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Method Article

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# A Diagnostic Accuracy Study to Validate Fatty Liver Index as Predictor for Fatty Liver

**Bhargav VY[1*], Jain M[2], Karthikeyan M[2] and Venkataraman J[2]**

[1]Department of Hepatology, Sri Ramchandra Institute of Higher Education & Research, Chennai, India

[2]Department of Gastroenterology, Arihant Hospital and Research Centre, Indore, India

***Corresponding author:**

Bhargav VY,
Department of Hepatology, Sri Ramachandra Institute of Medical Sciences and Research, Porur, Chennai, India
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**Keywords:**

Fatty Liver Index; Ultrasound; Fatty liver

**Abbreviations:**

US: Ultrasound; FL: Fatty liver; FLI: Fatty liver index; GGT: Gamma glutamyl transferase; TGL: Triglycerides; PPV: Positive predictive value; NPV: Negative predictive value; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio; CI: Confidence interval; AUROC: Area under the receiver operator characteristic curve

## 1. Abstract

**1.1. Introduction:** Ultrasound (US) is the first- line investigation to document a fatty liver (FL) but is operator dependent. Hence there is a need to establish simple and accurate predictors replacing US. Fatty liver index (FLI) is a validated marker.

**1.2. Methods:** Subjects with an ultrasound diagnosis of normal or FL were included. Basic patient data obtained, FLI was calculated. A total of 522 subjects formed the study population. Of these, 326 had FL (group1) and 196 had normal liver on US (group 2).

**1.3. Statistical Analysis:** Considering US as the gold standard, the sensitivity, specificity, negative and positive predictive values of FLI scores were determined. Area under the receiver operator characteristic curve (AUROC) was used to indicate the predictive validity of the FLI.

**1.4. Results:** Patients (males and females) with FL were significantly older, with a significantly greater BMI and WC compared to those without FL. Serum GGT and TGL likewise were significantly higher in individuals with FL. The FLI score in below 10 negated the presence of FL, with a NLR of 0.22 and a NPV of 73.08%. A score of 80 and above predicted the presence of FL with a PLR of 3.61 and above and a PPV of 85.71%. The AUROC of the FLI for predicting FL liver was 0.702 (95% CI: 0.655–0.749).

**1.5. Conclusion:** FLI is likely to have different cut off amongst different ethnic populations in the Indian subcontinent. Hence FLI cut off determinants for the respective population is necessary to predict FL.

## 2. Introduction

Ultrasound (US) is the first- line investigation to document a fatty liver (FL). FL is further better characterized with advanced imaging like computed tomography or magnetic resonance imaging, histopathology, fibroscan and liver biochemistry. Compared to these advanced imaging techniques, US is readily available and less costly. However, it is operator dependent. Thus, in a resource limited country like India, there is a need to establish simple and accurate predictors of FL

Fatty liver index (FLI) is a validated marker that was first introduced by Bedogni et al [1]. The index includes a combination of four predictors - body mass index (BMI), waist circumference (WC), serum triglycerides (TGL) and serum gamma glutamyl transferase (GGT). The FLI scores range between 1 and 100 [1]. The authors reported that FLI score of < 30 ruled out the possibility of FL on US, while FLI of 60 and above indicated FL with a positive likelihood ratio of 4.3. FLI scores between 30 and below 60 remained inconclusive. The study concluded that FLI index was an accurate predictor of hepatic steatosis, with a good diagnostic accuracy (area under the receiver operating characteristic curve =0.85; 95% CI =0.81–0.88).

We undertook a prospective study to determine the validity of FLI as a predictor of FL on US in our population. Further, we compared the obtained cut offs with the most validated cut off derived by Bedogini et al [1] i.e., <30 for absence and >60 for presence of FL.

## 3. Methods

Subjects who were residents of Tamil Nadu state, and registered in the master health check between January and December 2019 with an ultrasound diagnosis of normal or FL were included. Baseline patient information included age, gender, state of origin, details of medications for co-morbid disease like diabetes mellitus, hypertension, coronary artery disease, cerebrovascular accident, history of significant alcohol consumption and details of medication related to hepatitis B or C virus infection.

Anthropometric measurements - height (in cm), weight (in kg), waist and hip circumference (in cm) were recorded during the first visit. Laboratory data included complete hemogram, blood sugar (both fasting and post prandial), HbA1C, liver biochemistry, lipid profile, HBsAg and anti HCV antibody tests.

FLI was calculated using the "Med Calculator". US abdomen was performed by dedicated experienced radiologists using conventional B-mode ultrasonography. Parenchymal brightness, liver-to-kidney contrast, deep beam attenuation, bright vessel walls, and gallbladder wall definition were assessed. Qualitative grades were labeled as grade 0 to 3 [2]. For analysis, controls were patients with normal ultrasound; cases were those with FL (irrespective of the grades of fatty liver). Considering US as the gold standard, the sensitivity, specificity, negative and positive predictive values of FLI scores were determined to obtain the cut off value that predicted a normal liver or a FL.

Following causes of FL were excluded after detailed history and appropriate investigations- excess alcohol consumption, known case of cirrhosis of liver with portal hypertension, hepatitis B or Hepatitis C virus infection, metabolic liver disease, drug induced liver injury, those on total parenteral nutrition and prior history of major abdominal surgery. Patients with >3 times elevation of liver enzymes were also excluded.

Ethics committee of the Institution approved the study: Informed consent was obtained for collection of data and confidentiality of data was maintained. IEC reference number - CSP-MED 20/DEC/64/211.

## 4. Statistical Analysis

Continuous variables were presented as means ± standard deviation (SD) for normal distributed variables, or medians (interquartile range) for skewed variables. Categorical variables were presented as numbers (proportion).

Area under the receiver operator characteristic curve (AUROC) was used to indicate the predictive validity of the FLI. The most appropriate cutoff value of FLI was identified by Youden Index. Sensitivity (SN), specificity (SP), positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV), negative predictive value (NPV) and diagnostic accuracy of 10-value intervals of the FLI were calculated. The adequacy of sample size for the cut off of FLI obtained in the present study was compared with the validated FLI quoted by Bedogini et al.

Results: A total of 522 subjects formed the study population. Of these, 326 had FL (group1) and 196 had normal liver on US (group 2). Table 1 shows the comparison of baseline parameters in group 1 and group 2. Patients (males and females) with FL were significantly older, with a significantly greater BMI and WC compared to those without FL. Serum GGT and TGL likewise were significantly higher in individuals with FL (Table 1).

The FLI score in our study population ranged from 1 to 100 (Table 2). A score below 10 negated the presence of FL, with a NLR of 0.22 and a NPV of 73.08%. A score of 80 and above predicted the presence of FL with a PLR of 3.61 and above and a PPV of 85.71%. FLI scores between 10 and <80 remained indeterminant (Table 2).

Comparing the present findings with the earlier study by Bedogini et al, we observed that the sample size under each cut off was adequate with a comparative sensitivity for a cut off of 30 and a comparable specificity with cut off of 70 (Table 3). The AUROC of the FLI for predicting FL liver was 0.702 (95% CI: 0.655–0.749) (Figure 1). The optimal cut-off point was FLI ≥45.5, with the maximum Youden index of 0.3 and sensitivity, specificity, PPV and NPV of 63.27%, 66.26%, 52.99% and 75% respectively (Table 4). The level of agreement between FL as diagnosed by FLI>45.5 and final diagnosis was 0.083 (0.06 to 0.11) indicating poor agreement (Table 5). Considering the Area Under the Curve (AUC) value of FLI in predicting FL as 0.70 as per our results, 0.5 AUC as null value, with 5% two-sided alpha error (negative to positive cases ratio as 1:2), the study had attained 100% power.

**Table 1:** Baseline patient profile and biochemistry in subjects with (group 1) and without fatty liver (group 2).

| Baseline information | | Group 1 (FL) (326) | Group 2 (No FL) (196) | P value |
|---|---|---|---|---|
| Age in years (mean± SD) | Overall | 49.07±12.58 | 45.68±12.57 | 0.001 |
| | Male: | 48.7 ±12.58 | 45.76±12.55 | 0.024 |
| | Female: | 50.2± 12.6 | 45.57±12.57 | 0.005 |
| Sex | Male : Female | 2.8:1 | 1.2:1 | 0.00001 |
| BMI | Male | 27.1± 4.6 | 24.7±4.5 | 0.00001 |
| | Female | 28.7±4.5 | 26.2±4.5 | 0.0006 |
| Waist circumference | Male | 97.6±11.04 | 91.6±11.01 | 0.00001 |
| | Female | 93.6±11.03 | 86.72±11.12 | 0.00001 |
| Laboratory determinants of FLI | Gamma GT | 27 (7-262) | 18 (4.2-72) | 0.002 |
| | Triglyceride | 137.5 (37-540) | 116 (44-382) | 0.0004 |
| FLI (median, range) | Overall | 56 (4-99) | 33 (2-97) | 0.00001 |

**Table 2:** FLI scores 0 to 100 in predicting fatty liver in ultrasound

| FLI score | Patients (%) | Sensitivity | Specificity | PLR | NLR | PPV | NPV | Diagnostic accuracy |
|---|---|---|---|---|---|---|---|---|
| >10 | 496 (95) | 97.85 | 9.69 | 1.08 | 0.22 | 64.31 | 73.08 | 64.75 |
| ≥20 | 432 (82.7) | 92.02 | 32.65 | 1.37 | 0.24 | 69.44 | 71.11 | 69.73 |
| ≥30 | 374 (71.6) | 83.44 | 36.72 | 1.32 | 0.45 | 62.67 | 63.51 | 62.89 |
| ≥40 | 319 (61.1) | 73.31 | 59.18 | 1.8 | 0.45 | 74.92 | 57.14 | 68.01 |
| ≥50 | 263 (50.4) | 59.51 | 64.8 | 1.69 | 0.62 | 73.76 | 49.03 | 61.49 |
| ≥60 | 197 (37.7) | 46.01 | 76.02 | 1.92 | 0.71 | 76.14 | 45.85 | 57.28 |
| ≥70 | 124 (23.7) | 30.67 | 87.76 | 2.51 | 0.79 | 80.65 | 43.22 | 52.11 |
| ≥80 | 77 (14.7) | 20.25 | 94.39 | 3.61 | 0.84 | 85.71 | 41.57 | 48.08 |
| ≥90 | 26 (4.9) | 6.44 | 97.45 | 2.53 | 0.96 | 80.77 | 38.51 | 40.61 |

**Table 3:** Comparison of FLI cutoffs in the present study with reference article (shaded (Bedogini et al)

| FLI score | Patients (%) | **%** | SN | **SN** | SP | **SP** | PLR | **PLR** | NLR | **NLR** | PPV | NPV | Accuracy |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| >10 | 496 (95) | 90 | 97.85 | 98 | 9.69 | 17 | 1.08 | 1.2 | 0.22 | 0.1 | 64.31 | 73.08 | 64.75 |
| ≥20 | 432 (82.7) | 74 | 92.02 | 94 | 32.65 | 44 | 1.37 | 1.7 | 0.24 | 0.1 | 69.44 | 71.11 | 69.73 |
| ≥30 | 374 (71.6) | 60 | 83.44 | 87 | 36.72 | 64 | 1.32 | 2.4 | 0.45 | 0.2 | 62.67 | 63.51 | 62.89 |
| ≥40 | 319 (61.1) | 53 | 73.31 | 82 | 59.18 | 72 | 1.8 | 2.9 | 0.45 | 0.3 | 74.92 | 57.14 | 68.01 |
| ≥50 | 263 (50.4) | 43 | 59.51 | 70 | 64.8 | 80 | 1.69 | 3.5 | 0.62 | 0.4 | 73.76 | 49.03 | 61.49 |
| ≥60 | 197 (37.7) | 36 | 46.01 | 61 | 76.02 | 86 | 1.92 | 4.3 | 0.71 | 0.5 | 76.14 | 45.85 | 57.28 |
| ≥70 | 124 (23.7) | 28 | 30.67 | 49 | 87.76 | 91 | 2.51 | 5.2 | 0.79 | 0.6 | 80.65 | 43.22 | 52.11 |
| ≥80 | 77 (14.7) | 18 | 20.25 | 35 | 94.39 | 96 | 3.61 | 9.3 | 0.84 | 0.7 | 85.71 | 41.57 | 48.08 |
| ≥90 | 26 (4.9) | 9 | 6.44 | 18 | 97.45 | 99 | 2.53 | 15.6 | 0.96 | 0.8 | 80.77 | 38.51 | 40.61 |

%: percent; SN: sensitivity; SP: specificity; PLR: Positive likelihood ratio; NLR: Negative Likelihood Ratio, PPV: Positive predictive value; NPV: Negative predictive Value

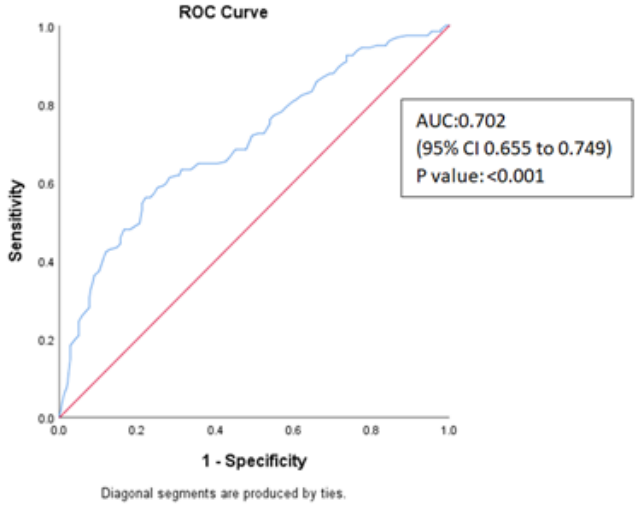


**Figure 1:** ROC analysis of fatty liver index predicting fatty liver

**Table 4:** Predictive validity of FLI cut off point 45.50 in predicting FLI (N=522)

| Parameter | Value | 95% CI | |
|---|---|---|---|
| | | Lower | Upper |
| Sensitivity | 63.27% | 56.10% | 70.02% |
| Specificity | 66.26% | 60.84% | 71.38% |
| False positive rate | 33.74% | 28.62% | 39.16% |
| False negative rate | 36.73% | 29.98% | 43.90% |
| Positive predictive value | 52.99% | 46.38% | 59.53% |
| Negative predictive value | 75.00% | 69.58% | 79.89% |
| Diagnostic accuracy | 65.13% | 60.87% | 69.22% |

**Table 5:** Comparison of FLI with FLI cut point 45.50 (N=522)

| FLI Cut Point 45.50 | FLI | | Chi square | Kappa statistics (95% CI) | p value |
|---|---|---|---|---|---|
| | Fatty Liver (N=196) | Normal (N=326) | | | |
| ≤45.50 | 124 (63.27%) | 110 (33.74%) | 43.138 | 0.083 (0.06 to 0.11) | <0.001 |
| >45.50 | 72 (36.73%) | 216 (66.26%) | | | |

## 5. Discussion

FLI has been validated in several other populations and has shown a very high sensitivity and specificity in predicting the presence of nonalcoholic fatty liver disease (NAFLD) [3]. It has also been shown to have a high concordance with imaging and histological criteria for NAFLD [4]. Our study validated the FLI index quoted by Bedogini et al for predicting FL by US. We observed that a lower cut off of <10 predicted absence of FL (NPV 73.08) while a cut off of >80 predicted the presence of FL (PPV 85.71%) with AUROC value of FLI in predicting FL was 0.70. A wide range of score between >10 and <80 remained in determinant, quite unlike the cut offs proposed by Bedogini et al.

Different studies have used arbitrary cut offs convenient for their individual study. For example, Khang et al, in a study to determine components of metabolic syndrome (MeS), used FLI to predict fatty liver. The authors revised the original cut off of FLI from < 30 to < 20 to predict absence of fatty liver in >91% and FLI of ≥ 60 for predicting fatty liver in >78% Authors found a cut off value of 20 to predict the presence of MeS (AUROC 0.849, sensitivity of 0.828 and a negative PPV of 91.9%).

## 6. Limitations and Recommendations

The differences in FLI cut off in our study may be related to an over diagnosis of grade I FL which may be overlapping with a normal US. A comparative study between the 3 grades of FL would have been informative. Our study however had very few patients with grade 2 and 3 FL. This is expected in a master health check where fewer cases are likely to have higher grades of FL. Correlation between fibroscan with US is likely to sort out the issue, taking fibroscan as the gold standard.

Recommendations: FLI is likely to have different cut off amongst different ethnic populations in the Indian subcontinent, as it is based on 2 anthropometric parameters such as BMI and waist circumference. Hence centres which do not have an access to US, should have FLI cut off of determinants for their respective population to pre-

dict FL, especially in the present COVID times.

## 7. Author Contributions

JV made the study concept and design; acquisition of data done by VYB, TSS; statistical analysis done by MJ and JV; drafting of manuscript done by VYB, MJ; critical revision of manuscript done for important intellectual content done by JV, MJ and TSS; administrative and technical support by JV.

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