Research Article

Correlation Between Alanine Aminotransferase and Left Ventricular Mass in Patients with Non-Alcoholic Fatty Liver Disease

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Abstract

Background: Non-alcoholic fatty liver disease (NAFLD) is considered a risk factor for chronic kidney disease, endocrinopathies, cardiovascular disease (CVD), cerebrovascular disease and osteoporosis. Many prospective follow-up studies demonstrated cardiovascular mortality as an important cause of death in these patients. However, the exact relationship between ALT and CVD especially LVH is undetermined.

Objective: The objective of this study was to determine the correlation between raised ALT levels and left ventricular mass (LVM) in NAFLD patients.

Methods: In this cross sectional analytical study, 115 patients (both male and female) were selected through non-probability purposive sampling technique after meeting inclusion and exclusion criteria. These patients, aged 20-60 years, were diagnosed cases of NAFLD with transaminitis (ALT ≥40 unit/L). Venous samples were collected for ALT, viral serology and fasting lipid profile. All the patients underwent ultrasound abdomen and echocardiography for LVM.

Results: Mean age of patients was 44.63±1.03 while gender distribution showed 55(47.8%) male and 60(52.2%) female patients with a mean body mass index (BMI) of 26.75±5.048. Mean ALT level was 56.68±9.08 and mean LVM was 190.60±14.23 grams. Correlation coefficient for ALT and LVM was 0.571 which showed moderate correlation between these two parameters. A positive moderate correlation existed between ALT and LVM after stratifying the data according to age, gender and BMI.

Conclusion: Elevated ALT levels in NAFLD patients can serve as a screening tool for cardiovascular risk assessment. Whether there is a temporal relationship between transaminitis and an increased risk of cardiovascular events needs further statistical evidence.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is accumulation of >5% liver fat per liver weight in the presence of <10 g of daily alcohol consumption. NAFLD, seen in 10—25% of the populations, manifests itself as hyperechoic texture on ultrasonography (due to diffuse fatty infiltration) and transaminitis.[1] In addition to the liver related complications, NAFLD is now considered a risk factor for extrahepatic diseases such as colorectal cancer, chronic kidney disease, endocrinopathies (type 2 diabetes

mellitus and thyroid dysfunction), cardiovascular disease (CVD), cerebrovascular disease and osteoporosis.[2]

Many prospective follow-up studies demonstrated cardiovascular mortality as an important cause of death in these patients. In 2018, Masood et al explained the vascular phenomenon in NAFLD patients as increased coronary arterial calcifications, endothelial dysfunction, high pulse wave velocity and increased carotid intima media thickness.[3] In 2016, Francque SM studied the association between NAFLD and cardiovascular mortality and found out that NAFLD was significantly associated with subclinical and clinical cardiovascular disease.[4] The evidence was further supported when Lonardo A showed that the development of diabetes mellitus and cardiovascular disease could be accelerated in the presence of fatty, inflamed or fibrotic liver disease in patients who are suffering from NAFLD, HCV or HIV.[5] Ybarra et al used ALT to predict left ventricular mass (LVM) and interventricular septum (IVS) thickness in patients with NAFLD.[6] However, the exact relationship between ALT and CVD especially LVH is undetermined. This was studied by Hagstrom H who concluded that although NAFLD patients have a higher risk of CVD as compared to the matched control group but the histological parameters are not independent risk factors.[7] Minhas AM conducted a systemic review and identified the paucity of high-quality evidence to prove an existing association between cardiovascular diseases and NAFLD.[8]

The objective of this study was to determine the correlation between raised ALT levels and left ventricular mass in NAFLD patients.

Methods

In this cross sectional analytical study, after approval from the institutional review board 130 patients (both male and female) were selected through non-probability purposive sampling technique and 115 patients were enrolled. These patients, aged 20-60 years, were diagnosed cases of NAFLD with transaminitis (ALT ≥40 unit/L). All the patients who had a history of heart failure, valvular heart disease, ischemic/ dilated or hypertrophic obstructive cardiomyopathy, hypertension, hepatitis due to any etiology, psychiatric illness, substance abuse or use of hepatotoxic drugs and malignancy were excluded. Pregnant or lactating patients were not included in the study.

After an informed consent, demographic profile was recorded. Venous samples were collected for ALT, viral serology and fasting lipid profile. All the patients then underwent an ultrasound abdomen for the diagnosis of fatty liver disease and echocardiography for left ventricular mass. The collected data was then processed and analyzed to establish the association of transaminitis with left ventricular mass.

Results

In this study, mean age of patients was 44.63±1.03 while gender distribution shows 55(47.8%) male and 60(52.2%) female patients. Mean body mass index of patients was 26.75±5.048 with a minimum of 19.2 and maximum was 35.98. Mean ALT level of patients was 56.68±9.08 (minimum and maximum ALT level was 40 and 70 respectively). Mean left ventricular mass among patients was 190.60±14.23 grams and minimum and maximum left ventricular mass was 160 and 215 respectively.

Figure 1 shows the correlation coefficient for ALT and LVM being 0.571 which means moderate correlation between these two parameters. Data was

Table 1: *Descriptive statistics of the patients with respect to Age, Gender, BMI, ALT and LVM*

Age Distribution		
n	*115*	
Mean	44.63	
SD	1.03	
Gender Distribution		
	Male	Female
Frequency	55	60
%age	47.8	52.2
Descriptive statistics for Body Mass Index		
n	115	
Mean	26.75	
SD	5.048	
Descriptive statistics for ALT (U/L)		
N	115	
Mean	56.68	
SD	9.08	
Descriptive statistics for Left Ventricular Mass (Grams)		
n	115	
Mean	190.60	
SD	14.23	

stratified for age and patients were divided into 2 groups i.e. 25-45 years and 46-60 years. In both these age groups a positive significant moderate correlation exists between ALT and LVM i.e. 25-45 years (correlation coefficient: 0.604) & 46-60 years (correlation coefficient: 0.547) as shown in figure 2. Among male and female patients significantly positive moderate correlation was observed between ALT and LVM i.e. male (correlation coefficient: 0.593) & female (correlation coefficient: 0.549) as shown in figure 3. Positive moderate significant correlation was seen between ALT and LVM in patients who had normal BMI as well as those patients who were overweight and obese as depicted in figure 4.

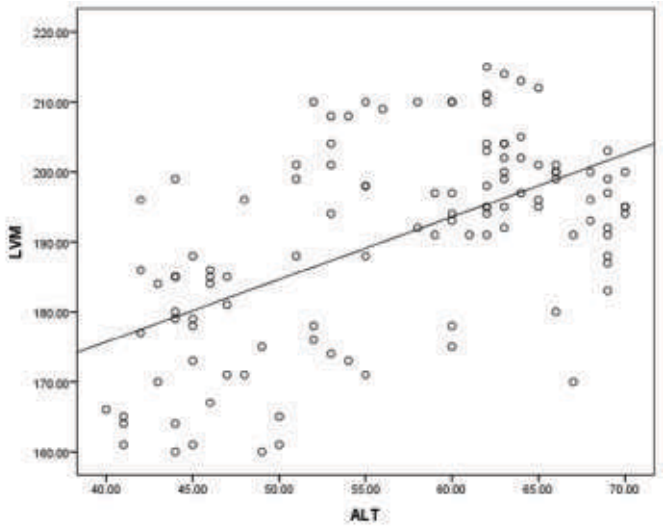

Figure-1: *Correlation between ALT and LVM*
*Correlation Coefficient (r) = 0.571***
*Note. **p < 0.01*

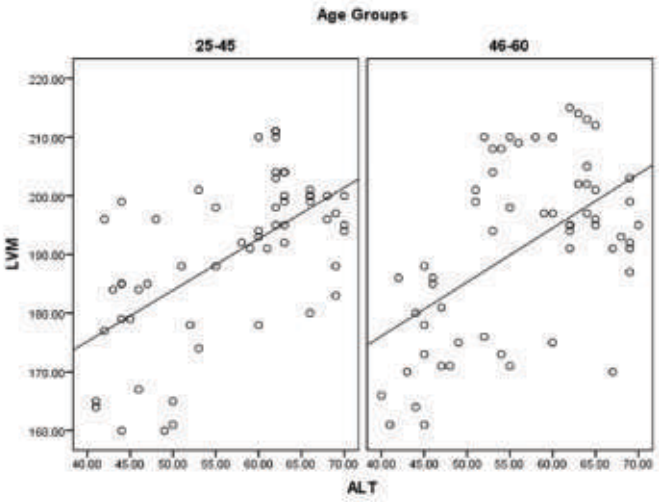

Figure-2: *Correlation between ALT and LVM Stratified for Age of Patients*

Age Groups	*ALT vs. LVM*
	Correlation coefficient (r)
25-45	0.604**
46-60	0.547**
Note. **p < 0.01	

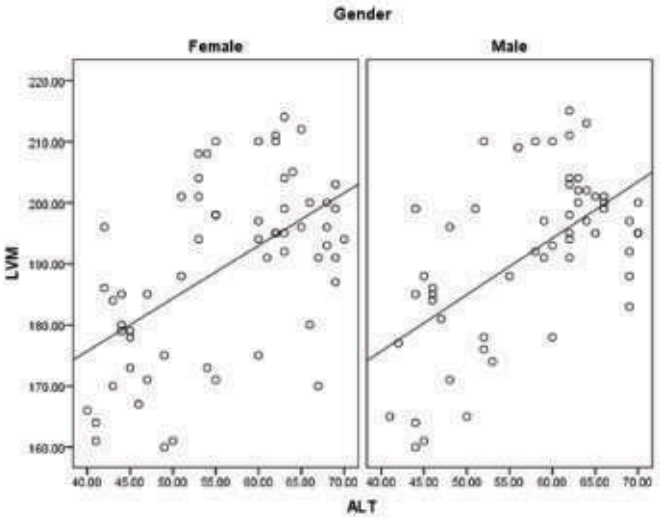

Figure-3: *Correlation between ALT and LVM stratified for gender of patients*

Gender	*ALT vs. LVM*
	Correlation coefficient (r)
Male	0.593**
Female	0.549**
Note. **p < 0.01	

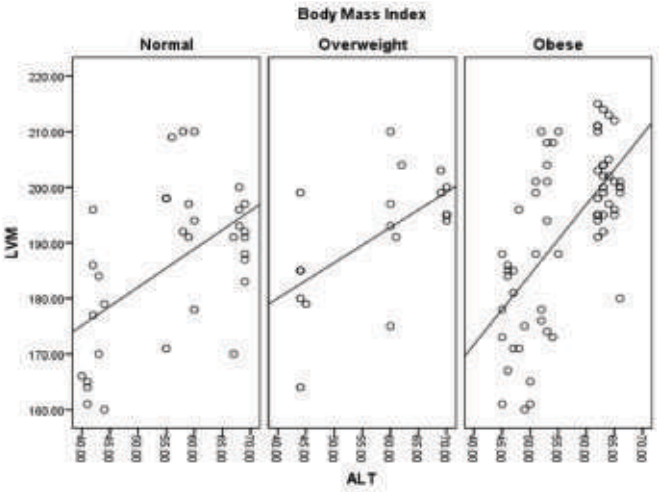

Figure-4: *Correlation between ALT and LVM Stratified for Body Mass index of Patients*

Body Mass Index	*ALT vs. LVM*
	Correlation coefficient (r)
Normal	0.536**
Overweight	0.597**
Obese	0.639**
Note. **p < 0.01	

Discussion

Nonalcoholic fatty liver disease (NAFLD) is accumulation of >5% liver fat per liver weight in the presence of <10 g of daily alcohol consumption. NAFLD, seen in 10—25% of the populations, manifests itself as hyperechoic texture on ultrasonography (due to diffuse fatty infiltration) and transaminitis.[1] The progression in NAFLD is associated with micro- and macrovascular complications in addition to the metabolic manifestation. These complications include metabolic syndrome, insulin resistance leading to type II diabetes mellitus. During the natural course of disease, however, NAFLD can be fatal and the leading causes of death in these patients are cardiovascular disease, chronic liver disease and malignancy in the descending order.[9]

Park HE et al studied the impact of NAFLD on coronary artery calcification (CAC) after enrolling 1732 patients for serial CAC evaluation. The results of the study showed that in NAFLD patients, CAC development or progression was higher as compared to the patients without NAFLD (48.8 Vs 38.4%; P < .01). NAFLD had a significant effect on the change in CAC when compared to the CAC score at baseline. In subjects without calcification at baseline, after adjustment of metabolic risk factors, NAFLD significantly affected the development of calcification (odds ratio, 1.49; 95% confidence interval, 1.01-2.21; p = .045).[10]

Sanyal et al. recorded the profile of liver enzymes in patients with NAFLD and concluded that high ALT and GGT were prevalent in these patients however ALP levels were within normal range in patients who had other co-morbid conditions like impaired glucose tolerance and diabetes mellitus.[11] Hence, serum ALT is a marker of NAFLD and predicts the incidence of metabolic syndrome and diabetes mellitus.[12] Recent data reports an independent association between elevated ALT and cardiovascular mortality once CV risk factors are adjusted. In 2018, Masood et al studied the association between transaminitis and carotid intima media thickness (CIMT) and showed that NAFLD patients have an elevated risk of CIMT, reduced endothelial function, increased coronary artery calcification and increased arterial stiffness.[3] The results of the HOORN 10-year prospective study further affirmed the value of ALT in predicting coronary events independently of conventional risk factors in a population-based cohort.

Zhou et al reviewed the data regarding CV events in NAFLD patients and established that these patients have a significantly higher risk for AF however they suggested that the evidence needs further strengthening regarding a linear relationship between NAFLD and CV events.[13] Goland et al. asserted that in the absence of obesity, hypertension and diabetes, NAFLD patients had variable LV geometry and left ventricular diastolic dysfunction. They found increased thickness of the inter-ventricular septum, posterior wall and an increased left ventricular mass NAFLD group in comparison with normal controls. These findings were further supported by Mantovani et al. when they confirmed a significant association between NAFLD and CV end points. They studied the risk of coronary heart disease alongwith LV dysfunction, valvular heart diseases and atrial fibrillation reviewing the structural, functional and arrhythmic heart conditions and pointed out a higher risk in patients with NAFLD.[14]

In this study significantly moderate positive correlation was seen between ALT and LVM in patients presenting with NAFLD. Mean ALT level of patients in this study was 56.68±9.08 and mean LVM among patients was 190.60±14.23. Correlation coefficient between ALT and LVM was 0.571 which shows positive moderate correlation between these two parameters. This positively moderate correlation shows interdependency of both parameters. In 2015, Azzam concluded similar findings and suggested that NAFLD patients have a higher risk of developing cardiovascular disease which is evident through changes in (both systolic and diastolic) left ventricular function, endothelial function and arterial stiffness. They suggested that all the patients with NAFLD should undergo an echocardiography to diagnose left ventricular hypertrophy, systolic and diastolic dysfunction which may translate into an increased risk for cardiovascular mortality.[15] Karabay studied LV geometry in patients with NAFLD using 2D speckle tracking echocardiography and showed evidence of subclinical myocardial dysfunction in addition to insulin resistance.[16]

The findings reported in this study are consistent with Juan Ybarra regarding significant correlation between ALT and LVM as the similar correlation pattern was

observed between ALT and LVM in patients with NAFLD. In NAFLD patients, serum ALT predicts both LVM and IVS irrespective of age, gender, BMI, diabetes and hypertension. Moreover, ALT acts as a surrogate marker for LVH in overweight and obese patients with NAFLD.[17] Similar findings were reported by Zhang et al when they showed that more than one-third of patients with CHF had a co-existent NAFLD which was associated with the severity of LV fibrosis.[18]

In this study, the results showed a positive significant moderate correlation between ALT and LVM when the data was stratified into age groups i.e. 25-45 years (correlation coefficient: 0.604) & 46-60 years (correlation coefficient: 0.547). Similarly, a significantly positive moderate correlation was observed between ALT and LVM in either gender i.e. male (correlation coefficient: 0.593) & female (correlation coefficient: 0.549). This is in accordance with the study of Chumlea WC et al where they showed that obesity has a linear relationship with LVM/ht2.7 in both men and women. The results showed that a possible positive covariate relationship of overall muscle mass with LVM/ht2.7 exists due to a significant linear association of BMI and physical activity with LVM/ht2.7 and a curvilinear association of abdominal circumference but the impact among the elderly and the known inadequacy of BMI at these ages remains an area for continued clinical study.[19]

LVM was high among over weight and obese patients as compared to those with normal body mass index. In overweight patients, LVM was 191.55 & among obese, it was 192.62. In our study, correlation between ALT and LVM in relation to body mass index was significant i.e. Normal BMI (r): 0.536, p-value<0.01, Overweight(r): 0.597, p-value < 0.01 & Obese(r): 0.639, p-value<0.01. These findings were supported by Karakan when the results of their study concluded that in hypertensive patients, body fat percentage was associated with a high LVMI.[20] Wykrętowicz studied the correlation between body fat index, renal morphology and hemodynamics and proved that intra-abdominal fat compartment is strongly correlated with LVM.[21]

The current data shows a strong evidence for cardiovascular mortality in NAFLD cases which is evident from coronary artery disease and atherosclerotic changes. A raised LVM is a direct consequence of atherosclerosis seen in NAFLD and predicts cardiovascular events. The results of the study showed that there is a moderate correlation between ALT and LVM with the correlation coefficient being 0.571 in patients with NAFLD. The correlation was significant after stratifying the data for age, gender and all categories of BMI. This means ALT can be considered a significant positive predictor to diagnose LVM in NAFLD patients and all the patients with NAFLD who have transaminitis on their liver profile should undergo immediate echocardiography to detect an increase in LVM which in turn will be predicting cardiovascular events in such patients. Hence, a rise in ALT should raise the concern about an increase in the risk of cardiovascular mortality and these patients should remain under surveillance for possible cardiovascular events.

The study did not follow the patients over an extended period of time or estimate the progression of disease so the temporal relationship was not identified and a specific follow-up surveillance routine was not suggested on the basis of these results. A large, multicentre prospective study that investigates the temporal relationship of NAFLD and cardiovascular end points in terms of transaminitis and LVM should be conducted to address the concerns raised in this study.

Conclusion

Elevated ALT levels in NAFLD patients can be used to predict and serve as a screening tool to detect the presence of atherosclerotic changes in case of cardiovascular risk assessment as evidenced by the presence of increased LVM. Whether there is a temporal relationship between transaminitis and an increased risk of cardiovascular events in NAFLD patients needs further statistical evidence.

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