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ORIGINAL CONTRIBUTIONS

The HAALT Non-invasive Scoring System for NAFLD in Obesity

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Abstract

Background The prevalence of NAFLD increases in obese diabetics. Accurate diagnosis of NAFLD requires invasive liver biopsies, which is costly, and time consuming and labor intensive. Currently, there is a lack of non-invasive diagnostic methods to identify those with NASH, in obese Indians.

Objectives To develop an accurate non-invasive scoring system using clinical and biochemical parameters to predict the risk of developing non-alcoholic steatohepatitis (NASH).

Methods Clinical and biochemical parameters were recorded pre-operatively from 290 patients who were posted for bariatric/metabolic surgery, between September 2017 and October 2018 and compared with the result of intra-operative liver biopsy NAFLD activity scores (NAS).

Results The mean weight and BMI of the patients were 120.3 ± 24.6 and 45.5 ± 7.8 respectively. In the final histopathological examination, 196/290 (67.6%) had simple steatosis, 92/290 (31.7%) had NASH, and 2/290 (0.007%) had cirrhosis. Binary logistic regression analysis of multiple independent predictors yielded five independent factors that were statistically significant (HbA1c, AST, ALT, liver span on USG, and serum triglycerides). These were used to create a scoring system, with a range of scores from 0 to 6, with maximum predictability at a score of 6. Patients with scores of ≧ 3 were at high risk of NASH diagnosis. The sensitivity of this scoring system was 85.87% and diagnostic accuracy was 75.35%.

Conclusions Our study not only confirms the significant association of NAFLD with obesity but also outlines a simple non-invasive scoring system to identify obese individuals at high risk for NASH.

Keywords Obesity · Metabolic syndrome · Non-alcoholic fatty liver disease · Non-alcoholic steatohepatitis · Liver biopsy · Type 2 diabetes mellitus · Bariatric surgery · Scoring system · Predictive model · Hepatosteatosis · Morbid obesity

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Introduction

Obesity is rapidly gaining notoriety as one of the most lethal diseases worldwide. An estimated 107 million Indians alone are suffering from obesity, which accounts for roughly 8–10% of the population [1]. Obesity is accompanied by several co-morbidities (most of which are life threatening). With the rising number of obese individuals, the prevalence of co-morbidities is also on the rise [2]. Non-alcoholic fatty liver disease (NAFLD) is one of these co-morbidities presenting in 30–100% of all obese individuals and alarmingly in 53% of all obese children [3, 4].

NAFLD is caused by significant lipid accumulation (5–10%) in the hepatic tissue in the absence of significant chronic alcohol intake. It is the commonest liver disease worldwide [5]. The natural history of NAFLD ranges from simple steatosis (without inflammation and fibrosis) to steatohepatitis (with inflammation and fibrosis), which can eventually lead to progressive hepatic fibrosis in up to 20% of patients, causing hepatic cirrhosis and liver failure over time [6]. In a fraction of these patients who develop cirrhosis, it eventually progresses to hepatocellular carcinoma [6].

Metabolic syndrome is a cluster of conditions; inclusive of, but not limited to obesity, insulin resistance, hyperinsulinemia, hypertriglyceridemia, and hypertension [7]. NAFLD is commonly referred to as the hepatic component of metabolic syndrome. Studies suggest that hepatic fat content influences the degree of insulin resistance in type-2 diabetes mellitus (T2DM), with the amount of fat deposited in the liver commonly influencing the daily insulin requirement [8]. Additional factors associated with the development of NAFLD include chronic inflammation, oxidative stress, and adipokine dysregulation [8]. A large Indian population-based study revealed that the majority (91%) of subjects with a BMI > 30 kg/m^2 had some evidence of steatosis on ultrasound [9].

Various scoring systems have been published from the Western countries to predict the prevalence of non-alcoholic steatohepatitis (NASH) [10–14]. However, some of the studies have not been validated and the ones that have been validated have various inconsistencies [15]. Radiological investigations like ultrasound will diagnose NAFLD but cannot distinguish between simple steatosis and steatohepatitis [16]. The "gold standard" to identify the type of NAFLD is only histological examination of a liver biopsy [15]. However, performing an ultrasound-guided liver biopsy is invasive and cost-intensive and has its own set of complications (2–4%), such as uncontrolled hemorrhage and bile leak. In contrast, performing an intra-operative liver biopsy has the advantage of ensuring strict hemostasis under vision following a liver biopsy [16].

The prevalence of NAFLD in the general population in the USA is 30%, which corroborates with the prevalence of obesity in the USA [15]. The prevalence of NAFLD in Asian populations varies from 20 to 45% as per various studies [17, 18]. Obesity is on the rise in India and other Asian countries, which can be attributed to changing lifestyles and dietary habits. Obesity coupled with insulin resistance and T2DM has possibly caused a rise of NAFLD in India. Various studies on NAFLD have been published from the Western countries, but its presentation and etiology in Asian populations have not been studied extensively [19]. This study has been designed to estimate prevalence of various components of NAFLD and aims to provide a simple and reproducible scoring system to identify those patients who have a higher risk of NASH diagnosis.

Materials and Methods

Aims and Objectives

The goal of this study is to highlight the importance of NAFLD in obese patients and emphasize the need for its inclusion as a separate component in the definition of metabolic syndrome. This study was conducted to estimate the prevalence of the various types of NAFLD in obese Indian patients, study the association of the various components of metabolic syndrome and biochemical markers with NAFLD, and formulate a simple non-invasive scoring system from these markers, to identify those patients at a high risk for NASH, and be used as a screening tool. This will enable decision making, as not all bariatric/metabolic surgeries (BS/MS) are suitable for patients with NASH or fibrosis.

Study Design

This prospective observational study included patients consenting for BS/MS with liver biopsy at a single high-volume center in Mumbai, India. The study was approved by the Institutional Ethics Committee. All patients met the criteria for undergoing BS/MS in obese Indians.

Exclusion criteria included the following: age less than 18 years, average alcohol consumption of more than 40 g/day for men and 30 g/day for women, patients with pre-existing acute or chronic liver disease of proven infective (hepatitis A, B, C, E), auto-immune, congenital or malignant cause, patients using hepato-toxic drugs, proven cirrhosis, patients not consenting to intra-operative liver biopsy.

Two hundred ninety patients, who fit the inclusion criteria, were enrolled, between September 2017 and October 2018. Two patients were excluded in view of cirrhosis on the final biopsy report. Hence, the final analysis was carried out on data from 288 patients.

Methods

All patients who fit the BMI criteria for BS/MS in Asia, as per IFSO-APC guidelines [20], and consented for surgery with liver biopsy, were subjected to different BS/MS, as per institutional practice (77.5% had a Roux-en-Y gastric bypass, 11.25% had a one anastomosis gastric bypass, and 11.25% had a sleeve gastrectomy).

Weight and height were measured for all patients at initial assessment and BMI was calculated. All patients underwent routine pre-operative work-up with blood and radiological investigations, which included liver functions tests (bilirubin, AST, ALT, GGTP), diabetic profile (HbA1c, fasting and post-prandial blood glucose, serum insulin and serum c-peptide), and lipid profile (total cholesterol, LDL cholesterol, HDL cholesterol, triglycerides), ultrasound (US) of the abdomen (to measure liver span) amongst other routine tests. US was carried out using an abdominal probe 2–5 MHz. Longitudinal, subcostal, ascending, and oblique scans were performed. The size of both lobes was measured. The right lobe measurements used were MCL dome to tip and MCL max AP. Midline max

AP was used for the left lobe. FibroScan as a routine test was not performed in all patients.

Patients underwent BS/MS as per standard practice, following which a laparoscopic-guided liver biopsy was taken with a tru-cut biopsy needle (MAX-CORE® Disposable Core Biopsy Instrument, BARD® Peripheral Vascular, Inc., AZ, USA) from the left lobe of the liver (Fig. 1). Hemostasis was achieved by using mono-polar electro-cautery over the site of the biopsy.

Biopsy samples were examined by the same team of pathologists at the institute and were scored as per the NAFLD activity score (NAS) developed by EM Brunt et al. [21]. Patients with cirrhosis on the final histopathological report were excluded from analysis [22].

Statistical Analysis

All categorical data was expressed as percentages, and continuous data was expressed as mean (with standard deviation). Comparison between the patients diagnosed with non-alcoholic fatty liver disease (NAFLD) with those suffering from non-alcoholic steatohepatitis (NASH) was performed by using the chi-square (χ^2) test or the unpaired Student's *t* test for qualitative and quantitative data respectively.

Binary logistic regression analysis was used, with the NAS score being the dependent factor and the biochemical parameters and co-morbidities being independent factors in the analysis.

The analysis yielded β regression coefficients, *p* values, and 95% confidence intervals (CI) for each of the independent variables. All p values ≤ 0.05 were considered statistically significant. The significantly associated variables were picked out and a scoring system was formulated. The β coefficient was utilized as the score for each individual significantly associated parameter. Receiver operating characteristic (ROC) curve was then created to identify a cutoff score for identifying patients with NASH.

The scoring system thus derived was then cross-validated to assess the predictive capabilities of the scoring system, that might be expected in actual clinical practice. The risk of having NASH was estimated in 10 randomly selected and mutually exclusive subsets of the study population using the scoring system from 90% of the study population, with the same methods used as for the derivation of the primary scoring system. The scores from the cross-validated cohort were then compared with the true prevalence of NASH and simple steatosis. The performance of the scoring system was estimated by measuring sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). All data was evaluated and analyses performed using Microsoft Excel 2016 (Microsoft Corporation, WA, USA).

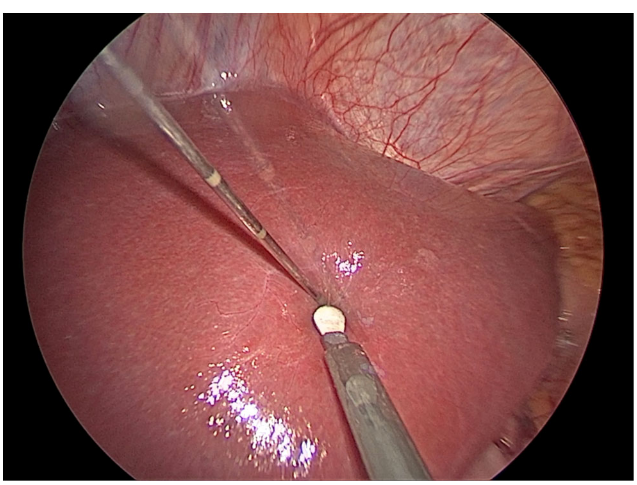


Fig. 1 Receiver operator characteristic (ROC) curve with an area under the curve (AUC) of 0.84, corresponding to a score of 3 on the scoring system

Results

The average age of the enrolled patients was 44.95 ± 11.5 years, with 117 (40.6%) males and 171 (59.4%) females. The mean weight was 120.3 ± 24.6 and mean BMI was 45.5 ± 7.8. BMI stratification is depicted in Fig. 2. One hundred ninety-six (67.6%) patients had simple steatosis, 92 (31.7%) patients had NASH, and 2 (0.007%) patients had cirrhosis (and were excluded in the final analysis) on the final histopathological examination. Results of various parameters were compared between the various stages of NAFLD and are illustrated in Table 1.

Liver span on ultrasonogram (USG), AST, ALT, GGTP, HbA1c, serum c-peptide (fasting), and serum triglycerides were significantly different in the two groups. Hypertension was not significantly associated with the type of NAFLD ($p = 0.5$) (Table 2). Eleven independent risk factors were then compared with the dependent variable (NASH or simple steatosis) by applying a multivariate regression analysis. Five independent risk factors were found to be statistically significant. Each significant risk factor was assigned a numerical score

HAALT scoring system

Independent variable		Score
HbA1c	> 6	2
AST	> 30 IU/l	1
ALT	> 35 IU/l	1
Serum triglyceride levels	> 150 mg/dl	1
Liver span on USG	> 16 cm	1
Total		6

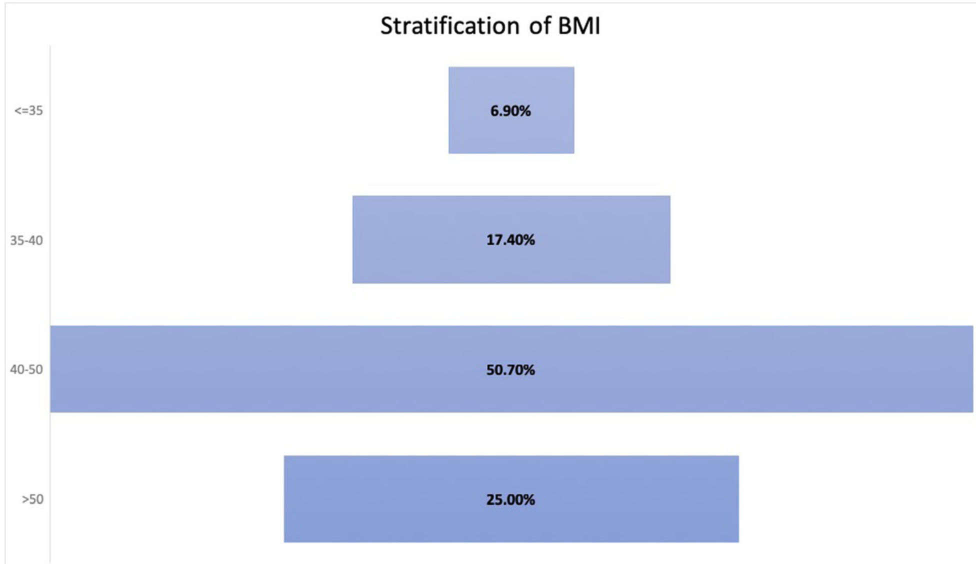


Fig. 2 Stratification of obese patients (undergoing bariatric/metabolic surgery) as per body mass index (BMI)

corresponding to the β coefficient as described in Table 3. The range of the summation of each individual score is 0 to 6.

The cutoff value was determined by the receiver operating characteristic (ROC) curve with an area under the curve (AUC) of 0.84 (Fig. 3). The cutoff point was observed as a score of 3. The percent of patients with simple steatosis and NASH for each scoring point is depicted in Table 4. Patients with a score of ≧ 3 were at a higher risk of NASH, whereas patients with a score of 0, 1, and 2 were at a lower risk for the development of NASH. The sensitivity and specificity of this model were estimated as 85.87% and 70.41% respectively. The PPV and NPV were 60.2% and 91.4% respectively. The diagnostic accuracy of this model was 75.35%.

Discussion

Obesity has always been associated with various degrees of NAFLD. The spectrum of NAFLD ranges from simple steatosis to NASH to cirrhosis [6]. In our study, 100% (290/290) patients were diagnosed with some form of NAFLD, 67.6% with simple steatosis, 31.7% with NASH, and 0.007% with cirrhosis. The global prevalence of NASH in obese patients varies between 20 and 35% in various studies, of which 70% have simple steatosis [11].

In 1975, Haller proposed that hyperuricemia and steatosis were associated with metabolic syndrome not as risk factors, but as a consequence [23]. Hypertension, insulin resistance,

Table 1 Comparison of various parameters between patients with simple steatosis and NASH USG, ultrasonography; AST, aspartate transaminase; ALT, alanine transaminase; GGTP, γ-glutamyl transaminase; HbA1c, glycosylated hemoglobin; LDL, low-density lipoprotein

$n = 288$	Simple steatosis ($n = 196$)	NASH ($n = 92$)	p values
Age	44.97 ± 11.79	44.9 ± 10.8	0.96
Weight	119.61 ± 24.64	121.79 ± 24.37	0.49
BMI	45.47 ± 8.11	45.47 ± 7.17	1
Liver span on USG	14.54 ± 1.81	16.09 ± 2.24	< 0.001
Total Bilirubin	0.55 ± 0.25	0.56 ± 0.24	0.692
AST	20.51 ± 9.9	30.3 ± 15.59	< 0.001
ALT	24.36 ± 13.11	36.28 ± 18.25	< 0.001
GGTP	31.78 ± 21.12	41.87 ± 31.54	0.001
HbA1c	6.56 ± 1.34	7.33 ± 1.59	< 0.001
Serum insulin (fasting)	25.59 ± 28.04	27.95 ± 14.69	0.45
Serum c-peptide (fasting)	3.74 ± 1.38	4.37 ± 1.27	< 0.001
Total cholesterol	177.31 ± 40.52	182.88 ± 38.25	0.271
LDL cholesterol	115.75 ± 40.61	119.09 ± 34.71	0.498
Serum triglycerides	134.93 ± 61.46	168.33 ± 113.34	0.001

Table 2 χ^2 test depicting association of hypertension with liver disease

Hypertension	Simple steatosis	NASH	Total
Observed			
Yes	100	43	143
No	96	49	145
Total	196	92	288
Expected			
Yes	97.32	45.68	143
No	98.68	46.32	145
Total	196	92	288
p value	0.50		

T2DM, and hyperlipidemia are central components of the metabolic syndrome (syndrome X), which is related to the development of NAFLD in patients [24, 25]. Hyperlipidemia is associated with NAFLD in 20–92% of patients. Amongst the various parameters, triglyceride levels have been associated with NAFLD, albeit inconsistently [24, 26]. Hypertension has been identified as an independent predictor for the development of NAFLD by Dixon et al. [27]. The possible mechanism was postulated to be via angiotensin II causing the release of the profibrogenic cytokine transforming growth factor β1, which results in hepatic stellate cell activation [27]. There is conflicting data regarding this, as hypertension has been implicated as "guilty by association," rather than a truly independent risk factor for NASH [28]. In this study, only serum triglyceride levels and poorer control of blood glucose levels (secondary to either T2DM or insulin resistance) have shown a significant correlation with NAFLD, whereas hypertension has no significant correlation.

Most scoring systems for prediction of NAFLD used serum fasting insulin levels, serum fasting c-peptide levels, HOMAIR, or T2DM as a component of metabolic syndrome [10–15, 27]. Poor glycemic control as reflected by HbA1c has been underutilized as a predictor of NAFLD [13]. It is a significant risk factor in the development and progression of NAFLD in obese subjects. In a population-based study, higher HbA1c levels (especially over 6%) were associated with increased prevalence of NAFLD [29]. In a cross-sectional study by Chao Yu et al., HbA1c levels in those with insulin resistance, but not proven T2DM, correlated with severity and risk of progression of NAFLD, leading him to recommend the use of HbA1c as a potential index for prediction of the severity of NAFLD [30]. Obese patients present with insulin resistance, as well as T2DM, both of which may be associated with an elevated HbA1c [29]. In our study, we found no statistical significance between serum fasting insulin and c-peptide levels and the development of NASH; however, HbA1c levels were significantly different between the steatosis and NASH groups (7.33 vs 6.56, $p < 0.001$). We have taken a lower cutoff for HbA1c (6%) as per the ROC curve to increase predictive sensitivity.

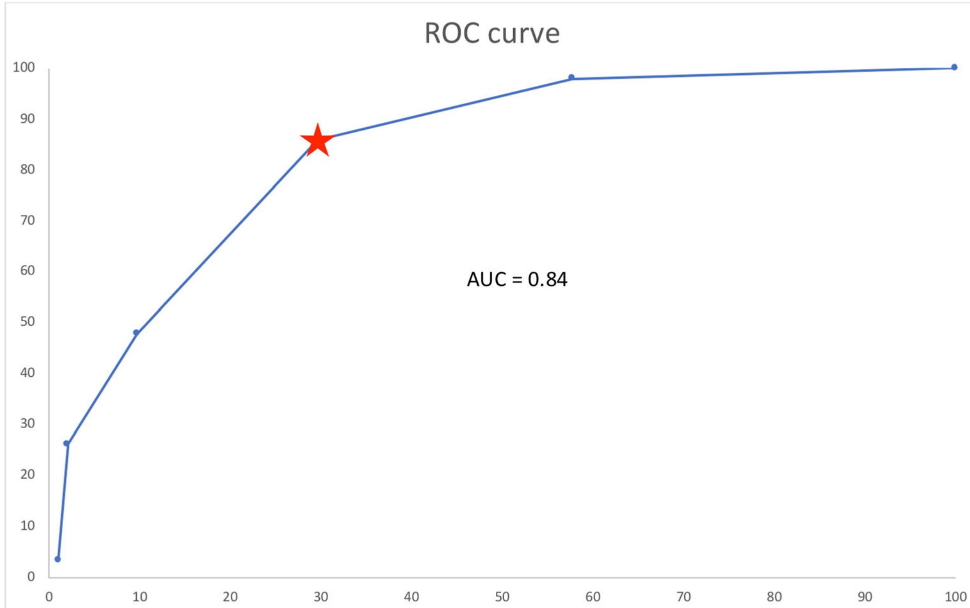
Liver enzymes may be elevated in patients with NAFLD, especially NASH as these are released by damaged and dying hepatic cells into the bloodstream. However, not all patients with NASH may have elevated liver enzymes [31]. The derangement in liver enzymes amongst obese patients ranges from 9.9 to 30.5% [15]. Ulitsky et al. noticed that enzymatic derangements may exist in 23.1% of patients with NASH [13]. The cutoff values taken by them were 40 U/l, which may have presented a higher PPV, but a lower sensitivity. Lower cutoff points increase the sensitivity of liver enzymes in the diagnosis of NASH as observed by Campos et al. [11].

Table 3 Results of multivariate regression analysis with assigned scores

Variables			β coefficient	Standard error	*p* values	Scores
HbA1c	>	6	2.407	0.565	0.000	2
AST	>	30	0.999	0.419	0.017	1
ALT	>	35	0.961	0.427	0.024	1
GGTP	>	35	0.158	0.342	0.644	
Fasting insulin	>	20	0.216	0.341	0.526	
c-peptide	<	4	0.25	0.342	0.466	
Total cholesterol	>	200	− 0.799	0.591	0.187	
LDL cholesterol	>	130	0.55	0.516	0.287	
Triglycerides	>	150	0.785	0.358	0.029	1
Liver span on USG	>	16	1.132	0.346	0.001	1

HbA1c, glycosylated hemoglobin; *AST*, aspartate transaminase; *ALT*, alanine transaminase; *GGTP*, γ-glutamyl transaminase; *LDL*, low-density lipoprotein; *USG* ultrasonography

Fig. 3 Method of performing an intra-operative liver biopsy. Hemostasis achieved with monopolar coagulation



In our study, the best cutoff points selected by the ROC curve were 30 U/l for AST and 35 U/l for ALT.

Ultrasonography (USG) to detect steatosis and hepatomegaly has been utilized in scoring systems previously [14]. Morbidly obese patients may pose a challenge in the diagnosis of fatty infiltration in the liver because of excessive fat. Besides, the sensitivity of USG is lower in mild fatty infiltration. Both these factors combined may give an unreliable result [26]. However, Liang et al. have shown that USG is acceptable and reliable in morbidly obese patients [32]. There is no arguing that USG is heavily operator dependent and requires software for analysis etc. Alteration in liver echo-texture exhibits a high intra- and inter-operator variability and hence was not considered in this study [14]. To reduce the variability, we considered liver span on USG as the only marker, using modes of measurement which has the least inter- and intra-operator variability [33]. FibroScans were not used in the final analysis, because of a host of reasons.

Table 4 Frequency of simple steatosis and non-alcoholic steatohepatitis (NASH) for each score

Scores	Simple steatosis		NASH		% NASH	
0	47	(24%)	1	(1%)	1/48	(2%)
1	36	(18%)	1	(1%)	1/37	(3%)
2	55	(28%)	11	(12%)	11/66	(17%)
3	39	(20%)	35	(38%)	35/74	(47%)
4	15	(8%)	20	(22%)	20/35	(57%)
5	2	(1%)	21	(23%)	21/23	(91%)
6	2	(1%)	3	(3%)	3/5	(60%)
Total	196		92			

1. It requires expensive capital equipment and is not freely available in India.
2. Though FibroScans show a better sensitivity, specificity, and NPV with a greater degree of fibrosis, not all NASH patients show fibrosis on histopathology. Hence, FibroScans may not be as useful in predicting and differentiating NASH from simple steatosis.

Magnetic resonance elastography (MRE) is another procedure which has a high sensitivity and specificity to detect liver fibrosis. However, it is not readily available across the world, and it is expensive as a screening tool [34].

Our study represents a unique data set which encompasses obese patients and the varying grades of NAFLD in these patients. Various components of metabolic syndrome and liver span on ultrasound were compared with the type of NAFLD and a scoring system was generated by running a multivariate regression analysis, which was then correlated with the NAS on histopathological examination. Five independent predictors that were found to be statistically significant (HbA1c, Triglycerides, AST, ALT, liver span on ultrasound) were then used in the HAALT scoring system with scores ranging from 0 to 6, where a score of 6 was the most predictive value (ROC curve showing an AUC = 0.84). Most scoring systems rely on a higher sensitivity and negative predictive value in order to screen potentially at-risk patients for further investigation. This scoring system compares favorably to other scoring systems as well as imaging modalities as depicted in Table 5.

BMI was not a significant risk factor in our study, as was the case with most other predictive scoring systems [10–15, 27]. Our study included a majority (75.7%) patients with BMI above 40 kg/m^2. This probably accounts for the non-significance of BMI in our study, as compared to the other

Table 5 Comparison of the HAALT scoring system with other scoring systems and imaging modalities

Scoring systems	HAALT scoring system	Pierre Gholam et al.	Campos et al.	Ulitsky et al.	Anty et al.	Pulzi et al.	Chi-Ming Tai et al.	FIB-4	FibroScan	MRE
Aims	NASH vs simple steatosis	NASH vs SNSI	NASH vs simple steatosis	NASH vs simple steatosis	NASH vs simple steatosis	NASH vs simple steatosis	NASH vs simple steatosis	Fibrosis vs no fibrosis	Fibrosis vs no fibrosis	Fibrosis vs no fibrosis
Sensitivity	85.87%	76%	–	80%	84%	70%	73%	77.2–90.1%	100%	80–98%
Specificity	70.41%	66%	–	89%	86%	88.60%	75%	65.4–71.6%	73.90%	90–100%
Positive predictive value (PPV)	60.20%	–	80%	75%	44%	63.60%	77%	–	77.80%	–
Negative predictive value (NPV)	91.20%	–	93%	89.70%	98%	91.20%	72%	–	100%	–
Diagnostic accuracy	75.35%	70%	–	–	–	84.40%	74%	–	86.40%	89–99%
Cost	$	$	$	$	$	$	$	$$	$$$	$$$
Screening tool	+++	+	+++	+++	+++	+++	+	−−−−	−−−−	−−−−

SNSI, steatosis with or without non-specific inflammation; *NASH*, non-alcoholic steatohepatitis; *MRE*, magnetic resonance elastogram

Asian study by Chi-Ming Tai et al., where only 52.8% patients had a BMI > 40 kg/m^2 [15]. Chi-Ming Tai et al. had stated in their study that if only those patients with a BMI > 40 kg/m^2 were included in their study, BMI may not have been significant, which was mentioned as a drawback in their study [15].

The goal of our study was to formulate a scoring system which was easy to use, non-invasive, and cheap and identifies patients at a higher risk for NASH. Additionally, those patients with severe degrees of NASH may not tolerate malabsorptive procedures, as these may cause hepatic decompensation. USG-guided liver biopsies are time-consuming, expensive, and potentially dangerous [17]. This non-invasive scoring system can predict patients at higher risk of NASH, allowing physicians and surgeons to prioritize treatment in those patients with obesity and metabolic syndrome. The correct BS/MS procedure can benefit patients with varying degrees of NAFLD, by not only preventing progression but also causing regression of the disease [35–37]. Our next step is to identify the performance of this scoring system in a prospective cohort of patients.

This study has been conducted on those with a single ethnic origin (mainly native Indians), albeit with varying cultural and socio-economic backgrounds. This has proven to be its major strength but also has its own drawbacks. Enrolling patients from a similar phenotype provides a robust, accurate, and reproducible scoring system for patients of similar ethnic origin, which probably covers the entire South Asian population. However, its usefulness in people with different phenotypes and ethnic backgrounds needs to be validated. Secondly, this scoring system could not be used for predicting fibrosis and cirrhosis, owing to the small number of cirrhotic patients (2/290) we had in this study cohort.

Conclusions

In our study, we have a 100% incidence of NAFLD in the obese population. Thus, emphasizing on the need to include NAFLD as an important component of metabolic syndrome. We developed a simple non-invasive HAALT scoring system for predicting NASH vis a vis simple steatosis in obese patients as a screening tool. This HAALT scoring system will allow physicians and surgeons to prioritize and escalate treatment options for obese patients, be it medical or surgical.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Ethical Approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional ethics committee and with the 1964 Helsinki declaration and its later amendments.

Informed Consent Informed consent was obtained from all individual participants included in the study.

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