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ABDA Score: A Non-invasive Model to Identify Subjects with Fibrotic Non-alcoholic Steatohepatitis in the Community☆

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Background: **Non-alcoholic fatty liver disease and non-alcoholic steatohepatitis (NASH) are prevalent in the community, especially among those with metabolic syndrome. Patients with fibrotic NASH are at increased risk of liver-related-events. Currently available non-invasive tests have not been utilized for screening for fibrotic NASH among the community. We aimed to develop a screening tool for fibrotic NASH among community members.** ***Methods:*** **We included two large cohorts aimed at assessing cardiovascular disease among community members. Fibrotic NASH was defined using the FibroScan-aspartate aminotransferase score of ≥0.67 that identifies ≥F2 fibrosis and a non-alcoholic fatty liver disease activity score ≥4 with a specificity of 90%. Metabolic parameters, biochemical tests and anthropometry were used to develop a multivariate model.** ***Results:*** **The derivation cohort (n = 1660) included a population with a median age 45 years, 42.5% males, metabolic syndrome in 66% and 2.7% (n = 45) with fibrotic NASH. Multivariate analysis identified the four significant variables (Age, body mass index , Diabetes and alanine aminotransferas levels) used to derive an ABDA score. The score had high diagnostic accuracy (the area under receiver-operating characteristic curve, 0.952) with adequate internal validity. An ABDA score ≥−3.52 identified fibrotic NASH in the derivation cohort with a sensitivity and specificity of 88.9% and 88.3%. The score was validated in a second cohort (n = 357) that included 21 patients (5.9%) with fibrotic NASH, where it demonstrated a high area under receiver-operating characteristic curve (0.948), sensitivity (81%) and specificity (89.3%).** ***Conclusions:*** **ABDA score utilizes four easily available parameters to identify fibrotic NASH with high accuracy in the community. (J Clin Exp Hepatol xxxx;xxx:xxx)**

Non-alcoholic fatty liver disease (NAFLD) is the commonest liver disease worldwide, with an estimated prevalence of about 25%.[1] One-fifth patients with NAFLD develop chronic hepatitis and are at risk of organ impairment, referred to as non-alcoholic steatohepatitis (NASH). Despite the prevalence of NAFLD being as high as 60% in the community, the American Association for the Study of the Liver Diseases and the European Association for the Study of the Liver advise against community screening.[2,3,4] A poor predictive value of the available diagnostic tests, cost of screening, lack of understanding of the natural history of the disease, and limited therapeutic options form the basis of these recommendations.[5] Even in a high-risk group of patients (those with diabetes), screening for NASH was not found to be cost-effective.[6]

Patients with NASH can be further subdivided, based on the severity of fibrosis on histology, into early NASH (F0–F1 fibrosis), fibrotic NASH (≥F2 fibrosis) and NASH-cirrhosis (F4 fibrosis). One-stage progression in fibrosis occurs in 14.3 and 7.1 years in patients with NAFLD and NASH, respectively.[7] To improve the long-term outcomes, identifying subjects with fibrotic NASH is essential as they are at risk of complications, disease

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Abbreviations: ALT: alanine aminotransferase; AST: aspartate aminotransferase; BMI: body mass index; CAP: controlled attenuation potential; FAST: FibroScan-AST; FIB-4: fibrosis-4; FPG: fasting plasma glucose; HOMA-IR: homeostatic model assessment-insulin resistance; HL: Hosmer–Lemeshow; LSM: liver stiffness measure; NAFLD: Non-alcoholic fatty liver disease; NAS: NAFLD activity score; NASH: non-alcoholic steatohepatitis; NFS: NAFLD fibrosis score
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progression and may benefit from potential pharmacological therapy.[8] The NAFLD fibrosis score (NFS)[9] and the the body mass index (BMI), aspartate aminotransferase (AST) to alanine aminotransferase (ALT) ratio and diabetes (BARD) score [10] are validated models for predicting advanced fibrosis in patients with NAFLD. However, their utility in identifying fibrotic NASH (≥F2 fibrosis) among asymptomatic individuals in the community has not been evaluated.

The FibroScan-AST (FAST) score is a composite score based on the ultrasonographic transient elastography parameters of liver stiffness measure (LSM), controlled attenuation potential (CAP), as well as AST.[11] At the cut-off of a FAST score ≥0.67, biopsy-proven fibrotic NASH (NAFLD with a histological NAFLD activity score [NAS] ≥4, and fibrosis ≥2) can be ruled-in with a 90% specificity. We aimed to evaluate fibrotic NASH (FAST ≥0.67) community prevalence in asymptomatic individuals and develop an identification model. We also validated the model in a separate cohort of asymptomatic family members of patients with NAFLD.

PATIENTS AND METHODS

Study Setting and Subjects

A retrospective analysis of two prospectively maintained databases of asymptomatic subjects was done. The derivation cohort comprised of prospectively evaluated consecutive asymptomatic subjects 30–60 years of age, residing in North India, between March 2017 to February 2020. The urban cohort from New Delhi included 828 subjects randomly selected from the ongoing Centre for cArdiac Risk Reduction in South Asia study,[12] aimed at assessing the cardiovascular risk in urban South-Asia. The rural cohort from Ballabgarh town of Haryana comprised of 832 subjects randomly selected from an ongoing study by the Indian Council of Medical Research, the Coronary Heart Disease repeat survey, that aims to estimate the risk of coronary artery disease in the rural community. The study was approved by the institute ethics committee (IEC/NP-307/05-09-2014). Subjects with significant alcohol consumption (>20 g/day or 140 g/week), a previous history of cirrhosis, hepatocellular carcinoma, hepatitis B and C infection, pregnant females and bedridden individuals were excluded.

The validation cohort comprised of prospectively screened consecutive asymptomatic family members (>13 years of age) of patients with NAFLD evaluated at a tertiary care hospital in New Delhi. They were evaluated as part of the study to estimate the NAFLD prevalence and predictors in the family members of patients with NAFLD. The subjects were recruited between April 2019 and July 2020, and the study was approved by the institute ethics committee (IECPG-229/22.04.2019). All subjects in the derivation and validation cohorts underwent an estimation of anthropometric parameters (height, weight, BMI, waist circumference and hip circumference), blood investigations (fasting plasma glucose [FPG] and insulin levels, total cholesterol, triglyceride and low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, very low-density lipoprotein-cholesterol, AST, ALT and glycosylated hemoglobin A1c levels [HbA1c]), and ultrasonography of the abdomen using a 3.5–5 MHz curvilinear transducer (either Siemens – Model: ACUSON X300 or PHILIPS-Model: IU22 G Cart) and transient elastography (FibroScan 502 Touch®, ECHOSENS, Paris, France) for the estimation of LSM and CAP.[4]

Definitions

NAFLD diagnosis was based on bright liver echotexture on ultrasonography with negative serology for hepatitis B and C and without significant alcohol intake. Hypertension was diagnosed based on two separate seated blood pressure readings of ≥140/90 mmHg.[13,14] Diabetes mellitus was diagnosed if FPG was ≥126 mg/dL after no calorie intake for at least 8 h or HbA1C ≥6.5%; post-load blood glucose estimation was not done.[15] Metabolic syndrome was defined based on the presence of three out of the five criteria (elevated FPG, elevated blood pressure [≥130/85 mm Hg or use of medications], increased waist circumference, increased triglyceride and decreased high-density lipoprotein-cholesterol) as defined by the National Cholesterol Education Program-Adult Treatment Panel III guidelines modified for the Asian population.[16,17] Increased homeostatic model assessment-insulin resistance (HOMA-IR) was defined as ≥2.5.[18] Few subjects in the validation cohort could not undergo all investigations due to the ongoing coronavirus disease pandemic. In subjects with missing data for metabolic syndrome components, the missing variable was assumed to be absent.

Estimation of LSM, CAP, and FAST Scores

All subjects underwent estimation of LSM and CAP scores using FibroScan touch 502 (ECHOSENS, Paris, France). The protocols for the assessment of LSM and CAP scores have been previously validated in our cohort.[19] All measurements were recorded using M and XL probes in subjects with BMI <30 kg/m^2 and ≥30 kg/m^2, respectively. AST estimation was done within one month of the estimation of LSM and CAP. The FAST score was calculated using the LSM, CAP and AST values.[11] The presence of fibrotic NASH was diagnosed based on the rule-in cut-off of the FAST score ≥0.67. The FAST score has been previously validated to predict fibrotic NASH in our population.[20] The study was done in asymptomatic individuals in the community and relatives of subjects with NAFLD, and none underwent a liver biopsy.

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Table 1 Baseline Characteristics of Subjects in the Derivation and Validation Cohorts.

	Derivation cohort (n = 1660)	Validation cohort (n = 357)	*P*-value
Age (years)	45 (39–52)	33 (22–45)	**<0.001**
Sex (Male) (%)	705 (42.5%)	196 (54.9%)	**<0.001**
Weight (kg)	66.5 ± 13.8	67.9 ± 15.6	0.111
Height (cm)	159.2 ± 9.2	163 ± 10.3	**<0.001**
BMI (kg/m^2)	26.2 ± 4.9	25.5 ± 5.0	**0.021**
WC (cm)	91.2 ± 12.0	90.8 ± 13.2	0.627
HC (cm)	98.6 ± 10.0	94.5 ± 12.6	**<0.001**
Diabetes (%)	372 (22.4%)	42 (11.8%)	**<0.001**
Hypertension (%)	483 (29.1%)	85/337 (25.2%)	0.151
Metabolic syndrome (%)†	1100 (66.3%)	158 (44.3%)	**<0.001**
SBP (mmHg)	122.5 ± 18.2	122.1 ± 14.7	0.715
DBP (mmHg)	81.4 ± 11.0	77.8 ± 9.0	**<0.001**
AST (IU/L)	26 (22–33)	25 (20–34)	0.212
ALT (IU/L)	27 (19–40)	27 (18–45)	0.324
FPG (mg/dL)	108 (102–120)	94 (86–103)	**<0.001**
Insulin (mIU/L)	9.6 (5.6–14.6)	5.3 (2.7–8.4)	**<0.001**
HOMA-IR	2.6 (1.5–4.4)	1.2 (0.6–2.0)	**<0.001**
HbA1C (%)	5.5 (5.2–6.0)	5.6 (5.2–6.1)	0.171
Cholesterol (mg/dL)	185 (162–214)	173 (144–200)	**<0.001**
TG (mg/dL)	133 (99–182)	120 (91–161)	**<0.001**
LDL-C (mg/dL)	113 (94–134)	112 (90–134)	0.111
HDL-C (mg/dL)	44 (38–50)	41 (37–47)	**<0.001**
VLDL-C (mg/dL)	26 (20–35)	17 (14–24)	**<0.001**
LSM (kPa)	4.6 (3.8–5.6)	5.0 (4.3–6.1)	**<0.001**
CAP (dB/m)	268 (229–313)	275 (220–315)	0.940
NAFLD	1057 (63.7%)	204/356 (57.3%)	**0.024**
FAST ≥0.67	45 (2.7%)	21 (5.9%)	**0.002**
Metabolic risk abnormality components			
• 0	34 (2.0%)	26 (7.3%)	**<0.001**
• 1	174 (10.5%)	75 (21.0%)	
• 2	352 (21.2%)	98 (27.5%)	
• 3	538 (32.4%)	88 (24.6%)	
• 4	413 (24.9%)	51 (14.3%)	

Values expressed as mean ± standard deviation, median (interquartile range) or frequency (percent), as appropriate.
Footnote: †- Diagnosed according to the National Cholesterol Education Program- Adult Treatment Panel III criteria.
Abbreviations: ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; BP: blood pressure; BMI: body mass index; CAP: controlled attenuation parameter; DBP: diastolic blood pressure; FAST: FibroScan-aspartate aminotransferase; FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin; HC: hip circumference; HDL-C: high-density lipoprotein cholesterol; HOMA-IR: homeostatic model assessment-insulin resistance; LDL-C: low-density lipoprotein cholesterol; LSM: liver stiffness measure; NAFLD: non-alcoholic fatty liver disease; SBP: systolic blood pressure; TG: triglyceride; VLDL-C: very-low density lipoprotein cholesterol; WC: waist circumference.

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Table 2 Characteristics of Patients With and Without Fibrotic NASH in the Derivation Cohort.

	Subjects with fibrotic NASH (n = 45)	Subjects without fibrotic NASH (n = 1615)	*P*-value
Age (years)	47.2 ± 8.7	45.3 ± 7.9	0.096
Sex (Male) (%)	27 (60%)	678 (42%)	**0.016**
Weight (kg)	77.1 ± 13.9	66.2 ± 13.6	**<0.001**
Height (cm)	160.4 ± 10.0	159.2 ± 9.1	0.368
BMI (kg/m^2)	30.0 ± 4.9	26.1 ± 4.9	**<0.001**
WC (cm)	102.3 ± 10.0	90.8 ± 11.9	**<0.001**
HC (cm)	103.1 ± 9.1	98.5 ± 10.0	**0.002**
Diabetes (%)	31 (68.9%)	341 (21.1%)	**<0.001**
Hypertension (%)	24 (53.3%)	459 (28.4%)	**<0.001**
Metabolic syndrome (%)†	39 (86.7%)	1061 (65.7%)	**0.003**
SBP (mmHg)	130.9 ± 18.1	122.2 ± 18.2	**0.002**
DBP (mmHg)	86.2 ± 10.7	81.3 ± 10.9	**0.003**
AST (IU/L)	73 (57–90)	26 (22–32)	**<0.001**
ALT (IU/L)	81 (60–119)	26 (19–39)	**<0.001**
ALP (IU/L)	124 (99–159)	93 (76–111)	**<0.001**
FPG (mg/dL)	148 (117–213)	108 (101–119)	**<0.001**
Insulin (mIU/L)	17.9 (10.9–26.0)	9.5 (5.5–14.3)	**<0.001**
HOMA-IR	6.7 (4.1–10.7)	2.6 (1.5–4.3)	**<0.001**
Increased HOMA-IR (%)	39 (86.7%)	854 (52.9%)	**<0.001**
HbA1C (%)	6.7 (5.7–9.6)	5.5 (5.2–5.9)	**<0.001**
Cholesterol (mg/dL)	182 (169–228)	185 (161–214)	0.340
TG (mg/dL)	143 (100–210)	133 (99–182)	0.149
LDL-C (mg/dL)	115 (102–143)	113 (93–136)	0.184
HDL-C (mg/dL)	43 (34–48)	44 (38–50)	0.148
VLDL-C (mg/dL)	28 (20–38)	26 (20–35)	0.170
LSM (kPa)	12.0 (9.0–20.2)	4.5 (3.7–5.5)	**<0.001**
CAP (dB/m)	355 (311–378)	266 (229–309)	**<0.001**
Metabolic risk abnormality components			
• 0	0 (0%)	34 (2.1%)	**<0.001**
• 1	0 (0%)	174 (10.8%)	
• 2	6 (13.3%)	346 (21.4%)	
• 3	9 (20.0%)	529 (32.8%)	
• 4	23 (51.1%)	390 (24.1%)	
• 5	7 (15.6%)	142 (8.8%)	

Values expressed as mean ± standard deviation, median (interquartile range) or frequency (percent), as appropriate.
Footnote: †- Diagnosed according to the National Cholesterol Education Program- Adult Treatment Panel III criteria.
Abbreviations: ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; BP: blood pressure; BMI: body mass index; CAP: controlled attenuation parameter; DBP: diastolic blood pressure; FAST: FibroScan-aspartate aminotransferase; FPG: fasting plasma glucose; HbA1c: glycosylated haemoglobin; HC: hip circumference; HDL-C: high-density lipoprotein cholesterol; HOMA-IR: homeostatic model assessment-insulin resistance; LDL-C: low-density lipoprotein cholesterol; LSM: liver stiffness measure; NASH: non-alcoholic steatohepatitis; SBP: systolic blood pressure; TG: triglyceride; VLDL-C: very-low density lipoprotein cholesterol; WC: waist circumference.

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Outcomes

The primary objective was to estimate the prevalence of fibrotic NASH in asymptomatic individuals in the community. We developed a model to predict the presence of fibrotic NASH in the community and validated it in a cohort of asymptomatic family members of patients with NAFLD. In addition, we compared the discriminative ability of the model in predicting fibrotic NASH, compared to other validated fibrosis prediction scores such as the NFS, BARD, and fibrosis-4 (FIB-4) score.[9,10,21] The transparent reporting of a multivariable prediction model for individual prognosis or diagnosis guidelines were followed for developing and validating the model.

Statistical Analysis

Categorical variables were expressed as frequency (%), and the association between two qualitative independent variables was assessed using a Chi-square test/Fisher's exact test. Continuous variables, depending on the normalcy of distribution, were expressed as mean ± standard deviation or median (interquartile range) and analyzed using the Independent Sample t test or Mann–Whitney U test, respectively. A stepwise multivariable logistic regression procedure was used to identify the factors associated with fibrotic NASH. Variables were considered for model building based on their association at the level of significance up to $P = 0.25$ under a crude association analysis or their clinical relevance. Accordingly, covariates were considered for the stepwise procedure with an entry probability 0.050 and a removal probability 0.051. Results were expressed as odds ratio (OR), and corresponding 95% confidence interval (CI) and a predictive model was created using the beta coefficient of the independent variables predicting fibrotic NASH. The performance of the model was assessed using measures of calibration, discrimination and clinical usefulness. Internal validation was assessed using a bootstrap simulation analysis. Calibration of the predicted probabilities calculated by the model was investigated using the Hosmer–Lemeshow (HL) goodness of fit test and calibration plots, which were constructed using predicted and estimated probabilities incorporating locally estimated scatterplot smoothening. The 95% CI of the slope and intercept was estimated. The slope and intercept were considered within the acceptable range if the CI included one and zero, respectively. A specification error in the model was assessed by a link test, and the covariates which did not fulfill the linearity assumption were log transformed. The model's discriminative power was assessed by plotting a receiver operating characteristic curve, an estimating area under the curve (AUC) and the correctly classified value. An appropriate cut-off for predicting fibrotic NASH was estimated based on the sensitivity and specificity.

The model performance was also evaluated in the validation cohort by assessing its discrimination ability on the validation dataset.[22] Additionally, the DeLong test was used to compare the model's performance to other fibrosis prediction scores (NFS, BARD, and FIB-4) by comparing their AUC. All statistical analysis was done using statistical software, SPPS (version 23.0 Chicago, IL, USA) and STATA/SE version 14.2 (StataCorp LP, College Station, TX, USA).

RESULTS

Baseline Characteristics of the Derivation Cohort

Over the study period, 1660 subjects (828 urban and 832 rural) were evaluated in the derivation cohort (Supplementary Figure 1). The median (interquartile range) age was 45 (39–52) years, and 705 (42.5%) subjects were males (Table 1). Diabetes, hypertension and metabolic syndrome were present in 372 (22.4%), 483 (29.1%) and 1100 (66.3%) subjects, respectively. The median LSM, CAP and AST values were 4.6 kPa, 268 dB/m and 27 IU/L, respectively. Of 1660 subjects, 45 (2.7%) had fibrotic NASH (FAST ≥0.67), with significantly higher prevalence in the urban cohort 38/828 (4.6%) compared to the rural cohort 7/832 (0.8%), $P < 0.001$. Subjects with fibrotic NASH had significantly higher weight, BMI, waist circumference and hip circumference than those without fibrotic NASH (Table 2). The prevalence of metabolic dysregulation—diabetes, hypertension, metabolic syndrome and increased HOMA-IR—was higher in the former group. Subjects with fibrotic NASH had significantly higher median LSM and CAP, 12.0 kPa and 355 dB/m, compared to 4.5 kPa and 266 dB/m in those without fibrotic NASH ($P < 0.001$ for both comparisons).

Predictors of Fibrotic NASH

Independent predictors for fibrotic NASH were evaluated in the derivation cohort including both the rural and urban cohort (Supplementary Table 1). To avoid collinearity, metabolic syndrome components such as impaired fasting glucose and elevated blood pressure (≥130/85 mm Hg) were not included in the model with diabetes and hypertension. The aim of the predictive model was to predict fibrotic NASH based on the FAST score. Therefore, the FAST score components, LSM, CAP, and AST, were not included for the univariate analysis. In the univariate analysis, male gender (OR 2.07, 95% CI 1.13–3.97, $P = 0.018$), increased waist circumference (OR 8.52, 95% CI 2.06–35.31, $P = 0.003$), diabetes (OR 8.27, 95% CI 4.35–15.73, $P < 0.001$), hypertension (OR 2.88, 95% CI 1.59–5.22, $P = 0.001$), increased HOMA-IR (OR 5.79, 95% CI 2.44–13.76, $P < 0.001$), BMI (OR 1.14, 95% CI 1.08–1.20, $P < 0.001$) and ALT (OR 1.05, 95% CI 1.04–1.06,

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Table 3 Predictors of Fibrotic NASH (FAST ≥0.67) in the Derivation Cohort.

Risk factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age	1.03	0.99–1.07	0.097	1.05	1.00–1.10	**0.034**
BMI	1.14	1.08–1.20	**<0.001**	1.15	1.07–1.24	**<0.001**
Diabetes	8.27	4.35–15.73	**<0.001**	4.09	1.88–8.92	**<0.001**
ln (ALT)[a]	25.70	13.32–49.58	**<0.001**	38.47	17.08–86.63	**<0.001**

Abbreviations: ALT: alanine BMI: body mass index; CI: confidence interval; FAST: FibroScan-aspartate aminotransferase; NASH: non-alcoholic steatohepatitis; OR: odds ratio.
[a]Log transformed ALT.

$P < 0.001$) were independent predictors for fibrotic NASH. However only four variables were selected for the model after a stepwise procedure. In an multivariable analysis, diabetes (OR 4.09, 95% CI 1.87–8.92, $P < 0.001$), BMI (OR 1.15, 95% CI 1.07–1.24, $P < 0.001$), ln ALT (38.47, 95% CI 17.08–86.63, $P < 0.001$) and age (OR 1.05, 95% CI 1.00–1.10, $P = 0.034$) were significantly associated factors of fibrotic NASH (Table 3).

Development of a Predictive Model

A predictive model was developed based on the four parameters (ALT, BMI, diabetes, and age) which were significant in the multivariable analysis. The addition of each parameter increased the model's discriminative power to a maximum when all four components were incorporated (AUC 0.952). A composite score (**ABDA** score) was calculated from using the regression coefficient of the four parameters (**A**LT in IU/mL, **B**MI in kg/m^2, **D**iabetes as present or absent and **A**ge in years), and was calculated as:

ABDA score = −24.74 + (3.65*ln (**ALT**)) + (0.14***BMI**) + (1.41***Diabetes[present (1)/absent (0)]**) + (0.05***Age**).

Evaluating Model Performance in the Derivation Cohort

Regarding internal validity under a bootstrap simulation analysis (with replacement) considering thousand iterations, the AUC was calculated as the same (AUC 0.952). This suggests satisfactory internal validity of the developed model. Also, the HL goodness of the fit test indicated that the model fits the data satisfactorily ($P = 0.28$) and there was no specification error under the link test (hatsq $P = 0.53$). The calibration plot also supports the same results (Figure 1A). Discrimination was assessed by estimating the AUC for the model in predicting fibrotic NASH. The model showed excellent AUC in the derivation cohort (0.952, 95% CI: 0.921–0.983) (Figure 1B). At the cut-off of ≥-3.52, the ABDA score had a sensitivity, specificity and correctly classified value of 88.9%, 88.3% and 88.3% respectively (Figure 2).

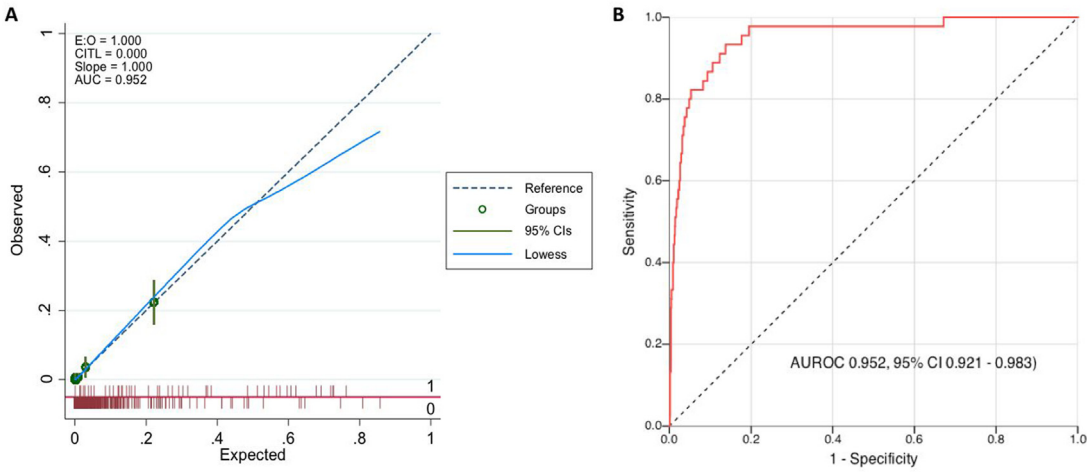

Figure 1 (A) The Hosmer–Lemeshow calibration plot, with Loess smoothing, for the prediction model in the overall derivation cohort showing satisfactory fit. EO: expected/observed ratio; CITL: calibration-in-the-large; AUC: area under the curve; Loess: locally estimated scatterplot smoothening (B) Receiver operating characteristic curve for the ABDA score in predicting fibrotic non-alcoholic steatohepatitis in the derivation cohort.

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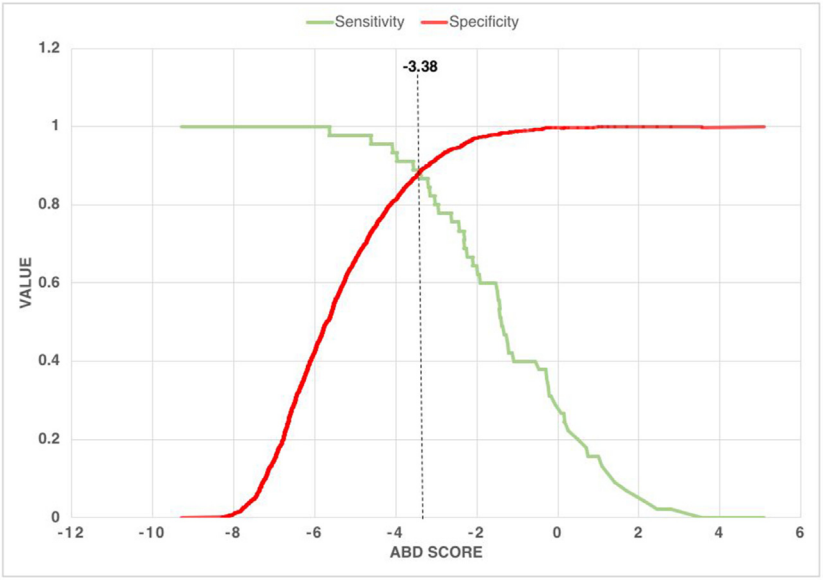

Figure 2 Line diagrams showing the sensitivity and specificity of various ABDA scores in predicting subjects with fibrotic non-alcoholic steatohepatitis.

The ABDA score could identify 40/45 (88.9%) subjects with fibrotic NASH in the derivation cohort (Table 4). At ALT of 30 IU/L, BMI of 23 kg/m^2, the presence of diabetes and the age of 30 years, the estimated ABDA score was −6.20, which rules out the presence of fibrotic NASH with a sensitivity of 97.8% and specificity of 54.3%. Similarly, at ALT of 60 IU/L, BMI of 30 kg/m^2, diabetes and the age of 50 years, the ABDA score was −1.69, which rules-in the presence of fibrotic NASH with a sensitivity of 62.2% and specificity of 97.4% (Figure 2).

Model Validation

The model was validated in the cohort of asymptomatic family members of subjects with NAFLD. Out of 357 asymptomatic family members, 356 had an available ultrasound report. The median age was 33 years, and 42 (11.8%), 85 (25.2%) and 158 (44.3%) subjects had diabetes, hypertension and metabolic syndrome, respectively. NAFLD and fibrotic NASH were present in 204 (57.3%) and 21 (5.9%) subjects, respectively (Table 1). The validation cohort had a lower prevalence of diabetes, metabolic syndrome and NAFLD, likely due to a younger age. The HL goodness of the fit test showed that the model fits the data satisfactorily (P = 0.98), and the calibration plot is shown in Figure 3A. Under validation data, the AUC of the developed model was also excellent (AUC 0.948, 95% CI: 0.918–0.977) (Figure 3B). An ABDA score at a cutoff of −3.52 could identify 17/21 (81.0%) patients with fibrotic

Table 4 Performance of the ABDA Score in the Derivation and Validation Cohorts.

	Derivation cohort (n = 1660)	Validation cohort (n = 357)
Prevalence of fibrotic NASH	45/1660 (2.7%)	21/357 (5.9%)
AUC for ABD score	0.952 (0.921–0.983)	0.948 (0.918–0.977)
ABD score ≥ −3.52 in patients with fibrotic NASH	40/45 (88.9%)	17/21 (81.0%)
ABD score ≥ −3.52 in patients without fibrotic NASH	188/1615 (11.6%)	36/336 (10.7%)
Sensitivity[a]	88.9% (75.9–96.3)	81.0 (58.1–94.6)
Specificity[a]	88.3% (86.7–89.9)	89.3 (85.5–92.4)
PPV[a]	17.5 (12.8–23.1)	32.1 (24.6–40.7)
NPV[a]	99.7 (99.2–99.9)	98.7 (96.9–99.5)
Positive LR[a]	7.6 (6.4–9.0)	7.6 (5.2–11.0)
Negative LR[a]	0.1 (0.1–0.3)	0.2 (0.1–0.5)

Abbreviations: AUC: area under curve; LR: likelihood ratio; NASH: non-alcoholic steatohepatitis; NPV: negative predictive value; PPV: positive predictive value.
[a]At a cutoff of ABDA score −3.52 points.

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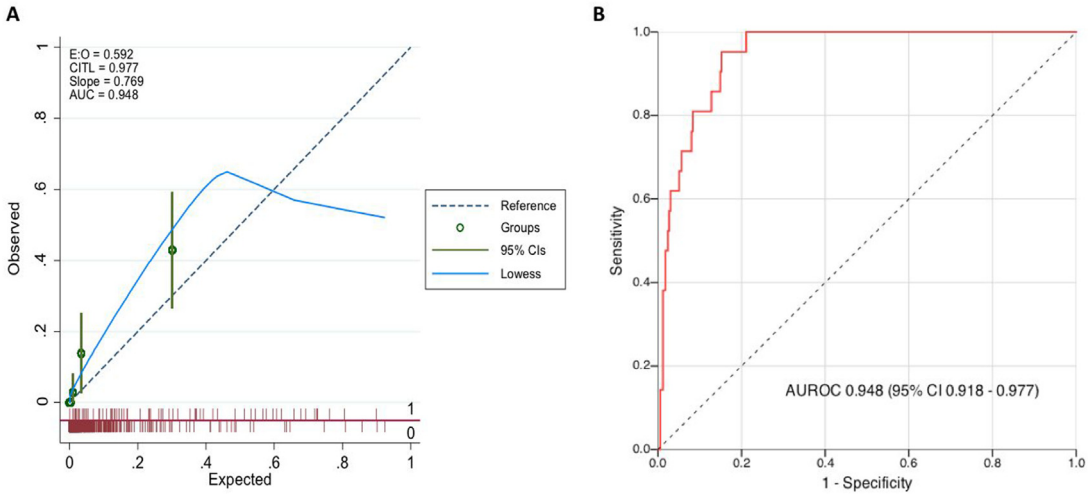

Figure 3 (A) The Hosmer–Lemeshow calibration plot, with Loess smoothing, for the prediction model in the validation cohort showing satisfactory fit. EO: expected/observed ratio; CITL: calibration-in-the-large; AUC: area under the curve; Loess: locally estimated scatterplot smoothening (B) Receiver operating characteristic curve for the ABDA score in predicting fibrotic non-alcoholic steatohepatitis in the validation cohort.

NASH (Table 4). There were no differences in the diagnostic performance (AUC) of the developed model on validation data compared to the derivation cohort (P = 0.85). The ABDA score also performed well when AUC was calculated for diagnostic performance among only adult participants older than 18 years (n = 310, AUC 0.94 [95% CI 0.90–0.97]) in the validation cohort as well as among those above 30 years of age (n = 203, AUC 0.93 [95% CI 0.88–0.97], as was the inclusion criteria for the derivation cohort.

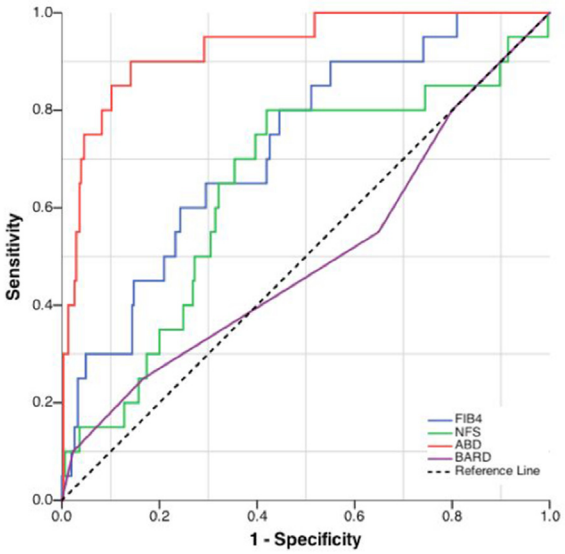

Figure 4 Receiver operating characteristic curve for the ABDA score, non-alcoholic fatty liver disease fibrosis score, fibrosis-4 and body mass index, aspartate aminotransferase to alanine aminotransferase ratio and diabetes score in predicting fibrotic non-alcoholic steatohepatitis. The ABDA score showed a better discriminative ability than all other predictive scores (P < 0.05, Delong test).

Comparison of the ABDA Score with Other Fibrosis Prediction Scores in the Validation Cohort

The ABDA score was compared to other non-invasive scores (NFS, BARD, and FIB-4) for fibrosis in the validation cohort. The median NFS, BARD and FIB-4 scores were −2.49 (−3.46 to −1.34), 2.0 (1.0–2.0) and 0.81 (0.49–1.30), respectively. The AUC for the NFS, BARD and FIB-4 score in predicting fibrotic NASH was 0.642 (0.510–0.774), 0.501 (0.357–0.645) and 0.726 (0.617–0.835), respectively (Figure 4).

DISCUSSION

It is important to identify those subjects with NAFLD who have NASH and significant fibrosis because they are at the highest risk of disease progression and warrant lifestyle modifications with/without pharmacological therapy. Our results show that the prevalence of fibrotic NASH in the community is 2.7%, with higher prevalence in the urban compared to the rural population. This is indeed alarming because our study subjects included asymptomatic individuals in the community. In the validation cohort of the family members of patients with NAFLD, the prevalence was even higher. We developed and validated a novel predictive score, the ABDA score, to identify subjects with fibrotic NASH in the community. The model was well calibrated, had an excellent discriminative ability and predicted fibrotic NASH with a high sensitivity and specificity of about 90%. In the validation cohort too, which included younger subjects with lower prevalence of metabolic risk-factors, the model had a similar discriminative ability.

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A recent meta-analysis suggests one in three Indians have NAFLD.[23] The prevalence of NASH varies between 3 and 5% worldwide, whereas the prevalence of ≥F3 fibrosis in subjects with NAFLD varies between 4.35% and 6.90%.[24,25] The community prevalence of fibrotic NASH is difficult to estimate because of the limitations in obtaining a liver biopsy in asymptomatic individuals in the community. This subgroup of subjects warrants therapeutic interventions and should, therefore, be identified early. Subjects with fibrotic NASH have significantly higher metabolic risk factors, and early identification of this subgroup can prevent future cardiovascular and hepatic complications.

Multiple scores predict fibrosis in subjects with NAFLD. The NFS was developed to predict advanced fibrosis (≥F3) in subjects with NAFLD.[9] The FIB-4 score was developed to predict significant fibrosis in patients with human immunodeficiency virus and hepatitis C virus co-infection and has been validated as a predictor of fibrosis in NAFLD too.[21,26] More recently, the magnetic resonance imaging(MRI)-AST score that utilizes MRI-based proton density fat fraction and elastography has been shown to be superior to FAST, FIB4 and NFS scores as well.[27] The requirement of a MRI or FibroScan prohibits any clinical utility of the FAST or MRI-AST scores for screening for fibrotic NASH in the primary care setting.[11] Fatty liver index was used to identify subjects with fatty liver in the community; however, NAFLD is extremely common in the community and, in the absence of advanced fibrosis, has a lower rate of liver-related events or mortality.[28] Thus, current guidelines do not recommend screening individuals for NAFLD in community.[3,25] Existing non-invasive tests to detect fibrotic NASH or NAFLD with advanced fibrosis have been reported and validated only in patients with specific risk factors, such as those with ultrasonogram-identified NAFLD,[29] diabetes with metabolic syndrome,[30] or those undergoing colonoscopy.[31] To the best of our knowledge, ours is the first clinical model that identifies fibrotic NASH in the community. The ABDA score incorporates readily available anthropometric and laboratory parameters, can be easily calculated using app-based calculators and predicts fibrotic NASH with excellent accuracy. Subjects with an ABDA score ≥−3.52 had a high probability of having fibrotic NASH and should be further evaluated.

Our study has a few limitations. The derivation and validation cohorts included subjects evaluated at two centers in North India, and need further validation of our results in diverse populations. The study was performed in asymptomatic individuals in the community and hence, a liver biopsy was not performed in any subject. However, we have previously shown that the FAST score has a good predictive accuracy in identifying subjects with fibrotic NASH in our population.[20] The validation cohort was significantly younger and had lesser metabolic risk factors compared to the derivation cohort. We included all the subjects in order to evaluate our model performance across different age groups, and found no differences in the diagnostic performance of the model in the two cohorts. We could not estimate the platelet count and albumin in the derivation cohort, and the ABDA score could not be compared to other non-invasive markers (NFS and FIB-4) in the derivation cohort. However, the ABDA score had a better discriminative ability than other non-invasive scores in the validation cohort. The ABDA score has a low positive predictive value and should be used to rule out significant fibrosis.

The use of this score can aid clinicians identify subjects with fibrotic NASH in the community using easily available anthropometric and laboratory investigations. The ABDA score can be used as a screening tool to identify subjects with fibrotic NASH in the community, thereby, identifying those asymptomatic subjects who have the most advanced disease and need therapeutic interventions.

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CONFLICTS OF INTEREST

The authors have none to declare.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jceh.2023.03.008.

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