SERUM URIC ACID LEVEL AS A PROGNOSTIC INDICATOR IN ACUTE MYOCARDIAL INFARCTION

By

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Dissertation submitted to the

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Under the guidance of

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LIST OF ABBREVIATIONS USED

DALY	- Disability adjusted life years
CVD	- Cardio Vascular Diseases
MI	- Myocardial Infarction
UA	- Uric Acid
XO	- Xanthine Oxidase
HF	- Heart Failure
NO	- Nitric Oxide
XDH	- Xanthine Dehydrogenase
NOS	- Nitric Oxide Synthase
ECG	- Electrocaridography
PCI	- Percutaneous Intervention
CABG	- Coronary Artery Bypass Graft
AMI	- Acute Myocardial Infarction
ACS	- Acute Coronary Syndrome
HTN	- Hypertension
DM	- Diabetes Mellitus

ABSTRACT

BACKGROUND:

Acute myocardial infarction continues to be a significant health problem In industrialized countries & increasingly significant problem in developing Countries. ST elevation MI constitutes approximately 40% of all AMI. Serum uric acid produced from xanthine & hypoxanthine (purines) by xanthine oxidase. Serum uric acid (UA) levels reflect circulating xanthine oxidase activity and oxidative stress production. Hyperuricemia is associated with deleterious effects on endothelial dysfunction, oxidative metabolism, platelet adhesiveness, haemorrheology, and aggregation. Hence this study is conducted to know the prognostic significance of serum uric acid levels in acute myocardial infarction.

AIMS:

To estimate serum uric acid levels in acute myocardial infarction patients and its correlation with killip's classification of heart failure.

Methods :

100 Patients with Acute myocardial infraction admitted between october 2011 to April 2013 were studied. Serum uric acid level was measured on day 0, 3 & 7 of MI. A detailed history and physical examination with reference to killip's classification were carried out. 2D Echocardiography & routine investigations was performed.Statistical analysis: Data presented with mean $\pm$ SD. Uric acid levels and killip's class compared with spearman correlation coefficient.

Results:

The mean age of the patients was 58.43 ± 13.77. The male to female ratio was 65:35 showing a male predominance. Mean uric acid levels on day 0 is 5.179 ± 1.910, on day 3 is 5.0325 ± 1.755, on day 7 is 4.953 ± 1.446. Uric acid levels was compared with killip class on day 0 and it is found to be significant($r = 0.7374$ and $p < 0.0001$) and results remain significant on day 3($r = 0.5898$ $p<0.0001$).In case of patients who expired ($n = 20$) the mean serum uric acid level was 6.845±2.715 and in other 80 patients was 4.783± 1.386($t= 4.828$, $p<0.0001$).Out of 20 patients who expired, 16 patients were having elevated serum uric acid levels(>7mg/dl). 19 patients were in Killip's class IV at the time of death. On all the days serum uric acid levels were higher in patients who were in higher Killip class.

Conclusion:

Patients with elevated serum uric acid levels belonged to higher killip's classification and were associated with higher mortality. Hence we can use serum uric acid as an inexpensive cardiovascular risk marker and prognostic marker in MI patients.

Key words :

Serum uric acid, Acute Myocardial infarction.

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INTRODUCTION

Coronary heart disease is the leading cause of death in India and the leading cause of death worldwide. Previously thought to affect primarily high-income countries, Coronary heart disease 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. Coronary heart disease 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. Effective screening, evaluation, and management strategies for coronary heart disease are well established in high-income countries, but these strategies have not been fully implemented in India.

CORONARY HEART DISEASE Mortality in India[1]

Coronary heart disease is the leading cause of death in India, leading to:

- 1.46 million deaths (14% out of a total of 10.3 million deaths)
- 130.7 deaths per 100,000
- 207.7 age-standardized deaths per 100,000
- 15,588,000 DALYs
- 1,931 age-adjusted DALYs per 100,000

Prevalence and incidence of coronary heart disease in India[2]

Unadjusted coronary heart disease rates have ranged from 1.6% to 7.4% in rural populations and 1% to 13.2% in urban populations. In 2000, there were an estimated 29.8 million people with coronary heart disease in India, out of a total estimated population of 1.03 billion people.

Coronary heart disease affects Indians with greater frequency and at a younger age than counter parts in developed countries, as well as many other developing countries. Age standardized CVD death rates in people 30-69 years old are 180 per 100,000 in Britain, 280 per 100,000 in China, and 405 per 100,000 in India. Also, 50% of coronary heart disease-related deaths in India occur in people <70 years of age, whereas only 22% of coronary heart disease-related deaths in Western countries occur in this age group.

Coronary heart disease prevalence appears to be worsening in India. In developed countries, ischemic heart disease is predicted to rise 30-60% between 1990 and 2020. In developing countries, rates are predicted to increase by 120% in women and 137% in men from 1990to 2020.

The prognosis of post myocardial infarction varies depending on a person's health, the extent of the myocardial damage and the treatment given. Median Mortality at 30 days was 16.6% with a range from 10.9%to 24.9% depending on hospital. Using variables available in the emergency room, people with a higher risk of adverse outcome can be identified. Elevation of cardiac markers following MI such as proteins (myoglobin) and enzymes (CK MB, Troponin T,I)are released into blood stream from necrotic heart muscle and have a temporal profile in MI. However they do not correlate with myocardial function.

Epidemiological studies have shown that elevated uric acid may be a risk factor for cardiovascular diseases and has a negative prognostic marker for mortality.

Elevated serum uric acid is highly predictive of mortality in patients with heart failure and coronary artery disease and in cardiovascular events in patients[3].

Adenosine synthesized locally by vascular smooth muscle in cardiac tissue is rapidly degraded by endothelium to uric acid, Which undergoes rapid efflux to the vascular lumen due to low PH, and negative membrane potential[4]. Uric acid and Xanthine oxidase levels are increased in vivo under ischemic conditions and hence uric acid acts as a marker of underlying ischemic conditions[5].Uric acid has a pathogenic role in cardiovascular disease. Hyperuricaemia is associated with deleterious effects on endothelium dysfunction, oxidative metabolism, platelet adhesiveness, haemorheology and aggregation. There is evidence that high uric acid is a negative prognostic factor in patients with mild to severe heart failure[5,6]. A study showed a close correlation between serum uric acid concentration and killip's classification in patients of acute myocardial infarction[7].

Hence as a predictor for mortality and morbidity following acute myocardial infarction this is one such study in which the prognostic role of serum uric acid in acute myocardial infarction is validated.

OBJECTIVES

- To estimate serum uric acid levels in acute myocardial infarction patients and its correlation with killip's classification of heart failure.

REVIEW OF LITERATURE

URIC ACID

Uric acid is a heterocyclic compound of carbon, nitrogen, oxygen and hydrogen with the formula C5H4N4O3. It is the final breakdown product of purine metabolism in humans.

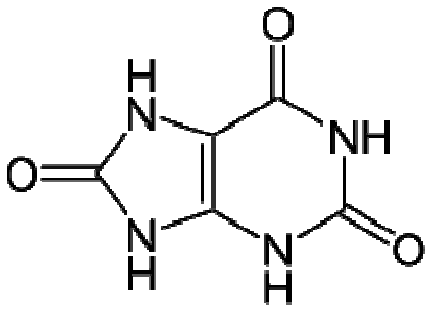


Figure-1

HISTORY

In 1776, the Swedish chemist Scheele[8] isolated uric acid from a calculus of urinary tract and in 1797, the British chemist Wollaston isolated the substance from a tophus which he removed from his own ear[9]. 50 years later, these observations led the British Physician, Alred Barry Garrod to show by chemical isolation, the presence of higher concentrations of uric acid in the blood of gouty patients.[10] Garrod's subsequent studies formulated, for the first time, a rational relationship between hyperuricemia and the clinical symptomatology of gouty arthritis. Later, in 1913,[11] Folin F. Denin developed a more reliable method of chemical determination of uric acid which led to rejection of Garrod's concept.[12]

STRUCTURE AND CHEMISTRY

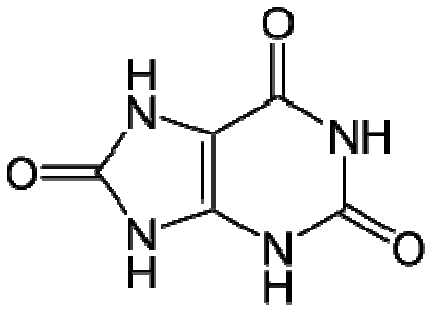


Figure - 2

The chemical nature of uric acid was shown by Fisher to be 2,6,8 trihydroxypurine.[13] Uric acid is a diprotic acid with pka1=5.4 and pka2=10.3. Thus in strong alkali at high pH or in the presence of carbonic acid or carbonate ions, it forms the singly charged hydrogen or acid uric acid ion as its pKa2 is greater than the pKa1 of carbonic acid. As its second ionization is so weak, the full uric acid salts tend to hydrolyze back to hydrogen uric acid salts and free base at pH values around neutral. It is aromatic because of the purine functional group.

SOLUBILITY

Generally, the water solubility of uric acid and its alkali metal and alkaline earth salts is rather low. All these salts exhibit greater solubility in hot water than cold, allowing for easy recrystallization. This low solubility is significant for the etiology of gout. The solubility of the acid and its salts in ethanol is very low or negligible. In ethanol water mixtures, the solubilities are somewhere between the end values for pure ethanol and pure water.

BIOLOGY

The enzyme xanthine oxidase makes uric acid from xanthine and hypoxanthine, which in turn are produced from purines. Uric acid is released in hypoxic conditions.[14]

In humans and higher primates, uric acid is the final oxidation (breakdown) product of purine metabolism and is excreted in urine. In most other mammals, the enzyme uricase further oxidizes uric acid to allantoin. The loss of uricase in higher primates parallels the similar loss of the ability to synthesize ascorbic acid, leading to the suggestion that uric acid may partially substitute for ascorbate in such species. Both uric acid and ascorbic acid are strong reducing agents (electron donors) and potent antioxidants.[15]

In humans, over half the antioxidant capacity of blood plasma comes from uric acid. The Dalmatian dog has a genetic defect in uric acid uptake by the liver and kidneys, resulting in decreased conversion to allantoin, so this breed excrete uric acid, and not allantoin, in the urine[16]. In birds and reptiles, and in some desert dwelling mammals (e.g., the kangaroo rat), uric acid also is the end product of purine metabolism, but it is excreted in feces as a dry mass. This involves a complex metabolic pathway that is energetically costly in comparison to processing of other nitrogenous wastes such as urea (from urea cycle) or ammonia, but has the advantage of reducing water loss.

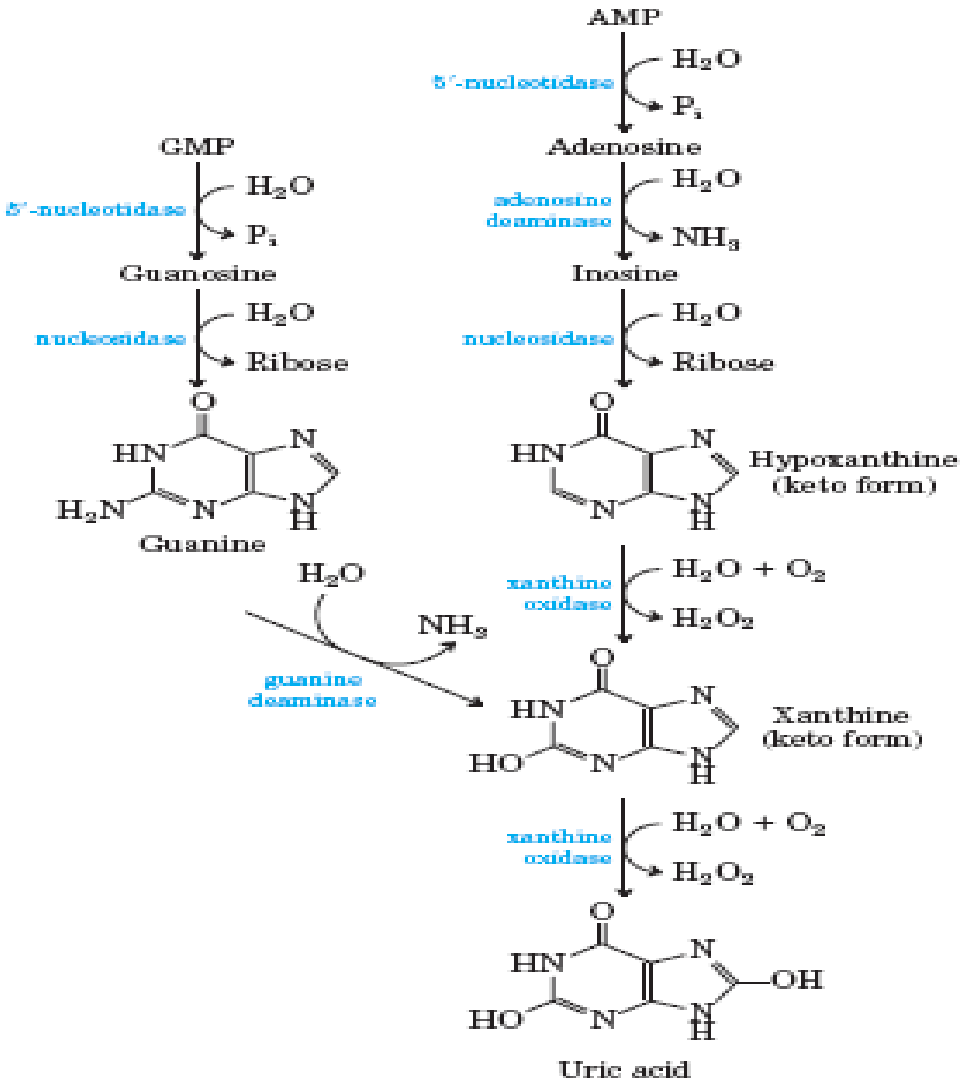
In humans, about 70% of daily uric acid disposal occurs via the kidneys, and in 5-25% of humans, impaired renal (kidney) excretion leads to Hyperuricemia.

GENETICS

A proportion of people have mutations in the proteins responsible for the

excretion of uric acid by the kidneys. Nine genes have so far been identified: SLC2A9; ABCG2; SLC17A1; SLC22A11; SLC22A12; SLC16A9; GCKR; LRRC16A; and PDZK1.SLC2A9 is known to transport both uric acid and fructose.[17]

SYNTHESIS



Synthesis of Uric Acid Figure-3

Degradation of Purines and Pyrimidines Produces Uric Acid and Urea, Respectively. Purine nucleotides are degraded by a pathway in which they lose their phosphate through the action of **5'-nucleotidase**. Adenylate yields adenosine, which is deaminated to inosine by **adenosine deaminase,** and inosine is hydrolyzed to

hypoxanthine (its purine base) and D-ribose. Hypoxanthine is oxidized successively to xanthine and then uric acid by **xanthine oxidase,** a flavoenzyme with an atom of molybdenum and four iron-sulfur centers in its prosthetic group. Molecular oxygen is the electron acceptor in this complex reaction. GMP catabolism also yields uric acid as end product. GMP is first hydrolyzed to guanosine, which is then cleaved to free guanine. Guanine undergoes hydrolytic removal of its amino group to yield xanthine, which is converted to uric acid by xanthine oxidase.

DIETARY INTAKE

Diet provides an important exogenous source of purines. Dietary intake of purines, nucleic acids contribute to the serum uric acid level and the daily excretion of uric acid, this contribution being proportional to the intake. However, the magnitude of this component of daily uric acid production is usually relatively small, since serum uric acid levels decrease by only 1 mg/dl or less when an individual changes from a normal to purine free diet. On the other hand, diets unusually high in purines (such as liver, meat sweet breads, kidney and anchovy) have the potential to raise the plasma uric acid concentration significantly. Because about 50% of the ingested RNA purine and 25% of the ingested DNA purine appear in urine as uric acid, foods high in nucleic acid content have a significant effect on the serum uric acid level.

NORMAL VALUES

Usually, the uric acid pool size of an adult male, is about, 1200mg, and 700mg uric acid is produced daily.[18] The production is balanced by the excretion of 500mg of uric acid into the urine and 200mg into the small intestine, Any imbalance in the two, results in hyperuricemia or hypouricemia.

The normal serum values vary with age and sex. Most children have serum uric acid concentrations of 3 to 4 mg/dl. Levels start rising during puberty in males, but remain low in females till menopause. The gender variation could probably be due to higher excretion in females. Normal values in **females are 2.5-5.6 mg/dl** and **males is 3.1-7mg/dl**.

After menopause, values for women increase to approximate those at men. Among adults, concentrations vary with height, body weight, blood pressure and renal function as well as alcohol intake.

URIC ACID EXCRETION

In a normal person on a normal diet about 700-1000 mg of uric acid is produced daily. If a person takes a diet rich in nucleoproteins (meat, particularly glandular meat, meat extracts, legumes) he/she will excrete little excess of uric acid.

On a purine free diet some uric acid is constantly excreted in urine amounting to about 200-500 mg/day. This fraction is referred to as endogenous uric acid. If it is determined for a given individual, the excess above this figure which he/she excretes on a purine containing diet is termed exogenous.

About 70% of uric acid is excreted by the kidneys. The remainder is excreted via the gastro intestinal tract, where it is degraded by uricolytic bacteria to carbon dioxide and ammonia. In patients with renal insufficiency, this extra renal elimination of uric acid may be a major route of disposal.

The mechanisms controlling intestinal elimination of uric acid are not well understood. The amount secreted into the lumen is probably related to the plasma concentration, so that a higher fraction of daily uric acid production may be excreted

via gastro intestinal tract in hyperuricemic individuals than in normal. It is not thought that intestinal elimination of uric acid represents an important regulator of the plasma uric acid concentration.[19]

On the other hand, renal excretion is the major regulator of plasma uric acid, decreases or increases in renal clearance are readily reflected by inverse changes in plasma uric acid concentration.

Steele and Rieselbach[20] proposed the four component model of renal handling of uric acid mechanism. It includes-

1. Glomerular filtration
2. Presecretory tubular reabsorption.
3. Tubular secretion
4. Postsecretory reabsorption

Normally, uric acid is totally filtered in the renal glomeruli and then the filtered load is completely reabsorbed in the proximal tubules. 5-10% is later secreted into the distal tubules and excreted in the urine. The filtered uric acid undergoes extensive absorption with atleast 98% of the filtered load reabsorbed. Recent evidences suggest that much of the secreted uric acid undergoes extensive reabsorption[21]. All four components are influenced by other factors. Since uric acid binding by plasma protein is thought not to be important, the rate of uric acid filtration should vary directly with changes in glomerular filtration rate. Tubular reabsorption is an active process closely related to sodium reabsorption. Expansion of extracellular fluid volume increases the uric acid clearance by inhibiting its tubular reabsorption[22]. Conversely, contraction of extracellular fluid volume, decreases the uric acid clearance, enhancing its tubular reabsorption, thereby leading to hyperuricemia.

The tubular secretory component is directly proportional to plasma uric acid concentration. Secretion may be decreased, if the transport pathway is competitively inhibited by other organic acids. In summary, normally kidneys excrete an amount equivalent to 5-10% of the filtered load of uric acid.

Altered renal excretion of uric acid exhibiting hyperuricemia could be due to -

1. Reduced filtration of uric acid
2. Enhanced reabsorption.
3. Decreased secretion.

No unequivocal data establish any one of these mechanisms as the basic defect, and it is likely that all three are operative within the hyperuricemic population.

Patients with renal disease usually have a reduction in glomerular filtration rate leading to decreased filtered load of uric acid and thus hyperuricemia.

Tubular reabsorption of uric acid is an active process that is closely related to sodium reabsorption. Therefore states of volume contraction (with enhanced sodium reabsorption) are accompanied by increased uric acid reabsorption and decreased uric acid clearance. Diuretic induced volume depletion leads to enhanced tubular reabsorption of uric acid as well as decreased uric acid filtration.

In some situations hyperuricemia has been attributed to competitive inhibition of uric acid secretion by excess organic acids thought to be secreted by the same renal tubular mechanism responsible for uric acid secretion. Examples include starvation (ketosis and free fatty acids), alcoholic ketosis, diabetic ketoacidosis, maple syrup urine disease and lactic acidosis of any cause.

HYPERURICEMIA

This may either be due to increased production or decreased excretion of uric acid or from a combination of the 2 processes. It is defined as a serum concentration more than 420 μmol/L is 7mg/dl[23] as based on physicochemical, epidemiologic and disease-related criteria, in epidemiologic studies, hyperuricemia is defined as the mean plus 2 standard deviations of values determined from a randomly selected healthy population. When measured, in unselected individuals, 95% have serum uric acid concentration <420μmol/L (7mg/dl). In relation to the risk of the disease, uric acid levels 420μmol/L is associated with the risk of gouty arthritis and escalates in proportion to the degree of elevation. Hyperuricemia is reported in 2-13.2% of ambulatory adults.

CAUSES:[24-27]

1) **Uric acid overproduction**

- Primary idiopathic
- HGPRT deficiency
- PRPP synthetase overactivity
- Hemolytic processes
- Lymphoproliferative diseases
- Myeloproliferative diseases
- Polycythemia vera
- Psoriasis
- Paget's disease
- Rhabdomyolysis
- Exercise
- Alcohol
- Obesity

- Purine-rich diet
- Glycogen storage diseases (types V, VII)

2) URIC ACID UNDER EXCRETION

- Primary idiopathic
- Renal insufficiency
- Polycystic kidney disease
- Diabetes insipidus
- Hypertension
- Acidosis-lactic acidosis, ketoacidosis
- Berylliosis
- Hypothyroidism
- Hyperparathyroidism
- Toxemia of pregnancy
- Lead intoxication
- Bartter's syndrome
- Down's syndrome
- Drugs
  - Salicylates (>2 g/d)
  - Diuretics
  - Alcohol
  - L- dopa
  - Ethambutol
  - Pyrazinamide
  - Nicotinamide
  - Cyclosporine

3) COMBINED MECHANISM

- Glucose-6-phosphate Dehydrogenase deficiency
- Alcohol
- Shock
- Fructose-1-phosphate aldolase deficiency.
- Physical exercise
- Status epilepticus
- Myocardial infarction
- Acute respiratory failure

HYPOURICEMIA:

It is defined as a serum uric acid concentration less than 180 μmol/L; i.e. 3mg/dl. It may occur as a consequence of decreased formation of uric acid or increased renal clearance of uric acid[28,29,30]. It can also result when the activity of xanthine oxide is reduced, either because of deficiency of the enzyme, as in xanthinuria, or when there is pharmacologic inhibition of xantine oxidase by allopurinol.

Renal causes of hypouricemia range from isolated defects of uric acid reabsorption to more complex abnormalities of renal tubular function.[31] The amount of uric acid finally excreted in urine appears to depend on the balance between tubular secretion of uric acid and the so-called post- secretory reabsorption of secreted uric acid. In contrast to hyperuricemia, which has been studied extensively, only recent

observations have suggested that hypouricemia may prove an important clue for the existence of underlying disease processes.

30 years ago, Ramsdell and Kelley[32] in a short communication, looked at the clinical significance of hypouricemia in a hospital population, but some of their plasma uric acid determinations were performed using the colorimetric phosphotungstate method which is not as specific for uric acid as the uricase method which is now preferred[33].

In a study done in UK, the prevalence of hypouricemia in hospital population was studied. Prevalence was reported to be 6.5% among the males and 4.8% among the females. The large group displaying hypouricemia, was intensive care patients, possibly due to a combination of alteration in the renal handling of uric acid and reduced dietary intake of protein. The author reports That in the study, a large group of patients (14%) who manifested hypouricemia[34], were those with diabetes mellitus, 10% of whom were on insulin and 4% on sulphonylureas.

CAUSES[35] OF HYPOURICEMIA:

- Total parenteral nutrition
- Cirrhosis
- Neoplasms
- Diabetes mellitus
- Syndrome of inappropriate secretion of ADH
- Fanconi syndrome
- Xanthine oxidase deficiency
- Drugs

- Ascorbic acid
- Dicoumarol
- Diflunisal
- Sulfinpyrazone
- NSAIDs
- Probenecid
- Estrogen
- Gucocorticoids

OXIDATIVE STRESS[36]

UA is a marker of oxidative stress, and may have a potential therapeutic role as an antioxidant .On the other hand, like other strong reducing substances such as ascorbate, UA can also act as a pro oxidant, particularly at elevated levels. Thus, it is unclear whether elevated levels of uric acid in diseases associated with oxidative stress such as stroke and atherosclerosis are a protective response or a primary cause. Some researchers propose Hyperuricemia-induced oxidative stress is a cause of metabolic syndrome. On the other hand, plasma uric acid levels correlate with longevity. In primates and other mammals. This is presumably a function of uric acid's antioxidant properties.

INDICATIONS FOR URIC ACID LOWERING THERAPY:[37]

- Initiation of chemotherapy or radiation therapy.
- History of kidney stones.
- History of gouty attacks (>2 per year), tophi.

- Moderate Renal function impairment (creatinine clearance <42 mL/min) Renal dysfunction.
- Markedly elevated uric acid levels (12 mg/dL in men or women).

Hyperuricemia is a biochemical abnormality, Not a disease. Indications for lowering uric acid is clear. Drug therapy to lower UA (ULT) for CVD prevention is not advised as per current evidence.

Potential mechanisms for increased uric acid in heart failure[38].

UA is a metabolic byproduct of purine metabolism .Serum UA 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 UA production in HF,including increased abundance and activity of XO, increased conversion of xanthine dehydrogenase (XDH) to XO or increased XO substrate resulting from enhanced ATP breakdown to adenosine and hypoxanthine. As UA is excreted primarily by the kidney, decreased renal perfusion could lead to increased UA levels. To the extent that HF leads to tissue ischemia (in advanced HF) and a rise in serum Lactate, renal UA excretion can be further impaired as lactate competes with uric acid via an organic anion exchanger in the proximal tubule..

Pathophysiological role of the xanthine oxidase pathway in heart failure:[39]

There is increasing evidence that strongly supports a direct pathophysiological role for the metabolic pathway leading to UA production in the failing circulation. In

this regard, the two terminal steps in uric acid production are catalyzed by XO, which also produces a molecule of superoxide for each reaction. XO is the product of the xanthine oxido reductase gene that encodes XDH, an 150 Kda protein, which functions as a homo dimer. XDH is converted to XO by proteolytic cleavage or sulfhydryl modification.

The elevation in serum UA may reflect increased XO pathway activity and in turn the generation of superoxide and resultant oxidative stress via the XO system. XO is upregulated within the heart in both experimental and human heart failure. Much had previously been made of the difficulty in identifying XO within the hearts of certain mammalian species, including humans; nevertheless, it is clear that XO, which is produced in highest abundance in the liver and gut, may circulate in the blood and adhere to endothelium in distant sites. Moreover, XO is expressed in cardiac myocytes, as shown by immunohistochemistry and may participate in intracrine signaling.

From a functional standpoint, XO activity participates in both mechanoenergetic uncoupling and vascular dysfunction in the failing circulation. Mechanoenergetic uncoupling is the process whereby cardiac energy consumption remains the same or increases while cardiac work falls dramatically, and is increasingly being perceived as a potential key lesion in the failing heart. Inhibition of XO with allopurinol restores depressed myocardial energetics toward normal,and this effect can be mimicked by the antioxidant ascorbate.

Furthermore, several recent studies have demonstrated that XO inhibition improves endothelial dysfunction in patients with congestive heart failure in

association with reduction in circulating markers of oxidative stress, thereby providing evidence that XO inhibition reduces oxidant generation.

Interaction of xanthine oxidase and uric acid with nitric oxide pathways: [40]

Both XO activity and UA may also affect cardiac and renal nitric oxide signaling, which exerts key cardiac and vascular effects. The impact of XO inhibition to restore depressed myocardial energetics requires intact NO pathway activity.UA may also impair NO production directly, as suggested by the finding that UA infusion into forearm veins of humans attenuates acetylcholine-stimulated vasodilation. Likewise, the hypertension associated with Hyperuricemia in rats is associated with reduced expression of macula densa , neuronal nitric oxide synthase (NOS) and can be partially reversed by the NOS substrate l-arginine. This finding has interesting implications for cardiac function, as neuronal NOS plays a key role in modulating cardiac excitation-contraction coupling by facilitating sarcoplasmic reticulum calcium release.

CLINICAL UTILITY OF URIC ACID MEASUREMENTS.[41]

From a clinical perspective, there raises the issue of whether serum UA levels should be routinely measured in HF patients. Indeed this should be more likely, 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 HF patients. Much in the same way as BNP has been evaluated, it will be of great

value to assess whether UA levels change in response to HF therapy in a manner that predicts clinical outcome.

UA levels are ready for clinical use, the observation that UA levels possess prognostic information adds an extremely intriguing finding to mounting evidence that XO and UA play pathophysiological roles in HF. 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 XO pathway and UA itself may be of pathophysiological importance in heart failure progression. The available evidence has established a link between Hyperuricemia and cardiovascular disease and this may be causal. Without waiting for the resolution of causality arguments, one can start using serum uric acid concentration as an inexpensive cardiovascular risk marker[42].

THE KILLIP'S CLASSIFICATION[43].

This is a system used in individuals with an acute myocardial infarction and heart failure, in order to risk stratify them. Individuals with a low Killip class are less likely to die within the first 30 days after their myocardial infarction than individuals with a high Killip class. Patients were ranked by Killip's class in the following way:

Killip class I :	Includes individuals with no clinical signs of heart failure.
Killip class II :	Includes individuals with rales or crackles in the lungs, an S3, and elevated jugular venous pressure.
Killip class III:	Describes individuals with frank acute pulmonary edema.

Killip class IV: Describes individuals in cardiogenic shock or hypotension (measured as systolic blood pressure lower than 90 mmHg) and evidence of peripheral vasoconstriction (oliguria,cyanosis or sweating).

The Killip classification system and mortality rate :

Killip class I: Mortality rate was found to be at 6%.

Killip class II: Mortality rate was found to be at 17%.

Killip class III: Mortality rate was found to be at 38%.

Killip class IV: Mortality rate 67%.

URIC ACID ESTIMATION [44].

The method used for analysis is enzymatic method (Uricase method) by using auto analyzers. In our laboratory, values taken as normal range is as follows :

Males 3.1 – 7.0 mg/dl

Females 2.5 – 5.6 mg/dl

Methods using Uricase, the enzyme that catalyses the oxidation of uric acid to allointoin are most specific. The simplest of these methods measures the differential absorption of uric acid and allointoin at 293nm.The differential absorption before and after incubation with Uricase is proportional to uric acid concentration.

This method has been proposed as candidate reference method.and is the most specific method.

MYOCARDIAL INFARCTION

Myocardial infarction is a common presentation of ischemic heart disease.

The who estimated in 2002, that 12.6 percent of worldwide deaths were from IHD, with it being the leading cause of death in developed countries, Worldwide more than 3 Million people have STEMIs and 4 million have NSTEMIs a year. CAD is responsible for 1 in 5 deaths worldwide overall. It is becoming more common in the developing world such as in India where cardiovascular disease (CVD) is one of the leading cause of death. The deaths due to CVD in India were 32% of all deaths in 2007. Although a relatively new major health issue in India, deaths due to CVD is expected to double during 1985–2015.Mortality estimates due to CVD vary widely from state to state, ranging from 10% in Meghalaya to 49% in Punjab (percentage of all deaths). Punjab (49%), Goa (42%), Tamil Nadu (36%) and Andhra Pradesh (31%) have the highest CVD related mortality estimates. State-wise differences are correlated with prevalence of specific dietary risk factors in the states. Moderate physical exercise is associated with reduced incidence of CVD in India (those who exercise have less than half the risk of those who don't).[45,46,47,48]

REVISED DEFINITION OF MYOCARDIAL INFARCTION [49] :

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

- Typical rise and gradual fall (troponin) or more rapid rise and fall (CK MB) of biochemical markers of myocardial necrosis

1) With at least one of the following:

a) Ischemic symptoms.

b) Development of pathologic Q waves on ECG reading.

c) ECG changes indicative of ischemia (ST elevation ordepression).

d) Coronary artery intervention(e g: coronary angiography).

2) Pathological findings of 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 reading. 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 finding of healed or healing MI.

CLASSIFICATION OF MI

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

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

   There are two basic types of acute myocardial infarction:

   a) Transmural: associated with atherosclerosis involving major coronary artery and are usually a result of complete occlusion of the area's blood supply.

b) **Subendocardial:** involving a small area in the subendocardial wall of the left ventricle, ventricular septum or papillary muscles.

Clinically, Myocardial infarction can be further sub classified into a ST elevation MI (STEMI) versus a non-ST elevation MI (non-STEMI) based on ECG changes. A 2007 consensus document classifies myocardial infarction into five main types:

Type 1 – Spontaneous myocardial infarction related to ischemia due to a primary Coronary event such as plaque erosion and/or rupture , fissuring, or dissection.

Type 2 – Myocardial infarction secondary to ischemia due to either increased oxygen demand or decreased supply, e.g. coronary artery spasm, coronary embolism, anemia, arrhythmias, hypertension, or hypotension.

Type 3 – Sudden unexpected cardiac death, including cardiac arrest, often with Symptoms suggestive of myocardial ischemia, accompanied by presumably new ST elevation, or new LBBB, or evidence of fresh thrombus in a coronary artery by angiography and/or at autopsy, but death occurring before blood samples could be Obtained, or at a time before the appearance of cardiac biomarkers in the blood.

Type 4 – Associated with coronary angioplasty or stents:

Type 4a – Myocardial infarction associated with PCI

Type 4b – Myocardial infarction associated with stent thrombosis as documented by angiography or at autopsy.

Type 5 – Myocardial infarction associated with CABG.

RISK FACTORS

AGE [50]

Men acquire an independent risk factor at age 45, Women acquire an independent risk factor at age 55; in addition individuals acquire another independent risk factor if they have a first-degree male relative (brother, father) who suffered a coronary vascular event at or before age 55.Another independent risk factor is acquired if one has a first-degree female relative(mother, sister) who suffered a coronary vascular event at age 65 or younger.

Heart failure (HF) is one of the most unfavorable consequences of the acute myocardial infarction (AMI), resulting in increased hospitalization level and mortality. The patients of advanced age constitute the major part among patients with HF due to AMI.

In a study of 123 patients a number of variables of the acute phase were investigated as potential predictors of developing HF within 12 months after AMI and the role of age was assessed. The relation of HF, echocardiographic variables measured 12 months after infarction and age was also studied. On completion a one-year follow-up, 54 patients (44%) developed HF, mainly of 2nd NYHA class.

The age of the patients was the only independent predictor of HF among the variables of the acute phase (OR = 1.06 under 95% CI (1.01-1.12).

The age over 65 years demonstrated 78% sensitivity and specificity in predicting development of HF. Among parameters estimated at the end of 12- months follow-up, age (OR = 0.934 under 95% CI (0.889-0.983) and echocardiographic wall motion score index (WMSI) (OR = 0.031 under 95% CI (0.003-0.333) independently influenced the presence of HF The factor of age had decisive importance for HF

development in group of the patients with medium infarct size. At WMSI range 1.6-1.89, 11 of 20 patients younger than 65 had no HF, whereas 8 of 9 patients older than 65 developed HF ($p < 0.05$). Thus, age is a major independent predictor of development of HF within the first year after AMI .The patients of the senior age group 65years and above have a higher risk of HF with medium infarct size, which does not result in HF in patients of younger age.

GENDER:[51,52]

The study was done to examine the association of Joint National Committee (JNC-V) blood pressure and National Cholesterol Education Program (NCEP) cholesterol categories with coronary heart disease (CORONARY HEART DISEASE) risk, incorporating them into coronary prediction algorithms, and to compare the discrimination properties of this approach with other non-categorical prediction functions.

Prospective, single - center study in the setting of a community-based cohort. During the 12 years of follow-up, a total of 383 men and 227 women developed CORONARY HEART DISEASE. A number of studies have indicated that women who have a Myocardial infarction have higher mortality rates than men. Study was done to review the literature on sex differences in mortality after myocardial infarction to determine whether female sex is independently associated with lower survival.

Much of the increased early mortality after myocardial infarction in women is explained by the older age and more unfavorable risk characteristics of the women.

National Academy of Clinical Biochemistry Recommendations for Use of Biochemical Markers for Risk Stratification in ACS (NACB):[53]

Class I

1. Patients with suspected ACS should undergo early risk stratification based on an integrated assessment of symptoms, physical examination findings, ECG findings, and biomarkers (Level of Evidence: C).
2. A cardiac troponin is the preferred marker for risk stratification and, if available, should be measured in all patients with suspected ACS. In patients with a clinical syndrome consistent with ACS, a maximal (peak) Concentration exceeding the 99th percentile of values for a reference control group should be considered indicative of increased risk of death and recurrent ischemic events (Level of Evidence: A).
3. Blood should be obtained for testing on hospital presentation followed by serial sampling with timing of sampling based on the clinical Circumstances. For most patients, blood should be obtained for testing at hospital presentation, and at 6 to 9 hours (Level of Evidence: B).

Class II a

4. Measurement of Hs-CRP may be useful, in addition to a cardiac troponin, for risk assessment in patients with a clinical syndrome consistent with ACS. The benefits of therapy based on this strategy remain uncertain (Level of Evidence: A).
5. Pro BNP may be useful, in addition to a cardiac troponin, for risk assessment in patients with a clinical syndrome consistent with ACS. The benefits of therapy based on this strategy remain uncertain (Level of Evidence: A).

Class II b

6. Measurement of markers of myocardial ischemia, in addition to cardiac troponin and ECG, may aid in excluding ACS in patients with a low Clinical probability of myocardial ischemia (Level of Evidence: C).
7. A multi-marker strategy that includes measurement of two or more path biologically diverse biomarkers in addition to a cardiac troponin, may aid in enhancing risk stratification in patients with a clinical syndrome Consistent with ACS. BNP and hs-CRP are the biomarkers best studied using this approach. The benefits of therapy based on this strategy remain uncertain (Level of Evidence:C).

   Early repeat sampling of cardiac troponin (e.g., 2 to 4 hours after presentation) may be appropriate if tied to therapeutic strategies (Level of Evidence: C).

Class III

8. Biomarkers of necrosis should not be used for routine screening of patients with low clinical probability of ACS (Level of Evidence: C).

The ACC/AHA and NACB guidelines recommend cTnI or cTnT as the preferred first-line markers, but note that CK-MB (by mass assay) is an acceptable alternative. The preference for cardiac troponins reflects the greater specificity of these markers compared with CK-MB and the prognostic value of troponin elevations in the presence of normal CK-MB levels. If the initial set of markers is negative in patients who have presented within the first 6 hours of the onset of pain, the guidelines recommend that another sample be drawn in the next 6 to 12 hours.

Management [54]:

The pre hospital care:

Patients with suspected STEMI is a crucial element bearing directly on the likelihood of survival. Accordingly, the importance of the immediate implementation of definitive resuscitative efforts and of rapidly transporting the patient to a hospital cannot be overemphasized. Major components of the delay from the onset of symptoms consistent with acute myocardial infarction (MI) to reperfusion include the following.

a. The time for the patient to recognize the seriousness of the problem and seek medical attention;
b. Prehospital evaluation, treatment, and transportation;
c. The time for diagnostic measures and initiation of treatment in the hospital. (e.g., "door-to-needle" time for patients receiving a thrombolytic agent and Fibrinolysis)[55]

Assessment of Reperfusion Options for STEMI Patients

Step 1: Assess time and risk.

- Time since onset of symptoms
- Risk of STEMI
- Risk of fibrinolysis
- Time required for transport to a skilled PCI laboratory

Step 2: Determine if fibrinolysis or invasive strategy is preferred.

Fibrinolysis is generally preferred if:

- Early presentation (≤3 hour from symptom onset and delay to invasive strategy)
- Invasive strategy is not an option
- Catheterization laboratory occupied or not available
- Vascular access difficulties.
- Lack of access to a skilled PCI laboratory.
- Prolonged transport.
- Door-to-Balloon time more than 90 minutes.

An invasive strategy is generally preferred if:

- Skilled PCI lab is available with surgical backup
- Door -to-balloon time less than 90 min
- High risk from STEMI.
- Cardiogenic shock.
- Killip class ≥3.

Contraindications to fibrinolysis:

- Increased risk of bleeding and ICH
- Late presentation.
- Diagnosis of STEMI is in doubt.

MATERIALS AND METHODS

1. SOURCE OF DATA:

- The material of present study collected from the patients who are admitted in B.L.D.E.U'S Shri B.M.Patil Medical College hospital and research centre, Bijapur who were diagnosed with acute myocardial infarction.
- The patients were informed about study in all respects and informed consent was obtained.
- Period of study is from October 2011to April 2013.

2. METHOD OF COLLECTION OF DATA:

A total of 100 patients taken for the study, every case was included after

- Detail history (chest pain lasting more than 20 minutes).
- ECG changes (including ST segment elevation, ST depression or pathological Q waves).
- CPK more than 2 times the upper limit of the normal.
- Patients were followed for 7 days from the date of admission, and total number of mortality and signs of heart failure (killip classification) that occurred in these 7 days are noted.

LABORATORY ASSESSMENT OF URIC ACID

SAMPLE COLLECTION

Oral and written consent was taken from the subjects prior to the collection of specimens. Approximately 3ml of venous blood was collected in a clean dry test tube and transported to the laboratory. On day 0 uric acid sample is obtained immediately after admission. On day 3 and 7 early morning blood samples were taken.

URIC ACID ESTIMATION:

PRINCIPLE:

Uricase converts uric acid into allantoin and hydrogen peroxidase . In the presence of peroxidase, hydrogen peroxide oxidatively couples with phenolic chromogens to form a red coloured compound , which has maximum absorbance at 510 nm .

The concentration of red coloured compound is propotional to the amount of uric acid in specimen.

$$\text{Uric acid} + H_2O \xrightarrow{\text{uricase}} \text{Allantoin} + H_2O_2$$

$$H_2O_2 + \text{phenolic chromogen} \xrightarrow{\text{peroxidase}} \text{Red colour compound .}$$

PROCEDURE :

Serum will be separated from blood within 30 minutes. 0.025 ml of serum is mixed with 1 ml of reagent (peroxidase , uricase , ascorbate oxidase , chromogen). The assay mixture incubated for 5 minutes at 37 degree C. After completion of the incubation .The assay mixture will be measured against reagent blank at 510 nm.

CALUCLATION:

1. With standard

$$\text{Serum Uric acid Concentration} = \frac{\text{Absorbance of sample}}{\text{Absorbance of standard}} \times \text{Concentration of standard (mg \%)}$$

3. SAMPLE SIZE:

- Time period of study from October 2011 to April 2013
- With prevalence of acute myocardial infarction – 7%(API text book of Medicine ,8th edition 2008 , K.K. Sethi)
- At confidence interval of 95% allowing $\pm$ 5 margin of error
- The calculated sample size is 100 using the below statistical formula.

$$n = \frac{(1.96)^2 (p) (1-p)}{d^2}$$

1. **STATISTICAL ANALYSIS:**

To analyze the data following methods was applied

- Data presented with mean $\pm$ SD.
- The levels of serum uric acid on day 0,3rd day, 7th day following acute myocardial infarction compared by Wilcoxon Matched Pairs Signed Rank test .
- Uric acid levels and killip's class compared with spearman correlation coefficient .

4. INCLUSION CRITERIA :

All AMI patients

1. Patients more than 18 yr of age.
2. Characteristic chest pain more than 20 minutes.
3. ECG changes (including ST segment elevation, ST depression or pathological Q waves).
4. CPK more than 2 times the upper limit of the normal.

5. EXCLUSION CRITERIA:

Any patient with a condition known to elevate uric acid level e.g.

- Chronic kidney disease.
- Gout.
- Hematological malignancy.
- Hypothyroidism.
- Patients on drugs which increase serum uric acid e.g. salicylates (>2 gm/d), Diuretics, Ethambutol, Pyrazinamide.
- Chronic alcoholics.

METHODS OF STUDY

- 136 patients presented with acute myocardial infarction. Out of which 30 patients were chronic alchoalic.6 patients had chronic kidney disease. These patients were excluded from the study. 100 Patients of acute MI who fulfilled inclusion criteria enrolled in study
- A detailed history and physical examination with special reference to Killip class was carried out.
- All patients underwent routine investigations including Hb, CBC, ECG, renal function tests.
- Serum uric acid level was measured on day 0, 3 & 7 of AMI.
- Patients were followed for 7 days from the date of admission.
- Total number of mortality and heart failure according to killip classification that occurred in these 7 days were noted and correlated with serum uric acid levels.

KILLIP CLASSIFICATION

I – No clinical signs of heart failure

II – Rales or crackles in the lungs, an S3, elevated JVP .

III – Frank pulmonary edema.

IV – Cardiogenic shock or hypotension (measured as systolic blood pressure lower than 90 mmHg), and evidence of peripheral vasoconstriction (oliguria, cyanosis or sweating).

RESULTS

During the 18 month study period from October 2011 to April 2013 a total of 100 patients with acute myocardial infarction were studied.

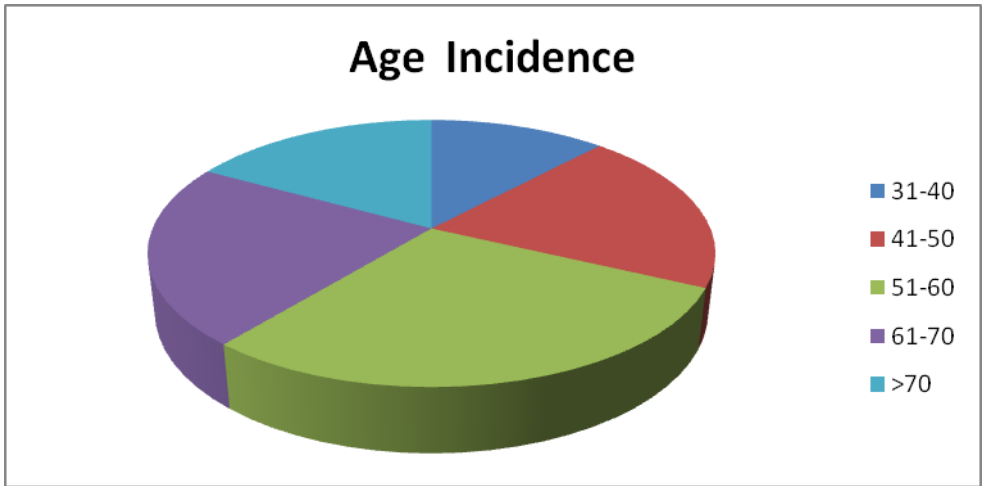
AGE:

The mean age of the patients included in the study is 58.43 ± 13.77 ranging from 35 years to 88 years. Out of 100 patients 12 were in the age group of 31 – 40 years, 20 were in age group of 41 – 50 years, 29 were in age group of 51 – 60 years, 22 were in age group of 61 – 70 years, 17 were in age group of more than 70 years. There was significant number in the age group of patients belonging to 51 – 70 years.

Table 1

Age(Years)	**Frequency**	**Percentage**
31 – 40	12	**12**
41 -50	20	**20**
51 – 60	2 9	**29**
61 – 70	22	**22**
>70	17	**17**
Total	100	**100**

Graph-1



SEX

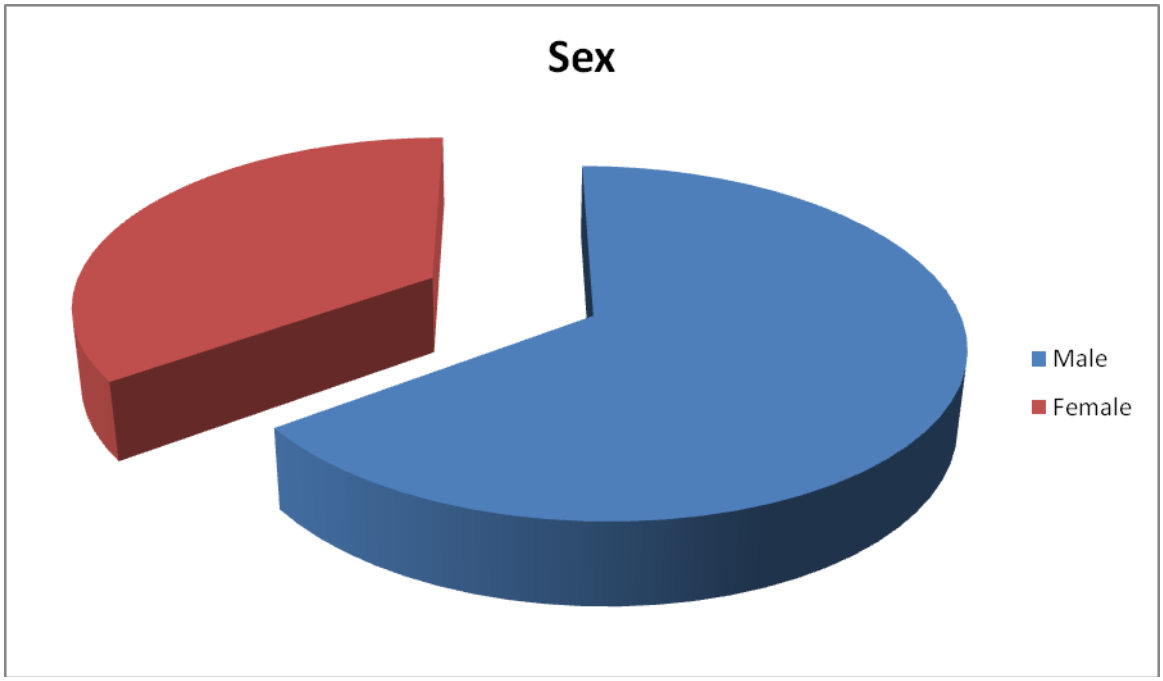
Total number of male patients were 65 and female patients were 35.Mean uric acid levels in male patients on day 0 is 5.244 ± 1.986 and female is 5.057 ± 1.781.

Table – 2

SEX	Frequency	Percentage	Mean UA level (Day 0)
MALE	65	65	5.244 ± 1.986
FEMALE	35	35	5.057 ± 1.781

Mann whitney test. U = 1073.5, P = 0.6463 (not significant)

Graph - 2



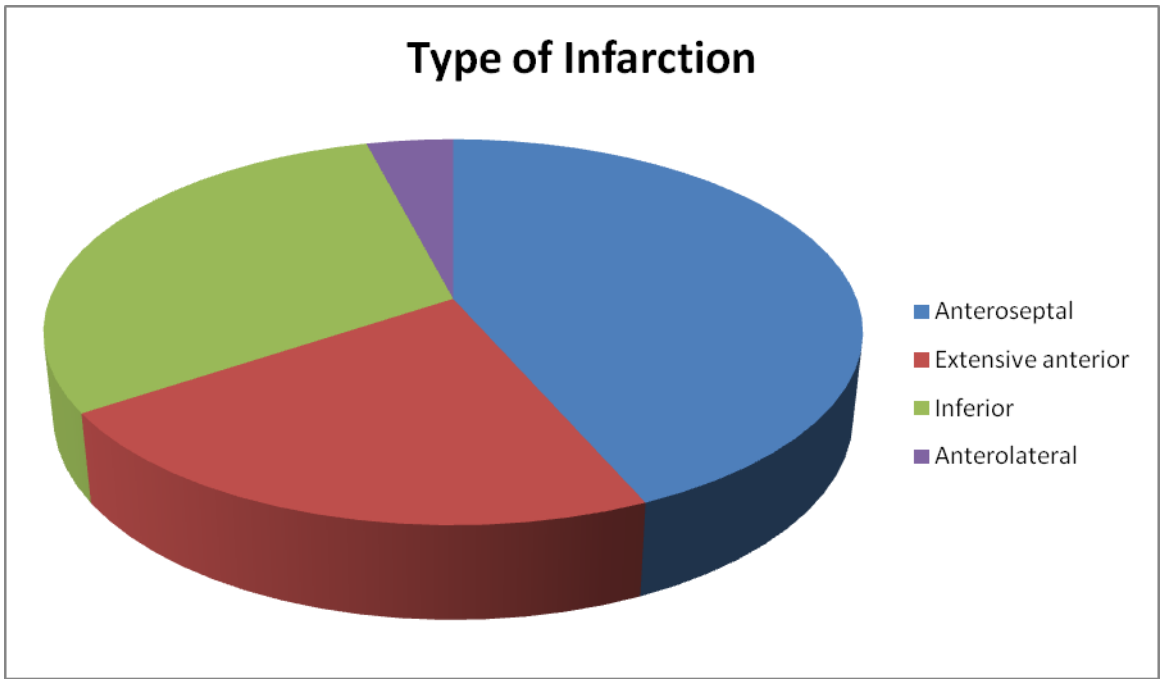
TYPE OF INFARCTION

Out of 100 patients, Anteroseptal wall MI was seen in 44 patients, Extensive anterior wall MI was seen in 22 patients, Inferior wall MI in 30 patients, Anterolateral wall MI in 4 patients.

Table-3

TYPE OF INFARCTS	Frequency	Percentage
Anteroseptal wall MI	44	44
Extensive anterior wall MI	22	22
Inferior wall MI	30	30
Anterolateral wall MI	4	4
Total	100	100

Graph – 3



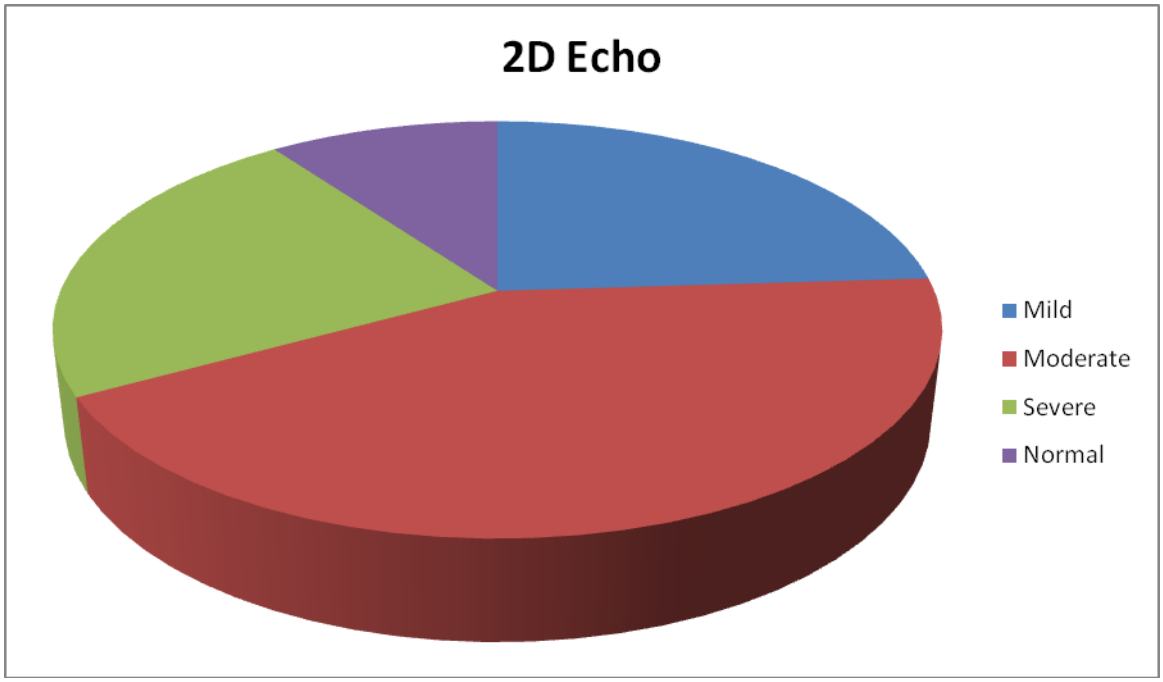
ECHOCARDIOGRAPHY:

2D Echocardiogram was performed and looked for LV dysfunction, Ejection fraction, and wall motility. Mild LV dysfunction was seen in 24 patients, Moderate LV dysfunction in 43 patients, Severe in 23 patients. In 10 patients it was normal LV function.

Table-4

LV dysfunction	Frequency	Percentage
Mild	24	24
Moderate	43	43
Severe	23	23
Normal	10	10
Total	100	100

Graph -4

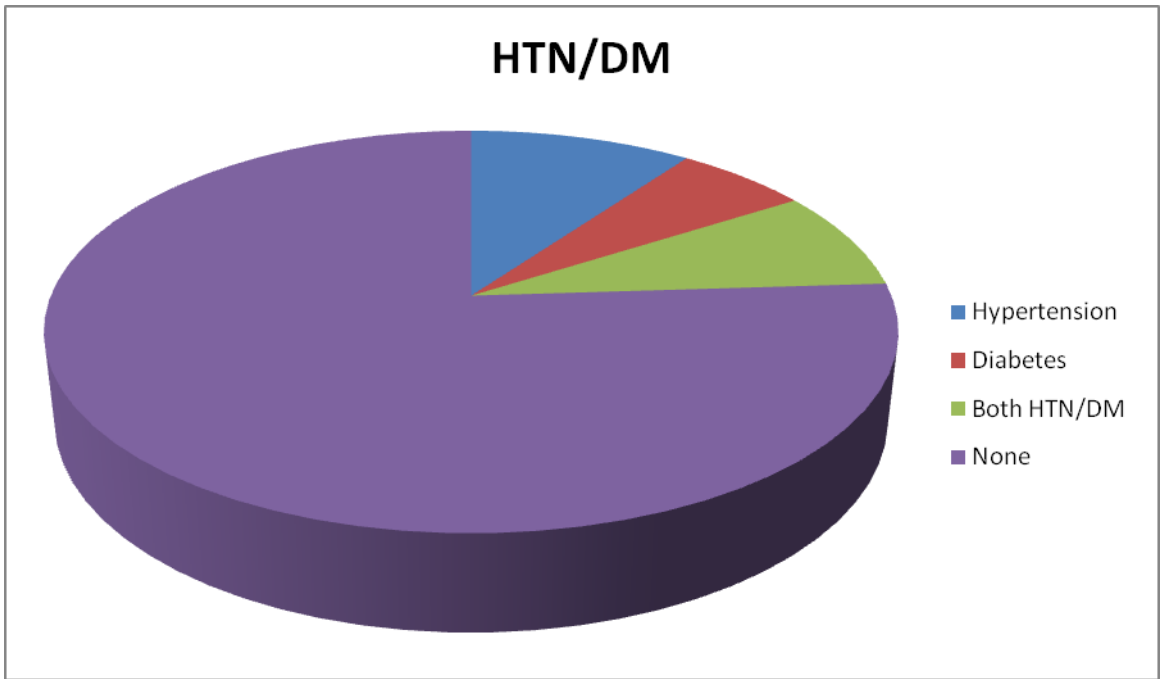


HYPERTENSION & DIABETES MELLITUS : Out of 100 patients, 10 patients had only Hypertension, 6 patients had only Diabetes and 8 patients had both Diabetes and Hypertension.

Table 5

VARIABLES	YES	NO	STATISTICAL ANALYSIS
HYPERTENSION Sr uric acid on Day 0	18 5.505 ± 1.624	82 5.107 ± 1.969	Mann whitney test. U = 608.10 P = 0.2463(not significant)
DIABETES MELLITUS Sr uric acid on Day 0	14 4.55 ± 1.029	86 5.28 ± 2.003	Mann whitney test. U = 483.5 P = 0.2411(not significant)

Graph-5



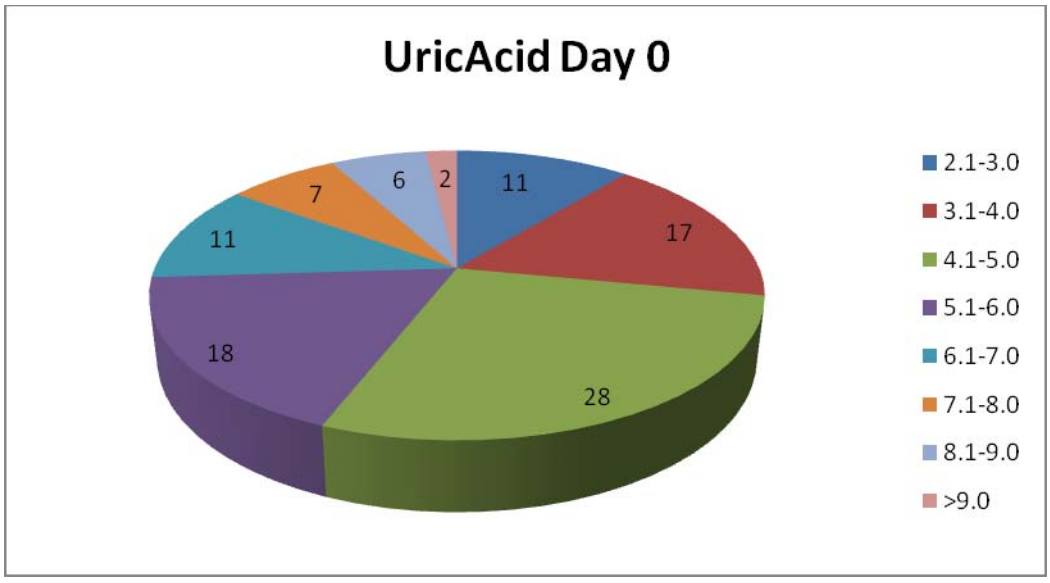
URIC ACID LEVELS DAY 0

Out of 100 patients, Serum uric acid levels in 11 patients is between 2.1 – 3.0 mg/dl, 17 patients in 3.1-4.0 mg/dl, 28 patients in 4.1-5.0mg/dl, 18 patients in 5.1-6.0mg/dl, 11 patients in 6.1-7.0 mg/dl, 7 patients in 7.1-8.0mg/dl, 6 patients in 8.1-9.0 mg/dl, 2 patients in >9mg/dl. Mean uric acid level on day 0 is 5.179 $\pm$ 1.910 mg/dl.

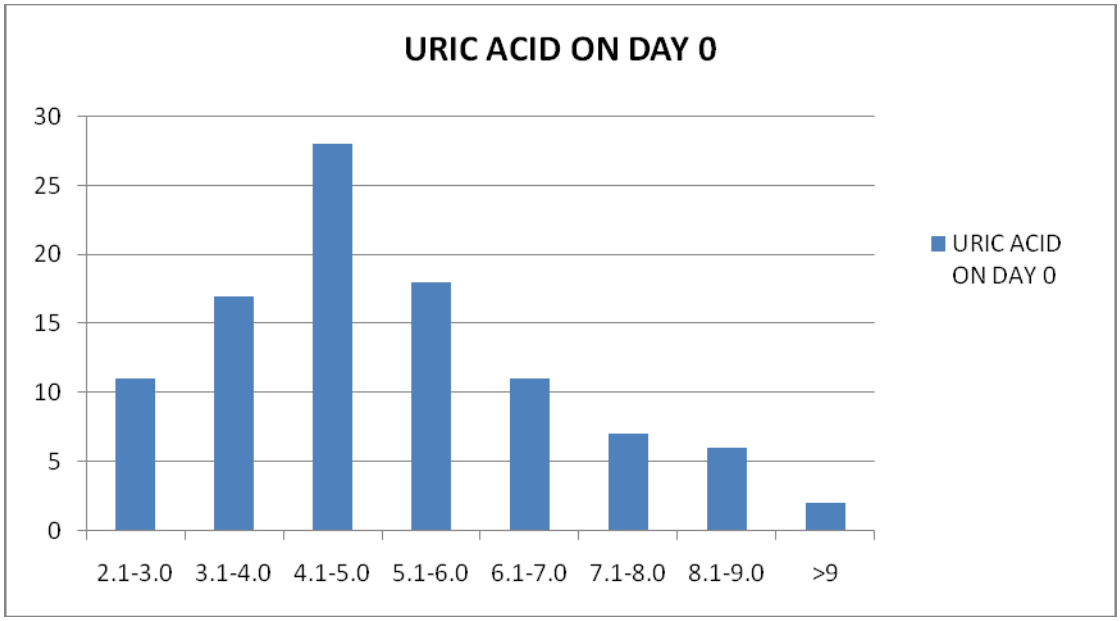
Table -6

Uric acid(mg/dl)	Frequency	Percentage
2.1-3.0	11	11
3.1-4.0	17	17
4.1-5.0	28	28
5.1-6.0	18	18
6.1-7.0	11	11
7.1-8.0	07	07
8.1-9.0	06	06
>9.0	02	02
Total	100	100

Graph – 6



Graph - 7


URIC ACID ON DAY 0
30
25
20
15
10
5
0
2.1-3.0
3.1-4.0
4.1-5.0
5.1-6.0
6.1-7.0
7.1-8.0
8.1-9.0
>9
URIC ACID ON DAY 0

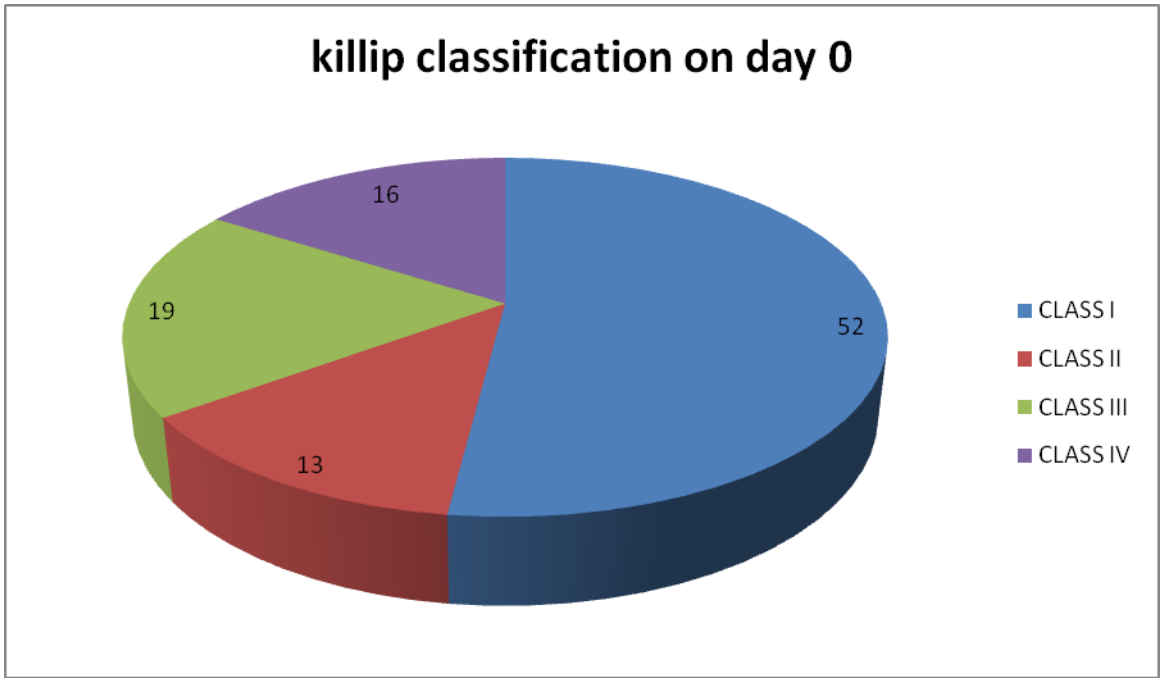
KILLIP CLASSIFICATION ON DAY O

Out of 100 patients 52 patients in class I, 13 patients in class II, 19 patients in class III, 16 patients in class IV.

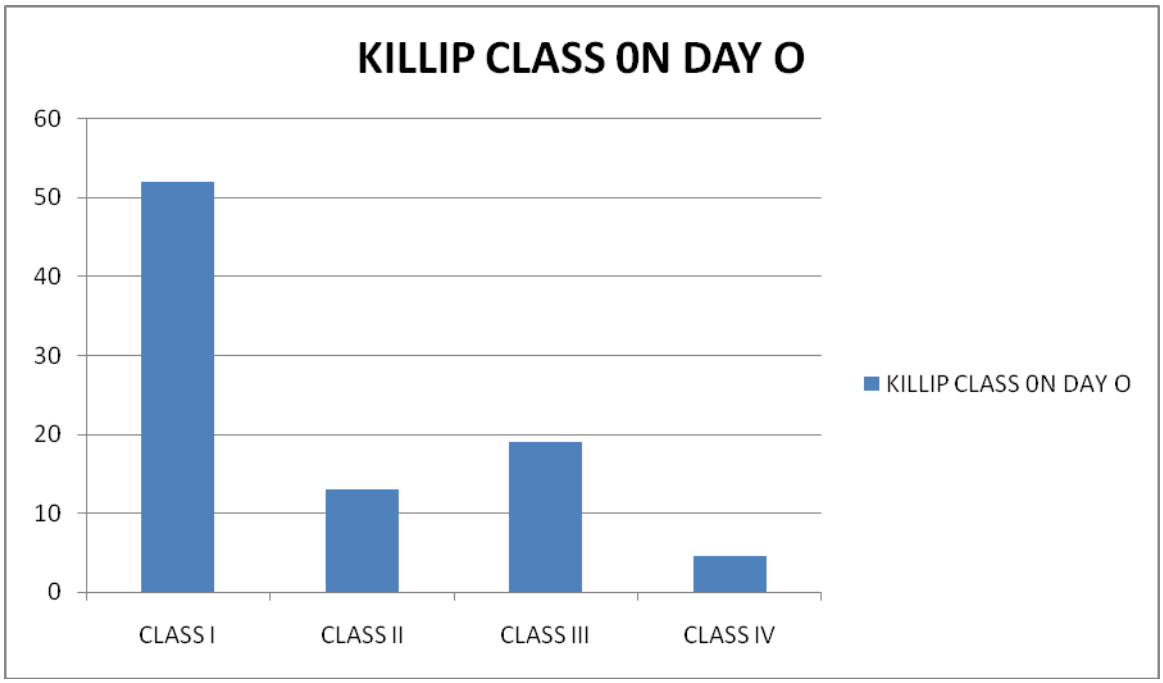
Table - 7

Killip classification	Frequency	Percentage
I	52	52
II	13	13
III	19	19
IV	16	16
Total	100	100

Graph - 8



Graph- 9



COMPARISON OF SERUM URIC ACID LEVEL AND KILLIP CLASS ON DAY O

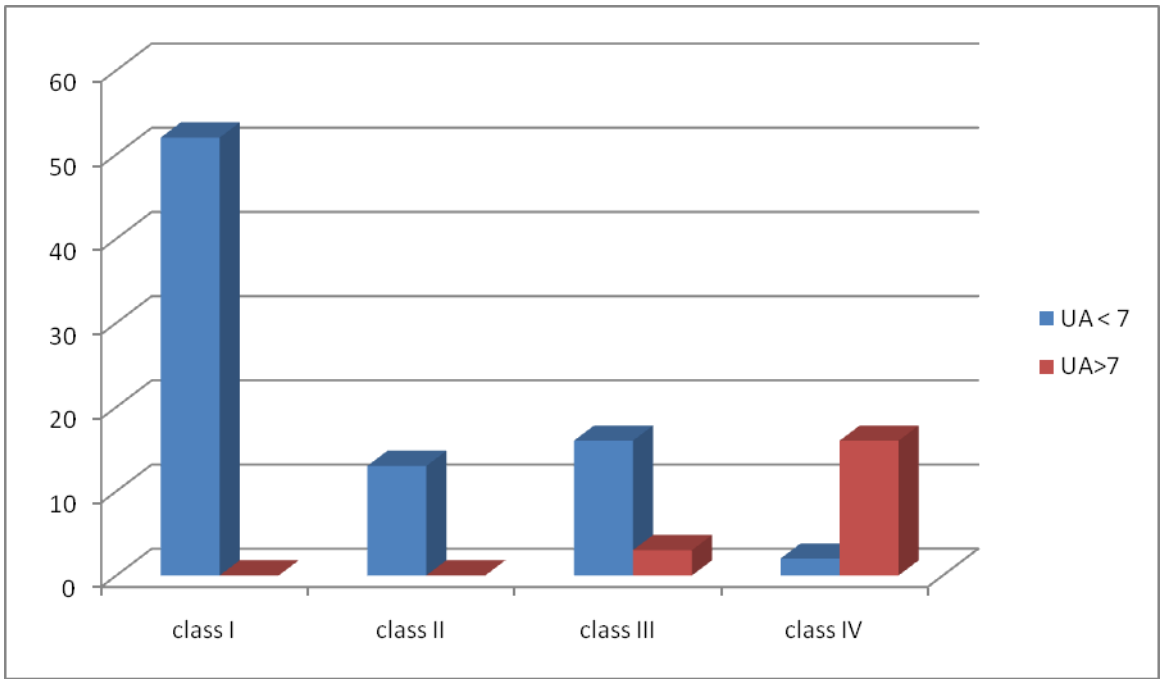
Out of 100 patients, 84 patients had uric acid level <7mg/dl and 16 patients had uric acid level >7mg/dl, out of 16 patients 3 were in killip class III and 13 were in class IV.14 patients died on Day 0

Table- 8

KILLIP CLASS	URIC ACID <7mg/dl	URIC ACID >7mg/dl	TOTAL
I	52	0	52
II	13	0	13
III	16	03	19

IV	02	13	16
TOTAL	84	16	100

Graph - 10



URIC ACID LEVELS VERSUS KILLIP CLASS CORRELATION ON DAY 0

SPEARMAN CORRELATION COEFFICIENT

r = 0.7374.

p < 0.0001 (Highly significant).

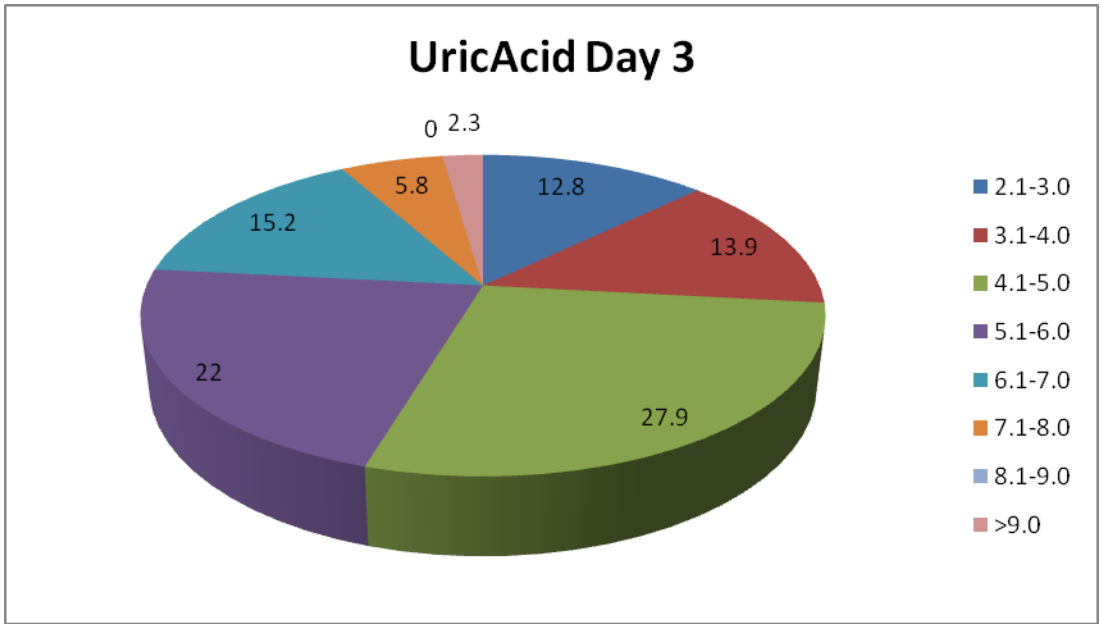
URIC ACID ON DAY 3

Out of 86 patients, Serum Uric acid levels in 11 patients is between 2.1–3.0mg/dl, 12 patients in 3.1-4.0mg/dl, 24 patients in 4.1–5.0mg/dl, 19 patients in 5.1–6.0mg/dl, 13 patients in 6.1-7.0mg/dl, 05 patients in 7.1-8.0mg/dl, 02 patients in >9.0mg/dl. Mean uric acid level on day 3 is 5.0325 $\pm$ 1.755

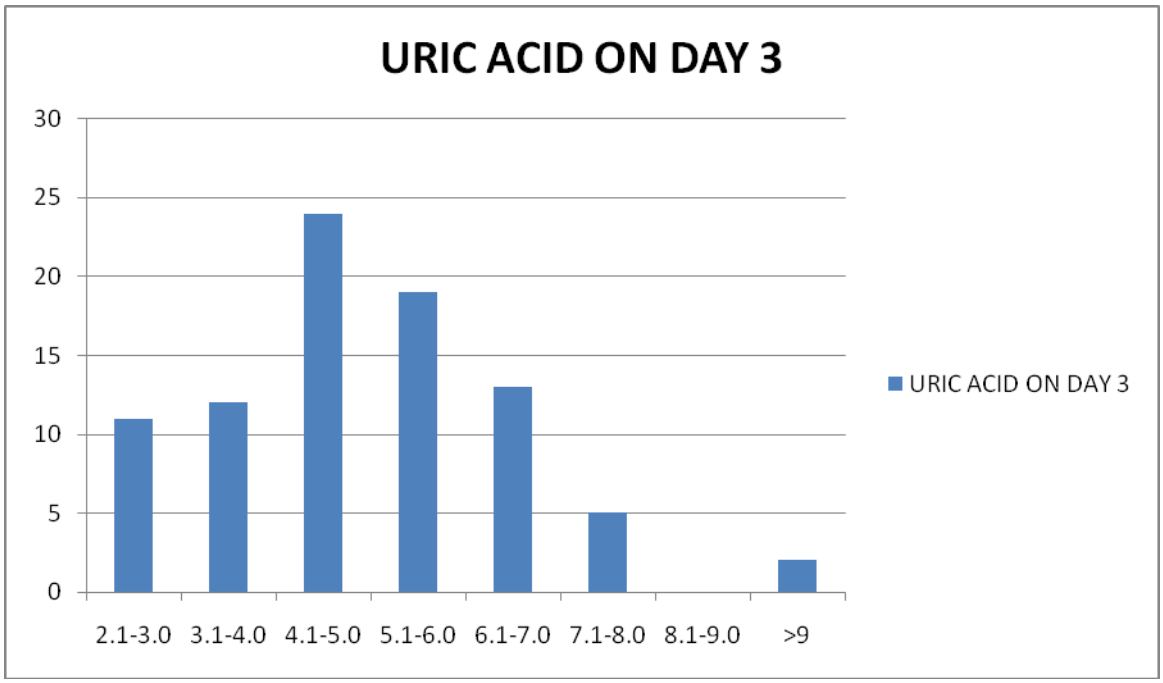
Table – 9

Uric acid(mg/dl)	Frequency	Percentage
2.1-3.0	11	12.8
3.1-4.0	12	13.9
4.1-5.0	24	27.9
5.1-6.0	19	22
6.1-7.0	13	15.2
7.1-8.0	05	5.8
8.1-9.0	00	00
>9.0	02	2.3
Total	86	100

Graph - 11


UricAcid Day 3
0
2.3
5.8
12.8
15.2
13.9
22
27.9
2.1-3.0
3.1-4.0
4.1-5.0
5.1-6.0
6.1-7.0
7.1-8.0
8.1-9.0
>9.0

Graph – 12


URIC ACID ON DAY 3
30
25
20
15
10
5
0
2.1-3.0
3.1-4.0
4.1-5.0
5.1-6.0
6.1-7.0
7.1-8.0
8.1-9.0
>9
URIC ACID ON DAY 3

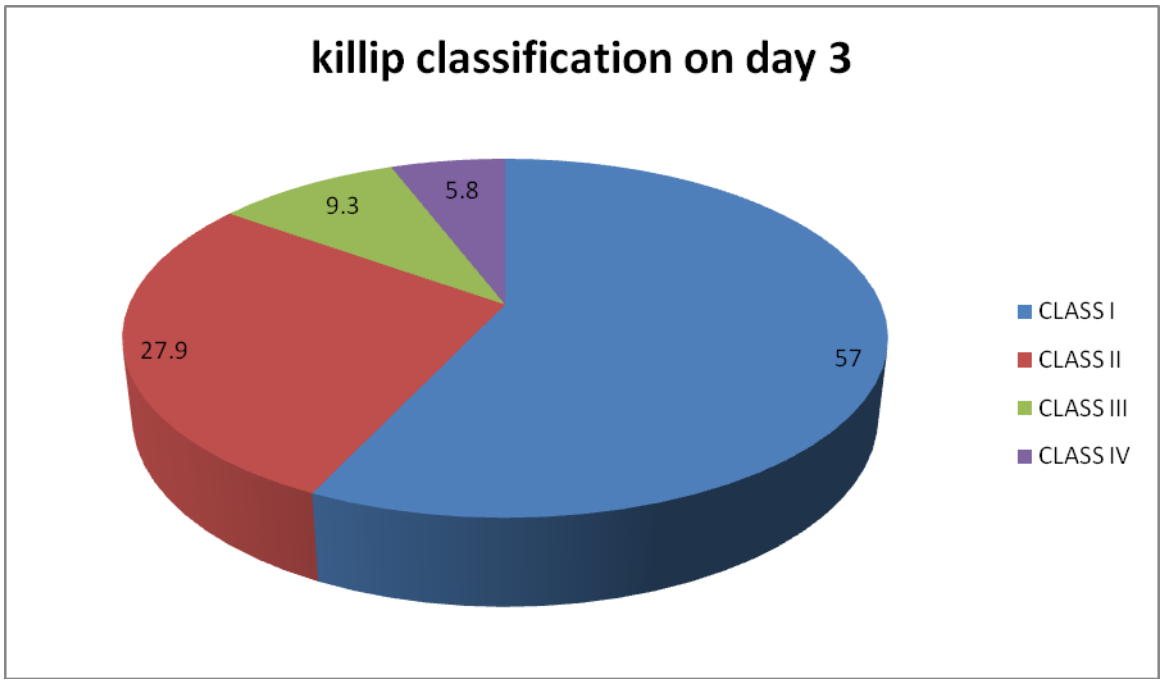
KILLIP CLASS ON DAY 3

Out of 86 patients 49 patients in class I, 24 patients in class II, 8 patients in class III, 5 patients in class IV.

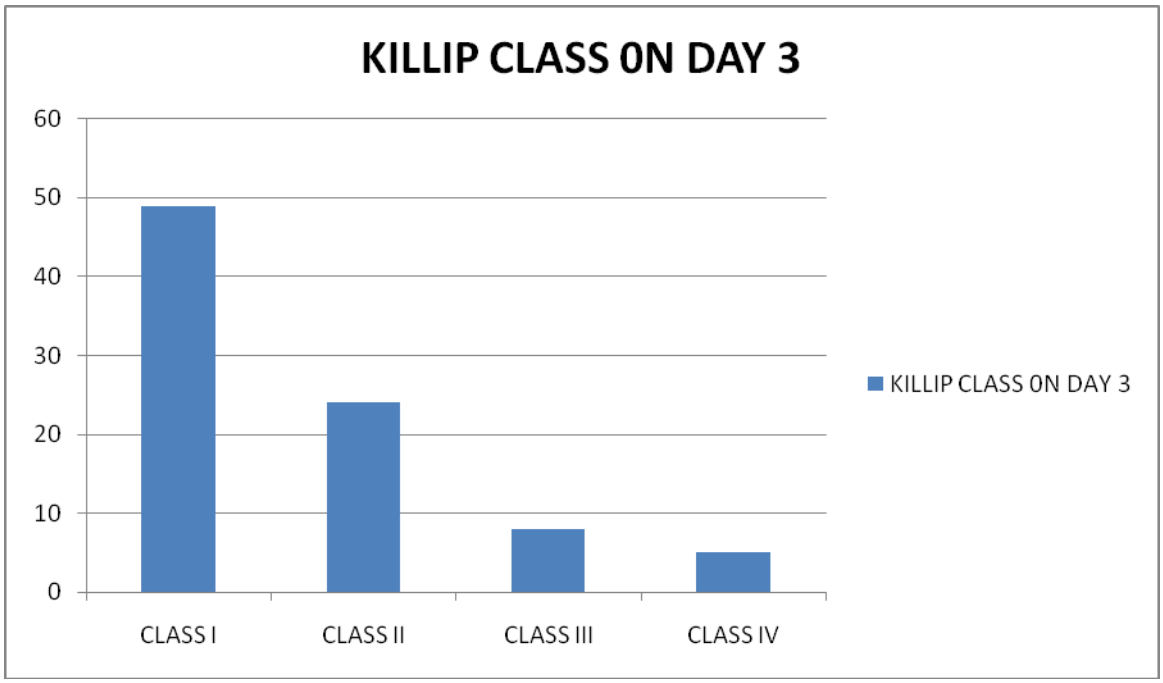
Table 10

Killip classification	Frequency	Percentage
I	49	57
II	24	27.9
III	08	9.3
IV	05	5.8
Total	86	100

Graph – 13



Graph-14



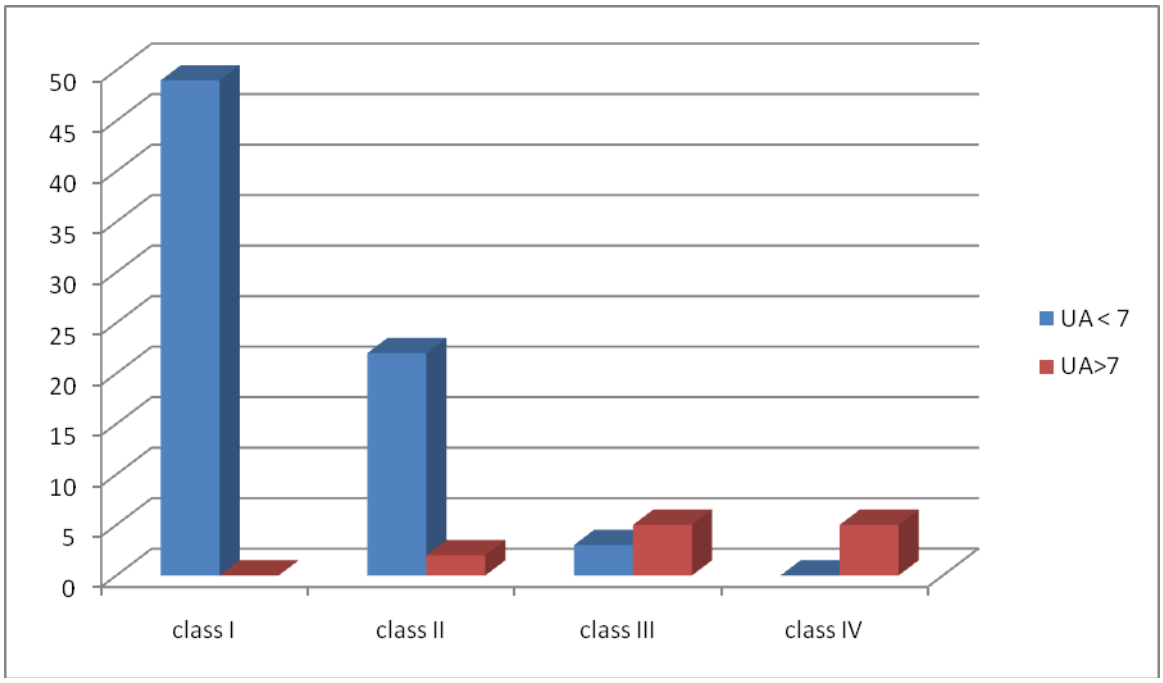
COMPARISON OF SERUM URIC ACID LEVEL AND KILLIP CLASS ON DAY 3

Out of 86 patients, 74 patients had uric acid < 7mg/dl and 12 patients had uric acid >7 mg/dl. Out of 12 patients 2 were in class II, 5 were in class III and 5 were in class IV.

Table-11

KILLIP CLASS	URIC ACID <7mg/dl	URIC ACID >7mg/dl	TOTAL
I	49	00	49
II	22	02	24
III	03	05	08
IV	00	05	05
TOTAL	74	12	86

Graph-15



URIC ACID LEVELS VERSUS KILLIP CLASS CORRELATION ON DAY 3

SPEARMAN CORRELATION COEFFICIENT

r = 0.5898.

p < 0.0001 (Highly significant).

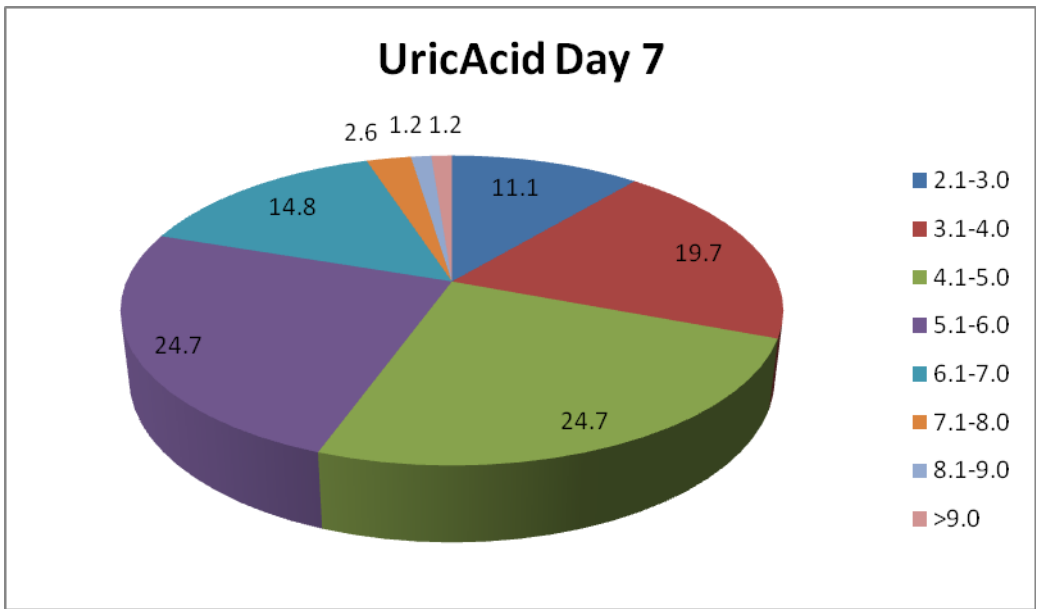
URIC ACID ON DAY 7

Out of 81 patients, Serum Uric acid levels in 9 patients is between 2.1–3.0mg/dl, 16 patients in 3.1-4.0mg/dl, 20 patients in 4.1–5.0mg/dl, 20 patients in 5.1–6.0mg/dl, 12 patients in 6.1-7.0mg/dl, 2 patients in 7.1-8.0mg/dl, 1 patient in 8.1-9.0mg/dl, 1 patient in >9mg/dl. Mean uric acid level on day 7 is 4.953 $\pm$ 1.446.

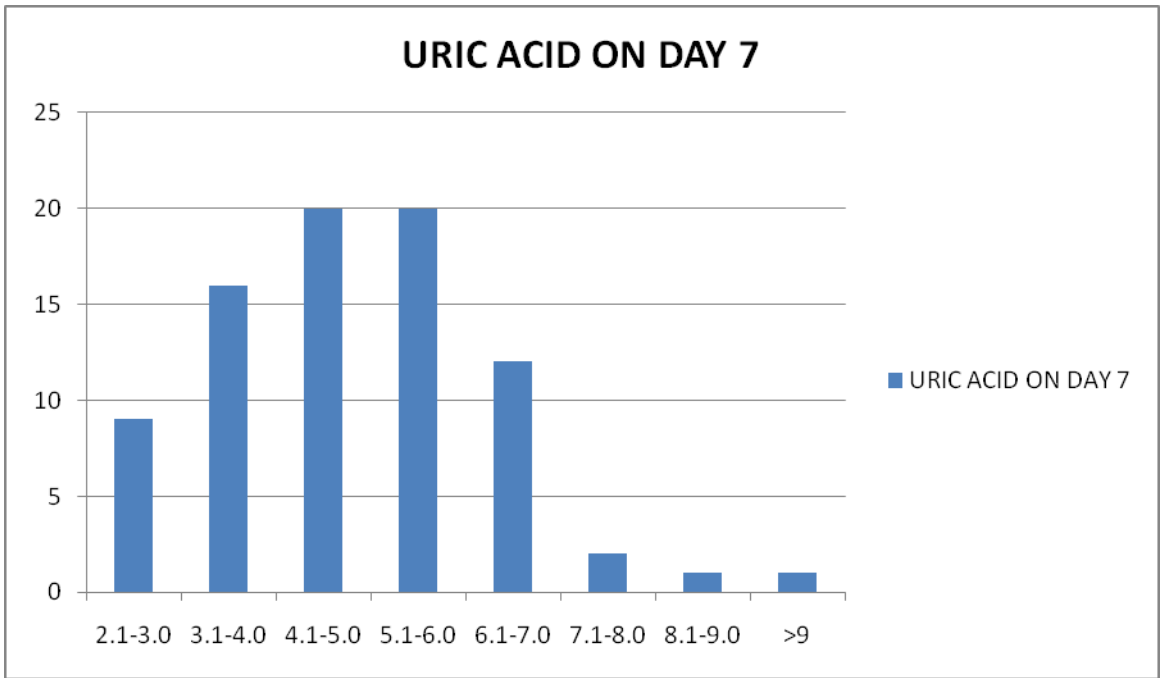
Table -12

Uric acid(mg/dl)	Frequency	Percentage
2.1-3.0	09	11.1
3.1-4.0	16	19.7
4.1-5.0	20	24.7
5.1-6.0	20	24.7
6.1-7.0	12	14.8
7.1-8.0	02	2.6
8.1-9.0	01	1.2
>9.0	01	1.2
Total	81	100

Graph - 16



Graph -17


URIC ACID ON DAY 7
25
20
15
10
5
0
2.1-3.0
3.1-4.0
4.1-5.0
5.1-6.0
6.1-7.0
7.1-8.0
8.1-9.0
>9
URIC ACID ON DAY 7

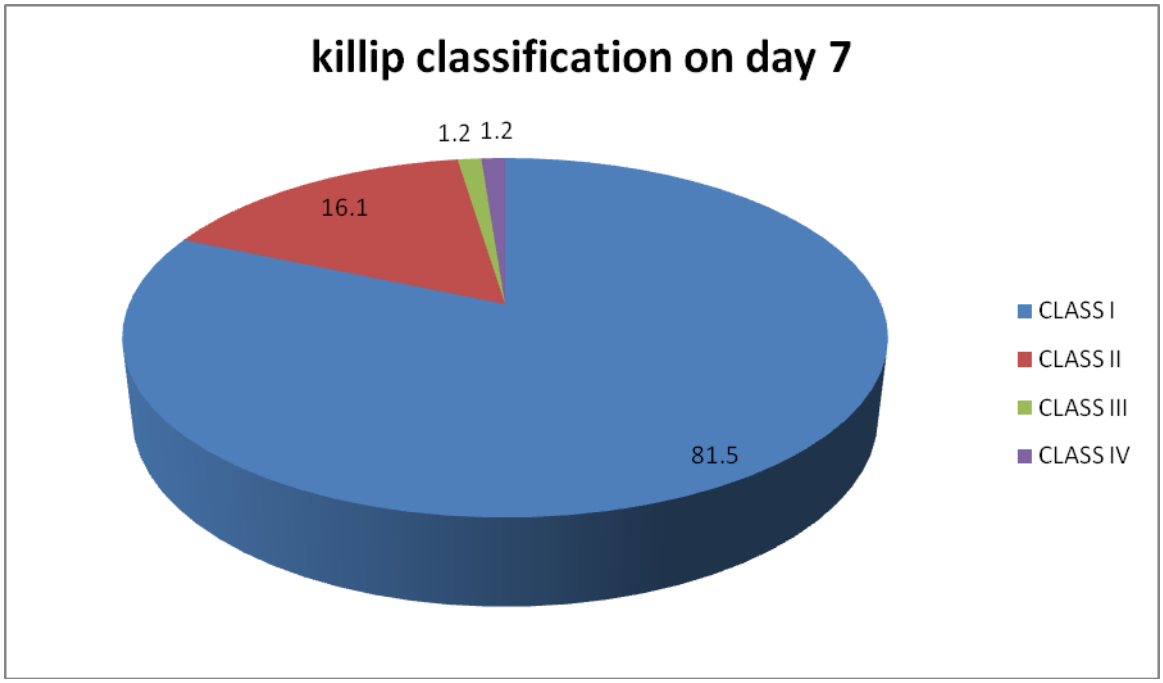
KILLIP CLASS ON DAY 7

Out of 81 patients 66 patients in class I, 13 patients in class II, 1 patient in class III, 1 patient in class IV.

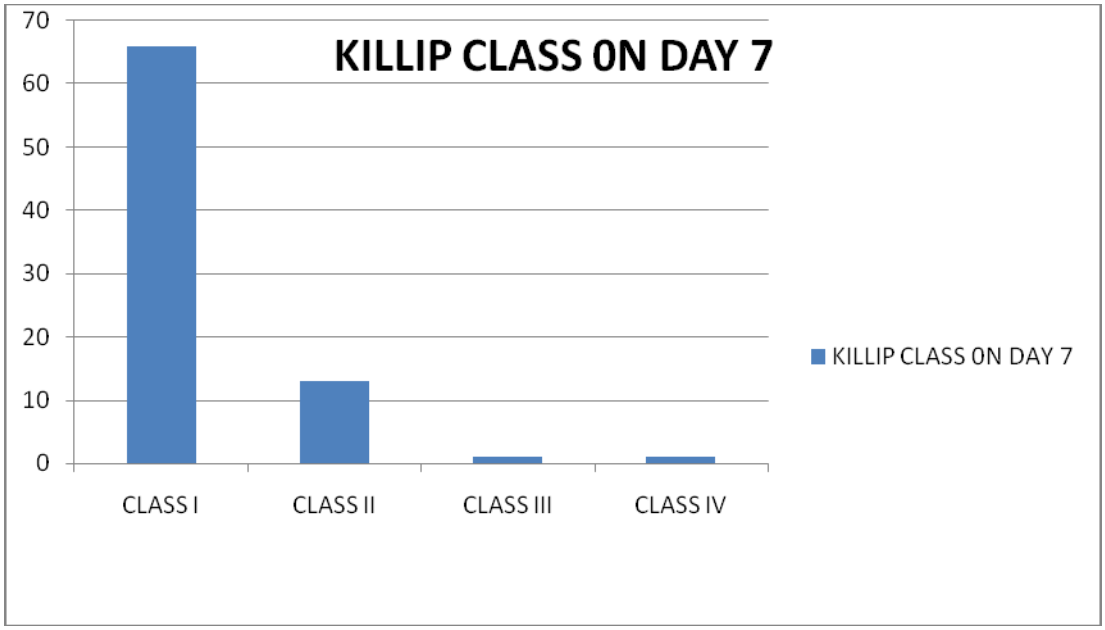
Table - 13

Killip classification	Frequency	Percentage
I	66	81.5
II	13	16.1
III	01	1.2
IV	01	1.2
Total	81	100

Graph - 18



Graph - 19



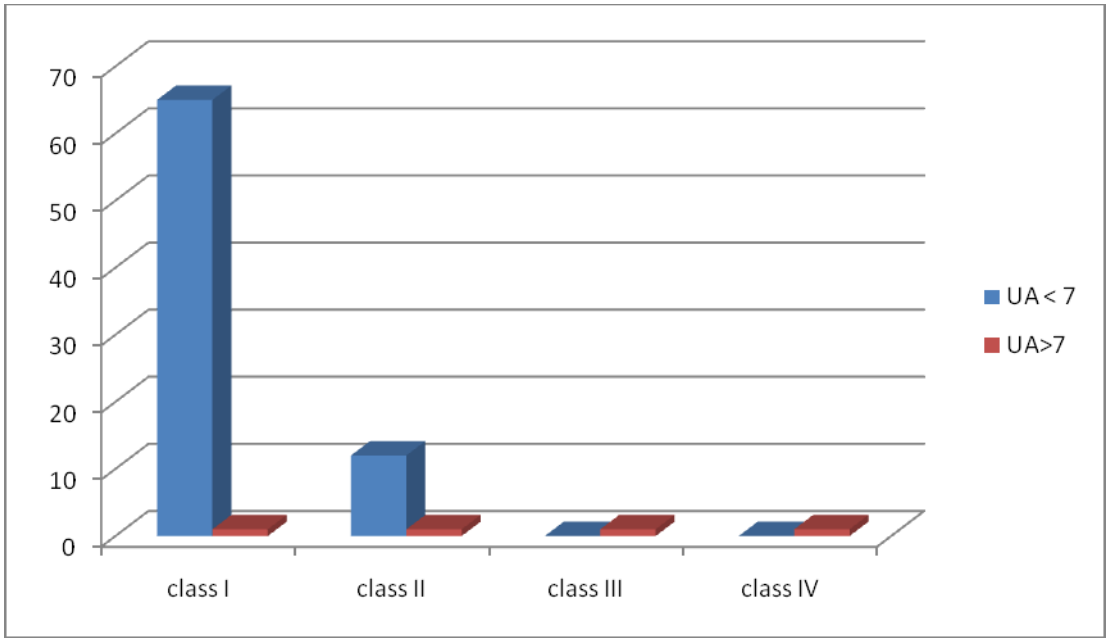
COMPARISON OF SERUM URIC ACID LEVEL AND KILLIP CLASS ON DAY 7

Out of 81 patients, 77 patients had uric acid < 7 mg/dl and 4 patients belong to uric acid >7 mg/dl, Out of 4 patients, 1 was in class I, 1 was in class II, 1 was in class III, 1 was in class IV.

Table 14

KILLIP CLASS	URIC ACID <7mg/dl	URIC ACID >7mg/dl	TOTAL
I	65	01	66
II	12	01	13
III	00	01	01
IV	00	01	01
TOTAL	77	04	81

Graph - 20



URIC ACID LEVELS VERSUS KILLIP CLASS CORRELATION ON DAY 7

SPEARMAN CORRELATION COEFFICIENT

r = - 0.0968.

p = 0.3921 (Not significant).

SERUM URIC ACID COMPARISON ON DAY 0 AND DAY 3

Day 0 Uric acid level (mean) – 5.179 $\pm$ 1.91.

Day 3 Uric acid level (mean) – 5.032 $\pm$ 1.75

Wilcoxon Matched Pairs Signed ranks test

P = 0.0605 (not significant)

SERUM URIC ACID COMPARISON ON DAY 0 AND DAY 7

Day 0 Uric acid level (mean) – 5.179 $\pm$ 1.91.

Day 7 Uric acid level (mean) – 4.953 $\pm$ 1.446

Wilcoxon Matched Pairs Signed ranks test

P = 0.0274 (significant)

SERUM URIC ACID COMPARISON ON DAY 3 AND DAY 7

Day 3 Uric acid level (mean) – 5.032 $\pm$ 1.75

Day 7 Uric acid level (mean) – 4.953 $\pm$ 1.446

Wilcoxon Matched Pairs Signed ranks test

P = 0.0424 (significant)

MORTALITY

Out of 100 patients, 20 expired during 7 day follow up. Out of the 20 patients who died, 16 had serum uric acid level more than 7.0 mg/dL.

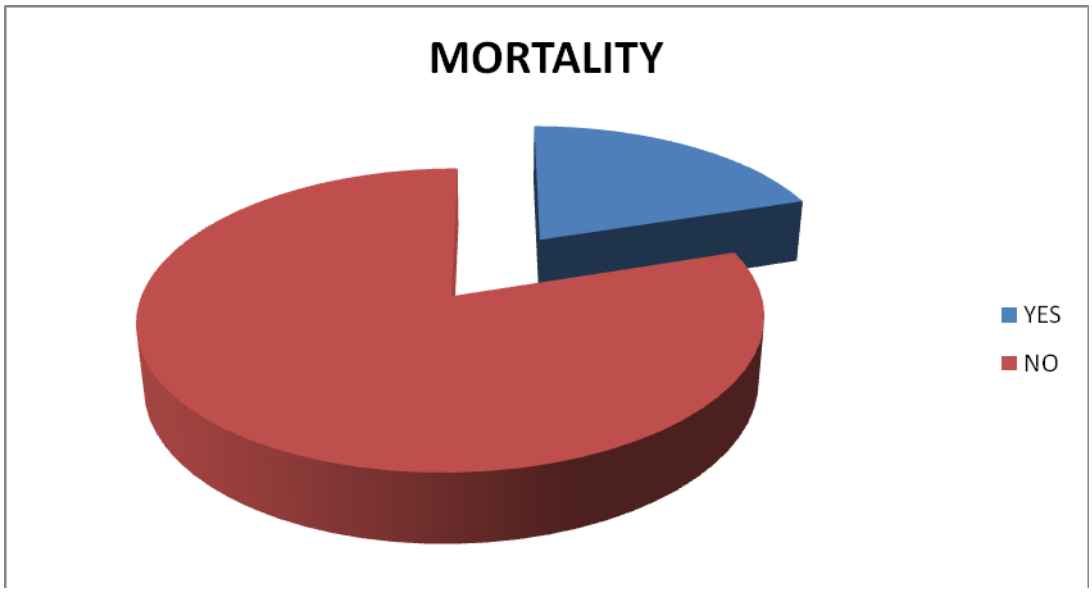
Of these 20 patients, 2 was in killip class I, 6 in class III and 12 in class IV at the time of admission. Thus 90 % of patients who died were in higher class i.e., class III and IV at time of admission. 1 patient of killip class I and 2 patients of killip class III shifted to killip class IV on day 3.Out of these 20 patients, 16 patients had uric acid more than 7 mg/dl. Therefore it shows that serum uric acid concentration is significantly correlated with killip class.

Table - 15

MORTALITY	YES	NO	TOTAL
	20	80	100
Mean serum uric acid level	6.845 $\pm$ 2.715	4.783 $\pm$ 1.386	

Unpaired t test. $t = 4.82$, $p < 0.0001$ (highly significant)

Graph – 21



MORTALITY AND SERUM URIC ACID CORRELATION

Table - 16

Variables	UA < 7 mg/dl	UA > 7 mg/dl	Total
Day 0	04	10	14
Day 3	0	05	05
Day 7	0	01	01
Total	04	16	20

MORTALITY AND KILLIP CLASS CORRELATION

Table - 17

Variables	Class I	Class II	Class III	Class IV	Total
Day 0	1	0	3	10	14
Day 3	0	0	0	5	5
Day 7	0	0	0	1	1
Total	1	0	3	16	20

DISCUSSION

In a study done in Japan in 2005 by Kojima et al, it was shown that Combination of Killip class and serum uric acid level after acute myocardial infarction is a good predictor of mortality in patients who have acute myocardial infarction. Using this study as referral study, we tried to find correlation between serum uric acid and Killip class and their prognostic value in our patients.

Present study was conducted in 100 patients of acute STEMI, who presented to hospital with in 24 hrs of onset of symptoms.

Out of 100 patients 65 were male and 35 were female, mean uric acid levels on day 0 in male patients was 5.244 $\pm$ 1.986 and in female is 5.057 $\pm$ 1.781.In this study there was no significant difference in uric acid levels between male and female patients(p = 0.6463 - NS). (Table 2) however in referral study males had higher uric acid levels as compared to females.[7]

In this study higher incidence of Acute MI is seen in the age group of 41-60 years (49% Table 1).

Out of 100 patients, 18 patients were hypertensive and 14 patients had diabetes, mean uric acid levels on day 0 in hypertensive patients was 5.505 $\pm$ 1.624 and in Non hypertensive patient was 5.107 $\pm$ 1.969. There was no significant difference in uric acid levels between hypertensive and Non hypertensive patients (P = 0.2463 - NS). This is different than other studies which showed that hypertensive patients had more hyperuricaemia.[7,56] Mean uric acid levels on day 0 in diabetic patients was 4.55 $\pm$ 1.029 and in Non diabetic patient was 5.28 $\pm$ 2.003. There was no significant difference in uric acid levels between diabetic and Non diabetic patients (P = 0.2411- NS). This finding is consistent with study by Tuomilheto et al[57] in which

there was no significant association between serum uric acid level and diabetic status. However, this finding is in contrast to other study by Safi et al[58] which showed that hyperuricaemia is significantly associated with type 2 diabetes mellitus.

Killip classification used as an indicator of severity of heart failure. There was a correlation between serum uric acid level and Killip class on day of admission as in earlier study[7]. On day of admission out of 100 patients, 16 patients had serum uric acid >7mg/dl in which 13 patients in killip class IV and 3 patients in killip class III (Table-8) ($p<0.0001$-highly significant).100% of patients who had serum uric acid >7mg/dl were in higher killip class (class III&IV).

On day 3, out of 84 patients 12 patients had serum uric acid >7mg/dl in which 5 patients in killip class IV and 5 patients in killip class III (Table 11) ($P<0.0001$-highly significant). 83% of patients who had serum uric acid >7mg/dl were in higher killip class.

On day 7 out of 81 patients 4 patients had serum uric acid >7mg/dl in which 1 patient in killip class IV and 1 patient in killip class III (Table 14) ($p<0.3921$-not significant).50 percent of patients who had serum uric acid >7mg/dl were in higher killip class. Thus patients of killip class III&IV had higher levels of uric acid as compared to patients of killip class I&II.

Out of 100 patients, 20 expired during 7 day follow up. The mean uric acid level in expired patients is 6.845 ± 2.715 and in other patients is 4.783 ± 1.386, which was a statistically significant difference($t = 4.82$, $p < 0.0001$ -highly significant).

Out of the 20 patients who died, 16 had serum uric acid level more than 7.0 mg/dl and 4 patients had serum uric acid less than 7mg/dl (Table 16). Of these 20

patients, 2 was in killip class I, 6 in class III and 12 in class IV at the time of admission. Thus 90 % of patients were in higher class i.e class III and IV at time of admission.

Out of 20 patients, 14 died on day of admission in which 10 patients were in killip class IV, 3 patients in killip class III and 1 patient in killip class I 5 patients died on day 3 follow up of these 1 patient was in killip class I, 2 patients in killip class III initially, later shifted to killip class IV on day 3, who died later. 1 patient died on day 7 follow up who was initially in killip class III at the time of admission, killip class II on day 3,shifted to killip class IV,who died later($p=0.0003$-highly significant).

Thus, 19 patients who expired were in killip class IV and 16 patients had serum uric acid levels >7mg/dl at the time of death. Therefore 80% patients had higher serum uric acid levels. Therefore it shows that mortality significantly correlated with serum uric acid concentration and killip class.

Prompt restoration of myocardial blood flow is the therapeutic goal in AMI because early reperfusion decreases mortality rates. In patients who had AMI, were in a high Killip's class, and had high UA concentrations. A failing heart due to AMI may cause tissue hypoperfusion and hypoxia, which trigger xanthine oxidase activation and oxidative stress production. Xanthine oxidase and oxidative stress as reflected by UA may form a vicious cycle that promotes severe heart failure. Therefore, UA may not be only a bystander marker but also a causative marker of mortality in patients who have AMI[59]. In this regard, improvement of coronary reperfusion alone may be less effective in ameliorating heart failure and decreasing mortality rate in patients who have AMI and high UA level and are in a high Killip's class.

Adjunctive therapy designed to decrease xanthine oxidase activity and inhibit oxidative stress production is expected to sever the vicious cycle. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) study demonstrated that lowering serum UA concentrations by losartan was associated with a beneficial effect on cardiovascular outcome.[60] The UA-lowering effect of atorvastatin may have contributed to the decrease in cardiovascular mortality in the Greek Atorvastatin and Coronary Heart Disease Evaluation (GREACE) study.[61]

Therefore, any drug interventions, such as therapy to decrease serum UA level in addition to coronary reperfusion, may have a favorable effect on mortality in patients who have AMI.

CONCLUSION

Patients with elevated serum uric acid levels belonged to higher killip's classification and had higher mortality.

Hence we can use serum uric acid as an inexpensive cardiovascular risk marker and prognostic marker in MI patients.

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I

ANNEXURES

INFORMED CONSENT FORM

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

TITLE OF THE PROJECT - SERUM URIC ACID LEVEL AS A PROGNOSTIC INDICATOR IN ACUTE MYOCARDIAL INFRACTION

.

PRINCIPAL INVESTIGATOR - DR. AMITH GUPTA B.A

P.G.GUIDE NAME - **DR. L.S.PATIL**
PROFESSOR OF GENERAL MEDICINE

All aspects of this consent form are explained to the patient in the language understood by him/her.

I) **INFORMED PART**

1) PURPOSE OF RESEARCH:

I have been informed that this study is about measuring serum uric acid levels in acute myocardial infarction patients. I have also been given a free choice of participation in this study.

2) PROCEDURE:

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

3) RISK AND DISCOMFORTS:

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

4) BENEFITS:

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

5) CONFIDENTIALITY:

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

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

6) REQUEST FOR MORE INFORMATION:

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

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

7) REFUSAL OR WITHDRAWAL OF PARTICIPATION:

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

8) INJURY STATEMENT:

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

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

_____ _____

Dr. AMITH GUPTA Date

(Investigator)

II) **STUDY SUBJECT CONSENT STATEMENT:**

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

_____ _____

Participant / Guardian Date

_____ _____

Witness to signature Date

BLDE'S SHRI B.M.PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTRE, BIJAPUR

SERUM URIC ACID LEVEL AS A PROGNOSTIC INDICATOR IN ACUTE MYOCARDIAL INFRACTION

SCHEME OF CASE TAKING

Name: CASE NO:

Age: IP NO:

Sex: DOA:

Religion: DOD:

Occupation:

Residence:

Presenting complaints with duration:

Chest pain

-Duration

-Site

-Radiation

-Type

-Aggravating factors

-Relieving factors

Palpitation

-Duration

-Site

-Radiation

-Type

-Aggravating factors

-Relieving factors

Breathlessness

-Duration

-Grade

-Orthopnea

-PND attack

Other symptoms

-Sweating

-Haemoptysis

-Cough

History of presenting complaints:

Past History:

History of hypertension

History of diabetes mellitus

Past history of IHD

Personal History:

Diet

Appetite

Sleep

Bladder and bowel habits:

Smoking/Tobacco chewing/Snuff Inhalation

Duration

Number of cigarettes/beedis pack year smoked

Amount of tobacco chewed/snuff inhaled

Alcohol

Duration

Quantity/Frequency

Type

Family History:

History of suggestive of Ischemic Heart Disease/hypertension/ diabetis mellitus

Treatment History:

General Physical Examination

Pallor: present/absent

Icterus: present/absent

Clubbing: present/absent

Generalized lymphadenopathy: present/absent

Built: Poor/Middle /Well

Nourishment: Poor / Middle / Well

Vitals

PR:

BP:

RR:

Temp:

SYSTEMIC EXAMINATION.

- Cardiovascular system

  Arterial system

  BP

  Pulse

  -PR

  -Character

  -Rhythm

  -Volume

-condition of the arterial wall

-Comparison of the arterial wall

-Radio femoral delay

-Any special character

-Other peripheral pulses

Ulnar artery

Brachial artery

Subclavian artery

Carotid artery

Femoral artery

Popliteal artery

Posterior tibial artery

Dorsalis pedis artery

Venous System

Engorged veins in neck

JVP

Inspection

-Precordial bulge

-Parasternal heave

-Epigastric pulsation

-Visible apical impulse

-Any engorged veins

Palpation

Apical impulse

Site

Character

Thrill

Palpable P2

Percussion

Auscultation

Mitral area

Heart sounds

Murmurs

Tricuspid area

Heart sounds

Murmurs

Aortic area

Heart sounds

Murmurs

Pulmonary area

Heart sounds

Murmurs

- Respiratory System

Position of treachea

Chest symmetry

Liver dullness

Breath sounds

Any added sounds

Per Abdomen

Organomegaly

Any evidence of free fluid

Central Nervous System

Consciousness

Orientation

Any focal neurological defect

INVESTIGATIONS

HAEMATOLOGY –

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

BIOCHEMISTRY–

Serum uric acid	Day 0	Day 3	Day 7

Serum creatinine	
Random blood sugar	

URINE EXAMINATION -

Protein	
Sugar	
Microscopy	

Liver function tests:

Chest X Ray PA view:

12 lead ECG

CPK-MB:

2D ECHOCARDIOGRAPHY AND COLOR DOPPLER:

FINAL DIAGONOSIS :

KEY TO MASTER CHART

UA	- Serum Uric acid
HTN	- Hypertension
DM	- Diabetes Mellitus
ECG	- Electrocardiography
LV Dys	- Left ventricular dysfunction
ASWMI	- Anteroseptal wall Myocardial infarction
EXTAWMI	- Extensive Anterior wall Myocardial infarction
IFWMI	- Inferior wall Myocardial infarction
ALWMI	- Anterolateral wall Myocardial infarction
N	- No
Y	- Yes