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Comparison of Non-Invasive Scoring Systems with Ultrasound and Liver Elastography in Predicting Non-Alcoholic Fatty Liver Disease in Healthy Population

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Abstract

***Introduction:** Non-Alcoholic Fatty Liver Disease (NAFLD) is a common but frequently overlooked entity in the general population. Though liver biopsy is the gold standard, Ultrasound (USG) is the benchmark modality for diagnosing NAFLD. Since it is observer dependent and subjective, hence newer markers or scoring systems are the need of the hour.*

***Methods:** 55 apparently healthy individuals were recruited as cases for the study and subjected to 2-D USG, Transient elastography (TE) and routine laboratory investigations and various scores were calculated. Appropriate statistical methods were applied.*

***Results:** Amongst all 55 cases, the prevalence of NAFLD as per USG and TE was found to be 32.73% and 30.91% respectively. A statistically significant correlation was found between NAFLD and NAFLH- liver fat score (NAFLD-LFS) (P = 0.046), Aspartate aminotransferase to platelet ratio index (APRI) (P = 0.006) and Fibrosis-4 Score (FIB-4) (P = 0.011). Multivariate analysis revealed only NAFLD-LFS to be a significant independent predictor of NAFLD in healthy population. No correlation of Lipid accumulation product (LAP) score, Hepatic Steatosis Index (HSI), Fatty Liver Index (FLI) and Homoeostatic Model Assessment of Insulin Resistance/Beta (HOMA-IR) score was found with the occurrence of NAFLD.*

***Conclusion:** NAFLD-LFS, FIB-4 and APRI scores can be used for the diagnosis of NAFLD. These are cheap, precise, handy tools with good objectivity and hence may be used for monitoring of disease in future.*

Introduction

Non-alcoholic fatty liver disease (NAFLD) has become one of the most important emerging public health issues. NAFLD represents a spectrum of liver disease ranging from simple fatty infiltration (steatosis) to significant inflammation, i.e., steatohepatitis (NASH) leading to fibrosis and cirrhosis, in the absence of excessive alcohol consumption.

Liver biopsy is the conventional gold standard technique to confirm NAFLD, but it is an expensive, invasive procedure that needs hospitalisation and is associated with the rare risk of death. Ultrasonography (USG) of the liver is an optimum, accurate and reliable non-invasive approach for the detection of NAFLD and has become the imaging modality of choice, replacing liver biopsy for the diagnosis of NAFLD[1]. However, USG abdomen is an observer dependent, time consuming qualitative system and is not useful for serial measurements or monitoring of the disease. Another non-invasive technique is Transient Elastography (TE), marketed and commonly known as fibroscan, that measures liver fibrosis by measuring the liver stiffness. This technique takes approximately five minutes to perform, is painless and does not require fasting, sedation, or analgesia[2]. However, it is again expensive and meant primarily for diagnosing fibrosis and not simple steatosis, is not available everywhere and is not ideal for repeated evaluation, especially in a developing country like India.

To overcome these shortcomings, many easily available non-invasive scoring systems such as NAFLD-Liver Fat Score (NAFLD-LFS), Fibrosis-4 Score (FIB-4), Lipid accumulation product (LAP) score, Hepatic Steatosis Index (HSI), Fatty Liver Index (FLI) and aspartate aminotransferase-to-Platelet Ratio Index (APRI) have been proposed and are being used frequently. However, their validation in a normal healthy population is still lacking and very little literature is available regarding the same in this part of the world and hence the present study was executed.

Methods

This was a cross-sectional observational study done among fifty five non-alcoholic, non-obese (BMI < 25kg/1.76 m^2), healthy individuals, less than sixty years of age without any co-morbidities. These subjects were enrolled from the community, i.e., apparently healthy relatives of patients visiting the hospital. All subjects with history of diabetes,

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hypertension, dyslipidaemia, metabolic syndrome, cardiac, kidney or liver disease, or on any medication including vitamin/calcium supplements were excluded. All cases were subjected to a thorough history and examination. 10 ml fasting venous sample was withdrawn for routine laboratory parameters. Ultrasound was done using Samsung-Medison Ultrasound Machine (serial number-SOQQM3HF400117L) and was performed by a single observer using a 2-5 MHz convex transducer and staged as grade 1 (when the echogenicity is just increased), grade-2 (when the echogenic liver obscures the echogenic walls of portal vein branches) and grade-3 (when the echogenicity of liver obscures the diaphragmatic outline). We could not use liver biopsy – the gold standard in diagnosis of NAFLD – as cases subjects did not give consent and also deemed it ethically incorrect to subject healthy individuals to an invasive procedure. Instead we used USG as a surrogate gold standard for the diagnosis as it is also a highly accurate and non-invasive method to pick up steatosis and early fibrosis. Transient elastography/fibroscan was done using fibroscan 402, ECHOSENS by a single observer. It was performed with a curved array ultrasound probe at 4 MHz for B-mode imaging. A normal liver's shear stiffness was taken between 6.5-7 kPa. Ten successful acquisitions were performed in each patient, and the median value was determined and used as a representative measurement of the liver elasticity. We did not use the CAP parameter as it is not measured in our machine.

The following non-invasive scores were calculated for every subject.

1. FIB-4 score was calculated by using age, liver enzymes values (AST/ALT) and platelet counts. A FIB-4 score of < 1.3 indicates the absence of advanced disease and the presence of fibrosis denoted by a score of ≥ 1.3[3].
2. NAFLD liver fat score (NAFLD-LFS) uses the values of AST/ALT and whether T2DM is present or not. Value ≤ 0.640 rules-out and values > 0.640 rules in NAFLD[4].
3. Hepatic steatosis index (HSI) includes AST/ALT, BMI, sex and DM presence or absence in calculations. With values < 30 ruling-out, and values > 36 ruling in steatosis[4].
4. Fatty liver index (FLI) uses BMI, triglycerides, and waist size for calculations. Values < 30 rules-out and values ≤ 60 rules in steatosis[4].
5. Aspartate aminotransferase-to-platelet ratio index (APRI) uses AST and platelet count for determination of liver fibrosis. At a threshold value of ≤ 0.3, it rules-out significant fibrosis; and at a threshold of ≤ 1.5, it rules in significant fibrosis[5].
6. Lipid Accumulation Product (LAP) Index is calculated using triglyceride levels and waist circumference. The cut-off values for LAP in men and women were taken as 30.5 and 23.0 respectively[6].
7. HOMA-IR and HOMA-Beta uses fasting glucose and insulin levels[7].

Statistical Analysis

Categorical variables are presented in number and percentage (%) and continuous variables are presented as mean ± SD and median. P value ≤ 0.05 was considered statistically significant. The data was entered in MS EXCEL spreadsheet and analysis was done using Statistical Package for Social Sciences (SPSS) version 16.0 (IBM, Chicago).

Results

Amongst all 55 subjects (12 males and 43 females), 37 (67%) had ultrasonographically documented normal liver morphology (gpA) and 18 (33%) had NAFLD (gpB) out of which 12 had grade 1, six had grade 2 and none had grade 3 NAFLD. Majority of the cases were in the age group of 30 - 50 years and the mean age was 43.4 ± 12.4 years. The prevalence of NAFLD was found to be 32.73% by USG and 30.91% by liver elastography. The laboratory parameters of all subjects have been depicted in Table I.

Table I: Laboratory parameters amongst all subjects.

Haematological and biochemical parameters	Cases (n = 55)
Haemoglobin (mg/dl)	12.68 ± 1.27
Total leucocyte count (per cubic mm)	6817.45 ± 1836.36
Platelet count (per cubic mm)	270 ± 84
Urea (mg/dl)	37.24 ± 12
Serum creatinine (mg/dl)	0.61 ± 0.27
Uric acid (mg/dl)	4.21 ± 0.95
Total bilirubin (mg/dl)	0.61 ± 0.22
Direct billirubin (mg/dl)	0.24 ± 0.08
Indirect bilirubin (mg/dl)	0.36 ± 0.18
Aspartate transaminase (U/L)	34.11 ± 11.79
Alanine transaminase (U/L)	32.98 ± 10.34
Alkaline phosphatase (U/L)	70.71 ± 21.28
Total protein (gm/dl)	7.38 ± 0.8
Albumin (gm/dl)	4.23 ± 0.63
Globulin (gm/dl)	3.16 ± 0.57
Total cholesterol (mg/dl)	173.33 ± 33.93
HDL (mg/dl)	45.71 ± 11.69
LDL (mg/dl)	92.33 ± 31.98
Triglyceride (mg/dl)	168.36 ± 51.33
Gamma-glutamyl transferase (U/L)	33.65 ± 24.65

The mean waist circumference was found to be 85.97 ±

9.26 cm and 89.5 ± 10.34 cm amongst cases in gpA and gpB, respectively (p = 0.207). Similarly, no difference was found in mean body mass index between gpA and gpB [24.7 ± 2.7 kg/m^2 vs 24.9 ± 2.6 kg/m^2 respectively (p = 0.775)].

The mean shear pressure value in liver elastography (kPa) in Group B was 7.86 ± 0.87, which was significantly higher as compared to 4.75 ± 1.25 in Group A (p < 0.001).

Table II: Comparison of mean shear pressure between gp A and gp B.

Fibroscan (kPa)	Group A (n = 37)	Group B (n = 18)	p value
< 7	36 (97.30%)	2 (11.11%)	< .0001
7 - 8.6	1 (2.70%)	13 (72.22%)	
8.7 - 10.2	0 (0%)	3 (16.67%)	
Mean ± Stdev	4.75 ± 1.25	7.86 ± 0.87	< .0001
Median (IQR)	4.6 (4.1 - 5.4)	7.85 (7.375 - 8.1)	
Range	1.9 - 7.3	5.8 - 9.5	

The mean shear pressure was found to be significantly higher in cases with grade 2 fatty liver (8.68 ± 0.68) as compared to 7.44 ± 0.64 in cases with grade 1 fatty liver (p = 0.001) implying that not only liver elastography accurately picks up NAFLD, it can even significantly stage its severity.

Table III: Association of non invasive scoring systems with ultrasonographically proven NAFLD.

Non-invasive scores of NAFLD	Group A (n = 37)	Group B (n = 18)	P value
HIS			
< 30	4 (10.81%)	2 (11.11%)	0.512
30 - 36	26 (70.27%)	10 (55.56%)	
> 36	7 (18.92%)	6 (33.33%)	
Mean ± Stdev	33.47 ± 2.88	35.14 ± 4.88	0.116
FLI			
< 30	13 (35.14%)	5 (27.78%)	0.748
30 - 59	18 (48.65%)	9 (50%)	
> = 60	6 (16.22%)	4 (22.22%)	
Mean ± Stdev	38.86 ± 16.71	42.94 ± 22.81	0.455
NAFLD-LFS			
< = .64	37 (100%)	18 (100%)	
Mean ± Stdev	-3.1 ± 1.33	-2.28 ± 1.28	0.046
APRI			
< = .3	30 (81.08%)	8 (44.44%)	0.006
.4 - 1.4	7 (18.92%)	10 (55.56%)	
Mean ± Stdev	0.28 ± 0.13	0.48 ± 0.29	0.01
FIB-4			
< 1.3	32 (86.49%)	10 (55.56%)	0.011
> = 1.3	5 (13.51%)	8 (44.44%)	
Mean ± Stdev	0.88 ± 0.39	1.53 ± 0.72	0.001
HOMA-IR			
< 2	26 (70.27%)	15 (83.33%)	0.346
> = 2	11 (29.73%)	3 (16.67%)	
Mean ± Stdev	1.87 ± 1.11	1.51 ± 0.58	0.197
HOMA-Beta			
< = 86.2	24 (64.86%)	14 (77.78%)	0.372
> 86.2	13 (35.14%)	4 (22.22%)	
Mean ± Stdev	67.97 ± 90.26	56.94 ± 69.82	0.65
LAP for women			
< 23	2 (10%)	1 (10%)	1
> 23	18 (90%)	9 (90%)	
LAP for men			
< 30.5	3 (17.65%)	1 (12.50%)	1
> 30.5	14 (82.35%)	7 (87.50%)	
LAP			
Mean ± Stdev	45.43 ± 19.2	53.67 ± 21.26	0.155

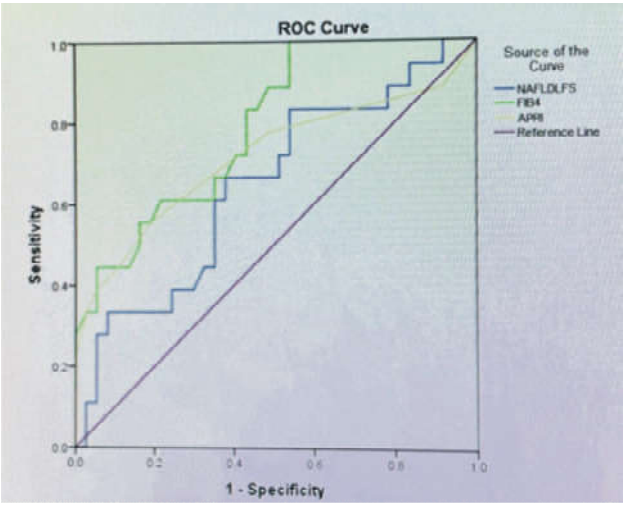

Fig. 1: *Comparison of receiver operating characteristic curve of NAFLD-LFS, APRI, FIB-4 in predicting NAFLD in study subjects.*

The AUROC for NAFLD-LFS to diagnose NAFLD was found to be 0.643 (CI = 0.481 - 0.801). At a value of ≥ - 3.37, the sensitivity and specificity to diagnose NAFLD was found to be 77.2% and 51% respectively. The AUROC for FIB - 4 to diagnose NAFLD was found to be 0.789 (CI = 0.661 - 0.911). At a value of ≥ 0.895, the sensitivity and specificity to diagnose NAFLD was found to be 72% and 60% respectively.

Similarly the AUROC for APRI to diagnose NAFLD was found to be 0.715 (CI = 0.55 - 0.87). At a value of ≥ 0.250, the sensitivity and specificity to diagnose NAFLD was found to be 78% and 52% respectively.

A statistically significant higher value of NAFLD-LFS score (p = 0.046) was found in gp B as compared to gp A. Higher values of APRI (p = 0.006) and FIB-4 score (p = 0.011) were observed in gp B indicating that healthy population with NAFLD not only can have just simple fatty liver but concomitant liver fibrosis also. Hence, these three scores, i.e., NAFLD-LFS, APRI and FIB-4, needing just a platelet count, liver function tests and basic lipid profile, can accurately pick up most cases with NAFLD in normal healthy population. There is always a trade-off between sensitivity and specificity so while choosing that variable as best in which a combination of sensitivity and specificity gives the maximum predictive value, i.e., maximum diagnostic accuracy and hence overall NAFLD-LFS, FIB-4 and APRI were found to be the best predictors of NAFLD and all three markers together can satisfactorily pick up most cases of NAFLD and also rule-out false positives. Since these three scoring systems depend upon three basic routine cheap tests, i.e., LFT, lipid profile and platelets counts, hence not only these novel scoring systems are affordable, repeatable but may also be used for monitoring of the disease. HSI, FLI, and LAP were not found to be predictive of NAFLD. The traditional markers of central obesity and NAFLD like HOMA-IR and HOMA-α were not found to be helpful in predicting NAFLD in our healthy non obese population. On performing multivariate logistic regression analysis, only NAFLD-LFS was found to be a significant independent predictor of NAFLD in healthy population (p < 0.01).

Discussion

Various risk factors like central obesity, diabetes, dyslipidaemia and metabolic syndrome have long been regarded as predictors of NAFLD[8]. Age, gender, and ethnicity also influence the prevalence of NAFLD as mentioned in a study by Chalasaini N *et al* in 2012[2]. During the selection of cases for this study, we excluded all people with obesity, diabetes, dyslipidaemia and metabolic syndrome; hence the biasing by these risk factors was automatically removed. USG and TE were found to be suggestive of NAFLD in 32.7% and 30.9% of subjects respectively in our study, which correlates well with the data available in literature suggesting 30 - 35% NAFLD in healthy Indian population. In our study, NAFLD-LFS, FIB-4 and APRI were also found to be significantly predictive of NAFLD in our healthy subjects.

Kotronen A *et al* in 2009 stated that NAFLD-LFS score can be helpful in identification of NAFLD using easily available variables[9]. On the contrary Kahl S *et al* in 2004 did not find NAFLD-LFS suitable for the prediction of hepato-cellular lipid content (quantified by magnetic resonance spectroscopy) at least in the non-obese and non-diabetic individuals[4]. In our cases, the mean NAFLD-LFS in group B (-2.28 ± 1.28) was significantly higher than that in group A (-3.1 ± 1.33) (p = 0.046) and the most significant to suggest NAFLD amongst all scoring systems. This was similar to the study by Chueng *et al* in 2014, in which NAFLD-LFS was found to be the best non-invasive prediction score for NAFLD out of FLI, HIS, LAP and NAFLD-LFS[10].

FIB-4 marker was initially derived in patients in hepatitis C and HIV co-infection by Dyson J *et al* in 2014 and they found FIB-4 to be one of the most useful non-invasive tests for diagnosing advanced fibrosis in NAFLD[11]. In our study also, 86.49% of subjects without NAFLD had FIB-4 score < 1.3 while 44.44% of subjects with NAFLD had FIB-4 score >/=1.3, both of which were significant. (p = 0.011). Further, the mean of FIB-4 in cases with NAFLD was 1.53 which was significantly higher as compared to mean 0.88 in those without NAFLD (p = 0.001).

Kruger FC *et al* in 2010 found that APRI compared favourably to NAFLD Liver Fibrosis Score (which was already a validated marker) and was superior to AST/ALT for the prediction of advanced fibrosis[12]. Even in our study, 81% of cases in gpA had APRI of </= 0.3 and 55% of cases with NAFLD, i.e., gpB had APRI in the range of 0.4 - 1.4, both of which were significant (p = 0.006). The median of APRI in cases with NAFLD was 0.48 which was significantly higher as compared to 0.28 amongst cases without NAFLD (p = 0.01).

Bedogni G *et al* in 2006 found FLI to be an accurate and simple predictor of hepatic steatosis in the general population[13]. Huang X *et al* in 2015 also demonstrated that FLI could detect NAFLD accurately in the middle-aged and elderly Chinese population[14]. We could not find any significant association between FLI with ultrasonographically documented NAFLD (p = 0.455). Similarly in our study, no significant association was seen between HIS and NAFLD (p = 0.116). This was contrary to the results of Lee H *et al* in 2010 who concluded HIS to be a simple and efficient screening tool for NAFLD in the general population[15]. The reason behind no correlation of FLI and HIS with NAFLD in our study may be that BMI is an important component of HIS and FLI and hence, having already chosen only those people who were non-obese with mean BMI 24.7 kg/m^2, the absence of correlation between FLI and HIS and NAFLD in our study can thus be explained.

Fujii H *et al* in 2019 concluded that HOMA-IR is an independent predictor of advanced fibrosis in non-diabetic patients with NAFLD[16]. In a study conducted by Salgado AL *et al* in 2010, the universal concurrence of insulin resistance (IR) was suggestive of it being a parameter for the diagnosis

of NAFLD[17]. However, no correlation of HOMA-IR was found with NAFLD in our subjects. In fact, mean HOMA-IR was numerically lower (1.51 +/- 0.58 vs 1.87 +/- 1.11) in cases without NAFLD (p = 0.19). The reason for this is that HOMA-IR is mostly useful in comparing IR between or within the groups. It has little relevance in individual patients due to several factors including non-standardised insulin assays and the pulsatile insulin secretion occurring normally in every individual.

In a study conducted by Siddiqui MS *et al* in 2005, the subjects with NAFLD had higher HOMA-α as compared to both lean and obese controls[8]. In our study, no significant association between HOMA- α and NAFLD was found to be present in cases (p = 0.746). Most of our cases with NAFLD had grade-1 steatosis and very few cases with NAFLD in our study had evidence of high-grade inflammation in the liver, (i.e., grade 2 and 3 fatty liver) and hence, pancreatic damage might be absent or only minimally present in these cases. Also, since all the cases were already healthy (without any obvious evidence of inflammation anywhere), the pancreatic beta-cell functions were expected to be relatively preserved hence with no correlation found between NAFLD and HOMA-α.

Bedogni G *et al* in 2010 found LAP to be a reasonably accurate approach to identify individuals with ultrasonographic liver steatosis[18]. In our study, no significant association was seen between LAP and NAFLD (p = 0.98). Waist circumference is a surrogate measure of central obesity and it is a component of LAP score as well and hence because of the lack of significant central obesity in our cases (mean waist circumference = 87.13 cm) no correlation was found between LAP and NAFLD. The limitation of our study was that we did not use the gold standard technique of liver biopsy in diagnosing NAFLD. Also, the controlled attenuation parameter (CAP) was not available in our hospital machine, hence may be we could have missed out on very mild cases.

Conclusion

NAFLD is rampant even in non obese healthy population of India. USG abdomen has been the gold standard investigative modality of choice but it is expensive, observer dependant, not meant for repetitive monitoring and in this COVID-19 era may not be advisable (because of the need to visit diagnostic centre and the risk of transmission of COVID-19 via bed linen). NAFLD-LFS, FIB-4 and APRI score can be a useful tool in the diagnosis and monitoring of the disease. Not only are these novel scoring systems cheaper, but are also reproducible, repetitive, bedside, and can be used for monitoring of the disease. However, long-term prospective studies with large number of cases are required for further validation.

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