SERUM URIC ACID LEVELS AND END ORGAN DAMAGE IN ESSENTIAL HYPERTENSION

A Dissertation submitted to

THE TAMIL NADU DR.M.G.R. MEDICAL UNIVERSITY

in partial fulfilment of the Regulations

for the award of the degree of

M.D (GENERAL MEDICINE) BRANCH - I

DEPARTMENT OF GENERAL MEDICINE

GOVERNMENT KILPAUK MEDICAL COLLEGE AND HOSPITAL,

CHENNAI

MAY 2023

Reg. No: 200120102021

CERTIFICATE

This is to certify that this dissertation entitled, **"SERUM URIC ACID LEVELS AND END ORGAN DAMAGE IN ESSENTIAL HYPERTENSION"** is the original Bonafide work done by **DR SARATH KUMAR K** Post graduate in General Medicine, under my overall supervision in the Department of General Medicine, Govt. Kilpauk Medical College in partial fulfillment of the regulations of The Tamilnadu Dr. M.G.R Medical University for the award of **M.D. DEGREE IN GENERAL MEDICINE.**

DR. P.PARANTHAMAN, M.D.,
Professor and HOD,
Department of General Medicine,
Govt. Kilpauk Medical College

Professor & HOD
Department of Medicine
Govt. Kilpauk Medical College
Chennai-10.

DR. R. SHANTHIMALAR, M.D., D.A.,
DME (FAC) / DEAN,
Govt. Kilpauk Medical College and
Hospital, Chennai - 600010

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation **"SERUM URIC ACID LEVELS AND END ORGAN DAMAGE IN ESSENTIAL HYPERTENSION"** at Govt. Kilpauk Medical College Hospital is a bonafide and genuine research work carried out by me in the Department of General Medicine, Government Kilpauk Medical and Hospital, Chennai-10, under the guidance of our **HOD and Prof. DR. P. Paranthaman MD,** Government Kilpauk Medical College and Hospital.

This dissertation is submitted to **THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI** in partial fulfillment of the University regulations for the award of M.D degree (General Medicine) Branch I, examination to be held in MAY 2023.

Date: 5/12/2022

Place: Chennai

Dr. SARATHKUMAR K

CERTIFICATE OF THE GUIDE

This is to certify that this dissertation entitled, "**SERUM URIC ACID LEVELS AND END ORGAN DAMAGE IN ESSENTIAL HYPERTENSION**" is the original Bonafide work done by **DR SARATH KUMAR K** Post graduate in General Medicine, under my overall supervision in the Department of General Medicine, Govt. Kilpauk Medical College in partial fulfillment of the regulations of The Tamilnadu Dr. M.G.R Medical University for the award of **M.D. DEGREE IN GENERAL MEDICINE.** "

DR PARANTHAMAN MD
Professor & HOD
Department of General Medicine,
Govt. Kilpauk Medical College,
Chennai- 600 010.

HOD & PROFESSOR
DEPARTMENT OF GENERAL MEDICINE
GOVT. KILPAUK MEDICAL COLLEGE & HOSPITAL
CHENNAI - 600 010.

GOVERNMENT KILPAUK MEDICAL COLLEGE,

INSTITUTIONAL ETHICS COMMITTEE

Reg.No. ECR/1385/Inst/TN/2020

CERTIFICATE OF APPROVAL

IEC PROTOCOL NO	: **716/2022**
TITLE OF THE STUDY	: **SERUM URIC ACID LEVELS AND END ORGAN DAMGE IN ESSENTIAL HYPERTENSION ; CROSS SECTIONAL STUDY AT A TERTIARY CARE HOSPITAL IN CHENNAI**
PRINCIPAL INVESTIGATOR	: DR.SARATH KUMAR K
DESIGNATION	: IIND YEAR POST GRADUATE
DEPARTMENT:	: DEPT OF GENERAL MEDICINE GOVT. KILPAUK MEDICAL COLLEGE, CHENNAI-10.

The request for an approval from the Institutional Ethics Committee (IEC) was considered on the IEC meeting held on **08/04/2022** at Government Kilpauk Medical College, Chennai-10.

The members of the Committee, the secretary and the Chairman are pleased to inform that the proposed work mentioned above, submitted by the principal Investigator is **APPROVED.**

The Principal Investigator and their team are directed to adhere to the guidelines given below:

1) You should inform the IEC in case of changes in study procedure, site, Investigator, Investigation, Guide or any other changes.
2) You should not deviate from the area of the work for which you applied for Ethical Clearance.
3) You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4) You should abide to the rules and regulations of the Institution(s)
5) You should complete the work within the specific period and if any extension of time is required, you should apply for permission again and do the work.
6) You should submit the summary of the work to the Ethical Committee on completion of the work.

MEMBER SECRETARY

Institutional Ethics Committee,
Kilpauk Medical College,Chennai.

DME(OSD)/DEAN

Kilpauk Medical College,
Chennai.

13/6/22

CERTIFICATE - II

This is to certify that this dissertation work titled **SERUM URIC ACID LEVELS AND END ORGAN DAMAGE IN ESSENTIAL HYPERTENSION**

of the candidate **DR. SARATH KUMAR** with registration Number **200120102021** for the award of **MD DEGREE** in the branch of **GENERAL MEDICINE**. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows **11%** percentage of plagiarism in the dissertation.

Guide & Supervisor sign with Seal.

HOD & PROFESSOR
DEPARTMENT OF GENERAL MEDICINE
GOVT. KILPAUK MEDICAL COLLEGE & HOSPITAL
CHENNAI - 600 010.

Ouriginal
by Turnitin

Document Information

Analyzed document	Final 1.docx (D152497506)
Submitted	2022-12-07 14:50:00
Submitted by	SARATH KUMAR K
Submitter email	sarathkajendiran@gmail.com
Similarity	11%
Analysis address	sarathkajendiran.tnmg@analysis.urkund.com

Sources included in the report

W	URL: http://repository-tnmgrmu.ac.in/5862/1/200100712santosh_kumar.pdf Fetched: 2021-11-02 11:01:37	6
SA	**STUDY OF SERUM URIC ACID LEVELS IN PATIENTS VISITING GOA MEDICAL COLLEGE AND HOSPITAL.docx** Document STUDY OF SERUM URIC ACID LEVELS IN PATIENTS VISITING GOA MEDICAL COLLEGE AND HOSPITAL.docx (D23042110)	9
SA	**thesis changed file.docx** Document thesis changed file.docx (D22705074)	3
SA	**abilash thesis.docx** Document abilash thesis.docx (D31629963)	6
SA	**The Tamil Nadu Dr. M.G.R. Medical University / Abisekha Plagiarism Check.docx** Document Abisekha Plagiarism Check.docx (D151547649) Submitted by: abichellathurai@gmail.com Receiver: abichellathurai.tnmg@analysis.urkund.com	2
SA	**THESIS FINAL.docx** Document THESIS FINAL.docx (D123646013)	10
SA	**THESIS FINAL.docx** Document THESIS FINAL.docx (D123636046)	2

ACKNOWLEDGEMENT

At the outset, I would like to thank my beloved Dean, Govt. Kilpauk Medical College & Hospital, Prof. Dr. R. SHANTHIMALAR, M.D., D.A. for her kind permission to conduct the study in Kilpauk Medical College. I express my indebtedness to my Guide Prof. Dr. P. Paranthaman M.D, Professor & HOD of Medicine, Department of General Medicine, Kilpauk Medical College & Hospital for permitting me to carry out this study and for his constant encouragement and guidance which had enabled me to complete my dissertation.

I thank my Assistant Professors, DR. V. MADHAVAN MD, DR. AGILA SARAVANAN MD and DR.ANURADHA MD for their constant help and support.

TABLE OF CONTENTS

LIST OF TABLES

18	Left ventricular hypertrophy and serum uric acid levels	
19	Serum uric acid levels in patients with coronary artery disease	
20	Albuminuria and serum uric acid levels	
21	Serum uric acid levels correlation with retinopathy	

LIST OF FIGURES

18	Serum uric acid levels correlation with left ventricular hypertrophy	
19	Correlation of serum uric acid levels with coronary artery disease	
20	Serum uric acid levels correlate with albuminuria	
21	Retinopathy and serum uric acid levels	

ABBREVIATION

UA	-	Uric acid
SUA	-	Serum uric acid
AT	-	Angiotensin
CVD	-	Cardiovascular disease
ESRD	-	End-stage renal disease
BP	-	Blood pressure
SBP	-	Systolic blood pressure
DPB	-	Diastolic blood pressure
JNC	-	Joint national committee
CKD	-	Chronic kidney disease
OAT	-	Organic anion transporters
URAT1	-	Urate transporter 1
hUAT	-	Human uric acid transporter
GWAS	-	Genome-wide association studies

INTRODUCTION

Hypertension is a cardiovascular disease that is increasing in developing countries. The disorder negatively affects an individual's lifespan and increases the risk of stroke, coronary heart disease, and target organ damage. [1]

In most studies, a patient is often diagnosed late with hypertension and comorbid conditions such as target organ damage. This leads to high morbidity and mortality among patients, which can be due to altered renal and cognitive functioning. [2]

Uric acid (UA) levels have often elevated in hypertension patients. The European Society of Hypertension has recommended laboratory testing for serum UA (SUA) levels in patients with hypertension. Elevated UA levels are considered a risk factor for the development of cardiovascular disease and can lead to organ damage. [3]

It has been demonstrated that serum uric acid levels are associated with multiple cardiovascular risk factors, including metabolic syndrome, diabetes, renal disease, and hypertension; however, the studies also reported that serum uric acid levels are often used for independently predicting cardiovascular events in patients with hypertension. [4]

Several pathological mechanisms are linked with SUA levels and cardiovascular damage, including the proliferation of vascular smooth muscle cells, stimulation

of the inflammatory pathway, and prothrombic effects due to platelet activation. [5] [6] [7]

The prevalence of subclinical hypertension and organ damage indicates an increased risk for cardiovascular events and renal morbidity among patients. Studies have reported that UA levels can be used as a prognostic marker for tissue ischemia, endothelial dysfunction, and the development of atherosclerosis. [8] [9] [10]

An increased hypertensive stage has been associated with targeted organ damage and renal dysfunction. The role of SUA in the development of cardiovascular diseases has been in research to understand the exact mechanism. The ruling out of the mechanism can help clarify the pathological involvement, which can be used in prompt diagnosis and improving the treatment outcome in patients.

The present study aims to evaluate the association of serum uric acid levels with end-organ damage in hypertensive patients.

LITERATURE REVIEW

Hypertension is the leading cause of the global burden of disease. Elevated blood pressure affects more than one billion individuals and causes 9.4 million deaths annually. It can lead to a severe cardiovascular disorder that includes; congestive heart failure, ischemic and hemorrhagic stroke, coronary heart disease, and peripheral heart disease. [11]

Epidemiology of hypertension

Countries and subpopulations within a country differ in blood pressure levels, the rate of age-related increases in blood pressure, and the prevalence of hypertension. All populations, except for a small number of people who live in isolated societies, suffer from hypertension. Blood pressure steadily rises in industrialised societies during the first 20 years of life. Blood pressure and growth and maturation are linked in children and adolescents. In young children and between adolescence and young adulthood, blood pressure "tracks" over time. [11]

The prevalence of hypertension has increased over the past four decades due to the widespread use of antihypertensive drugs. Data have suggested that the incidence rate of hypertension was higher in low-income populations than in high-income populations. [12] Risk factors such as salt intake, low potassium intake, alcohol consumption, obesity, sedentary lifestyle, and unhealthy diet can be differentiated based on regional heterogeneity. [12]

Both genetic and environmental factors may cause variations in the prevalence of hypertension among different regions and racial groups. Studies of " acculturating " societies and research on people who move from less to more urbanised areas suggest that the environment significantly impacts blood pressure. Weight gain and obesity are both significant, independent risk factors for hypertension. 60% of hypertensives are thought to be overweight by >20%. Population-level hypertension prevalence correlates with dietary NaCl intake, and a high NaCl intake may contribute to the age-related rise in blood pressure. [1] [11] [12]

Low dietary calcium and potassium intakes may also increase the risk of developing hypertension. A stronger predictor of blood pressure than sodium or potassium alone is the urine sodium-to-potassium ratio (a measure of both sodium and potassium intakes). Hypertension may also be influenced by alcohol use, psychosocial stress, and a lack of exercise. [1] [11] [12]

MECHANISM OF HYPERTENSION

The cardiac output and peripheral resistance play a determinant role in understanding the overall mechanism involved in the development of hypertension.

Cardiac output is determined by the stroke volume and heart rate, whereas the stroke volume is based on the myocardial contractility and the size of vascular compartments. [11]

Peripheral resistance is determined by functional and anatomic changes in the small arteries and arterioles (lumen diameter between 100-400 um). [11]

Intravascular volume

The sodium ion is one of the predominant and independent factors related to extracellular fluid volume. An excessive amount of NaCl can initially produce high excretion of sodium ions from the kidney, which results in volume expansion and increased cardiac output. Auto-regulation of blood flow maintains the pressure between the arteries to prevent increased arterial pressure. However, with the increased face of arterial pressure, resistance within the vascular bed increases which can elevate the blood pressure. However, the peripheral resistance increases in such situations and reverts the cardiac output to normal.

$$\text{Blood Flow} = \frac{\text{pressure across the vascular bed}}{\text{vascular resistance}}$$

Figure 1 denotes the determining factors for arterial pressure

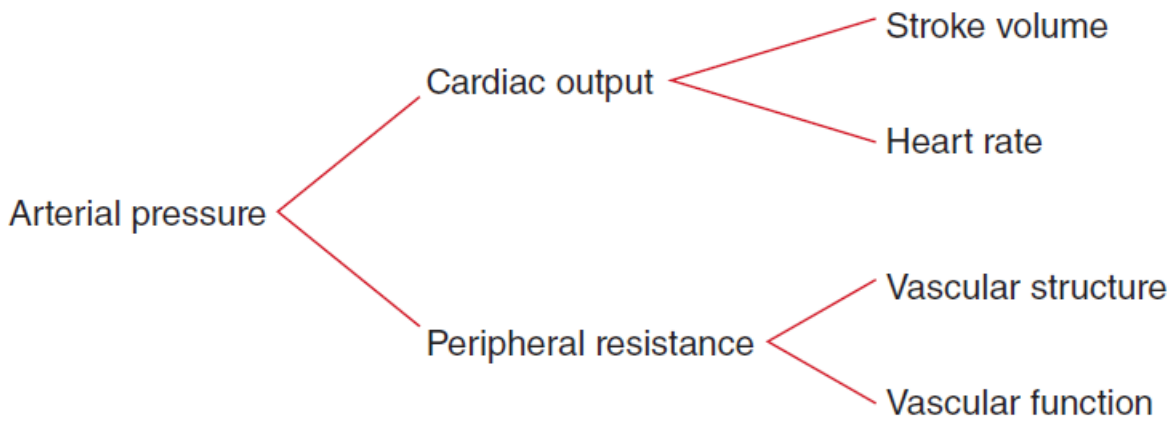


Figure 1 – Determinants of the arterial pressure

Sodium salts without chloride have little to no effect on blood pressure, whereas sodium salts with chloride have a significant impact. This is because urinary sodium excretion rises as arterial pressure increases in response to a high sodium intake, maintaining sodium balance at the expense of an increase in blood pressure. This "pressure-natriuresis" phenomenon may be caused by a subtly elevated glomerular filtration rate, decreased renal tubular absorbing capacity, and perhaps hormonal components like the atrial natriuretic factor. To achieve natriuresis and sodium balance, greater increases in arterial pressure are needed" n people with impaired sodium excretion capacity.

A decrease in the kidney's ability to excrete sodium may result from intrinsic renal disease or from increased production of the hormone mineralocorticoid, which causes an increase in the reabsorption of sodium by the renal tubules. Increased neural activity in the kidney may also help increase renal tubular

sodium reabsorption. Higher arterial pressure might be necessary to achieve sodium balance in these cases. On the other hand, low blood pressure is related to disorders that cause salt loss. A severe case of volume-dependent hypertension is ESRD. In ~80% of these patients, vascular volume and hypertension can be controlled with adequate dialysis; in the other 20%, the mechanism of hypertension is related to increased renin-angiotensin system activity. [11]

Autonomic nervous system

In conjunction with hormonal and volume-related factors, Adrenergic function contributes to the long-term regulation of arterial pressure. In addition, adrenergic reflexes modify blood pressure in the short term. Finally, dopamine, epinephrine, and norepinephrine contribute significantly to tonic and phasic cardiovascular regulation.

Guanosine nucleotide-binding regulatory proteins (G proteins) and intracellular concentrations of downstream second messengers mediate the actions of the adrenergic receptors. The effectiveness of receptor-effector coupling at a site "distal" to receptor binding may affect physiologic responsiveness to catecholamines in addition to receptor affinity and density. The transmitter substance and receptor site occupancy response are relatively specific to the receptor sites. The two main types of adrenergic receptors are: and based on their physiology and pharmacology.

Recent molecular cloning studies have found additional subtypes. Norepinephrine occupies and activates receptors more eagerly than epinephrine, and the opposite is true for receptors. In smooth muscle, receptors are found on postsynaptic cells and cause vasoconstriction. Receptors are on the presynaptic membranes of postganglionic nerve terminals, which produce norepinephrine. Catecholamines that activate the two receptors function as negative feedback controllers, preventing further norepinephrine release. The activation of 1-adrenergic receptors increases the kidney's renal tubular sodium reabsorption.

The increased sympathetic outflow is frequently linked to hypertension in people of both normal and obese weight. According to recordings of postganglionic muscle nerve activity made using a microelectrode inserted into the peroneal nerve in the leg, people with hypertension typically have higher sympathetic outflow than people with normotension. The sympathetic flow increases in obesity-related hypertension and hypertension linked to obstructive sleep apnea. In patients with "resistant" hypertension, baroreceptor activation via electrical stimulation of carotid sinus afferent nerves reduces blood pressure. Drugs that block the sympathetic nervous system are effective antihypertensives, proving that the sympathetic nervous system can contribute to elevated blood pressure without necessarily being the cause.

Renin-angiotensin-aldosterone

The increased sympathetic outflow is frequently linked to hypertension in people of both normal and obese weight. According to recordings of postganglionic muscle nerve activity made using a microelectrode inserted into the peroneal nerve in the leg, people with hypertension typically have higher sympathetic outflow than people with normotension. The sympathetic outflow increases in obesity-related hypertension and hypertension linked to obstructive sleep apnea. In patients with "resistant" hypertension, baroreceptor activation via electrical stimulation of carotid sinus afferent nerves reduces blood pressure. Drugs that block the sympathetic nervous system are effective antihypertensives, proving that the sympathetic nervous system can contribute to elevated blood pressure without necessarily being the cause.

The three major stimuli for renin secretion include;

1) Decreased NaCl transport in the distal portion of the thick ascending limb of the loop of Henle that abuts the corresponding afferent arteriole
2) Reduced pressure or stretch within the renal afferent arteriole (baroreceptor mechanism)
3) Stimulation of renin-secreting cells by the sympathetic nervous system via β_1 adrenoreceptors

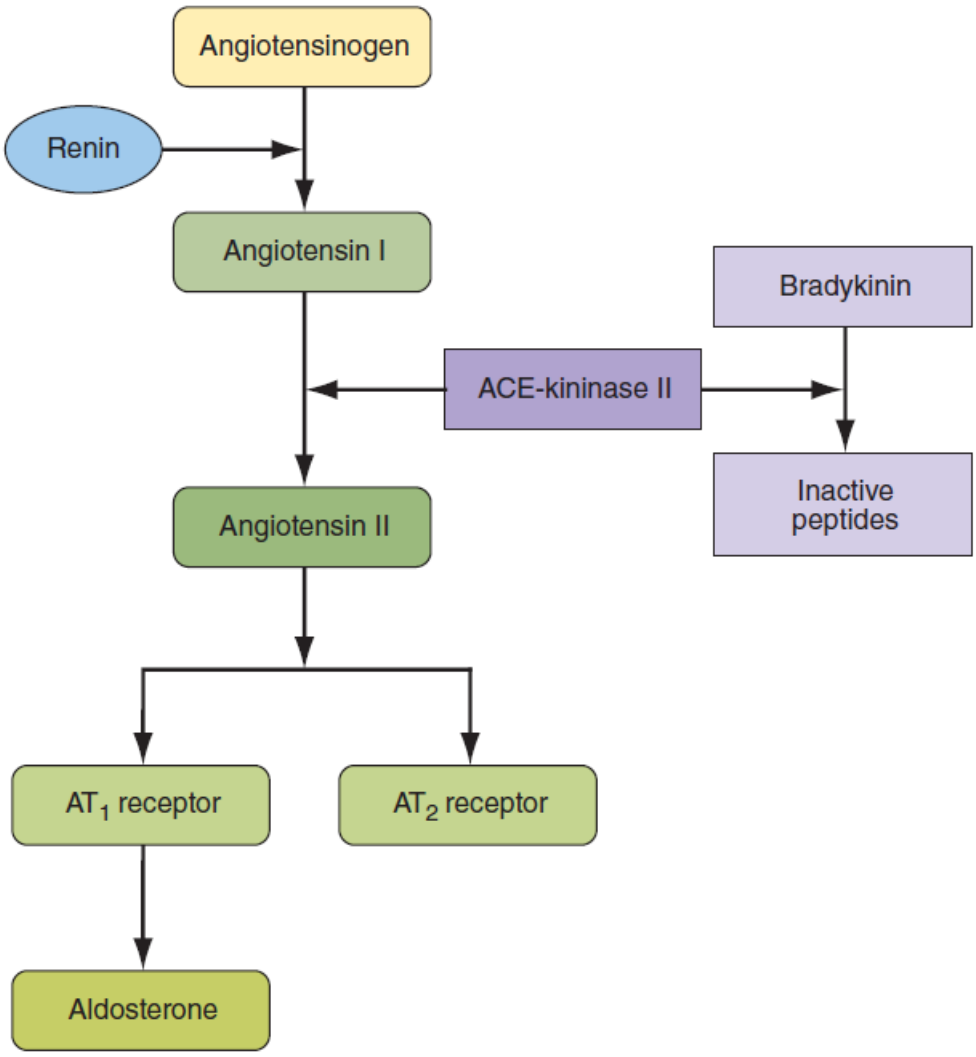


Figure 2 – Renin-angiotensin-aldosterone axis

Angiotensin I is converted to the active octapeptide, angiotensin II, by a converting enzyme primarily found in pulmonary circulation. This conversion occurs by releasing the C-terminal histidyl-leucine dipeptide. The vasodilator bradykinin is among the peptides that the same converting enzyme cleaves, rendering it inactive. Angiotensin II is a potent pressor substance that primarily acts on cell membranes through angiotensin II type 1 (AT1) receptors. It is the main tropic factor for the secretion of aldosterone by the adrenal zona

glomerulosa. Angiotensin II may contribute to the anthogenesis of atherosclerosis independent of its hemodynamic effects through a direct cellular action on the vessel wall. [11]

Hypertension is not always linked to increased renin-angiotensin-aldosterone axis activity. A low-NaCl diet or volume contraction may cause the renin-angiotensin-aldosterone axis to become more active, maintaining arterial pressure and volume homeostasis. In edematous conditions like CHF and liver disease, secondary aldosteronism—increased aldosterone brought on by increased renin-angiotensin—but not hypertension—is also seen. [13]

Vascular Mechanism

Important determinants of arterial pressure include vascular radius and the compliance of resistance arteries. Small reductions in lumen size significantly increase flow resistance because it varies inversely with the fourth power of the radius. Structure, mechanics, or functional modifications may cause smaller small arteries and arterioles in hypertensive patients. Remodelling describes changes in the vessel wall's geometry without affecting the volume of the vessel. Either eutrophic (reduced lumen size) or hypertrophic (increased cell size and increased intercellular matrix deposition), vascular remodelling increases peripheral resistance. [13]

Remodelling is also aided by apoptosis, low-grade inflammation, and vascular fibrosis. The elasticity of the vessel and lumen diameter are both related. A small

increase in volume causes a relatively large increase in pressure in a semirigid vascular system. In contrast, vessels with a high degree of elasticity can accommodate an increase in volume with only a small change in pressure. [13]

Pathological consequences due to hypertension [13]

1. Cardiovascular abnormalities

The hypertensive state can result in structural and functional deformities due to adaption of the heart, which can lead to left ventricular hypertrophy, CHF, blood flow abnormalities, atherosclerotic disease, diastolic dysfunction, microvascular complications, and cardiac arrhythmias.

2. Central nervous system effects

Patients with hypertension are often associated with impaired cognitive skills with progressive age, and the incidence of stroke rises in such patients. In addition, hypertensive encephalopathy can be seen due to failure of autoregulation of the cerebral blood flow resulting in vasodilation and hyperperfusion. Untreated hypertensive encephalopathy can result in seizures, coma, and death within a few hours of onset.

3. Renal effects

Both a target and a contributor to hypertension is the kidney. Secondary hypertension's most prevalent aetiology is primary renal disease. Reduced sodium excretion, excessive renin secretion related to volume status, and an overactive

sympathetic nervous system are some mechanisms underlying kidney-related hypertension. On the other hand, renal damage and ESRD are risk factors for hypertension. The elevated risk brought on by high blood pressure is gradual, ongoing, and pervasive throughout the range of blood pressure levels above the ideal range.

Clinical Disorders of Hypertension

1. Metabolic Syndrome
2. Essential Hypertension
3. Renovascular Hypertension
4. Primary Aldosteronism
5. Cushing's syndrome
6. Pheochromocytoma
7. Other causes: obstructive sleep apnea, coarctation of the aorta, acromegaly, hypercalcemia, hyper or hypothyroidism
8. Monogenetic Hypertension

Key recommendations for hypertension [14]

1. Diagnosis of hypertension should be made at primary health centres and facilities above that level using validated and calibrated BP measurement devices and following the standardised BP measurement procedure
2. Diagnosis of hypertension should be based on at least two measurements taken in the clinic or by a healthcare provider on at least two visits, which

are at least 1-4 weeks apart, except in the case of hypertensive urgencies and hypertensive emergencies, where hypertension is diagnosed during the first visit itself. Ambulatory blood pressure monitoring and home-based BP monitoring are not feasible for diagnosis for most patients with hypertension in India and are therefore not recommended

3. Hypertension should be diagnosed when BP is persistently above a systolic of 140mm and diastolic of 90 mm

Classification of Hypertension [14]

Based on the standard treatment guidelines, hypertension is classified as;

Grade	**Systolic BP**	**Diastolic BP**
Grade 1	140-159 mm Hg	90-99 mm Hg
Grade 2	160-179 mm Hg	100-109 mm Hg
Grade 3	180 or above	110 or above
Isolated systolic hypertension	Systolic > 140 mm Hg	Diastolic < 90 mm Hg
Hypertensive urgency	Systolic > 180 mm Hg	Diastolic < 90 mm Hg **Asymptomatic**

JNC 8 Guidelines for the Management of Hypertension in Adults [15]

- When the systolic or diastolic pressure is 150 mm Hg or higher in the general population of adults 60 years of age and older, pharmacologic treatment should be started. Target systolic and diastolic pressures for patients should be less than 150 mm Hg and 90 mm Hg, respectively. If the course of treatment leads to a systolic pressure of less than 140 mm Hg, as long as this does not harm the patient's health or quality of life, there is no need to change the course of treatment
- In populations below 60 years of age, pharmacological treatment should be started when the systolic pressure is 140 mm Hg or higher or when diastolic pressure is 90 mm Hg or higher. The targeted systolic pressure is less than 140 mm Hg, and the diastolic pressure is less than 90 mm Hg

Hypertension in patients presented with CKD or Diabetes [15]

- For patients 18 years or older presenting with CKD or diabetes, the treatment goal is similar to the general population; to maintain the blood pressure threshold within the specified limit.
- A systolic pressure of 140 mm Hg or threshold diastolic pressure of 90 mm Hg
- The targeted diastolic pressure is less than 90 mm Hg

Management of Hypertension and End organ damage

Subclinical end organ damage	
Left-ventricular hypertrophy	ACEI, ARB, CA
Elevated albuminuria	ACEI, ARB
Renal dysfunction	ACEI, ARB
I**rreversible hypertensive end-organ damage**	
Prior stroke	Any antihypertensive
Prior myocardial infarction	BB, ACEI, ARB
Angina pectoris, CHD	BB, CA
Heart failure	Diuretics, BB, ACEI, ARB, MR antagonists
Chronic renal insufficiency	ACEI, ARB, and Loop diuretics
Peripheral arterial occlusive disease	Calcium antagonist

Serum Uric Acid and Hypertension

Hyperuricemia is commonly associated with the presence of arterial hypertension. Recent literature has reported that 25-40% of patients with hypertension are diagnosed with hyperuricemia. [16]

The association between high uric acid levels and cardiovascular disease have been reported since the 19th century. Several studies have stated the relationship and considered uric acid levels as an independent risk factor for cardiovascular events, including congestive heart failure and cerebrovascular disease. [17] A large

study conducted in hypertensive patients with diabetes found a higher level of serum uric acid levels than 7 mg/dl, which was significantly related to cardiovascular mortality. [18]

Uric acid metabolism

Uric acid is the final metabolite product formed by the purine degradation, the urates (an ionised form of uric acid) show high concentration in the extracellular plasma and synovial fluid, with 98% concentrated as monosodium urate at normal pH of 7.4. The solubility of uric acid is generally dependent on the pH of urine, the kidney excretes two-thirds of the urate, and the majority of the concentrated form is excreted through the intestine. [11]

The kidney clears the urate from the plasma to maintain the physiological balance by the organic anion transporters (OATs), which comprise urate transporter 1 (URAT1) and human uric acid transporter (hUAT). The mechanism involved in the excretion process is as follows;

1. Glomerular filtration
2. Tubular reabsorption
3. Secretion
4. Post-secretory reabsorption

The URAT1 directly inhibits the uric acid compounds on the apical side of the tubular cells. The production of urate is influenced by the dietary intake of purine and the rates of de novo biosynthesis of purines from the precursors (nonpurine). Hyperuricemia is generally caused by increased production, decreased excretion, or a combination of both. The deposition of urate precipitate is seen in tissues as tophi in hyperuricemia. [11]

Hyperuricemia

An elevated serum uric acid concentration of more than 6.0 mg/dl in females and more than 7.0 mg/dl in males is characterised as hyperuricemia. [19]

Aetiology of Hyperuricemia

The cause for the elevated uric acid levels can be due to the overproduction of urate or decreased uric acid excretion.

The overproduction can be due to the following;

1. Purine-rich diet
2. Cell breakdown or turnover: Paget disease, psoriasis, tumour lysis, hemolysis, rhabdomyolysis, myeloproliferative disease
3. Error in purine metabolism

A decreased uric acid excretion includes; Acidosis (lactic acidosis, ketoacidosis), hypovolemia, medication/toxin (diuretic, niacin, pyrazinamide, ethambutol, cyclosporin, beryllium, salicylates, lead, alcohol), sarcoidosis,

hyperparathyroidism, hypothyroidism, Bartter syndrome, and Down syndrome are all examples of kidney diseases that can be either acute or chronic, [20]

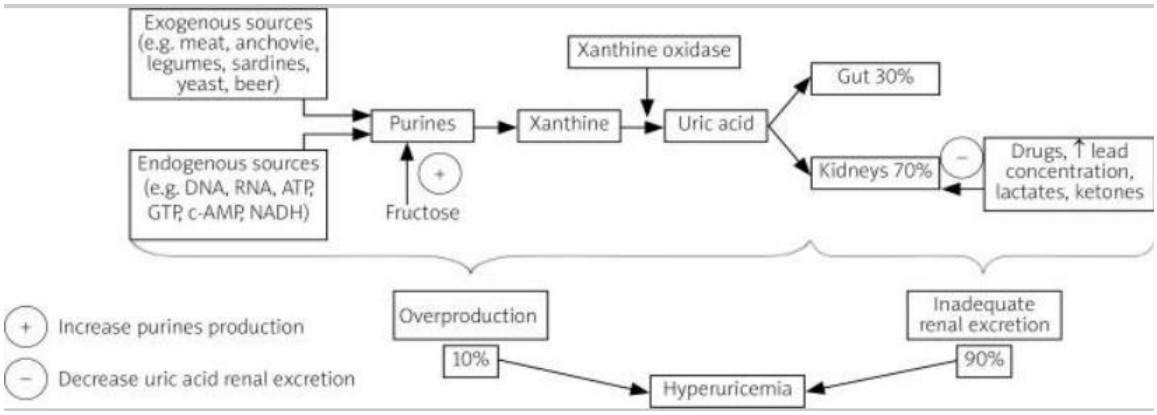


Figure 3 – Causes of Hyperuricemia [21]

Classification of hyperuricemia based on pathophysiology

Urate Overproduction		
Primary idiopathic	Myeloproliferative diseases	Rhabdomyolysis
HPRT deficiency	Polycythemia vera	Exercise
PRPP synthetase Overactivity	Psoriasis	Alcohol
Hemolytic Processes	Paget's disease	Obesity
Lymphoproliferative diseases	Glycogenosis III, V, and VII	Purine – rich diet
Decreased Uric Acid Excretion		
Primary idiopathic	Starvation ketosis	Drug ingestion
Renal insufficiency	Berylliosis	Salicylates (>2g/d)
Polycystic kidney	Sarcoidosis	Diuretics
Diabetes insipidus	Lead intoxication	Alcohol
Acidosis	Hypothyroidism	Ethambutol
Lactic acidosis	Toxemia of pregnancy	Pyrazinamide
Diabetic ketoacidosis	Bartter's syndrome	Nicotinic acid
Down's syndrome	Cyclosporine	

Hyperuricemia and cardiovascular disease [21]

The most frequently occurring comorbidities of hyperuricemia are modifiable cardiovascular risk factors. Notably, recommended lifestyle changes like weight loss, regular exercise, and dietary adjustments lower UA levels, gout risk, and insulin resistance. [22] Whether to use ULT as a primary, secondary, or tertiary prevention of cardiovascular events arises due to known associations between UA and cardiovascular risk. [20]

Asymptomatic hyperuricemia in patients with cardiovascular disease (CVD) has a variety of causes, clinical implications, and treatment options. High levels of UA in people suffering from CVD could result from reduced glomerular filtration rate, renal vasoconstriction, hyperinsulinemia, tissue ischemia, oxidative stress and diuretic treatment. [23] [24]

The relationship between arterial hypertension and hyperuricemia is one of the topics that has been researched the most. On animal models, the first observations were made. Blood pressure (BP) levels in rats were inversely correlated with UA levels, and lowering UA led to a drop in BP. [25]

In people, UA causes vasoconstriction of the kidneys and UA-induced vasoreactivity hypertension by decreasing nitric oxide production, increasing the production of reactive oxygen species, and stimulating the renin-angiotensin system. These mechanisms apply to hypertension with early onset.

However, hyperuricemia is primarily linked to kidney microcirculation damage in the late stages of arterial hypertension, and its direct link to elevated BP values is less certain. Increased platelet aggregation, in-stent restenosis, and the Patho mechanism mentioned above may all play a role in the well-established link between hyperuricemia and ischemic heart disease. [26]

Epidemiology of Uric acid and Hypertension

Through the majority of the 20th century, relatively little progress was made in studying a possible connection between uric acid and hypertension. Most researchers concluded that uric acid was an associated surrogate marker for more significant risk factors like obesity, diabetes, and chronic kidney disease, even though some cardiovascular risk trials measured uric acid and suggested an association between uric acid and hypertension or cardiovascular disease. [27] [28]

Clinical Evidence of Uric Acid and Hypertension [27]

Study Conducted (Year)	Population	The relative risk of hypertension
Israeli Heart (1972)	10,000 Israeli men, aged 17–25 y, enrolled at military induction	Two-fold risk at 5
Fessel et al. (1973)	224 White men in Western United States, age >35 y	Greater increase in systolic blood pressure at four y
NHANES (1993)	6768 Healthy children aged 6–17 y	Uric acid predicts adolescent hypertension
Olivetti Heart Study (1994)	619 Adult men from Southern Italy	Two-fold risk at 12 y

Framingham (2005)	3329 Men and women in the Framingham cohort	1.6-fold at four y
ARIC (2006)	9104 Mixed race (black and white) men and women aged 45–64 y at enrollment	1.5-fold at nine y
GOCADAN (2012)	1078 Alaskan native Americans with chronic kidney disease II or III	1.2-fold age-adjusted risk
Fadrowski (2012)	6036 Adolescents, aged 11–17 y, evaluated in the National Health and Nutrition Examination Survey	Uric acid >5.5 mg/dL, 2.03-fold risk

Animal model of Hyperuricemia Hypertension

Although there was a lot of epidemiological data to support the idea that uric acid might be linked to hypertension, it wasn't until Johnson and colleagues' experiments in 2001 that a logical mechanism could be established using a rat model of hyperuricemia. Within two weeks, hyperuricemia leads to hypertension,

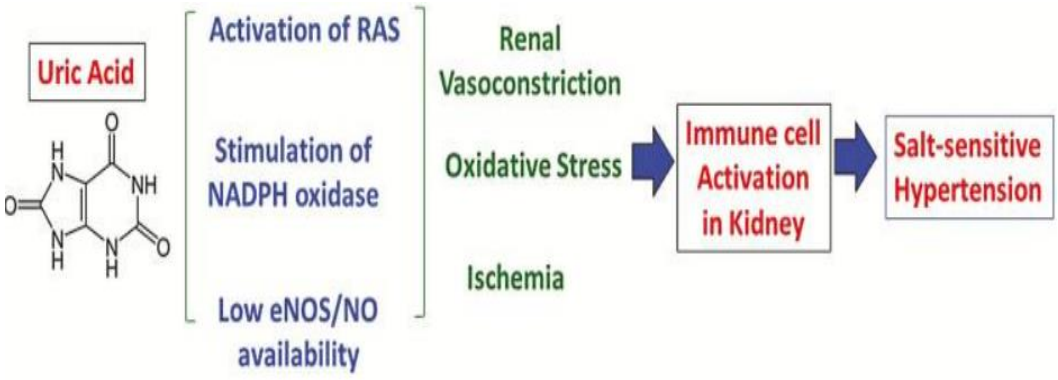
with an increase in systolic and diastolic blood pressure proportional to serum uric acid. The effects of uric acid-lowering medications can be mitigated (allopurinol or benziodarone). Urate reduction can completely reverse early-stage hypertension, but persistent hyperuricemia causes irreversible sodium-sensitive, uric acid-independent hypertension. [29]

Current evidence for target organ damage due to uric acid levels in hypertension

- The cross-sectional study conducted among 130 patients by Sandra et al. shows that uric acid levels were significantly higher in patients with hypertension when compared with the control group. In addition, the prevalence of hyperuricemia was 46.9% more among hypertensive patients. [29]
- A severe condition of left ventricular hypertrophy was much higher in patients with hyperuricemia and hypertension. The study also reported a linear relationship between the target organ damage in essential hypertension, which can be assessed based on serum uric acid levels. [29]
- Francesca et al. evaluated the role of uric acid as the independent risk factor for cardiovascular and renal morbidity among 425 patients. The study reported a 75% higher risk of cardiac hypertrophy and a 2-fold greater risk of having carotid abnormalities. [30]

- The development of a genetic scoring system to assess the risk for hypertension in large population studies was made possible by using genome-wide association studies (GWAS), which have been used to identify genetic polymorphisms that control serum urate levels. The genetic risk scores for hyperuricemia have been found to predict the risk for gout using a method known as Mendelian randomisation. Still, they have not been found to predict the development of hypertension, CKD, or cardiometabolic diseases. [31]
- Pleiotropy, in which genetic polymorphisms affect serum urate and cardiometabolic disease through shared pathways, is thought to be the cause of the findings in studies that link genetic scores for hyperuricemia with hypertension and metabolic diseases. [32] [33]

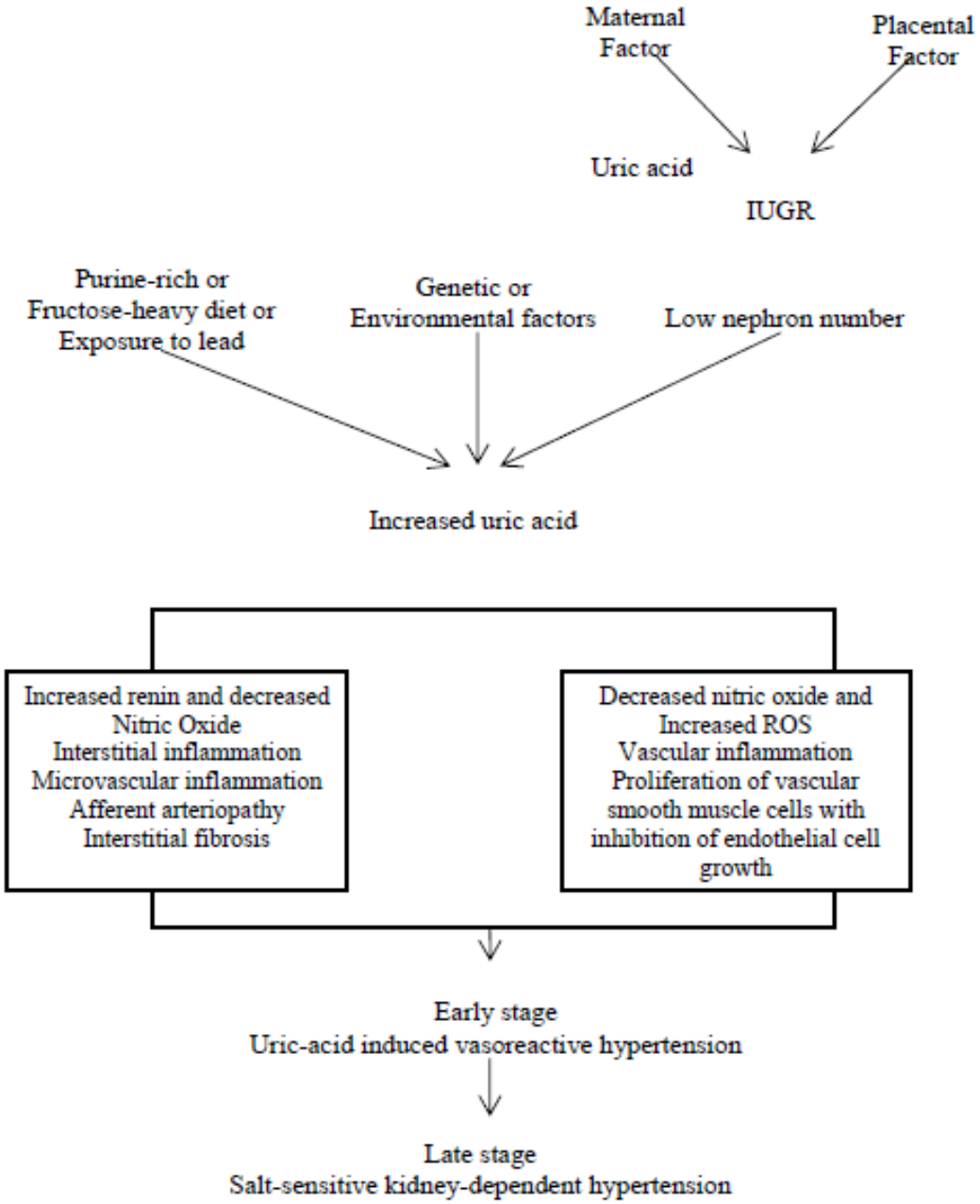
Figure 4 – Uric acid-associated pathways for hypertension



The recent findings suggest that uric acid levels can be used to diagnose hypertension among patients at risk of developing end-organ damage. In addition,

uric acid levels can be used as a prognostic marker during initial evaluation to control and treat the disease accordingly.

The pathway involved in uric acid-mediated hypertension



Management of Hyperuricemia [34]

Since most patients never experience gout or nephrolithiasis, they do not require medical treatment for hyperuricemia. The unnecessary expense and risk of side effects outweigh the benefits of starting medication. Urate-lowering medications in asymptomatic patients are only indicated in those undergoing cytolytic therapy for malignancy to prevent tumour lysis syndrome.

However, the medication that lowers urate levels includes;

- Allopurinol is a xanthine oxidase inhibitor used to prevent gouty arthritis, nephrolithiasis, and hyperuricemia associated with chemotherapy.
- Probenecid is a second-line treatment for gout because it inhibits URAT1 and causes an increase in uric acid secretion.
- Rasburicase, a recombinant uricase used as a preventative measure against chemotherapy-related hyperuricemia, converts uric acid to allantoin, which is significantly more water soluble and easily excreted from the kidneys. [35]

AIM AND OBJECTIVES

Aim

To evaluate the correlation between serum uric acid levels and the presence of end-organ damage in essential hypertension.

Objectives

To identify the patients with essential hypertension and to measure serum uric acid levels

1) To measure albuminuria

2) To assess LV dysfunction by ECHO

3) To examine the fundus for retinopathy

METHODOLOGY

STUDY DESIGN:

OBSERVATIONAL CROSS-SECTIONAL STUDY

STUDY POPULATION:

Patients with essential hypertension were admitted to the general medicine department of Govt. Kilpauk Medical College.

STUDY PERIOD

Six months from the date of approval of the ethical committee.

INCLUSION CRITERIA

- Patients with essential hypertension of one year

EXCLUSION CRITERIA

- Age more than 70 yrs
- Diabetes mellitus
- Cardiac diseases

- Chronic kidney disease
- Patients on diuretics, ACE inhibitors, Angiotensin receptor blockers
- Secondary hypertension
- Patients in hypertensive emergency

SAMPLE SIZE:

Formula

$$n = \frac{Z^2_{1-\alpha/2}\, p\,(1-p)}{d^2}$$

Where,

p : Expected proportion

d : Absolute precision

1- α/2 : Desired Confidence level

The sample size was estimated using nMaster software Version 2.0 by applying the following details in the above formula. Based on the study "Serum uric acid and target organ damage in primary hypertension" by Francesca viazzi and group (The overall prevalence of left ventricular hypertrophy was 46% obtained from the study group of 425 patients). Based on the above parameter with an alpha of 0.05 (2-sided) and precision level of 5%, the estimated sample size using the sample size formula for a single proportion. The above parameter and formula give us a sample size of 100 subjects.

Methods

Patients with essential hypertension admitted to kilpauk medical college were assessed during the period described above. Patients fulfilling the inclusion criteria were enrolled on the study after obtaining informed consent. Serum uric acid levels were measured.

Serum Uric Acid levels

It was calculated using the enzymatic calorimetric test, with the normal range for adult males being 3.6 -7 and adult females being 2.3 -6.1. Therefore, hyperuricemia was defined as SUA >7 in males and SUA >6 in females.

1) LV EF by ECHO
2) Albuminuria by dipstick method
3) Retinopathy by KEITH WAGNER CLASSIFICATION

DIPSTICK PROTEIN READING	PROTEIN EXCRETION(MG/DL)
Negative	<10
Trace	10 to 20
1+	30
2+	100
3+	300
4+	>1000

KEITH WAGNER CLASSIFICATION

GRADE	FUNDUS CHANGES
I	Slight constriction of retinal arterioles
II	Group 1 + Focal narrowing of retinal arterioles+ AV nicking
III	Group 2 + Flame shaped haemorrhages + Cotton wool spots + Hard exudates
IV	Group 3 + Optic disc swelling

STATISTICAL ANALYSIS:

The collected data will be analysed with IBM.SPSS statistics software 23.0 Version. To describe the data, descriptive statistics, frequency analysis, and percentage analysis will be used for categorical and continuous variables, and the mean and SD will be used.

The Chi-Square test or Fisher's exact test will be used to find the association of significance in categorical data. In all the above statistical tools, the probability value of .05 will be considered a significant level.

RESULTS

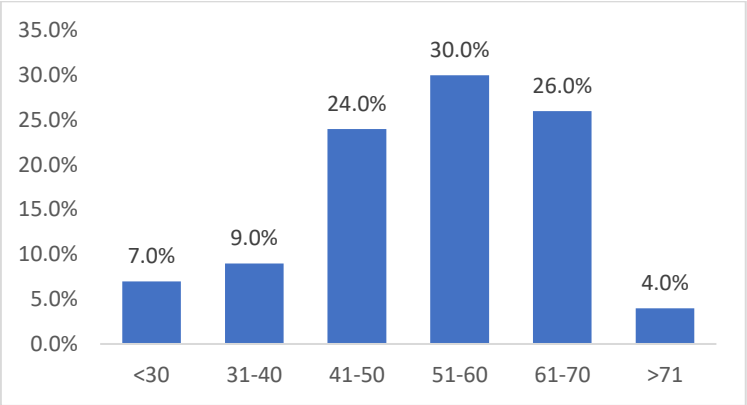
1. Age distribution

The current study reports a high prevalence of hypertension in the age group of 51-60 years of age (30.0%), followed by 61-70 years of age (26%), and the age range of 41-50 years (24%). In addition, a low prevalence was observed in the age group of 31-40 (9%) and <30 years of age (7%).

Table 1 – Age distribution of patients

Age group	Frequency	Percent
<30	7	7.0%
31-40	9	9.0%
41-50	24	24.0%
51-60	30	30.0%
61-70	26	26.0%
>71	4	4.0%
Total	100	100.0%

Figure 1 - % distribution of age



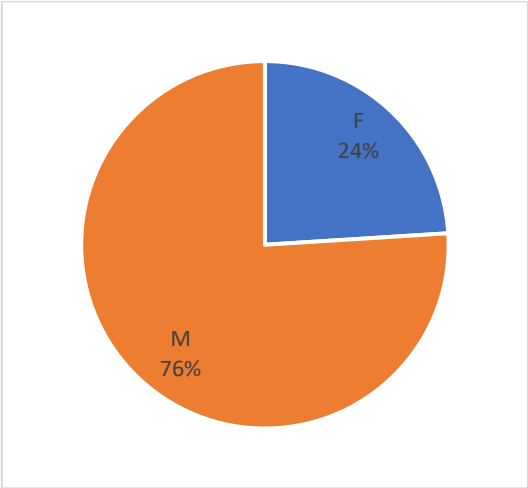
2. Gender distribution

A high male predominance was reported in the current study comprising 76 males (76%) and 24 females.

Table 2 – Distribution of gender

Gender	Frequency	Percent
F	24	24.0%
M	76	76.0%
Total	100	100.0%

Figure 2 – % distribution of gender



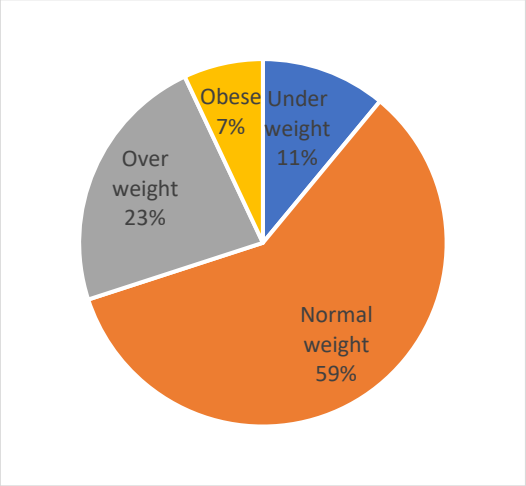
3. BMI of patients

Most of the patients were reported to be in the normal range of BMI, comprising 59 individuals (59%). However, an overweight BMI range was reported in 23 individuals (23%), and obesity was reported in 7 individuals (7%). In addition, 11 individuals (11%) observed an underweight range of BMI.

Table 3 – BMI distribution of patients

BMI	Frequency	Percent
Underweight	11	11.0%
Normal weight	59	59.0%
Overweight	23	23.0%
Obese	7	7.0%
Total	100	100.0%

Figure 3 - % distribution of BMI



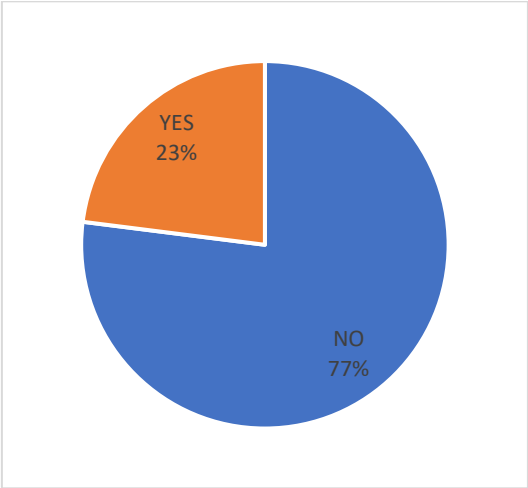
4. Social habits and smoking history

Of 100 patients, 23 were reported to have a social habit of alcohol consumption (23%), and 77 patients did not report any alcohol consumption history.

Table 4 – Alcohol consumption among patients

Alcohol	Frequency	Percent
NO	77	77.0%
YES	23	23.0%
Total	100	100.0%

Figure 4 - % distribution of alcohol consumption

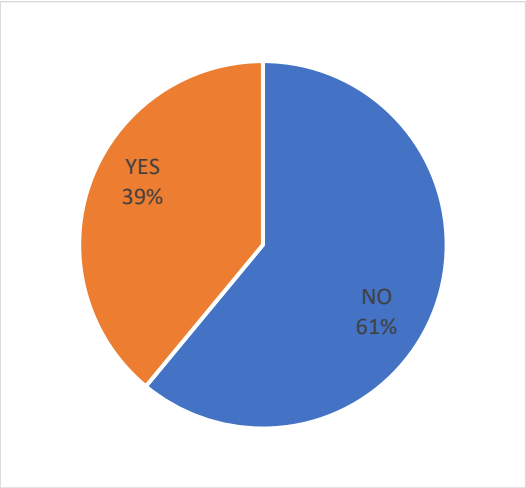


Smoking was reported in 39 patients (39%), and 61 reported no history or social habit of smoking.

Table 5 – Smoking among patients

Smoking	Frequency	Percent
NO	61	61.0%
YES	39	39.0%
Total	100	100.0%

Figure 5 - % distribution of smoking



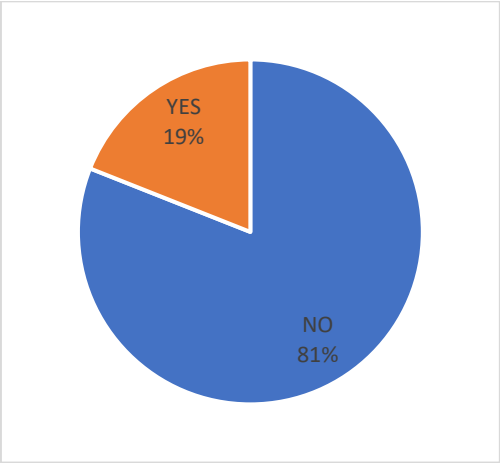
5. **Comorbid conditions**

a. Diabetes mellitus – A history of diabetes was reported in 19 patients (19%) from the overall study.

Table 6 – Prevalence of diabetes

Diabetes mellitus.	Frequency	Percent
NO	81	81.0%
YES	19	19.0%
Total	100	100.0%

Figure 6 - % prevalence of diabetes among patients



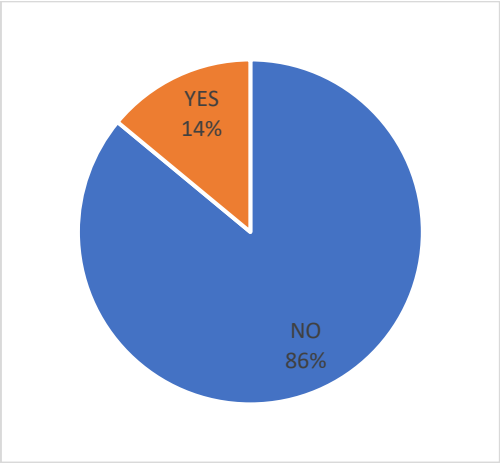
b. Left ventricular hypertrophy

A total of 14 patients was diagnosed with left ventricular hypertrophy, whereas 86 patients did not have any significant finding.

Table 7 – Left ventricular hypertrophy in patients

Left ventricular hypertrophy	Frequency	Percent
NO	86	86.0%
YES	14	14.0%
Total	100	100.0%

Figure 7 - % distribution of left ventricular hypertrophy



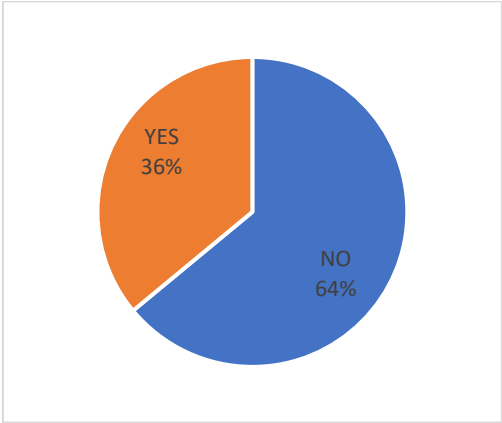
c. Coronary artery disease

Thirty-six patients were reported to be diagnosed with coronary artery disease comprising 36% of the participants from the overall study.

Table 8 – CAD among patients

Coronary artery disease	Frequency	Percent
NO	64	64.0%
YES	36	36.0%
Total	100	100.0%

Figure 8 - % prevalence of coronary artery disease

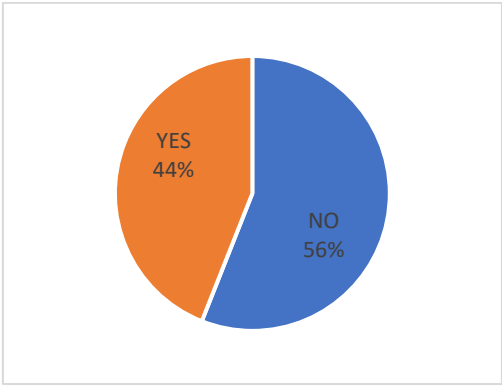


Albuminuria was seen in 44 patients (44%), whereas 56 patients were not diagnosed with such a condition.

Table 9 – Albuminuria in patients

Albuminuria	Frequency	Percent
NO	56	56.0%
YES	44	44.0%
Total	100	100.0%

Figure 9 - % prevalence of albuminuria

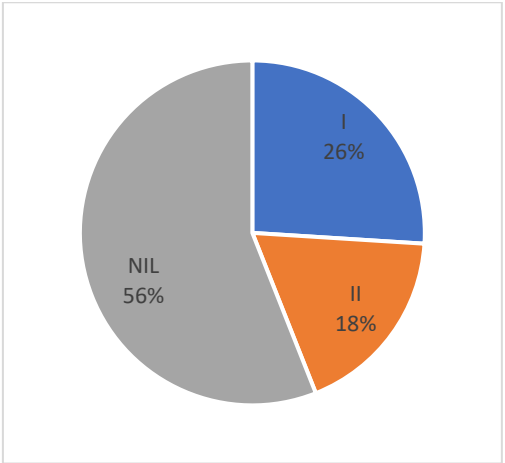


Retinopathy was reported in 44 patients, out of which stage I retinopathy was reported in 26 patients (26%) and stage II retinopathy was seen in 18 patients (18%). In addition, 56 patients did not report retinopathy.

Table 10 – Retinopathy in patients

Retinopathy	Frequency	Percent
I	26	26.0%
II	18	18.0%
NIL	56	56.0%
Total	100	100.0%

Figure 10 – Retinopathy % distribution



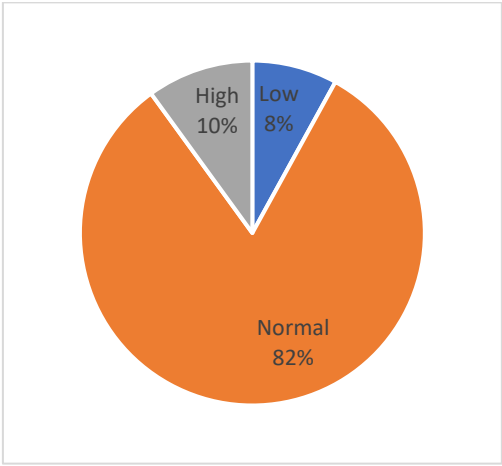
6. Serum uric acid levels among patients and their correlation

From 100 patients, elevated serum uric acid levels were observed in 10 patients (10%), and 8 (8%) reported low or serum uric acid levels. Eighty-two patients were seen with normal levels of serum uric acid.

Table 11 – Serum uric acid levels in patients

Serum uric acid	Frequency	Percent
Low	8	8.0%
Normal	82	82.0%
High	10	10.0%
Total	100	100.0%

Figure 11 -% distribution of serum uric acid levels in patients



a. **Correlation of serum uric acid levels with essential hypertension and different age groups**

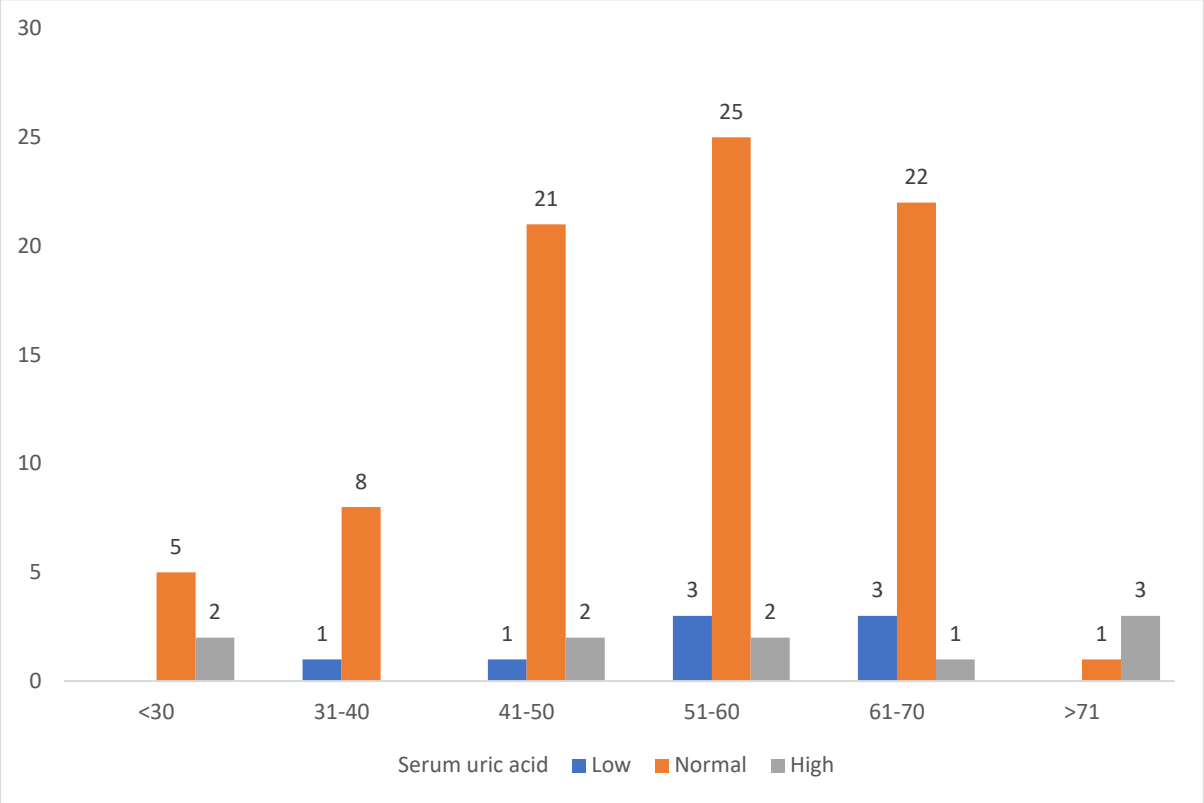
In the current study, elevated levels of serum uric acid were seen in 10 patients with essential hypertension, out of which the age group of >71 was seen with 3 cases of high serum uric acid levels, followed by the age group of 41-50 and 51-60 with two individuals for each of the group. In addition, those aged <30 years reported 2 cases of high serum uric acid levels, and 1 case was seen between 61-70 years of age. The study reports a p-value of 0.005 for the correlation between age and serum uric acid levels.

Table 12 – Serum uric acid levels correlation with age

			Serum uric acid			Total	P value
			Low	Normal	High		
Age group	<30	Count	0	5	2	7	0.005
		% within serum uric acid	0.0%	6.1%	20.0%	7.0%	
	31-40	Count	1	8	0	9	
		% within serum uric acid	12.5%	9.8%	0.0%	9.0%	

	41-50	Count	1	21	2	24
		% within serum uric acid	12.5%	25.6%	20.0%	24.0%
	51-60	Count	3	25	2	30
		% within serum uric acid	37.5%	30.5%	20.0%	30.0%
	61-70	Count	3	22	1	26
		% within serum uric acid	37.5%	26.8%	10.0%	26.0%
	>71	Count	0	1	3	4
		% within serum uric acid	0.0%	1.2%	30.0%	4.0%
Total		Count	8	82	10	100
		% within serum uric acid	100.0%	100.0%	100.0%	100.0%

Figure 12 - % prevalence of serum uric acid levels in patients



b. Serum uric acid levels correlation with gender

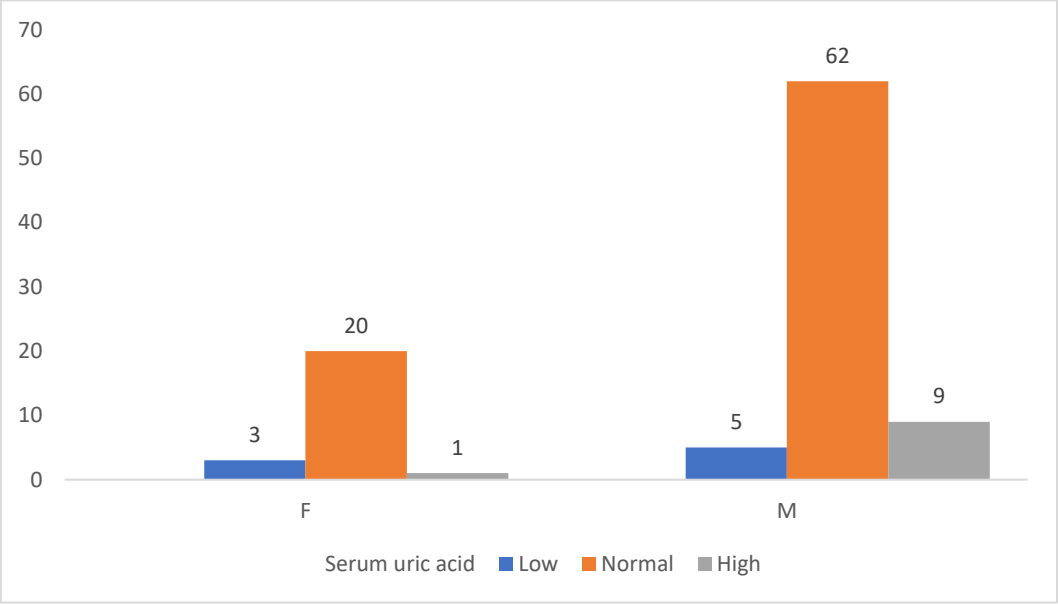
The current study reports that high serum uric acid levels were seen in males comprising nine individuals, whereas low levels were seen higher in males (5 individuals) and females (3 individuals). However, the study did not report any significant difference in gender and serum uric acid levels (p-value 0.39).

Table 13 – Uric acid level correlation with gender

			Serum uric acid			Total	P value
			Low	Normal	High		
Gender	F	Count	3	20	1	24	0.39

		% within serum uric acid	37.5%	24.4%	10.0%	24.0%	
	M	Count	5	62	9	76	
		% within serum uric acid	62.5%	75.6%	90.0%	76.0%	
Total		Count	8	82	10	100	
		% within serum uric acid	100.0%	100.0%	100.0%	100.0%	

Figure 13 – Uric acid levels in correlation with gender



c. Serum uric acid levels correlation with BMI

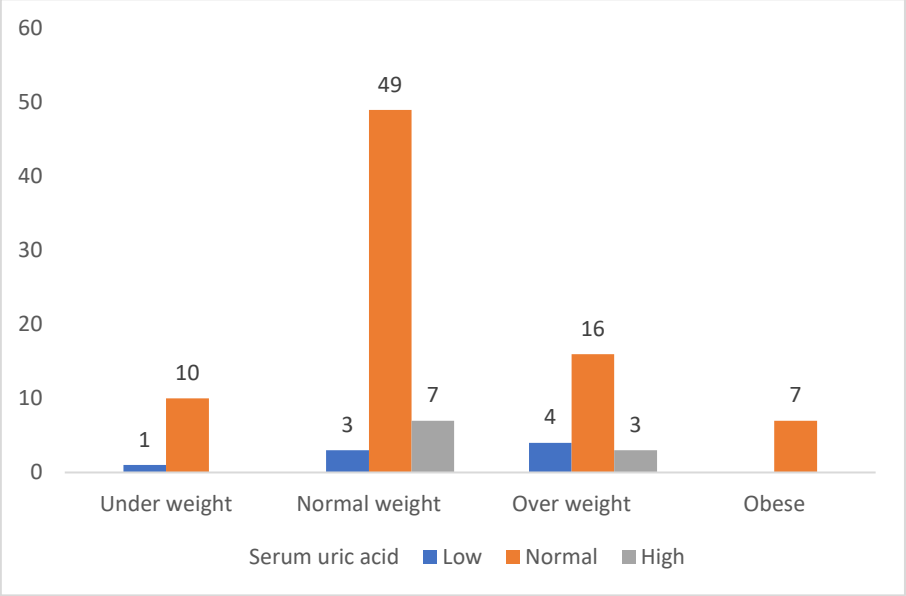
The study did not report any significant difference between the BMI and serum uric acid levels (p-value 0.342). However, high uric acid levels were reported in 3 overweight patients and seven patients with normal BMI.

Table 14 – Serum uric acid correlation with BMI

			Serum uric acid			Total	P value
			Low	Normal	High		
BMI	Underweight	Count	1	10	0	11	0.342
		% within serum uric acid	12.5%	12.2%	0.0%	11.0%	
	Normal weight	Count	3	49	7	59	
		% within serum uric acid	37.5%	59.8%	70.0%	59.0%	
	Overweight	Count	4	16	3	23	
		% within serum uric acid	50.0%	19.5%	30.0%	23.0%	
	Obese	Count	0	7	0	7	
		% within serum	0.0%	8.5%	0.0%	7.0%	

		uric acid					
Total		Count	8	82	10	100	
		% within serum uric acid	100.0%	100.0%	100.0%	100.0%	

Figure 14 – Serum uric acid level correlation with BMI



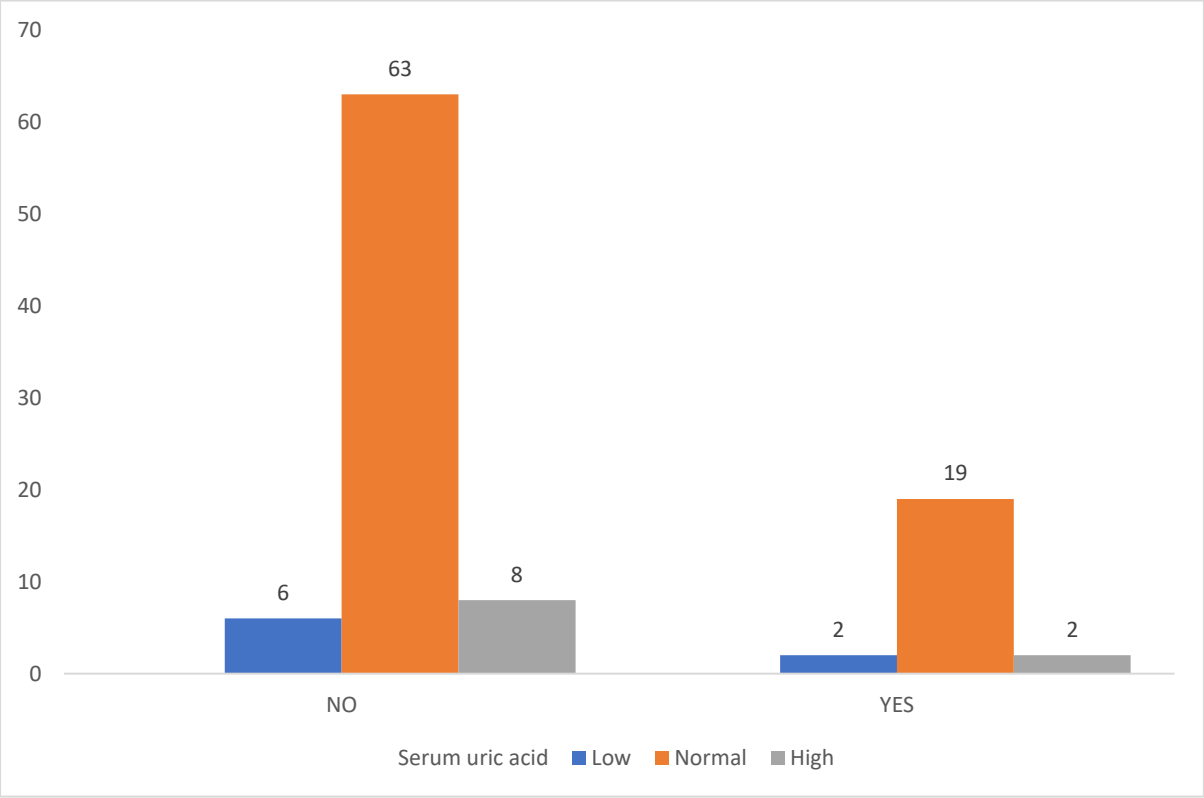
d. Serum uric acid correlation with alcohol consumption

The study did not report a significant difference between alcohol consumption and serum uric acid levels (p-value = 0.965). Elevated uric acid levels were seen in 2 patients with a history of alcohol consumption.

Table 15 – Serum uric acid levels correlation with alcohol consumption

			Serum uric acid			Total	P value
			Low	Normal	High		
Alcohol	NO	Count	6	63	8	77	0.965
		% within serum uric acid	75.0%	76.8%	80.0%	77.0%	
	YES	Count	2	19	2	23	
		% within serum uric acid	25.0%	23.2%	20.0%	23.0%	
Total		Count	8	82	10	100	
		% within serum uric acid	100.0%	100.0%	100.0%	100.0%	

Figure 15 – Serum uric acid levels in patients with alcohol consumption



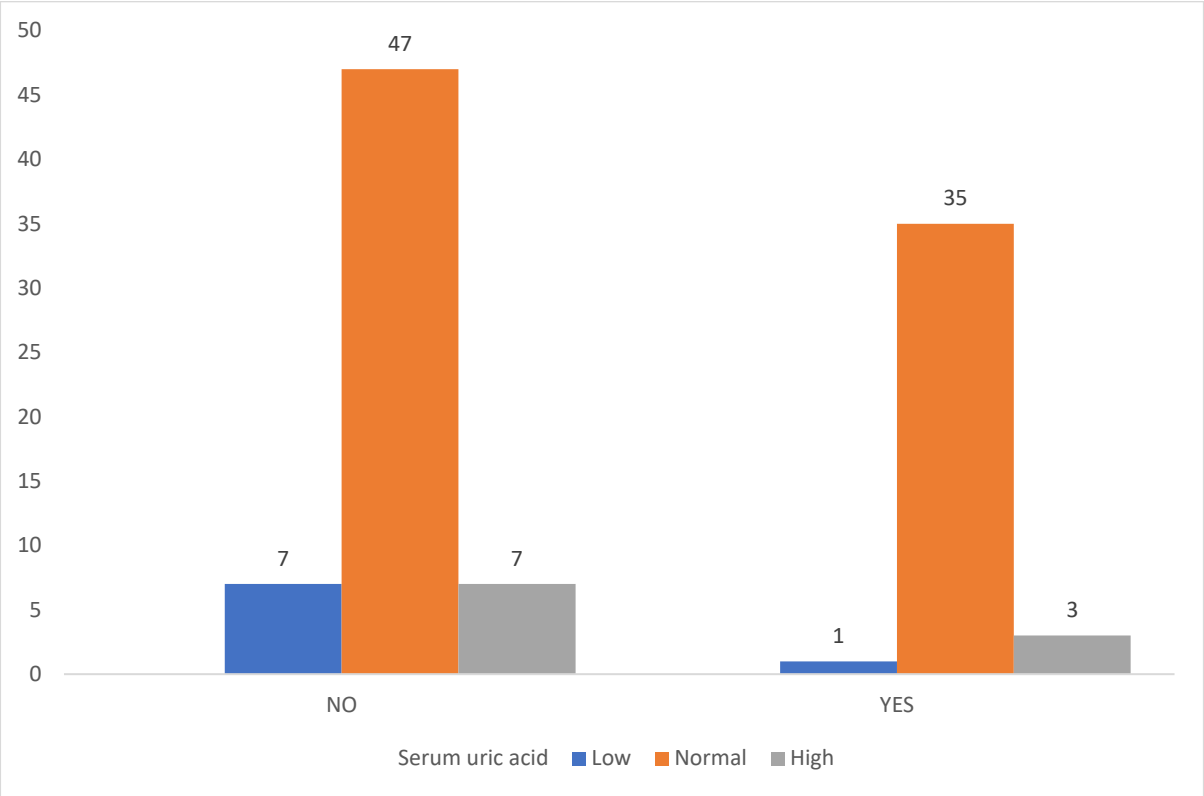
e. Serum uric acid levels correlation with smoking

High serum uric acid levels were reported in 10 patients, of which 3 had a smoking history and 7 had no smoking habit. In addition, low serum uric acid levels were seen in one patient with a smoking habit. Normal serum uric acid levels were seen in 35 patients with a smoking history. The study found no significant correlation between smoking and serum uric acid levels (p-value = 0.205).

Table 16 – Serum uric acid in patients with smoking habit

			Serum uric acid			Total	P value
			Low	Normal	High		
Smoking	NO	Count	7	47	7	61	0.205
		% within serum uric acid	87.5%	57.3%	70.0%	61.0%	
	YES	Count	1	35	3	39	
		% within serum uric acid	12.5%	42.7%	30.0%	39.0%	
Total		Count	8	82	10	100	
		% within serum uric acid	100.0%	100.0%	100.0%	100.0%	

Figure 16 – Smoking habit and serum uric acid levels



7. **Comorbidities and serum uric acid levels**

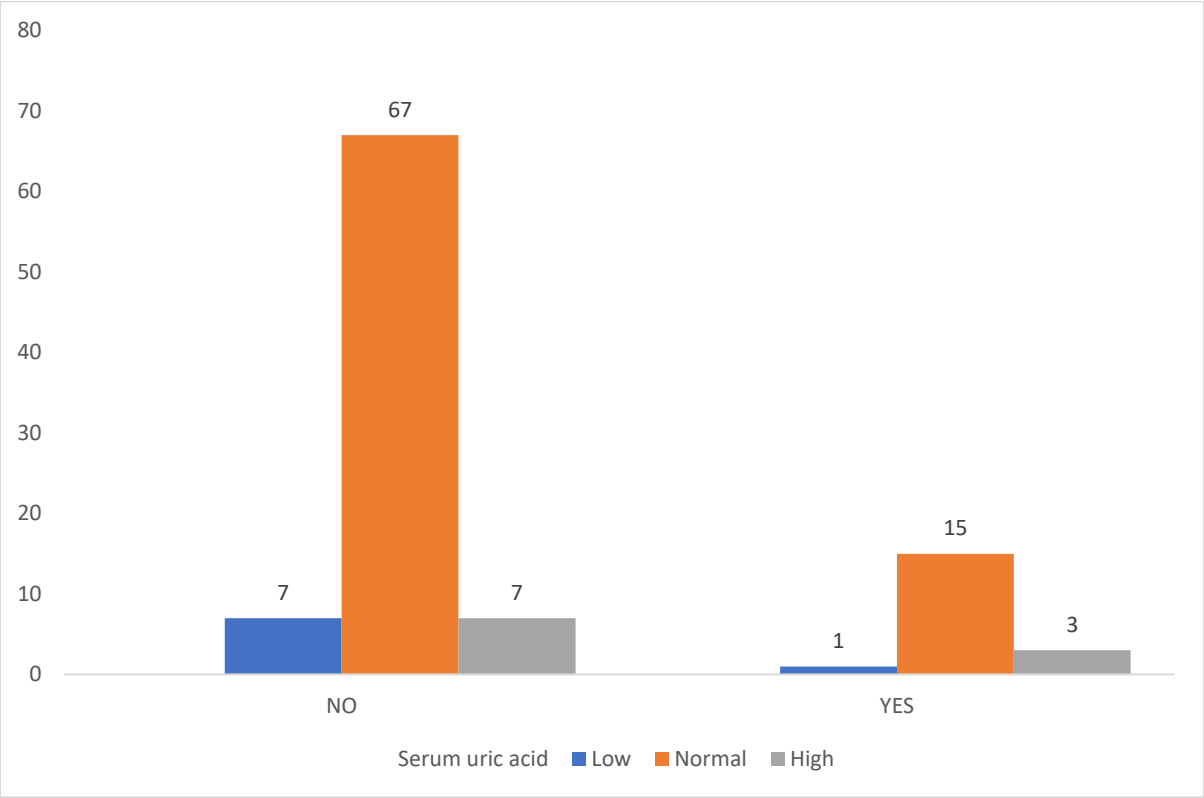
a. Diabetes mellitus

Patients with diabetes mellitus revealed normal serum uric acid levels in 15 patients (18.3%). High uric acid levels were reported in 3 patients, and low levels were reported in one patient with diabetes mellitus. The study did not find any significant correlation or difference between diabetes mellitus and serum uric acid levels (p-value = 0.591).

Table 17 – Serum uric acid levels in diabetic patients

			Serum uric acid			Total	P value
			Low	Normal	High		
Diabetes mellitus.	NO	Count	7	67	7	81	0.591
		% within serum uric acid	87.5%	81.7%	70.0%	81.0%	
	YES	Count	1	15	3	19	
		% within serum uric acid	12.5%	18.3%	30.0%	19.0%	
Total		Count	8	82	10	100	
		% within serum uric acid	100.0%	100.0%	100.0%	100.0%	

Figure 17 – Diabetes correlation with serum uric acid levels



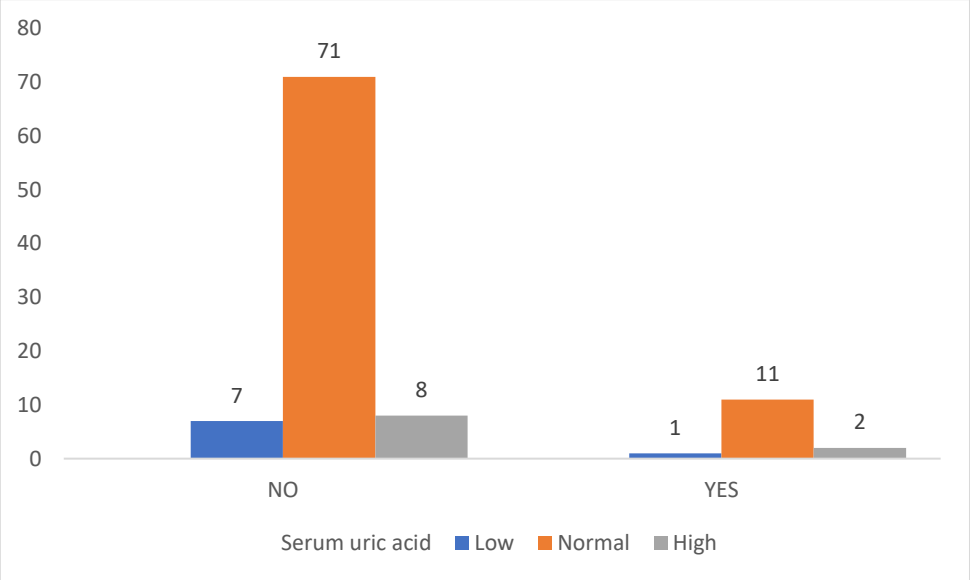
b. **Left ventricular hypertrophy and serum uric acid levels**

The current study did not report a significant difference between left ventricular hypertrophy and serum uric acid levels (p-value = 0.845). 2 patients were seen with elevated serum uric acid levels and left ventricular hypertrophy.

Table 18 – Left ventricular hypertrophy and serum uric acid levels

			Serum uric acid			Total	P value
			Low	Normal	High		
Left ventricular hypertrophy	NO	Count	7	71	8	86	0.845
		% within serum uric acid	87.5%	86.6%	80.0%	86.0%	
	YES	Count	1	11	2	14	
		% within serum uric acid	12.5%	13.4%	20.0%	14.0%	
Total		Count	8	82	10	100	
		% within serum uric acid	100.0%	100.0%	100.0%	100.0%	

Figure 18 – Serum uric acid levels correlation with left ventricular hypertrophy



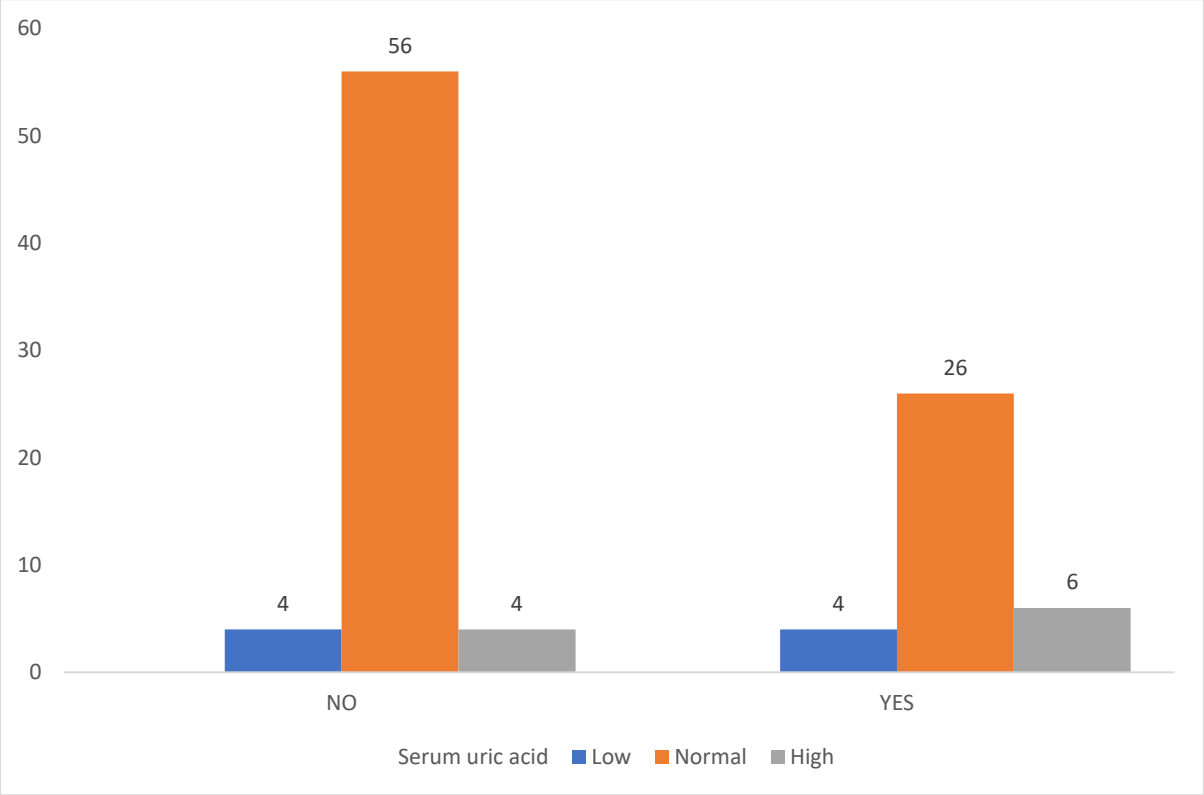
c. **Coronary artery disease and serum uric acid levels**

Patients with coronary artery disease reported higher serum uric acid levels in 6 patients, and low levels were seen in 4 patients. However, the study did not find any significant correlation between serum uric acid levels and the prevalence of coronary artery disease (p-value = 0.147).

Table 19 – Serum uric acid levels in patients with coronary artery disease

			Serum uric acid			Total	P value
			Low	Normal	High		
Coronary artery disease	NO	Count	4	56	4	64	0.147
		% within serum uric acid	50.0%	68.3%	40.0%	64.0%	
	YES	Count	4	26	6	36	
		% within serum uric acid	50.0%	31.7%	60.0%	36.0%	
Total		Count	8	82	10	100	
		% within serum uric acid	100.0%	100.0%	100.0%	100.0%	

Figure 19 – Correlation of serum uric acid levels with coronary artery disease



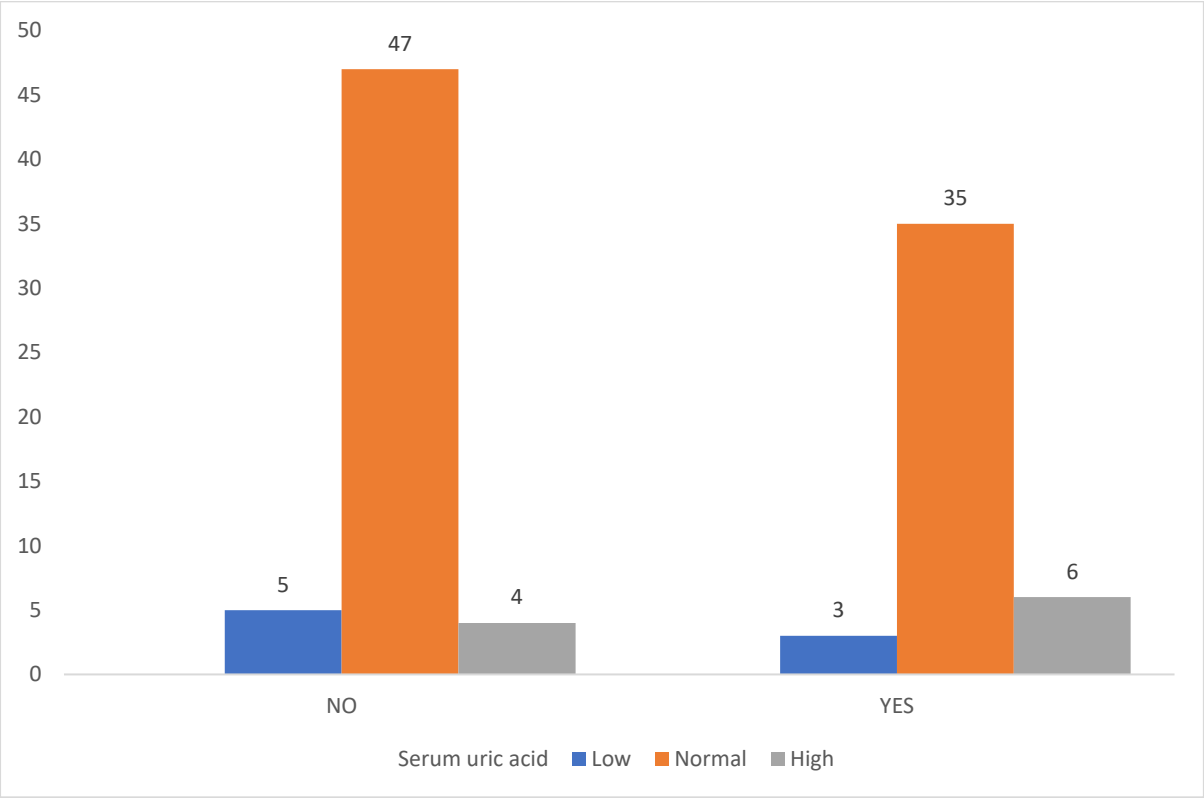
d. Albuminuria and serum uric acid levels

We did not find any significant correlation between albuminuria and serum uric acid levels (p-value = 0.54); however, six patients with albuminuria reported high serum uric acid levels.

Table 20 – Albuminuria and serum uric acid levels

			Serum uric acid			Total	P value
			Low	Normal	High		
Albuminuria	NO	Count	5	47	4	56	0.54
		% within serum uric acid	62.5%	57.3%	10.0%	56.0%	
	YES	Count	3	35	6	44	
		% within serum uric acid	37.5%	42.7%	60.0%	44.0%	
Total		Count	8	82	10	100	
		% within serum uric acid	100.0%	100.0%	100.0%	100.0%	

Figure 20 – Serum uric acid levels correlate with albuminuria



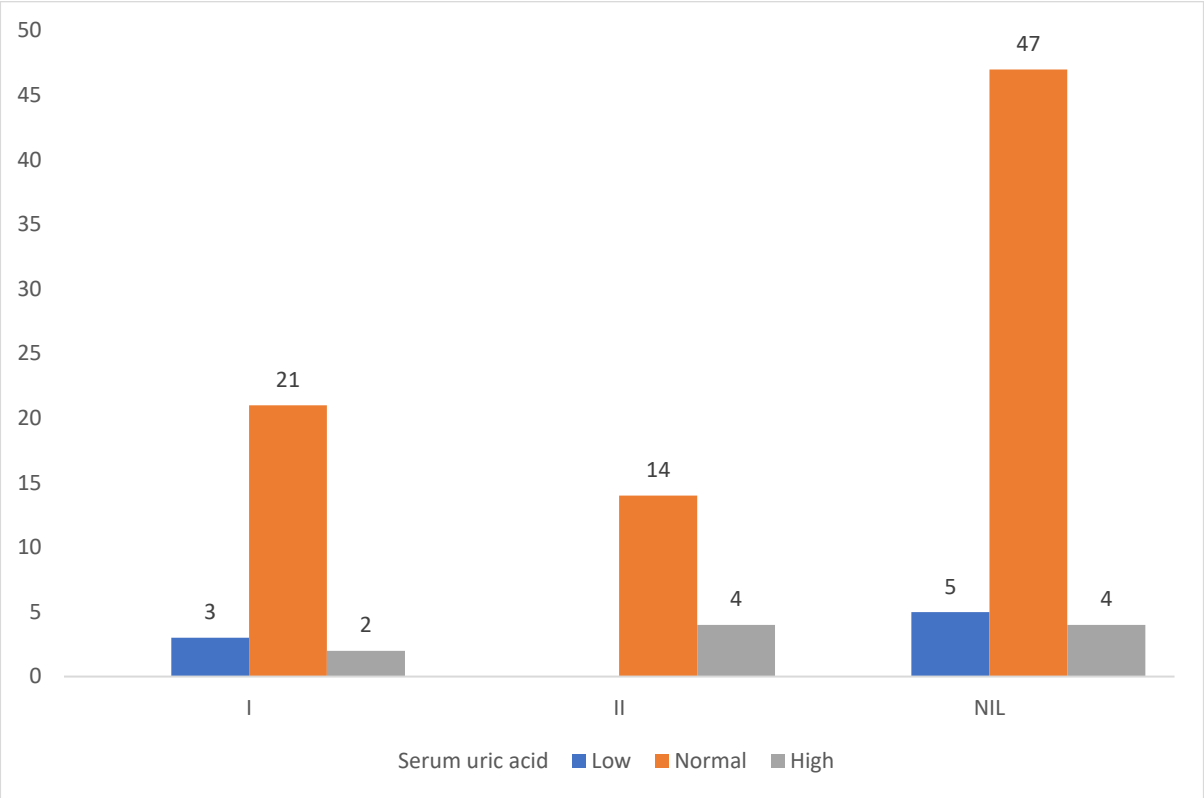
e. Retinopathy and serum uric acid levels

Most patients with retinopathy show normal levels of serum uric acid; however, grade I retinopathy reported two patients with elevated serum uric acid levels and three patients with reduced serum uric acid levels. In addition, grade II retinopathy revealed four patients with a high level of serum uric acid. However, the study did not report any significant correlation concerning the prevalence of retinopathy and serum uric acid levels (p-value = 0.262).

Table 21 – Serum uric acid levels correlation with retinopathy

			Serum uric acid			Total	P value
			Low	Normal	High		
Retinopathy	I	Count	3	21	2	26	0.262
		% within serum uric acid	37.5%	25.6%	20.0%	26.0%	
	II	Count	0	14	4	18	
		% within serum uric acid	0.0%	17.1%	40.0%	18.0%	
	NIL	Count	5	47	4	56	
		% within serum uric acid	62.5%	57.3%	40.0%	56.0%	
Total		Count	8	82	10	100	
		% within serum uric acid	100.0%	100.0%	100.0%	100.0%	

Figure 21 – Retinopathy and serum uric acid levels



DISCUSSION

Several kinds of literature have established the direct association between serum uric acid levels and hypertension. One such finding was reported by a cross-sectional study which stated that each 1mg/dL increase in serum uric acid levels could increase a 20% prevalence of hypertension in the general population if adequate treatment measures are not adopted. [37] The current study reports a fluctuation in serum uric acid levels depending on the comorbid condition, BMI, age, gender, and clinical condition. It is postulated that hyperuricemia is more common among hypertensive patients compared to normotensive (28.8% versus 13.7%, respectively, p-value < 0.0001). [38]

A retrospective study of 351 patients with essential hypertension revealed hyperuricemia as the most common clinical condition compared to normotensive individuals. The current study finding reports a high prevalence of essential hypertension among the age group between 51-60 years of age (30%), followed by 61-70 years of age (26%). Similar findings were noted by Ofori et al., with a mean age of 46.8 years. [39]

However, our study did not report a higher level of patients with elevated serum uric acid levels in patients with essential hypertension. Therefore, the patients in our study did not have elevated serum uric acid levels, which can be due to the hypertensive stage, gender, age, or other comorbid conditions.

In the current study, we find that 23% of the patients with essential hypertension were overweight as per BMI measurement, and 7% were obese, similar to the study conducted by Ofori et al., where overweight patients were reported with high levels of serum uric acid levels.

Social habit is also considered an independent risk factor for hypertension and elevated serum uric acid levels reported by Tatsumi et al. in retrospective cohort data in 7848 patients. The study reported that alcohol consumption and hyperuricemia was the independent factor for the development of hypertension, with an HR ratio of 1.37 in men and 1.54 in women. Furthermore, the interaction between gender and alcohol consumption with hyperuricemia was not significant, parallel to the findings of our study. It can be postulated that hyperuricemia can predict the development of hypertension independently of alcohol intake. [40] However, we observed a high level of uric acid and low levels in patients with essential hypertension presented with the comorbid condition, including; left ventricular hypertrophy (LVH), coronary artery disease, and diabetes. In a recent study by Yoshimura et al. of 1943 hypertensive and normotensive patients, the study reports a significant association between serum uric acid levels and LVH only among males [41]. In some studies, the association was seen in females. [42] These gender differences can be due to hormone alteration, which is yet to be clinically proven. [43]

The current study did not find a significant correlation between serum uric acid levels to age, gender, social habit, comorbid condition, or social habits, which can be due to the limited size of the participants and initial clinical stages of hypertension. However, the study found that individuals with elevated serum uric acid levels were seen with retinopathy grade I and grade II, which can be seen in other literature. [38] [39]

We found few differences between hypertensive and normotensive patients in the current study. However, the plausible relation between serum uric acid levels and the development of targeted organ damage can be seen due to the formation of free radicals resulting in oxidative stress and leading to renal dysfunction, which has been reported bother studies have reported Studies between serum uric acid levels reported the positive correlation and hypertension was the development of grade I and II retinopathy in the majority of the individuals.

The classical proposed mechanism for uric acid leading to the development of hypertension is the primary harmful effects on the kidney, which is related to the activation of the intrarenal renin-angiotensin system and the deposition of urate crystal in the urinary tract. In addition, recent evidence has stated that uric acid can cause endothelial dysfunction and injury directly, concerning the study by Klauser et al., which revealed the deposits of urate crystals in patients' aorta and coronary arteries. [44]

SUMMARY

- The current study reports a high prevalence of hypertension in the age group of 51-60 years of age (30.0%), followed by 61-70 years of age (26%), and the age range of 41-50 years (24%).
- A high male predominance was reported in the current study comprising 76 males (76%) and 24 females.
- Most of the patients were reported to be in the normal range of BMI, comprising 59 individuals (59%).
- Twenty-three reported having a social habit of alcohol consumption (23%), and 77 patients did not report any alcohol consumption history.
- Smoking was reported in 39 patients (39%), and 61 reported no history or social habit of smoking.
- A history of diabetes was reported in 19 patients (19%) from the overall study.
- A total of 14 patients was diagnosed with left ventricular hypertrophy, whereas 86 patients did not have any significant finding.
- Thirty-six patients were reported to be diagnosed with coronary artery disease comprising 36% of the participants from the study.
- Albuminuria was seen in 44 patients (44%), whereas 56 patients were not diagnosed with such a condition.

- Retinopathy was reported in 44 patients, out of which stage I retinopathy was reported in 26 patients (26%) and stage II retinopathy was seen in 18 patients (18%).
- Elevated serum uric acid levels were observed in 10 patients (10%), and eight (8%) reported low or serum uric acid levels.
- Elevated levels of serum uric acid were seen in 10 patients with essential hypertension, out of which the age group of >71 was seen with 3 cases of high serum uric acid levels
- high levels of serum uric acid were seen in males comprising nine individuals, whereas low levels were seen higher in males (5 individuals) and females (3 individuals).
- There is no significant difference in BMI, alcohol consumption, smoking, diabetes mellitus left ventricular hypertrophy with serum uric acid levels.
- There is no significant correlation between albuminuria and retinopathy with serum uric acid levels.

CONCLUSION

The current study reports that serum uric acid levels can be seen as an independent factor for the development of hypertension and, without adequate treatment, can lead to target organ damage. The prevalence of hyperuricemia was reported in 10 individuals (10%), and hypouricemia was seen in 8 individuals (8%) from the total study.

The study did not report any significant correlation of serum uric acid levels with age, gender, BMI, social habits, or comorbid condition. However, based on the literature and clinical requirements, hyperuricemia can be seen in patients with essential hypertension.

BIBLIOGRAPHY

1. British Cardiac Society; British Hypertension Society; Diabetes UK; HEART UK; Primary Care Cardiovascular Society; Stroke Association JBS 2: Joint British Societies' guidelines on preventing cardiovascular disease in clinical practice. *Heart.* 2005;**91**(Suppl 5):v1–v52.
2. Whitworth JA, World Health Organization, International Society of Hypertension Writing Group 2003 World Health Organization (WHO)/ International Society of Hypertension (ISH) statement on management of hypertension. *J Hypertens.* 2003;**21**(11):1983–1992.
3. Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and renal hypertension. *N Engl J Med.* 1966;**275**(9):457–464.
4. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med. 1999; 131: 7–13.
5. Mazzali M, Kanellis J, Han L, Feng L, Xia YY, Chen Q, Kang DH, Gordon KL, Watanabe S, Nakagawa T, Lan HY, Johnson RJ. Hyperuricemia induces a primary renal arteriolopathy in rats by a blood pressure-independent mechanism. Am J Physiol Renal Physiol. 2002; 282: F991–F997.

6. Kanellis J, Watanabe S, Li JH, Kang DH, Li P, Nakagawa T, Wamsley A, Sheikh-Hamad D, Lan HY, Feng L, Johnson RJ. Uric acid stimulates monocyte chemoattractant protein-1 production in vascular smooth muscle cells via mitogen-activated protein kinase and cyclooxygenase-2. Hypertension. 2003; 41: 1287–1293.
7. Rao GN, Corson MA, Berk BC. Uric acid stimulates vascular smooth muscle cell proliferation by increasing platelet-derived growth factor A-chain expression. J Biol Chem. 1991; 266: 8604–8608.
8. Langlois M, De Bacquer D, Duprez D, De Buyzere M, Delanghe J, Blaton V.Serum uric acid in hypertensive patients with and without the peripheral arterial disease. Atherosclerosis. 2003; 168: 163-168
9. Kang DH, Finch J, Nakagawa T, Karumanchi SA, Kanellis J, Granger J, Johnson RJ. Uric acid endothelial dysfunction and pre-eclampsia: searching for a pathogenetic link. J Hypertens, 2004;22:229-235
10. Patetsios P, Song M, Shutze WP, Pappas C, Rodino W, Ramirez JA, Panetta TF. Identification of uric and xanthine oxidase in atherosclerotic plaque. Am J Cardiol. 2001; 88:188-191,
11. Jameson, Fauci, Kasper, Hauser, Longo, and Loscalzo. Harrison's Principal of Internal Medicine. 20th Edition. Mc.Graw Hill Education. Page no – 1891.
12. Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. Nat Rev Nephrol. 2020 Apr;16 (4):223-237.

13. Iqbal AM, Jamal SF. Essential Hypertension. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
14. Hypertension. Standard Treatment Guidelines. Ministry of Health and Family Welfare Government of India. 2016.
15. JNC 8 Guidelines for the Management of Hypertension in Adults. Practice Guidelines.
16. Cannon PJ, Stason WB, Demartini FE, Sommers SC, Laragh JH. Hyperuricemia in primary and renal hypertension. *The New England journal of medicine.* 1966;275:457–464.
17. Moriarity JT, Folsom AR, Iribarren C, Nieto FJ, Rosamond WD. Serum uric acid and risk of coronary heart disease: Atherosclerosis risk in communities (ARIC) study. *Ann Epidemiol.* 2000;10:136–143.
18. Chen JH, Chuang SY, Chen HJ, Yeh WT, Pan WH. Serum uric acid level as an independent risk factor for all-cause, cardiovascular, and ischemic stroke mortality: a Chinese cohort study. *Arthritis and rheumatism.* 2009; 61:225–232.
19. George C, Minter DA. Hyperuricemia. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2022.
20. Dong H, Xu Y, Zhang X, Tian S. Visceral adiposity index is strongly associated with hyperuricemia independently of metabolic health and obesity phenotypes. Sci Rep. 2017 Aug 18;7(1):8822

21. Skoczyńska M, Chowaniec M, Szymczak A, Langner-Hetmańczuk A, Maciążek-Chyra B, Wiland P. Pathophysiology of hyperuricemia and its clinical significance - a narrative review. Reumatologia. 2020;58(5):312-323.
22. Choi HK. A prescription for lifestyle change in patients with hyperuricemia and gout. Curr Opin Rheumatol. 2010;22:165–172.
23. Messerli FH, Frohlich ED, Dreslinski GR, et al. serum uric acid in essential hypertension: an indicator of renal vascular involvement. Ann Intern Med. 1980;93:817–821.
24. Quińones Galvan A, Natali A, Baldi S, et al. Effect of insulin on uric acid excretion in humans. Am J Physiol. 1995;268:E1–5.
25. Soletsky B, Feig DI. Uric acid reduction rectifies prehypertension in obese adolescents. *Hypertension.* 2012; 60:1148–1156.
26. Joo HJ, Jeong HS, Kook H, et al. Impact of hyperuricemia on clinical outcomes after percutaneous coronary intervention for in-stent restenosis. *BMC Cardiovasc Disord.* 2018; 18:114.
27. Feig DI. The role of uric acid in the pathogenesis of hypertension in the young. J Clin Hypertens (Greenwich). 2012 Jun;14(6):346-52.
28. Culleton BF, Larson MG, Kannel WB, Levy D. Serum uric acid and risk for cardiovascular disease and death: the Framingham Heart Study. Ann Intern Med. 1999;131:7–13.

29. Ofori SN, Odia OJ. Serum uric acid and target organ damage in essential hypertension. Vasc Health Risk Manag. 2014 May 2;10:253-61.

30. Viazzi F, Parodi D, Leoncini G, Parodi A, Falqui V, et al. Serum uric acid and target organ damage in primary hypertension. Hypertension. 2005 May;45(5):991-6.

31. Jordan DM, Choi HK, Verbanck M, Topless R, et al. No causal effects of serum urate levels on the risk of chronic kidney disease: a Mendelian randomisation study. PLoS Med 2019; 16:e1002725.

32. Yang Q, Guo CY, Cupples LA, Levy D, Wilson PW, Fox CS. A genome-wide search for genes affecting serum uric acid levels: the Framingham Heart Study. Metabolism 2005; 54:1435–1441.

33. Li X, Meng X, He Y, Spiliopoulou A, Timofeeva M, Wei WQ, et al. Genetically determined serum urate levels and cardiovascular and other diseases in UK Biobank cohort: a phenome-wide Mendelian randomisation study. PLoS Med 2019; 16:e1002937

34. Yang N, Yu Y, Zhang A, Estill J, Wang X, Zheng M, Zhou Q, et al. Reporting, presentation and wording of recommendations in clinical practice guideline for gout: a systematic analysis. BMJ Open. 2019 Jan 29;9(1):e024315.

35. Yakupova SP. Gout. New opportunities for diagnosis and treatment. Ter Arkh. 2018 May 11;90(5):88-92.

36. Schmieder RE. End organ damage in hypertension. Dtsch Arztebl Int. 2010 Dec;107(49):866-73.
37. Kuwabara M, Niwa K, Nishi Y, Mizuno A, Asano T, Masuda K, et al. Relationship between serum uric acid levels and hypertension among Japanese individuals not treated for hyperuricemia and hypertension. Hypertens Res. 2014;37:785–9.
38. Emokpae AM, Abdu A. Serum uric acid levels among Nigerians with essential hypertension. Niger J Physiol Sci. 2013;28(1):41–44.
39. Ofori SN, Odia OJ. Serum uric acid and target organ damage in essential hypertension. Vascular Health and Risk Management. 2014 ;10:253-261.
40. Tatsumi Y, Asayama K, Morimoto A, Satoh M, Sonoda N, Miyamatsu N, et al. hyperuricemia predicts the risk for developing hypertension independent of alcohol drinking status in men and women: the Saku study. Hypertens Res. 2020;43:442–49.
41. Yoshimura A, Adachi H, Hirai Y, et al. Serum uric acid is associated with the left ventricular mass index in males of a general population. Int Heart J. 2014;55(1):65–70.
42. Matsumura K, Ohtsubo T, Oniki H, Fujii K, Iida M. Gender-related association of serum uric acid and left ventricular hypertrophy in hypertension. Circ J. 2006;70(7):885–888.
43. Viazzi F, Parodi D, Leoncini G, et al. Serum uric acid and target organ damage in primary hypertension. Hypertension. 2005;45(5):991–996.

ந ோயோளி ஒப்புதல் படிவம்

ஆய்வு விவரம்: "வளர்சிததமோற்ற ந ோய்க்குறிகள் மற்றும் இதய ோள அபோயக் கோரணிகள் கோண்ட கழுத்துப் பகுதியில் உள்ள சங்கத்தத மதிப்பிடுவதற்கு-ஒரு குறுக்கு கவட்டு ஆய்வு"

ஆய்வு தமயம்: அரசு கீழ்போக்கம் மருத்துவக் கல்லூரி, கசன்தை

ந ோயோளி கபயர்:

ந ோயோளி வயது:

புறந ோயோளி எண்:

ந ோயோளி இந்தப் கபட்டிகள் உள்ளகசய்யலோ

ஈநல உள்ள ஆய்வின் தடமுதறயின் ந ோக்கத்தத ோன் புரிந்துகோண்டன்

ை உறுதிப்படுத்துகிறன். நகள்வி நகட்பதற்கு ைக்கு வோய்ப்பு உள்ளது, ைது முழு திருப்திக்கு ைது நகள்விகளும் சந்நதகங்களும் பதிலளிக்கப்பட்டை. ☐

-இந்த ஆய்வில் ோன் பங்நகற்பது தன்ைோர்வத்திலோை மற்றும் ைது சட்டபூர்வ உரிதமகள் போதிக்கப்படோமல் எந்த ந ரத்திலும் எந்தக் கோரணமும் கூறோமல் விலகிக்ககோள்வதற்கு ோன் கதந்திரமோக உள்நளன் என்பதத ோன் புரிந்துகோண்நடன். ☐

-சிகிச்தசயக ஆய்தவ வழங்கும் றுவைம், ஆய்தவ வழங்கும் றுவைத்தின் சோர்போக பணிபுரியும் மற்றவர்கள், க றிமுதறக் குழு மற்றும் ஒழுங்குமுதற அதமப்புகள், தற்நபோததய ஆய்வு மற்றும் அவற்றில் இருக்கக் கூடிய எந்த ஒரு ஆநரோய்ச்சியிலும் ைது உடல் லப் பதிநவடுகதளப் போர்ப்பதற்கு ைது அனுமதி நததவயில்தல என்று ோன் புரிந்துகோண்நடன். அது கதோடர்போக டத்தப்படும், ோன் ஆய்விலிருந்து விலகிைோலும் கூட இந்த அனுகதல ஒப்புக்ககோள்கிநறன். ைினும், சட்டத்தின் கீழ் நததவப்பட்நடோல் ஒழிய, மூன்நறோம் தரப்பிைருக்கு கவளியிடப்படும் அல்லது பிரகரிக்கப்படும் எந்தத் தகவல்களில் ைது அதடயோளம் கவளிப்படுத்தப்படோது என்பதத ோன் புரிந்துகோண்நடன். இந்த ஆய்விலிருந்து எழும் தரவுகள் அல்லது முடிவுகளின் பயன்போட்தட கட்டுப்படுத்தோமல் இருக்க ோன் ஒப்புக்ககோள்கிநறன் ☐

.நமநல உள்ள ஆய்வில் பங்நகற்க ோன் ஒப்புக்ககோள்கிநறன், ஆய்வின் நபோது அளிக்கப்பட்ட அறிவுதரகளுக்கு இணங்க நவண்டும். ஆய்வுக் குழுவுடன் விகவோசத்துடன் ஒத்துழக்கவும், ைது உடல் லத்தில் அல்லது ல்வோழ்வுத் தில் ஏநதனும் சர்நகடு ஏற்பட்நடோல் அல்லது எதிர்போரோத அல்லது வழக்கத்திற்கு ோறோை அறிகுறிகள். ☐

இந்த ஆய்வில் பங்நகற்பதற்கு ோன் ஒப்புதல் அளிக்கிநறன்.

இரத்தவியல், உயிர்நவதியியல், நரடிநயோலோஜிக்கல் பரிநசோததைகள் உட்பட முழுதமயோை மருத்துவ பரிநசோததை மற்றும் பகுப்போய்வு பரிநசோததைகதள நமற்ககோள்ள ோன் அனுமதி ககோடுக்கிநறன்.

[redacted]

ந ோயோளியின் கபயர் மற்றும் முகவரி: ஆய்வோளரின் நததி தகயோப்பம்:

சுய ஒப்புதல் படிவம்

ஆய்வு செய்யப்படும் தலைப்பு: கடுமையான பக்க வாதத்துடன் தொடர்புடைய சீரம் ஃபெரிடின்சிஆர்பி,மற்றும் ஆர்.டி.டபிள்யூ.

இடம் : அரசு கீழ்பாக்கம் மருத்துவகல்லூரி மற்றும் மருத்துவமனை, சென்னை

பங்குபெறுபவரின் பெயர்:

பங்குபெறுபவரின் வயது:

பங்குபெறுபவரின் எண்:

மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விவரங்கள் எனக்கு விளக்கப்பட்டது. நான் இவ்வாய்வில் [redacted]கிறேன்.

PATIENT CONSENT FORM

Study details : **SERUM URIC ACID LEVELS AND END ORGAN DAMAGE IN ESSENTIAL HYPERTENSION ' A Cross sectional Study.**

Study centre : GOVT. KILPAUK MEDICAL COLLEGE, CHENNAI

Patient Name :
Patient Age :
OP number :

Patient may check in ( )these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well-being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination and diagnostic tests including haematological, biochemical, radiological tests.

Signature/thumb impression:

Patient Name and Address: Place: Date:

Signature of investigator :

Study investigator's Name : Place: Date :

S.No.	Age	Age group	Gender	BMI	BMI	SBP	DBP	Alcohol	Smoking	Diabetes mellitus.	LVH	Coronary artery disease	Cerbrovascular accident.	Albuminuria	Retinopathy	Random blood sugar	Blood urea	Serum creatinine	Serum uric acid
1	61	5	F	31.7	4.0	160	100	NO	NO	NO	NO	YES	NO	YES	II	71	40	0.7	4.2
2	52	4	F	21.1	2.0	150	90	NO	NO	NO	NO	NO	NO	NO	NIL	89	30	0.9	4
3	55	4	M	17.4	1.0	160	100	NO	YES	NO	NO	NO	YES	YES	II	96	30	1.4	5.5
4	46	3	F	27.6	3	150	100	NO	NO	NO	NO	YES	NO	NO	NIL	108	20	0.8	4.5
5	41	3	M	16.6	1.0	160	110	YES	YES	NO	NO	NO	YES	YES	I	90	23	1.1	5.2
6	44	3	M	22.7	2.0	160	110	YES	YES	NO	NO	NO	NO	NO	NIL	95	26	0.9	4.7
7	47	3	M	16.8	1.0	210	110	NO	YES	NO	NO	YES	NO	YES	III	120	40	1.4	6.2
8	59	4	M	25.3	3	170	84	YES	NO	NO	NO	YES	NO	NO	NIL	118	36	1.1	3.5
9	63	5	M	26.5	3	150	90	YES	YES	NO	NO	YES	NO	NO	NIL	88	30	1.1	4.8
10	55	4	M	23.6	2.0	170	100	NO	NO	YES	NO	YES	NO	YES	II	170	40	0.8	7.42
11	51	4	M	20.5	2.0	170	110	NO	YES	NO	NO	NO	YES	NO	NIL	77	28	1	5.2
12	59	4	M	24.1	2.0	190	120	NO	NO	NO	NO	NO	NO	YES	I	89	32	1.1	5.5
13	48	3	M	19.9	2.0	160	100	YES	NO	NO	NO	NO	YES	NO	NIL	110	22	0.7	5.3
14	30	1	M	21.8	2.0	170	100	NO	YES	NO	NO	NO	NO	YES	I	112	24	0.9	4.7
15	40	2	M	22.4	2.0	160	120	NO	NO	NO	NO	NO	YES	NO	NIL	98	18	0.9	3.6
16	62	5	M	25.2	3	150	100	NO	YES	NO	NO	NO	NO	NO	NIL	105	30	1	4.8
17	59	4	M	24.8	2.0	160	100	YES	YES	YES	NO	NO	NO	YES	I	162	26	1.1	4.6
18	60	4	M	23.6	2.0	160	100	NO	NO	YES	NO	NO	NO	NO	NIL	180	30	0.8	4.4
19	48	3	M	22.1	2.0	164	100	YES	YES	NO	NO	YES	NO	NO	NIL	77	24	0.9	6.5
20	33	2	M	21.9	2.0	146	90	NO	YES	NO	NO	NO	NO	YES	I	125	40	1	4.5
21	74	6	M	27.5	3	160	100	NO	NO	NO	NO	NO	NO	YES	I	74	20	0.9	7.7
22	55	4	M	32.8	4.0	170	110	NO	YES	YES	YES	YES	NO	NO	NIL	203	30	0.8	6.4
23	70	5	M	23.3	2.0	150	100	NO	NO	NO	YES	YES	NO	YES	II	68	19	0.7	4.1
24	54	4	M	24	2.0	160	100	YES	YES	YES	YES	NO	NO	YES	I	179	30	0.7	4.6
25	26	1	M	27.4	3	150	100	NO	NO	NO	NO	NO	NO	NO	NIL	90	26	0.8	5.8
26	64	5	M	22.5	2.0	186	106	NO	NO	NO	NO	NO	YES	NO	NIL	115	26	0.9	3.7
27	55	4	M	27.7	3	190	120	NO	NO	NO	YES	NO	NO	YES	II	164	40	1	6.2
28	65	5	F	16.4	1.0	166	110	NO	NO	NO	NO	NO	NO	YES	I	79	24	0.8	6.8
29	40	2	F	24.3	2.0	164	96	NO	NO	NO	NO	NO	NO	NO	NIL	92	30	0.9	5.7
30	42	3	F	20.7	2.0	150	100	NO	NO	NO	NO	NO	NO	NO	NIL	78	24	0.8	5.5
31	50	3	F	19.4	2.0	180	100	NO	NO	NO	NO	NO	YES	NO	NIL	87	22	0.7	4.3
32	26	1	M	24.8	2.0	156	90	NO	NO	NO	NO	NO	NO	NO	NIL	70	30	1	5.9
33	30	1	M	22.5	2.0	148	100	NO	NO	NO	NO	NO	NO	NO	NIL	74	24	0.9	6
34	62	5	M	25.2	3	150	90	NO	NO	NO	NO	NO	NO	NO	NIL	88	24	0.8	5.8
35	63	5	M	31.1	4.0	150	100	NO	YES	NO	NO	NO	NO	NO	NIL	106	28	1	6.2
36	55	4	M	21.5	2.0	140	100	NO	NO	NO	NO	YES	NO	NO	NIL	96	30	0.8	6.4
37	63	5	M	25	3	180	100	YES	NO	NO	NO	YES	NO	YES	I	114	24	1	5.5
38	74	6	M	22.8	2.0	150	92	NO	NO	NO	NO	YES	NO	NO	NIL	109	26	0.7	3.9
39	60	4	M	27.2	3	170	110	NO	YES	NO	NO	YES	NO	YES	I	83	32	0.8	5.2
40	70	5	M	32.8	4.0	150	100	NO	NO	NO	NO	NO	NO	NO	NIL	117	28	0.7	4.1
41	67	5	M	24.6	2.0	160	100	NO	YES	NO	NO	NO	NO	NO	NIL	73	28	1	3.9
42	55	4	M	23.4	2.0	170	80	NO	NO	NO	NO	NO	NO	NO	NIL	99	30	1.1	5.1
43	51	4	F	27.3	3	170	90	NO	NO	NO	NO	NO	NO	YES	II	101	29	0.9	4.9
44	40	2	F	22.4	2.0	160	100	NO	NO	NO	NO	NO	NO	NO	NIL	65	24	0.9	7
45	63	5	F	26.7	3	150	90	NO	NO	NO	NO	NO	NO	NO	NIL	82	30	1.1	5.5
46	48	3	M	22	2.0	170	100	YES	YES	NO	NO	YES	NO	NO	NIL	110	28	1	8.8
47	45	3	F	24.9	2.0	166	96	NO	NO	YES	NO	NO	NO	YES	I	167	30	0.9	6.5

46	48	3	M	22	2.0	170	100	YES	YES	NO	NO	YES	NO	NO	NIL	110	28	1	8.8
47	45	3	F	24.9	2.0	166	96	NO	NO	YES	NO	NO	NO	YES	I	167	30	0.9	6.5
48	30	1	M	22.4	2.0	160	100	YES	NO	NO	NO	YES	NO	NO	NIL	94	26	0.7	8.4
49	47	3	M	21.6	2.0	156	96	NO	NO	NO	NO	NO	NO	NO	NIL	101	20	0.8	4.5
50	28	1	F	27.1	3	140	100	NO	NO	YES	NO	YES	NO	NO	NIL	217	32	0.7	7.35
51	56	4	M	15.8	1.0	180	100	NO	YES	NO	YES	NO	NO	YES	II	66	40	1.5	4.9
52	63	5	M	22.7	2.0	180	100	YES	NO	NO	NO	YES	YES	YES	I	74	34	1.3	4.8
53	60	4	F	16.9	1.0	170	80	NO	NO	NO	NO	YES	YES	YES	I	67	28	0.7	4.5
54	48	3	M	20.4	2.0	170	120	NO	YES	NO	NO	YES	NO	YES	II	73	30	0.7	7.5
55	39	2	M	25.3	3	146	90	YES	NO	YES	NO	YES	NO	YES	II	69	29	1.2	5.3
56	66	5	M	22.2	2.0	140	100	NO	YES	NO	YES	YES	NO	YES	I	83	32	1.4	5.5
57	48	3	M	20.8	2.0	150	110	NO	NO	YES	NO	NO	NO	NO	NIL	134	24	0.8	3.9
58	65	5	M	23.5	2.0	220	130	NO	YES	NO	YES	NO	YES	YES	II	72	26	0.8	7.62
59	79	6	M	19.8	2.0	210	120	NO	NO	NO	YES	NO	NO	NO	NIL	70	38	1.5	7.4
60	49	3	M	21.9	2.0	140	100	NO	YES	NO	NO	YES	NO	NO	NIL	69	30	1.3	4.6
61	60	4	M	22.8	2.0	150	100	NO	YES	YES	NO	YES	NO	NO	NIL	220	26	1	4.1
62	60	4	F	27.2	3	210	120	NO	NO	NO	YES	NO	YES	YES	I	148	40	1.3	4.3
63	45	3	F	33.8	4.0	150	100	NO	NO	YES	NO	YES	NO	NO	NIL	180	34	1	5.6
64	62	5	F	23.2	2.0	144	100	NO	NO	YES	NO	NO	NO	NO	NIL	185	32	0.8	4.4
65	38	2	M	23.4	2.0	160	90	NO	YES	YES	NO	YES	NO	NO	NIL	112	26	0.9	4.8
66	54	4	F	27.3	3	170	110	NO	NO	YES	YES	NO	NO	NO	NIL	172	24	0.8	3.1
67	61	5	M	22	2.0	160	100	NO	YES	NO	NO	NO	YES	YES	I	96	25	0.9	3.3
68	65	5	M	28.4	3	170	100	NO	NO	NO	NO	NO	NO	NO	NIL	79	40	1	4.95
69	70	5	M	16.1	1.0	170	100	NO	NO	NO	NO	YES	NO	NO	NIL	83	35	1.1	3.24
70	49	3	F	24.3	2.0	160	100	NO	NO	NO	NO	NO	NO	YES	I	69	19	0.6	4.1
71	65	5	M	18.6	2.0	170	100	NO	YES	NO	NO	NO	NO	YES	II	95	24	0.9	3.66
72	67	5	M	16.9	1.0	180	100	YES	NO	NO	YES	NO	NO	NO	NIL	87	21	1	4.15
73	56	4	F	23.8	2.0	150	100	NO	NO	NO	NO	NO	NO	YES	I	72	20	0.8	3.44
74	53	4	M	20.8	2.0	170	100	NO	NO	NO	NO	NO	NO	YES	II	83	39	1.3	3.77
75	45	3	F	25.1	3	150	100	NO	NO	NO	NO	YES	NO	YES	I	78	29	0.8	3.44
76	64	5	F	31.7	4.0	150	100	NO	NO	NO	NO	YES	NO	YES	II	66	40	0.7	5.46
77	48	3	F	22.5	2.0	160	110	NO	NO	NO	NO	NO	NO	NO	NIL	104	26	0.8	4.25
78	50	3	F	20	2.0	160	110	NO	NO	NO	NO	NO	NO	NO	NIL	80	30	0.9	4.14
79	65	5	M	16	1.0	160	100	NO	YES	NO	NO	NO	YES	YES	II	94	33	1.3	4.15
80	43	3	F	27.6	3	150	100	NO	NO	NO	NO	YES	NO	NO	NIL	104	19	0.9	4.5
81	40	2	M	15.6	1.0	160	110	YES	YES	NO	NO	NO	YES	YES	I	88	23	1.1	5.3
82	42	3	M	22.7	2.0	160	110	YES	YES	NO	NO	NO	NO	NO	NIL	93	26	1	4.49
83	45	3	M	16.9	1.0	210	110	NO	YES	NO	NO	YES	NO	YES	III	118	40	1.2	6.3
84	64	5	M	25.2	3	170	90	YES	NO	NO	NO	YES	NO	NO	NIL	119	36	1.4	3.6
85	60	4	M	26.3	3	150	90	YES	YES	NO	NO	YES	NO	NO	NIL	86	30	1.1	4.3
86	56	4	M	22.6	2.0	190	110	NO	NO	YES	NO	YES	NO	YES	II	170	40	0.6	7.8
87	52	4	M	20.9	2.0	170	90	NO	YES	NO	NO	NO	YES	NO	NIL	76	28	0.9	5.3
88	60	4	M	24.1	2.0	160	100	NO	NO	NO	NO	NO	NO	YES	I	88	32	1.2	5.6
89	46	3	M	19.9	2.0	150	100	YES	NO	NO	NO	NO	YES	NO	NIL	108	22	0.7	5.2
90	30	1	M	21.8	2.0	170	100	YES	YES	NO	NO	NO	NO	YES	I	112	24	1.1	4.9
91	40	2	M	22.4	2.0	140	110	NO	NO	NO	NO	NO	YES	NO	NIL	96	18	0.9	3.8
92	65	5	M	27.2	3	150	100	NO	YES	NO	NO	NO	NO	NO	NIL	82	30	1	4.9
93	58	4	M	24	2.0	160	100	YES	YES	YES	NO	NO	NO	YES	I	162	26	1.1	4.6
94	60	4	M	23.6	2.0	160	100	NO	NO	YES	NO	NO	NO	NO	NIL	180	30	0.8	4.51
95	48	3	M	21.9	2.0	170	100	YES	YES	NO	NO	YES	NO	NO	NIL	72	24	0.9	6.6
96	39	2	M	22.3	2.0	144	96	NO	YES	NO	NO	NO	NO	YES	I	126	37	1	4.2
97	73	6	M	27.3	3	160	100	NO	NO	NO	NO	NO	NO	YES	I	72	22	0.9	7.45
98	55	4	M	32.8	4.0	150	100	NO	YES	YES	YES	YES	NO	NO	NIL	208	30	0.8	6.6
99	70	5	M	23.3	2.0	146	100	NO	NO	NO	YES	YES	NO	YES	II	60	25	0.7	4.5
100	54	4	M	22.4	2.0	150	100	YES	YES	YES	YES	NO	NO	YES	I	140	35	0.7	4.4