Baseline Values of Nonalcoholic Fatty Liver Disease Scores and Its Risk Assessment in Patients with Type 2 Diabetes Mellitus

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Keywords

Nonalcoholic fatty liver disease · Type 2 diabetes · Obesity · Noninvasive nonalcoholic fatty liver disease scores · Metabolic syndrome · Body mass index

Abstract

Introduction: The prevalence of nonalcoholic fatty liver disease (NAFLD) is increasing and is fueled by a twin-epidemic of obesity and diabetes mellitus in India. The objective of the study was to estimate various noninvasive NAFLD scores (NINS) for the baseline risk-assessment of NAFLD in patients with type 2 diabetes mellitus (T2DM). **Methods:** An observational, cross-sectional, open label, study of investigator-rated NINS was conducted ensuring adherence to relevant ethical standards. **Results:** In a 3-month period, 29 patients with T2DM were enrolled (age [mean $\pm$ SD]: 55.8 ± 9.72 years; men [n, %]: 18, 62%). One patient (3.45%) by fibrosis-4 index (cutoff for advanced fibrosis ≥ 2.67) and by AST to platelet ratio index (cutoff ≥ 0.98); 2 (6.90%) by NAFLD fibrosis score (cutoff ≥ 0.676); 20 (69%) by body mass index (BMI), AST to ALT ratio, and DM score (BARD; cutoff ≥ 2); and 27 (93.10%) by BMI, age, ALT, triglyceride score (cutoff ≥ 1) indicated high risk for advanced hepatic fibrosis. Only the BARD score (median

[min-max]: 3 [1–4]) was elevated above the cutoff values while other scores were below cutoff values. The study failed to demonstrate any correlation between age, gender, anthropometric and metabolic parameters, and NINS. **Conclusion:** While this study did not demonstrate significant elevation of NINS, scores were found to be elevated in some T2DM patients and they may be at high risk of advanced liver fibrosis. Further well-designed studies in this domain are required for early detection, management, and reducing the burden of liver disease in Indian patients with diabetes.

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Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide. The prevalence of NAFLD in general population in western countries varies from 9 to 40% which is similar to the prevalence in India (9–32%) depending on various studies [1, 2]. It is usually associated with type 2 diabetes mellitus (T2DM) along with systemic arterial hypertension, obesity, and dyslipidemia. The prevalence of obesity and T2DM is on rise in India and that may lead to parallel in-

Table 1. BMI, WHR, and various NINS and their cutoff values

Sr. No.	Parameter	Formula	Cutoff	Interpretation/comment*
1	BMI (kg/m ²)	$=(\text{body weight in kg})/(\text{height in meters})^2$	Underweight: <18.5 kg/m ² ; Normal: 18.5–22.5 kg/m ² Overweight: 23–25 kg/m ² Obese class I: 25–29.5 kg/m ² Obese class II: ≥ 30 kg/m ²	The BMI was categorized as per WHO criteria for South Asians which is stricter than the cutoffs for BMI for Westerns/other populations
2	WHR	$= \text{Waist circumference (WC; cm)} / \text{Hip circumference (HC; cm)}$	A ratio >0.89 for men and 0.81 for women for South-Asian Indian origin is considered as abnormal	Indian patients tend to have higher upper body obesity despite of lower lean body mass as compared to Western patients; WHR is useful indicator in such cases.
3	AAR	$= \text{AST (IU/L)} / \text{ALT (IU/L)}$	AAR >1 was considered as abnormal	
4	APRI	$\text{AST ([ULN]; IU/L)} / \text{platelet ratio (10}^9\text{/L)} \times 100$	A ratio above 0.98 is considered as a significant marker for liver fibrosis	
5	BARD score	A composite of 1. BMI ≥ 28 kg/m ² = 1 point; 2. AST/ALT ≥ 0.8 = 2 points; 3. T2DM = 1 point.	A ratio of BARD ≥ 2 was considered as abnormal	
6	FIB-4	$=(\text{age [years]} \times \text{AST IU/L}) / (\text{platelet [10}^9\text{/L]} \times \text{ALT [IU/L]})$	Score <1.30 indicates: low risk	Low risk (for advanced liver fibrosis): correlates with F0–F1 stage of fibrosis on histology
			1.30–2.67: indeterminate risk	Indeterminate risk
			>2.67: high risk	High risk: correlates with F3–F4 histology grading for fibrosis
7	NFS	$= -1.675 + [0.037 \times \text{age (years)}] + [0.094 \times \text{BMI (kg/m}^2\text{)}] + [1.13 \times \text{hyperglycemia/T2DM (yes = 1, no = 0)}] + [0.99 \times \text{AST/ALT ratio}] - [0.013 \times \text{platelet (10}^9\text{/L)}] - [0.66 \times \text{albumin (g/dL)}]$	Score <–1.455 indicates low risk of hepatic fibrosis NFS	Low risk (for developing advanced liver fibrosis): histology grading for fibrosis: F0–F2
			1.455–0.675: indeterminate	Intermediate
			>0.675: High risk	High risk: (histology grading for fibrosis: F3–F4)
8	BAAT score	Calculated by 1 point for each variable; 1. BMI ≥ 28 kg/m ² ; 2. ALT (IU/L) ≥ 2 -times ULN; 3. Age ≥ 50 years and 4. Triglycerides ≥ 150 mg/dL	A value of BAAT score >1 was considered abnormal	A score of <1 has a negative predictive value of 100% in predicting septal fibrosis/cirrhosis (Ratziu et al. [5])
9	HAALT score**	A total 6-point scoring system based on 5 independent variables 1. HbA1c >6 (score 2) 2. AST >30 IU/L (score 1), 3. ALT >35 IU/L (score 1), 4. Sr. triglyceride levels >150 mg/dL (score 1) 5. Liver span on USG >16 cm (score 1)	A score above 3 is considered as abnormal	

BAAT, BMI, age, ALT, and triglycerides score; APRI, AST to platelet ratio; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ULN, upper normal limit; T2DM, type 2 diabetes mellitus; FIB-4, fibrosis-4 index; HbA1c, glycosylated hemoglobin; HAALT, HbA1c, AST, ALT, Sr, triglyceride, liver span on ultrasonography; WHR, waist to hip circumference ratio; NINS, noninvasive NAFLD scores; NAFLD, nonalcoholic fatty liver disease; BARD, BMI, AAR, and T2DM score; AAR, AST to ALT ratio; NFS, NAFLD fibrosis score. * Liver fibrosis was graded on a scale of 0–4. F0, absent; F1, portal fibrosis with no fibrosis beyond the portal tracts; F2, portal fibrosis with a few septa; F3, portal fibrosis with numerous septa; and F4, cirrhosis. Further, liver fibrosis was treated as a categorical variable either being absent/minimal (F0, F1) or septal (F2, F3, F4) (Ratziu et al. [5]). ** If patients have done USG-abdomen for other reasons in last 3 months, HAALT score was calculated, otherwise it was omitted.

crease in the prevalence of NAFLD. Hence, it is imperative to determine risk-assessment for development of NAFLD. Various studies in India reported prevalence of NAFLD from 12 to 84% in T2DM; however, most of the studies indicate prevalence about 50–56%.

While liver biopsy is a gold standard technique, risk-assessment for liver damage can be done using numerous non-invasive methods such as fibroscan, MR-elastography as well as simple, cost-effective, OPD-based noninvasive NAFLD scores (NINS) such as fibrosis-4 index (FIB-4) score; NAFLD fibrosis score (NFS); AST to platelet ratio (APRI); AST to ALT ratio (AAR); body mass index (BMI), age, ALT, and triglycerides score (BAAT); BMI, AAR, and T2DM score (BARD); and HAALT score [3]. However, there are fewer studies done in India in diabetes mellitus patients to assess the risk of liver damage/NAFLD using these various scores.

The aim of this pilot study was to assess the baseline values of NINS, so that it can be helpful for future large-scale studies to the risk of liver damage/fibrosis in patients in patients with diabetes mellitus. We conducted this study in a tertiary care diabetes OPD in Mumbai, India. We further assessed NAFLD risk in patients with T2DM in subgroups of patients with obesity and metabolic syndrome. Also, the objective of the study was to correlate the NINS with various demographic, anthropometric and laboratory parameters.

Methodology

Study setting

This was an observational, cross-sectional, open label, study of investigator-rated NINS in T2DM patients. No active intervention or investigations or extra-follow up visits were done. The study was conducted at diabetes OPD in a tertiary care facility in Mumbai.

Patient Population

All patients with T2DM attending to diabetes OPD and who were willing to provide written informed consent were enrolled in the study. Patients were diagnosed diabetic as per ICMR guidelines for diagnosis of Indian patients with diabetes if they fulfilled any one of the following criteria: symptoms of diabetes plus random plasma glucose ≥ 200 mg/dL (casual means without regard to time of last meal); fasting plasma glucose (FPG) ≥ 126 mg/dL; 2-h post 75 g glucose ≥ 200 mg/dL (as part of OGTT) and glycated hemoglobin $\geq 6.5\%$ [4]. Those who were unwilling to provide consent; those who were suffering from other medical conditions such as known renal failure, hepatic failure, heart failure etc.; those patients with diabetic keto-acidosis; those with history/known viral hepatitis/other types of hepatitis; those with excessive consumption of alcohol defined as >60 mL/day were excluded from the study. Patients with incomplete records/investigations were also excluded.

Table 2. Baseline characteristics

Baseline characteristics	Mean $\pm$ SD or <i>n</i> (%)
Age (mean $\pm$ SD), years	55.8 (9.7)
Men, <i>n</i> (%)	18 (62)
Women, <i>n</i> (%)	11 (38)
Duration since diagnosis of T2DM (mean $\pm$ SD)	8.43 (6.59)
BMI (mean $\pm$ SD), kg/m ²	26.71 (3.81)
WHR (mean $\pm$ SD)	0.98 (0.05)
BSL-F (mean $\pm$ SD), mg/dL	172.0 (87.3)
BSL-PP (mean $\pm$ SD), mg/dL	243.6 (110.3)
HbA1c (mean $\pm$ SD), %	9.15 (2.69)

Outcome Parameters

Calculation of NINS is dependent on some of the routine investigations: complete blood count, liver function tests, and lipid profile along with the anthropometry (BMI) which were captured at the same visit along with age, body weight and other parameters. This was obtained from the available information in patient records. No additional investigations/visits were performed. The details of evaluation parameters are mentioned in Table 1.

Statistical and Analysis Plan

Total population sampling technique, a type of purposive sampling was used to collect data. All cases attending diabetes OPD for 3 months after IEC approval and willing to provide the written informed consent were included in study. Data were entered and analyzed in Microsoft Excel 2016. Data are presented as mean (SD) for normally distributed numerical variables, median (min-max) for skewed numerical variables, and count (%) for categorical variables. To assess correlation, Pearson's correlation test was applied for parametric data, whereas for nonparametric data, Spearman's rank correlation test was applied. The normality of data was assessed online using the Kolmogorov-Smirnov test of normality using the Website (<https://www.socscistatistics.com/tests/kolmogorov/default.aspx>). For comparison of difference between 2 groups, *t* test was applied for parametric data and Mann-Whitney U test was applied for nonparametric data. Data were rounded off to 2 decimal points and *p* value <0.05 was considered as statistically significant.

Results

In the duration of 3 months, 29 patients (mean $\pm$ SD age: 55.8 ± 9.7 years; 18 [62%] men) were recruited into the study. However, due to COVID-19 pandemic situation, further enrolment was terminated. The baseline characteristics of the patients are presented in Table 2.

The primary end point, distribution of various NINS was variable for every score. The AAR score was abnormal (cutoff ≥ 1) in none of the patients and all 29 patients were deemed as low risk for NAFLD. The APRI score was abnormal (cut off ≥ 0.98) in one patient (3.45%). The BARD score

Fig. 1. Distribution of various NINS in patients with T2DM ($n = 29$). NINS, noninvasive NAFLD scores; NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.

Table 3. Various NINS at the baseline visit

NAFLD score	AAR ($n = 28$)	APRI ($n = 27$)	BARD ($n = 29$)	FIB-4 ($n = 27$)	NFS ($n = 28$)	BAAT ($n = 29$)
Cutoff values	≥ 1	≥ 0.98	≥ 2	≥ 2.67	≥ 0.676	≥ 1
Finding*	0.98 (0.34)	0.32 (0.37)	3 (0–4)	1.18 (0.89)	–1.13 (1.47)	1.0 (0–3)

* Mean ($\pm$ SD) or median (range). NINS, noninvasive NAFLD scores; FIB-4, fibrosis-4 index; AAR, AST to ALT ratio; APRI, aspartate aminotransferase-to-platelet ratio index; BARD, BMI, AAR, diabetes score; NFS, NAFLD fibrosis score; BAAT score, BMI, ALT, age, triglycerides score; BMI, body mass index; NAFLD, nonalcoholic fatty liver disease; T2DM, type 2 diabetes mellitus.

was abnormal (cutoff ≥ 2) in 20 (approx. 69%) patients. FIB-4 score was abnormal (cutoff ≥ 2.67) in 1 (3.45%) patient. NFS score was abnormal (cut off ≥ 0.676) in 2 patients (approx. 7%). BAAT score was elevated (cutoff ≥ 1) in 27 patients (approx. 93%) (Fig. 1). The mean ($\pm$ SD; for normally distributed data) or median (min-max range for skewed data) values for AAR, APRI, BARD, FIB-4, NFS, and BAAT scores were 0.98 (0.34), 0.18 (0.12–1.99), 3 (1–4), 1.18 (0.89), –1.13 (1.47), and 1 (0–4), respectively (Table 3). FIB-4 and NFS scores further were categorization into low risk (no advanced fibrosis), intermediate risk (indeterminate), and

high risk (advanced fibrosis) was present in 22 (75.86%) and 11 (37.94%); 6 (20.68%) and 16 (55.17%); and 1 (3.45%) and 2 (approx. 7%) patients, respectively (Fig. 2).

Among the secondary outcome measures, there was no correlation between age of the patient, duration of diabetes since diagnosis, and gender on the baseline scores. Even anthropological parameters like WHR and BMI did not show any correlation with baseline NAFLD scores except BMI correlating with BARD score ($r = 0.76$, $p < 0.001$; Spearman's rank correlation). The study did not report significant difference in NINS in patients with and those

Fig. 2. FIB-4 and NFS score further sub-categorization. FIB-4, fibrosis-4 index; NFS, NAFLD fibrosis score.

Fig. 3. Distribution of various NINS in the BMI subgroups as per the WHO criteria for Asians. *n* = 7 for obesity category II – some of the scores were obtained from 6 patients. BMI is calculated by dividing weight (kg) by height (m) squared (expressed as kg/m²). The BMI was categorized as per the WHO criteria into not overweight (underweight <18.5 or normal weight: 18.5–22.5 kg/m² were clubbed together) or overweight (at risk: 23–25, obese class I: 25–29.5 and obese class II as BMI ≥30 kg/m²). BMI, body mass index; NINS, noninvasive NAFLD scores; NAFLD, nonalcoholic fatty liver disease.

without metabolic syndrome. The AAR mean score was 1.03 and 0.93 (*t* test, *p* = 0.48), APRI mean score was 0.24 and 0.38 (*t* test, *p* = 0.17), median BARD score was 3 and 3 (Mann-Whitney U test, *p* = 0.25), FIB-4 mean score was 1.03 and 1.3 (*t* test, *p* = 0.22), NFS mean score was –0.69

and –1.5 (*t* test, *p* = 0.07), median BAAT score was 1 and 1.5 (Mann-Whitney U test, *p* = 0.74) in patients with T2DM with and without metabolic syndrome; respectively. There was no significant correlation that was observed in metabolic parameters such as blood sugar levels (fasting

Fig. 4. Distribution of various NINS across men and women ($n = 16$ for BAAT, NFS, and FIB-4; $n = 17$ for rest scores for men; $n = 11$ for women). NINS, noninvasive NAFLD scores; NAFLD, nonalcoholic fatty liver disease; BAAT, BMI, age, ALT, and triglycerides score; NFS, NAFLD fibrosis score; FIB-4, fibrosis-4 index.

of post-prandial) and lipid parameters with NAFLD scores. Again, this pattern was seen when patients were divided into subgroups of BMI categories as per the WHO criteria or gender (Fig. 3, 4).

Discussion

This study assessed baseline NAFLD scores in the patients with type 2 diabetes in a cross-sectional manner. Among NAFLD scores assessed, HAALT could not be assessed since no patient came up with suitable ultrasonography reports. Other scores were calculated for all the study participants.

Our study indicated on median value BARD score was elevated in patients with type 2 diabetes; whereas other scores were not elevated. This could be contributed to the small sample size. Our study indicated variability – as many as 1 patient (3.45%) by APRI and FIB-4 score to 27 patients (93%) by BAAT score to suffering from advanced fibrosis stage (F3 level). In a large cohort of patients with diabetes with biopsy-proven NAFLD patients the sensitivity non-invasive scores like AAR, APRI, FIB-4, and NFS ranged from 38% to 95% [6, 7]. In yet another study, tran-

sient elastography – confirmed NAFLD (an imaging technique to assess the fibrosis, >8 kPa indicates intermediate-advanced fibrosis), FIB-4 values (>1.3 for intermediate to advanced fibrosis) progressively increased in patients without diabetes (8%), pre-diabetes (15%), and diabetes (31%) [8]. A third study also reported highly variable advanced fibrosis using noninvasive scoring ranging from 1% by APRI to 33% by NFS [9]. Even in an Indian study of patients with diabetes, 24/319 (7.5%) had and NFS score >0.67 , which is very similar to our study [10]. In a study by Mohan et al. [11], the prevalence of the NAFLD was 24.5% in patients with diabetes by a separate score, IDRS.

There can be number of arguments than can be made towards this variability of advanced fibrosis using noninvasive scores. First, there is an inherent variability in the construct of the scores; some are more of functional markers while others are structural markers. It can be debated which ones should be preferred – whether serum enzyme markers (e.g., AAR score) over fibrosis markers (e.g., NFS score) [12]. These tests appear to be less sensitive and more specific. Some studies indicate FIB-4 score and NFS score have better correlation with radiological investigations like VCTE [13]. Second, these scores are mere snapshot in the time and may not accurately reflect

changes over long-term aspect of the disease. Hence, they cannot be accurate prognostic markers of repeated variable injury to liver [14, 15]. Last would be inherent variability associated with the scores many of which were designed for hepatitis C related liver injury rather than being specific tool for NAFLD. This makes these tests variable, less accurate than optimal and prone for error. However, these tests are quick, easy, cost-effective, and noninvasive and can be done bed-side at community or non-specialist setting. Nevertheless, numerous guidelines/position statements such as The European Association for the Study of the Liver (EASL 2010), The Italian Association for the Study of the Liver (AISF) and The American Association for the Study of Liver Diseases (AASLD), American College of Gastroenterology (ACG), and The American Gastroenterology Association (AGA) recommend various scores to be used in the evaluation of NAFLD [5]. However, there is a significant difference in guideline recommendation about the routine screening of NAFLD in primary care setting and a global consensus is currently missing. AASLD do not recommend routine screening, whereas the joint guidelines by EASL-EASD-EASO (European Association of Study for the Liver; European Association for Study of Diabetes, and European Association for Study of the Obesity, respectively) recommend screening of NAFLD in primary care setting in patients with obesity or metabolic syndrome [16]. However, given the diabetes, obesity, and metabolic syndrome pandemic in India, it might be prudent for a primary care physician to observe high index of suspicion for NAFLD in patients with diabetes till definitive studies/guidelines are available.

While this study has numerous methodological limitations associated with small sample size and only a cross-sectional study, the results were similar with previous reported studies. While BMI was correlated with some scores, it was not a consistent trend and small sample size can be the reason for lack of correlation between anthropometry, metabolic parameters, age and scores. Our study may serve as a beginning step for planning well-designed robust studies. This study also provides evidence for the possibility of community level screening of patients with diabetes for NAFLD and may help reduce the burden of liver disease by raising early index of suspicion, preventive strategies, and early referral to a hepatologist as well as by helping raise awareness about NAFLD amongst physicians. Since we are currently facing an epidemic of diabetes in India, further innovative research is promptly needed to modify the course of NAFLD.

Conclusion

In this study, we found NINS elevated in some patients with T2DM. The study leads to an assumption that of raised burden of liver disease in patients with T2DM. Health-care professionals should have high index of suspicion in such patients. Further well-designed studies in this domain are required for early detection, management, and reducing the burden of liver disease in Indian patients with diabetes.

Statement of Ethics

Institutional Ethics Committee approval (Institutional Ethics Committee for Biomedical and Health Research, Dr DY Patil Medical College, Navi Mumbai India; IEC Ref. No. DYP/IECBH/2019/111 date of approval: 19 December 2019) was obtained before patient enrolment. All investigations pertaining to obtaining this score were part of routine care of patients and no additional interventions/investigations/extra-follow up visits were done. Written informed consent was obtained by patients before enrolling the patients. The study was conducted in accordance to ICH-GCP criteria and as per Helsinki Declaration. Data were reported in an anonymized manner.

Conflict of Interest Statement

K.J. is a full-time employee and holds shares of a GSK. However, this study was not sponsored by GSK and has no role in it whatsoever. Others have no conflict of interest to report.

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Author Contributions

K.J. wrote the protocol, captured data, checked for completeness, and wrote the manuscript. S.P. and S.C. contributed by screening and inclusion of the patients, capturing data, and contributed to the manuscript writing.

Data Availability Statement

The data are currently not registered in any repository being an observational study and can be made available with appropriate permissions from the authors and the institute (Dr. Smita Patil, email: Smita.patil@dypatil.edu).

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