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RESEARCH ARTICLE
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URIC ACID AND CARDIOVASCULAR DISEASE: A RETROSPECTIVE ANALYSIS IN ESRD

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ABSTRACT

BACKGROUND

Chronic kidney disease has become rampant among the present Indian population, mainly due to progressively increasing numbers of non-insulin-dependent diabetes mellitus. While hypertension, diabetes mellitus, and obesity increase susceptibility, hypoalbuminemia and hyperuricemia represent indicators of susceptibility and progression of CKD, which, along with nephrotoxins, lead to end-stage renal disease (ESRD).[1] In this study, we intend to analyze uric acid levels along with renal function parameters to predict cardiovascular involvement due to ESRD. Cardiovascular dysfunctions contribute to major causes of mortality in ESRD when it forms as a renal-cardiac syndrome that affects both systolic and diastolic functions of the heart.

AIMS AND OBJECTIVES

1. To evaluate uric acid level as a co-marker of cardiovascular dysfunction in ESRD.
2. To derive left ventricular dysfunction from echocardiographic parameters and compare it with uric acid levels.
3. To evaluate left atrial diameter as an indicator of severe cardiac dysfunction in ESRD.

MATERIALS AND METHODS

Material: All renal transplant recipients who were carefully evaluated and recommended for renal transplantation, who attended the pre-anesthetic clinic, were taken up for the study. PAC charts and investigation reports were taken up retrospectively. All patients underwent successful renal transplantation.

Study Type: Retrospective Analysis
Study Period: October 2024 to February 2025
Study Place: D.S.M.C.H, Siruvachur.

METHODS

The pre-anesthetic evaluation charts and investigation reports, both biochemistry and echocardiogram, were noted for 30 renal transplant recipients. The above-mentioned parameters were tabulated and analyzed.

PARAMETERS

Age, Gender, Creatinine, Uric Acid, Ejection Fraction, Left Atrial Diameter.

RESULTS
Age distribution was from 25 to 64 years, with the maximum number of patients between 34 and 42 years. The creatinine levels in males ranged from 3 to 13 mg/dl, whereas in females, it ranged from 5 to 9 mg/dl. Ejection fraction ranged from 35% to 65%, with most patients having an EF between 45% and 55%. Females had a better EF than males. Among the 30 patients, only 6 were female. Uric acid levels ranged from 3 to 10 mg/dl and were consistently high in all females. Uric acid and creatinine showed an R-value of 0.5. Uric acid levels greater than 6 mg/dl were associated with an ejection fraction of less than 45%. The left atrial diameter showed variable uric acid levels. A direct correlation between left atrial end-systolic diameter and uric acid levels was observed in only 8 out of 30 cases.

CONCLUSION
In order to differentiate between normal and abnormal biological processes to predict adverse outcomes, standard biomarkers are indicated in CKD progression.[2] In addition to conventional biomarkers such as albuminuria, serum albumin, and anemia, serum uric acid appears to be a co-marker for CKD progression, with high levels associated with poor ejection fraction. Though novel biomarkers such as plasma asymmetric dimethyl arginine[3] are under research, simple routine tests like serum uric acid may provide insights into cardiovascular dysfunction, a major cause of mortality in end-stage renal disease. However, larger studies are needed to substantiate the relationship between uric acid levels and cardiac dysfunction.

KEYWORDS: CKD, ESRD, Uric Acid, Ejection Fraction, Creatinine, Markers of CKD & Progression.

INTRODUCTION
Cardiovascular disease is the major cause of morbidity and mortality in patients with chronic kidney disease (CKD).[4] According to the National Kidney Foundation, kidney disease outcomes quality initiative (NKF-KDOQI) recommendations, patients with CKD, regardless of the stage of disease, should be considered the highest risk group for cardiovascular events.
Uric acid is the final oxidation product of purine metabolism, with 70% excreted by the kidney. Though compared to creatinine, which is excreted by 11 mmol per day, uric acid excretion is only 4 mmol per day as excreted by the normal kidney. Renal organic anion transport system on the proximal tubule is affected in renal dysfunction.[5] Hyperuricemia has a casual role in pathophysiology of chronic kidney disease. Uric acid has been studied as a marker for mainly detecting the progression of CKD to end-stage renal disease.[6] Along with top pathways affected by CKD such as tricarboxylic acid cycle, tyrosine metabolism and nitrogen metabolism, purine metabolism is also affected due to the loss of organic anion transport system.[7]
The association of uric acid with progressive renal disease and relationship with cardiac dysfunction has been extensively studied. This study tries to evaluate uric acid as a part of protein investigation to denote severity of renal disease and left ventricular dysfunction that is first affected in uremia.

AIMS AND OBJECTIVES
1. To evaluate uric acid levels as a co-marker of cardiovascular dysfunction in ESRD.
2. To derive left ventricular dysfunction from echocardiographic parameters and compare it with uric acid levels.
3. To evaluate left atrial diameter as an indicator of severe cardiac dysfunction in ESRD.

MATERIALS AND METHODS
This is a retrospective analysis conducted on renal transplant recipients who were carefully evaluated and recommended for renal transplantation. Patients who attended the pre-anesthetic clinic were included in the study. PAC charts and investigation reports, including biochemical and echocardiographic findings, were collected and analyzed.

Study Type
Retrospective Analysis

Study Period
October 2024 to February 2025

Study Place
D.S.M.C.H, Siruvachur

Parameters Studied
- Age
- Gender
- Creatinine levels
- Uric Acid levels
- Ejection Fraction (EF)
- Left Atrial Diameter

RESULTS
Age distribution ranged from 25 to 64 years, with the highest number of patients between 34 and 42 years. The creatinine levels in males ranged from 3 to 13 mg/dl, whereas in females, it ranged from 5 to 9 mg/dl.
Ejection fraction varied between 35% and 65%, with most patients exhibiting an EF between 45% and 55%. Females demonstrated better EF than males. Only 6 out of the 30 patients were female. Uric acid levels ranged from 3 to 10 mg/dl and were consistently high in all female patients.
A statistical correlation was found between uric acid and creatinine levels, with an R-value of 0.5. Uric acid levels exceeding 6 mg/dl were associated with an ejection fraction below 45%. Left atrial diameter demonstrated variable uric acid levels. A direct correlation between left atrial end-systolic diameter and uric acid levels was observed in 8 out of 30 cases.

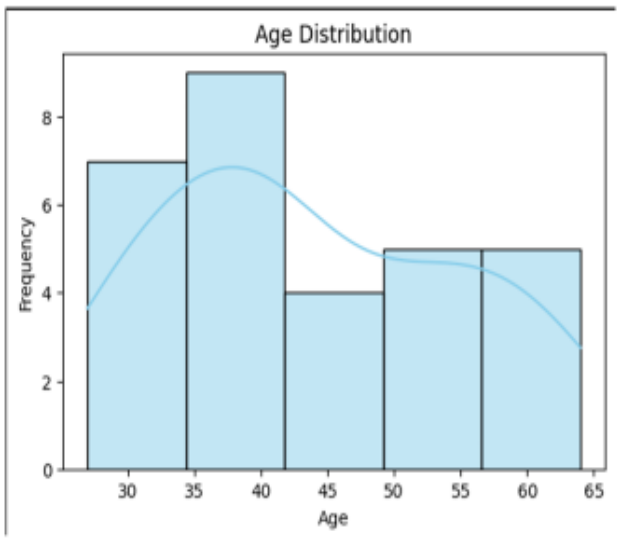


Figure 1: Age Distribution

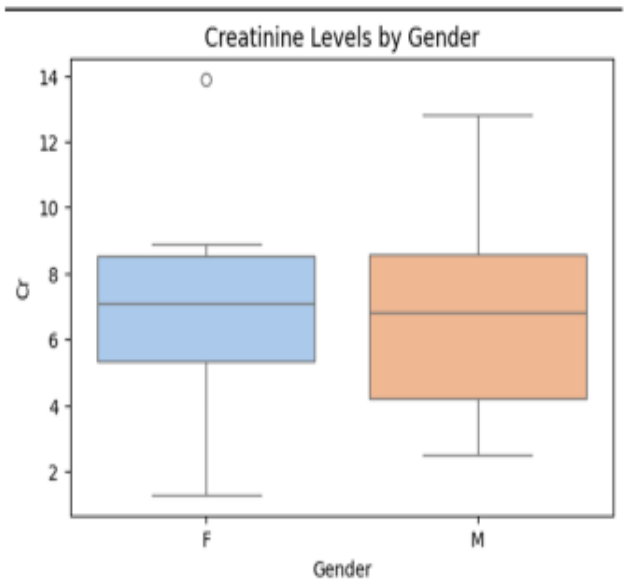


Figure 2: Creatinine Levels by Gender

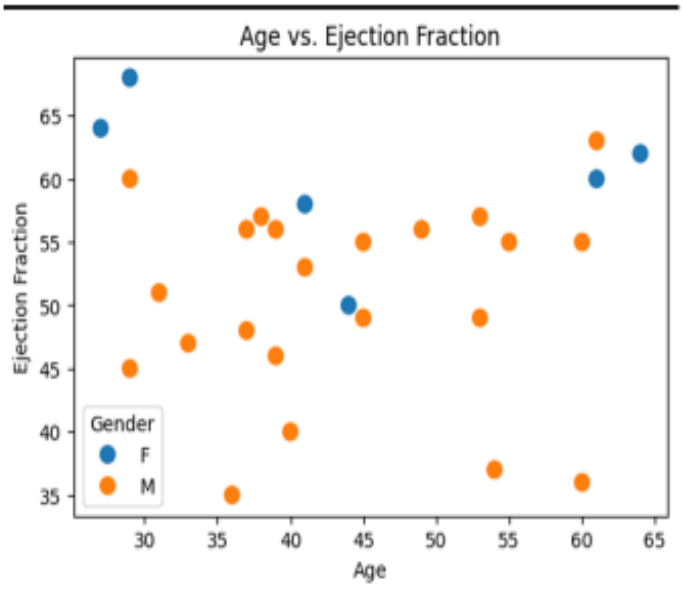


Figure 3: Age vs. Ejection Fraction

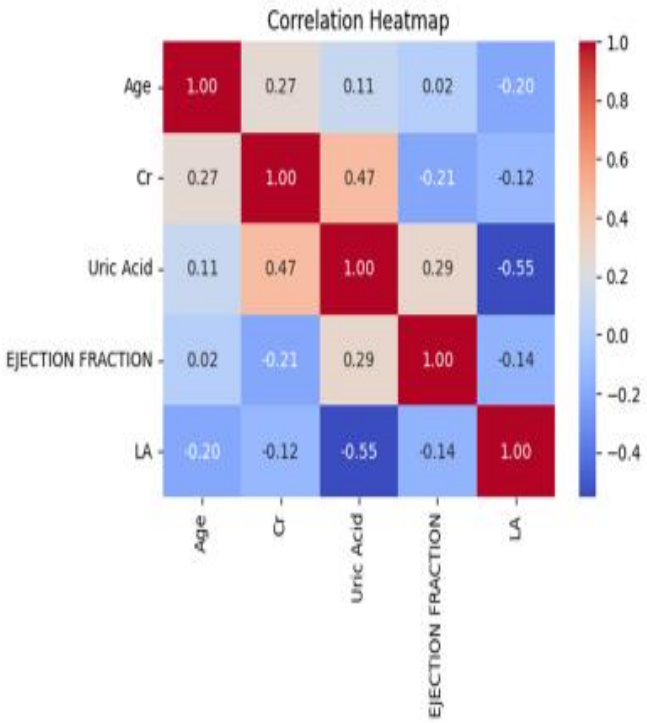


Figure 4: Correlation Heatmap

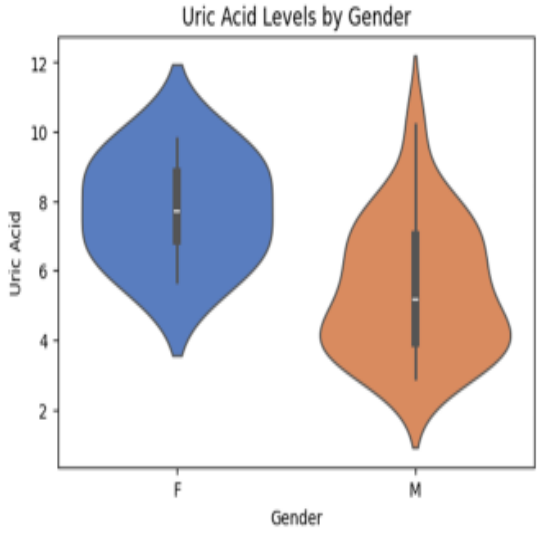


Figure 5: Uric Acid Levels by Gender

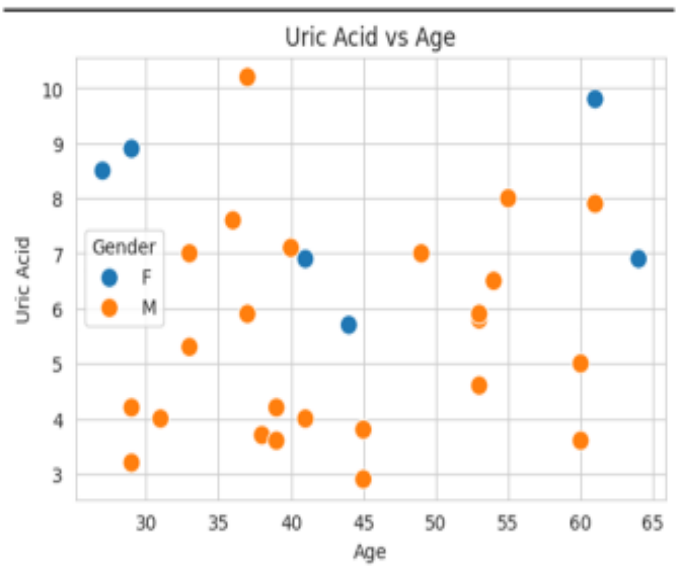


Figure 6: Uric Acid vs Age

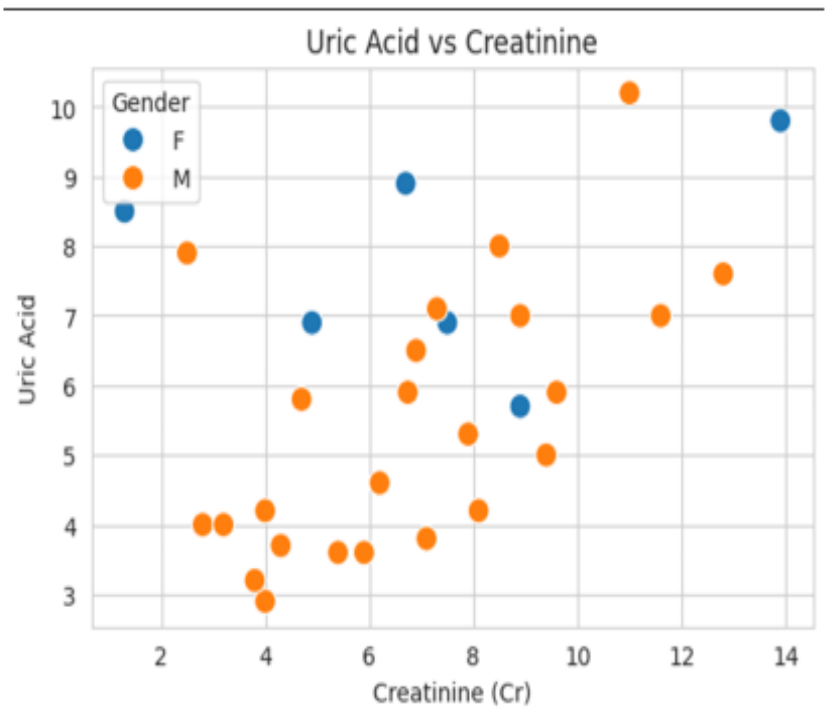


Figure 7: Uric Acid vs Creatinine

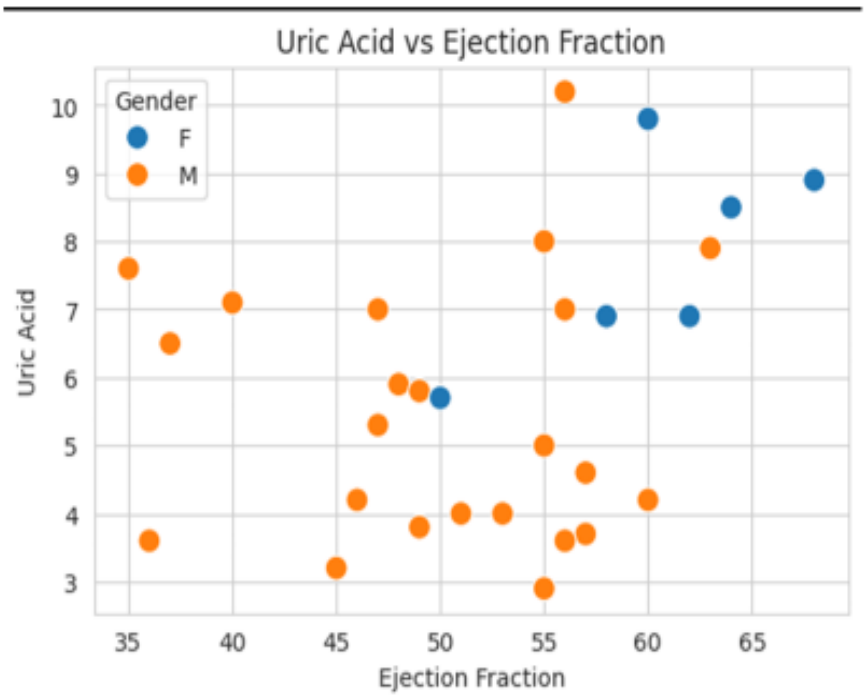


Figure 8: Uric Acid vs Ejection Fraction

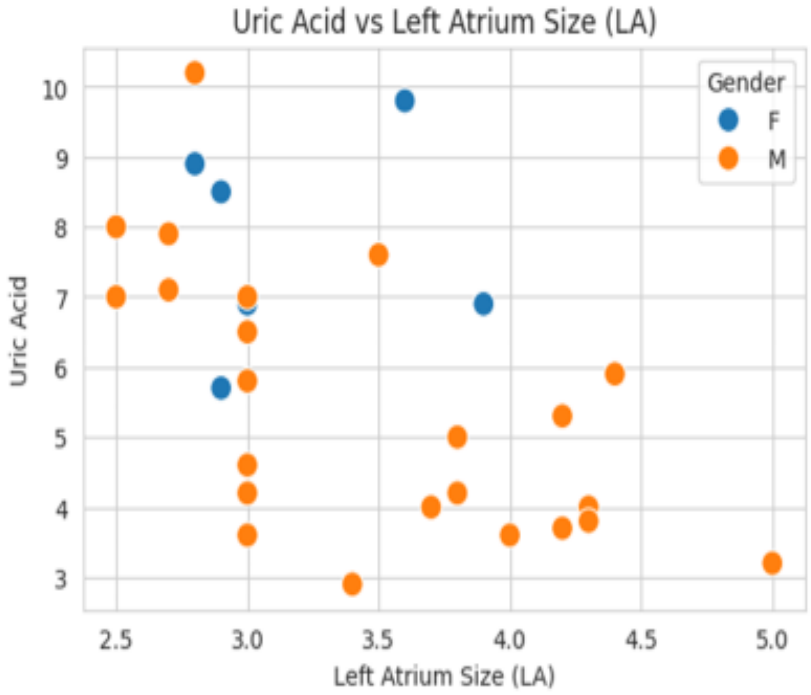


Figure 9: Uric Acid vs Left Atrium Size (LA)

DISCUSSION

Uremia is largely caused by the accumulation of organic waste products that are normally cleared by the kidneys. The European Uremic Toxin Work Group listed 80 to 250 uremic solutes.[8] In view of

the multiplicity of solutes, Bergstrom suggested criteria to identify uremic toxins. However, no uremic solute has so far fully satisfied the criteria. Many of the effects of uremia are difficult to quantify. Metabolic effects, symptoms, and signs of uremia are multiple and of complex origin. They have been classified into metabolic, neural and muscular, and other categories, as shown in the table below.

Category	**Symptoms and Signs of Uremia**
Metabolic	Increased oxidant levels, Reduced resting energy expenditure, Reduced body temperature, Insulin resistance, Muscle wasting, Amenorrhea and sexual dysfunction
Neural and Muscular	Fatigue, Loss of concentration (ranging to coma and seizures), Sleep disturbances, Restless legs, Peripheral neuropathy, Anorexia and nausea, Diminution in taste and smell, Itching, Cramps, Reduced muscle membrane potential
Other	Serositis (including pericarditis), Hiccups, Granulocyte and lymphocyte dysfunction, Platelet dysfunction, Shortened erythrocyte life span, Albumin oxidation
Table 1: Metabolic effects, symptoms, signs of uremia	

Major uremic solutes include urea, D-amino acids, peptides and proteins, guanides, phenols and aromatic compounds, indoles and other tryptophan metabolites and aliphatic amines.[9]
Uric acid, which is a purine metabolite, is the only known organic substance with a plasma level actively regulated by variation of its renal excretion. With advanced CKD, the capacity of the kidney to increase the fractional excretion of uric acid is exceeded, and uric acid levels increase along with those of its precursor molecules xanthine and hypoxanthine.

Uric acid is eliminated 60-70% by kidney and 30-40% by intestine, hence a declining renal function is associated with elevation in serum uric acid. 40-80% of patients with end-stage renal disease have hyperuricemia defined as levels more than 7mg per deciliter.[9] In patients treated with hemodialysis, uric acid is effectively removed from blood, given its clearance pattern and sieving coefficient(1.01) similar to that of urea. Detrimental pathophysiological effects have been attributed to uric acid and linked to pathogenesis of cardiovascular disease, the main cause of osmolarity in dialysis patients.[10] Despite its antioxidant properties, uric acid was found to activate inflammatory pathways in the body such as NALP3 inflammasome, leading to secretion of interleukin-1-beta and reactive oxygen species. In addition, uric acid triggers endothelial dysfunction and stimulates RAAS, thus contributing to vascular smooth muscle cell growth and arterial function impairment.[11]

Task Force City Elderly Health Examination Program found a U-shaped association between serum uric acid 4-8mg per deciliter and all-cause mortality. This form of association appears to be independent of patient's body composition.[12]

Uric acid is cleared from body by glomerular filtration and secretion by proximal tubule cells and asymptomatic hyperuricemia 12-15mg per deciliter is typical in established AKI. Higher levels suggest increased production of uric acid and may point to a diagnosis of acute urate nephropathy. Urinary uric acid to creatine ratio on a random specimen has been proposed as a means to distinguish between hyperuricemia caused by overproduction of and impaired excretion. This ratio was more than 1 in acute uric acid nephropathy and less than 1 in acute kidney injury due to other causes.

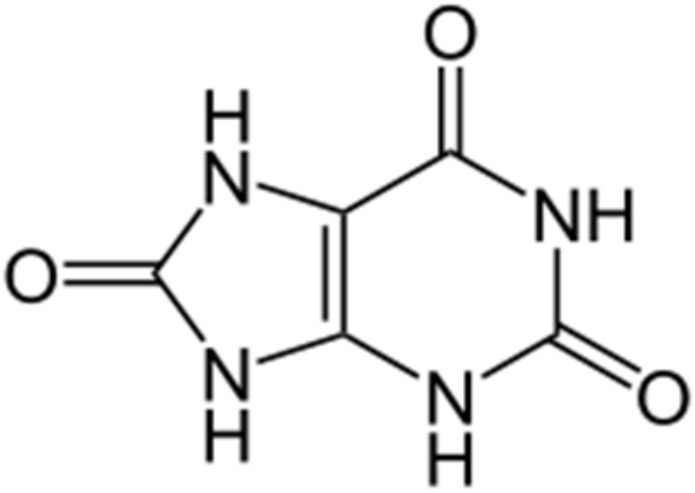
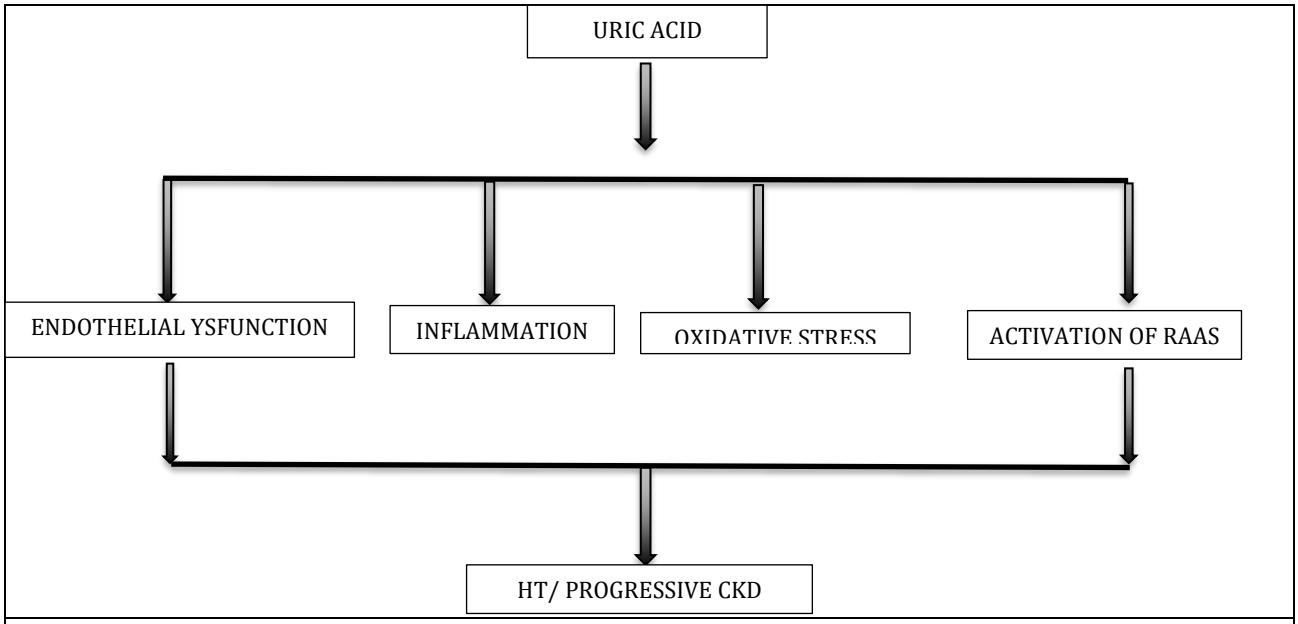


Figure 10: Structure of Uric Acid



Flow Chart

Uric acid solubility is pH and concentration dependent. Uric acid crystallization in tubules collecting system or outflow tract or deposition on uric acid within interstitium result in inflammation up to 11% of chronic interstitial disease where attributed to disorders of uric acid for every 1mg per deciliter increase in baseline uric acid.

CARDIORENAL SYNDROME (CRS) General Definition: Pathophysiological disorder of the heart and kidneys wherby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in other organ.
CRS TYPE 1 (Acute Cardiorenal syndrome) Abrupt worsening of cardiac function.(eg Acute Heart Failure) leading to acute kidney injury
CRS TYPE 2 (chronic Cardiorenal syndrome) Chronic abnormalities of renal function (eg chronic heart failure) causing progressive and permanent chronic kidney disease
CRS TYPE3 (Acute Renovardiac Syndrome) Abrupt worsening of of renal function (eg acute kidney injury)causing acute cardiac disorder(eg volume overload, heart failure, hyperkalemia)
CRS TYPE 4(chronic Reno cardiac syndrome) Chronic kidney disease (eg diabetic nephropathy) contributing to decreased cardiac function, cardiac fibrosis or hypertrophy and/ or increased risk of adverse cardiovascular events
CRS TYPE 5(SECONDARY CARDIO RENAL SYNDROME)

Systemic condition (eg multiple trauma, sepsis) causing both cardiac and renal disfunction	
CRS TYPE 1	Acute of cardiac function leading to kidney injury and/or dysfunction
CRS TYPE 2	Chronic abnormalities in cardiac function leads to kidney injury and/or dysfunction
CRS TYPE 3	Acute of kidney function leads to cardiac injury and/or dysfunction
CRS TYPE 4	Chronic kidney disease leads to heart injury and/or dysfunction
CRS TYPE 5	Systemic extra enal and extracardiac condition leading to Simon tennis injury and or dysfunction of both the heart and kidney
Table 2: CRS Classification	

A 7% increased risk for developing kidney disease was noted after adjustment for confounders.[13] Acquired cause of urinary tract obstruction due to intraluminal intrinsic processes include uric acid nephropathy as a foremost factor.

High serum and uric acid levels could occur due to lack of enzyme uricase which transform uric acid into more soluble allantoin. Uricase deficiency is partially compensated by repression of xanthine oxidase but the high serum uric acid may also be due to low renal fractional excretion of uric acid and underlying urinary pH is one of the major contributor of uric acid nephrolithiasis.

After controlling for baseline serum creatinine and other variable, presence or absence of baseline hyperuricemia, defined as more than 7mg per deciliter in men and 6mg per deciliter in women, markedly increased the risk of developing end-stage kidney disease requiring dialysis. The urate crystals have been associated with arteriosclerosis and stimulate inflammasomes in lesions similar to cholesterol crystals and this is expected to increase risk for plaque extension or rupture. This explains cardiovascular dysfunction and mortality in patients with even mild increased uric acid levels coexisting with end-stage renal disease. Lowering serum uric acid level was beneficial in estimated GFR and blood pressure.[14]

Condition	**Initiation**	**Maintenance**
Hypertension	Uric acid dependent oxidative stress, reduced nitrous oxide activated RAS,no kidney damage	Autoimmune inflammation in kidney maintains renal vasoconstriction
Obesity	Uric acid dependent decrease in mitochondrial function, inhibit AMPK, less ATP generation	Loss of mitochondria resets weight to higher level
Diabetes	Uric acid induced insulin resistance, gluconeogenesis reduced insulin secretion	Chronic islet injury leads to diabetic state in setting of Persistent insulin resistance
CKD	Uric acid dependent glomerular hypertension, vaso construction, endothelial disfunction, inflammation	Chronic kidney injury leads to persistent hyperfiltration and glomerular hypertension independent of uric acid levels
Table 3: Role of Uric Acid in Systemic Illness		

The interplay between heart and kidney is key to pathophysiologic process that occur in heart failure and end-stage renal disease and synergistic failure of both organs have been termed as Cardiorenal syndrome. Cardiorenal syndrome refers to disorders of heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction in the other. The three key mechanical contributors to heart failure in end-stage renal disease include pressure overload, volume overload and cardiomyopathy.[15] The risk of developing cardiovascular disease CKD 3-30 times depending on the stage of CKD. Risk factors for the development of CVD in patients with CKD can be divided into traditional factors and non-traditional factors. Traditional factors include hyperlipidemia, hypertension, diabetes and smoking. Non-traditional factors include volume overload, increased sympathetic tone, activation of reactive RAAS, oxidative stress, uremic toxins, abnormal mineral metabolism, anemia and malnutrition.[16] Three important mechanisms contribute to CVD progression in CKD. Autonomic dysfunction, vascular pathology, cardiac pathology, diuretic resistance has been attributed as one of the factors indicating poor volume and electrolyte homeostasis. This is often considered as a predictor of worse outcomes independent of GFR.[17]

Classification of cardio-renal syndromes describes five popular terms namely acute cardio-renal syndrome, chronic cardio-renal syndrome, acute renal cardiac syndrome, chronic renal cardiac syndrome class 4 and systemic cardio-renal syndromes. Of these, chronic kidney disease leading to

cardiac injury or progression of cardiac disease including heart failure which is CRS4 is the most relevant to our topic of consideration. In 42 percent of patients with heart failure estimated GFR less than 60 ml per minute per 1.73 meter square is frequently present as per the definition of CKD. Conversely, on patient with CKD the prevalence of heart failure in subjects with GFR less than 60 ml per 1.73 meter square is between 2 to 20 fold higher than in patient with preserved GFR.

Systemic modulating factors designated as cardio-renal connectors which include endothelial dysfunction, inflammation, sympathetic nervous system activation, running angiostensin, aldosterone system activation, reactive oxygen species activation, affects GFR and RBF. In CRS, 3rd and 4th endothelial dysfunction and inflammation have increased markers such as TNF-alpha and IL-6 which have detrimental effect on cardiac function.[18] In patient with ESRD, left ventricular dysfunction and hypertrophy due to myocardial stiffening and fibrosis are bound to occur.

Left ventricular diastolic dysfunction in early stages of CKD may present with heart failure with preserved ejection fraction. Left ventricular diastolic dysfunction associated with elevated mortality and hospitalization due to heart failure, echocardiogram with the use of two-dimensional and Doppler imaging is the simplest method to assess LVD. Consequences of LVDD are increased signs of left atrium, elevation of left ventricle and diastolic pressure, development of pulmonary hypertension, heart failure. Left atrium plays an important role in cardiovascular hemostasis. Though modulation of cardiac filling and output as well as regulation of circulatory volume and tone. Left atrial remodeling is characterized by dynamic alteration in atrial structure function in retrophysiology. LA dilation is a hallmark of atrial remodeling and prognostic monitor of cardiovascular and thromboembolic events. Atrial fibrosis, hypercoagulability contractile and endothelial dysfunction may force the concept of atrial cardiomyopathy.[19]

Generally, a left atrial diameter of 3.5 to 4 cm was considered as an upper limit of normal. End systolic LA measurement given by echocardiograms aims to give a simple solution of severity of cardiac dysfunction in ESRD, and correlating with LVDD and the marker we have taken into consideration, that is, uric acid, which is often more than 6.1 In ESRD, the LA (ES) of more than 3.2 cm has been considered abnormal and associated with LA strain and an important prognostication index of end-stage renal disease and cardiac dysfunction.

Novel LA measurements using cardiac magnetic resonance such as phasic LA strain, LA ejection fraction, and LA minimum volume seem to be of present interest and analysis.[20] Though all LA metrics were associated with cardiovascular mortality, still several studies and multi-variate analysis are going on for better model discrimination.

CONCLUSION

Cardiovascular dysfunction is a major cause of mortality in progressive CKD and end-stage renal disease. Prognostication is becoming an essential compartment of counseling in ESRD. Simple co-biomarkers serve to economize and provide incremental information regarding cardiovascular outcome in ESRD. Markers for susceptibility, initiation, and progression of CKD and end-stage renal disease have been identified. In our study of 30 cases, 20% were females, all had history of pregnancy-induced hypertension, and all had high uric acid levels more than 7 mg per deciliter, along with poor ejection fraction and borderline LA measurement of more than 3.5-4.1 cm. Middle-aged males were more severely affected. Larger intensive studies are needed to establish uric acid level as an important biomarker associated with cardiac dysfunction in ESRD.

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