A retrospective study to find out the correlation between NAFLD, diabetes, and obesity in Indian patients

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Abstract

Background: Nonalcoholic fatty liver disease (NAFLD) is present in the body with metabolic disorders such as Type 2 diabetes mellitus (T2DM), obesity, and cardiovascular disease. However, no significant evidence has been found till date exhibiting their association epidemiologically in Indian patients. Objective: To assess the association among NAFLD, T2DM, and obesity, and to validate the scoring system with grades of fatty liver (severity of liver disease) estimated by ultrasound vs. NAFLD fibrosis score, BARD score, and aspartate aminotransferase to platelet ratio index (APRI) score. Methodology: A retrospective, observational study was conducted out in patients with NAFLD (n = 316) where diagnosis and grades of fatty liver were established via ultrasound reports. The patients were divided into two groups, Group A (n = 114, NAFLD with T2DM) and Group B (n = 202, NAFLD without T2DM). R 4.0.0 was used for statistical analysis. Results: The mean age (in years) of the patients was 54.08 ± 10.78 in Group A and 48.10 ± 15.36 in Group B. The mean BMI in Group A was found to be slightly higher as compared to Group B, 27.49 ± 4.94 and 26.56 ± 4.68, respectively, and the difference was found to be statistically significant (p-value <0.05). The overall predictive ability of the NAFLD scoring system matched that to ultrasonography liver grading fibrosis report for approximately 53% of patients. The BARD scoring system was found to be matched with ultrasonography reported Grade 1 fatty liver (198/316). In the case of the APRI scoring system, the association was not observed with ultrasonography reports in any grades of fatty liver. Conclusion: Body mass index might be an independent risk factor for NAFLD. NAFLD fibrosis score appears to be a reliable non-invasive tool to determine the severity of liver fibrosis in NAFLD patients. BARD score may predict Grade 1 liver fibrosis. However, APRI scores do not correlate with imaging evidence of fibrosis like NAFLD and BARD scores.

Keywords: NAFLD score, non-alcoholic fatty liver disease, obesity, type 2 diabetes

Introduction

Non-alcoholic fatty liver disease (NAFLD) is currently the most prevalent form and major cause of liver disease in the world, affecting about 50% of adult population.[1,2] It is characterised by the accumulation of excess of hepatic fat (≥ 5%) without significant alcohol intake, hepatitis virus infection, or due to any other secondary causes of accumulation of hepatic fat.[3] The severity of NAFLD ranges from simple NAFLD (characterised by accumulation of intrahepatic triacylglycerol (IHTAG)) to non-alcoholic steatohepatitis (NASH) (NASH is characterised by the presence of hepatocyte injury and fibrosis), which might ultimately lead to cirrhosis (accumulation of scar tissue), hepatocellular carcinoma or liver failure. NAFLD and NASH are usually “silent” liver diseases. The accumulation of pathological ectopic fat and low-grade chronic inflammation of liver with...
inability to accumulate fat are the other common manifestations of NAFLD.

The early stages of NAFLD are typically asymptomatic. The most common findings in patients of NAFLD are increase in levels of liver enzymes that include alanine aminotransferase (ALT), aspartate transaminase (AST), and/or gamma-glutamyl transferase (γGT). However, about 80% of the patients with NAFLD exhibit levels of liver enzymes within the normal range. Over 70% of T2D patients suffer from NAFLD. As per various observational epidemiologic studies, metabolic disorders such as T2D and obesity have been strongly linked with NAFLD. In order to prevent the progression of the disease, especially in the people who are at high risk of developing complications of disease, it is very important to understand the causal relationships among the three diseases to identify the aetiology of the disease and develop effective diagnostic, therapeutic, and preventive strategies.

There are two to three folds increased risk of developing T2D in NAFLD patients while there is a higher prevalence of steatohepatitis, liver fibrosis, and end-stage liver disease in T2D patients. There appears to exist a complex bi-directional relationship between NAFLD and diabetes where one drives progression of the other. T2D patients have elevated IHTAG as compared to age, gender, and body mass-matched subjects without T2D. T2D patients having NAFLD may have increased insulin requirement, that may also have implications on their body weight.

In obese persons, the prevalence of NAFLD increases to ~50–75%, indicating that there is a relationship between IHTAG and total adiposity. The prevalence of NAFLD is similar to that of obesity as increased caloric intake, sedentary lifestyle, and consequent development of obesity are the major risk factors for the development of NAFLD. The fat distribution, adipose tissue (AT) functionality, and IR constitute the basis of metabolic disturbances such as MetS, diabetes and NAFLD.

Liver biopsy is the “gold standard” for diagnosing NAFLD. It helps to determine the stage and severity of fibrosis by assessing the pathological features such as hepatocyte ballooning, lobular inflammation, and fibrosis. As the technique is invasive and is associated with complications, it is not widely accepted.

Ultrasound (USG) is the most common imaging modality used to detect hepatic steatosis because of its less cost, safety, and availability; USG represents the first line in diagnosing NAFLD. It has a sensitivity and specificity of 60–94% and 84–95% for detecting fat, respectively.

There are non-invasive systems available to evaluate fibrosis in NAFLD patients biochemically which include NAFLD fibrosis score, BARD score, and APRI score. Such clinical scoring systems are useful in early detection of NAFLD and predicting fibrosis. The NAFLD fibrosis score (NFS), is a composite score of age, hyperglycemia, body mass index, platelet count, albumin, and aspartate aminotransferase and alanine aminotransferase (AST/ALT) ratio. It was found to independently identify NAFLD patients with and without advanced fibrosis at initial NAFLD diagnosis. A study from Japan validated the NFS and reported it to have an acceptable sensitivity, specificity, positive, and negative predictive values for advanced liver fibrosis of 100%, 83%, 63%, and 100%, respectively.

Another clinical score, BARD score, composed of body mass index (BMI) ≥ 28 kg/m², AST/ALT ratio ≥ 0.8 and history of diabetes mellitus, is used to predict increased chances of liver fibrosis. However, the BARD score cannot differentiate the severity of fibrosis in patients with a higher BMI or a higher AST/ALT ratio. Aspartate aminotransferase to platelet ratio index (APRI) score is used for predicting liver cirrhosis by using AST and platelet levels.

Thus, the study of the correlation between NAFLD, T2D, and obesity in Indian patients may help to better manage the condition.

The present study was conducted to find the relationship between NAFLD, T2D, and obesity. The study further will help enlighten the knowledge of physicians as it is aimed to explore the predictability of various liver fibrosis scoring systems in determining the severity of liver fibrosis vis-à-vis USG grading system.

**Materials and Methods**

In this retrospective cohort study, the EMR records of 316 OPD patients fulfilling the inclusion and exclusion criteria were reviewed and analysed (Group A – 114, NAFLD with T2DM and Group B – 202, NAFLD without T2DM). The Institutional Ethics Committee Clearance was taken from Royal Independent Ethics Committee with IEC no. RPIEC191020.

The severity of fibrosis was defined based on the USG findings.

The grades of fatty liver are:

- **Grade 1 (Mild)** – minimal diffuse increase in hepatic echogenicity with normal visualization of diaphragm and intrahepatic vessel borders.
- **Grade 2 (Moderate)** – moderate diffuse increase in hepatic echogenicity with slightly impaired visualization of intrahepatic vessels and diaphragm.
- **Grade 3 (Severe)** – marked increase in echogenicity with poor penetration of posterior segment of right lobe of liver and poor or no visualization of hepatic vessels and diaphragm.
In the study, the patients were assessed by demographic (age, gender), anthropometric (BMI), and biochemical parameters (serum ALT, AST, albumin, serum triglycerides, platelet count).

The data generated was used to score the patients using the NAFLD fibrosis score, BARD, and APRI score.

**NAFLD fibrosis score**[^19]

The NAFLD fibrosis score calculated according to the following formula:

\[-1.675 + 0.037 \times \text{age (years)} + 0.094 \times \text{BMI (kg/m}^2\text{)} + 1.13 \times \text{IFG/diabetes (yes = 1, no = 0)} + 0.99 \times \text{AST/ALT ratio} - 0.013 \times \text{platelet (} \times 109/L) - 0.66 \times \text{albumin (g/dL)}.

- NAFLD score ≤1.455 = less probability of fibrosis
- NAFLD score >1.455-0.675 = indeterminate score
- NAFLD score >0.675 = high probability of fibrosis

**BARD score**[^18]

BARD score calculated as weighted sum:

- BMI ≥28 = 1 point + AAR of ≥0.8 = 2 points + DM = 1 point.

- BARD score of more than 2 indicates fibrosis.

NAFLD patients divided into different groups based on T2D and BMI:

- Group A – NAFLD Patients with T2D
- Group B – NAFLD Patients without T2D
- Group C – NAFLD Patients with Normal BMI (18.0-24.9)
- Group D – Overweight NAFLD Patients with BMI (25.0-29.9)
- Group E – Obese NAFLD Patients with BMI (>30.0)

**APRI score**[^16]

APRI score was calculated as:

\[(\text{AST/upper limit of normal AST range}) \times 100]/\text{Platelet count}

- APRI score ≤0.5 = Completely free of fibrosis or mild scarring
- APRI score ≥1.5 = Scarring in liver and likely some cirrhosis

The main outcome measures were T2D (estimated by patient history) and obesity (estimated by BMI). Based on the patient history of T2D and BMI, the NAFLD stages were compared as diabetic vs non-diabetic and obese vs non-obese patients.

The patients were categorised by the presence or absence of T2D, and their statistical significance calculated in different age groups, gender, BMI ranges, and biochemical tests. The difference between the primary endpoints of Group A (Diabetic) and Group B (Non-diabetic) in different age groups was calculated based on t-test. Continuous outcomes were depicted as the mean ± SD, and categorical data were depicted as numbers (percentage). Logistic regression analysis was used to identify the factors that were significantly associated with the severity among NAFLD patients.

**Statistical analysis**

R 4.0.0 was used for statistical analysis.

**Results**

The majority of diabetic NAFLD patients were in the average age group of 54.08 ± 10.78 years while non-diabetics were in the age group of 48.10 ± 15.36 years. The comparison between both the groups was found to be statistically significant. The majority of the NAFLD patients were females in diabetic and non-diabetic groups. The mean BMI was 27.49 ± 4.94 and 26.56 ± 4.68 in diabetic and non-diabetic groups, respectively, but the comparison between the groups was found to be statistically non-significant.

The mean BMI, albumin, and triglycerides were slightly higher in Group A as compared to Group B. While the mean AST and ALT values were found to be higher in the non-diabetic group (33.84 ± 25.21 and 38.60 ± 26.80) as compared to the diabetic group (29.88 ± 14.29 and 33.40 ± 15.91) but the comparison between the groups was found to be statistically non-significant.

The groups based on BMI ranges (Group C, D, and E) were analysed based on age, gender, diabetes, and triglycerides using analysis of variance (ANOVA). The mean ages according to BMI were 51.09 ± 14.58, 51.10 ± 14.52 and 47.43 ± 12.70 in Group C, D, and E, respectively. The majority of NAFLD patients with normal BMI are non-diabetic, however the percentage of diabetics increased in overweight and obese groups but the comparison among the groups was found to be statistically non-significant.

In both diabetic and non-diabetic groups, the severe fibrosis can be seen in younger age as compared to mild and moderate fibrosis. Other clinical parameters (BMI and AST) were directly proportional to the severity of fatty liver in both diabetic and non-diabetic groups. The comparison among the grades of fatty liver with respect to age in diabetics and levels of albumin in non-diabetics was found to be statistically significant. All other comparisons among the groups were found to be statistically non-significant. [Table 1].
According to the NAFLD scoring system, the mild fibrosis group ($F_1$, $F_2$) with T2D has a mean age of 51.21 ± 12.02 years while the severe fibrosis group with T2D has a mean age of 60.53 ± 9.18 years. The mean BMI and AST were higher in severe fibrosis cases, while the mean ALT, albumin and triglycerides were found to be lower in severe fatty liver cases for both the groups but the comparison among the groups was found to be statistically non-significant.

Data were analysed using ANOVA for multivariate analysis. $P$ and $F$ values were obtained for estimating relation between the scores and increasing grade of fatty liver on imaging. In NAFLD scoring system, the average NAFLD fibrosis scores were compared with grades of fatty liver. The mean difference in NAFLD scores was found to be highly statistically significant ($p$-value = 0.0001) across all the grades [Table 2].

In BARD scoring system, only the mean BMI was found to be higher in the severe fibrosis group in both the groups. The $P$ value was 0.0008 for Grade 1 which was statistically significant while it was much higher for Grade 2 and 3 (1.64 and 0.41) [Table 3 and 4].

In case of APRI scoring system, both the scorings found to be statistically insignificant ($p$-value > 0.05) for all the Grades (Grade 1, 2, and 3).

### Discussion

This study was conducted to find out the correlation between NAFLD, T2D, and obesity based on demographic, anthropometric, and biochemical parameters. Patients were categorised by the presence or absence of Type 2 diabetes and their statistical significance was calculated in different age groups, gender, BMI ranges, and biochemical tests. The majority of NAFLD patients with diabetes were in the age group 51–60 years and without diabetes were in the age group 41–50 years. The correlation between the presence of diabetes and NAFLD among the patients with advancing age found to be statistically significant ($p$-value < 0.05). A meta-analysis including 10897 Type 2 diabetes mellitus patients also indicated the overall prevalence of NAFLD among Type 2 diabetes mellitus is significantly higher.[24]

At the same time, correlation between NAFLD, gender, and BMI were found to be statistically insignificant in the present study. However, the mean BMI in diabetic group (Group -A) was found to be slightly higher as compared to the non-diabetic group (Group B).

The groups based on BMI ranges (Group C, D, and E) were analysed based on age, gender, diabetes, and triglycerides, however, no statistical significance was found. The obese group (Group E) was found to have the lowest mean BMI. Bhatt. K et al.[23] found that BMI was significantly on the higher side in patients with NAFLD than a control group without NAFLD. A cohort study conducting on 103 subjects also found the mean BMI in obese group (35.4 ± 3.8 kg/m²) much higher than the non-obese group (27.6 ± 1.8 kg/m²). This study concluded that the prevalence of NAFLD is much higher than previously believed in overweight/obese patients with T2D. The odds ratio was calculated in NAFLD patients based on occurrence of diabetes and their BMI. The odds ratio is 1.25 [CI (0.78-2.01)]

### Table 1: Comparison of NAFLD patients with and without T2D with different grades of fatty liver

| Variable          | Type of Case | Grade of fatty liver (Mean±SD) | $P$  |
|-------------------|--------------|--------------------------------|------|
|                   |              | 1          | 2             | 3          |      |
| Age (Group A)     | 56.93±9.99   | 50.51±10.80| 46.83±6.96    | 0.002*     |
|                   | 48.40±16.59  | 47.75±12.86| 45.50±10.29   | 0.882      |
| BMI (Group A)     | 27.35±4.52   | 27.49±5.41 | 29.14±5.30    | 0.701      |
|                   | 25.93±4.14   | 27.61±5.42 | 28.70±4.46    | 0.031      |
| AST (Group A)     | 29.15±13.66  | 30.90±14.07| 31.05±19.81   | 0.812      |
|                   | 31.82±17.64  | 36.72±35.86| 45.60±15.05   | 0.202      |
| ALT (Group A)     | 32.75±14.60  | 34.36±16.15| 34.02±24.38   | 0.875      |
|                   | 38.00±26.07  | 38.31±27.87| 55.00±       | 0.315      |
| Albumin (Group A) | 3.88±0.48    | 3.87±0.37  | 3.97±0.44     | 0.884      |
|                   | 3.92±0.46    | 3.70±0.41  | 3.97±0.42     | 0.007      |
| Triglycerides (Group A) | 149.32±59.69 | 182.32±100.39 | 180.78±126.23 | 0.115      |
|                   | 139.00±64.67 | 150.62±80.45| 221.33±52.32 | 0.016      |

$^*P<0.05$=Statistically significant

### Table 2: Comparison of NAFLD Fibrosis score according to USG fatty liver grade in study group

| F0-F2 (Mean NAFLD Fibrosis Score value±SD) | F3-F4 (Mean NAFLD Fibrosis Score value±SD) | Indeterminate (Mean NAFLD Fibrosis Score value±SD) | $P$  | $F$  |
|-------------------------------------------|-------------------------------------------|-----------------------------------------------|------|------|
| Grade 1 (n=198)                           | 2.87±1.21                                 | 1.14±0.37                                     | <0.0001** | 149.05 |
| Grade 2 (n=106)                           | 2.71±0.92                                 | 1.40±0.64                                     | <0.0001** | 105.28 |
| Grade 3 (n=12)                            | 2.55±0.75                                 | 0.39±0.26                                     | 0.0001*  | 37.32  |

$^*$P<0.05=Statistically significant; **P<0.001
at 95% times higher indicating that the NAFLD patients with abnormal BMI are more susceptible to Type 2 diabetes mellitus as compared to normal BMI group. The grade of fatty liver has direct correlation with diabetic group (Group A).

According to the NAFLD scoring system, the mild fibrosis group (F0-F2) with T2D has a mean age of 51.21 ± 12.02 years while the severe fibrosis group has a mean age of 60.53 ± 9.18 years. The age, BMI, and albumin were statistically correlated to NFS system in Cases (Group A).

In NAFLD scoring system, the average NAFLD fibrosis scores were compared with grades of fatty liver. Out of 316 (53%) patients, there was less or high probability of fibrosis in 167 patients. However, in 47% of patients, the indeterminate probability of fibrosis was found. The relation between the two was statistically significant in different grades of fatty liver. This finding was not in agreement with the study findings of Kakrani et al.,[16] who reported that biochemical evidence of NAFLD or fibrosis in the form NAFLD fibrosis scores did not correlate with Ultrasonography evidence of fatty liver. This discrepancy between the present studies could be due to differences in the selection criteria of the subjects. The participants in the Kakrani et al.,[16] study (106 patients) had a BMI >25, whereas in our study the participants belonged to different BMI categories.

In BARD scoring system, the correlation between different grades of fatty liver and BARD scores was statistically significant only for Grade 1. Ageely et al. in their cross-sectional study observed that Grade 3 ultrasonographic fatty liver significantly correlates with advanced fibrosis, based on BARD score.[23] In the present study, the overall observation based on BARD scoring system was similar to Ageely et al., showing the prevalence of higher BARD scores in patients with advanced age, higher BMI, higher AST/ALT ratio, and T2D. In case of APRI scoring system, the relation between the two was not statistically significant in any grade of fatty liver.

In this study, we validated different non-invasive scoring system that composed of routinely measured and easily available variables including clinical and laboratory ones to discriminate between the presence or absence of advanced fibrosis in NAFLD patients which is important as a part of diagnosis for physicians. Using the ranges defined by the scoring systems, a prediction of absence or presence and higher or lower probability of fibrosis was made in all the subjects. Based on NFS scoring system, the risk of fibrosis could be determined in 53% (167/316) of subjects. Around 149 patients of the total 316 were considered “indeterminate”. This implies that by applying NFS, liver biopsy can be avoided in 47% of patients in the total cohort. A significant consistency was observed in the results of NFS scores and USG grades of fatty liver. Only 18 (6%) patients out of the total cohort have the risk of advanced fibrosis. On the other hand, the imaging fatty liver grading identified 12 (4%) out of 316 individuals with severe liver fibrosis, suggesting the comparable severity results from NFS and imaging.

We also attempted to correlate the BARD and APRI scores with the imaging results. The P value obtained was >0.05 indicating the relationship was not statistically significant. Thus, the BARD and APRI score do not correlate with imaging evidence of fibrosis like NAFLD score. Overall, USG has reported 60–94% of sensitivity and 84–95% specificity for detecting fat, but both fat and fibrosis can turn up a hyperechoic liver in 98.7% of patients that is known as ‘fatty fibrotic pattern.’ Sensitivity depends on the amount of fat present in liver, however, both sensitivity as well as specificity are poor in morbid obesity. Patients with steatosis have marked rise in echogenicity and non-visualisation. Ultrasound has the disadvantage of being subjective and less sensitive and specific in obese patients.[19] Hence, the use of biochemical parameters along with imaging together can provide more accurate estimation and validation of fibrosis in NAFLD patients.

**Conclusion**

It can be concluded that there is a complex bi-directional relationship between the progression of NAFLD and

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**Table 3: Clinical profile in NAFLD patients with or without T2D based on BARD scores**

| Variable | Type of Case | Bard risk Score (Mean±SD) | P |
|----------|--------------|---------------------------|---|
| Age      | Group A      | 54.42±10.60               | 0.431 |
|          | Group B      | 50.18±15.18               | <0.0001 ** |
| BMI      | Group A      | 28.07±5.04                | 0.003*  |
|          | Group B      | 26.70±5.00                | 0.439   |
| AST      | Group A      | 30.94±14.98               | 0.057   |
|          | Group B      | 33.40±26.54               | 0.658   |
| ALT      | Group A      | 32.42±15.89               | 0.12    |
|          | Group B      | 32.07±18.12               | <0.0001 ** |
| Albumin  | Group A      | 3.88±0.44                 | 0.762   |
|          | Group B      | 3.82±0.44                 | 0.083   |
| Triglycerides | Group A  | 163.31±84.48              | 0.889   |
|          | Group B      | 141.11±59.31              | 0.147   |

**Table 4: Comparison of BARD score according to USG fatty liver grade in study group**

| Grade | (Mean BARD Fibrosis Score value) (Mean±SD) | P | F |
|-------|--------------------------------------------|---|---|
|       | (Mean BARD Fibrosis Score value) (Mean±SD) | (Mean BARD Fibrosis Score value) (Mean±SD) | 0.0008** | 7.42 |
| Grade 1 | 1.88±1.11                   | 2.42±1.18       | 2.48±1.04 | 0.198 |
| Grade 2 | 2.01±1.09                   | 2.50±0.95       | 2.36±1.02 | 1.64 |
| Grade 3 | 2.42±0.49                   | 2.00±1.67       | 2.00±1.67 | 0.537 |

*P<0.05=Statistically significant; **P<0.001
development of T2D. The concomitant presence of both disorders might result in an increase in both hepatic and diabetic mortalities. While genetic and environmental factors affecting obesity causally increases the risk of NAFLD, no significant correlation could be established based on our study. The non-invasive fibrosis scoring system, NFS can be relied on to great extent to determine the probability of fibrosis to develop effective diagnostic, therapeutic and preventive strategies. The other two non-invasive tests, BARD, and APRI cannot be solely adopted to validate the degree of severity of fibrosis. This study suggests estimation of fibrosis in patients of NAFLD using USG and biochemical parameters together as additive evidence for better validation. Further research is needed to validate the NFS score for predicting liver complications and mortality in NAFLD patients.

Limitations
Due to the lack of availability of duration of T2D, we cannot conclude whether NAFLD was the by-product of diabetes or NAFLD led to diabetes.

Key Points
• The concomitant presence of NAFLD and T2DM might result in increase in hepatic and diabetic mortalities.
• To determine the probability of fibrosis to develop effective diagnostic, therapeutic and preventive strategies, NFS can be used.
• To validate the degree of severity of fibrosis, BARD and APRI can be used.
• As an additive evidence, USG and biochemical parameters can be used for estimation of fibrosis in NAFLD patients.

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Conflicts of interest
There are no conflicts of interest.

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