Diagnostic performance of serum steatosis biomarkers in Prediction of Non Alcoholic Fatty Liver Disease in Adult Asymptomatic Egyptians

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Abstract

Background: Non alcoholic fatty liver disease (NAFLD) is the most common liver disease involving about 25% of the world's population. Liver biopsy is the current gold standard for the diagnosis and assessment of the severity of hepatic steatosis. However, because of its invasive nature and the risk of complications, many non invasive imaging modalities and laboratory markers were evaluated for the assessment of the hepatic steatosis.

Objectives: To evaluate the diagnostic performance of noninvasive indices to predict NAFLD in Egyptian patients.

Patients and methods: A cross-sectional study was conducted in a series of adult asymptomatic subjects. NAFLD was diagnosed in 100 cases by ultrasonography for whom controlled attenuation parameters (CAP) examination was done. General, anthropometric and biochemical data were collected. Fatty liver indexes (FLI), Zhejiang University index (ZJU) and hepatic steatosis index (HSI) were calculated. Roc curve analysis was used to detect the optimal cutoff of different models that predict steatosis.

Results: The area under the receiver operating characteristic (AUROC) curve of the FLI, ZJU index, and HSI was 0.999, 0.929, and 0.898, respectively. The (AUROC) curve of the FLI and ZJU index were significantly higher than that of HSI (P=0.0001 and P=0.001, respectively). The optimal cut off values for the FLI, ZJU index, and HSI were 30, 40.3, and 39.6, respectively.

Conclusion: FLI, ZJU and HSI could be accurate and applicable tools for the noninvasive diagnosis of NAFLD in Egyptian patients.

Key words: NAFLD**,** steatosis indices, non invasive, CAP.

DOI: 10.21608/svuijm.2022.122580.1281
***Correspondence**: m_metwally88@yahoo.com.
Received: 12 February,2022.
Revised: 20 February, 2022.
Accepted: 3 March, 2022.
Cite this article as: Moustafa Abd El Hamid Ali, Ghada Moustafa Kamal, Moustafa Adel Ahmed Younis ,Amr Mohammed Zaghloul. Diagnostic performance of serum steatosis biomarkers in Prediction of Non Alcoholic Fatty Liver Disease in Adult Asymptomatic Egyptians. (2022).. *SVU-International Journal of Medical Sciences*. Vol.5, Issue 2, pp: 51-.63

Introduction

Nonalcoholic fatty liver disease (NAFLD) is the most common chronic liver disease worldwide affecting about 25% of the general population **(Younossi, 2019).** NAFLD represents a spectrum of histological findings that range from simple increase of intrahepatic lipid content (steatosis, non-alcoholic fatty liver, NAFL) to an inflammatory progressive disease known as non-alcoholic steatohepatitis (NASH), NASH could result in fibrosis, cirrhosis, and subsequently hepatocellular carcinoma (HCC) **(LaBrecque et al., 2014).**

Liver biopsy is still the gold standard for diagnosing fatty liver disease and assessment of its severity. However, in addition to its invasive nature, it carries the risk of several complications including pain, bleeding and infection **(Rockey et al., 2009)**. It is also susceptible to sampling errors and assesses only a small fraction (1/50,000th) of the liver parenchyma **(Bonekamp et al., 2014).**

Because of these limitations, the clinical importance of NAFLD and its high prevalence, several noninvasive imaging modalities and laboratory biomarkers were suggested to evaluate NAFLD. In clinical practice, Liver US is the most commonly used imaging modality to detect hepatic steatosis as it is available, simple and non invasive. However, it is susceptible to inter-observers variability and its sensitivity is much reduced when liver fat content is lower than 30% or in patients with morbid obesity **(Stern and Castera, 2017).** Controlled attenuation parameter (CAP) is an imaging technique available on the FibroScan system (Echosens, Paris, France) measuring the attenuation of the US beam that is used for evaluation of the hepatic steatosis **(Sasso et al., 2012).**

There are several indices for predicting NAFLD including fatty liver index (FLI) **(Bedogni et al., 2006),** Zhejiang University (ZJU) index **(Wang et al., 2015),** and hepatic steatosis index (HSI) **(Lee et al., 2010).** In this study, we aimed to evaluate the diagnostic performance of the (FLI, HSI and ZJU indices) as non invasive biomarkers to predict the presence of steatosis, in a series of patients with NAFLD.

Patients and methods

Study design

This study was a hospital-based cross-sectional, nested case–control study. Participants were selected by simple random sampling from asymptomatic adults (aged18-75 years) accompanying patients attending either the Tropical Medicine and Gastroenterology Outpatient Clinic or the Inpatient section of the department, Sohag University Hospital. In the present study subjects were excluded if they met any of the following criteria:

- Participants aged <18 years or >75 years.
- Those with a diagnosis of liver diseases (other than NAFLD) or any end-stage liver diseases, including viral

hepatitis, drug-induced liver injury, autoimmune liver disease, Wilson's disease, primary biliary cholangitis or any other CLD that might coexist with NAFLD.

- We also excluded participants with significant alcohol intake (≥30 g/day for men or ≥20 g/day for women).

All included individuals were subjected to a thorough medical history, clinical examination and anthropometric measures including BMI and waist circumference (WCir). We calculated BMI using the following formula (BMI = weight (kg)/ (height $(m)^2$) **(Keys et al., 1972).** WCir was measured as described by **WHO (2000)** at a level midway between the lower rib margin and iliac crest with the tape all around the body. The diagnosis of Metabolic syndrome (MetS) requires the presence of 3 of the following criteria: Fasting Glucose ≥100 mg/dl, WCir >102 cm in men and >88 cm in women , TG ≥150 mg/dl**,** HDL-C < 40 mg/dl in men and< 50 mg/dl in women, Blood Pressure ≥130 (systolic) or ≥85 mm Hg (diastolic) **(National Cholesterol Education Program, 2002).**

Ultrasonographic examination (US)

US was used for screening because it is noninvasive, safe, of low cost without exposure to radiation. A convex-type transducer of an ultrasound device with 3.5–5-MHz frequency **(Mindray DP-2200)** was used to identify participants with fatty liver.

NAFLD was diagnosed according to the following features:(a) the echo level of the liver compared to that of the kidney, (b) impaired or no visualization of portal vein wall and (c) impaired appearance of the diaphragm **(Shannon et al., 2011).**

CAP assessment

All patients had fibroscan examination after overnight fasting and CAP score was obtained using Fibroscan 502 Touch **(Echosens, Paris, France)**. FibroScan examination was performed by a single operator using either the M or the XL probe, according to the recommendation by the software. Adequate pressure of the probe on the skin surface over the right hepatic lobe through intercostal spaces with the patients in dorsal decubitus with the right arm maximally abducted. LSM score was represented by the median of 10 measurements and was considered reliable only if at least 10 successful acquisitions were obtained, success rate was ≥ 60% and the IQR-to-median ratio of the 10 acquisitions was ≤0.3.

The median optimal cut-off value of CAP for S ≥S1,S≥S2 and S≥ S3 were 215dB/m, 252dB/m and 296 dB/m respectively **(de Lédinghen et al., 2012).**

Laboratory tests

After fasting for 8 h overnight and under complete aseptic conditions, peripheral venous blood sample was collected for assays of Viral hepatitis markers, Liver function

tests, Renal function test , GGT, Lipid profile, Complete blood count, Fasting blood glucose level.

Indices calculation

The following scores were calculated:

- **Fatty liver index (FLI):** calculated according to the following equation:

FLI= ($e^{0:953*\log e\ (triglycerides) + 0:139*BMI+0:718*\log e\ (ggt) +0:053*waist\ circumference-15:745}$)/ ($1+e^{0:953*\log e(triglycerides)+0:139*BMI+0:718*\log e(ggt)+0:053*waist\ circumference-15:745}$)*100. **(Bedogni et al., 2006).**

Hepatic Steatosis Index (HSI)

HSI=8 x ALT/AST ratio+ BMI (+2 if DM; +2 if female) **(Lee et al., 2010).**

- **ZJU index**

ZJU index= BMI (kg/m^2) + FBG (mmol/l) +TG (mmol/l) + 3 x ALT (IU/l)/AST (IU/L) ratio (+2 if female) **(Wang et al., 2015).**

Ethical considerations

The study protocol was approved by the Sohag Faculty of Medicine Ethical Committee. Informed written consent was taken from all participants.

Statistical analysis

Data were analyzed using STATA version 16.0 (Stata Statistical Software: Release 16.0 College Station, TX: StataCorp LP) and MedCalc program version 19.1. Quantitative data were represented as mean, standard deviation, median and range. Data were analyzed using student t-test to compare means of two groups and ANOVA for comparison of the means of three groups or more. When data were not normally distributed Kruskal Wallis test for comparison of three or more groups and Mann-Whitney test was used to compare two groups. Nonparametric test for trend across ordered groups was used to compare ordered variable. Qualitative data were presented as number and percentage and compared using either Chi square test or fisher exact test. Roc curve analysis was used to detect best cutoff of different variables that predict steatosis. We also calculated Sensitivity, specificity, positive predicted value and negative predictive values. Graphs were produced by using Excel or STATA program. P value was considered statistically significant if it was less than 0.05.

Results

Our study included 100 patients diagnosed to have NAFLD by abdominal ultrasound (59 females and 41males with mean age of 45.76±11.01 years), for whom fibroscan was done for assessment of hepatic steatosis. Another group of 50 subjects with no sonographic evidence for fatty liver were randomly selected as controls (32 females and 18 males) their mean age was 36.64± 12.47 years.

The basic clinical characteristics and anthropometric measures of the studied groups were summarized in (**Table.1**). Patients with NAFLD were statistically significant older in age (P<0.0001) with higher body mass index and waist circumference (P<0.0001). NAFLD

prevalence among patients with the different grades of obesity was 78% which was higher than that in overweight patients (16%). While its prevalence was about (6%) among those with normal BMI**.** The prevalence of metabolic syndrome was significantly higher in patients with NAFLD compared to those without NAFLD (P<0.0001).

The laboratory data of the studied groups were presented in (**Table.2**). Patients with NAFLD showed statistically significant higher levels of GGT (P=0.02), serum cholesterol, triglycerides, LDL, and VLDL (P<0.0001for each), and lower levels of HDL (P<0.0001).

The performance of the studied steatosis indices and compares the best cut off values in our sample (optimal) and the originally described (Low and High) cut off values of these scores were analyzed in (**Table.3**). FLI had the highest AUROC (0.999) with 98% sensitivity, 100% specificity, 100% PPV and 96.2 % NPV at a cut off value > 30. Using the high cut-off value (≥60), FLI detected NAFLD with 100% specificity and a 100% positive predictive value. FLI excluded NAFLD with 98 % sensitivity and a 96.2 % negative predictive value using the low cut-off value (<30).

ZJU had the next AUROC (0.929) with 87% sensitivity, 94 % specificity, 96.7 % PPV and 78.3 % NPV at a cut off value > 40.3. Using the high cut-off value (>38), ZJU detected NAFLD with 86 % specificity and a 92.9 % positive predictive value. ZJU excluded NAFLD with 100 % sensitivity and a 100 % negative predictive value using the low cut-off value (<32).

HSI had an AUROC (0.898) with 80% sensitivity, 94% specificity, 96.4% PPV and 70.1 % NPV at a cut off value > 39.6.Using the high cut-off value (>36), HSI detected NAFLD with 54 % specificity and a 71.4 % positive predictive value. HSI excluded NAFLD with 96% sensitivity and a 42.9 % negative predictive value using the low cut-off value (<30).

The performance of the studied steatosis indices is shown in **Fig.1.** FLI showed the best performance, followed by ZJU and lastly HSI (AUROC 0.999, 0.929, 0.898 respectively).

Table 1. Baseline clinical characteristics and anthropometric measures of the studied groups

Variables	**NAFLD N=100**	**Non-NAFLD N=50**	**P value**
Age/year Mean ± SD	45.76±11.01	36.64±12.47	**<0.0001**[a]
Gender			
Female	59 (59.00%)	32 (64.00%)	0.56[b]
Male	41 (41.00%)	18 (36.00%)	

DM	24 (24.00%)	12 (24.00%)	1.00[b]
Hypertension	18 (18.00%)	8 (16.00%)	0.76[b]
BMI Mean ± SD	34.35±6.20	25.22±1.73	**<0.0001[a]**
WCir (cm) Mean ± SD	112.18±13.16	73.46±6.85	**<0.0001[a]**
Obesity class Normal weight Overweight Obesity grade 1 Obesity grade 2 Obesity grade 3	 6 (6.00%) 16 (16.00%) 36 (36.00%) 23 (23.00%) 19 (19.00%)	 22 (44.00%) 28 (56.00%) 0 0 0	**<0.0001[b]**
Metabolic syndrome	57 (57.00%)	3 (6.00%)	**<0.0001[b]**

DM, diabetes mellitus; **BMI**, Body mass index; **WCir,** Waist circumference; **SD**, standard deviation.

[a] *Student-t* test; [b] *Chi square* test.

Table 2. Laboratory findings of the studied groups

Variable s	NAFLD (N=100)	Non-NAFLD (N=50)	P value
ALT(IU/L) Mean ± SD	24.64±14.72	21.24±6.69	0.62[a]
AST(IU/L) Mean ± SD	23.69±10.27	21.78±6.51	0.50[a]
Albumin (g/dL) Mean ± SD	4.29±0.68	4.39±0.33	0.32[a]
Bilirubin (mg/dL) Mean ± SD	0.73±0.26	0.68±0.22	0.33[a]
GGT (IU/L) Mean ± SD	26.45±23.30	17.18±7.54	**0.02**[a]
S. creatinine (mg/dL) Mean ± SD	0.97±0.98	0.79±0.20	0.06[a]
WBCs (10^3/ µL) Mean ± SD	7.09±2.20	8.40±1.98	**0.0005**[a]
Hb (gm/dL) Mean ± SD	12.37±1.82	11.98±1.50	0.20[a]
Platelets (10^3/µL) Mean ± SD	266.11±69.28	279.52±67.64	0.25[a]
Triglycerides (mg/dL) Mean ± SD	192.38±81.38	119.58±19.25	**<0.0001**[a]
Cholesterol (mg/dL) Mean ± SD	205.94±45.26	169.48±13.14	**<0.0001**[a]

HDL (mg/dL) Mean ± SD	39.17±6.60	45.16±7.95	**<0.0001**[a]
LDL (mg/dL) Mean ± SD	120.05±39.81	101.93±13.95	**0.0001**[a]
VLDL (mg/dL) Mean ± SD	37.18±18.69	24±3.95	**<0.0001**[a]
FBG (mg/dL) Mean ± SD	111.52±45.91	102.4±28.90	0.61[a]

[a] *Student-t* test.

AST, Aspartate aminotransferase; **ALT**, Alanine aminotrasferase; **Hb**, Heamoglobin; **WBCs**, white blood cells; **GGT**, Gamma-glutamyl transpeptidase; **HDL**, High -density lipoprotein; **LDL**, Low-density lipoprotein; **VLDL**, Very low-density lipoprotein; **SD**, standard deviation; **FBG**, Fasting blood glucose.

Table 3. Diagnostic performance of HSI, ZJU index, and FLI in predicting hepatic steatosis.

Variables	**HSI**			**ZIU index**			**FLI**		
AUROC (95% CI)	0.898 (0.838:0.941)			0.929 (0.875:0.964)			0.999 (0.997:1.00)		
Cut off value	Low (30)	High (36)	Optimal (>39.6)	Low (32)	High (38)	Optimal (>40.3)	Low (30)	High (60)	Optimal (>30)
Sensitivity (%)	96.0	88.0	80.0	100	92.0	87.0	98.0	83	98.0
Specificity (%)	6.0	54.0	94.0	8.00	86.0	94.0	100	100	100
PPV (%)	67.1	81.5	96.4	68.5	92.9	96.7	100	100	100
NPV (%)	42.9	71.4	70.1	100	84.3	78.3	96.2	74.6	96.2

Roc curve analysis was used to detect best cutoff of different indices, *Sensitivity, specificity, positive predicted value and negative predictive value*s

HSI, Hepatic steatosis index; **PPV**, positive predictive value; **NPV**, negative predictive value; **AUROC**, area under the receiver-operator curve.

AUROCs are given with 95% confidence interval (95%CI).

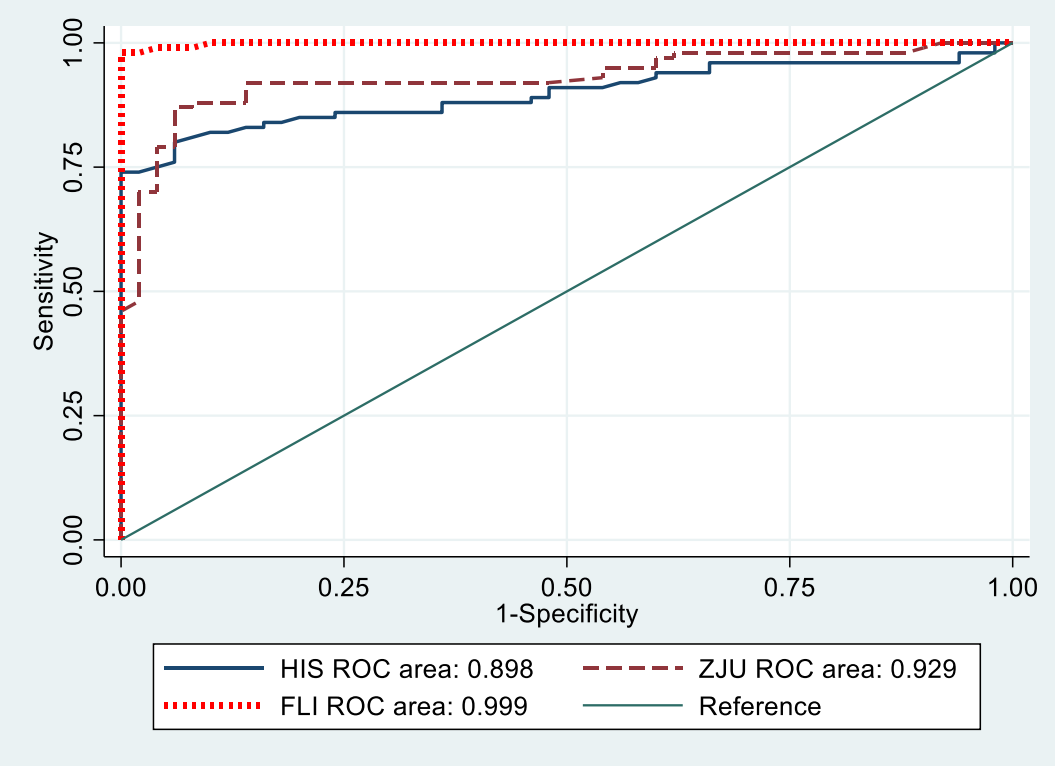

Fig .1. ROC curve of the HSI, ZJU index, and FLI for detecting NAFLD.
Comparison between the ZJU index and HSI (P=0.053).
Comparison between the FLI and HSI (P=**0.0001**).
Comparison between ZJU index and FLI (P=**0.001**).

Discussion

NAFLD is one of the MetS features **(DeFronzo and Ferrannini, 1991).** It is commonly associated with the different components of MetS such as visceral obesity, type 2diabetes, dyslipidemia **(Cortez-Pinto et al., 1999).** In the present study, the prevalence of metabolic syndrome was significantly higher in NAFLD patients than those with no NAFLD (57% *vs* 6%, p<0.0001). In their study, **Zaki et al. (2014)** found that MetS was diagnosed in 83.7% of Egyptian patients affected by NAFLD. **Marchesini et al. (2003)** studied the components of MetS in 304 individuals with NAFLD, and reported that more than 90% of NAFLD patients had at least one component of this syndrome, and about one third of individuals had all components.

Multiple studies confirmed that the increased BMI is associated with NAFLD **(Ju et al., 2013; Amirkalali et al., 2014; Motamed et al., 2016; Borai et al., 2017; Dai et al., 2017; Lin et al., 2017; Chen et al., 2019).** Our results showed that BMI was significantly higher in patients with NAFLD than in those without NAFLD.

In our study, we compared the diagnostic performance of FLI, ZJU and HSI as non invasive markers for the prediction of steatosis in

asymptomatic adults. FLI among the three steatosis indices had the best diagnostic performance (AUROC: 0.999) higher than that compared to its original description (AUROC: 0.85) reported by **Bedongi et al. (2006).** A possible explanation for this difference is the higher WCir and BMI in our studied population (mean WCir: 112.18±13.16) and (mean BMI:34.35±6.20) compared to (mean WCir:98 ±16) and (mean BMI:29.5 ±5.8) in the original description. Many studies validated the FLI in variable accuracy according to the studied populations. **Zhang et al. (2021)** validated FLI in eastern Chinese with good applicability (AUROC: 0.852). **Murayama et al. (2021)** also used FLI for prediction of hepatic steatosis in Japanese with good applicability (AUROC: 0.884)**. Cuthbertson et al. (2014)** also validated FLI in participants recruited from four research centres and reported that FLI could discriminate between patients with and without NAFLD.

ZJU had a good diagnostic performance (AUROC: 0.929) higher than that of its original description (AUROC: 0.822) reported by **Wang et al. (2015).** A possible explanation for this difference is the higher BMI in our studied population (mean BMI: 34.35±6.20) compared to (mean BMI: 24.53±3.18) in the original description. Compared to FLI and HSI it performed better than HSI but less than FLI. Our results agree with **Murayama et al. (2021)** and **Zhang et al. (2021)** who compared FLI and ZJU in Eastern Chinese and found that FLI (AUROC: 0.852) performed better than ZJU (AUROC: 0.847).

HSI had a good diagnostic performance (AUROC: 0.898) higher than that of its original description (AUROC: 0.812) reported by **Lee et al. (2010).** A possible explanation for this difference is the higher BMI in our studied population (mean BMI: 34.35±6.20) compared to (mean BMI: 24.1±2.8) in the original description. In our results it had a lower performance than that of FLI and ZJU. These results agree with **Zhu et al. (2018), Li et al. (2019), Jung et al. (2020), Zhang et al. (2021) and Murayama et al. (2021)**

Our study has some limitations that should be taken into consideration. **Firstly,** the relatively small number of patients and controls. **Secondly,** it was performed in one center. **Thirdly,** although abdominal ultrasonography is a good diagnostic tool for NAFLD, it is not useful when fat accumulation is less than 30% of liver volume. Thus it may underestimate the actual prevalence of NAFLD.

Conclusion: FLI, ZJU and HSI can be used as screening tools for NAFLD in Egyptian patients. FLI shows better performance in diagnosing NAFLD than ZJU followed by HSI. The optimal FLI, ZJU and HSI cut-off values to detect NAFLD in our patients are (30, 40.3 and 39.6 respectively) with an acceptable sensitivity and specificity.

List of abbreviations:
ALT: Alanine aminotrasferase.
AST: Aspartate aminotransferase.
AUROC: area under the receiver-operator curve.
BMI: Body mass index.
CAP: Controlled attenuation parameter.
DM: diabetes mellitus.
FBG: Fasting blood glucose**.**
FLI: fatty liver index**.**
GGT: Gamma-glutamyl transpeptidase
Hb: Hemoglobin.
HCC: Hepatocellular carcinoma.
HDL: High -density lipoprotein
HSI: Hepatic steatosis index.
kPa: Kilo Pascal.
LDL: Low-density lipoprotein.
LSM: Liver stiffness measurement**.**
NAFLD: non-alcoholic fatty liver disease.
NAFL: non-alcoholic fatty liver.
NASH: non-alcoholic steatohepatitis**.**
NPV: negative predictive value.
MetS: metabolic syndrome.
PPV: positive predictive value.
SD: standard deviation.
TGs: Triglycerides.
US: Ultrasonography.
VLDL: Very low-density lipoprotein.
WBCs: white blood cells.
WCir: Waist circumference.
WHO: World Health Organization.
ZJU: Zhejiang University index.

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