, Fig 9&10). It was observed that among 44 Heart failure patients, 36 patients had high uric acid level and 8 patients had normal uric acid level, 28 cases had concurrent high uric acid,sugar & cholesterol levels. So patients who had high uric acid level and normal uric acid level contributed to 82 %and 18 % respectively to Heart failure. (Table 10, Fig. 10)

It was also found that 36 patients out of 56 patients with high uric acid level had Heart failure amounting to an incidence of 64.2 % Heart failure in this group. While only 8 out of 44 patients with normal uric acid level had Heart failure. ie. Only 18.1 % of patients with normal uric acid level had Heart failure. (Table 13,14,15,16 & 17 & fig 11,12,13, 14 & 15).

The above figures suggest that the occurrence of Heart failure is high in patients with high uric acid level. Moreover incidence of heart failure in cases with concurrent elevation of uric acid, sugar, cholesterol is 77.8 %.concurrent elevation of serum uric acid along with blood sugar & total cholesterol predicts short term outcome. Our studies comparable with other studies who showed similar findings and elevated serum uric acid level is an early predictor of short term outcome. Kojima S. Sakamoto et al, (American

journal of cardiology 2005 Aug 15) Anker SD, Doehner W et.al., (Circulation 2003, Apr 22; circulation 2003 Nov 25) Sakai H, Tsutamoto T et. al.,(J cardiol.2006 May), Joshua M, Hare MD et.al., (circulation 2003, American Heart association), Virendra singh, RK Goyal et.al., (Journal of the Indian Medical association 1977 Sep 1) studies support this study. Their studies revealed that serum uric acid level reflects circulatory xanthine oxidase activity and oxidative stress production. Increased serum uric acid level along with sugar & cholesterol has been identified in patients who have congestive cardiac failure and is a marker of poor prognosis in such patients.

ECHOCARDIOGRAM:

In high uric acid population, 4 patients had normal LV function, 8 patients had mild LV dysfunction, 26 patients had moderate LV dysfunction, 18 patients had severe LV dysfunction. In normal uric acid level population, 28 patients had normal LV function, 7 patients had mild LV dysfunction, 6 patients had moderate LV dysfunction, 3 patients had severe LV dysfunction. (Table 18, Fig 16). So serum uric acid level can also be associated with Echocardiographic cardiac dysfunction later, retrospectively with clinical findings earlier.

So uric acid level can be used as a definite predictor of cardiac failure.

ARRHYTHMIAS :

12 out of 100 patients developed Arrhythmias in this study. So the incidence of Arrhythmias was 12 % of which 5 (41.7 %) were males, 7 (58.3 %) was female. 4 patients had ventricular tachycardia and 6 patients had heart block & 2 had supraventricular tachycardia (Table 19 & 20, Fig 17&18).

It was observed that among 12 Arrhythmias 9 patients had high uric level and 3 patients had normal uric acid level. So patients who had high uric acid level and normal uric acid level contributed to 75 % and 25 % respectively to Arrhythmias (Table 21 , Fig 19) .

It was also found that 9 patients out of 56 patients with high uric acid level had Arrhythmias amounting to an incidence of 16 % Arrhythmias in this group. While only 3 out of 44 patients with normal uric acid level had Arrhythmias. ie. only 6.8 % of patients with normal uric acid level had Arrhythmias. (Table 22&23, Fig 20 & 21).

The above findings suggest that the occurrence of Arrhythmias is also high in patients with high uric acid level. This observation can be matched with the outcome of a large randomized double blind placebo control clinical trial “Oxypurinol therapy for CHF” conducted in 2003, which could establish a beneficial effect for oxypurinol in reducing the incidence of

Arrhythmias and other adverse cardiac events by lowering serum uric acid level. The above trial & our trial tells there is a high incidence of Arrhythmias when there is an elevated serum uric acid level and it is hypothetical an increased uric acid level may be arrhythmogenic. Further studies are needed to conclude.

MORTALITY :

15 out of 100 patients died due to their cardiac ailments in this study. This amounts to mortality rate of 15% of which 8 (53.3%) were males, 7 (46.7 %) was female. (Table 24&25, Fig 22&23). To find out the prognostic significance of elevated uric acid level following Acute Myocardial Infarction, mortality rate in patients with normal and high uric acid level were separately calculated. It was observed that among 15 deaths 12 deaths were contributed by patients with high uric acid levels and 3 deaths by those who had normal uric acid levels. Thus 80% of death in post infarction period occurred in those who had a high uric acid level and only 20% in those who had a normal uric acid level. (Table 26 & Fig 24)

It was also found that 12 out of 56 patients with high uric acid level died. This implies a mortality rate of 21.4 %. Like wise a mortality rate of 6.8 % was observed for patients with normal uric acid level following Myocardial Infarction (Table 27, Fig 25). This striking difference in the mortality figures for both group of patients implies uric acid level can be

used as a predictor of mortality following Myocardial Infarction. Out of 15 deaths, 2 patients in the age group of 31-40 years, 1 patient was in the age group of 41-50 years, 7 patients were in the age group of 51-60 years, 3 patients were in the age group of 61-70 years, 2 patients was in the >70 years. (Table 28, Fig 26)

Kojima S, Sakamoto et. al.,(American journal of cardiology 2005 Aug 15) Fang J, Alderman M H et. al., (Serum uric acid and cardiovascular mortality, JAMA 2000) Bengtsson C, Lapidus L et.al., (Acta Med Scand 1998) Freedman DS, Williamson DF et.al., (Relation of serum uric acid to mortality and Ischemic Heart disease Am. J. Epidemiol 1995) Culleton BF, Lasonmia et.al ., (Serum uric acid and risk of cardiovascular disease and death Ann. Intern. Med July 6. 1999) studies supports this study. This study revealed that patients who developed short term adverse events like mortality following Myocardial Infarction had high uric acid concentrations. Our study also parallels with previous authors and uric acid can be used as a good predictor of mortality.

ATYPICAL PRESENTATION :

In the study only 46 patients presented with classical anginal pain. So atypical presentation of myocardial infarction were more common in type 2 diabetes (table 29 & 27).

Conclusion

CONCLUSION

1. Measuring serum Uric acid level along with sugar & cholesterol is one of the predictable prognostic indicators in Acute Myocardial Infarction and one of the early and short term predictor.
2. A high serum Uric acid level associated with short term mortality in Acute Myocardial Infarction.
3. .Atypical presentation in myocardial infarction were much more common in diabetic patients.
4. Elevated serum Uric acid is strongly associated with cardiac Arrhythmias as against controls and can be used as an immediate prognostic indicator in Acute Myocardial Infarction.
5. Elevated serum Uric acid level may be Arrhythmogenic. Further studies require to confirm and to treat.
6. There is a strong association of elevated serum Uric acid and cardiac failure.
7. Patients with high Uric acid level belonged to higher Killip class status (III & IV) .

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Appendix

ABBREVIATIONS

MI	-	MYOCARDIAL INFARCTION
IHD	-	ISCHEMIC HEART DISEASE
DM	-	DIABETES MELLITUS
UA	-	URIC ACID
TC	-	TOTL CHOLESTEROL
RBS	-	RANDOM BLOOD SUGAR
HDL	-	HIGH DENSITY LIPOPROTEIN
LDL	-	LOW DENSITY LIPOPROTEIN
SD	-	STANDARD DEVIATION
STEMI	-	ST ELEVATION MYOCARDIAL INFARCTION
CK-MB	-	CREATINE KINASE MB
HF	-	HEART FAILURE
BNP	-	BRAIN NATRIURITIC PEPTIDE

ANNEXURE

CERTIFICATE OF CONSENT

I have been invited to participate in research on “Metabolic factors and their impact on prognosis and early complications of acute myocardial infarction in type 2 diabetes mellitus (serum uric acid , blood sugar & total cholesterol)”. I understand that it will involve answering a detailed questionnaire, undergoing a thorough physical exam, giving blood samples .I have been informed that the risks are minimal and may include only slight pain and redness at sight of needle prick. I am aware that there may be no benefit to me personally and that I will not be compensated monetarily. I have been provided with the name of a researcher who can be easily contacted using the number and address I was given for that person.. I have had the opportunity to ask questions about it and any questions I have asked have been answered to my satisfaction. I consent voluntarily to participate as a participant in this research and understand that I have the right to withdraw from the research at anytime without in anyway affecting my medical care.

Name of the participant : _____

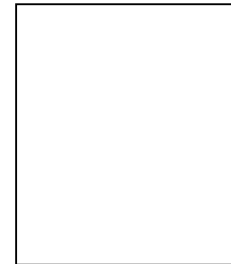
Signature of the participant : _____

Date : _____

If illiterate, a witness must sign (if possible, this person should be selected by the participant and must have no connection to the research team).

I have witnessed the accurate reading of the consent form to the potential participant, translated to his/ her mother tongue , and the individual has had opportunity to ask questions. I confirm that the individual has given the consent freely.

Name of witness : _____ AND Thumb print of participant
Signature of witness: _____
Date : _____



(Day/Month/Year)

I have accurately read or witnessed the accurate reading of the consent form to the potential participant, I confirm that the individual has given the consent freely.

Name of the researcher :
Signature of the researcher with date :

PROFORMA

NAME : AGE : SEX: OCCUPATION : I.P.NO:

ADDRESS : D.O.A : D.O.D :

SYMPTOMS AT THE TIME OF ADMISSION:

CHEST PAIN, DYSPNOEA, SWEATING, PALPITATIONS

OLIGURIA PAIN & SWELLING IN JOINTS

PAST HISTORY :

RENAL DISEASE GOUT CHRONIC ALCOHOLISM

IHD DIABETES ASPIRIN & DIURETIC THERAPHY

ECG :

KILLIP'S CLASSIFICATION : I II III IV

THROMBOLYSED : NOT THROMBOLYSED :

CLINICAL EXAMINATION :

a. PR :

b. BP :

c. JVP elevation : Yes / No

d. Pedal edema : Yes / No

e. Basal Rales : Yes / No

INVESTIGATIONS :

a. Hb % : b. TC : c. DC : d. URINE : ALB : SUGAR : DEPOSITS :

e. BLOOD SUGAR : f. BLOOD UREA:

g. SERUM CREATININE : h. SERUM ELECTROLYTES : Na⁺ : K⁺ :

i. SERUM URIC ACID LEVEL ON ADMISSION : j. SERUM CHOLESTEROL k.

ECHOCARDIOGRAM :

ADVERSE CARDIAC EVENTS:

a. CARDIAC FAILURE :

b. ARRHYTHMIAS

c. SHOCK

d. DEATH

f. HOSPITAL STAY

MASTER CHART

S.No	AGE	SEX	ANGINA	VOMITIN	GIDDINES	DKA	CVA	LVF	URIC ACID	GLUCOSE	CHOLEST	AWMI	EX AWMI	MUL MI	IWMI	IW+RWMI	KIL I & II	KIL III & IV	HF	ECHO	ARRTHY	DEATH
1	43	F	Y	N	N	N	N	N	8.1	268	205	N	N	Y	N	N	Y	N	N	MILD	N	N
2	65	F	N	Y	N	N	N	Y	9.1	356	321	N	Y	N	N	N	N	Y	Y	SEVERE	Y	Y
3	57	M	Y	N	N	N	N	Y	9.2	288	268	Y	N	N	N	N	N	Y	Y	MODERAT	N	N
4	71	M	N	N	N	Y	N	Y	9.2	546	344	N	Y	N	N	N	N	Y	Y	SEVERE	N	Y
5	68	F	N	N	N	N	N	Y	7.6	168	222	Y	N	N	N	N	N	Y	Y	MODERAT	N	N
6	51	M	Y	N	N	N	N	N	8.1	198	168	N	Y	N	N	N	N	Y	Y	MODERAT	N	N
7	59	F	Y	N	N	N	N	Y	7.6	326	286	Y	N	N	N	N	N	Y	Y	SEVERE	N	Y
8	46	M	N	N	N	Y	N	N	6.2	586	166	N	N	Y	N	N	Y	N	N	NORMAL	N	N
9	52	F	Y	N	N	N	N	N	9.1	156	178	N	N	N	Y	N	N	Y	Y	MODERAT	N	N
10	49	M	N	N	Y	N	N	N	7.4	174	194	Y	N	N	N	N	Y	N	N	NORMAL	N	N
11	59	F	N	N	Y	N	N	N	7.2	302	336	N	N	N	Y	N	Y	N	N	NORMAL	N	N
12	35	F	Y	N	N	Y	N	N	5.4	504	268	Y	N	N	N	N	Y	N	N	MILD	N	N
13	55	F	N	N	N	N	Y	Y	7.5	348	294	N	N	Y	N	N	N	Y	Y	MODERAT	N	N
14	47	F	Y	N	N	N	N	N	6.7	186	178	N	N	N	Y	N	Y	N	N	NORMAL	N	N
15	67	F	N	N	N	N	N	Y	7.4	262	284	Y	N	N	N	N	N	Y	Y	SEVERE	N	N
16	49	M	N	N	N	Y	N	N	7.4	588	234	N	Y	N	N	N	Y	N	N	NORMAL	N	N
17	52	M	Y	N	N	N	N	Y	7.5	322	348	N	N	N	Y	N	N	Y	Y	MODERAT	N	N
18	37	M	Y	N	N	N	N	Y	7.2	189	162	Y	N	N	N	N	N	Y	Y	MODERAT	N	N
19	45	F	N	Y	N	N	N	N	7.5	268	205	N	N	Y	N	N	Y	N	N	MILD	N	N
20	48	M	Y	N	N	N	N	Y	7.4	286	302	Y	N	N	N	N	N	Y	Y	SEVERE	N	N
21	64	M	N	N	N	Y	N	Y	5.6	542	198	N	Y	N	N	N	Y	N	N	MILD	N	N
22	69	F	N	N	N	N	N	Y	8.2	265	256	Y	N	N	N	N	N	Y	Y	MODERAT	N	N
23	47	M	Y	N	N	N	N	Y	4.5	283	184	N	N	N	Y	N	N	Y	Y	MODERAT	N	N
24	35	M	N	N	N	Y	N	N	3.6	604	173	N	Y	N	N	N	Y	N	N	NORMAL	N	N

25	59	F	N	N	Y	N	N	Y	7.6	296	316	N	Y	N	N	N	N	Y	Y	MODERAT	N	N
26	46	M	Y	N	N	N	N	Y	6.6	164	196	N	N	N	Y	N	Y	N	N	SEVERE	Y	Y
27	36	M	N	N	N	Y	N	N	5.4	508	168	Y	N	N	N	N	Y	N	N	NORMAL	N	N
28	55	F	N	N	Y	N	N	N	7.7	174	174	N	N	Y	N	N	Y	N	N	MODERAT	N	N
29	51	F	Y	N	Y	N	N	Y	7.5	292	306	N	Y	N	N	N	N	Y	Y	MODERAT	N	N
30	33	M	N	N	Y	N	N	N	8.2	364	282	Y	N	N	N	N	Y	N	N	MILD	N	N
31	53	F	Y	N	N	N	N	N	7.5	169	194	Y	N	N	N	N	Y	N	N	NORMAL	N	N
32	49	F	N	N	N	N	N	Y	8.4	308	356	N	N	N	Y	N	N	Y	Y	MODERAT	Y	N
33	59	M	N	N	N	N	N	Y	6.2	184	168	Y	N	N	N	N	N	Y	Y	SEVERE	N	N
34	58	M	Y	N	N	N	N	Y	8.5	194	158	N	N	Y	N	N	N	Y	Y	MODERAT	N	N
35	48	F	Y	N	N	N	N	Y	8.5	268	288	N	N	N	Y	N	N	Y	Y	MODERAT	N	N
36	47	M	N	N	Y	N	N	N	7.2	163	169	Y	N	N	N	N	Y	N	N	MILD	N	N
37	51	M	Y	N	N	N	N	Y	8.3	298	308	N	Y	N	N	N	N	Y	Y	MODERAT	N	N
38	64	F	N	N	Y	N	N	N	4.3	178	176	N	N	N	Y	N	Y	N	N	NORMAL	N	N
39	35	M	N	Y	N	N	N	Y	9.4	308	366	Y	N	N	N	N	N	Y	Y	SEVERE	N	Y
40	45	M	Y	N	N	N	N	Y	4.4	163	169	N	N	N	N	Y	N	Y	Y	MODERAT	N	N
41	53	F	N	N	Y	N	N	N	5.6	198	159	Y	N	N	N	N	Y	N	N	MILD	N	N
42	59	M	N	N	Y	N	N	Y	9.4	568	368	N	N	Y	N	N	N	Y	Y	SEVERE	N	Y
43	36	F	Y	N	N	N	N	N	3.5	333	168	Y	N	N	N	N	Y	N	N	NORMAL	N	N
44	49	F	N	N	N	N	N	Y	8.2	346	268	Y	N	N	N	N	N	Y	Y	MODERAT	N	N
45	55	F	N	Y	N	N	N	N	5.6	205	194	N	N	N	Y	N	Y	N	N	SEVERE	Y	Y
46	45	M	Y	N	N	N	N	N	3.4	207	176	Y	N	N	N	N	Y	N	N	NORMAL	N	N
47	69	F	Y	N	N	N	N	Y	8.4	404	346	N	N	N	N	Y	N	Y	Y	SEVERE	N	Y
48	37	M	N	N	Y	N	N	Y	6.2	208	184	N	N	Y	N	N	N	Y	Y	MODERAT	N	N
49	53	M	Y	N	N	N	N	N	8.1	243	300	Y	N	N	N	N	Y	N	N	NORMAL	N	N
50	48	M	Y	N	N	N	N	Y	3.4	248	148	N	N	N	N	N	N	Y	Y	MODERAT	N	N

51	57	M	N	N	N	Y	N	Y	3.4	608	158	Y	N	N	N	N	N	Y	Y	SEVERE	N	N
52	52	F	Y	N	N	N	N	N	7.4	295	274	N	N	N	N	Y	Y	N	N	MILD	N	N
53	47	M	N	N	Y	N	N	N	5.5	236	194	N	Y	N	N	N	Y	N	N	NORMAL	N	N
54	36	F	N	N	N	Y	N	N	4.4	642	186	N	N	Y	N	N	Y	N	N	NORMAL	N	N
55	63	F	N	N	N	N	N	Y	8.1	306	268	Y	N	N	N	N	N	Y	Y	SEVERE	N	Y
56	48	M	Y	N	N	N	N	N	6.4	222	176	N	N	Y	N	N	Y	N	N	MILD	N	N
57	48	M	N	N	Y	N	N	N	4.5	158	184	Y	N	N	N	N	Y	N	N	NORMAL	N	N
58	37	M	Y	N	N	N	N	Y	8.4	356	283	N	N	N	Y	N	N	Y	Y	SEVERE	Y	Y
59	52	F	N	N	Y	N	N	N	3.4	184	182	Y	N	N	N	N	Y	N	N	NORMAL	N	N
60	48	F	Y	N	N	N	N	Y	7.8	289	322	N	N	N	N	Y	N	Y	Y	MODERAT	N	N
61	51	M	N	Y	N	N	N	N	5.6	228	195	Y	N	N	N	N	Y	N	N	NORMAL	N	N
62	57	M	N	N	N	N	N	Y	8.2	226	268	N	N	Y	N	N	N	Y	Y	MODERAT	N	N
63	63	M	Y	N	N	N	N	N	4.3	137	168	N	Y	N	N	N	Y	N	N	NORMAL	N	N
64	52	F	N	Y	N	N	N	Y	9.2	394	308	N	Y	N	N	N	N	Y	Y	SEVERE	N	Y
65	58	M	Y	N	N	N	N	N	5.4	194	148	N	N	N	Y	N	Y	N	N	NORMAL	N	N
66	55	F	N	N	Y	N	N	N	5.5	138	171	Y	N	N	N	N	Y	N	N	NORMAL	N	N
67	52	M	N	N	N	Y	N	N	7.3	567	268	N	N	N	N	Y	Y	N	N	MILD	N	N
68	46	M	Y	N	N	N	N	N	5.3	111	186	N	Y	N	N	N	Y	N	N	NORMAL	N	N
69	39	M	N	N	Y	N	N	Y	8.2	463	258	N	Y	N	N	N	Y	N	N	MODERAT	N	N
70	52	F	Y	N	N	N	N	N	3.3	92	179	N	N	Y	N	N	Y	N	N	NORMAL	N	N
71	48	F	N	N	Y	N	N	N	8.4	168	196	Y	N	N	N	N	N	Y	Y	MODERAT	N	N
72	58	M	Y	N	N	N	N	N	5.4	308	268	N	N	Y	N	N	N	Y	Y	MODERAT	N	N
73	77	M	N	N	Y	N	N	Y	5.6	242	194	Y	N	N	N	N	N	Y	Y	SEVERE	Y	Y
74	49	F	N	N	Y	N	N	N	3.5	168	196	N	N	N	N	Y	Y	N	N	NORMAL	N	N
75	58	M	N	N	N	Y	N	Y	8.6	587	304	N	Y	N	N	N	N	Y	Y	MODERAT	N	N
76	59	M	N	Y	N	N	N	N	4.8	164	182	Y	N	N	N	N	Y	N	N	NORMAL	N	N

77	61	F	Y	N	N	N	N	Y	8.2	284	249	N	N	Y	N	N	N	Y	Y	MODERAT	Y	N
78	44	M	N	N	Y	N	N	N	6.5	188	174	N	Y	N	N	N	Y	N	N	NORMAL	N	N
79	52	M	N	Y	N	N	N	N	8.2	194	159	N	N	N	Y	N	Y	N	N	MODERAT	N	N
80	53	M	Y	N	N	N	N	Y	9.1	308	266	Y	N	N	N	N	N	Y	Y	SEVERE	Y	Y
81	44	F	N	N	N	Y	N	N	5.6	642	148	N	N	N	N	Y	Y	N	N	MILD	N	N
82	48	M	N	N	Y	N	N	N	6.3	194	183	N	N	Y	N	N	Y	N	N	SEVERE	N	N
83	73	F	Y	N	N	N	N	N	8.1	158	159	N	N	Y	N	N	Y	N	N	MILD	N	N
84	59	M	N	N	N	N	Y	Y	9.2	542	298	N	N	Y	N	N	N	Y	Y	SEVERE	Y	Y
85	57	M	Y	N	N	N	N	N	6.3	158	158	N	Y	N	N	N	Y	N	N	NORMAL	N	N
86	44	F	Y	N	N	N	N	N	8.5	128	184	N	N	Y	N	N	Y	N	N	MILD	N	N
87	49	M	N	N	Y	N	N	N	6.3	148	169	N	N	Y	N	N	Y	N	N	NORMAL	N	N
88	58	F	Y	N	N	N	N	N	8.1	186	183	N	N	Y	N	N	Y	N	N	MODERAT	Y	N
89	69	M	N	N	Y	N	N	N	5.2	348	266	Y	N	N	N	N	Y	N	N	NORMAL	N	N
90	51	F	Y	N	N	N	N	Y	7.2	393	308	N	Y	N	N	N	N	Y	Y	SEVERE	Y	Y
91	59	M	N	Y	N	N	N	N	4.8	186	206	N	N	N	N	Y	Y	N	N	NORMAL	N	N
92	42	F	Y	N	N	N	N	N	4.6	226	205	N	Y	N	N	N	Y	N	N	MILD	N	N
93	47	F	N	N	Y	N	N	Y	9.2	228	258	N	N	Y	N	N	N	Y	Y	MODERAT	N	N
94	53	M	Y	N	N	N	N	N	6.3	158	228	N	Y	N	N	N	Y	N	N	NORMAL	N	N
95	63	F	Y	N	N	N	N	Y	7.4	246	286	Y	N	N	N	N	N	Y	Y	SEVERE	Y	N
96	57	F	Y	N	N	N	N	N	5.3	246	284	N	N	Y	N	N	Y	N	N	MODERAT	N	N
97	47	M	N	Y	N	N	N	N	7.2	158	268	N	N	N	Y	N	Y	N	N	MODERAT	N	N
98	48	F	Y	N	N	N	N	N	5.3	126	262	N	N	N	N	Y	Y	N	N	NORMAL	N	N
99	64	F	Y	N	N	N	N	N	6.7	184	198	N	Y	N	N	N	Y	N	N	NORMAL	N	N
100	36	M	Y	N	N	N	N	Y	5.6	186	198	N	Y	N	N	N	Y	N	N	MILD	N	N