Liver Enzymes and Uric acid in Acute Heart Failure

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Background: Acute heart failure (AHF) is defined as the new onset or recurrence of gradual or rapidly worsening signs and symptoms of heart failure, requiring urgent or emergent therapy.

Objectives: This study attempts to assess the association of liver function tests (LFT) and uric acid level with in hospital outcome and echocardiography parameters, in patients with acute decompensated heart failure.

Patients and Methods: A total of 100 patients (aged 16 - 90 years, 60% men) admitted with AHF were enrolled. LFTs and uric acid levels were assessed on first day and before discharge, and patients were followed for 3 months.

Results: In-hospital outcomes were considered. Mean Left Ventricular Ejection Fraction (LVEF) was 35% (20 - 45%). Mean Uric acid level was 8.4 mg/dL, significantly higher than chronic HF and normal groups (P < 0.02). Elevated liver enzymes were seen in 52% patients, mostly (87%) in transaminases. Liver enzymes were decreased in 85% patients before discharge. LFT and uric acid levels were inversely and significantly correlated with LVEF on echocardiography (P = 0.02), but not with diastolic parameters. Although there was no significant correlation between uric acid level and in-hospital mortality, risk of intubation and rehospitalization in 3 months, enzyme levels increased in these groups. Increased aspartate transaminase (AST level) was associated with inotrope infusion in AHF patients (42 vs. 82 mg/dL, P = 0.03).

Conclusions: Abnormal transaminases and uric acid levels are seen in AHF patients. Increased AST levels may be a predictor of the need for inotrope during hospital course in these patients.

Keywords: Heart Failure; Live function; Uric Acid

1. Background

Acute heart failure (AHF) is defined as the new onset or recurrence of gradual or rapidly worsening signs and symptoms of heart failure, requiring urgent or emergent therapy (1). It is among the most common causes for hospitalization and represents a major burden in the general health of the developed world, with high morbidity and mortality (2). Although numerous parameters, like Pro-B type natriuretic peptide (ProBNP), indicate the prognosis of heart failure (HF), most are costly to evaluate and are assessed only in research. The relation between organs, such as kidneys and heart, is also clarified in various diagnostic and treatment strategies, and also liver involvement has been reported in patients with heart failure (3). The prognostic value of abnormal transaminases is reported variable, by different surveys, in chronic heart failure (CHF) and decompensation. Similarly, as changes in liver function tests (LFTs) are generally due to necrosis of hepatocytes (reflecting as transaminases increment) it may be secondary to the hemodynamic disturbances and congestion in AHF (4). Recently, an increasing interest in uric acid has also emerged, as a number of studies have shown that hyperuricemia is a constant feature of inflammation and oxidative stress in heart failure (5). Although inotropes are useful and lifesaving drugs, sometimes they are harmful, they are being used commonly in acute heart failure. Signs of low blood pressure (BP) or low cardiac output are mentioned indications in guidelines. They can lead to major organ damage, in some critical scenarios. There are several valuable markers in predicting timely inotrope administration.

2. Objectives

In this study, we investigated liver enzymes and uric acid level and their association with echocardiography parameters, in hospital mortality and need for inotrope in AHF patients.

3. Patients and Methods

3.1. Study Population

This single-center case series enrolled a total of 100 con-

secutive AHF patients, who were admitted to our center between January 2013 and April 2014. Patients with acute dyspnea, having two major, or one major and two minor criteria of Framingham (2) and ProBNP more than 450 pg/mL, in patients younger than 50 years, or more than 900 pg/mL, in patients older than 50 years (1) enrolled. The exclusion criteria comprised uncontrolled diabetes, known previous liver disease (chronic viral/autoimmune/drug-related hepatitis, liver malignancy, and known biliary tract disease), significant congenital heart disease and severe RV dysfunction (Tapse < 8 mm), significant rheumatic heart disease, known hematological disease, other than anemia of chronic disease (hemoglobinopathies and hemolytic states), continuous consumption of xanthine oxidase inhibitor and furosemide > 80 mg, and a history of gout, kidney stone, and renal dysfunction (creatinine > 2 mg/dL or glomerular filtration rate (GFR) < 30 mL/min/m²). For all the patients, a thorough history taking was followed by a complete physical examination. Additionally, clinical signs of heart failure such as rales, edema, and paroxysmal nocturnal dyspnea, as well as standard New York Heart Association (NYHA) functional class were determined. In the second day, transthoracic echocardiography was done by GE ultrasonograph (GE Healthcare AS, Oslo, Norway) equipped with a S4 Probe 2 MHz and the lab tests were repeated predischarge. Patients were followed and hospital stay, inotrope administration, mortality, cardio-renal and rehospitalization, during 3 months, were assessed. Inotropes were prescribed according to the American Society of Cardiology/American Heart association (ACC/AHA) guidelines in HF (1), low BP (less than 90/60), leading to cardio renal involvement, intractable dyspnea or cognitive disorders, in patients during hospital admission.

3.2. Laboratory Measurements

Blood samples were obtained intravenously, immediately on admission, and repeated predischarge. The serum uric acid level and LFTs were measured by uricase-peroxidase method (ADVIA® 1650 Chemistry System, Siemens Medical Solutions Diagnostics, Tarrytown, NY, USA). Other biochemical parameters were measured according to the standard techniques. Liver function tests that were extracted included aspartate aminotransferase (upper limit of normal [ULN] = 40 U/L), ALT (ULN = 40 U/L), alkaline phosphatase (ALP) (ULN = 120 U/L), direct bilirubin (ULN = 0.5 mg/dL), and total bilirubin (ULN = 1.1 mg/dL). Serum uric acid > 6.4 mmol/L was defined as abnormal.

Numbers are in accordance to laboratory references mentioned in internal medicine texts, in the general population. Mean uric acid level was evaluated in CHF patients in AMIN study and it was 7.4 mg/dL (6), which is more than the mean level in normal patients. Data in this study have been discussed according to the levels mentioned. LV systolic and diastolic function, systolic pulmonary arterial pressure (PAP) and right ventricular (RV) function were evaluated by echocardiography.

3.3. Study Endpoint

Hospital stay, inotrope administration, mortality, cardio renal and rehospitalization during 3 months were considered.

3.4. Statistical Analysis

Continuous variables were expressed as mean ± standard deviations (SD). Independent groups were compared using the unpaired Student's t test. Categorical data were compared with the chi-squared test, and Fisher's exact test was performed, when relevant. Pearson correlation test was used to assess the relation of two continues variables. Statistical analyses were performed using SPSS version 15.0 (SPSS Inc., Chicago, IL, USA). Statistical significance was set at $P < 0.05$.

4. Results

Baseline characteristics of the patient population are shown in Table 1. Men accounted for 60% of the study population (aged 19 - 82, mean: 48 years), and mean hospital stay duration was 7 days. Mean uric acid serum level was 8.4 ± 2.2 mg/dL, which was significantly higher than that chronic heart failure (mean uric acid serum level was 7.6 mg/dL) and normal subjects (mean uric acid serum level was 6.4 mg/dL), P = 0.02 and 0.05, respectively. Predischarge mean uric acid level was 7.7 mg/dL, slightly decreased after treatment. Mean AST was 54 mg/dL and mean ALT was 86 mg/dL. Mean AST in the day of discharge was 41 mg/dL and mean ALT was 67 mg/dL. Mean total bilirubin level was 3.2 mg/dL and mean direct bilirubin level was 1.8 mg/dL. At predischarge evaluation, total bilirubin level returned to lower than 0.6 mg/dL in 60% of patients. According to the reference thresholds mentioned in the textbooks, 54% had high AST levels (> 40 mg/dL), 48% high ALT levels (> 40 mg/dL), 68% high ALP levels (> 150 mg/dL), while 41.2% had total bilirubin level > 1.5 mg/dL, and 58.8% had direct bilirubin level > 0.5 mg/dL. The respective mean systolic PAP was 32 mmHg. Mean LVEF was 28% on echocardiography. In the evaluation of the RV function, according to echocardiographic data, mean Tapse was 15 mm. There was no significant association with diastolic parameters like E/EA, diastolic PAP, systolic PAP, left atrium size and liver enzymes, but there was a significant inverse association between LVEF and liver function tests and also uric acid levels (R = 0.4), P = 0.04 and 0.03 respectively (Table 2).

4.1. Study Outcomes

A total of 30 patients received inotropes. LFTs and uric acid were higher in this group and there was significant association with AST levels and inotrope use (P = 0.03). Twenty seven patients suffered from worsening renal function, while LFTs and uric acid levels were higher in this group, it was not significant (P = 0.07). Twenty patients had more than one admission due to AHF and 10 patients were

intubated, there was a trend to higher LFTs but it was not statistically significant (P = 0.09). Seven patients died and

ProBNP and uric acid levels were higher in this group, although without statistical significance. (P = 0.12) (Table 3).

Table 1. Baseline Characteristics in Heart Failure Group[a]

Variables	Maximum	Minimum	Mean ± SD
Age, y	92	16	43 ± 17.29
AST, U/L	406	5	54 ± 65.13
ALT, U/L	855	9	86 ± 147.47
Total Bilirubin, mg/dL	8.1	0.3	1.8 ± 1.41
Direct Bilirubin, mg/dL	4.2	0.1	0.8 ± 0.8
Uric Acid, mg/dL	16.8	2.7	8.4 ± 2.2
Hospital stay (days)	20	4	7 ± 3.6
ProBNP, pg/dL	2870	870	1007 ± 191.34
sysPAP, mmHg	75	15	32 ± 13.98
LA area, cm2	69	14	27 ± 6.76
E/Ea	28	14	19 ± 4.2
LVEDD, mm	85	17	48 ± 0.9
TAPSE, cm/sec	3.2	9	1.9 ± 0.28
LVEF, %	50	22	28 ± 9.9

[a] Abbreviations: AST, (aspartate transaminase); ALT, (alanine transaminase); E/Ea, mitral E velocity/septal mitral annular velocity in Tissue Doppler Imaging; left ventricular end diastolic diameter(LVEDD); LVEF(left ventricular ejection fraction); PAP, (pulmonary artery pressure); Tapse, (Tricuspid annular plane systolic excursion).

Table 2. Pearson Correlation of Liver Enzymes and Serum Uric Acid level to Echocardiography Parameters[a]

Echo Parameters	AST, U/L		ALT, U/L		Uric Acid, mg/dL		Total Bilirubin mg/dL		Direct Bilirubin, mg/dL	
	r	P Value	r	P Value	r	P Value	r	P Value	r	P Value
E/Ea	-0.05	0.5	-0.02	0.8	-0.18	0.06	-0.01	0.9	-0.04	0.6
LVEDD, mm	0.14	0.15	0.15	0.13	0.14	0.15	0.1	0.12	0.1	0.1
Tapse, cm/sec	0.5	0.9	0.7	0.9	0.09	0.3	0.15	0.9	0.14	0.7
LA area, cm^2	0.04	0.6	0.08	0.4	0.07	0.9	0.12	0.2	0.08	0.6
Sys PAP, mmHg	-0.22	0.02	-0.16	0.1	0.08	0.4	-0.01	0.8	-0.05	0.5
EF, %	-0.26	0.008	-0.23	0.01	-0.26	0.007	-0.27	0.006	-0.26	0.008

[a] Abbreviations: ALT, liver aminotransferases; E/Ea, mitral E velocity/septal mitral annular velocity in Tissue Doppler Imaging; EF, ejection fraction; LA, left atrium; LVEDD, left ventricular end diastolic diameter; LVEF, left ventricular ejection fraction; PAP, pulmonary artery pressure ; r, Pearson Correlation Coefficient.

Table 3. Pearson Correlation of Liver Function tests and Uric Acid Serum Level With in-Hospital and 3 Months Outcome in Acute Heart Failure Patients

Study Endpoints	(n = 100)	AST, (U/L)		ALT, U/L		URICACID, mg/dL		PROBNP, pg/dL	
		Mean ± SD	P Value	Mean ± SD	P Value	Mean ± SD	P Value	Mean ± SD	P Value
Inotrope	30		0.03		0.16		0.06		0.7
Positive cases		82 ± 96		142 ± 208		9.3 ± 3.2		1067 ± 292	
Negative cases		42 ± 41		63 ± 104		8 ± 2.3		981 ± 120	
Mortality			0.6		0.8		0.4		0.11
Positive cases	13	66 ± 70.7		82 ± 117		8.9 ± 3.4		1147 ± 419	
Negative cases	87	52 ± 64.4		87 ± 152		8.3 ± 2.5		983 ± 119	
Intubation			0.3		0.5		0.3		0.4
Positive cases	10	110 ± 129		145 ± 189		9.3 ± 4		1014 ± 118	
Negative cases	90	48 ± 51		80 ± 141		8.2 ± 2.5		1006 ± 198	
Cardiorenal			0.6		0.4		0.3		0.1
Positive cases	27	68 ± 92		114 ± 182		9.3 ± 3.6		1008 ± 207	
Negative cases	73	49 ± 51		76 ± 132		8.1 ± 2.1		1005+-143	
Hospitalization			0.33		0.23		0.21		0.16
Positive cases	20	70 ± 90		98 ± 126		9.1 ± 2.6		1067 ± 345	
Negative cases	80	50 ± 57		84 ± 152		8.2 ± 2.7		992 ± 126	

5. Discussion

Liver dysfunction and also serum uric acid level have been investigated in chronic heart failure, as the association between hyperuricemia and increases in wedge pressure and cardiac index decline were documented (7). Also, an inverse relationship was found between serum bilirubin level and cardiac output, in which total bilirubin was the strongest predictor for mortality in the CHF (8). However, there are few studies assessing this relationship in AHF. One documented prognostic factor, known in AHF, is ProBNP. Nevertheless, recently, several novel markers like serum uric acid level are considered. Some articles suggested the relationship between uric acid level and cardiovascular risk factors or adverse cardiac events (9). Uric acid is a marker of oxidative stress and is independently associated with poor prognosis and increased mortality (10). It is independent of renal function, serum sodium, serum urea, diuretic usage, and patient age. In our study, mean uric acid level in AHF patients was 8.4 mg/dL on admission, and 7.7 mg/dL at predischarge evaluation, however, mean uric acid level is defined as 7.2 mg/dL in CHF and 6.4 mg/dL in normal subjects. Uric acid level, as an oxidative marker, is increased in AHF patients and has an inverse relation with ejection fraction (P ≤ 0.01). High uric acid level is correlated with severity of LV dysfunction in AHF patients (11). Inotropic agents are among the most important and lifesaving drugs in AHF and represent a cornerstone in critical situations. However, they do have adverse effects with negative impact on patient survival (12). Although, it was found that impaired organ perfusion, resulting from both forward failure (reduced cardiac output and backward failure (increased central venous pressure), are important indications for inotrope administration, it is important to find markers to predict inotrope need before complications occur. Transaminase increment was seen in more than half of the AHF patients in our study and there was significant association of AST levels with inotrope administration. Seventy percent of acute heart failure patients had blood pressure more than 90 mmHg, so hepatic dysfunction can predict inotrope need in AHF. Liver function tests abnormalities are frequently found in heart failure patients and related to poor outcome (12). There are two mechanisms responsible for liver dysfunction in HF: hepatic congestion, especially in those with significant RV dysfunction (13) and liver ischemia, due to low cardiac output state (14). In a study on 323 patients with history of HF, the prognostic value of liver function failure was suggested, independently of the hemodynamic situation (15). In other studies, changes in LFTs and hepatocyte necrosis were the most common pathologic findings in severe hypovolemic shock (16) and AHF patients (17). Biochemistry signs of cholestasis were in accordance with systemic congestion and increases in right side filling pressure and also, biochemistry signs of hepatic cytolysis were correlated with clinical signs of hypoperfusion. Conges-

tive hepatopathy is associated with long term mortality (18). We showed that increased transaminase levels rapidly improve to the near normal range in response to the invasive treatment with inotropic agents, as several studies have suggested similar results (19). van Deursen et al. showed that AST and ALT improved to the normal ranges during five days of inotrope use and AST decreased faster than ALT (20). We proposed that the increased level of transaminases is a reflection of hepatic ischemia, secondary to the hypoperfusion, due to the rapid deceleration of cardiovascular function, and this fact was supported with adverse short term prognosis in these patients, in our study. We found an inverse correlation between liver enzymes and echocardiographic parameters, such as ejection fraction, although it was not meaningful (however, doubtful) with diastolic parameters, left atrial size and ProBNP. In the Nikolaou study, the prognostic value of abnormal ALT-normal AST- was reported, independent of acute myocardial infarction. Transaminase increment was a marker of hepatic dysfunction and high right atrial pressure (6, 21). In our survey, like Nikolaou et al. (21), increasing in the transaminases did not affect the short term prognosis parameters, such as mortality. The bilirubin level was abnormal in 60% of our patients, mostly seen in the chronic heart failure. In Amin et al. bilirubin and uric acid levels were in correlation with increased wedge pressure and ProBNP, in patients with chronic heart failure (23). Although we did not found this relationship between diastolic markers and ProBNP in echocardiography, we demonstrated its reverse correlation with ejection fraction. It seems that ejection fraction and cardiac output are related to liver dysfunction, in the acute phase of heart failure. Trend to the transaminase increment was more pronounced in the mortality or intubation requiring groups, and LFTs decreased with inotrope treatment, measured on the day of discharge. This fact suggested that sinusoidal compression and perfusion derangement caused liver injury, however, hemodynamic improvement with inotropic agents would correct liver dysfunction (21). We found a significant relationship between AST increment and inotrope need during admission. Other outcome parameters did not have significant correlation, which can be due to this fact that liver, is a compliant organ and its dysfunction is affected in end stage HF or in the hyperacute setting. Therefore, appropriate and timely initiation of these agents can help in the stabilization of clinical situation and preventing the organ damages.

5.1. Conclusions

We clarified cardio-hepatic disturbance in more than half of our patients with AHF diagnosis. Uric acid significantly increased in these patients, which imply inflammatory conditions in AHF patients. Abnormalities in the liver function tests inversely correlated with ejection fraction in echocardiography. Significant relationship

was found between AST increment and inotrope need during hospital admission, therefore, AST can be used in predicting inotropic need in patients with diagnosis of AHF. However, we did not find this specification for uric acid and ALT level. More studies are required to clarify this issue.

5.2. Study Limitations

The main limitations of the present study are lack of control group and relatively small sample size. Another limitation is related to lack of long-term follow-up.

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Authors' Contributions

Study concept and design: Dr. Farveh Vakilian; Acquisition of data: Dr. Amir Hossein Rafighdoost, Farveh Vakilian; Analysis and interpretation of data: Dr. Salehi, Farveh Vakilian; Drafting of the manuscript: Dr. Farveh Vakilian. Dr. Ahmad Amin; Critical revision of the manuscript for important intellectual content: Dr. Amir Hossein Rafighdoost; Statistical analysis: Dr. Mayam Salehi; Administrative, technical, and material support: Dr. Abbas Ali Rafighdoost Dr. Farveh Vakilian; Study supervision: Dr. Abbas Ali Rafighdoost DR. Ahmad Amin.

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