

## A STUDY ON ASSOCIATION OF METABOLIC RISK FACTORS AND DEGREE OF HEPATIC STEATOSIS WITH RISE OF LIVER ENZYME

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### Abstract

**Background:** Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disease from simple steatosis to steatohepatitis with or without cirrhosis, hepatocellular carcinoma occurring in persons who lack secondary causes of liver fat accumulation such as significant alcohol consumption. The aim is to study the relationship between number of metabolic risk factors and degree of hepatic steatosis (according to CAP value) and rise of liver enzyme (ALT). **Materials and Methods:** This was a cross sectional study conducted at a tertiary care hospital in Guwahati, Assam, India among NAFLD patients. We estimated prevalence of various metabolic risk factors such as overweight/obesity, waist circumference, Type 2 Diabetes Mellitus (T2DM) & Dyslipidemia. Fibroscan was done to determine CAP value. Association between number of metabolic risk factors and rise in the level of liver enzyme (ALT) and presence of severe hepatic steatosis (defined by CAP  $\geq$  293dB/m) was calculated. **Result:** Study showed that significantly higher number of patients having all 3 metabolic risk factors (T2DM, dyslipidemia & Overweight/obesity) had raised ALT ( $\geq$  50 U/L) as compared to patients having less than 3 risk factors (OR= 2.373, p= 0.0164). Similarly, presence of all 3 metabolic risk factors was significantly associated with presence of severe hepatic steatosis (CAP  $\geq$  293 dB/m) as compared to patients having less than 3 risk factors (OR = 2.811, p = 0.126). **Conclusion:** Presence of more metabolic risk factors in patients with NAFLD had significant association with presence of severe hepatic steatosis and raised ALT levels.

## INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is considered as the hepatic manifestation of the metabolic syndrome and has become the most common chronic liver disease in the world.<sup>[1]</sup> NAFLD is defined as presence of evidence of hepatic steatosis (HS), either by imaging or histology, and

lack of secondary causes of hepatic fat accumulation such as significant alcohol consumption, long term use of steatogenic medication, or monogenic hereditary disorder. According to a meta-analysis, global prevalence of NAFLD is around 25.4%.<sup>[2]</sup> The prevalence of NAFLD among the general population in India, ranges from 9% to 53%.<sup>[3,4]</sup> NAFLD is frequently accompanied in the majority of patients by metabolic comorbidities such as obesity,

Type 2 diabetes mellitus (T2DM) and dyslipidemia. NAFLD may also affect the lean population, despite the increased prevalence of the illness in obese people and its link to the metabolic syndrome. Lean NAFLD in Indian context is defined as presence of nonalcoholic fatty liver (NAFL) in individuals with BMI < 23 kg/m<sup>2</sup>.<sup>[5]</sup> According to data from Das et al.<sup>[6]</sup> from Eastern India, almost 5.1% of lean, non-drinking population had NAFLD.

Histologically speaking, NAFLD can be divided into NAFL and non-alcoholic steatohepatitis. NAFL is characterised as the presence of > 5% HS without hepatocyte ballooning, which is a sign of hepatocellular damage. Nonalcoholic steatohepatitis (NASH) is characterised by the presence of >5% HS, inflammation, hepatocyte damage (such as ballooning), and fibrosis, whether or not present. Serum AST (Aspartate aminotransferase) or ALT (Alanine aminotransferase) levels may be mildly to moderately elevated (1.5 to 4 times), or both, with serum ALT often higher than AST. Metabolic syndrome might also be related to raised ALT levels.<sup>[7]</sup>

The controlled attenuation parameter (CAP), a new technology for the quantitative detection of liver fat content, is based on the idea of ultrasonic attenuation of liver transient elastography. In addition, it is a noninvasive technique that can replace needle biopsy to evaluate liver steatosis and fibrosis.<sup>[8]</sup> Few previous studies have suggested that individuals having more number of metabolic risk factors might have higher CAP values.<sup>[9,10]</sup>

The present study was undertaken to determine the prevalence of various metabolic risk factors among patients of NAFLD. It further intended to assess the prevalence of lean NAFLD and NAFLD patients with normal liver enzyme (ALT). There is a dearth of literature regarding the association of metabolic risk factors with CAP and liver enzymes in individuals with NAFLD in the Indian context. So we also studied the relationship between number of metabolic risk factors and degree of hepatic steatosis (according to CAP value) and rise of liver enzyme (ALT).

## MATERIALS AND METHODS

This single centre, cross sectional study was conducted on patients belonging to North eastern states of India and attending Guwahati Medical College and Hospital on OPD basis from August 2021 to March 2022. We included all the patients diagnosed with fatty liver disease on abdominal imaging (mostly Ultrasound abdomen).

### Exclusion Criteria Included

1. History of significant alcohol intake defined as ongoing alcohol consumption of > 21 standard drinks on average per week in men and > 14 standard drinks on average per week in women<sup>[11]</sup>
2. Recent use of medications implicated in causing fatty liver,

3. Diagnosed patients of Wilsons disease, Hepatitis C,
4. Patients diagnosed with inborn error of metabolism known to cause fatty liver,
5. Patients unwilling to undergo Fibroscan (for CAP measurement)
6. Patients who did not give consent for participation in the study.

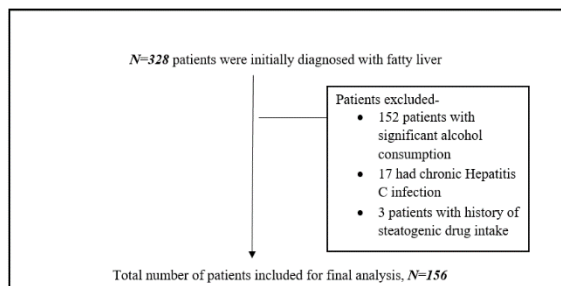
All patients included in the study underwent waist circumference, height and weight measurement. Body mass index (BMI) was calculated for all patients. 131 patients underwent Fibroscan for determination of CAP value. All patients underwent routine blood examinations to determine liver function (particularly serum ALT), lipid profile (particularly serum triglyceride and HDL), glycated hemoglobin (HbA1C), fasting and post prandial blood sugar.

The quantitative determination of liver fat was performed by a skilled operator using FibroScan (502 model, M probe; Echosens, France). Each subject was required to be successfully tested for ≥10 times, and the median of all effective measurements was defined as the final result. An effective measurement should meet the following requirements: the ratio of the interquartile range (IQR) to the median (IQR/med) of all measurements was <30% and the success rate (successful detection number/total test number) was ≥60%. Patients were also assigned a steatosis grade (S0–S3) (based on CAP scores in decibels per meter, which is a calculation of the attenuation of ultrasonic signals used for transient elastography) as described elsewhere by Sasso et al.<sup>[12]</sup> The grades are assigned as follows: S0, no steatosis (0%–10% fat; 0–237 dB/m); S1, mild steatosis (11%–33% fat; 238–259 dB/m); S2, moderate steatosis (34%–66% fat; 260–292 dB/m); and S3, severe steatosis (>67% fat; ≥293 dB/m).

For the present study upper limit of normal for serum ALT is taken as 50 U/L in accordance with the laboratory value used in our institute. Type 2 Diabetes mellitus was diagnosed if patient had fasting plasma glucose ≥ 126 mg/dL or post prandial blood glucose ≥ 200 mg/dL or Glycated hemoglobin(A1C) ≥ 6.5%.<sup>[13]</sup> Dyslipidemia was diagnosed with serum HDL (high density lipoprotein) cholesterol < 40 mg/dL for male and < 50 mg/dL for female, or serum triglyceride ≥ 150 mg/dL.<sup>[14]</sup> Increased waist circumference was defined as ≥ 90 cm for male and ≥ 80 cm for female.<sup>[14]</sup> Patients with BMI ≥ 23kg/m<sup>2</sup> were considered overweight/obese.<sup>[15]</sup> Lean NAFLD was defined as BMI < 23 kg/m<sup>2</sup> and evidence of hepatic steatosis on imaging.<sup>[5]</sup> For our analysis we included 3 metabolic risk factors - Oberweight/obesity, Type 2 DM and Dyslipidemia. Patients having all the 3 risk factors were compared with patients having ≤ 2 risk factors for the presence of severe hepatic steatosis (CAP ≥ 293 dB/m) and raised ALT(≥ 50 U/L).

Overall during the study period 328 patients were diagnosed with fatty liver on the basis of imaging. Among them 152 patients had significant

consumption of alcohol, 17 had Hepatitis C infection, 3 had history of intake of steatogenic drugs and hence were excluded from the study. So, 156 patients diagnosed with NAFLD were included for final analysis [Figure 1]. Among them 25 patients did not undergo Fibroscan. Hence for CAP analysis 131 patients were included.



**Figure 1: Flow diagram for patient inclusion and exclusion**

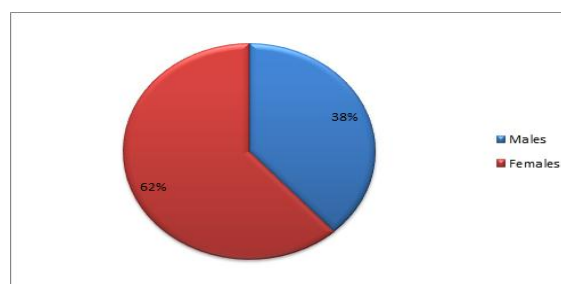
**Ethics:** The study procedures adhered to the guidelines of the Declaration of Helsinki.

**Statistics:** Data was entered into Microsoft excel and analysed using Statistical Package for Social Sciences (SPSS) version 26.0. Normality of the data was checked using Shapiro-Wilk test. Categorical variables were described using frequency, percentages along with their means and SD.

Inferential statistics for comparative analysis using chi square test was done to look for association between metabolic risk factors with the levels of ALT and CAP. The level of statistical significance was set at 0.05.

## RESULTS

The baseline characteristics have been depicted in [Table 1]. The present study comprised of 62% females and 38% males; the mean age of the participants was 38.58±9.45 [Figure 2 & Table 1]. Among the participants, 124 (79%) were overweight/obese, 68(43.5%) had Type 2 DM, 102(65.4%) of them had dyslipidemia and 116(74.3%) had a increased waist circumference [Table 2].



**Figure 2: Gender distribution**

**Table 1: Baseline characteristics.**

Parameter	Number of patients	Mean±SD
Age (years)	156	38.58±9.45
ALT ≥ 50 U/L	76	90.76±25.43
ALT<50 U/L	80	40.58±5.30
TG (mg/dL)	156	193.51±68.38
HDL (mg/dL)	156	44.51±9.50
HbA1c (%)	156	6.64±1.20
Waist circumference(cm) (Male)	60	96.73±8.10
Waist circumference(cm) (Female)	96	89.95±10.15

**Table 2: Distribution of metabolic risk factors among NAFLD patients**

Factor	Number of patients (%)
BMI ≥ 23 kg/m <sup>2</sup>	124(79%)
Type 2 DM	68(43.5%)
Dyslipidemia (TG ≥ 150 mg/dL, HDL< 40 mg/dL for male and HDL < 50 mg/dL for female)	102(65.4%)
Waist circumference (≥90 cm for males, ≥80 cm for females)	116(74.3%)

For BMI, it was observed that 20.5% of the participants had BMI < 23 kg/m<sup>2</sup> (Normal/underweight) 12.8% were overweight and 66.6% of them were obese [Table 3].

**Table 3: Distribution of patients according to BMI**

BMI (kg/m <sup>2</sup> )	Number of patients (%)	Mean±SD
<23	32(20.5%)	22.18±0.50
23-24.9	20(12.8%)	24.16±0.52
≥25	104(66.6%)	28.83±2.33

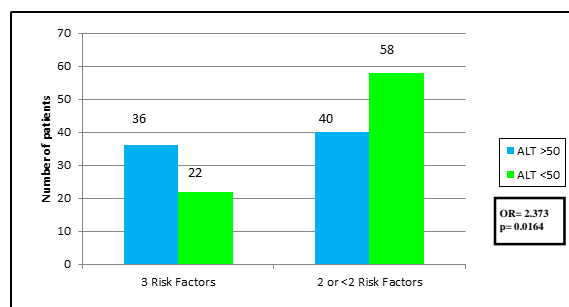
Among NAFLD patients, 80 (51.3%) had normal ALT levels (<50 U/L) as compared to 76 patients (48.7%) with raised ALT ≥ 50 U/L). For analysis we included 3 of the above-mentioned risk factors (Type 2 DM, overweight/obesity & dyslipidemia). Among the patients, 58 (37%) of them had all the above-mentioned risk factors as compared to 98(63%) patients who had ≤ 2 risk factors.

The distribution of participants according to the number of risk factors and CAP values; 13(9.92%) of them had no risk factors with CAP ranging in between 240-300dB/m, 32(24.42%) of them had one risk factor with the CAP value in the range of 244-322dB/m, 44(33.58%) had the presence of two risk factors and CAP of 258-330dB/m and 42(32.06%) exhibited all three risk factors with CAP in the range of 252-364dB/m [Table 4].

**Table 4: Distribution of CAP values with number of metabolic risk factors**

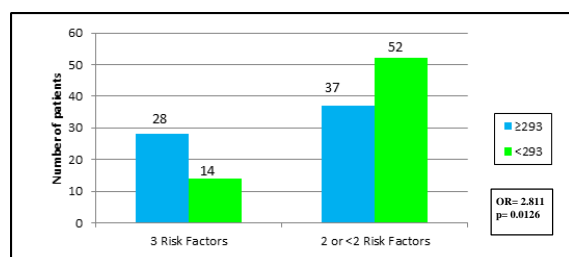
Number of risk factors	Number of patients (%)	Range of CAP(dB/m)	Mean±SD
0	13(9.92%)	240-300	265.69±19.59
1	32(24.42%)	244-322	273.78±21.13
2	44(33.58%)	258-330	292.52±18.76
3	42(32.06%)	252-364	308.52±29.25

As shown in [Figure 3], 62% (36/58) patients with three metabolic risk factors and 41% (40/98) of them with  $\leq 2$  risk factors had elevated levels of ALT ( $\geq 50$  U/L) indicating a positive association between presence of 3 metabolic risk factors (BMI  $\geq 23$  kg/m<sup>2</sup>, Type 2 DM, Dyslipidemia) and raised ALT [OR= 2.373, p=0.0164].



**Figure 3: Association of number of metabolic risk factors with increased levels of ALT ( $\geq 50$  U/L) (Risk factors analysed- BMI  $\geq 23$  kg/m<sup>2</sup>, Type 2 DM, Dyslipidemia)**

Similarly, 66.66% (28/42) patients with three metabolic risk factors and 42% (37/89) of them with  $\leq 2$  risk factors had severe steatosis (CAP  $\geq 293$  dB/m) indicating a positive association of between presence of 3 metabolic risk factors (BMI  $\geq 23$  kg/m<sup>2</sup>, Type 2 DM, Dyslipidemia) and presence of severe hepatic steatosis (CAP  $\geq 293$ dB/m) [OR 2.811, p=0.0126] [Figure 4].



**Figure 4: Association of number of metabolic risk factors with presence of severe hepatic steatosis (CAP  $\geq 293$  dB/m) (Risk factors analysed- BMI  $\geq 23$  kg/m<sup>2</sup>, Type 2 DM, Dyslipidemia)**

## DISCUSSION

This cross-sectional study aimed to determine the prevalence of various metabolic risk factors among patients of NAFLD. It further intended to assess the prevalence of NAFLD with normal liver enzyme (ALT) and the participants with lean NAFLD. It also studied the relationship between number of metabolic risk factors and degree of hepatic steatosis (according to CAP value) and rise of liver enzyme (ALT).

Among the study participants, 79% were obese/overweight, 43.5% had Type 2 DM, 65.4% of them had dyslipidemia and 74.3% had increased waist circumference. These results are in accordance with previous studies which shows frequent association of metabolic risk factors with NAFLD.<sup>[16-19]</sup>

The prevalence of lean/non obese nonalcoholic fatty liver disease (NAFLD) ranges widely in studies. The present study showed a greater prevalence of lean NAFLD (20.5%) which is similar to studies done in the eastern India by Singh et al,<sup>[20]</sup> (16.3%) and western India by Chalmers et al,<sup>[21]</sup> (16%). In contrast to this, Yiwen et al,<sup>[22]</sup> conducted a study which analysed 45 studies across the world comprising of 7351 NAFLD patients in which prevalence of lean NAFLD was found to be 10.2%. An ongoing multicentric study by Duseja et al,<sup>[23]</sup> on 3553 participants in India showed the prevalence of lean NAFLD to be 10.6%.

As suggested earlier, many of the NAFLD patients presents with raised ALT levels. In the present study 51.3 % of patients had normal ALT which is similar to a study conducted in eastern India by Sanyal et al (57%).<sup>[24]</sup> A meta-analysis of studies comprising 4084 patients across the world suggested that 25% of the patients had normal ALT.<sup>[25]</sup> These differences might have aroused due to lack of a uniform cut off to describe upper limit of normal for ALT level across studies.

In the present study, patients who had all the metabolic risk factors (BMI  $\geq 23$  kg/m<sup>2</sup>, dyslipidemia and T2DM) had significantly higher chances of an elevated ALT level ( $\geq 50$ U/L) indicating a positive association (OR- 2.373; p= 0.0164). Similar findings were observed in a study undertaken by Chen et al,<sup>[26]</sup> where among NAFLD patients ALT levels were significantly higher in subjects with metabolic syndrome (MetS) as compared to those without MetS. The Aus Diab study conducted by Farrell et al,<sup>[27]</sup> also suggested that among metabolic associated fatty liver disease (MAFLD) patients having higher ALT levels also had higher median BMI, more T2DM and a large proportion met the criteria of MetS. So the results of these studies signify that greater transaminitis might be associated with more metabolic risk factors which can lead to greater liver damage.

It was observed that patients with NAFLD and the presence of all three metabolic risk factors (Type 2 DM, Obesity & dyslipidemia) had significant association with presence of severe steatosis (CAP  $\geq 293$  dB/m) (OR- 2.811 ; p=0.0126). Likewise, Hu et al,<sup>[9]</sup> in their study found a positive correlation of increasing CAP with the prevalence of MetS and its



components and concluded that CAP may be an indicator of risk of MetS and the severity of metabolic disorders in middle-aged and elderly NAFLD patients. Similarly Nuria et al,<sup>[10]</sup> deduced that subjects with metabolic risk factors had higher CAP value as compared to controls. In view of these studies it can be assumed that increased CAP may be associated with increased presence of metabolic components in NAFLD patients.

The present study had certain limitations. Firstly, it was a single center cross-sectional study with a small sample size of 156 patients. Secondly, follow-ups were not conducted to observe the association of changes in CAP and ALT values with metabolic risk factors. A large-scale multicentric study with follows ups of an adequate number of middle-aged and elderly NAFLD patients is needed for generalizability of the results to the entire population.

## CONCLUSION

Our findings suggests that among NAFLD patients, presence of more number of metabolic risk factors might lead to greater extent of transaminitis and presence of severe hepatic steatosis thus leading to liver damage.

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