



ORIGINAL RESEARCH PAPER

General Medicine

A STUDY OF CORRELATION BETWEEN SERUM URIC ACID AND EJECTION FRACTION IN HEART FAILURE PATIENTS

KEY WORDS:

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ABSTRACT

BACKGROUND:Heart failure (HF) is a clinical syndrome that occurs in patients who, because of an inherited or acquired abnormality of cardiac structure and or function.30%of elderly between 70-80 years develop heart failure.Hence there is a need for a biomarker which is cheap. In a developing country like India where uric acid evaluation can be done in rural set up at the cost of about Rs 50, the present study aims at establishing the evaluation of uric acid levels in heart failure.

Methods:This observational study was conducted in a tertiary care hospital in Hyderabad.100 patients admitted with symptoms and signs of Heart Failure.Baseline clinical examination,ECG,2DECHO were performed and if tested positive were evaluated for serum uric acid levels along with blood counts,biochemistries, serum electrolytes,cardiac enzymes. Levels of uric acid were compared with LVEF (Left Ventricular Ejection Fraction) to asses its prognostic significance and also with functional NYHA class.

Results: The mean age of study population was 47.3 ± 13.4. 24 % patients each were present in the age group of, 51 – 60 yrs 41 – 50 yrs and 31 – 40 yrs respectively followed by 14 % patients in the age group of 61 – 70 yrs.47 % were males and 53 % were females male : female ratio was 1.12:1.55% of males and 54%females had acute caronary syndrome as precipitating event. In the present study the range of uric acid was observed between 7.1 – 10 mg/dl, the mean uric acid levels were observed to be 8.6 ± 0.67. There was a significant and inverse correlation observed between uric acid levels and ejection fraction $r = -0.808$ $p < 0.001$ and positive correlation observed between NYHA class and uric acid levels $r = 0.844$, $p < 0.005$.

Conclusions:Excessive uric acid levels in chronic heart failure has lead to the chronic inflammation thereby contributing to the oxidative damage to the myocardium .In heart failure patients,with serum uric acid is more than 7 mg / dl, then either RWMA or Global hypokinesia positive OR LVEF < 50%. Serum uric acid levels are more in the severe functional disability patients (NYH III AND IV). In rural set up due to financial constraints uric acid levels can be used as a prognostic marker.

INTRODUCTION

Heart failure (HF)¹ is a clinical syndrome that occurs in patients who, because of an inherited or acquired abnormality of cardiac structure and or function, develop a constellation of clinical symptoms (dyspnea and fatigue) and signs (edema and rales) that lead to frequent hospitalizations, a poor quality of life, and a shortened life expectancy. The mean age of patients with heart failure is 75 years.

In developing countries, two to three percent of the population suffers from heart failure, but in those 70 to 80 years old, it occurs in 20 - 30 percent. Men and women have equivalent incidence and prevalence of heart failure.However **Women** tend to develop heart failure later in life, have preserved systolic function, more pronounced, signs and symptoms ,survive longer with heart failure than men do.

In tropical countries, the most common cause of HF is valvular heart disease,followed by Rheumatic heart disease,anemia or some type of cardiomyopathy. Moreover there has also been an increase in diabetes, hypertension and obesity which has resulted in heart failure.

Heart failure is associated with significantly reduced physical and mental health, resulting in a markedly decreased quality of life. The condition usually worsens with time and the progressive disease is associated with an overall annual mortality rate of 10%.

Patients with Symptoms at rest [New York Heart Association (NYHA) class IV] have a 30–70% annual mortality rate, whereas patients with symptoms with moderate activity (NYHA class II) have an annual mortality rate of 5–10%.Community-based studies indicate that 30–40% of patients die within 1 year of diagnosis and 60–70% die within 5 years.

Uric acid is a product of xanthine metabolism. Elevated levels of xanthine oxidase causes conversion of hypoxanthine to xanthine and to uric acid which acts as an oxidative stress in heart failure. There are some studies showing that there is evidence of increased uric acid levels in heart failure patients and uric acid as a prognostic marker in heart failure.

In a developing country like India where uric acid evaluation can be done easily even in rural set up, the present study aims at establishing the evaluation of uric acid levels in heart failure.

BIOMARKERS IN HEART FAILURE:

"Biomarker" is a parameter reflecting or characterizing a certain biological process. It may include variety of indices/parameters derived from clinical images, physiological tests, tissue biopsies, and even genetic variants, but most often, this term is reserved for blood or urine based assessments. Finally, the assay should be relatively easy to perform and analyze so that the information is readily available to the clinician while the patient is still in the treatment area.

2. Biological validity of the biochemical marker:

One could also make the argument that the ideal biomarker should make physiological sense|| that is, there should be a pathophysiological basis for believing that changes in the level of the biomarker are linked to changes in the clinical status of the patient.

NEWER BIOMARKERS IN HEART FAILURE:1. Chromogranin 2. Galectin 3. Osteoprotegerin 4. Adiponectin5. Growth differentiation factor 15

IMPORTANCE OF BIOMARKERS IN HEART FAILURE:

Aid in elucidating the pathogenesis of heart failure, enhance risk stratification, identify subjects at risk,in the diagnosis of heart failure and in monitoring therapy.

Uric acid as a biomarker in heart failure: The activation of the xanthine oxidase (XO) system by tissue hypoxia increases UA production and causes hyperuricaemia, thus, hyperuricemia is a marker for impaired oxidative metabolism.

Cell death, tissue hypoxia, and impaired metabolism in HF increase XO activity, leading to an overproduction of UA.Numerous studies like Anker etal, Sakai et al.a have demonstrated the prognostic importance of hyperuricemia in patients with CHF. UA trans cardiac gradient correlates with left ventricular ejection fraction,

and that a high serum UA level is an important predictor of mortality, independent of factors such as glomerular filtration rate and BNP level, which are known predictors of poor prognosis in patients with mild to severe CHF.

AIMS and OBJECTIVES OF THE STUDY

1) To study correlation of uric acid levels with ejection fraction in heart failure patients (both acute & chronic).

METHODS:

This study is an observational study done in the department of General Medicine in Osmania General Hospital Hyderabad with tertiary care facilities between november 2015 and March 2018. All patients who are admitted with symptoms and signs of Heart Failure in the wards like Intensive Care Unit, Acute Medical Care, Intensive Cardiac Care unit, Medical Wards, Cardiac Wards both paid and general rooms were recruited in the study. The sample size was 100 patients after evaluation by clinical and 2D echocardiography findings and by satisfying inclusion and exclusion criteria were recruited after informed consent

INCLUSION CRITERIA: Age more than 18 years of both sexes, informed consent from patients with signs and symptoms of heart failure

EXCLUSION CRITERIA: Patients of chronic kidney disease and on hemodialysis, gout, Chronic liver failure, patients on treatment with drugs like cyclosporine, pyrazinamide, ethambutol, levodopa, Children, Immunosuppressed patients like Malignancy. Uric acid in all patients was measured at the time of admission with informed consent.

LAB INVESTIGATIONS PERFORMED: Include Complete Hemogram, Blood urea, Serum Creatinine, Blood Sugar, Complete urine analysis, Serum Electrolytes, Cardiac enzymes CPK, CPK MB, Coagulation profile, Prothrombin time, Activated partial thromboplastin time, Electrocardiogram, X ray Chest, 2D Electrocardiography and Serum Uric acid.

METHOD: Uric acid in the sample originates, by means of the coupled reactions described below, a coloured complex that can be measured by spectrophotometry.

REFERENCE VALUE OF SERUM URIC ACID: Serum and Plasma: a) Men : 3.5 to 7.2 mg / dl = 210 – 420 µ mol / L b) Women : 2.6 to 6.0 mg / dl = 150 – 350 µ mol / L.

RESULTS AND STATISTICAL ANALYSIS : After obtaining informed consent, A total of 100 patients with heart failure and ejection fraction less than 50 who presented to the department of general medicine were enrolled. In the present study it was observed that 47 % were males and 53 % were females male : female ratio was 1.12:1. 24 % patients each were present in the age group of, 51 – 60 yrs, 41 – 50 yrs and 31 – 40 yrs respectively followed by 14 % patients in the age group of 61 – 70 yrs.

Table 1: Distribution of patients based on age

Age Group yrs	Total	
	No.	%
< 20 yrs	1	1
21 - 30 yrs	9	9
31 - 40 yrs	24	24
41 – 50 yrs	24	24
51 – 60 yrs	24	24
61 – 70 yrs	14	14
> 70 yrs	4	4
Total	100	100.0
Mean ± SD	47.3 ± 13.4	

In the present study it was observed that 47 % were males and 53 % were females male : female ratio was 1.12:1.

In the present study it was observed that there is no statistically significant difference observed in the age wise distribution in male and females p >0.05. the mean age group in males was 49.17 compared to 45.64 in females.

Table 3: Age and gender wise distribution

Age	MALE		FEMALE	
	No.	%	No.	%
< 20	0	.0	1	1.9
21 - 30	5	10.6	4	7.5
31 - 40	12	25.5	12	22.6
41 - 50	6	12.8	18	34.0
51 - 60	12	25.5	12	22.6
61 - 70	10	21.3	4	7.5
> 70	2	4.3	2	3.8
Total	47	100.0	53	100.0
chi square	9.36		p value 0.155	

In the present study 38.3 % were males had history of CAD compared to 22.6 % females there was no statistically significant difference between gender and history of CAD p >0.05.

34 % were males had history of DM compared to 52.8 % females there was no statistically significant difference between gender and history of DM p >0.05

68.1 % were males had history of HTN compared to 73.6 % females there was no statistically significant difference between gender and history of HTN p >0.05.

0 % were males had history of HF compared to 5.7 % females there was no statistically significant difference between gender and history of HF p >0.05.

Table 4: Risk factors in study population

History of	MALE		FEMALE		chi square	p value
	No.	%	No.	%		
CAD	18	38.3	12	22.6	2.9	0.08
DM	16	34	28	52.8	3.57	0.059
HTN	32	68.1	39	73.6	0.366	0.545
HF	0	0	3	5.7	2.74	0.09

Table 5: Cause and gender comparison

CAUSE	MALE		FEMALE	
	No.	%	No.	%
ACS(AWMI)	14	29.8	18	34.0
ACS(IWMI)	12	25.5	11	20.8
DCM	18	38.3	15	28.3
OLD AWMI	1	2.1	1	1.9
OLD IWMI	1	2.1	3	5.7
OLDAWMI	1	2.1	5	9.4
Total	47	100.0	53	100.0
chi square	4.14		p value 0.53	

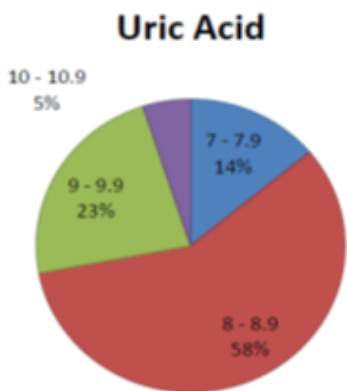
26 male patients had ACS as the precipitating cause of heart failure compared to 29 female patients.

18 male patients had DCM as the precipitating cause of heart failure compared to 15 female patients.

3 male patients had old ACS as the precipitating cause of heart failure compared to 9 female patients.

There was no statistically significant difference in gender and causative factor of heart failure in the study population p > 0.05.

Uric Acid	No.
7 - 7.9	14
8 - 8.9	58
9 - 9.9	23
10 - 10.9	5
Total	100



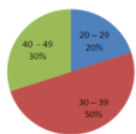
In the present study the range of uric acid was observed between 7.1 – 10 mg/dl, the mean uric acid levels were observed to be 8.6 ± 0.67.

In the present study the range of Ejection fraction was observed between 28 – 48%, the mean ejection fraction was observed to be 34.8 ± 6.65.

Ejection Fraction in Study Population

Ejection Fraction	No.
20 – 29	20
30 – 39	50
40 - 49	30
Total	100

Ejection Fraction



In the present study it was observed that there was a significant and inverse correlation observed between uric acid levels and ejection fraction $r = -0.808$ $p < 0.001$.

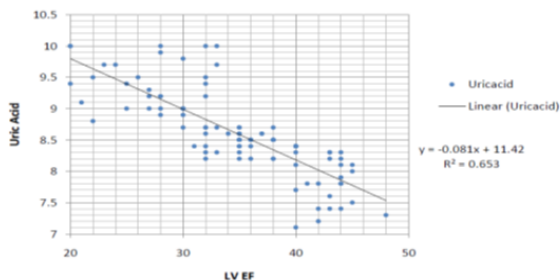


Table 8: Linear regression analysis

Dependent Variable: URIC ACID

Variable	No	Mean
Ejection Fraction	100	34.8 ± 6.65
Uric acid	100	8.6 ± 0.67

	R	Adjusted R Square	Std. Error of the Estimate
R	.808 ^a	.653	.39496

Predictors: (Constant), EF

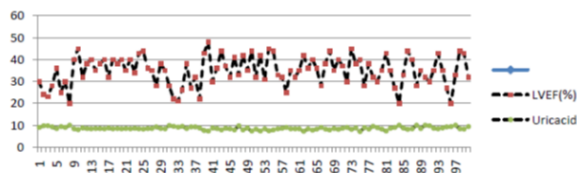
b Dependent Variable: URIC ACID

Coefficients ^a	Unstandardized Coefficients B	Std. Error	Standardized Coefficients Beta	t	Sig.
(Constant)	11.421	.211		54.050	.000
LVEF	-.081	.006	-.808	-13.581	.000

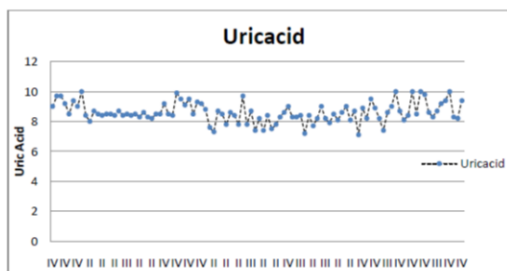
Coefficient factor (r) = 0.808
 $R^2 = 0.653$ It was found that the linear regression line obtained reestablished 65.3% of dependency of uric acid ($R^2 = 0.653$).

Linear regression analysis was done with uric acid as a dependent factor and ejection fraction as a independent factor and it was found that there is a significant impact of Ejection fraction on uric acid .($P < 0.001$).

URIC ACID LEVELS AND EJECTION FRACTION



CORRELATION BETWEEN URIC ACID LEVELS AND NYHA CLASS:



	Correlation	URIC ACID
NYHA	r value	.844
	p value	.000

There was a significant and positive correlation observed between NYHA class and uric acid levels $r = 0.844$, $p < 0.005$.

DISCUSSION:

Our study showed an inverse correlation between serum uric Acid levels with ejection fraction in patients with heart failure i.e. higher the uric acid levels lower the ejection fraction. Similar results were observed by Pinelli et al.

Study by XuDuan et al, showed increase of serum UA level was found to be inversely associated with disease severity, cardiac function (LVEF) and prognosis of CHF.

Xanthine oxidase metabolic pathway as an important contributor to both symptoms of CHF as well as progression of the disease was observed by Doenher W et al in Germany.

In a study by Vaduganathan et al, it was reported that the mean uric acid levels was higher in males than that of females, though we have not observed such association.

Our analysis also proves that serum uric acid levels are more in the severe functional disability patients(NYH III AND IV).

Monitoring a combination of BNP and UA may be useful for the management of patients with CHF -**Sakai H, et al .circ.J.2006.**

Prevalence of Hyperuricemia in Patients With Acute Heart Failure With Either Reduced or Preserved Ejection Fraction.

Palazzuoli A, et al AM J cardiology 2017. This study concluded that In AHF hyperuricemia is common in both in HFpEF and in HFrEF.

There have been recent studies on heart failure and it was observed that apart from XO activity, Uric acid itself is found to play a role in the effect on heart failure. Long term Allopurinol is associated with less mortality with heart failure.

uric acid can be a better marker than 2D Echo for the detection of HF

In the present study it was observed that ,there was a significant and inverse correlation observed between UA levels and LVEF ($r=-0.808$; $p<0.001$)

We have therefore conducted this observational study to correlate the association between high UA levels with LVEF during HF.

Limitations of the study :Study was conducted on limited population of 100 normal healthy patients. Cardiac angiograms studies to quantify the atherosclerotic burden on selected patients could not be carried due to financial constraints.

CONCLUSIONS:

Elevated levels of xanthine oxidase causes conversion of hypoxanthine to xanthine and to uric acid which acts as an oxidative stress in heart failure.

This finding of excessive uric acid levels due to overproduction in chronic heart failure has lead to the recognition of association between heart failure and chronic inflammation thereby contributing to the oxidative damage to the myocardium.

The analysis of correlation conclusively proves that when serum uric acid is more than 7 mg / dl, then either RWMA or Global hypokinesia positive OR LVEF < 50 % in heart failure patients.

Serum uric acid levels are more in the severe functional disability patients (NYH III AND IV).

In the rural setup of India, where due to cost constraints and infrastructural constraints 2D ECHO is beyond the reach of several village patients, serum uric acid could be used as a prognostic marker for Heart Failure

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