Diagnostic Utility of Non-invasive Steatosis and Fibrosis Biomarkers in Metabolic Dysfunction- Associated Steatotic Liver Disease Patients

Original Article

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ABSTRACT

Background: Metabolic dysfunction-associated steatotic liver disease (MASLD) represents a major causative agent of hepatic pathology-related to morbidity and mortality on a global scale. The detection of straightforward, non-surgical biomarkers for the diagnosis of MASLD holds great importance.

Aim: To investigate the reliability of serum biomarkers in determining the extent in investigating the severity of hepatic steatosis and fibrosis in individuals diagnosed with MASLD and analyzing the determinants of disease progression.

Methods: The current study enrolled 87 asymptomatic adults with bright liver on ultrasound. Steatosis/fibrosis were assessed using Transient Elastography. MASLD, this diagnostic approach adhered to internationally endorsed criteria.

Results: Of the 87 MASLD patients, moderate/ advanced steatosis was present in 68 patients (78.2%), and moderate/advanced fibrosis was found in 25 patients (28.7%). ROC curve analysis revealed that AUROCs of steatosis biomarkers were: FLI (0.681), HSI (0.676), and VAI (0.627) and TyG (0.566). Fatty degree by Ultrasound, and right hepatic lobe span were the significant predictors of moderate/ advanced steatosis in multiple logistic regression analysis. AUROCs of fibrosis scores were FIB-4 (0.949), APRI (0.868), NFS (0.632), BARD (0.615). FIB-4 was identified as the only significant factor associated with moderate or advanced fibrosis in the final regression model.

Conclusions: Fatty degree by ultrasound and right hepatic lobe span independently predicted moderate and advanced steatosis in MASLD patients, while FIB-4 served as the sole marker of moderate to advanced fibrosis among the patients evaluated. These simple tests may be used safely as an alternative to Transient Elastography where the machine is not available.

Key Words: MASLD, serum steatosis markers, serum fibrosis markers, transient elastography.

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INTRODUCTION

Metabolic dysfunction-associated steatotic liver disease (MASLD), formerly termed non-alcoholic fatty liver disease (NAFLD), affects 25%–30% of the global population and is currently the most widespread chronic liver condition worldwide[1]. MASLD prevalence worldwide surges at an equal pace with the prevalence of A combination of metabolic disturbances including insulin resistance, elevated blood lipids, increased waist circumference, and hypertension and is even considered its hepatic component [2].

MASLD comprises multiple pathological liver conditions, beginning with early-stage hepatic steatosis (metabolic dysfunction-associated steatotic liver, MASL) and progressing to metabolic dysfunction-associated steatohepatitis (MASH), with potential advancement to hepatic fibrosis and cirrhosis. MASLD has been closely linked to an elevated risk of serious liver outcomes, including decompensated progressive liver dysfunction and hepatocellular carcinoma [1].

Among the diagnostic tools of MASLD, Liver biopsy persists to serve as the reference standard for diagnosing liver conditions used to evaluate steatohepatitis and

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fibrosis. However, its invasive nature, histopathological discrepancies with samples heterogeneity, potential complications and inconvenience as a screening tool due to requisite costs and expertise has resulted into robust studies evaluating non-invasive methodologies and biomarkers to enable timely detection and assessment in evaluating the intensity and course of progression of steatosis and fibrosis in MASLD patients [3]. The novel procedures have included a variety of imaging, biomarkers and artificial intelligence-based technologies [4].

Among the imaging modalities Transient wave-based elastographic assessment combined with the controlled attenuation parameter (CAP) has recently become a reliable, highly reproducible, and non-invasive assessment tools for detecting steatosis and progressive fibrotic processes associated with different chronic liver disorders including MASLD [5, 6]. However, the high cost of the device has limited its wide spread clinical use [7].

Egypt has shown a prohibitive and mounting incidence of MASLD, this underscores the urgent necessity in support of the execution of effective public health regulations to mitigate the escalating burden. In view of the high prevalence of Chronic hepatic disease with scarce resources, there is a momentous necessity of verification of biomarkers enabling rapid and accurate diagnosis of MASLD [8]. Also, the advancement of economical and accessible diagnostic approaches modalities is imperative to facilitate early intervention strategies and attenuate the overall disease burden of MASLD in our population. In light of this, our study intended to 1) assess the performance of some serum biomarkers in assessment concerning assessment of steatosis severity and fibrosis staging in Egyptian individuals diagnosed with MASLD. 2) Identify variables connected to the development of moderate and advanced steatosis and fibrosis in the studied patients.

ETHICAL CONSIDERATION

The Ethical Committee of Egypt's Sohag Faculty of Medicine gave their approval to this hospital-based cross-sectional (IRB Registration number: Soh-Med-25-4—3PD). Following the guidelines laid out in the Declaration of Helsinki, all procedures pertaining to the study were carried out. Participants were people without symptoms who were either admitted to the department's inpatient section or were relatives of patients at the Tropical Medicine and Gastroenterology Outpatient Clinic. Participation in the study was contingent upon all individuals signing an informed consent form.

METHODS

To determine MASLD using internationally recognized criteria, patients were evaluated from June 2021 through December 2023 using a battery of procedures, including a full clinical evaluation, abdominal ultrasonography, transient elastography (FibroScan), and laboratory testing[9]. Thus, 87 individuals were classified as MASLD and included in the research if they had radiographic evidence of hepatic steatosis together with any cardiometabolic risk factor (CMRF) and no other reasons for hepatic steatosis.

The adult CMRF [9] are listed below:

Body mass index (BMI) II ≥25 kg/m^2 OR waist circumference >94 cm (males) 80 cm (females).

Indicators of diabetes mellitus (DM) include fasting serum glucose levels of 5.6 mmol/L (100 mg/dL) or higher, 2-hour post-load glucose levels of 7.8 mmol/L (140 mg/dL) or higher, HbA1c levels of 5.7% (39 mmol/L), or treatment for type 2 diabetes.

Hypertension (HTN) medication treatment or blood pressure equal to or more than 130/85 mm Hg.

At least 1.7 mmol/L (150 mg/dL) of plasma triglycerides or therapy to reduce lipids

Plasma HDL-cholesterol levels should be 40 mg/dL (males) or 1.3 mmol/L (no more than 50 mg/dL). (Women) OR low-fat diet therapy

- Inclusion and exclusion Criteria

The selection criteria for enrollment encompassed the following: asymptomatic cases with age 18-75 years, provision of informed consent to undergo abdominal ultrasound examination, Transient Elastography (FibroScan), laboratory and other study procedures.

Exclusion criteria encompassed participants with clinically relevant levels of alcohol intake were excluded from the study to avoid confounding effects (Typical daily amount taken of 30 grams for males and 20 grams for females), along with diagnoses of chronic liver conditions other than MASLD e.g., chronic hepatic conditions caused by viral infections, medication-related liver damage, or autoimmune processes, chronic decompensated illnesses, active autoimmune diseases and finally unwilling to provide the consent.

Methods:

Comprehensive medical history included gender, age, smoking status, DM, HTN. Complete clinical examination including blood pressure measuring, looking for any stigmata of chronic liver disease and abdominal examination for detection of organomegaly or ascites. Anthropometric parameters including waist circumferences, weight and height were obtained for each participant and hence BMI[10] was calculated.

Abdominal ultrasonographic examination:

The procedure was conducted following an overnight fast, with the patient positioned supine. A convex ultrasound

transducer operating the Mindray DP-2200 (China) at a frequency range of 3.5 to 5 MHz was utilized. Right lobe liver dimensions were taken in an oblique plane at the line running down from the middle of the clavicle and grouped as <11 cm (shrunken), 11–15 cm (normal), or >15 cm (enlarged)[11].

Fatty liver was classified into three grades according to changes in hepatic echogenicity[12]:

Hepatic steatosis was evaluated using conventional abdominal ultrasonography. The degree of liver echogenicity was assessed and classified into three grades based on established criteria:

Grade 1 (Mild): Slight increase in hepatic echogenicity compared to normal liver tissue.

GRADE 1: representing the region where the hepatic echogenicity is markedly elevated compared to normal.

GRADE 2: where the elevated hepatic echogenicity obscures the echogenic walls of the portal vein branches.

GRADE 3: where the patterns of the diaphragm are obscured by the highly echogenic parenchyma of the liver.

Transit Elastography:

Vibration Controlled Transient Elastography (VCTE) was implemented for the quantitative evaluation of hepatic steatosis utilizing the FibroScan 502 system (Echosens, Paris, France). Liver stiffness measurement (LSM) and controlled attenuation parameter (CAP) were obtained employing both M+ and XL+ probes, to facilitate accurate, assessment of hepatic fibrosis and steatosis using non-invasive methods, measurements were obtained after a minimum 4-hour fasting period. The procedure was performed with the patient positioned supine or in a slight left lateral decubitus posture, right arm placed in a superior extended posture to facilitate optimal access through the intercostal spaces. An intercostal approach was employed, targeting the site with the most favorable acoustic window for image acquisition [13]. Measurements were conducted in regions of liver parenchyma free from vessels or bone structures. Any readings affected by improper technique or excessive transducer pressure on the skin were automatically excluded. The liver stiffness measurement (LSM) score was calculated as the median of 10 valid acquisitions. To ensure reliability, criteria included a minimum of 10 successful measurements, a minimum success rate of 60%, and an interquartile range (IQR) to median ratio below 0.3.Based on the manufacturer's guidelines and corroborated by prior research, steatosis severity was categorized by steatosis grading based on CAP measurements (dB/m) was defined as: S0 (<215), S1 (216–252), S2 (253–296), and S3 (>296)[14]. Similarly, fibrosis stages were classified by Liver stiffness measurement (LSM) values, expressed in kilopascals (kPa), were categorized as follows: F0 (1–6 kPa), F1 (6.1–7 kPa), F2 (7–9 kPa), F3 (9.1–10.3 kPa), and F4 (≥10.4 kPa) [15].

Alongside the study course and to minimize the bias risk, Transient Elastography operators and statisticians had no access to the participants' clinical and laboratory records during the trial.

Laboratory tests

For all participants the following Laboratory tests were performed: fasting and or 2 hours-post prandial blood glucose, liver enzymes (AST, ALT, GGT), total bilirubin, albumin, hematological profile, and lipid profile markers such as cholesterol, triglycerides, HDL, LDL, and VLDL.

Serum steatosis and fibrosis scores

I. For assessment of hepatic steatosis, the indices listed below were determined:

Fatty Liver Index (FLI) [16] calculated as (e 0.953 *log (TGs) + 0.139 * BMI + 0.718 *log (GGT) + 0.053 * waist circumference - 15.745)/ (1 +e 0.953 * log (TGs) + 0.139 * BMI + 0.718 * log (GGT) + 0.053 *circumference - 15.745) * 100

Hepatic Steatosis Index (HSI) [17] calculated as 8 * (ALT/ AST ratio) + BMI (+ 2 if female; + 2 if DM)

Visceral Adiposity Index (VAI) [18] calculated as: In females: (WC/ (36.58+ (1.89*BMI)))*(TG/0.81) *(1.52/HDL).

In males: (WC/ (39.68+ (1.88*BMI))) *(TG/1.03) *(1.31/HDL).

Triglyceride x glucose index (TyG) [19] calculated as: fasting TGs (mg/dl) * fasting glucose (mg/dl)/ 2

II. For assessment of fibrosis, the following scores were calculated:

NAFLD fibrosis score (NFS) [20] calculated as: -1.675 + 0.037 * age (years) + 0.094 * BMI (kg/m^2) + 1.13* impaired fasting glycaemia or diabetes (yes = 1, no = 0) + 0.99 * AST/ ALT ratio -0.013 * platelet (* 10^9/litre) -0.66 * albumin (g/dl)

Fibrosis-4 (FIB-4) [21] calculated as: (age (years) * aspartate aminotransferase (AST (IU/L))/ (Platelet count (10^9/L) * (alanine aminotransferase (ALT) (IU/L)) 1/2)

APRI [22] calculated as: ((AST/ULN)/platelet count (10^9/L)) * 100

BARD score [23] Computed as a weighted combination of three variables: a BMI exceeding 28 contributes 1 point, an AST/ALT ratio above 0.8 contributes 2 points, and a diagnosis of diabetes adds 1 point.

Statistical analysis:

Data were analyzed using STATA version 14.2 (StataCorp LP, College Station, TX, USA). Quantitative

variables were reported as means, standard deviations, and ranges. Comparisons between two groups were conducted using the Student's t-test, whereas analysis of variance (ANOVA) was applied for comparisons involving more than two groups. For datasets that did not meet normality assumptions, the Kruskal-Wallis test was utilized for multiple group comparisons, and the Mann–Whitney U test was employed for comparisons between two groups. Trends across ordered groups were evaluated using a nonparametric trend test.

Categorical variables were summarized as frequencies and percentages. Group comparisons were conducted The chi-square (χ^2) test or Fisher's exact test was used as appropriate. Receiver Operating Characteristic (ROC) curve analysis was conducted to identify the optimal cutoff values for variables predicting advanced steatosis or fibrosis. Assessment of diagnostic accuracy involved calculating sensitivity, specificity, PPV, and NPV.Logistic regression was utilized to calculate odds ratios (ORs) for potential predictors. Visual data presentations were created using Microsoft Excel or STATA. A *p-value* less than 0.05 was considered statistically significant.

RESULTS

Data of 87 MASLD patients (32 males and 55 females) were statistically analysed. Their mean age was 46.62 ± 10.06 years. Hepatic Ultrasonographic and FibroScan results are demonstrated in (Table 1). Patients were sub-grouped (using FibroScan) according to the degree of steatosis (CAP score) into mild (S1) 19 patients (21.84%) vs moderate (S2) 31 patients (35.63%) and advanced (S3) 37 patients (42.53%). Similarly, depending on the fibrosis stage, they were categorized into no fibrosis (F0) 52 patients (59.77%) and minimal (F1) 10 patients (11.49%) vs moderate/advanced fibrosis (F2) 12 patients (13.79%), (F3) 7 patients (8.05%) and (F4) 6 patients (6.90%). (Figure 1) shows the results of FibroScan of 1 participant and their interpretation.

Table 1: Results of abdominal ultrasound examination of the liver and FibroScan in 87 MASLD cases:

Variable	Summary statistics
Right lobe span (cm)	
Mean ±SD	16.72±1.8
Median (range)	16.5 (13-22)
Fatty degree by ultrasound	
Mild	28 (32.18%)
Moderate	38 (43.69%)
Severe	21 (24.14%)
FibroScan results	
Steatosis degree (CAP score)	
Mild (S1)	19 (21.84%)
Moderate/advanced	
S2	31 (35.63%)
S3	37 (42.53%)
Fibrosis stage	
F0	52 (59.77%)
F1	10 (11.49%)
Moderate /advanced	
F2	12 (13.79%)
F3	7 (8.05%)
F4 (Cirrhosis)	6 (6.90)

Data are expressed as percentages (%), mean ± standard deviation (SD), median (range), and CAP refers to the controlled attenuation parameter.

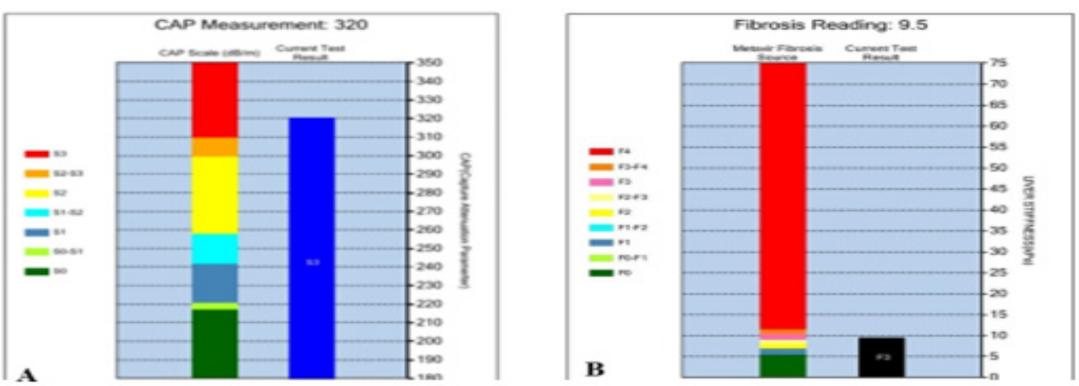

Fig. 1: A: Steatosis assessment by FibroScan with CAP Score of 320 corresponds to $3. B: Liver stiffness measurment by FibroScan (9.5 k Pascal) corresponds to F3.

Analysis for predictors of moderate and advanced steatosis

Findings detailed in (Table 2) of univariate analysis of the studied variables for prediction of moderate/ advanced steatosis. Active smoking, body weight, BMI, larger right hepatic lobe, fatty degree by ultrasound demonstrated a statistically significant association with advanced steatosis (*P*=0.02, 0.006, 0.003 and 0.01, 0.001 respectively). Among serum biomarkers of steatosis, only FLI and HSI were significantly associated with moderate and advanced steatosis (*P*=0.02 and 0.03 respectively). However, multiple-variable logistic regression analysis (Table 4) revealed that moderate and severe fatty degree by Ultrasound, (*P*=0.002 & 0.03), and larger right lobe span (*P*=0.01) were the significant predictors for moderate and advanced steatosis in the final logistic regression model.

Table 2: Univariable analysis of clinical, Ultrasonographic and laboratory data in predicting moderate and advanced steatosis:

Variable	Mild steatosis (S1) *N*=19	Moderate/ advanced steatosis (S2+S3) *N*=68	*P value*
Age/years (Mean ± SD)	48.11± 10.93	46.21± 10.60	0.49
Gender Female n (%) Male n (%)	 14 (73.68%) 5 (26.32%)	 41 (60.29%) 27 (39.71%)	0.29
Smoking Non-smoker n (%) Active smoker n (%) x-smoker n (%)	 15 (78.95%) 1 (5.26%) 3 (15.79%)	 43 (63.24%) 22 (32.35%) 3 (4.41%)	0.02
DM n (%)	4 (21.05%)	18 (26.47%)	0.77
Hypertension n (%)	4 (21.05%)	11 (16.18%)	0.73
Weight (kg) (Mean ± SD)	81.0± 13.86	94.10± 18.67	0.006
Height (cm) (Mean ± SD)	164.54± 10.34	164.81± 10.78	0.92
WC (cm) (Mean ± SD)	105.68± 11.64	112.12± 15.49	0.1
BMI (Mean ± SD)	29.84± 3.57	34.88± 6.87	0.003
Right lobe span (cm) (Mean ± SD)	15.76± 1.42	16.99± 1.82	0.01
Fatty degree by Ultrasound Mild Moderate Severe	 13 (68.42%) 5 (26.32%) 1 (5.26%)	 15 (22.06%) 33 (48.53%) 20 (29.41%)	0.001
Fasting blood glucose concentration (mg/dL), expressed as mean ± SD·	108.84± 37.93	112.29± 49.35	0.94
ALT (U/l) (Mean ± SD)	24.05± 12.03	22.66± 13.40	0.69
AST (U/l) (Mean ± SD)	29.63± 13.74	34.65± 13.94	0.28
Albumin (gm/dl) (Mean ± SD)	4.35± 0.43	4.19± 0.47	0.18
GGT (U/I)(Mean ± SD)	24.84± 18.72	27.12± 24.70	0.50
Platelets ((103/ul) (Mean ± SD)	231.63± 60.10	218.49± 69.64	0.17
Cholesterol (mg/dl) (Mean ± SD)	209.42± 60.14	203.18± 46.69	0.58
TGs (mg/dl) (Mean ± SD)	190.42± 79.52	178.57± 100.87	0.35
HDL (mg/dl) (Mean ± SD)	37.42± 7.27	40.51± 10.94	0.31
LDL (mg/dl) (Mean ± SD)	133.26± 58.42	127.24± 48.70	0.58
VLDL (mg/dl) (Mean ± SD)	36.39± 16.81	36.34± 20.71	0.83
FLI (Mean ± SD)	73.26± 18.91	83.60± 17.40	0.02
HSI (Mean ± SD)	40.79± 4.32	44.90± 7.30	0.03
VAI (Mean ± SD)	10.67± 6.28	8.44± 6.58	0.09
TyG (Mean ± SD)	4.90± 0.27	4.86± 0.30	0.63

Data are presented as percentages (%), mean ± standard deviation (SD). Abbreviations used include DM for diabetes mellitus, WC for waist circumference, BMI for body mass index, ALT for alanine transaminase, AST for aspartate transaminase, GGT for gamma-glutamyl transferase, TGs for triglycerides, HDL for high-density lipoproteins, LDL for low-density lipoproteins, VLDL for very low-density lipoproteins, FLI for fatty liver index, HSI for hepatic steatosis index, VAI for visceral adiposity index, and TyG for triglycerides-glucose index.

Table 3: Univariate analysis of clinical, Ultrasonographic and laboratory data in predicting moderate and advanced fibrosis.

Variable	No or minimal fibrosis (F0&F1) *N*=62	Moderate/advanced fibrosis (F2, F3, F4) *N*=25	*P value*
Age/years (Mean ± SD)	45.73±10.34	48.84±11.24	0.22
Gender Female Male	 43 (69.35%) 19 (30.65%)	 12 (48.00%) 13 (52.00%)	 0.06
Smoking Non-smoker n (%) Active smoker n (%) x-smoker n (%)	 43 (69.35%) 15 (24.19%) 4 (6.45%)	 15 (60.00%) 8 (32.00%) 2 (8.00%)	 0.70
DM n (%)	11 (17.74%)	11 (44.00%)	0.01
Hypertension n (%)	7 (11.29%)	8 (32.00%)	0.02
Weight (kg) (Mean ± SD)	88.11±14.58	99±24.40	0.01
Height (cm) (Mean ± SD)	163.97±9.99	166.68±12.05	0.28
WC (cm) (Mean ± SD)	108.73±13.99	115.64±16.23	0.04
BMI (Mean ± SD)	33.01±5.54	35.68±8.59	0.09
Right lobe span (cm) Mean ± SD	16.45±1.55	7.37±2.22	0.09
ALT (U/l) (Mean ± SD)	23.89±14.49	20.68±8.33	0.60
AST (U/l) (Mean ± SD)	27.89±11.91	47.6±7.07	0.001
Albumin (gm/dl) (Mean ± SD)	4.22±0.51	4.25±0.35	0.83
GGT (U/I) (Mean ± SD)	21.74±13.49	38.72±35.96	0.003
Platelets ((103/ul) (Mean ± SD)	242.58±68.05	168.72±23.14	0.0001
FIB-4 (Mean ± SD)	1.22±0.73	3.13±0.71	0.0001
APRI (Mean ± SD)	0.35±0.22	0.70±0.16	0.0001
NFS (Mean ± SD)	-1.55±1.33	-0.10±2.64	0.06
BARD 0 1 2 3 4	 0 12 (19.35%) 10 (16.13%) 34 (54.84%) 6 (6.68%)	 1 (4.00%) 3 (12.00%) 2 (8.00%) 11 (44.00%) 8 (32.00%)	 0.04

Data are shown as percentages (%); mean ± standard deviation (SD). Abbreviations include DM for diabetes mellitus; WC for waist circumference; BMI for body mass index; ALT for alanine transaminase; AST for aspartate transaminase; GGT for gamma-glutamyl transferase; FIB-4 for fibrosis index based on four parameters; APRI for aspartate to platelet ratio index; NFS for nonalcoholic fatty liver disease fibrosis score; and BARD for BMI-AST-ALT-Diabetes score.

Table 4: Multiple-variable Factors Associated with Moderate and Advanced Steatosis and Fibrosis: Logistic Regression respectively (Final model).

Variable	Odds ratio (95% confidence interval)	*P value*
Predictors of moderate and advanced steatosis		
Fatty degree by ultrasound Mild Moderate Severe	 Ref 9.35 (2.23:39.15) 15.88 (1.41: 178.56)	 0.002 0.03
RT lobe span (cm)	2.38 (1.09:5.20)	0.03
Predictors of moderate and advanced fibrosis		
DM	2.89 (0.50:16.65)	0.23
Hypertension	2.27 (0.35:14.56)	0.39
FIB-4	12.53 (3.91:40.18)	<0.0001

Data is presented as percentage (%); Mean ±SD: Standard deviation; VAI: Visceral adiposity index; DM: Diabetes mellitus; FIB-4: Fibrosis index- based on 4.

Diagnostic performance of steatosis indices: ROC curve analysis detected the cut-off points that demonstrated the highest diagnostic performance in our sample as shown in (Table 5). The AUROC of FLI was the highest 0.681 (0.57-0.78), followed by HSI 0.676 (0.57-0.77), then VAI 0.627 (0.52-0.73 and lastly, TyG 0.566 (0.46-0.67).

Table 5: Optimal cutoff values, area under the curve (AUC), sensitivity, and specificity, PPV, NPV and diagnostic accuracy of different indices and markers to predict moderate/ advanced steatosis and fibrosis respectively

Indices	Best cut off point	AUC (95% CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy (%)	*P value*
Steatosis indices								
FLI	>83	0.681 (0.572:0.777)	63.24	68.42	87.8	34.2	65.8	0.01
HSI	>46.5	0.676 (0.567:0.773)	36.76	100	100	30.6	68.4	0.003
VAI	≤11.31	0.627 (0.516:0.728)	82.4	52.6	86.2	45.5	67.5	0.08
TyG	≤4.94	0.566 (0.455:0.672)	66.2	57.9	84.9	32.4	62.1	0.9
Fibrosis indices								
FIB-4	>2.56	0.949 (0.880:0.985)	88.0	91.9	81.5	95.0	90.0	<0.0001
APRI	>0.06	0.868 (0.779:0.931)	92.0	77.4	62.2	96.0	84.7	<0.0001
NFS	>0.5	0.632 (0.521:0.733)	56.0	93.6	77.8	84.1	74.8	0.11
BARD	>3	0.615 (0.504:717)	32.0	90.3	57.1	76.7	61.2	0.11

Data are expressed as percentages (%). Abbreviations include FLI for Fatty Liver Index; HSI for Hepatic Steatosis Index; VAI for Visceral Adiposity Index; TyG for Triglyceride-Glucose Index; FIB-4 for Fibrosis-4 score; APRI for Aspartate to Platelet Ratio Index; NFS for Nonalcoholic Fatty Liver Disease Fibrosis Score; and BARD for BMI-AST-ALT-Diabetes score.

Analysis for predictors of moderate and advanced fibrosis

Univariate analysis of all studied variables (Table 3) shows that DM, hypertension, higher weight and WC exhibited a strong statistical association with moderate and advanced fibrosis (*P*= 0.01, *P*= 0.02, *P*=0.01 and *P*=0.04) respectively. Similarly, higher AST, GGT along with a diminished platelet count were markedly correlated with moderate and advanced fibrosis (*P*= 0.006, *P*=0.001, *P*=0.003 and *P*=0.0001 respectively). Regarding fibrosis scores, FIB-4, APRI and BARD scores were significantly correlated with moderate and advanced fibrosis (*P*=0.0001, 0.0001 and 0.04 respectively). Regression analysis using a logistic model incorporating multiple predictors of predictors of moderate and advanced fibrosis is shown in (Table 4). In the final multivariate analysis, only FIB-4 showed an independent association with moderate and advanced fibrosis ($P < 0.0001$).

Diagnostic performance of fibrosis indices:

ROC curve analysis detected the most discriminative cut-off points observed in our study population as shown in (Table 5). FIB-4 had the highest AUROC 0.949 (0.88-0.99) (Figure 2), followed by APRI with AUROC 0.868 (0.78-0.93), NAFLD-FS had the next AUROC 0.632 (0.52-0.73) and lastly, BARD had least AUROC 0.615 (0.50-0.72).

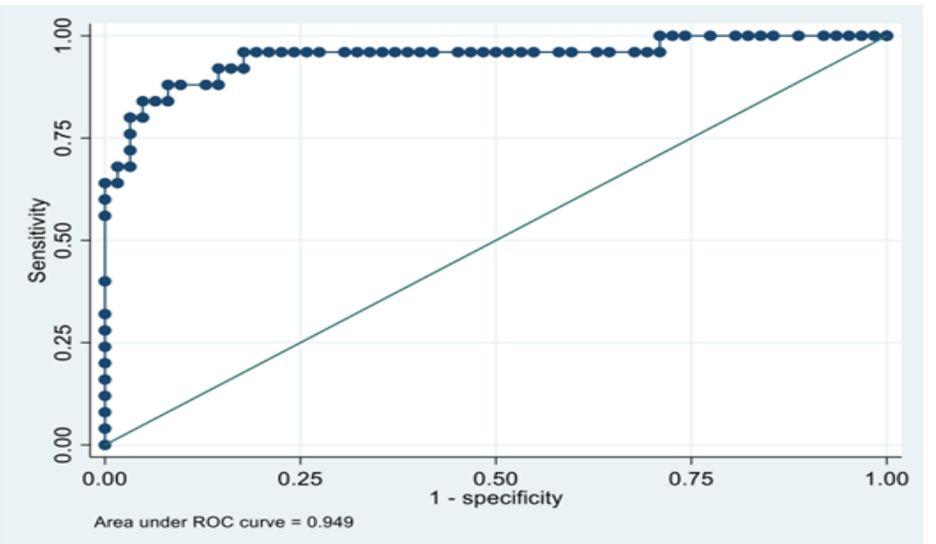

Fig. 2: ROC curve analysis of FIB-4 in predicting moderate/ advanced fibrosis. (AUROC=0.949 (0.88-0.99)

DISCUSSION

Currently, MASLD represents the leading cause of chronic liver disease across the globe[24]. The natural history of MASLD encompasses hepatic necro-inflammatory reactions, followed by hepatic fibrosis, cirrhosis, and ultimately hepatocellular carcinoma. Initial diagnostic assessment and proper management of MASLD can halt fibrosis progression and ameliorate MASLD-related health consequences [25]. Liver fibrosis is the fundamental event in MASLD pathogenesis and even in MASLD patients with advanced fibrosis, it serves as a separate risk factor linked to health complications and death in hepatic and extrahepatic contexts [26]. On the contrary, the mere incidence of steatosis is did not correlate Contributing to an augmented risk of hepatic morbidity [27].

During the previous decade, non-invasive biochemical and imaging techniques for assessing hepatic fat accumulation and fibrosis have significantly advanced. These methods include serological diagnostic scores including Fatty Liver Index (FLI), APRI, FIB-4, and NAFLD Fibrosis Score (NFS). Complementing these are radiological modalities like Transient Elastography (FibroScan), which provide reliable, non-invasive investigation of liver pathology [28]. Exploration and validation of these non-invasive tools Is widely recognized as a key topic in current research with a variety of tests being implemented to accurately recognize patients presenting with advanced liver fibrosis. Moreover, these tests are also steadily utilized to determine liver-related prognosis [29].

Our research focused on evaluating the effectiveness of several markers and scoring systems in distinguishing early from advanced stages of steatosis and fibrosis, comparing their performance to results from Transient Elastography. Univariate analysis of our data showed that body weight, BMI, fatty degree by ultrasound, right hepatic lobe span, FLI and HSI were significantly higher in moderate and advanced steatosis patients than those with mild steatosis. However, the final logistic regression model revealed that only moderate and severe fatty degree by ultrasound, and right lobe span were independent risk factors for moderate and advanced steatosis.

A comparison concerning the diagnostic capability of serum molecular markers associated with liver fat accumulation (FLI, HSI, VAI and TyG index) for predicting moderate and advanced steatosis in the present study revealed that FLI at a cut off >83 had the best AUROC (0.681), followed by HSI (0.676), VAI (0.627) and lastly TyG index (0.566).

Thomson et al. [30] studied non-invasive liver steatosis scores and demonstrated that FLI and VAI were among the highest predictive scores for early diagnosis of MASLD with AUROC of 0.65 (Sensitivity=63, Specificity=62.9%) and 0.628 (Sensitivity=50.8%, Specificity=65.7%) respectively. More recently and in partial concordance with our findings, a cross-sectional study conducted in China by ***Hu et al.*** [31] reported that during screening for MASLD among those with type 2 diabetes mellitus and their corresponding Lipid Accumulation Product (LAP) demonstrated the highest predictive accuracy for identifying MASLD, with AUROC of 0.786 (95%CI 0.76 - 0.81), followed by BMI (AUROC =0.785), VAI (AUROC =0.744) and TyG (AUROC =0.720).

Earlier studies [32] showed that AUROC of FLI and HSI for predicting moderate and severe steatosis (>33% by histopathology) were equal (0.65) and for both VAI and TyG index were (0.59).

A recent meta-analysis revealed that the Visceral Adiposity Index (VAI) possesses predictive capability for diagnosing NAFLD (AUROC = 0.767) and NASH (AUROC = 0.732). The study also found significantly elevated VAI values in adult patients with NAFLD and simple steatosis compared to healthy controls, as well as higher values in cases of severe steatosis relative to simple steatosis [33]. More recently, a large muti-center study evaluating biopsy-proven MASLD vs healthy controls concluded that TyG (AUROC= 0.814), HSI (AUROC= 0.795) and FLI (AUROC= 0.701) expressed a high discriminatory capacity to distinguish MASLD cases from controls [34].

In the current study, we examined the capability of some serum fibrosis markers to predict moderate and advanced fibrosis in MASLD patients. FIB-4, APRI, NFS and BARD scores showed higher values in patients with moderate and advanced fibrosis. These findings aligned with several studies that underscored the predictive value of these markers in MASLD patients [34-36]. However, upon multiple logistic regression analysis we found that only FIB-4 significantly predicted moderate and progressed fibrosis.

We investigated and compared the diagnostic potential of various serum fibrosis markers in prediction of moderate and progressed fibrosis. We found that FIB-4 at a cut-off >2.56 had the largest AUROC (0.949), followed by APRI at > 0.06 (AUROC= 0.868), NAFLD-FS at > 0.5 (AUROC =0.632) and lastly BARD score at >3 (AUROC =0.615). In a study conducted by ***Amernia et al.*** [37] APRI followed by FIB-4 were shown as the optimal non-invasive surrogate for FibroScan in the assessment of hepatic fibrosis among MASLD patients, quantifying the discriminative ability via the area under the receiver operating characteristic curve (AUROC) values of 0.923 and 0.913 for discriminating advanced fibrosis stages F3 and F4 from earlier stages F2 and F1, respectively. ***Xiao et al.*** [38] concluded in a meta-analysis study that APRI could distinguish advanced fibrosis and cirrhosis (AUROC= 0.75), though it had reduced sensitivities. Owing to its high NPV, APRI has manifested as an effective diagnostic tool in discriminating advanced fibrosis and no fibrosis. However, it showed poor performance for those with intermediate fibrosis [39]. A recent study reported that the Aspartate Aminotransferase to

Platelet Ratio Index (APRI) demonstrated high diagnostic efficacy in patients with MASLD, achieving an area under the receiver operating characteristic curve (AUROC) of 0.85, with a sensitivity of 16% and specificity of 99%, particularly for the detection of progressed fibrosis [34].

In our study, FIB-4 at a cut off >2.56 had 88% sensitivity, 91.9 % specificity, 81.5% PPV and 95% NPV. FIB-4 was advocated by European Association for the Study of the Liver (EASL) for the purpose of non-invasive fibrosis quantification due to excellent performance and subsequent validation in numerous studies from geographically distinct areas [40, 41]. Assessment of FIB-4 has been conducted recently in MAFLD patients to diagnose advanced fibrosis, However, these studies utilized different cut-offs with slightly lower accuracies in comparison to previous studies[42, 43]. More recently, upon evaluation in MASLD cohort, FIB-4 at a cut-off (>2.67) had 75.5% sensitivity, 70.1 % specificity, 81% PPV and 62.9% NPV with AUROC= 0.8-0.82 for fibrosis diagnosis [44].

This study confined by a relatively small number of participants and a single-center setting, potentially limiting the wider applicability of the results. Conclusion:

We concluded that using abdominal ultrasound can predict moderate and advanced steatosis in MASLD patients. FLI and HSI showed only moderate diagnostic performance for moderate and advanced steatosis. While FIB-4 was proved to be the exclusive significant predictor of moderate and advanced fibrosis and had a very good diagnostic accuracy. FIB-4 may be used in clinical practice together with ultrasound whenever Transient Elastography is not available.

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CONFLICT INTEREST

None to be declared.

AUTHORS' CONTRIBUTION

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by [Ghada M Galal], [Mohamed Abdulwahab Mohamed Ali] and [Ramy M Elsharkawy]. The first draft of the manuscript was written by [Sherif A Sayed] and [Noha M Abd El Rahman]. All authors commented on previous versions of the manuscript. All authors read and approved of the final manuscript.

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الاستخدام التشخيصي للدلالات الحيوية غير الاختراقية للتنكس الدهني والتليف في مرضي الكبد الدهني المصاحب للخلل الأيضي

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المقدمة: يعتبر الكبد الدهني المصاحب للخلل الأيضي من الأسباب الرئيسية علي مستوى العالم للأمراض والوفيات المرتبطة بالكبد. تعد عينة الكبد الطريقة التقليدية لتقييم عبء المرض. ان تحديد الدلالات الحيوية البسيطة غير الاختراقية لهذا المرض يشكل أهمية قصوى في تشخيصه.

الأهداف: ١- تقييم أداء المؤشرات المصلية الحيوية في قياس درجة التنكس الدهني ومرحلة التليف في مرضي الكبد الدهني المصاحب للخلل الأيضي. ٢- دراسة عوامل التنبؤبوجود تنكس دهني وتليف متقدم في هؤلاء المرضى.

المرضى والطرق المستخدمة: اشتملت الدراسة علي ٨٧ من الأشخاص البالغين الذين لا يعانون من أعراض ولديهم الكبد مشرق عند الفحص بالموجات فوق الصوتية. تم تقييم التنكس الكبدي والتليف بواسطة رسام المرونة العابر. تم تشخيص الكبد الدهني المصاحب للخلل الأيضي طبقا للمعايير المعتمدة دوليا.

تم تقييم دلالات التنكس الآتية في مصل الدم: FLI, HSI, VAI, TyG كما تم تقييم التليف بواسطة كل من

NFS, FIB-4, APRI, BARD

تم استخدام منحنيات (ROC) للتعرف على أفضل العوامل للتنبؤ بوجود التنكس الدهنى / التليف فى هؤلاء المرضى.

النتائج: وجد التنكس الدهني المتوسط والمتقدم فى ٦٨/ ٨٧ مريضا (٧٨,٢٪) بينما وجد التليف المتوسط والمتقدم في ٨٧/٢٥ مريضا (٢٨,٧٪). لقد كشف تحليل منحنى (ROC أن المنطقة تحت المنحنى الخاصة بدلالات التنكس كانت (٠,٦٨١) ل FLI، (٠,٦٧٦) ل HSI، (٠,٦٢٧) ل VAI و (٠,٥٦٦) ل TyG. كانت درجة التنكس الدهني في الفحص بالموجات فوق الصوتية وطول الفص الأيمن للكبد هما المتنبئان ذوا الدلالة الاحصائية بوجود تنكس دهني متوسط الي متقدم في تحليل الانحدار اللوجستي المتعدد. كانت المنطقة تحت المنحنى الخاصة بدلالات التليف كالآتي: (٠,٩٤٩) لمؤشر FIB-٤، (٠,٨٦٨) لمؤشر APRI، (٠،٦٣٢) ل NFS و (٠،٦١٥) لمؤشر BARD. أظهر النموذج النهائي لتحليل الانحدار اللوجستي المتعدد أن مؤشر FIB-٤ هو المتنبئ الوحيد ذو الدلالة الاحصائية لوجود تليف متوسط الي متقدم.

الاستنتاجات: ان درجة التنكس الدهني في الفحص بالموجات فوق الصوتية وطول الفص الأيمن للكبد يمكنها لبتنبؤ بشكل مستقل بوجود تنكس دهني متوسط/ متقدم في مرضى الكبد الدهني المصاحب للخلل الأيضى. في حين كان مؤشر FIB-٤ هو المتنبئ الوحيد بوجود تليف متوسط/ متقدم في هؤلاء المرضى. يمكن استخدام هذه الاختبارات البسيطة كبديل عن رسام المرونة العابرفي الأماكن التي لا يتوفر بها هذا الجهاز.