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Original Research Article

Uric Acid: New Prognostic Marker in Line for Heart Failure: A Hospital Based Cross Sectional Study

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Abstract

Introduction: It is widely known that there is a link between elevated uric acid levels and the risk of developing cardiovascular disease. Hyperuricemia influences the onset and progression of cardiovascular disease by affecting molecular signals like oxidative stress, insulin resistance, and inflammatory response. Insulin resistance can disrupt the uptake of myocardial glucose leading to myocardial energy metabolism disorder, all of which have an impact on the myocardium's diastolic and contractile function.

Materials and Methods: This cross-sectional study was conducted on 100 patients of heart failure, both new onset and decompensation of chronic heart failure, admitted in wards and MICU in department of medicine of JLNMC and attached Hospitals, Ajmer during the period of September 2021- September 2022.

Result: This study observed a statistically significant relation between serum uric acid level and NYHA class (P value<0.001). There was a strong negative correlation between serum uric acid and heart failure with reduced ejection fraction (r= -0.892, P value<0.001) which was statistically significant.

Discussion: In this study cases were divided based on serum uric acid level among NYHA class and it was observed that as the NYHA class of the severity of heart failure increased, Serum Uric Acid levels also increased to greater levels and this increase can be a preceding factor for progression to cardiorenal syndrome and various arrhythmias especially experienced by cases in NYHA III and IV class. The Mean± SD of uric acid was (8.23±0.71 mg/dl) while mean ±SD of left ventricular ejection fraction was (34.31± 8.73%). Serum Uric Acid can be used as a independent prognostic marker in assessing the severity of heart failure as it is easily available and inexpensive, in place of NT-proBNP which is expensive in a resource limited country and it may also be a useful tool in predicting the unfavorable outcomes in patients with heart failure.

Keywords: Serum Uric Acid, Heart Failure, Insulin Resistance, Cardiorenal, Oxidative Stress.

Introduction

Heart Failure is a complex clinical syndrome that results from structural or functional impairment of ventricular filling or ejection of blood, which in turn leads to cardinal clinical symptoms of dyspnoea and fatigue and signs of heart failure, namely rales and oedema[1]

Heart failure encompasses a broad range of Left ventricular function and is divided into 4 classes based on ejection fraction.[2]

HFrEF (HF with reduced EF)	LVEF ≤ 40%
HFimpEF (HF with improved EF)	Previous LVEF ≤40% and a follow-up measurement of LVEF >40%
HFmrEF (HF with mildly reduced EF)	LVEF 41%–49% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)
HFpEF (HF with preserved EF)	LVEF ≥50% Evidence of spontaneous or provokable increased LV filling pressures (eg, elevated natriuretic peptide, noninvasive and invasive hemodynamic measurement)

Prevalence of heart failure in a developed country is 2% and in an individual above 65 years of age it is increased to 6%, whereas in developing country it is estimated to be 1% according to INDUS study[3].

According to a recent research done by National Health and Nutrition Examination Survey (NHANES), patients with heart failure were found to have a prevalence of hyperuricemia of about 50%[4]. It is widely known that there is a link between high serum uric acid levels and the risk of developing cardiovascular disease.

High uric acid levels have been linked to a number of cardiovascular diseases, such as hypertension, coronary artery disease (CAD), cerebrovascular disease, atrial fibrillation, vascular dementia[5] and pre-eclampsia.In higher animals, the end product of purine metabolism is uric acid.

The body's UA synthesis and excretion are balanced under physiological circumstances and when this equilibrium is disturbed, hyperuricemia results. Normally, male UA levels greater than 7 mg/dl or female UA levels greater than 6 mg/dl are considered to be hyperuricemia[6]. After hypertension, hyperglycaemia, and hyperlipidaemia, hyperuricemia is the most often condition encountered as a result of an increasingly unhealthy lifestyle.

Hyperuricemia not only influences the onset but also promotes progression of cardiovascular disease by controlling certain molecular signals like insulin resistance[7], oxidative stress[8], and inflammatory response[9].

For people who already have heart failure, serum uric acid may be helpful in predicting their prognosis in terms of repeated hospitalisation, requiring intensive care unit admission, requiring invasive or non-invasive ventilation along with other biochemical parameters like NT-proBNP, inflammatory markers like IL-6, hs-CRP.

This study is being done to determine the link between serum uric acid levels and the severity of heart failure because there is some evidence to suggest that urate-lowering therapy may cut CV risk in this population

and, thus, may constitute a new method in risk reduction.

Objectives

1. To determine how the level of serum uric acid and ejection fraction are correlated.
2. To assess the relationship between the level of serum uric acid and the severity of heart failure.

Materials and Methods

Study Centre: The present study was conducted on patients attending the Department of Medicine at Jawaharlal Nehru Hospital, Ajmer.

Study Design: Hospital Based, Cross sectional study.

Study Duration: one year duration from September 2021 to September 2022

Study Population: Patients with Heart failure.

Inclusion criteria:

All heart failure patients above age >18 years

Exclusion criteria:

- Patient with solid tumors and haematological malignancy.
- Patient with gouty arthritis.
- Patient with renal involvement.
- All pregnant females.
- Patient with drugs that alter uric acid metabolism.
- Patient refuse to give written consent.

After ethical clearance from institutional ethical committee the cross-sectional study was conducted on 100 patients of heart failure admitted in wards in department of medicine in JLNMC and attached Hospitals, Ajmer during the period of September 21-September 22 considering inclusion and exclusion criteria.

All patients were subjected to a detailed history and clinical examination. The severity of Heart Failure was assessed using New York Health Association (NYHA) classification.

After stabilization of our patients and fasting of 8-10 hours sample of peripheral venous blood was taken under strict aseptic techniques and was sent to the hospital's

Central laboratory for measurement of relevant investigations as required in our study like Complete Blood Count which was estimated using Sysmex 6-part full automatic analyser XN-550, Renal Function Test, Liver Function Test, Lipid Profile, Serum Uric Acid, NT-proBNP, IL-6, hs-CRP and 2D-echocardiography.

All these parameters were performed under supervision of experienced pathologist, biochemists and cardiologists.

The New York Heart Association (NYHA) Class of heart failure classified cases in the various classes according to the severity of symptoms or functional limits.

Statistical Analysis

All data was stored in MS Excel spread sheet. Statistical analysis was performed using computer software (SPSS Trial version 23 and Primer). Quantitative data were expressed as mean and standard deviation. Qualitative data was expressed in Percentages. Correlation between quantitative outcomes was assessed using Pearson correlation coefficient. For all statistical analysis, a 5% probability level was considered significant i.e. P value equal to or less than .05.

Class I: Patient with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitations, dyspnoea or angina pain.
Class II: Patient with cardiac disease resulting in slight limitations of physical activities. They are comfortable at rest. Ordinary physical activity results in fatigue, dyspnoea, palpitations, or angina pain.
Class III: Patient with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, dyspnoea, palpitations, or anginal pain.
Class IV: Patient with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or angina syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.

Observation

On the basis of age wise distribution of 100 cases among NYHA class we have observed that there was no statistically significant difference among the groups. The Mean±SD of age was 59.62±10.44 years, 64.00±8.76 years, 65.10±9.52 years and 63.07±8.80 years in NYHA class I, II, III and IV respectively.

The value of chi-square =15.657 with 12 degrees of freedom, (P value=0.20). This study observed no statistically significant difference among the NYHA class based on Hemoglobin, Total leucocyte count, Platelet count, Hematocrit, SGOT and SGPT level. (Table 1)

Distribution of cases according to serum uric acid levels among NYHA class revealed a statistically significant relation between severity of heart failure and serum uric acid where Mean±SD of SUA was (7.81±0.79 mg/dl) in NYHA I, in NYHA II Mean±SD was (7.97±0.46 mg/dl), in NYHA III Mean±SD was (8.57±0.43mg/dl) and in NYHA IV Mean±SD was (9.25±0.72 mg/dl) (P value=0.001).(Table 2)

On comparison of the NYHA class according to inflammatory markers (Interleukin-6 and Hs-CRP), no statistically significant difference was observed among the 4 classes (P value = 0.53 and P value = 1.00, respectively). (Table 3)

In our study, Comparison of NT-proBNP according to NYHA classification revealed statistically significant relation (P<.001). In NYHA I Mean±SD of NT-proBNP was 6190.29±4546.75pg/ml, in NYHA II Mean±SD 7200.12±4014.69pg/ml, in NYHA III Mean±SD was 8203.15±4928.05 pg/ml and in NYHA IV Mean±SD was 12426.43±7808.29 pg/ml. (Table 4)

Study of Serum uric acid and NT-proBNP revealed a positive correlation between SUA and NT-proBNP and it was statistically significant. Mean±SD of SUA was (8.23±0.71) mg/dl and Mean±SD of NT-proBNP was (6864.16±5461.87) pg/ml (r=0.15, P value=0.004).(Table 5)

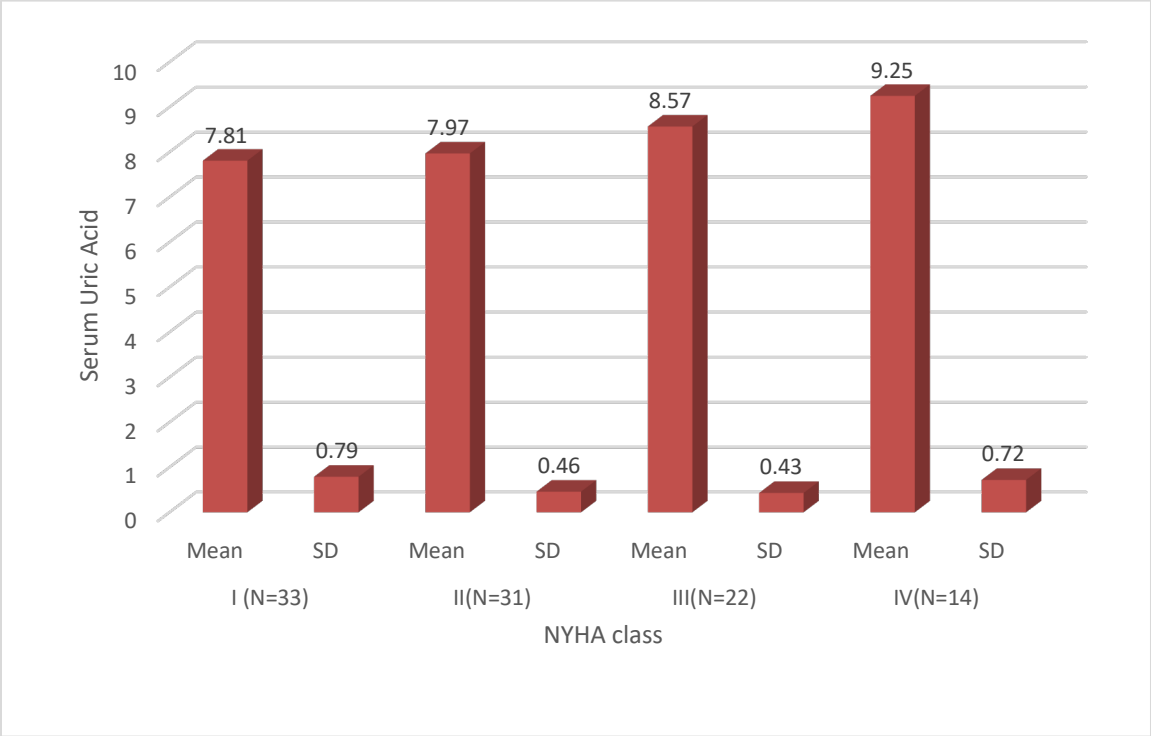
This study also observed a negative correlation between serum uric acid and heart failure with reduced ejection fraction which was statistically significant (r= -0.892, P value=0.001). Whereas a weak correlation was found between Serum uric acid and Heart failure with Preserved ejection fraction and it was not statistically significant (r=0.08, P value=0.732).(Table 6)

Table 1: Distribution of cases based on Age and Hematological and Biochemical parameters.

	NYHA I		NYHA II		NYHA III		NYHA IV		P Value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Age (years)	59.62	10.44	64.00	8.76	65.10	9.52	63.07	8.80	0.207
Haemoglobin(g/dl)	12.48	1.58	12.83	1.84	12	1.53	12.74	2.02	0.373 NS
Total Leucocyte count(µL)	9141. 21	3443. 29	9167. 23	3510. 23	9463. 33	2958. 14	9350. 29	3345. 54	0.330 NS
Haematocrit(%)	37.4	3.95	37.61	5.39	36.19	3.97	38.49	3.31	0.176 NS
Platelet count(x10^3/µL)	279	0.87	307	0.79	318	0.9	297	0.89	0.118 NS
SGOT(U/L)	59.5	39.25	70.56	64	77.86	69.48	61.21	37.02	0.628 NS
SGPT(U/L)	53.21	62.08	66.04	81.48	76.24	92.67	55.43	37.45	0.687 NS

Table 2: Comparison of following groups according to Serum Uric Acid(mg/dl)

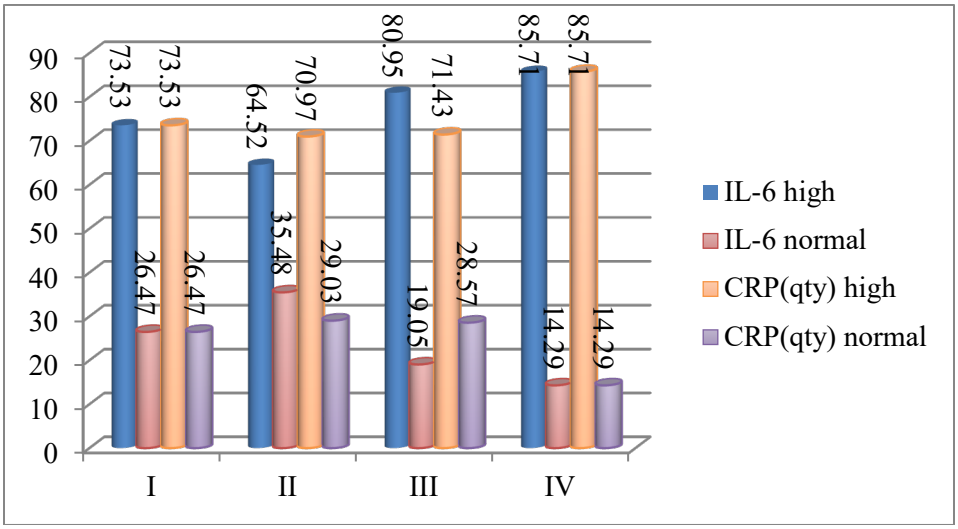
NYHA class	I (N=33)		II(N=31)		III(N=22)		IV(N=14)		P Value LS
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Serum Uric Acid(mg/dl)	7.81	0.79	7.97	0.46	8.57	0.43	9.25	0.72	.001



Graph 1: Comparison of NYHA Class according to Serum Uric Acid(mg/dl)

Table 3: Comparison of following groups according to Inflammatory markers (Interlukin-6, hs-CRP)

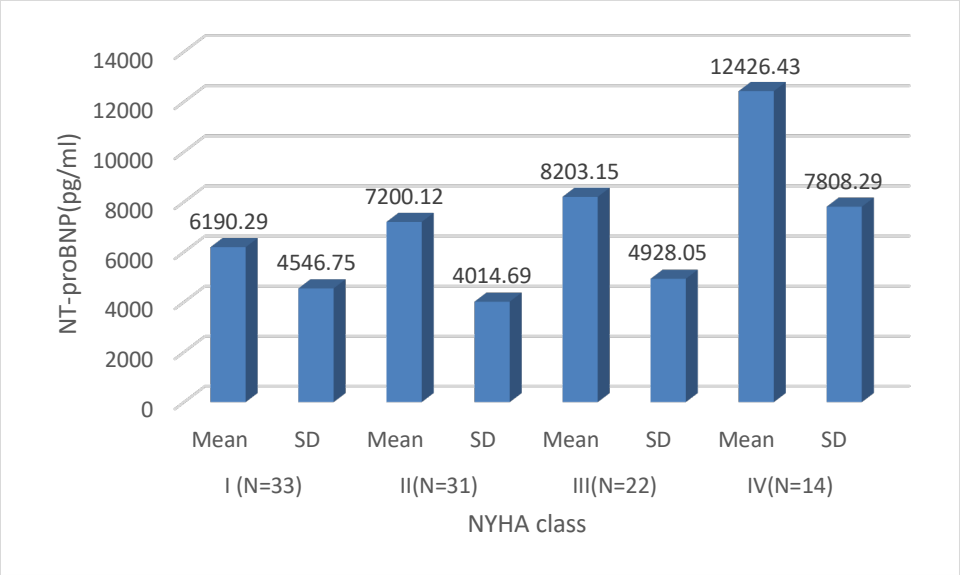
IL-6(pg/ml)	I		II		III		IV		
	N	%	N	%	N	%	N	%	P-Value
High	24	73.53	20	64.52	18	80.95	12	85.71	0.536NS
Normal	9	26.47	11	35.48	4	19.05	2	14.29	
Mean±SD	11.12±6.34		10.01±5.33		12.46±6.93		20.68±11.09		
hs-CRP(mg/L)									
High	24	73.53	22	70.97	16	71.43	12	85.71	1.000NS
Normal	9	26.47	9	29.03	6	28.57	2	14.29	
Grand Total	33	100	31	100	22	100	14	100	
Mean±SD	5.75±4.03		11.05±8.72		12.34±10.95		10.32±8.94		



Graph 2: Comparison of following groups according to Inflammatory markers (Interlukin-6, hs-CRP)

Table 4: Comparison of following groups based on NT-proBNP(pg/ml) according to NYHA classification.

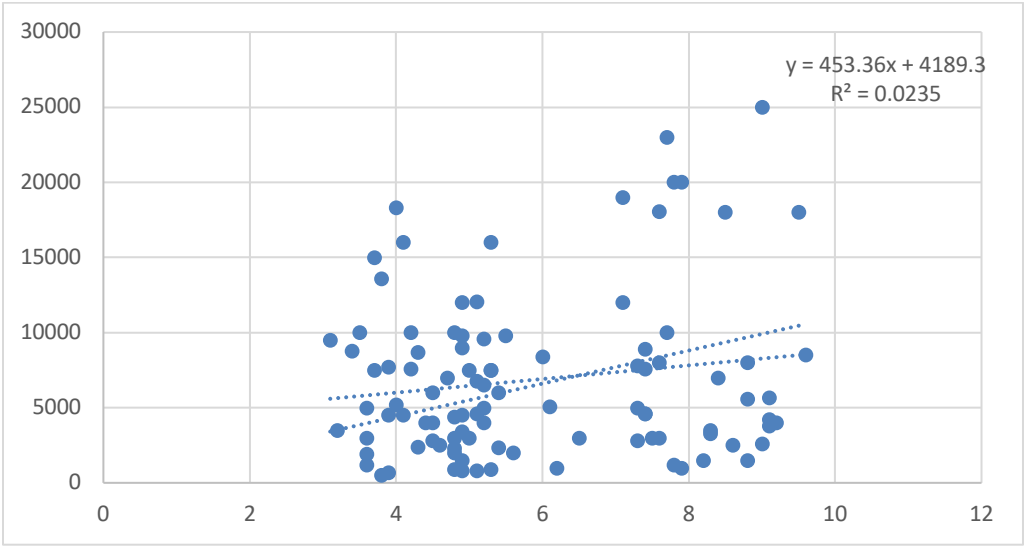
NYHA class	I (N=33)		II(N=31)		III(N=22)		IV(N=14)		P Value
	Mean	SD	Mean	SD	Mean	SD	Mean	SD	LS
NTproBNP(pg/ml)	6190.29	4546.75	7200.12	4014.69	8203.15	4928.05	12426.43	7808.29	0.001



Graph 3: Comparison based on NT-proBNP(pg/ml) according to NYHA classification.

Table 5: Correlations between Serum uric acid and NT-proBNP

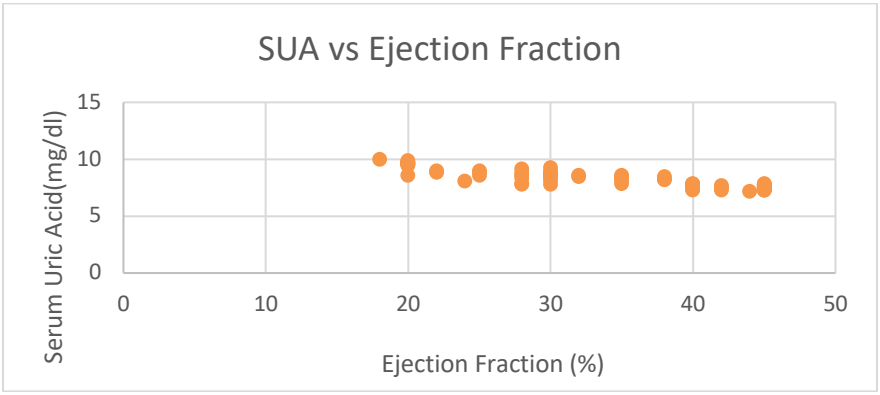
	Mean	SD	N	Pearson Correlation	P Value LS
Serum uric acid(mg/dl)	8.232	0.712	100		
NT-proBNP(pg/ml)	6864.160	5461.8741	100	.153	.004

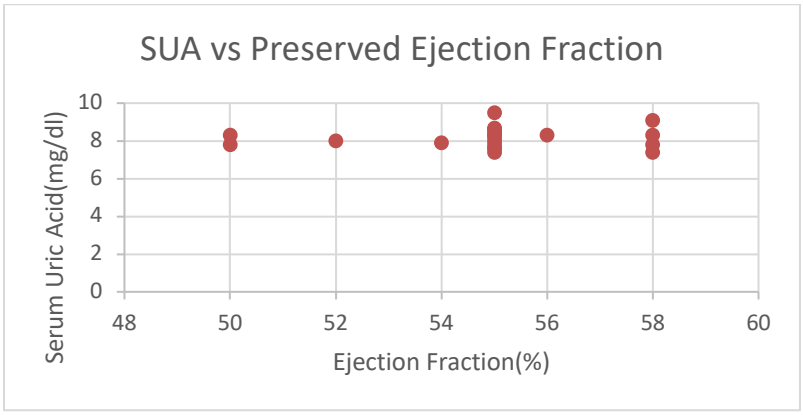


Graph 4: Correlations between Serum uric acid and NT-proBNP

Table 6: Correlation between Serum uric acid and Ejection fraction

	Mean	SD	N	Pearson Correlation	P Value LS
Serum uric acid(mg/dl)	8.23	0.71	100		
Reduced Ejection fraction (%)	34.31	8.73	80	-0.892	.001S
Preserved Ejection fraction (%)	54.95	2.20	20	0.081	0.732





Graph 5: Correlation between Serum uric acid and Ejection fraction

Discussion

Hyperuricemia is common in patients with HF and is related to advanced disease severity, higher concentrations of natriuretic peptides, higher ventricular filling pressure, and lower cardiac output [10,11].

In our study age wise distribution among 4 classes of NYHA observed that mean age of cases in NYHA I was 59.62±10.44 years, mean age in NYHA II was 64.00±8.76 years, mean age in NYHA III was 65.10±9.52 years and mean age in NYHA IV was 63.07±8.80 years and predominantly hyperuricemia with heart failure was observed more in middle aged to elderly population.

We observed similar level of hemoglobin in all 4 classes and our study did not *reveal* any significant difference between hemoglobin of a patient with NYHA class of severity. TLC were slightly higher in NYHA III-IV class likely due to more stressful condition, more activation of immune response and more sympathetic nervous system activation as compared to NYHA I and II class but no statistically significant relation was found between the TLC and NYHA severity. Also Hematocrit was divided into high(>50%), normal(36%-50%) and low(<36%) categories with 6 cases in high haematocrit category, 33 cases in low hematocrit, and 61

cases had their haematocrit in the normal range No statistical significant difference was observed between haematocrit and severity of heart failure (P value=0.176) because of the limited number of cases and our study was not a follow-up study.

3 groups were made which comprised of 3 cases in the high platelet count group(>450x10^3/μL), *27 cases* in low(<150x10^3/μL) and 70 cases in normal platelet count(150-450x10^3/μL) and no significant relation could be drawn between platelet count and NYHA severity(p >.05), although low platelet count was found in the majority of NYHA III and IV because cases in these groups are prone to more severe inflammation and septicemia. Ausra Mongerdiene, *et al*. (2021) [12] revealed that there were no differences between platelet counts (PLT) and NYHA severity (p = 0.972). Mojadidi MK, *et al*. (2016) [13] suggested that a higher degree of thrombocytopenia is associated with higher all-cause mortality.

In our study cases were divided based on serum uric acid level among NYHA classes we observed that in NYHA I (n=33) Mean ±SD of serum uric acid was (7.81±0.79 mg/dl), in NYHA II (n=31) Mean ± SD was(7.97 ± 0.46 mg/dl), in NYHA III (n=22) Mean ± SD was (8.57±0.43 mg/dl) and in NYHA IV (n=14) Mean ± SD was (9.25±0.72 mg/dl) indicating a statistically significant relationship between uric acid level and severity of heart failure (P value=0.001). So as the NYHA class of the severity of heart failure increased, Serum Uric Acid levels also increased to greater levels and this increase can be a preceding factor for progression to cardiorenal syndrome and various arrhythmias especially experienced at increased rate by cases in NYHA III and IV class. Mohamed Ezzat, *et al*. (2019) [14] observed that patients with congestive heart failure had significantly higher mean serum uric acid levels than apparently healthy people (P value = 0.02).

We also observed that although the levels of IL-6 were raised in all 4 NYHA class whether the cases presented acutely or were in a chronic state of heart failure but comparatively rise was greater in those who presented in NYHA III and IV class. Interlukin-6 can be one of the mediators in progression of ongoing inflammation but still this inflammatory marker alone cannot be linked to prognosis of heart failure in our study.

R J Raymond, *et al.* (2001) [15] also observed in his study IL-6 levels were elevated in both asymptomatic LV systolic dysfunction and those who presented with acute heart failure. Similarly, this study observed no statistically significant relation between hs-CRP level and NYHA class (P value=1.00NS) and that even though it was elevated in 74% of our heart failure patients but as of now it cannot be used as independent marker of severity and prognosis in heart failure in our study. Similar observation was made by Hilary M D, *et al.* (2018) [16] that hs-CRP was not significantly associated with heart failure symptom severity as assessed by the New York Heart Association (NYHA) functional class or Minnesota Living with Heart Failure Questionnaire score. CRP levels were not significantly associated with symptoms (orthopnea or peripheral edema) or signs (jugular venous pressure elevation) of congestion.

Turkery, *et al*.(2014) [17] observed in their study that median hs-CRP was 1.50 mg/l [0.90–3.50] in NYHA class I, in NYHA class II 2.73 mg/l [2.59–6.57], NYHA class III it was 5.20 mg/l [3.30–9.30] and NYHA IV: 4.07 mg/l [4.03–7.92] and that in Heart Failure patients hs-CRP was not correlated with LVEF and NYHA class. In this study we observed relation between levels of NT-proBNP and the severity of heart failure in

which Mean±SD of NT-proBNP in NYHA I was 6190.29 ±4546.75 pg/ml, Mean±SD in NYHA II 7200.12 ± 4014.69 pg/ml, in NYHA III Mean ±SD was 8203.15 ± 4928.05 pg/ml and in NYHA IV Mean ±SD was 12426.43±7808.29 pg/ml. In our study, NT-proBNP levels increased with the severity of heart failure and it was statistically significant (P value =0.001), suggesting that NT-proBNP is not only a diagnostic marker for heart failure but also serves as a prognostic marker in heart failure patients.

We observed a statistically significant positive correlation between SUA and NT-ProBNP. SUA had a Mean ±SD of 8.23±0.71 mg/dl and NT-ProBNP had a Mean± SD of 6864.16± 5461.87 pg/ml (r = 0.15, P =.004), demonstrating that as the severity of heart failure increased, Uric acid and NT-proBNP both showed a trend of increasing to higher levels (r =.153, p =.004).

P. Sabaka, *et al*. (2019) [18] also analysed linear regression of NT-pro-BNP and uric acid concentration and revealed that as the severity of heart failure increased (r = 0.263, p 0.0001; r = 0.293, p 0.0001), uric acid and NT-proBNP both showed a trend of increasing to higher levels. Park HS, *et al*. (2010) [19] observed that patients with UA levels > 8.0 mg/dL and NT-ProBNP levels > 4,210 pg/mL were at highest risk for cardiac events (p = 0.01).

This study observed a statistically significant negative correlation between serum uric acid and heart failure with reduced ejection fraction (r =-0.89, P value=0.001). The Mean ± SD of uric acid in our patients was 8.23±0.71 mg/dl with Mean ±SD of LVEF was 34.31± 8.73%. As the normal heart is subjected to mycoardial ischemia, inflammation sets in leading to increased apoptosis, increased remodeling of myocardium which in turn leads to increased formation of uric acid along with other natriuretic peptides. This increased uric acid in turn promotes more oxidative stress further altering the myocardial functional and structural parameters, and this vicious cycle continues. Ali Hasan I A, *et al*. (2022) [20] in their study used Pearson's product-moment correlation coefficient to assess the relationship between ejection fraction (%) and uric acid level (mg/dl) and they found There was a significant negative correlation between the two variables (correlation coefficient (r)=-0.21, p-value=0.039).

Conclusion

In this study we conclude that significant association was observed between high levels of uric acid and severity of heart failure. Serum uric acid is inversely related with heart failure with reduced ejection fraction. SUA and NT-proBNP are positively correlated with severity of heart failure. So, Serum Uric Acid can be used as a prognostic marker in assessing the severity of heart failure as it is easily available and inexpensive, in place of NT-proBNP which is expensive in a resource limited country. The reduction of uric acid can be expected to be a novel strategy in these patients.

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