Original Article JCMCTA 2022 ; 33 (1) : 56-65

# Risk Factor Evaluation of Non Alcoholic Fatty Liver Disease in Lean Individual

Mostafa Noor Mohsin[1*] Salahuddin Mohammed Ali Haider[1]
Farhana Akter[2] Ershad Uddin Ahmed [3] Binoy Paul[4]

## Abstract

**Background :** Non-Alcoholic Fatty Liver Disease (NAFLD) is epidemic around the world. Bangladesh is also experiencing an increasing trend of NAFLD.Obesity is a common clinical phenotype associated with NAFLD, which is linked to metabolic syndrome and related comorbidities, including type II diabetes, hypertension and dyslipidemia. Clearly, not all obese subjects develop NAFLD and NAFLD also can be found in non-obese patients. This subset of individuals, known to have 'lean NAFLD' or 'non-obese NAFLD', is growing increasingly prevalent. NAFLD in lean patients appears to be more common among Asians. So it is important to look for risk factors for NAFLD in lean patients for prevention of advanced liver disease. The objective of our study was to find out the risk factors of NAFLD in lean (Nonobese) individual.

**Materials and methods:** It was prospective observational study done on 100 patients attending in the Gastroenterology Department and OPD of Chittagong Medical College Hospital after approval of Ethical and Review Committee of CMC and grant from DGHS. Total 100 patients having 18 to 65 years of age, were taken as study subjects who met inclusion criteria. Informed written consent was obtained from the patients or attendant after full explanation of the purpose of the study. Fasting Blood Glucose (FBS) Fasting lipid profile, SGPT, SGOT, Ultrasonography of hepatobiliary system and Fibrosan were done . All necessary data was included in the data collection sheet and was analyzed by Microsoft excel and SPSS-23.

**Results:** 100 patients were included in this study. Mean age of this study with age was in between 18 years to 65 years.Male to female ratio was 3:1 in the studied population.The majority of the lean patient with NAFLD (31%) was in the age group 40-49 years. The majority of the lean patient with NAFLD (83%) was in normal BMI range 18.5-22.99 kg/m$^2$ and 13% had BMI <18.50 kg/m$^2$. Out of 100patients diabetes and hypertension were found 22% and 17% of patients respectively. 22% and 17% patients. 65% and 37% patients had raised SGPT and SGOT respectively. Out of 100 subjects, 50% had raised triglyceride level (50%) and 18% had raised LDL cholesterol (18%) level.According to Ultrasonography findings 68% were in Grade I, 11% in Grade II and only 1 patient was in Grade III fatty liver. Fibroscan of 100 subjects, Significant fibrosis (≥2 F) was observed in 9%, while advanced fibrosis (F4) was seen in 4% of patients. As per steatosis score 36% was in S2 and 34% were in S3 grade. Median fibrosis score and steatosis score was significantly higher in patients with high SGPT compared to patients with normal SGPT (p <0.005) whereas median fibrosis score and steatosis score was higher in patients with high SGOT compared to patients with normal SGOT, but only the difference in steatosis score reached statistical significance (p<.042). AUC of SGPT for discriminating fibrosis grade F0-F1 from Grade F2-F4 was 0.565 (95% CI: 0.404-0.726, p=0.519). AUC of SGOT for discriminating fibrosis grade F0-F1 from Grade F2-F4 was 0.573 (95% CI: 0.342-0.803, p=0.474). This indicated that there was no significant role of SGPT or SGOT values for prediction of significant fibrosis (≥2F).AUC of SGPT for discriminating steatosis grade S0-S2 from Grade S3-S4 was 0.565 (95% CI: 0.404-0.726; p=0.519). AUC of SGOT for discriminating steatosis grade S0-S2 from Grade S3-S4 was 0.573 (95% CI: 0.342-0.803, p=0.474). This indicated that both SGPT and SGOT had significant role for prediction of significant steatosis (≥3S).Higher age (p <0.028) and female sex (p<0.013) were revealed as independent predictive factors for significant fibrosis (≥F2) in non-obese NAFLD patients on performing multivariate binary logistic regression.

**Conclusion**

Lean NAFLD is now frequently recognized in day-to-day clinical practice, however, the data on epidemiology, risk factors, physiopathology, distinctive histologic changes, natural history and treatment of this entity are still scanty. From a biological point of view, lean NAFLD be haves much like obese NAFLD. Our study may help to find out risk factors in nonobese NAFLD which may help prevention of advance liver disease by early intervention.

**Key words:** AUC; Fibroscan; NAFLD; SGPT; SGOT; Ultrasonography.

1. Assistant Professor of Gastroenterology Chittagong Medical College, Chattogram.
2. Associate Professor of Endocrinology Chittagong Medical College, Chattogram.
3. Professor of Gastroenterology Chittagong Medical College, Chattogram.
4. Associate Professor of Gastroenterology Chittagong Medical College, Chattogram.

***Correspondence:** **Dr. Mostafa Noor Mohsin**
*Cell : 01819 38 21 62*
*E-mail: mostafamohsin14@gmail.com*

*Submitted on : 07.05.2022*
*Accepted on : 20.06.2022*

## Introduction

Non Alcoholic Fatty Liver Disease (NAFLD) is rapidly becoming the most common cause of chronic liver disease in Western Countries, and a similar trend is expected in Eastern Countries in the next years. Non-Alcoholic Fatty Liver Disease (NAFLD) includes a spectrum of disorders ranging from the simple fatty liver to non-alcoholic steatohepatitis, with increasing fibrosis leading to cirrhosis.[1] The prevalence of NAFLD is alarmingly growing worldwide in adult and children/adolescent populations, with a bidirectional association between NAFLD and metabolic syndrome.[2] Obesity, insulin resistance, type 2 diabetes mellitus, and dyslipidemia are the most relevant metabolic conditions related to this spectrum of diseases.[1,2]

Obesity is a common clinical phenotype associated with NAFLD, which is linked to metabolic syndrome and related comorbidities, including type II diabetes, hypertension, and dyslipidemia. Clearly, not all obese subjects develop NAFLD and NAFLD also can be found in non-obese patients.[3,4] NAFLD may represent a group of conditions in which several pathogenetic processes may be in play that may be disparate between obese and non- obese patients, despite similar clinical and histopathologic presentation.

Globally, the reported prevalence of nonobese NAFLD varies widely, ranging from 3% to 30%. The variability may be attributed to differences in study subject selection, diagnostic modalities, and lifestyle and dietary customs of the specific population. The prevalence data on nonobese NAFLD between the East and West are not directly comparable at least in part because of the different Body Mass Index (BMI) cut-off values for Asians. The recommended BMI cut-off value for Asians for being overweight is 23 to 25 kg/m$^2$ and for obesity is greater than 25 kg/m$^2$, in contrast to 25 to 30 kg/m$^2$ and greater than 30 kg/m$^2$, respectively, for subjects of other races[5].

Overall, the global trends of NAFLD prevalence in lean individuals track the march of the obesity pandemic globally.[6] Evenwithin the normal Body Mass Index (BMI) range, there is an ongoing increase of obesity worldwide, which is linked to expanded, dysfunctional, inflamed adipose tissue.[7] In cross-sectional studies, 7–20% of individuals with NAFLD have a lean habitus. Initially described in Asian populations and considered as a “third world phenotype”, this subset of NAFLD has since been described in other populations, including in Europe and the USA.[8,9] In Asia, the prevalence of NAFLD has been reported to vary from 12.6% of unselected patients to 27% of lean individuals.[10,11,12]

Questions of obvious practical importance may include the following: i) what is the clinical significance of nonobese NAFLD as a liver disease ii) if nonobese NAFLD is a clinically significant condition, what are indicators to identify patients at risk.

## Materials and methods

It was prospective observational study done on 100 patients attending in the Gastroenterology Department and OPD of Chittagong Medical College Hospital after approval of Ethical and Review Committee of CMC and grant from DGHS during the period of February 2021 to June 2021. Total 100 patients having 18 to 65 years of age, were taken as study subjects who met inclusion and exclusion criteria. Inclusion Criteria was age 18 to 65 years, BMI ≤23 and Ultrasound of hepatobiliary system showed fatty liver whereas exclusion criteria was Ultrasound of hepatobiliary system suggestive of chronic liver disease, BMI ≥23, Liver disease due to other causes and patient with severe co-morbid condition. Informed written consent was obtained from the patients or attendant after full explanation of the purpose of the study. All patients were interviewed by case record form and undergone through physical examination. Fasting Blood Glucose (FBS) Fasting lipid profile, SGPT, SGOT, Ultrasonography of hepatobiliary system and Fibrosan were done in all patients . All necessary data was included in the data collection sheet and was analyzed by Microsoft excel and SPSS-23.

## Results

**Table I** Demographic characteristics of the NAFLD patients with lean body mass (n=100)

| Variables | | Percentage (%) |
|---|---|---|
| Age, years | 20-29 years | 20 |
| | 30-39 years | 24 |
| | 40-49 years | 31 |
| | 50-59 years | 12 |
| | ≥60 years | 13 |
| Sex | Male | 75 |
| | Female | 25 |

Data were expressed as percentage only, as the frequency and percentages were same.
Age ranged from 20 and 75 years in the study with a mean (±SD) age of 41.61 (±12.05) years. The majority of the lean patient with NAFLD (31%) was in the age group 40-49 years, followed by the age group 30-39 years (24%) and 20-29 years (20%). There was male predominance (75%) with a male to female ratio of 3:1 in the studied population (Table I).

**Table II** BMI, diabetes and hypertension status of the NAFLD patients with lean body mass

| Variables | Total (n=100)* | Male (n=75) | Female (n=25) | p value |
|---|---|---|---|---|
| **Body mass index, kg/m$^2$** | | | | |
| 18.50-22.99 | 83 | 64 (85.3) | 19 (76.0) | 0.282 |
| <18.50 | 17 | 11 (14.7) | 6 (24.0) | |
| **Diabetes mellitus** | | | | |
| Present | 22 | 56 (73.3) | 21 (84.0) | |
| Absent | 76 | 19 (25.3) | 3 (12.0) | 0.292 |
| IGT | 2 | 1 (1.3) | 1 (4.0) | |
| **Hypertension** | | | | |
| Present | 17 | 61 (81.3) | 22 (88.0) | 0.442 |
| Absent | 83 | 14 (18.7) | 3 (12.0) | |

*Data were expressed as percentage only, as the frequency and percentages were same. IGT: Impaired Glucose Tolerance test.

BMI ranged from 13.12 and 22.96 kg/m$^2$ in the study with a mean (±SD) BMI of 20.45 (±1.86) kg/m$^2$. The majority of the lean patient with NAFLD (83%) was in normal BMI range 18.5-22.99 kg/m$^2$ and 13% had BMI <18.50 kg/m$^2$. Proportion of patients having diabetes and hypertension was 22% and 17% respectively (Table II).

**Table III** Distribution of biochemical parameters in the NAFLD patients with lean body mass (n=100)

| Biochemical parameters | Total (n=100)* | Male (n=75) | Female (n=25) | p value |
|---|---|---|---|---|
| **SGPT** | | | | |
| Normal | 35 | 18 (24.0) | 17 (88.0) | <0.001 |
| High | 65 | 57 (76.0) | 8 (32.0) | |
| **SGOT** | | | | |
| Normal | 63 | 43 (57.3) | 20 (80.0) | 0.042 |
| High | 37 | 32 (42.7) | 5 (20.0) | |
| **Total cholesterol** | | | | |
| Normal | 56 | 42 (56.0) | 14 (56.0) | 1.0 |
| High | 44 | 33 (44.0) | 11 (44.0) | |
| **HDL cholesterol** | | | | |
| Normal | 59 | 42 (56.0) | 17 (68.0) | 0.291 |
| Low | 41 | 33 (44.0) | 8 (32.0) | |
| **LDL cholesterol** | | | | |
| Normal | 82 | 61 (81.3) | 21 (84.0) | 0.764 |
| High | 18 | 14 (18.7) | 4 (16.0) | |
| **Triglyceride** | | | | |
| Normal | 50 | 35 (46.7) | 15 (60.0) | 0.248 |
| High | 50 | 40 (53.3) | 10 (40.0) | |

Data were expressed as percentage only, as the frequency and percentages were same.
The most common biochemical abnormality in the studied patient was high SGPT (65%), followed by high triglyceride level (50%), high total cholesterol (44%), low HDL cholesterol (41%) high SGOT (37%) and high LDL cholesterol (18%) (Table III).

**Table IV** Severity of NAFLD in the NAFLD patients with lean body mass (n=100)

| Severity parameters | Total (n=100)* | Male (n=75) | Female (n=25) | p value |
|---|---|---|---|---|
| **USG** | | | | |
| Fatty liver | 20 | 16 (21.3) | 4 (16.0) | |
| Grade I | 68 | 51 (68.0) | 17 (68.0) | 0.348 |
| Grade II | 11 | 8 (10.7) | 3 (12.0) | |
| Grade III | 1 | 0 (0) | 1 (4.0) | |
| **Fibrosis score** | | | | |
| F0-F1(1-7.4) | 91 | 72 (96.0) | 19 (76.0) | |
| F2-2.4-9.5 | 5 | 2 (2.7) | 3 (12.0) | 0.009 |
| F4 -12.5-75 | 4 | 1 (1.3) | 3 (12.0) | |
| **Steatosis score** | | | | |
| S0 | 15 | 12 (16.0) | 3 (12.0) | |
| S1 | 15 | 11 (14.7) | 4 (16.0) | 0.868 |
| S2 | 36 | 28 (37.3) | 8 (32.0) | |
| S3 | 34 | 24 (32.0) | 10 (40.0) | |

According to US findings 68% were in Grade I, 11% in Grade II and only 1 patient was in Grade III. Significant fibrosis (≥2 F) was observed in 9%, while advanced fibrosis (F4) was seen in 4% of patients. As per steatosis score 36% was in S2 and 34% were in S3 grade (Table IV).

**Table V** Comparison of fibroscan (Fibrosis and steatosis) score between NAFLD patients normal and high ALT

| Fibroscan parameters SGPT (n=35) | Patients with normal SGPT(n=65) | Patients with high | p value† |
|---|---|---|---|
| **Fibrosis score** | | | |
| Median (IQR) | 4.1 (3.7-5.6) | 5.1 (4.4-6.3) | 0.016 |
| **Steatosis score** | | | |
| Median (IQR) | 265.0 (240.0-293.0) | 297.0 (268.5-325.5) | 0.005 |

†p value obtained from Mann Whitney U test.

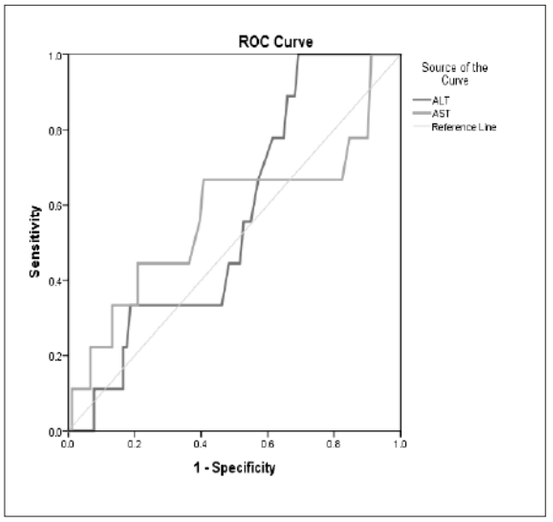
Median fibrosis score and steatosis score was significantly higher in patients with high SGPT compared to patients with normal SGPT (Table V).

**Table VI** Comparison of fibroscan (Fibrosis and steatosis) score between NAFLD patients normal and high AST

| Variables | Patients with normal SGOT (n=63) | Patients with high SGOT (n=37) | p value† |
|---|---|---|---|
| **Fibrosis score** | | | |
| Median (IQR) | 4.8 (4.0-5.8) | 5.3 (4.1-6.5) | 0.172 |
| **Steatosis score** | | | |
| Median (IQR) | 273.0 (241.0-310.0) | 297.0 (276.0-319.0) | 0.042 |

†p value obtained from Mann Whitney U test.

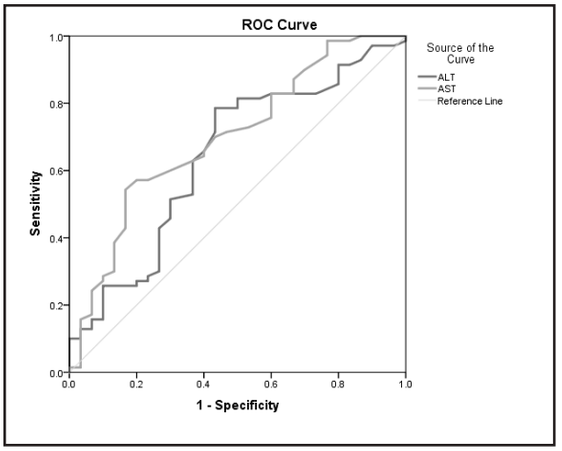
Median fibrosis score and steatosis score was higher in patients with high SGOT compared to patients with normal SGOT, but only the difference in steatosis score reached statistical significance (Table VI).




| Variables | Area under curve (95% CI for AUC) | p value |
|---|---|---|
| SGPT (ALT) | 0.565 (0.404-0.726) | 0.519 |
| SGOT (AST) | 0.573 (0.342-0.803) | 0.474 |

**Figure 1** ROC curve for SGPT and SGOT to discriminate fibrosis grade F0-F1 from Grade F2-F4

Figure 1 shows that, AUC of SGPT for discriminating fibrosis grade F0-F1 from Grade F2-F4 was 0.565 (95% CI: 0.404-0.726, p=0.519). AUC of SGOT for discriminating fibrosis grade F0-F1 from Grade F2-F4 was 0.573 (95% CI: 0.342-0.803; p=0.474). This indicated that there was no significant role of SGPT or SGOT values for prediction of significant fibrosis (≥2F).




| Variables | Area under curve (95% CI for AUC) | p value |
|---|---|---|
| SGPT (ALT) | 0.642 (0.521-0.764) | 0.025 |
| SGOT (AST) | 0.699 (0.587-0.811) | 0.002 |

**Figure 2** ROC curve for ALT and AST to discriminate steatosis grade S0-S2 from Grade S3-S4

Figure 2 shows that, AUC of SGPT for discriminating stetosis grade S0-S2 from Grade S3-S4 was 0.565 (95% CI: 0.404-0.726, p=0.519). AUC of SGOT for discriminating stetosis grade S0-S2 from Grade S3-S4 was 0.573 (95% CI: 0.342-0.803, p=0.474). This indicated that both SGPT and SGOT had significant role for prediction of significant steatosis (≥3S).

**Table VII** Multivariate logistic regression analysis for factors associated with significant fibrosis ≥F2 in non-obese NAFLD patients.

| Variables | B | Odds ratio | 95% CI for OR | | p value |
|---|---|---|---|---|---|
| | | | Lower | Upper | |
| Age, years | 0.101 | 1.106 | 1.011 | 1.210 | 0.028 |
| Sex (Female) | 2.349 | 10.479 | 1.651 | 66.502 | 0.013 |
| Diabetes mellitus | -0.319 | 0.727 | 0.083 | 6.330 | 0.773 |
| Hypertension | 0.258 | 1.294 | 0.158 | 10.593 | 0.810 |
| BMI, kg/m$^2$ | 0.017 | 1.017 | .987 | 1.048 | 0.265 |
| SGPT, IU/L | 0.022 | 1.022 | 0.985 | 1.061 | 0.251 |
| SGOT, IU/L | -0.002 | 0.998 | 0.969 | 1.027 | 0.883 |
| Total cholesterol, mg/dl | 0.040 | 1.041 | 0.961 | 1.128 | 0.327 |
| HDL cholesterol, mg/dl | 0.000 | 1.000 | 0.962 | 1.039 | 0.998 |
| LDL cholesterol, mg/dl | 0.000 | 1.000 | 0.989 | 1.012 | 0.959 |

OR: Odds Ratio, CI: Confidence Interval.

Higher age and female sex were revealed as independent predictive factors for significant fibrosis in non-obese NAFLD patients on performing multivariate binary logistic regression (Table VII).

**Discussion**

NAFLD in lean persons is now a widely recognized problem. Initially, described in Asian populations and considered as a "third world phenotype," this subset of NAFLD has since been described in other populations, including in Europe and the United States.[13,14] Therefore, risk factors associated with lean NAFLD are being studied worldwide.

Although age is non modifiable, in our study, the majority of the lean patient with NAFLD (31%) was in the age group 40-49 years, followed by the age group 30-39 years (24%) and 20-29 years (20%). There was male predominance (75%) with a male to female ratio of 3:1 (Table I).

This phenomenon may be explained by the protective effect of female sex hormones on the progression of hepatic fibrosis. The center at KAUH previously published research findings as well as national and international data on NAFLD that have shown that males are more commonly affected than females which was similar to our study.[15] Vos et al. reported that compared with obese NAFLD patients, lean NAFLD patients were younger, mostly male. Kumar R et al reported that A slight male preponderance has been found in the majority of studies on lean NAFLD, with the age ranging between 19 years and 56 years.[16]

The definition of normal weight using BMI varies depending on the racial background of the individual. Caucasians are considered as having normal weight when BMI is 18.5-25 kg/m2 with overweight being 25-30 kg/m2 and obese being > 30 kg/m$^2$. [17,18] However, lower BMI cutoffs are applied to Asians because a specific BMI reflects a higher percentage of body fat and higher health risk compared to Caucasians.[19] Accordingly, in Asians, normal weight is considered when BMI is < 23 kg/m$^2$, with overweight being 23-25 kg/m$^2$ and obese being > 25 kg/m$^2$.[17,18]

The prevalence of NAFLD is around 4 times lower in the lean population compared to the overweight/obese population.[20,21-26] Asians seem to have a higher prevalence of lean-NAFLD, and African Americans lower, which might be explained, at least to some extent, with different compartmentalization of fat depots and intrinsic differences in adipose tissue structure/function in individuals with different racial backgrounds.[27-29].

In our study, we included study population with BMI ≤23 kg/m$^2$. We found that BMI ranged from 13.12 and 22.96 kg/m$^2$ with a mean (±SD) BMI of 20.45 (±1.86) kg/m2. The majority of the lean patient with NAFLD (83%) was in normal BMI range 18.5-22.99 kg/m2 and 13% had BMI <18.50 kg/m2. Proportion of patients having diabetes and hypertension was 22% and 17% respectively (Table II).

Regarding metabolic outcomes in NAFLD obese and NAFLD non-obese/lean patients, in a retrospective study of 669 NAFLD patients in Italy, lean (BMI < 25 kg/m2) NAFLD patients had lower prevalence of hypertension, T2DM and metabolic syndrome than overweight (25 kg/m2 ≤BMI < 30 kg/m2) and obese (BMI≥30 kg/m2) NAFLD patients.[30] In the Indian population, Kumar et al reported that among NAFLD patients, lean (BMI < 23 kg/m2) patients had had lower prevalence of T2DM and metabolic syndrome than obese (BMI > 25 kg/m2) patients.[31] In a case control study from Sri Lanka, Niriellaet al reported a higher prevalence of hypertension in non-lean (BMI > 23 kg/m2) patients with NAFLD compared with lean NAFLD patients[32]. In studies performed in Japan, Yoshitaka et al reported lower blood pressure and fasting plasma glucose in lean (BMI < 23 kg/m2) than in overweight NAFLD patients.[33]

In our study we found that out of 100 lean NAFLD subjects, only 22 patients, 2 patients and 17 patients had diabetes mellitus, impaired glucose and hypertension respectively. Majority of our lean NAFLD subjects were non diabetic (76 subjects) and non hypertensive (83 subjects). These findings were similar to above study (Table II).

Several studies have revealed a frequent occurrence of dyslipidaemia in lean NAFLD patients.[34,35,36,37] The liver plays an important role in lipid metabolism and may be involved in the development of dyslipidaemia in NAFLD.[37] Impaired hepatic lipid handling may occur in patients with NAFLD, causing faulty lipid homeostasis and initiation of dyslipidaemia. Individuals with dyslipidaemia without obesity are termed as normal weight dyslipidaemia. The estimates of prevalence of normal weight dyslipidaemia in the general population range from 10% to 37%.[38] A study by Kim et al

demonstrated that triglyceride levels were significantly associated with both the development and regression of NAFLD among non-obese Koreans.[39] In particular, hypertriglyceridemia associates with a 2-fold increased risk for hepatic steatosis in lean.[40,41,42]

Several studies also found that lean and overweight/obese-NAFLD share a common lipid profile, with higher levels of triglycerides, total cholesterol and Low-Density Lipoprotein (LDL) cholesterol compared with both lean and overweight/obese controls.[43]

In our study, we found that 50% of our subjects had high triglyceride level and 44% had high total cholesterol level whereas 18% had high LDL level and 41% had low HDL level. This finding may be potentially linked to a disturbance of cholesterol metabolism and a higher dietary cholesterol carbohydrate consumption in this population. Our findings were also found similar to above studies (Table-III).

It is important to highlight that gene-environment interactions (e.g. diet, physical activity, metabolic comorbidities, or gut microbiota) seem to be crucial to modulate gene polymorphism-mediated liver damage in lean/non-obese NAFLD. On a predisposed genetic background, environmental factors could trigger the disease and related complications. Intriguingly, a recent cohort study of 1339 biopsy-proven NAFLD Caucasian patients (195 lean, BMI < 25 kg/m2) showed that NAFLD development and progression in lean individuals were independent of their PNPLA3 genotype.[44]

In our study, most of our patients were non diabetic (76%), non hypertensive (83%) and almost 50% of study subjects had no dyslipidaemia. In light of these studies, further research is needed to assess the role of genetic determinants in NAFLD pathophysiology and the impact of their interplay with other risk factors in lean individual NAFLD.

An elevated ALT level is the primary laboratory abnormality in patients with NAFLD, but not all patients with NAFLD have elevated levels of ALT and the diagnostic sensitivity of serum SGPT for NASH is only about 40%.[27,45-47] 65 % patients of our study subject had raised SGPT. Together our current results and previous findings indicate that ALT is an important bio- marker that is suggestive of but not diagnostic of hepatic steatosis and fibrosis. Regarding SGOT, it is considered that values twice as high as normal are an indicator of severity of liver fibrosis.[48] 37% patients of our study subjects had raised SGOT. However, there is also a percentage of approximately 10% of patients with NASH with normal levels of SGOTand SGPT.[49]

35% and 63% of our study subject had normal SGPT and SGOT level respectively. This funding does not similar to previous study which might be due to heterogenecity of Asian population (Tablet –III).

Therefore, although FibroScan screening to evaluate liver stiffness and steatosis is a priority with elevated SGPT and SGOT levels, this imaging method should be considered even for with normal SGPT and SGOT concentrations with ultrasonography revealed fatty liver.

USG is noninvasive and is certainly the most common method for diagnosing NAFLD in clinical practice. It has very high sensitivity and specificity for detecting hepatic steatosis, which may vary from 60% to 94% and 88% to 95%, respectively.[50] Among the three grades of NAFLD with ultrasonography , the prevalence of Grade I (26.10%) was higher in Bangladesh. Although this condition is benign, there may be significant changes in liver, to NASH or cirrhosis, if Grade I progresses to further stages.[51,52] In our study, we found that 68% had grade-I fatty change in liver whereas only 1% patients had grade-III fatty change at ultrasonography, showing accordance with previous study (Table IV).

In our study, fibroscan was done using FIBROSCAN (Echosens,France) for the grading of fibrosis in patients which showed that 4% belonged to grade F4 followed by 5% patients in F2 grade whereas 91% patients belonged to F0-F1 grade fibrosis (Table IV)

We also found that the median (IQR) value of fibrosis as per fibroscan in 35 patients with normal SGPT and in 65 patients with raised SGPT were 4.1 (3.7-5.6) and 5.1 (4.4-6.3) respectively. These findings in our study was not statistically significant (p=0.016) (Table V).

We also found that the median (IQR) value of steatosis as per fibroscan in 35 patients with normal SGPT and in 65 patients with raised SGPT were 265 (240-293) and 297 (268.5-325.5) respectively. These findings in our study was statistically significant (p=0.005) (Table V).

We also found that the median (IQR) value of fibrosis as per fibroscan in 35 patients with normal SGOT and in 65 patients with raised SGOT were 4.8 (4-5.8) and 5.3 (4.1-6.5) respectively. These findings in our study was not statistically significant (p=0.172) (Table VI).

We also found that the median (IQR) value of steatosis as per fibroscan in 35 patients with normal SGOT and in 65 patients with raised SGOT were 273 (241-310) and 297 (276-319) respectively. These findings in our study was not statistically significant (p=0.042) (Table: VI).

Andrea Marie Macabuag-Oliva et al found that,the primary laboratory abnormalities in NAFLD are elevated serum AST and ALT levels, they are seldom higher than 3 or 4 times the upper limit of normal. Changes of aminotransferases do not parallel changes in fibrosis stage, showing accordance to our study.[53]

In our study, AUC (Area under curve) of SGPT for discriminating fibrosis grade F0-F1 from Grade F2-F4 was 0.565 (95% CI: 0.404-0.726, p=0.519). AUC of SGOT for discriminating fibrosis grade F0-F1 from Grade F2-F4 was 0.573 (95% CI: 0.342-0.803; p=0.474). This indicated that there was no significant role of SGPT or SGOT values for prediction of significant fibrosis (≥2F) (Fig I).

AUC of SGPT for discriminating stetosis grade S0-S2 from Grade S3-S4 was 0.565 (95% CI: 0.404-0.726, p=0.519). AUC of SGOT for discriminating stetosis grade S0-S2 from Grade S3-S4 was 0.573 (95% CI: 0.342-0.803, p=0.474). This indicated that both SGPT and SGOT had significant role for prediction of significant steatosis (≥3S) (Fig 2). These finding might be due to development of NASH which may lead to cirrhosis and normalization of SGPT with increase SGOT level.

Therefore, although FibroScan screening to evaluate liver stiffness and steatosis is a priority with elevated SGPT and SGOT levels, this imaging method should be considered even for with normal SGPT and SGOT concentrations with ultrasonography revealed fatty liver when liver biopsy is not feasible.

In our study also found that Increasing age (p=0.028) and female sex (p=0.013) were revealed as independent predictive factors for significant fibrosis in non-obese NAFLD patients on performing multivariate binary logistic regression (Table VII).

**Limitation**

The study had limitation in several aspects. We have identified NAFLD with Ultrasonoghraphic (USG) findings which was further evaluated by Fibroscan without liver biopsy. Liver biopsy is the gold standard for diagnosing NAFLD.USG may miss NAFLD detection if liver fat less than 30%. As we lacked genotypic data, we were unable to assess the impact of genetic variability on the association of lean NAFLD. NAFLD and BMI status change over time, but we did not reflect longitudinal changes in these characteristics over follow-up.Other limitations of this study are small sample size and single centre confined to gastroenterology department.

**Conclusion**

Individuals who are lean or nonobese may also develop NAFLD. This is particularly true in populations that are mostly lean, as seen in Asia. These individuals thus represent a subset where the disease manifests at lower overall BMI thresholds but where there is increased visceral adipose tissue. In addition, in specific regions and clinical situations, there are other unique aetiologies for NAFLD that must be considered which require specific treatments. This study may help to find out risk factors in non obese NAFLD which may help prevention of advance liver disease by early intervention.

**Recommendation**

Lean NAFLD is an increasing condition that worsens metabolic profile and increases all-cause mortality. Individuals with lean/nonobese NAFLD, despite not presenting with obesity, have increased visceral adiposity, and Sarcopenia. Since both characteristics act synergistically, worsening the prognosis, the assessment of body composition could help to identify high-risk subjects. As patients with lean NAFLD can suffer from the whole spectrum of liver disease, accurate work-up and identify risk factors are required for evaluating the true prevalence of NASH, advanced liver fibrosis, or compensated cirrhosis and planning for therapeutic strategy.

**Acknowledgements**

The authors gratefully acknowledge the contribution of all staffs working in Department of Gastroenterology, Chittagong Medical College Hospital and DGHS for valuable grant.

**Contribution of authors**

MNM-Conception, design, acquisition data, interpretation of data, and final approval.
SMAH-Design, data collection, drafting & final approval.
FA-Interpretation of data, critical revision & final approval.
EUA-Data analysis, critical revision & final approval.
BP-Data analysis, drafting & final approval.

**Disclosure**

All authors declared no conflict of interest.

**References**

**1.** De Minicis S, Day C, Svegliati-Baroni G. FromToNAFLD to NASH and HCC: Pathogenetic mechanisms and therapeutic insights. Curr Pharm Des. 2013;19:5239–5249.

**2.** Schwimmer JB, Deutsch R, Kahen T, Lavine JE, Stanley C, Behling C. Prevalence of fatty liver in children and adolescents. Pediatrics. 2006;118:1388–1393.

**3.** Machado M, Marques-Vidal P, Cortez-Pinto H. Hepatic histol- ogy in obese patients undergoing bariatric surgery. J Hepatol. 2006;45:600–606.

**4.** Das K, Das K, Mukherjee PS et al. Nonobese population in a developing country has a high prevalence of nonalcoholic fatty liver and significant liver disease. Hepatology. 2010; 51:1593–1602.

**5.** Alberti KG, Zimmet P, Shaw J, et al. The metabolic syndrome–a new worldwide definition. Lancet. 2005;366:1059–1062.

**6.** Riquelme A, Arrese M, Soza A, Morales A, Baudrand R, Perez-AyusoRM,et al. Non-alcoholic fatty liver disease and its association with obesity,insulin resistance and increased serum levels of C-reactive protein in His-panics. Liver Int. 2009;29:82–88.

**7.** Collaboration NCDRF. Trends in adult body-mass index in 200 countriesfrom 1975 to 2014: a pooled analysis of 1698 population-based measure-ment studies with 19.2 million participants. Lancet. 2016;387:1377–1396.

**8.** Younossi ZM, Koenig AB, Abdelatif D, Fazel Y, Henry L, Wymer M. Globalepidemiology of nonalcoholic fatty liver disease-Meta-analytic assess-mentofprevalence,incidence, and outcomes. Hepatology. 2016;64:73–84.

**9.** Vernon G, Baranova A, Younossi ZM. Systematic review: the epide-miology and natural history of non-alcoholic fatty liver disease andnon-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther. 2011;34:274–285.

**10.** Deurenberg-Yap M, Schmidt G, van Staveren WA, Deurenberg P. Theparadox of low body mass index and high body fat percentage among Chinese, Malays and Indians in Singapore. Int J Obes Relat Metab Disord. 2000;24:1011–1017.

**11.** Vos B, Moreno C, Nagy N, Fery F, Cnop M, Vereerstraeten P et al. Leannon-alcoholic fatty liver disease (Lean-NAFLD): A major cause of crypto-genic liver disease. Acta Gastroenterol Belg. 2011;74:389–394.

**12.** Xu C, Yu C, Ma H, Xu L, Miao M, Li Y. Prevalence and risk factors for thedevelopment of nonalcoholic fatty liver disease in a nonobese Chi-nese population: the Zhejiang Zhenhai Study. Am J Gastroentero. l2013;108:1299–1304.

**13.** Shi Y, Wang Q, Sun Y et al. The prevalence of lean/nonobese nonalcoholic fatty liver disease: A systematic review and meta-analysis. J. Clin. Gastroenterol. 2020; 54: 378–387.

**14.** Albhaisi S, Chowdhury A, Sanyal AJ. Non-alcoholic fatty liver disease in lean individuals. JHEP Rep. 2019; 1: 19–341.

**15.** Shahinul Alam,, Shah Mohammad Fahim, Muhammad Abdul Baker Chowdhury et al. Prevalence and risk factors of non-alcoholic fatty liver disease in Bangladesh. An open access journal of gastroenterology and hepatology. 2018;2: 39–46.

**16.** Vos B, Moreno C, Nagy N, Féry F, Cnop M, Vereerstraeten P, et al. Lean non-alcoholic fatty liver disease (Lean-NAFLD): a major cause of cryptogenic liver disease. Acta Gastroenterol Belg. 2011;74:389–394.

**17.** Best CH, Hartroft WS, et al. Liver damage produced by feeding alcohol or sugar and its prevention by choline. Br Med J. 1949;2:1002-1006.

**18.** Weir CB, Jan A. BMI classification percentile and cut off points. StatPearls. Treasure Island (FL): StatPearls Publishing. 2020.

**19.** Consultation WHOE. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet. 2004;363:157-163.

**20.** Younossi ZM, Stepanova M, Negro F, et al. Nonalcoholic fatty liver disease in lean individuals in the United States. Medicine (Baltimore). 2012;91:319-327.

**21.** Bellentani S, Saccoccio G, Masutti F, et al. Prevalence of and risk factors for hepatic steatosis in Northern Italy. Ann Intern Med. 2000;132:112-117.

**22.** Feng RN, Du SS, Wang C, et al. Lean-non-alcoholic fatty liver disease increases risk For

metabolic disorders in a normal weight Chinese population. World J Gastroenterol. 2014;20:17932-17940.

**23.** Nishioji K, Sumida Y, Kamaguchi M, et al. Prevalence of and risk factors for non-alcoholic fatty liver disease in a non-obese Japanese population, 2011-2012. J Gastroenterol. 2015;50:95-108.

**24.** Wei JL, Leung JC, Loong TC, et al. Prevalence and severity of nonalcoholic fatty liver disease in non-obese patients: A population study using proton-magnetic resonance spectroscopy. Am J Gastroenterol. 2015;110:1306-1314.

**25.** Kim SS, Cho HJ, Kim HJ, et al. Nonalcoholic fatty liver disease as a sentinel marker for the development of diabetes mellitus in non-obese subjects. Dig Liver Dis. 2018;50:370-377.

**26.** Sinn DH, Kang D, Cho SJ, et al. Lean non-alcoholic fatty liver disease and development of diabetes: a cohort study. Eur J Endocrinol. 2019;181:185-192.

**27.** Young S, Tariq R, Provenza J, et al. Prevalence and profile of nonalcoholic fatty liver disease in lean adults: systematic review and meta-analysis. Hepatol Commun. 2020;4:953-972.

**28.** Browning JD, Szczepaniak LS, Dobbins R, et al. Prevalence of hepatic steatosis in an urban

population in the United States: Impact of ethnicity. Hepatology. 2004;40:1387-1395.

**29.** Alberti KG, Zimmet P, Shaw J, Group IDFETFC. The metabolic syndrome--a new worldwide definition. Lancet. 2005;366:1059-1062.

**30.** Fracanzani AL, Petta S, Lombardi R, Pisano G, Russello M, Consonni D, Di Marco V, Cammà C, Mensi L, Dongiovanni P, Valenti L, Craxì A, Fargion S. Liver and Cardiovascular Damage in Patients With Lean Nonalcoholic Fatty Liver Disease, and Association With Visceral Obesity. Clin Gastroenterol Hepatol. 2017; 15: 1604-1611.

**31.** Kumar R, Rastogi A, Sharma MK, Bhatia V, Garg H, Bihari C, Sarin SK. Clinicopathological characteristics and metabolic profiles of non-alcoholic fatty liver disease in Indian patients with normal body mass index: Do they differ from obese or overweight non-alcoholic fatty liver disease? Indian J EndocrinolMetab. 2013; 17: 665-671.

**32.** Niriella MA, Kasturiratne A, Pathmeswaran A, De Silva ST, Perera KR, Subasinghe SKCE, Kodisinghe SK, Piyaratna TACL, Vithiya K, Dassanayaka AS, De Silva AP, Wickramasinghe AR, Takeuchi F, Kato N, de Silva HJ. Lean non-alcoholic fatty liver disease (Lean NAFLD): Characteristics, metabolic outcomes and risk factors from a 7-year prospective, community cohort study from Sri Lanka. Hepatol Int. 2019; 13: 314-322.

**33.** Yoshitaka H, Hamaguchi M, Kojima T, Fukuda T, Ohbora A, Fukui M. Nonoverweight nonalcoholic fatty liver disease and incident cardiovascular disease: A post hoc analysis of a cohort study. Medicine (Baltimore). 2017; 96: e6712.

**34.** Kumar R, Rastogi A, Sharma MK, Bhatia V, Garg H, Bihari C, et al. Clinicopathological characteristics and metabolic profiles of non-alcoholic fatty liver disease in Indian patients with normal body mass index: Do they differ from obese or overweight non-alcoholic fatty liver disease? Indian J Endocrinol Metab. 2013;17:665–671.

**35.** Alam S, Gupta UD, Alam M, Kabir J, Chowdhury ZR, Alam AK. Clinical, anthropometric, biochemical, and histological characteristics of nonobese nonalcoholic fatty liver disease patients of Bangladesh. Indian J Gastroenterol. 2014;33:452–457.

**36.** Younossi ZM, Stepanova M, Negro F, Hallaji S, Younossi Y, Lam B, et al. Nonalcoholic fatty liver disease in lean individuals in the United States. Medicine (Baltimore). 2012;91:319–327.

**37.** Højland Ipsen D, Tveden-Nyborg P, Lykkesfeldt J. Normal weight dyslipidemia: Is it all about the liver? Obesity (Silver Spring). 2016;24:556–567.

**38.** Badoud F, Perreault M, Zulyniak MA, Mutch DM. Molecular insights into the role of white adipose tissue in metabolically unhealthy normal weight and metabolically healthy obese individuals. FASEB J. 2015;29:748–758.

**39.** Kim NH, Kim JH, Kim YJ, Yoo HJ, Kim HY, Seo JA, et al. Clinical and metabolic factors associated with development and regression of nonalcoholic fatty liver disease in nonobese subjects. Liver Int. 2014;34:604–611.

**40.** Chen CH, Huang MH, Yang JC, et al. Prevalence and risk factors of nonalcoholic fatty liver disease in an adult population of taiwan: metabolic significance of nonalcoholic fatty liver disease in nonobese adults. J Clin Gastroenterol. 2006;40:745-752.

**41.** Sookoian S, Pirola CJ. Systematic review with meta-analysis: risk factors for non-alcoholic fatty liver disease suggest a shared altered metabolic and cardiovascular profile between lean and obese patients. Aliment PharmacolTher. 2017;46:85-95.

**42.** Xu C, Yu C, Ma H, Xu L, Miao M, Li Y. Prevalence and risk factors for the development of nonalcoholic fatty liver disease in a nonobese Chinese population: The Zhejiang Zhenhai Study. Am J Gastroenterol. 2013;108:1299-304.

**43.** Feng, R.-N.; Du, S.-S.; Wang, C.; Li, Y.-C.; Liu, L.-Y.; Guo, F.-C.; Sun, C.-H. Lean-non-alcoholic fatty liver disease increases risk for metabolic disorders in a normal weight Chinese population. World J. Gastroenterol. 2014, 20, 17932–17940.

**44.** Vos, B.; Moreno, C.; Nagy, N.; Féry, F.; Cnop, M.; Vereerstraeten, P.; Devière, J.; Adler, M. Lean Non-Alcoholic Fatty Liver Disease (Lean-NAFLD): A Major Cause of Cryptogenic Liver Disease. Acta Gastro-Enterol. Belg. 2011;74:389–394.

**45.** Vajro P, Lenta S, Socha P, Dhawan A, McKiernan P, Baumann U, et al. Diagnosis of nonalcoholic fatty liver disease in children and adolescents: Position paper of the ESPGHAN Hepatology Committee. J Pediatr Gastroenterol Nutr. 2012; 54: 700–713.

**46.** Mofrad P, Contos MJ, Haque M, Sargeant C, Fisher RA, Luketic VA, et al. Clinical and histologic spec- trum of nonalcoholic fatty liver disease associated with normal ALT values. Hepatology. 2003; 37: 1286–1292.

**47.** Kunde SS, Lazenby AJ, Clements RH, Abrams GA. Spectrum of NAFLD and diagnostic implications of the proposed new normal range for serum ALT in obese women. Hepatology. 2005; 42: 650–656.

**48.** Fan JG, Saibara T, Chitturi S, Kim BI, Sung JJ, Chutaputti A, authors. What are the risk factors and settings for non-alcoholic fatty liver disease in Asia-Pacific. J Gastroenterol Hepatol. 2007;22(6):794–800. [PubMed].

**49.** European Association for the Study of the Liver (EASL), European Association for the Study of Diabetes (EASD). European Association for the Study of Obesity (EASO), authors. EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol. 2016;64(6):1388–1402.

**50.** Joy D, Thava VR, Scott BB. Diagnosis of fatty liver disease: is biopsy necessary? Eur. J. Gastroenterol. Hepatol. 2003; 15: 539–543.

**51.** Agarwal AK, Jain V, Singla S et al. Prevalence of non-alcoholic fatty liver disease and its correlation with coronary risk factors in patients with type 2 diabetes. J. Assoc. Physicians India. 2011; 59: 351–354.

**52.** Dixon JB, Bhathal PS, O'brien PE. Nonalcoholic fatty liver disease: predictors of nonalcoholic steatohepatitis and liver fibrosis in the severely obese. Gastroenterology. 2001; 121: 91–100.

**53.** A Comparison of the Sensitivity and Specificity of Ultrasound Elastography Compared to Liver Ultrasound, ALT, and AST in the detection of Fatty Liver and Fibrosis in Patients with Metabolic Syndrome and Type2 Diabetes Mellitus. Journal of the ASEAN federation of Endocrine Societies. 2014;29:59-64.