Original Article

Established and Emerging Biomarker in Chronic Heart Failure

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Abstract:

Background : More than one million hospital admissions each year are due to heart failure as the major diagnosis. One in six patients over 65 who visit a primary care facility complaining of dyspnea with exertion has undiagnosed HF. By far, the most thoroughly investigated, extensively used, and acknowledged biomarkers for heart failure are natriuretic peptides. B type natriuretic peptide (BNP) and its biologically inactive fragment N-terminal pro B-type natriuretic peptide (NT-ProBNP), which are both primarily released by the ventricles in response to stretching, have been suggested to be useful for determining the prognosis or disease severity of chronic heart failure in earlier studies[1]. Uric acid levels rise in CHF primarily due to increased production and occasionally due to decreased excretion or both. Elevated uric acid levels are a sign of developing heart failure and cardiac dysfunction. Numerous studies have demonstrated a connection between morbidity and death in CHF and elevated serum uric acid levels[2].

Objective: To find out the relationship between on admission serum uric acid level with established prognostic factors and Biomarkers such as different classes of NYHA, LVEF, NT-PROBNP, and their prognostic significance.

Methods: From April 2018 to March 2019, this study was carried out at the National Heart Foundation Hospital and Research Institute's Department of Cardiology. After considering the inclusion and exclusion criteria, 148 patients with chronic heart failure who had admission serum uric acid measurement and telephone follow-up within 30 days were included. The study patients were divided into two groups based on Serum uric acid level Group I (SUA in men<7mg/dl) (SUA in women <6mg/dl), Group II (SUA in men e"7mg/dl), (SUA in women e"6mg/dl) Baseline characteristics, Left ventricular ejection fraction (LVEF) were then compared between the two groups.

Results: On 148 patients, the level of serum uric acid was assessed, and follow-up was done, patients with chronic heart failure were shown to have significantly higher levels of hyperuricemia, and there was a strong association between the severity of the rise in serum uric acid (SUA) and the severity of the heart failure. Elevated blood uric acid levels and ejection fraction have an antagonistic relationship. The severity of heart failure can be predicted by hyperuricemia, as evidenced by the association between patients with elevated blood UA levels and a worse New York Heart Association (NYHA) functional class. Higher uric acid levels in patients were linked to negative outcomes and a poor prognosis..

Conclusion: As with NT Pro BNP or other well-established prognostic indicators, lower uric acid levels upon admission can be utilized to predict the prognosis of CHF patients.

Keywords: Serum Uric Acid, Chronic Heart Failure, Echocardiogram, Left Ventricular Ejection Fraction, NYHA Classification. Biomarkers.

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Introduction:

The leading cause of death worldwide during the past ten years has been cardiovascular disease (CVD). 28 percent of the 50.4 million fatalities worldwide in 1990 were caused by CVD. In 2001, 29 percent of all fatalities were attributable to CVD. By 2030, there will be 7.8 billion people on the planet, and cardiovascular disease will be the root cause of 32% of all deaths. A significant concern for the health sector is the increasing burden of cardiovascular diseases (CVDs) in developing nations, particularly in low- and middle-income nations. World Health Organization estimated that in 2012, CVDs caused 17.5 million deaths worldwide, accounting for 31% of all deaths, with 80% of these deaths occurring in LMICs (WHO, 2015). Additionally, CVDs were also responsible for 85% of all global disabilities[3]. More than one million hospital admissions each year are due to heart failure as the major diagnosis. One in six patients over 65 who visit to a primary care facility complaining of dyspnea with exertion have undiagnosed HF (mainly HFpEF). At age 55, the lifetime chance of having heart failure is 28% for women and 33% for men. For Americans over 40, the risk of having HF over their lifetime is 20%[4].

We lack information on the precise frequency and incidence of heart failure in Bangladesh. Heart failure affected about one-seventh of all hospitalized patients. The average age was 54.1 years (15.3). Ischemic heart disease (IHD) was the majority's main cause (35.79 percent), but it frequently coexisted with a history of hypertension (46.8 percent). In 29.14 percent of cases, high blood pressure was thought to be the main risk factor for heart failure. Diabetes Mellitus (DM) was shown to be more common in Dilated Cardiomyopathy (DCM) and co-existed with IHD in 41.4 percent of cases[5].

Congestive heart failure is a complex syndrome that can develop as a result of any anatomical or functional cardiac condition that hinders the heart's capacity to pump blood throughout the body adequately. Congestive heart failure is a complex syndrome that can develop as a result of any anatomical or functional cardiac condition that hinders the heart's capacity to pump blood throughout the body adequately. The syndrome of heart failure is characterized by symptoms such as breathlessness with features of circulatory congestion such as jugular venous distension, rales, peripheral edema, and ascites[6].

Insulin resistance and obesity are important risk factors for the onset of heart failure. It has been demonstrated that obesity alone is a risk factor for incident heart failure[7]. In addition to monitoring ventricular rate control in patients with atrial fibrillation, ECG monitoring is useful in the evaluation of individuals who exhibit symptoms that could indicate an arrhythmia or bradycardia, such as palpitations or syncope. Heart failure may be made worse by ventricular arrhythmias, episodes of ischaemia and bradycardia, and conduction defects[8].

Elevated NPs help establish an initial working diagnosis, identifying those who need additional cardiac testing; Patients do not need an echocardiogram if their readings are below the cutoff for significant heart dysfunction. It is unlikely that patients with normal plasma NP concentrations have heart failure[9]. The most extensively researched heart failure biomarkers are natriuretic peptides. The ventricles respond to stress by producing B type natriuretic peptide (BNP) and its physiologically inactive component NT-ProBNP[10].

For patients with suspected HF, an effective and commonly accessible diagnostic to make the diagnosis is echocardiography[11]. Since the late 19th century, researchers have recognized that gout, hypertension, and obesity are all related to serum uric acid (SUA)[12]. Chronic heart failure is frequently accompanied by hyperuricemia (CHF). As the condition gets worse, serum uric acid rises. In a cross-sectional study, hyperuricemia was present in 51% of patients with chronic heart failure who were hospitalized[13]. Patients with end-stage CHF and cachectic patients had greater SUA levels, and SUA is inversely correlated with functional NYHA class II.

SUA (Serum Uric Acid) was the most powerful predictor of survival for patients with severe CHF (NYHA class III or IV): in patients with high levels of SUA (> 9.5 mg/dl). Patients with higher uric acid levels were linked to long-term negative outcomes, and other studies have linked elevated serum uric acid levels in patients with congestive heart failure to higher rates of morbidity and mortality[14]. Heart failure brought on by hyperuricemia is caused by a number of processes. Higher XO substrate (ATP breakdown to adenosine and hypoxanthine) and up-regulated and increased XO activity may be the causes of the increased SUA formation. SUA can have adverse effects on the cardiovascular system and can influence the immunological response when it is released from necrotic tissue. Hyperuricemia in heart failure is a sign of activated XO[15].

Anemia, renal impairment, cardiac rhythm abnormalities, a long corrected QT interval, complete LBBB, and advanced age are prognostic factors for CHF. Left ventricular ejection fraction of 40% is also a poor prognostic factor[16]. High serum uric acid was present in HF patients. Elevation of serum uric acid in HF is multifactorial. Diuretic treatment, elevated production, and diminished renal function may explain this[17].

Serum SUA in this population may provide predicting data about the patient. This simple, low-cost marker can identify CHF high-risk individuals.

Objective:

To find out the relationship between on admission serum uric acid level with different classes of NYHA, LVEF, NT-PROBNP, and its prognostic significance

Methodology:

This was a prospective cohort study. The study was carried out in the Department of Cardiology, National Heart Foundation Hospital & Research Institute, Mirpur2 , Dhaka Bangladesh. After presentation and acceptance of the protocol and getting ethical clearance, the study was carried out from April, 2018 to March, 2019 (1 year). Considering inclusion and exclusion criteria, a total number of 148 patients of both sexes were included in the study.

Inclusion Criteria:

Patients of both sex between 20-80 years who were admitted with chronic heart failure to the Department of Cardiology in NHFH & RI, with heart failure (both with preserved as well as reduced ejection fraction).

Exclusion Criteria:

1. Patients who were not willing to enroll in the study.
2. Patients who were unable to be reached via phone for follow-up.
3. Patients with previously diagnosed hyperuricemia who are using anti hyperuricemic medication.
4. Patients with severe comorbid conditions, such as severe chronic obstructive pulmonary disease, severe renal impairment, pneumonia, pulmonary embolism, adult respiratory distress syndrome, and any cancer.
5. Renal Impairment (Serum creatinine e" 1.5 mg/dl)
6. Recent Acute Coronary Syndrome (< 1 month)

Data Collection and Analysis:

Data was gathered through in-depth patient assessment, extensive history taking, clinical examination, and conducting relevant investigations. Demographic information, age, gender, occupation, and BMI (kg/m2) were recorded. Each patient's height and weight were recorded in meters and kilograms for the purpose of calculating BMI. Hypertension, diabetes, and dyslipidemia was noted. NYHA Class of heart failure was noted. Routine Investigations like FBS, serum creatinine, fasting lipid profile, Pro BNP, Hemoglobin level was measured. Serum Uric acid assay was be carried out by using Siemens Dimension RXL Max analyzer and enzymatic colorimetric method. Left ventricular ejection fraction (LVEF), LVIDd, and LA size were assessed by 2D trans thoracic echocardiography. After 30 days, patients were followed up with either hospital records or trans-telephonic follow-up, whichever was appropriate. All the above data was collected by face to face interview using questionnaire. All available data were processed, and statistical analyses were then performed to determine their significance. The collected data were expressed as appropriate in the form of frequency, percentage, mean, and standard deviation. For continuous variables, Student's t-test was used to compare groups. By using the Chi-square test, categorical data was assessed. Logistic regression was done in order to adjust for established prognostic factors for chronic heart failure (Tachycardia, anemia, LVEF, serum uric acid, Anti- pro BNP, advancing age >70). Version 16 of the computer-based SPSS (Statistical Program for Social Science) program was used to conduct the entire analysis. P-value of <0.05 was considered significant.

Result:

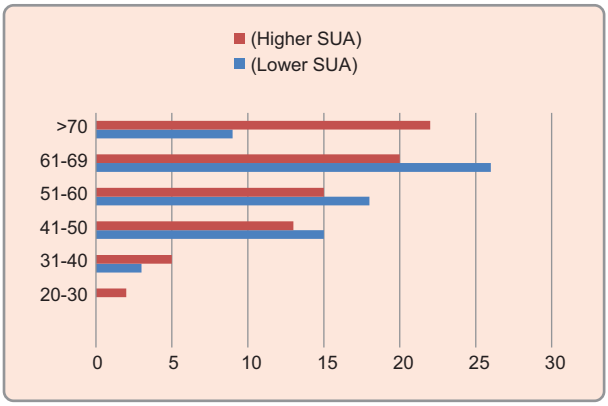

Fig.-1: *Showing Age Distribution among Group I & II*

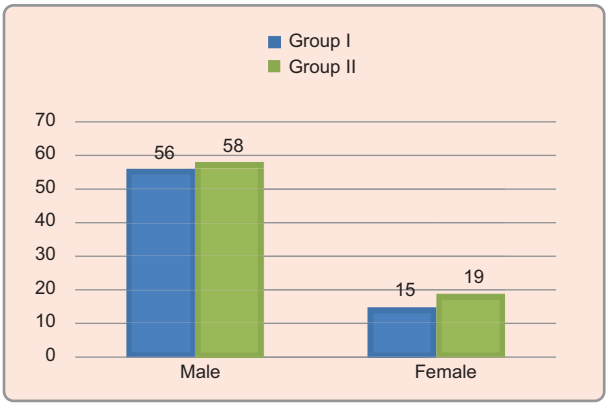

Fig.-2: *Bar Graph Showing Male And Female distribution among Group I & II*

Table-I

Association of BMI of the study patients between two groups

BMI (kg/m^2)			0.099^{ns}
Normal (18.5-22.9)	9(12.7%)	4(5.2%)	
Overweight (23.0-24.99)	8(11.3%)	12(15.6%)	
Obese (³25.0)	54(76.1%)	61(79.2%)	
Total	71(100%)	77(100%)	
Mean±SD	26.58±3.60	28.03±4.48	

ns = not significant

Table-II

Association drug history of the study patients between two groups (n=148)

Drug history	Group I (Lower SUA) (n=71) No. (%)	Group II (Higher SUA) (n=77) No. (%)	p value
Beta blockers	30(42.3)	34(44.2)	0.815^{ns}
ACE inhibitors	34(47.9)	43(55.8)	0.333^{ns}
ARB	34(47.9)	30(39.0)	0.273^{ns}
Loop diuretics	70(98.6)	74(96.1)	0.351^{ns}
Spironolactone	64(90.1)	62(80.5)	0.100^{ns}
Nitrates	35(49.3)	45(58.7)	0.264^{ns}
Anti-platelet Clopidogrel	53(74.6)	52(67.5)	0.341^{ns}
Aspirin	71(100.0)	74(96.1)	0.093^{ns}
Statin	32(45.1)	28(36.4)	0.281^{ns}
Digoxin	1(1.4)	4(5.2)	0.203^{ns}

Figures in the parentheses indicate corresponding percentage;
Chi-squared Test (χ^2) was done to analyze the data.
ns = not significant

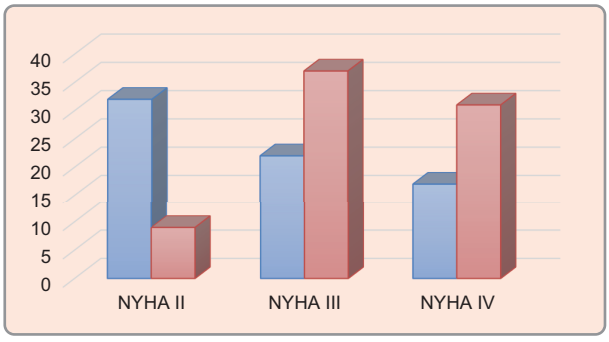

Fig.-3: *Bar Graph showing Uric acid levels higher with higher NYHA Class*

Table-III

Comparison of biochemical variables between two groups (n=148)

Biochemical variables	Group I (Lower SUA) (n=71) Mean±SD	Group II (Higher SUA) (n=77) Mean±SD	p value
Serum uric acid	5.57±1.01	9.46±1.99	
Hb	12.18±1.35	10.80±1.17	0.001^{s}
RBS	9.01±3.87	8.92±1.87	0.851^{ns}
NT PRO BNP	2889.11±1392.9	3594.59±1241.43	0.001^{s}
HBA1C	7.73±10.50	7.54±1.26	0.409^{ns}
Troponin I	0.04±0.03	0.04±0.04	0.528^{ns}
Serum creatinine	1.23±0.15	1.23±0.20	0.953^{ns}
SGPT	69.26±89.04	62.55±100.98	0.699^{ns}
Na	138.85±3.15	137.10±4.52	0.008^{s}
K	3.89±0.43	4.05±0.54	0.089^{ns}
Cl	97.46±7.23	99.85±8.92	0.077^{ns}

Data were expressed mean±SD
Unpaired student t-test was done to analyze the data.
s=significant, ns = not significant

Table-IV

Association of echocardiograph findings between two groups (n=148)

Echocardiographic findings	Group I (Lower SUA) (n=71)	Group II (Higher SUA) (n=77)	p value
LA size	35.15±4.36	37.23±5.15	0.009^{s}
LVED	53.48±8.99	56.92±6.25	0.008^{s}
LVEF	41.96±7.39	37.16±6.17	<0.001^{s}

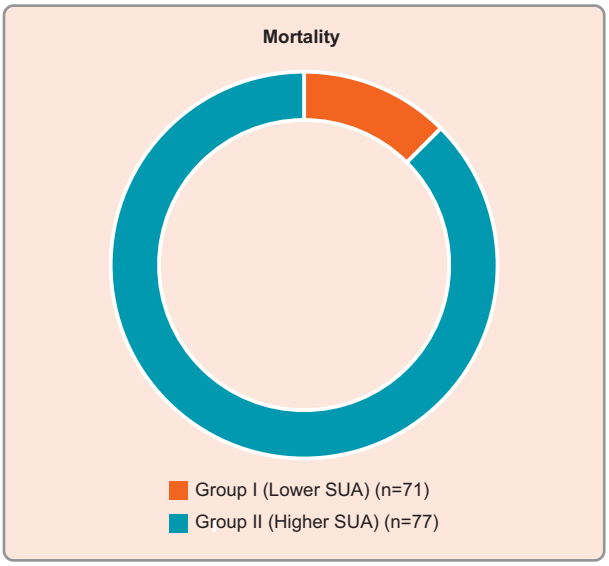

Fig 4: *Association of mortality between two groups (n=148)*

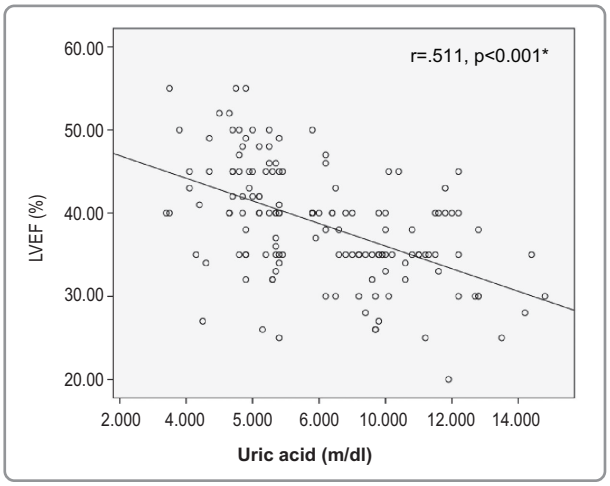

Fig.-5: *Scatter diagram showed correlation between LVEF and on admission Uric acid level of the study population (n=148). It showed statistically significant negative correlation with medium strength (r= -0.511, p= <0.001).*

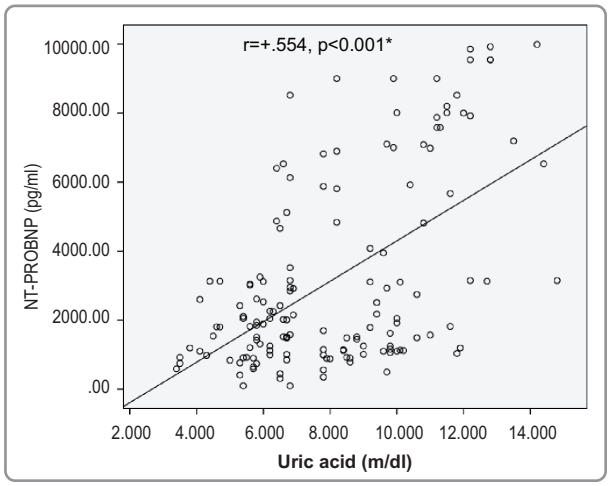

Fig.-6: *Scatter diagram showed correlation between NT-PROBNP and Uric acid level of the study population (n=148). It showed statistically significant positive correlation with medium strength (r= -0.554, p= <0.001).*

Table-V
Regression analysis (n=148)

Variables	p-value	OR	95% CI	
			Lower	Upper
Anemia d"11gm/dl	.637	.789	.294	2.114
LVEF (d" 40%)	.012 [s]	3.806	1.227	4.858
NT PRO BNP	.024 [s]	2.100	1.000	4.000
Serum uric acid	.033 [s]	2.004	2.475	3.767

Table V shows Regression analysis done to clarify the independent association of various prognostic factors

Discussion:

Previous research has demonstrated that serum uric acid in HF patients may also serve as a predictive risk factor. Increased ventricular filling pressures cause an adaptive increase in BNP, whereas increased xanthine oxidase activity causes a maladaptive increase in uric acid levels in HF. According to this study, which is consistent with Roberts' research investigations, hyperuricemia is present in the majority (73 %) of heart failure patients and is more common in men than in women [18].

Serum uric acid levels are markedly higher in acute decompensation than in chronic heart failure, indicating that acute heart failure syndromes are more likely to have hyperuricemia than chronic states, and that the majority of patients with acute decompensation-related hyperuricemia have severe clinical impairment. Acute heart failure patients with elevated uric acid levels had worsening left ventricular remodeling due to increased oxidative stress and xanthine oxidase activity [19].

There was no substantial difference in the drug use between Group I and Group II in this experiment. A statistically significant difference between the hyperuricemic group that received diuretics and the control group that did not was found in a study [20]. Classifying HF patients according to LVEF is essential because to disparities in aetiology, demographics, co-morbidities, and treatment response. Patients in Group I had an LVEF of 41.967.39, whereas those in Group II had an LVEF of 37.166.17. Patients with a greater SUA had a mean LVEF of 38.20 according to research by Ehmouda [21]. Consistent with Suresh [22], there was a

statistically significant (p 0.05) gap between the two groups in our investigation. Because individuals with HF have varied underlying etiologies, demographics, co-morbidities, and therapeutic responses, it is crucial to differentiate them based on LVEF [22]. In this study, LVEF in Group I patients was 41.96±7.39 in group II 37.16±6.17. Ehmouda [21] showed mean LVEF 38±20 in patients with higher SUA. In this study difference between two groups was statistically significant ($p < 0.05$) which was similar to Suresh [22].

Xanthine oxidase, an enzyme crucial in the conversion of purines to uric acid, has been linked to the production of superoxide free radicals. It has been demonstrated that coronary endothelial cells have ncreased xanthine oxidase activity during ischemia and increases even more after reperfusion [23]. Allopurinol decreases the size of infarcts and hastens the recovery of myocardium that has been stunned, presumably through reducing the generation of dangerous free radicals. Recent research reveals that xanthine oxidase activation and congestive heart failure are related [24].

Allopurinol may have enhanced LV function was by improving endothelial function, which therefore increased myocardial perfusion. Alternatively, allopurinol may improve myocardial oxygen consumption and other energy efficiency, which would then have the secondary impact of strengthening endothelial function, to directly affect LV function [25,26].

Even if improving LV function does contribute to improved endothelial function, the underlying process may still be related to oxidative stress reduction because oxidative stress is an interesting regulator of unfavorable LV remodeling. According to findings from a study in Germany, patients with CHF who had a high blood uric acid level were more likely to pass away if heart transplant is not done [2,6]. Given that hyperuricemia may be brought on by increased renal excretion of UA due to renal impairment or diuretics, it is unknown if serum uric acid is a standalone prognostic biomarker in relation to renal dysfunction in patients with CHF [18].

In this study, patients with high uric levels had an increased risk of severe heart failure, frequent hospital readmissions, longer hospital stays, and death within 30 days of follow-up compared to patients with normal uric acid levels. The use of uric acid as a prognostic marker may be very advantageous in patients with prior heart failure who have high blood uric acid levels and poor left ventricular ejection fraction. For individuals with persistent heart failure, individualized therapy is necessary for the best outcome. For this reason, it's crucial to accurately predict each patient's prognosis.

After Performing the multivariable logistic regression analysis in present study, it showed adjusted prognostic factors by multivariate logistic regression analysis for chronic heart failure. It was found serum uric acid is independently associated with outcome OR 2.004, p value 0.033. Analysis also showed LVEF (d" 40%) and NT PRO BNP as expected, remained strong predictor of outcome.

The critical importance of uric acid level as a prognostic marker may be demonstrated by the substantial association between the level of blood uric acid and reduced left ventricular ejection fraction in patients with established heart failure. In chronic heart failure, individualized treatment is needed to achieve optimal outcome. This requires a reliable assessment of individual prognosis.

Further prospective studies are required to show that routine measurement or lowering of blood uric acid levels will improve outcomes in patients with chronic heart failure, regardless of whether these levels are prepared for routine clinical use as a prognostic indicator.

Conclusion:

It was discovered that the severity of heart failure was correlated with the prevalence of hyperuricemia. The inverse relationship between elevated blood uric acid levels and ejection fraction suggests that growing hyperuricemia in chronic heart failure is a sign of deteriorating cardiac function. Patients with greater uric acid levels had a worse prognosis, as evidenced by their higher NYHA class at presentation, longer hospital stays, and higher 30-day mortality rate.

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