SCHOOL of MEDICINE STUDENTS' JOURNAL

SMSJournal.net

Original Article

Doi: 10.22037/smsj.v4i1.39588

Investigating the Predictive Ability of FLI for Non - Alcoholic Fatty Liver Disease Involvement

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ARTICLE INFO
Date Submitted: 6 October, 2022
Date Accepted: 24 December, 2022

KEYWORDS
Non - Alcoholic Fatty Liver Disease; Fatty Liver Disease; Fatty liver index

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ABSTRACT

Background and Aim: Non - alcoholic fatty liver disease (NAFLD) is one of the common concerns in the world. This disease has a correlation with obesity, type 2 diabetes, metabolic syndrome, and other diseases. So, prediction and diagnosis of NAFLD is important. Fatty liver index can be used as a good method for prediction of NAFLD involvement but there are few evidences about it. The aim of this study was to investigate the prediction and diagnostic power of FLI to predict and diagnosis of NAFLD.

Methods: In this diagnostic study, patients who were referred to our hospital from 2020 to 2021 were assessed. Patients with NAFLD (N = 108) were compared with normal people (N = 220) based on age, sex, anthropometric parameters, laboratory data, and FLI.

Results: The mean age among all participants was 45.62 ± 10.93 years. There were significant differences between NAFLD group and normal group about age, sex, height, weight, BMI, waist circumference, diabetes and hypertension history, TG, LDL, AST, ALT, ALK, GGT. The sensitivity, specificity, and accuracy of FLI in diagnosis of NAFLD were 73.15%, 81.36%, and 78.66%, respectively. The best cut - off point based on ROC analysis and Youden index for differentiation of grade 1 from grade 2 was 69.5 and the best cut - off point for differentiation of grade 2 from grade 3 was 72.5 when the high FLI level considered as 60.

Conclusion: FLI is good method for prediction and diagnosis of NAFLD.

INTRODUCTION

Non - alcoholic fatty liver disease (NAFLD), defined as hepatic steatosis in the absence of excessive alcohol consumption and other obvious factors of injury, is becoming the most common chronic liver disease in the world, affecting up to 46% of adults in some countries (1, 2). Its global prevalence is estimated for the general population about 25% for NAFLD (3, 4). With the increasing prevalence of obesity, type 2 diabetes and related metabolic disorders, NAFLD has become an important public health concern in Asia. The prevalence of NAFLD in China has almost doubled in the past 10-15 years (5, 6).

When individuals adopt a sedentary lifestyle and diet above normal Western standards, such as Asian, Hispanic, Indian, and Native American individuals, they are more susceptible to NAFLD than those of European and African ancestry (7). Prospective studies have shown that NAFLD progresses to nonalcoholic steatohepatitis and fibrosis, leading to cirrhosis

Please Cite This Paper As:
Rafieian B, Hatami B, Abdi S. Investigating the Predictive Ability of FLI for Non - Alcoholic Fatty Liver Disease Involvement. Sch Med Stud J. 2022;4(1):1-7.

(8-10). Recently, increasing evidence suggests that NAFLD may play an important role in the development of cardiovascular disease and chronic kidney disease. Therefore, more efforts are necessary for early detection of NAFLD. At the same time, a simple and effective diagnostic method will be useful for early diagnosis and better management of NAFLD patients (11, 12).

Fatty liver index (FLI) is an algorithm based on waist circumference, body mass index (BMI), triglycerides and gamma glutamyl transferase (GGT) to predict fatty liver and is easy to use. It is a common measurement in clinical practice (13, 14). There is also agreement of this method with imaging results and histological diagnostic features for NAFLD. In addition, FLI can be used as a marker for the diagnosis of cardiovascular diseases (15, 16). Many patients with NAFLD are asymptomatic, although some patients with NASH may have symptoms of fatigue, lethargy, and discomfort in the upper right part of the abdomen (17). But most of the patients are identified with abnormal and increased liver function tests or fatty deposits in the liver which are identified incidentally in abdominal imaging. Radiographic evidence in patients with NAFLD includes increased echogenicity in ultrasound and increased fat signal in MRI (9).

Until now, few studies have been conducted on the ability to predict nonalcoholic fatty liver disease by calculating the fatty liver index (FLI) as a practical method for predicting and preventing NAFLD; therefore, in this study, we decided to determine the power of prediction of NAFLD through FLI calculation.

METHODS

This is a diagnostic study that was conducted on patients were referred to the gastroenterology clinic of Ayatollah Taleghani Hospital (Tehran - Iran) from 2020 to 2021 who were involved with fatty liver disease.

The inclusion criteria were non - alcoholic fatty liver disease (NAFLD) involvement and age between 16 and 70 years old. The exclusion criteria were involvement with autoimmune hepatitis, acute hepatitis, chronic liver disease, Acquired Immunodeficiency Disease (AIDS), drug - related fatty liver, and history of alcohol consumption, age lower than 16 years, and not having consent to participate into the study.

In order to calculate the sample size, ROC analysis was used and the sample size based on 70% test effectiveness (Area under the ROC curve), 5% error (Type 1 Error) and 95% power was assessed at least 31 people in NAFLD group and at least 62 people in normal group. So the sample size was at least 93 people.

One hundred and eight patients with NAFLD based on ultrasound and 220 patients who did not have fatty liver on ultrasound were entered into the study. The diagnosis of NAFLD was based on liver imaging or liver biopsy and clinical examination of metabolic syndrome with or without abnormal liver enzymes. Fatty liver index was calculated in all patients.

Grading of fat infiltration in the liver was recorded as follows:

• Mild: echogenicity increases slightly and the diaphragm and borders of intrahepatic vessels have a normal appearance.

• Moderate: echogenicity increases to a moderate extent and the diaphragm and intrahepatic vessels are slightly disturbed in appearance.

• Severe: echogenicity increases markedly, and the diaphragm, intrahepatic vessels, and the posterior part of the right lobe change in appearance.

Collected data including age, gender, body mass index (BMI), type2 diabetes and hypertension, family history of liver disease and laboratory parameters were recorded for all patients. The laboratory parameters that were checked from the patient's blood sample included: triglyceride, HDL, cholesterol, LDL, aspartate aminotransferase, alanine transaminase and alkaline phosphatase. BMI was calculated based on weight and height (kg / m2), and high triglycerides were defined based on levels greater than the 95th percentile for age and sex. Low HDL cholesterol was defined as a level less than the 5th percentile for age and sex, hypercholesterolemia was defined as a level greater than 200 mg / dL, and high LDL - cholesterol was defined as a level greater than 130 mg/dL.

Fatty liver index was measured using the algorithm reported by Bedogni et al. in 2006 (18). The sensitivity and specificity of FLI and its cut point were obtained according to the analysis of received data.

$$FLI = (e^{(0.953 \times \ln(TG) + 0.139 \times BMI + 0.718 \times \ln(GGT) + 0.053 \times WC - 15.745)}) / (1 + e^{(0.953 \times \ln(TG) + 0.139 \times BMI + 0.718 \times \ln(GGT) + 0.053 \times WC - 15.745)}) \times 100$$

Statistical analysis

Mean, standard deviation, frequency and percentage were used to describe the data. After proving the normality of the distribution of the studied variables with the Kolmogorov Smirnov test, the t-test was used to compare the quantitative variables between the two groups, and Fisher's exact test was used for the qualitative variables.

To measure the diagnostic power of FLI in predicting the final result, we used the statistical indicators of sensitivity, specificity and Youden index. Also, to obtain the optimal point and a suitable cut point, ROC diagram was drawn. All analyzes were performed by SPSS 25.0 statistical software.

P-value less than 0.05 were considered statistically significant.

Ethical issue

This study was approved in ethical committee of Shahid Beheshti Medical University (IR.SBMU.MSP.REC.1400.394).

RESULTS

The purpose of this study was to investigate the power FLI to predict NAFLD. 108 patients with fatty liver and 220 controls were included in the study. In table 1 we represent anthropometrical, historical, and laboratory data of patients between the two groups of NAFLD and normal participants.

Table 1. Anthropometric, historical, and laboratory data of patients based on NAFLD and normal groups

		Group			
		Total	**NAFLD (N = 108)**	**Control (N = 220)**	**P-value**
Sex	Male	61 (18.6%)	29 (26.9%)	32 (14.5%)	0.01
	Female	267 (81.4%)	79 (73.1%)	188 (85.5%)	
age		45.62 ± 10.93	48.05 ± 9.6	44.42 ± 11.36	0.005
Height (cm)		159.96 ± 7.95	161.55 ± 8.45	159.18 ± 7.6	0.01
Weight (Kg)		72.44 ± 13.2	81.48 ± 13.15	68 ± 10.76	< 0.001
Waist circumference (cm)		94.42 ± 11.83	102.49 ± 10.25	90.75 ± 10.63	< 0.001
BMI		28.24 ± 4.6	31.08 ± 4.37	26.85 ± 4.05	< 0.001
		Group			
		Total	**NAFLD**	**Control**	**P-value**
Type 2 diabetes	No	290 (88.4%)	89 (82.4%)	201 (91.4%)	0.026
	Yes	38 (11.6%)	19 (17.6%)	19 (8.6%)	
Hypertension	No	269 (82.0%)	79 (73.1%)	190 (86.4%)	0.006
	Yes	59 (18.0%)	29 (26.9%)	30 (13.6%)	
		Group			
		Total	**NAFLD**	**Control**	**P-value**
Laboratory data	TG	126.6 ± 74.6	173.91 ± 95.7	103.37 ± 46.78	0.042
	Chol	179.14 ± 39.83	185.53 ± 37.49	176.01 ± 40.65	0.273
	HDL	47.06 ± 10.64	47.98 ± 10.71	46.61 ± 10.59	0.125
	LDL	104.01 ± 29.53	107.58 ± 26.49	102.26 ± 30.82	< 0.001
	AST	20.05 ± 6.86	23.15 ± 9.12	18.64 ± 4.95	< 0.001
	ALT	20.26 ± 11.23	26.79 ± 14.35	17.29 ± 7.89	0.036
	ALK	191.77 ± 68.08	203 ± 74.89	186.26 ± 63.94	< 0.001
	GGT	25.2 ± 24.7	34.49 ± 27.68	20.64 ± 21.74	< 0.001
	Ln¥TG	4.69 ± 0.55	5.04 ± 0.49	4.53 ± 0.51	< 0.001
	Ln¥GGT	3 ± 0.58	3.33 ± 0.58	2.84 ± 0.52	< 0.001

*Based on T-test **Based on Fisher Exact test ¥: logarithm

Mean FLI was calculated based on Bedogni algorithm in the two groups. FLI based in Bedogni algorithm is identified a score between 0 - 100. FLI more than 60 was considered as NAFLD. After this calculation, we assessed sensitivity, specificity, and cut-off point of FLI. The related data are seen in table 2.

Table 2. FLI assessment in patients based on group

		group		Sensitivity	Specificity	Accuracy (*)
		NAFLD	**Noraml**			
Diagnosis.FLI	NAFLD	79 (73.1%)	41 (18.6%)	0.7315 (63.76%	0.8136 (75.58%	0.7866 (73.82%

	Normal	29 (26.9%)	179 (81.4%)	to 81.22%)	to 86.28%)	to 82.97%)
Mean FLI		70.67 ± 21.08	34.83 ± 24.84			

Then we assessed the best cut-off point based on ROC analysis and Youden index. The best cut - off point is defined as a point that has the highest accuracy in differentiation of grade 1 from grade 2 fatty liver disease. The cut - off point is the point that has the highest Youden index based on this analysis (Table 3).

Table 3. The diagnostic power of FLI in differentiation of grade 1 from grade 2 fatty liver

	AUC	95% CI	P-value	Cutoff	Sensitivity (%)	Specificity (%)	Youden index
FLI index	0.754 ± 0.056	0.644 - 0.863	0.001	69.5	85	54	39.9

Youden index = Sensitivity + Specificity -1 AUC: area under ROC curve

Based on our results, this cut - off point is 69.5. The sensitivity and specificity of this cut - off point were 85% and 54%, respectively.

We also assessed the best cut - off point based on ROC analysis and Youden index for differentiation of grade 2 from grade 3 fatty liver disease, like above. The cut - off point FLI for differentiation grade 2 from grade 3 fatty liver disease was 72.5. The sensitivity and specificity of this cut-off point were 80% and 50%, respectively. These data are seen in table 4.

Table4. The diagnostic power of FLI in differentiation of grade 2 from grade 3 fatty liver

	AUC	95% CI	P-value	Cutoff	Sensitivity (%)	Specificity (%)	Youden index
FLI index	0.643 ± 0.126	0.388 - 0.881	0.274	72.5	80	50	30

ROC diagrams for FLI diagnostic power in differentiation grade 1 from grade 2 and for grade 2 from grade 2 fatty liver disease are seen in figure 1 and 2.

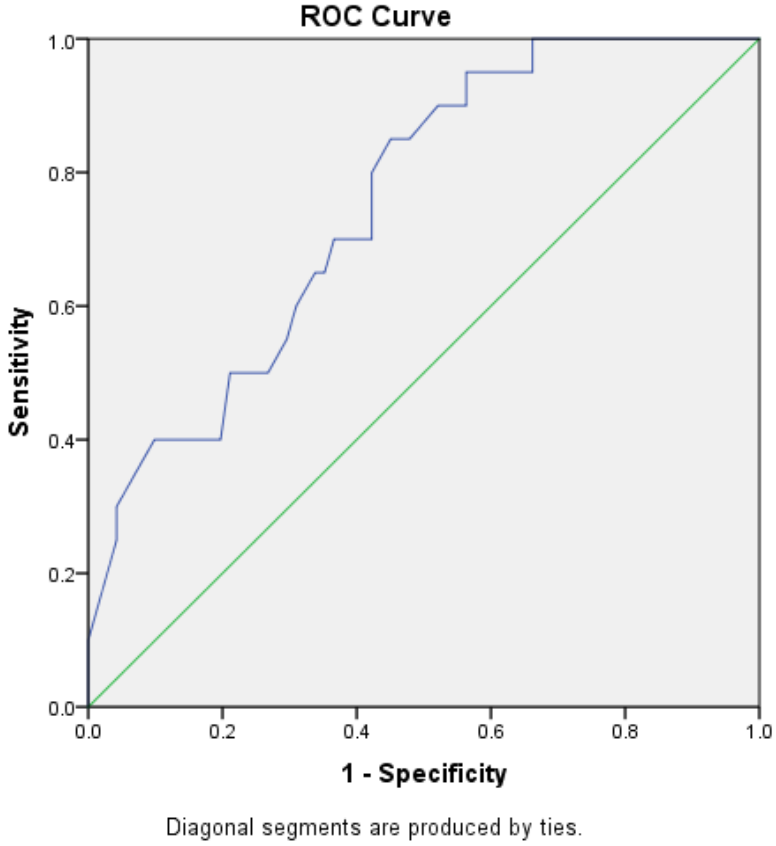

Figure 1. ROC diagrams for FLI diagnostic power in differentiation grade 1 from grade 2.

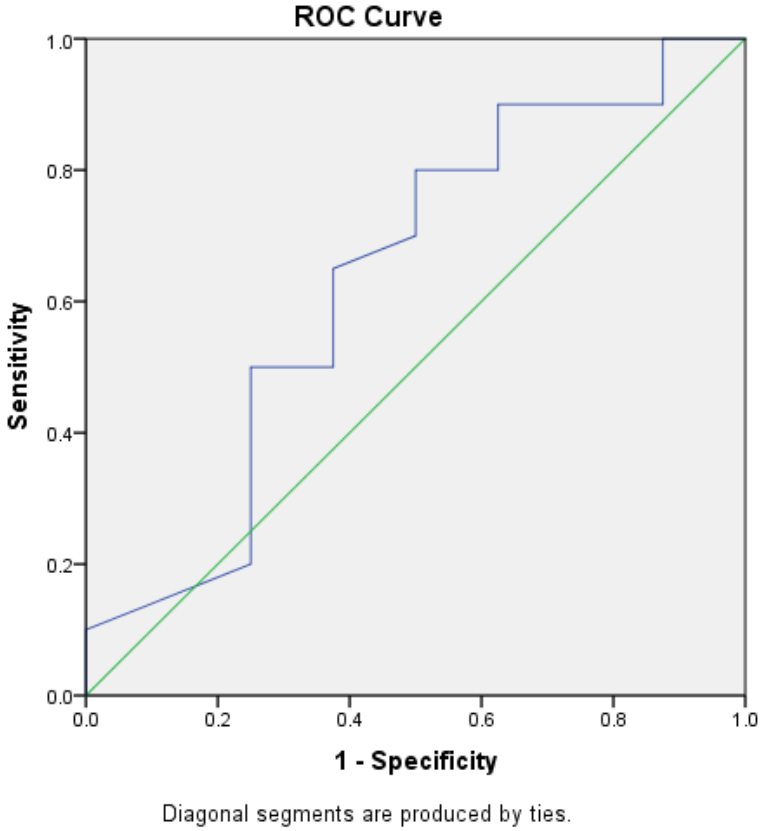

Figure 2. ROC diagrams for FLI diagnostic power in differentiation grade 2 from grade 3.

DISCUSSION

In the current study, which was conducted with the aim of investigating diagnostic power FLI for prediction of non- alcoholic fatty liver, 108 patients with fatty liver disease and 220 normal people as controls were included in the study. 73.1% of patients with fatty liver were women. The mean age in patients was 48.05 ± 9.6 years and in healthy people was 44.42 ± 11.36 years. Regarding gender and age, there was a significant difference between people with fatty liver disease and healthy people, and in people with fatty liver were older age and female gender were more common. The mean height, weight, waist circumference and BMI index in patients with fatty liver were significantly higher than healthy people. Type 2 diabetes and high blood pressure were more common in people with fatty liver, and this difference was significant between the two groups.

In our study, it was determined that the sensitivity, specificity and accuracy of FLI were 73%, 81% and 78%, respectively in diagnosis NAFLD, based on the FLI 60 criteria. In the study by Castellana et al., the prevalence of NAFLD in three classes of FLI was 14%, 42% and 67%. In the current study, the prevalence of NAFLD in three classes of FLI was not investigated. Sensitivity, specificity, positive predictive value, negative predictive value, odds ratio for positive results, odds ratio for negative results, and diagnostic odds ratio were 81%, 65%, 53%, 84%, 2.3, 0.3 and 7.8 for the lower cut - off, and 44%, 90%, 67%, 76%, 4.3, 0.6 and 7.3 for the higher cut - off. The higher cut - off in this study for FLI was equal to 60, which makes these two studies comparable. Regarding this limit of FLI, the two studies differed from each other. The sensitivity and specificity of this test in Castellana et al.'s study were 44% and 90%, but in the present study, these values were 73% and 81%. In our study, FLI had a higher sensitivity than the study by Castellana et al., but the specificity was almost the same. The conclusion of Castellana et al.'s study was that FLI had a well performance in NAFLD risk classification, but showed weak evidence of differential performance in excluding or diagnosing this disorder. In the current study, it was seen that 73.1% of 108 patients with fatty liver were correctly diagnosed using the FLI index, and 81.4% of the 220 people in the control group were correctly diagnosed as healthy group, using the FLI index. In fact, our findings indicate the appropriate differential performance of FLI for the diagnosis of fatty liver, and in this respect, these two studies are different from each other (19).

In Murayama et al.'s study, the area under receiver operating characteristic (AUROC) of the FLI index was 0.884. In subjects with a high risk of advanced fibrosis, the sensitivity of FLI was 83.3% with a low cut - off value and the specificity with a high cut - off value was 100%. In the current study, it was seen that the ROC for FLI for the accuracy in diagnosing grade 1 of 2 fatty liver was equal to 0.754. The sensitivity of the cut - off point of 69.5 for FLI was evaluated as 85% and the specificity of this point was 54%. Regarding the accuracy in diagnosing grade 2 of 3 fatty liver diseases in the ROC diagram for FLI, it was seen that ROC was 0.643 and at the cut - off point of 72.5, the sensitivity was 80% and the specificity was 50%. The FLI could not significantly differentiate between grade 2 and 3 in our study because the number of people with grade 3 fatty liver in the current study was few and therefore due to the lack of volume, contrary to clinical findings, FLI failed to differentiate significantly between grades 2 and 3 fatty liver (20).

In the study of Motamed et al., which was conducted in 2020 with the aim of evaluating the ability of FLI to predict new cases of NAFLD after a 7-year follow-up, the AUC of FLI in men and women was 0.712 (95% CI = 0.675 - 0.749) and was 0.721 (95% CI = 0.759 - 0.683). It was concluded that the FLI has a reasonable ability to predict the occurrence of new cases of NAFLD (21). As seen in this study, the AUC level was not different in men and women, but it showed that FLI had a high AUC level in detecting fatty liver. The accuracy and power of the test increases as it approaches 1. In the current study, it was also seen that FLI has a good ability to diagnose fatty liver and it can be used as a suitable method for diagnosing NAFLD, and these two studies were similar in this respect.

In the study by Khang et al., the findings indicated that patients with FLI above 60 had a higher prevalence of hypertension (49.7%), diabetes (DM; 20.4%) and METS (74.9%). FLI was positively correlated with age, body mass index, blood pressure, hemoglobin A1C and homeostasis model assessment of insulin resistance. In the current study, patients with FLI above 60 were diagnosed as fatty liver, and it was seen that the group with fatty liver had older age, higher body mass index, female gender, diabetes and higher blood pressure. The results of these two studies were similar. Of course, in the current study, it was seen that female gender is related to fatty liver. In another word, fatty liver is more common in women, which was not seen in the study by Khang et al. Khang et al.'s study concluded that FLI may be a useful screening tool to identify individuals who may require early management of METS and are at high risk for cardiovascular events. This issue was not investigated in our study, but it was seen that FLI is a suitable index for diagnosis of NAFLD (22).

In Hsu et al.'s study, it was seen that male gender, body mass index, body fat mass, fasting plasma glucose, uric acid, alanine aminotransferase, triglyceride and FLI values were associated with NAFLD. Compared with other biochemical markers, FLI had the best discriminating ability to predict LEAN - NAFLD. In the current study, it was seen that female gender, high BMI, diabetes, GGT, TG, GGT, LnTG, LnGGT, ALK, ALT, AST, LDL, were related to the presence of fatty liver, which in terms of tests and underlying disease, two studies are almost similar were, but there was a difference between the two studies in terms of gender, which requires further investigation in future studies (23).

In the study of Huang et al., it was seen that people with NAFLD diagnosed by FLI had worse metabolic characteristics than patients with NAFLD diagnosed by ultrasound. Therefore, more attention should be paid to the management and metabolic control of NAFLD. In the current study, this issue was not investigated, but this issue needs to be investigated in future studies because if this issue is proven, the value of FLI for the follow-up of patients with NAFLD becomes very remarkable (24).

CONCLUSION

FLI can be used as a suitable and good index to evaluate patients with NAFLD. This test has sensitivity, specificity and accuracy (respectively) equal to 73%, 81% and 78%, respectively. Of course, these values are true if the level of FLI is 60 or higher, and in fact, the definition of fatty liver is based on FLI above 60. The appropriate cut - off point for differentiating fatty liver grade 1 from 2 in FLI is 69.5 and in differentiating grade 2 from 3, it is 72.5. Also, the ROC levels for differentiating the mentioned grades are equal to 0.754 and 0.643, respectively. According to the findings of this study, it can be said that FLI has a high predictive and diagnostic power for assessment of NAFLD.

ACKNOWLEDGEMENTS

Not declared.

CONFLICT OF INTEREST

All authors declare no conflicts of interest.

FUNDING

None

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