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ASSESSMENT OF PROGNOSTIC SIGNIFICANCE OF SERUM URIC ACID LEVELS IN PATIENTS WITH CONGESTIVE CARDIAC FAILURE DURING HOSPITAL STAY IN A TERTIARY CARE TEACHING HOSPITAL.

General Medicine

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ABSTRACT

Background & Objectives: Congestive/Chronic Heart Failure (CHF), the main cause of hospitalization and healthcare expenditure has become a global catastrophe with its major threat to patients, health systems and societies. The importance of reliable, cheap and easily done prognostic tools cannot be over-emphasised in view of ever mounting gravity of HF with its present incidence of 64 million cases globally and an estimated 160,000 deaths annually in India alone. Many studies have found an association between increased serum uric acid (SUA) level and CHF. By this study, we attempt to evaluate the prognostic significance of SUA in CHF and its association with LVEF, NYHA classification and co-morbidities present. **Materials and Methods:** This study, a retrospective single centre observational study was carried out among 80 consecutive patients, diagnosed with CHF irrespective of aetiology, subject to inclusion/exclusion criteria during their stay in a hospital in central India. All patients were subjected to detailed clinical examination and the severity of their condition was evaluated using NYHA classification along with lab/X-ray/ECG/ECO/USG investigation outcomes. The data recorded in the case study proforma were then summarised, analysed and interpreted with appropriate statistical tools. **Results:** The population comprising 80 CHF patients -44 males and 36 females with mean age of 60.89 and 60.14 years showed maximum incidence (75%) in the age group – 51 to 70 years. Out of these, 58 patients (73%) had hyperuricemia. The mean SUA levels against LVEF categories of >50%; 40-49%; 30-39%;<30% were 5.63,6.83,8.42 & 9.14 mg/dL respectively, thereby showing a negative correlation between the two. The mean SUA levels of all patients across NYHA classes I to IV were 5.33, 5.94, 8.17 and 10.19 mg/dL respectively, resulting in a positive correlation. The average duration of hospital stay of the patients was increased from 5.89 to 11.35 days, while their mean SUA levels were increased from 6 to 9 mg/dL. CAD (42%), Hypertension (36%), DM (31%), CVA (11%), hypercholesteremia (10%) and smoking (9%) were found the major risk factors/comorbidities existed. Conclusion: Our study demonstrated that SUA has prognostic significance in CHF patients and hyperuricemia shall be a stand-alone prognostic indicator of worsening cardiac dysfunction and consequent hospitalisation and mortality. The study revealed statistically significant correlations between SUA levels and LVEF, NYHA classification and duration of hospital stay of the population. These associations render SUA levels prognostically significant. Our results and postulations support outcomes of many previous studies highlighting prognostic significance of hyperuricemia. Further, it revealed noticeable associations between SUA levels and co-morbidities such as coronary artery disease, Hypertension and Diabetes Mellitus. We found statistically significant association between Hyperuricemia and Diabetes mellitus while the relationship between hyperuricemia and hypertension was found insignificant.

KEYWORDS

INTRODUCTION

Heart Failure (HF) or congestive/chronic heart failure (CHF) is a leading aetiology for both morbidity and mortality on global level affecting at least 26 million people worldwide [1]. The estimated prevalence of HF is about 1% of the population or about 10-13 million people in India, while it accounts for about 0.16 million deaths annually.

The ageing population, increasing prevalence of cardiac risk factors and improved survival rate among acute cardiovascular disease patients have snow balled HF into a global catastrophe as it is a devastating, resource-intensive syndrome that results in premature mortality, disability, impaired functional capacity, reduced quality of life requiring multiple pharmaco therapies. HF is also a main cause of hospitalization and healthcare expenditure in many countries. For these reasons, HF represents a major threat to patients, health systems and societies; particularly in nations with resource-constrained systems and economies [2]

HF: Definition, Aetiology& Presenting symptoms

The universal definition emphasizes HF as a clinical syndrome with symptoms and/or signs caused by a structural and/or functional cardiac abnormality and corroborated by elevated natriuretic peptide levels and/or objective evidence of pulmonary or systemic congestion. [3] The majority of the CHF cases are due to CAD and MI while other structural causes include hypertension, valvular heart diseases, arrythmia, myocarditis and congenital heart diseases. The most common presenting symptoms include dyspnoea, arrythmia, oedema (legs and ankles), angina/chest discomfort cough and fatigue. Fatigue is due to under-perfusion of the skeletal muscles resulting in exercise intolerance. Accumulation of fluid may occur, resulting in pulmonary and peripheral congestion - hence the term 'congestive heart failure'.

Pathophysiology of CHF

In CHF, the normal adaptive cardiac mechanism for maintaining adequate contractile ability become maladaptive when trying to maintain cardiac performance. Cardiac physiology tries to adapt several compensatory mechanisms such as Frank-Starling mechanism, Myocyte regeneration changes, myocardial hypertrophy/hypercontractility. This eccentric remodelling mechanism further worsens the loading conditions and wall stress [4]

When the cardiac output is decreased, neuroendocrine system releases epinephrine, norepinephrine, endothelin-1 and vasopressin which leads to vasoconstriction and increased after load. Besides, an increase in cyclic adenosine monophosphate (cAMP) results in increased myocardial contractility and further prevents myocardial relaxation.

An increase in after load and myocardial contractility with impaired myocardial relaxation leads to increased myocardial oxygen demand which leads to cell death and apoptosis. Apoptosis and diminished cardiac output with increased demand leads to a perpetuating cycle of increased neurohumoral stimulation and maladaptive hemodynamic and myocardial responses.

A decrease in cardiac output also stimulates the renin-angiotensin-aldosterone system (RAAS), leading to increased salt and water retention, along with increased vasoconstriction. This further fuel the maladaptive mechanisms in the heart and cause progressive heart failure. In addition to this, the RAAS system releases angiotensin II, which has been shown to increase myocardial cellular hypertrophy and interstitial fibrosis. This maladaptive function of angiotensin II has

been shown to increase myocardial remodelling. In HFpEF, there is a decrease in myocardial relaxation and an increase in the stiffness of the ventricle due to an increase in ventricular after load. This perpetuates a similar maladaptive hemodynamic compensation and leads to progressive heart failure.[5]

Uric acid & HF

Uric acid (UA) is the end product of purine breakdown. Xanthine oxidase (XO) & Xanthine dehydrogenase, the enzymes responsible for breakdown of uric acid, contribute to generate oxidative stress-causing free-oxygen-radicals (ROS). Oxidative stress helps development of atherosclerosis and increase in cytokine production. [6]

In spite of many studies done on the relationship between uric acid and cardiovascular disease, the mechanisms by which UA could determine CV events still remains unclear. Up-regulated XO activity and increased production ROS are judged to be the core pathogenesis of HF with hyperuricemia which initiates a cluster of cardiovascular effects such as oxidative stress, endothelial dysfunction, vascular inflammation, left ventricular dysfunction and insulin resistance.

Despite the remarkable therapeutic advances, chronic heart failure remains a condition marked by progressive deterioration and premature mortality and it is the final common pathway for a multitude of cardiac insults.[7]. Therefore, introduction of simple and effective investigatory modalities is absolutely necessary for early diagnosis, risk stratification and prognosis.

Justification of the study

Epidemiological studies have found an association between increased serum uric acid (SUA) levels to an elevated vascular event rate and mortality in patients with co-morbidities [8,9]

SUA may be an important indicator for predicting prognosis of people with pre-existing heart failure. Not many studies have been conducted that evaluated increased SUA levels as an independent risk factor for heart failure among the general population. [10].

This study is an attempt to evaluate the prognostic significance of SUA and correlate SUA levels with the severity of Congestive Cardiac Failure (CHF), duration of hospital stay and comorbidities present in the population under the study.

AIMS AND OBJECTIVES

The primary objective of this study is to evaluate the efficacy of serum uric acid level as a prognostic tool and to find its correlation with left ventricular ejection fraction related to congestive /chronic heart failure. Study of association of SUA levels with comorbidities present being the secondary objective of the study.

MATERIALS AND METHODS

This study, a retrospective single centre observational study was carried out among 80 consecutive patients, subject to inclusion/exclusion criteria, diagnosed with CHF during their hospital stay in a tertiary care teaching hospital in central India during the period from July 2021 to August 2022.

Inclusion Criteria: Patients having age ≥18 years for both sexes and Individuals diagnosed as congestive cardiac failure patients irrespective of aetiology.

Exclusion criteria:1. Patients who are diagnosed with: Lung disease, ,Gout, Calcium pyrophosphatase disease (CPPD), Nephrolithiasis ,Rheumatic diseases, Liver diseases, Solid tumours, Haematological malignancy, Inflammatory Bowel Disease. 2. Patients on the medications: Allopurinol, Amiloride Cisplatin ,Cyclosporine A Ethacrynic acid ,Ethambutol , Levodopa ,Niacin, Tacrolimus ,Theophylline, Anagrelide,Cilostazol ,Amphetamines ,Carbamazepine ,Clozapine ,Ergot alkaloids, Pergolide 3.Patients with h/o alcohol, Chemotherapy medications, Tricyclic antidepressant

History, examination & Investigations

All patients were subjected to a detailed history and examination and the severity of Congestive Heart Failure was assessed using NYHA functional classification along with other investigations. A case study proforma is used for recording, all presenting symptoms/vital signs/clinical exam, lab/X-ray/ECG/ECO/USGinvestigation outcomes & personal/treatment/menstrual/Addiction/family history.

Data collection, recording and Statistical Analysis:

Individual patient's data recorded in the proforma sheets were entered in Microsoft Excel spread sheet, tabulated, summarised and analysed. Significance testing of the difference between means was done by unpaired 2 tailed student 't'- test for independent samples, and correlations were estimated by Pearson coefficient. Significance was considered, if the 'p' value was below 0.05.

Serum Uric Acid Measurements:

Reference Values for Serum Uric acid levels: In Men: 2.4 - 7.4 mg/dL: In Women: 1.4 – 5.8 mg/dL :Hyperuricemia is defined as serum uric acid levels >7.4 mg/dL in males and >5.8 mg/dL in females.

Patient Short Term Outcome:

All the patients included in the study were followed up for the period of their hospital stay.

RESULTS

Demographic features and SUA levels

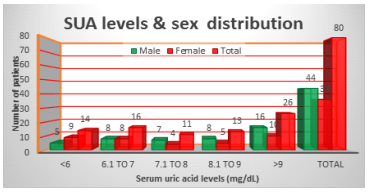
The total strength of the study group was 80 patients - 44 males and 36 females. The maximum incidence of the population was in the age group of 51 -70 years i.e. 33 (75%) males and 22 (61%) females. The mean age of the study group was 60.89 years, 60.14 years and 61.81 years for the population, males and females respectively.

Table 01: Gender and SUA levels of patients

S. No.	Age Category (in years)	No. of Males			No. of Females			No. of Males + Females		
		SUA levels			SUA levels			SUA levels		
		Normal	Hyper	Total	Normal	Hyper	Total	Normal	Hyper	Total
01	18 - 40	1	2	3	1	1	2	2	3	5
02	41 - 50	0	3	3	2	4	6	2	7	9
03	51 - 60	4	13	17	0	4	4	4	17	21
04	61 - 70	7	9	16	5	13	18	12	22	34
05	Above 70	2	3	5	0	6	6	2	9	11
Total	14	30	44	8	28	36	22	58	80	

Out of the total 80 patients, a total of 58 (73%) patients (30 males + 28 females) had hyperuricemia (above 7.4 mg/dL for males and 5.8 mg/dL for females) and a total of 22 (27%) (14 males and 8 females) had normal range (between 2.4 -7.4 mg/dL and 1.4 -5.8 mg/dL for males and females respectively) of SUA. The mean SUA levels for the whole group was 8.277 mg/dL, while the same for the male and female patients were 8.60 mg/dL and 7.88 mg/dL respectively.

Graph: 01: SUA levels & sex distribution



SUA levels and Left Ventricular Ejection Fraction

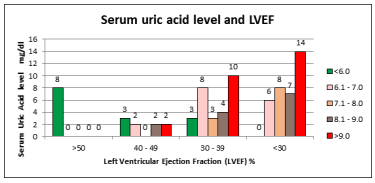
Out of total 80, 8 patients (10%) had LVEF >50 %, 6 were females and 2 were males. The figures for LVEF category 40 to 49 % and 30 to 39% were 9 (11% :Male 4+Female 5) and 28 (35%: Male 17 + Female11). 44 % or 35 patients had LVEF less than 30%. They were 21 males and 14 females. Further, out of 35 patients with LVEF below 30%, 21 patients (12 males + 9 females) belonged to the sub-category of LVEF % equal to or below 20 to 25.

Table No. 2: LVEF % and SUA levels

LVEF %	Serum Uric Acid levels (mg/dL)						P Value
	<6.0	6.1 -7.0	7.1-8.0	8.1 -9.0	>9.0	Total	
	Number of Patients						
>50	8	0	0	0	0	8	0.001
40 - 49	3	2	0	2	2	9	
30 - 39	3	8	3	4	10	28	
<30	0	6	8	7	14	35	
Total	14	16	11	13	26	80	

In summary, 63 patients (79%: 38 males plus 25 females) belonged to the broader category of LVEF less than 39 %, while 21 % or 17 patients (6 males +11 females) were from the category of LVEF equal to/or more than 40%. A negative correlation existed between SUA levels and LVEF % withp.value less than 0.001, making the association statistically significant.

Graph No.2 Serum Uric acid levels and LVEF



The mean SUA of the population against four classes of LVEF viz. > 50%, 40-49%, 30-39% and <30% were 5.63, 6.83, 8.42 and 9.14 mg/dL respectively.

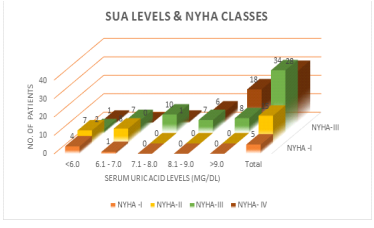
SUA levels and NYHA classes

A statistically significant association was found, reflecting a negative correlation, between various SUA levels and corresponding NYHA classes. P.value of the association was 0.001.

Table 3. SUA levels and NYHA classes

SUA (mg/dL)	Number of patients				P.value
	NYHA CLASSES				
	I	II	III	IV	
<6.0	4	7	2	1	0.001
6.1 – 7.0	1	8	7	0	
7.1 – 8.0	0	0	10	1	
8.1 – 9.0	0	0	7	6	
>9.0	0	0	8	18	
Total	5	15	34	26	

Graph 3: SUA levels & NYHA classes



The mean SUA levels of all patients across NYHA classes I to IV were 5.33, 5.94, 8.17 and 10.19 mg/dL. 50 patients (63%) classified as NYHA III and IV (25 patients in each class) had SUA levels more than 7.0mg/dL. Of the remaining 30 patients (37%), 5,15,9,1 x patients were classified as NYHA classes from I to IV respectively with SUA levels less than 7 mg/dL.

SUA levels and duration of hospital stay

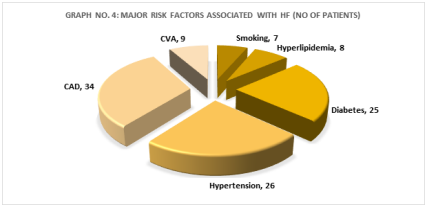
The mean number of days the patients stayed in the hospital is increased from 5.89 days to 11.35 days when their corresponding SUA levels were increased from below 6.0mg/dL to above 9.0 mg/dL. Thus, the association showed a positive correlation and it is significant with p.value<0.001.

Table No.4: SUA levels and duration of hospital stay

S. No.	Sua levels (mg/dL)	Total no. of patients	Number of patients No. of days stayed in hospital			Mean duration of hospital stay in days	p. Value
			<5 days	5-10 days	>10 days		
1	<6.0	14	10	2	2	5.89	<0.001
2	6.1 to 7.0	16	10	6	0	5.19	
3	7.1 to 8.0	11	1	8	2	7.55	
4	8.1 to 9.0	13	3	4	6	8.46	
5	>9.0	26	0	11	15	11.35	

Co-morbidities/Major risk factors

The major risk factors associated with CHF identified in our study were, CAD, Hypertension, DM, CVA, hypercholesteremia and smoking.



The number of patients having these co-morbidities were 34 (42%),26 (36%), 25 (31%), 9 (11%), 8 (10%) and 7 (9%) respectively . The mean SUA levels of the CAD, Hypertensive and diabetic patients were 8.4, 8.2 and 8.2 (all mg/dL) respectively.

DISCUSSION

It is still debated globally whether Serum Uric acid, is an independent risk factor or it's just a consequence of other disorders associated with cardiovascular diseases like hypertension, DM and dyslipidaemia. And a prognostic factor of HF.

Our study was conducted among a population of 80 inpatients diagnosed with different stages of heart failure as reflected in their NYHA grading, LVEF percentage and other relevant evaluations. The study designed to assess the significance of prognostic value of SUA levels of congestive heart failure (CHF) patients demonstrated that that Serum Uric Acid level signifies prognosis in CHF. The analysis of the data indicated that SUA levels have statistically significant association with LVEF%, NYHA grading and duration of hospital stay. Further, the study highlighted the statistically significant correlation between hyperuricemia and DM. However, the study indicated insignificant association between hyperuricemia and hypertension.

Demographic characteristics of the study

Predominance of male over female patients (55% vs 45%), higher mean age of females (61.81 years for females vs 60.14 years for males), higher prevalence of hyperuricemia cases among women (78 % against 68 % among males), higher number of HFpEF cases among females were the main noticeable demographic characteristics of the study. These features were in line with previous studies- Kirkwood et al (1996), Michelle and Uzma et.al (2009) and the study by Eljaaly Z et al (Dec 2021).

Role of oestrogen, lower cut-off point to meet the reference value of SUA among females may be some of the reasons behind higher incidence of hyperuricemia among females. [11]Studies such as Michele Arcopinto et al [12] found that prevalence of HFpEF is more among females than males. Difference in anthropometry, a different LV architecture, and EF in healthy males compared with females, the role of oestrogen's, differential gene expression, different tendency to maintain a systemic inflammation status, and the pattern of HF comorbidities acting together on coronary microvascular/endothelial inflammation are put forward for explaining this asymmetrical incidence.

Prognostic value of SUA levels

In a systemic review of meta analysis, Lina Mia et al. suggested that a high level of SUA independently predicted the risk of all-cause mortality, cardiovascular death and combined death or death events in CHF patients. These findings hold good in our studies as well since the mean duration of hospital stay in our study increased from 5.89 days to 11.35 days when the SUA levels increased from < 6.0 mg/dL to above 9.0 mg/dL. Our study demonstrated a statistically significant association between SUA levels and duration of hospital stay which substantiate previous findings that SUA predicts poor outcome in CHF. The exact molecular mechanisms by which UA is implicated in pathophysiology of HF is yet to be established unambiguously. However, many studies have established the role of Xanthine oxidase in explaining various cardiovascular events leading to and/or worsening HF.

Over expression of XO could have ROS-mediated detrimental effects such as endothelial disfunction, inflammatory activation, mitochondrial damage, or impaired cardiac contractility, all of which are commonly seen in HF. XO is a critical factor in upregulating

myocardial apoptosis - the central feature in the progression of HF.[13,14,15].Multiple experimental studies have demonstrated that hyperuricemia inhibits myocardial cell activity by activating extracellular signal-regulated kinase ERK/P38 signalling pathway and it impedes the mechano-energetic coupling in HF, bringing down the mechanical efficiency of myocardial contraction while the oxygen consumption remains the same [16,17,18]. All the above explanations suggest that hyperuricemia is an intrinsic feature of HF pathophysiology which in turn is in line with what the data analysis indicated in our study.

Correlation between SUA levels and LVEF

LVEF , as demonstrated in numerous studies, is a powerful predictor of mortality in HF patients based on which many drug and device therapeutic indications were defined. [19]

Our study revealed a negative correlation between LVEF % and SUA levels. The association is significant with a p.value of 0.001. The average SUA level moved from 6.83 mg/dL to 8.42 mg/dL to 9.14 mg/dL when the corresponding LVEF % was declined from below 50% to below 40% to below 30%. Further, the mean SUA level of 21 patients belonged to the sub-category of LVEF>20 to 25 %, which could be classified as very severe cardiac dysfunction cases, was as high as 9.61 mg/dL. Thus, this study supports the hypothesis that progressive hyperuricemia indicates cardiac dysfunction and its severity as reflected in LVEF%.

Several previous studies demonstrated the negative correlation of LVEF% with SUA levels. Anker et al. [20] showed that a high SUA level predicted poorer outcomes in patients with moderate to severe chronic HF. Giuseppe Abrosio et al [21] demonstrated that the adverse prognostic value of elevated SUA levels is not confined to HFrEF patients as it could be documented in other HF phenotypes categorised on the basis of LVEF. In a study conducted in the year 2016 ,Yohei Yamauchi et el [22] found that SUA is associated negatively with LVEF in both genders.

SUA levels and NYHA classification

Our study demonstrated a positive correlation between SUA levels and NYHA classification of patients. The association was found statistically significant with a p.value of 0.001

The mean SUA levels of all patients in our study moved from 5.33 to 5.94 to 8.17 to 10.19 (mg/dL) as the NYHA classifications changed from class I to class IV. Leyver et al. reported an inverse relationship between SUA and VO2 max and a positive correlation between UA levels and minute ventilation/carbon dioxide production (VE/VCO2), both of which suggest that increased SUA concentrations may reflect an impairment of the oxidative metabolism with consequent exercise intolerance in HF [23].This findings, along with the aforesaid negative correlation between SUA levels and LVEF %, logically explains the positive correlation between SUA levels and NYHA classes as found in our study where SUA levels increased sharply alongside NYHA classes.

SUA levels and risk factors/Co-morbidities of HF

The association between SUA and DM was found statistically significant (p.value = 0.001) while association between SUA and hypertension was found insignificant (p.value = 0.169).

Our study postulates a statistically significant association between hyperuricemia and DM with p.value 0.001. Many studies [24 & 25] have shown that hyperuricemia is closely related to insulin resistance and diabetes. The pathological mechanism between the association could be: reduction of insulin sensitivity due to UA induced inflammation [26], ROS caused oxidative stress resulting in lipid peroxidation, DNA/cellular damage and decreased insulin secretion [27], endothelial dysfunction and inhibition of insulin pathway.[28]
Claudio Bhorghi et al. [29] stated that Oxidative stress and intracellular urate activity with involvement of xanthine-oxidoreductase (XOR) are implicated in the mechanism of hypertension among hyperuricemia patients and the study further confirm significant association between SUA and hypertension. However, contrary to this hypothesis, our study revealed non-significant association between the two and assuch calls for further studies looking into the aspects of correct cardiovascular threshold of SUA levels, the time course of uricemia fluctuations, monitoring the effects of SUA lowering medications and closer monitoring of hypertension of larger HF population.

CONCLUSION

Our study demonstrated that SUA has prognostic significance in CHF patients and hyperuricemia shall be a stand-alone prognostic indicator of worsening cardiac dysfunction and consequent hospitalisation and mortality. The study revealed statistically significant correlations between SUA levels and LVEF, NYHA classification and duration of hospital stay of the population. These associations render SUA levels prognostically significant. Our results and postulations support outcomes of many previous studies highlighting prognostic significance of hyperuricemia. Further, it revealed noticeable associations between SUA levels and co-morbidities such as coronary artery disease, Hypertension and Diabetes Mellitus. We found statistically significant association between Hyperuricemia and Diabetes mellitus while the relationship between hyperuricemia and hypertension was found insignificant.

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