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Role of uric acid as a biomarker in patients with heart failure

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Abstract
Aim: The present study was done to find out the relationship between serum uric acid levels and Heart failure.
Material and Method: The study was carried out in Chattrapati Shivaji Subharti Hospital, Meerut in the Department of Medicine. 50 cases of both sex aged between 20 to 80 years with clinical evidence of heart failure were enrolled in this study. All patients with documented evidence (2D echo Based) of heart failure and having heart failure treatment were included in the study. The data was collected by a preformed structured interviewer-administered questionnaire that was pretested with modifications made prior to its use in the study. The patients were interviewed that requests for the demographic, medical history and previous history of taking any medications and supplements. Two-dimensional echocardiography was done in the cardiology department for all patients. Serum uric acid levels were measured on admission for all the 50 patients.
Results: Higher uric acid was reported among 68.42% and 44.44% of the male and female respectively. It can be appreciated from the results that as the NYHA class increases, Uric Acid level also increases. Mean uric acid level was 5.92±1.67 and 8.22±2.28 among survivor and non-survivor subjects respectively with statistically significant difference as $p<0.05$.
Conclusion: In conclusion, our study found that hyperuricemia is related to a more prominent frequency of heart failure and hyperuricemia is an indicator of all reason mortality in patients with heart failure.

Keywords: uric acid, echocardiography, heart failure, mortality

Introduction
Heart failure (HF) is one of the most prevalent clinical diagnoses in modern medicine. India is home to 16% of global population, 25% of the world's coronary heart disease (CHD) burden, 120 million hypertensives and a large number of individuals with RHD. CVD will be the leading cause of morbidity and mortality in India by 2020 [1, 2]. Hence heart failure is a thriving issue around the world.
Despite advances in its treatment, HF is the main cause of hospitalization in adults over 60 years of age and is a major cause of mortality. There is a need for a cost-effective, simple prognostic biomarker. Although several biomarkers, especially brain natriuretic peptide (BNP), are available and may be helpful for risk stratification, their utilization in guiding treatment remains controversial. The association between elevated levels of uric acid (UA) and worse outcomes in cardiovascular diseases has been known for over half a century. It was first described in respect to coronary artery disease [3, 4] but it soon became obvious that the relationship holds true for all cardiac conditions [5, 6] as well as hypertension, kidney disease, and diabetes[7]. In recent years, there has been growing interest regarding elevated UA in HF.
The potential molecular mechanisms that explain the role of SUA in development and advance of HF are traditionally structured in follow schematic consequences that are appeared to be counter directed. On the one hand, the hyperuricemia causes inflammation due to direct vascular injury and a production of various inflammatory cytokines and monocyte chemo attractant protein-1, inducing oxidative stress and activation of the local rennin-angiotensin system [8, 9]. Additionally, all these factors lead to endothelial dysfunction by a reduction in endothelial levels of vasodilator substances such as nitric oxide, inducing cellular proliferation, accelerating atherosclerosis, activating insulin resistance and microvascular inflammation [10]. On the other hand, urates are physiological substrate for myeloperoxidase acting as regulator of oxidative stress, but molecule of uric acid may act as intracellular scavengers of free radicals diminishing proinflammatory effect and increasing cell survival [11]. Thus, SUA links in vascular damage, endothelial dysfunction and oxidative stress that play important role across all stages of HF development and contributes in an impact of co-morbidities on risk of HF onset and advance [12].
Hence the association of SUA and coronary heart disease has long been recognised and has sparked enormous debate about the role of SUA as a risk factor for CHD and the treatment of hyperuricemia especially in hypertensive patients [13]. In more recent years several studies and meta-analysis have reported raised SUA to be associated with increased risk of incident HF in population studies [14]. Whether this association is causal is still a

matter of debate. However a recent Mendelian randomisation study provided no evidence that the association between SUA and HF is causal, suggesting that SUA may be only a risk marker rather than a causal factor in the development of HF [15].

Not many studies have been conducted that evaluated increased serum uric acid (UA) levels as an independent risk factor for heart failure among the general population. Hence the present study was done to find out the relationship between serum uric acid levels and Heart failure.

Material and Method

The study was carried out in Chattrapati Shivaji Subharti Hospital, Meerut in the Department of Medicine. 50 cases with clinical evidence of heart failure were enrolled in this study. All patients with documented evidence (2D echo Based) of heart failure and having heart failure treatment were included in the study. Informed consent was obtained from all patients. All participants were told about the study and informed consent was taken.

Patients of both sex aged between 20 to 80 years and patients with Heart failure both with preserved and decreased EF were included in the study. Patients with pre-existing gout, patients on long standing diuretics, anti-tubercular drugs, immune-suppressants, and on chemotherapy, K/C/O Chronic kidney disease/malignancy and patients with pre-existing gout and heart failure, patients on long-standing diuretics and heart failure were excluded from the study

The data was collected by a preformed structured interviewer-administered questionnaire that was pretested with modifications made prior to its use in the study. The patients were interviewed that requests for the demographic, medical history and previous history of taking any medications and supplements. Demographic data obtained from patient included age, sex, height and weight, and body mass index.

Patients were subjected to the routine work up for heart failure including

a. Complete blood count
b. Blood glucose (fasting and 2 hour post prandial)
c. Fasting serum lipid profile
d. Serum Uric Acid
e. Blood urea
f. Serum creatinine
g. Serum electrolytes
h. Chest X ray
i. Two-dimensional echocardiography

Methodology

1. A detailed physical examination was conducted to assess patients' volume status (edema, jugular venous distension), weight, height, body mass index, and orthostatic blood pressure changes.
2. Complete blood count, blood glucose (fasting and 2-hour postprandial), fasting serum lipid profile, blood urea, serum creatinine were measured in all patients.
3. Two-dimensional echocardiography was done in the cardiology department for all patients.
4. Serum uric acid levels were measured on admission for all the 50 patients who met the inclusion criteria.
5. All patients with documented evidence of heart failure and on heart failure treatment for at least one month were recruited for the study.
6. Patient history was collected by a structured pro-forma which includes general details of the patient, any illness history, and present complaints. All the data (like anthropometric measurements and clinical data) collected were also noted.

Instruments

1. Electrocardiogram

All patients had 12 lead ECG, which was reviewed for evidence of atrial enlargement, ventricular hypertrophy, evidence of antecedent myocardial infarction and conduction blocks.

2. Chest x ray

Chest x ray posteroanterior view was done in all patients to note pulmonary congestion, pleural effusion and to estimate cardio thoracic ratio.

3. Echocardiography

M-mode echocardiography was used to assess left ventricle dimensions. Left ventricle internal dimension in end systole (LVESD) and end diastole (LVEDD) were measured at the level of mitral valve leaflet tips in parasternal long axis view. Measurements were taken from the endocardium of the left surface of the interventricular septum to the endocardium of the left ventricle posterior wall. In adults the normal range of LVEDD is 3.5 to 5.6 centimeter. The normal range of LVESD is 2 to 4 centimeter. 2-D echo imaging in apical 4 chamber, parasternal long axis and parasternal short axis views were used to assess ventricular and valvular movement. Ejection fraction was estimated using Simpson's method. In this method multiple short axis views are taken along the LV long axis. Endocardial border is traced accurately and left ventricle cavity is divided into 20 slices of known thickness and diameter (D). Left ventricle end diastole and Left ventricle end systole volumes are estimated.

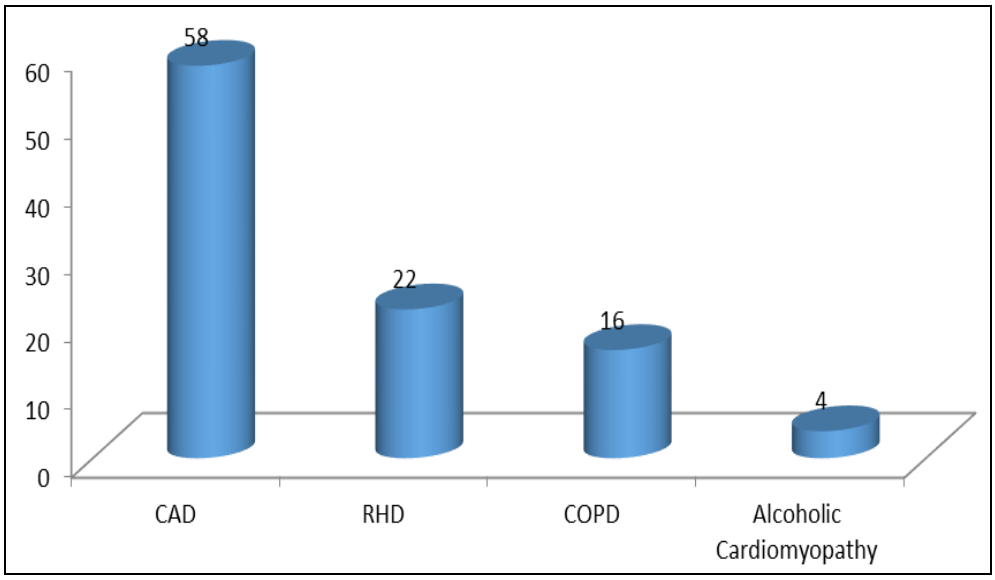
Area of each slice=$22/7(D/2)^2$

Volume of each slice = area X thickness.
LV volume= volume of each slice X number of slices (20)
EF = (Left ventricle end diastole volume -Left ventricle end systole volume) X 100/Left ventricle end diastole volume

Uric Acid (Normal values)
Serum Uric Acid (males) = 3.0 to 7.0 mg/dl
Serum Uric Acid (females) = 2.5 to 6.0 mg/dl

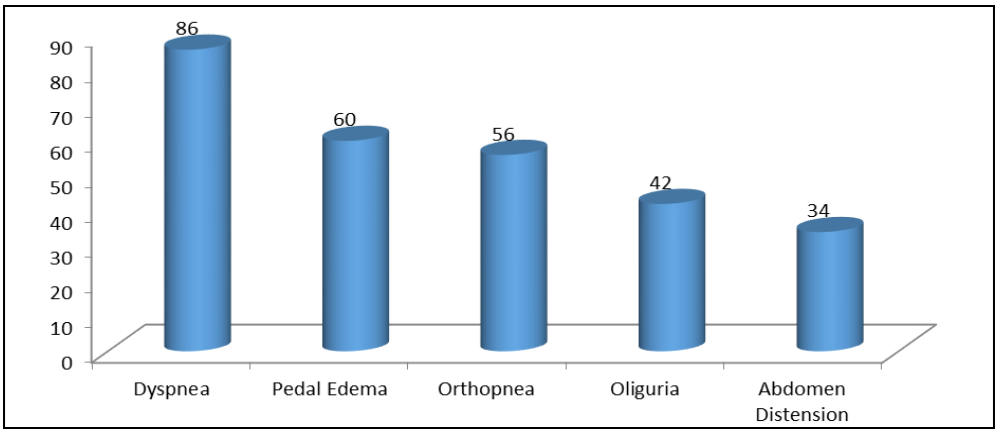
Statistical analysis
Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). For each assessment point, data were statistically analyzed using one way ANOVA. Difference between two groups was determined using student t-test as well as chi square test and the level of significance was set at $p<0.05$.

Results
Out of 50 subjects, there were 32 (64%) males and 18 (36%) females. 2%, 12%, 32%, 36% and 18% of the subjects belonged to 20-30, 31-40, 41-50, 51-60 and >60 years of age group respectively. Most common cause was CAD (58%) followed by RHD (22%) and COPD (16%). Alcoholic cardiomyopathy and RVD as a cause of heart failure was found among 4% each of the subjects (graph 1).



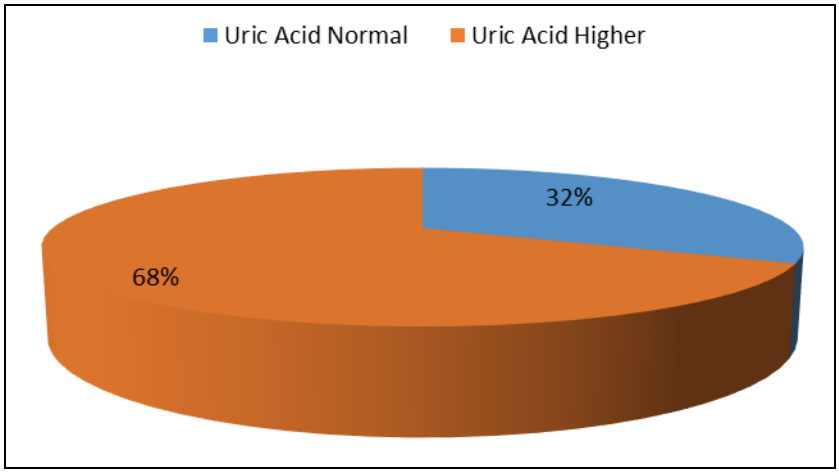
Graph 1: Cause of heart failure among the study subjects

Smoking, Alcoholism, Hypertension, Diabetes and Dyslipidemia was reported among 46%, 56%, 68%, 48% and 34% of the subjects respectively. Hence most common risk factor for heart failure in our study was Hypertension. Dyspnea, Pedal edema, Orthopnea, Oliguria and Abdominal Distension was found among 86%, 60%, 56%, 42% and 34% of the subjects respectively (graph 2).



Graph 2: Symptoms among the study subjects

Mean BMI (kg/m^2), SBP (mmhg) and DBP (mmhg) among the study subjects was 24.89±3.62, 155.63±12.91 and 88.26±7.38 respectively. In our study, normal uric (mg/dl) was revealed among 32% of the subjects while higher uric acid was found among 68% of the subjects (graph 3).



Graph 3: Uric acid (mg/dl) among the study subjects

Higher uric acid was reported among 68.42% and 44.44% of the male and female respectively. When male and female was compared according to uric acid level, it was found to be statistically significant as p<0.05 (table 1).

Table 1: Uric acid (mg/dl) among males and females

Gender	Normal		High (>7: Male, >6: Females)		p value
	N	%	N	%	
Male	12	31.58	26	68.42	0.02*
Female	10	55.56	8	44.44	
Total	16	32	34	68	

*: statistically significant

It can be appreciated from table 2 that as the NYHA class increases, Uric Acid level also increases. Mean uric acid level was 4.31±1.92, 6.98±2.34 and 9.03±2.09 among NYHA Class II, III and IV of heart failure respectively with statistically significant difference as p<0.05.

Table 2: Mean uric acid according to NYHA Class

NYHA Class	N	Uric Acid (mg/ml)	
		Mean	SD
Class II	7	4.31	1.92
Class III	39	6.98	2.34
Class IV	4	9.03	2.09
Anova Test		14.94	
p value		<0.01*	

*: statistically significant

Mean uric acid level was 5.92±1.67 and 8.22±2.28 among survivor and non-survivor subjects respectively with statistically significant difference as p<0.05 (table 3).

Table 3: Mean uric acid according to mortality

Outcome	N	Uric Acid (mg/ml)	
		Mean	SD
Survivor	42	5.92	1.67
Non-survivor	8	8.22	2.28
t Test		21.78	
p value		<0.01*	

*: statistically significant

Discussion

Increase in Uric acid are related to increased vascular tone and depressed myocardial contractility due to an increase in Xanthine Oxidase activity. Therefore Uric acid could be related to hemodynamic compromise in

heart failure [16]. The study was carried out in Chattrapati Shivaji Subharti Hospital, Meerut in the Department of Medicine among 50 cases with clinical evidence of heart failure. All patients with documented evidence (2D echo Based) of heart failure and having heart failure treatment were included in the study.

In our study, there was male dominancy in our study. Henry-Okafor *et al* [17] and Adnan Khan *et al* [18] in their study revealed similar male dominance.

In this study; maximum subjects were from the age group of 51-60 years. In a study by C.N. Sai Vigneshvar *et al* [19] revealed that the mean age of the participants was 56.08±8.48 years. The age ranges from 43 years to 76 years. This is similar to our study.

Most common cause was CAD (58%) followed by RHD (22%) and COPD (16%). Alcoholic cardiomyopathy and RVD as a cause of heart failure was found among 4% each of the subjects in our study. In a study by C.N. Sai Vigneshvar *et al* [19] reported that overall co-morbidities present were CAD (62%), RHD (28%), and COPD (10%). This is similar to our study.

In our study, normal uric (mg/dl) was revealed among 32% of the subjects while higher uric acid was found among 68% of the subjects. Higher uric acid was reported among 68.42% and 44.44% of the male and female respectively. When male and female was compared according to uric acid level, it was found to be statistically significant as $p<0.05$. NYHA Class II, III and IV heart failure was reported among 14%, 78% and 8% of the subjects respectively. Mean uric acid level was 4.31±1.92, 6.98±2.34 and 9.03±2.09 among NYHA Class II, III and IV of heart failure respectively with statistically significant difference as $p<0.05$.

Among patients with chronic cardiovascular dysfunction, serum uric acid concentrations are related to the more prominent movement of superoxide dismutase and endothelium-subordinate vasodilatation. Another potential pathophysiological interface among hyperuricemia and cardiovascular dysfunction may be through inflammation. Asymptomatic hyperuricemia is a proinflammatory state related to more significant levels of serum markers of inflammation, for example, C-responsive protein, interleukin-6, and neutrophil count[20]. Among patients with heart failure, hyperuricemia is related to more elevated levels of markers of endothelial activation, for example, the soluble intercellular adhesion molecule 1 and inflammatory markers, for example, interleukin-6, tumor necrosis factor-α, and its receptors [19].

According to C.N. Sai Vigneshvar *et al* [19], there were 28% in NYHA grade 2 followed by 62% in grade 3 and 10% in grade 4. The mean uric acid levels were 7.12 mg/dL. Adnan Khan *et al* [18] in their study demonstrated that 59.29% of these patients had elevated serum uric acid levels. SUA was significantly higher among symptomatic Congestive Heart Failure patients than in asymptomatic patients with 34.93% of the Hyperuricemic CHF patients were in NYHA III and NYHA IV whose SUA was above 8 mg/dl as compared to 31.57% Hyperuricemic CHF patients whose SUA was below 8 mg/dl. This fact may help to identify asymptomatic patients in followup. They also found that mean SUA levels increased significantly with NYHA class.

Existing literature is clashing on whether a decrease in serum uric acid will bring about quantifiable clinical advantage among those with established heart failure. Some studies have even indicated that that increased serum uric acid brought about by diuretic use may have a helpful job in itself. On the other hand, the Losartan Intervention for endpoint decrease in hypertension (LIFE) study has discovered that the uricosuric property of Losartan, has an advantageous impact among patients with hypertension and left ventricular remodeling and hypertrophy. The components by which uric acid reduction treatment is valuable is still not clear. In particular, it is hazy whether the notified advantage from the utilization of xanthine oxidase inhibitors intercedes through a decrease in serum uric acid levels or some other mechanism.

Mortality was found among 16% of the subjects in our study. Mean uric acid level was 5.92±1.67 and 8.22±2.28 among survivor and non-survivor subjects respectively with statistically significant difference as $p<0.05$. Numerous studies have reported that hyperuricemia indicates a higher relative risk of all cause mortality in patients with CHF, independent of other risk factors. In a recent study, high uric acid levels increased all-cause mortality in patients with both acute and chronic HF, which in turn, increases XO activity and subsequently SUA levels [21]. Jankowska EA *et al* [22] in their study revealed that in patients with mild to moderate CHF, elevated serum UA levels are strongly related to death, and this correlation is independent of Chronic Heart Failure severity and impaired renal function. In the same study, hyperuricemia was said to have predicted exercise intolerance and was an indicator of inflammatory activation in CHF. Serum UA levels increased extremely alongside with CHF severity expressed as NYHA class.

Limitations of the study

Our data on serum uric acid are essentially left truncated, that is we know the extent of hyperuricemia but not the period of hyperuricemia.

In outline, our study found that hyperuricemia is related to a more prominent frequency of heart failure and hyperuricemia is an indicator of all reason mortality in patients with heart failure. Future investigations utilizing different urate reduction treatment methodologies would be expected to decide if the essential counteraction of heart failure is conceivable. As the commonness of heart failure is increasing, even a little clinical advantage got from such investigations can be of gigantic benefit to the community.

Conclusion

In conclusion, our study found that hyperuricemia is related to a more prominent frequency of heart failure and hyperuricemia is an indicator of all reason mortality in patients with heart failure. Future investigations utilizing

different urate reduction treatment methodologies would be expected to decide if the essential counteraction of heart failure is conceivable. As the commonness of heart failure is increasing, even a little clinical advantage got from such investigations can be of gigantic benefit to the community.

References

1. Huffman MD, Prabhakaran D. Heart failure: Epidemiology and prevention in India. Natl Med J India,2010:23:283-8.
2. Reddy KS. Rising burden of cardiovascular disease in Indians. In: Sethi KK, editor. Coronary Artery Disease in Indians. A Global Perspective. Mumbai: Cardiological Society of India, 1998.
3. Kohn PM, Prozan GB. Hyperuricemia; relationship to hypercholesteremia and acute myocardial infarction. J Am Med Assoc,1959:170(16):1909-1912.
4. Gertler MM, Garn SM, Levine SA. Serum uric acid in relation to age and physique in health and in coronary heart disease. Ann Intern Med,1951:34(6):1421-1431.
5. Strasak A, Ruttmann E, Brant L, Kelleher C, Klenk J, Concin H *et al*. Serum uric acid and risk of cardiovascular mortality: a prospective long-term study of 83,683 Austrian men. Clin Chem,2008:54(2):273-284.
6. Tamariz L, Harzand A, Palacio A, Verma S, Jones J, Hare J. Uric acid as a predictor of all-cause mortality in heart failure: a meta-analysis. Congest Heart Fail 2011;17(1):25–30.
7. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. N Engl J Med,2008:359(17):1811-1821.
8. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, Krotova K, Block ER, Prabhakar S, Johnson RJ. Hyperuricemia induces endothelial dysfunction. Kidney international,2005:67(5):1739-42.
9. Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid–induced C-reactive protein expression: implication on cell proliferation and nitric oxide production of human vascular cells. Journal of the American Society of Nephrology,2005:16(12):3553-62.
10. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. New England Journal of Medicine,2008:359(17):1811-21.
11. Berezin A. Serum uric acid as a metabolic regulator of endothelial reparative processes in heart failure patients. Stem Cell and Translational Investigation, 2014, 1.
12. Berezin AE. Uric Acid in Heart Failure: Controversy factor in the multiple pathogenesis of the disease. Biomedical Journal of Scientific & Technical Research,2017:1(3):592-4.
13. Gois PH, Souza ER. Pharmacotherapy for hyperuricemia in hypertensive patients. Cochrane Database Syst. Rev, 2013, 1. CD008652.
14. Desai RV, Ahmed MI, Fonarow GC *et al*. Effect of serum insulin on the association between hyperuricemia and incident heart failure. Am. J. Cardiol,2010:106:1134-1138.
15. Wannamethee SG, Papacosta O, Lennon L, Whincup PH. Serum uric acid as a potential marker for heart failure risk in men on antihypertensive treatment: The British Regional Heart Study. International J. Cardiol,2018:252:187-92.
16. Omran AR. The epidemiologic transition: A theory of the epidemiology of population change. Milbank Mem Fund, 1971; 49: 501.
17. Henry-Okafor Q, Collins SP, Jenkins CA, *et al*. Relationship between uric acid levels and diagnostic and prognostic outcomes in acute heart failure. The open biomarkers journal,2012:5:9.
18. Khan A, Shah MH, Khan S, Shamim U, Arshad S. Serum Uric Acid level in the severity of Congestive Heart Failure (CHF). Pak J Med Sci,2017:33(2):330-334.
19. Vigneshvar CS, Arumugam E, Appandraj S. Uric acid level as a biomarker in heart failure patients in a rural population attending tertiary care hospital in Chengalpattu District, Tamil Nadu. IAIM, 2020; 7(12): 57-63.
20. Ruggiero C, Cherubini A, Ble A, *et al*. Uric acid and inflammatory markers. Eur Heart J,2006:27:1174-1181.
21. Tamariz L, Harzand A, Palacio A, Verma S, Jones J, Hare J. Uric acid as a predictor of all-cause mortality in heart failure: a meta-analysis. Congest Hear Fail,2011:17(1):25-30.
22. Jankowska EA, Ponikowska B, Majda J, *et al*. Hyperuricaemia predicts poor outcome in patients with mild to moderate chronic heart failure. Int J Cardiol,2007:115(2):151-155.