# Role of Controlled Attenuation Parameter in Metabolic Associated Fatty Liver Disease Patients

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**Background and study aim:** Metabolic associated fatty liver disease (MAFLD) is an increased serious clinical concern .Novel physical parameter, based on the properties of ultrasonic signals acquired by the Fibroscan®, is called the controlled attenuation parameter (CAP). This study aimed at assessing the role of CAP in disease staging in MAFLD patients.

**Patients and Methods:** This is a comparative cross sectional study conducted on 84 patients diagnosed as having fatty liver by abdominal ultrasonography and, features of MAFLD according to international consensus guideline. Patients classified as MAFLD with chronic liver disease, HCV, HBV (Group 2) and MAFLD without other chronic liver disease (Group 1).

**Results:** Most patients had marked hepatic steatosis. The diagnostic accuracy of CAP in disease staging in MAFLD patients was 88% at cut off value of >297 dB/m with sensitivity 88.5% and specifity 82.8%.The diagnostic accuracy of combined CAP and FLI(Fatty liver index) for liver steatosis diagnosis was 95% with sensitivity 96.2% and specifity 87.7%.

**Conclusion:** CAP may be used as a promising noninvasive tool for assessment and quantifying of steatosis in MAFLD patients. Combination of both noninvasive imaging technique (CAP) and laboratory score (FLI) may improve the diagnostic accuracy in assessing steatosis in MAFLD patients .

## INTRODUCTION

In the twenty-first century, the prevalence of non-alcoholic fatty liver disease (NAFLD) has expanded dramatically, with a current worldwide disease burden estimated to be around 25% of the global population. If total intrahepatic fat mass exceeds 5% of liver mass, hepatic steatosis is observed **[1, 2]**.

The crucial involvement of metabolic variables as significant pathogenic drivers is not covered or indicated in the NAFLD terminology. However, diagnosis of alcoholic liver disease and NAFLD may overlap, making it difficult to identify one from the other. To propose a more thorough redefinition of fatty liver disease linked with metabolic dysfunction to replace NAFLD, we propose, "Metabolic dysfunction associated fatty liver disease (MAFLD)." MAFLD diagnosis does not necessitate the exclusion of patients who consume alcohol or have other chronic liver disorders, nor does it necessitate the existence of a metabolic imbalance **[3]**.

Serum liver enzyme abnormalities are an important aspect of regular clinical tests for individuals with NAFLD; nevertheless, they are influenced by a variety of factors, including obesity, metabolic syndrome, diabetes, ethnicity, and genetics. **[4]**. The reference standard for the diagnosis of NAFLD and the assessment of NAFLD-related pathological abnormalities such as the degree of steatosis and liver fibrosis is often liver biopsy **[5]**. However, there are well-known disadvantages to liver biopsy, such as invasiveness and sample unpredictability. Noninvasive laboratory and radiographic assessment methods for hepatic steatosis and fibrosis in NAFLD have evolved, which may help overcome the limitations of liver biopsy, such as

the FIB4, APRI score, FLI, and NFS, as well as radiological methods such as Transient elastography **[6]**.

The FibroScan's vibration-controlled transient elastography (VCTE) method monitors the velocity of the shear wave, which is then translated to stiffness using the Young's module. It has been established as a quick and painless method for diagnosing and staging liver fibrosis **[7]**. The controlled attenuation parameter (CAP) is a physical parameter based on the FibroScan's ultrasonic signal characteristics. CAP detects ultrasonic attenuation at the VCTE's core frequency using a M or standard probe, which may aid in the diagnosis of steatosis **[8]**. This study aimed to assess role of CAP in disease staging in MAFLD patients.

## PATIENTS AND METHODS

This is a comparative cross sectional study conducted on 84 patients, diagnosed as having fatty liver by abdominal ultrasonography at Tropical Medicine Department, Faculty of medicine, Zagazig University from September 2021 to May 2022. Patients were classified as MAFLD with other chronic liver disease (HCV, HBV) (G2), and MAFLD without other chronic liver disease (G1).

**Inclusion Criteria:**

MAFLD is diagnosed based on the presence of hepatic steatosis detected by ultrasonography, as well as one of the three diseases listed below: 1- overweight/obesity, 2- diabetes mellitus (DM), or 3- metabolic dysregulation. The presence of two or more of the following conditions was considered as metabolic dysregulation: (a) Men's waist circumference > 102 cm, while women's waist circumference > 88 cm. (b) Blood pressure >130/85 mmHg or treatment with a specific medication. b) A TG of more than 1.70 mmol/L (150 mg/dl) or a specific pharmacological therapy (d) Male HDL-C < 1.0 mmol/L (40 mg/dl) and female HDL-C < 1.3 mmol/L (50 mg/dl). (e) Prediabetes (fasting glucose levels of 5.6 to 6.9 mmol/L (100 mg/dl to 125 mg/dl) or 2-hour post-load glucose levels of 7.8-11.0 mmol/L (140 mg/dl to 199 mg/dl) or HbA1c of 5.7 to 6.4%).(f) C-reactive protein (CRP) level >2 mg/L **[3]**.

**Exclusion Criteria:**

Hepatic decompensation, morbid obesity BMI>35 and presence of hepatocellular carcinoma

**Operational design:**

All cases were subjected to complete history taking included a history of alcohol consumption, drug use. Comorbidities such as type 2 diabetes, hypertension, and cardiovascular disease should also be identified. A comprehensive clinical examination with measurement of blood pressure, weight, height and waist circumference was performed. Body mass index (BMI) was calculated by dividing body weight (in kg) by the square of height (in meters).

**Imaging investigations:**

Abdominal Ultrasound was done to all patients. NAFLD suspected when sonographic features unique to NAFLD are standardized as (bright liver echoes, increased hepatorenal echogenicity and poor or no visualization of portal, hepatic vein or diaphragm) and hepatic steatosis grading was done according to Hernaez et al. **[9].**

**Biochemical assessment:**

Complete Blood Count, Liver function tests including: bilirubin level, serum albumin, ALT, AST. Kidney function tests including : serum creatinine and serum urea. Prothrombin time, INR. Virological markers as HCV antibody, HBVsAg, HCV RNA by PCR. Alfa feto protein and Fasting blood glucose (FBG) were done. Diagnosis of T2DM based on American Diabetes Association revised criteria, using a value of fasting blood glucose 126 mg/dl or greater on at least 2 occasions, postprandial blood glucose >200 mg/dl and glycosylated hemoglobin >6.5%. Lipid profile: Total cholesterol (TC), triglycerides (TG), LDL cholesterol and HDL cholesterol. Serum fibrosis markers include NAFLD fibrosis score (NFS) fibrosis 4 (FIB-4) and FLI(Fatty liver index) for hepatic steatosis were also done**[10]**.

a- NAFLD fibrosis score = −1.675 + 0.037 – age (years) + 0.094 BMI (kg/m$^2$) + 1.13 × [Impaired FBG/DM (yes = 1, no = 0)] + 0.99 × AST/ALT ratio – 0.013× platelet count (×109/l) – 0.66 × albumin (g/dl).

b- FIB-4 index = Age (years) × AST (U/L)/ [PLT (109/L) × ALT1/2 (U/L)].

c- FLI= (e0.953 × loge (triglycerides) + 0.139 × BMI + 0.718 × loge (GGT) + 0.053 × waist circumference − 15.745)/(1 + e0.953 × loge (triglycerides) + 0.139 × BMI + 0.718 × loge (GGT) + 0.053 × waist circumference − 15.745) × 100.

Fibroscan was done for all patients for measuring LSM defined in KPa, CAP defined in dB/m, using Fibroscan 502 (Echosens, Paris, France) device using two probes M+ and XL+.

**Controlled attenuation parameter:**

The controlled attenuation parameter (CAP) is a new physical parameter based on the FibroScan's ultrasonic signal characteristics. At the M or XL probes, CAP measures ultrasonic attenuation at the core frequency of Vibration-controlled transient elastography (VCTE).

**Statistical analysis:**

The collected data analyzed using SPSS program (Statistical Package for Social Sciences) software version 26.0, Microsoft Excel 2016 and MedCalC program software version 19.1. Descriptive statistics were done for numerical parametric data as mean ± SD and minimum & maximum of the range and for numerical non parametric data as median and 1st& 3rd inter-quartile range, while they were done for categorical data as number and percentage. Using independent t-test, Mann Whitney U, Chi square test and Spearman's method. The ROC Curve to evaluate the Sensitivity and specificity for quantitative diagnostic measures that categorize cases into one of two groups. Excellent accuracy =0.90 to 1 (%), Good accuracy = 0.80 to 0.90 (%), Fair accuracy = 0.70 to 0.80 (%), Poor accuracy = 0.60 to 0.70 (%), Failed accuracy = 0.50 to 0.60 (%). The level of significance was taken at P value <0.05 is significant.

## RESULTS:

This study included 84 MAFLD patients, their age ranged from 23-69 years old, 63 males and 21 females, classified as (group 1) MAFLD patients without chronic liver diseases, (group 2), MAFLD patients with chronic liver diseases. HBV (6 patients), HCV(20 patients). 30 MAFLD patients were hypertensive, 21 MAFLD patients were diabetics. BMI was 32.16 ± 2.7 kg/m2, waist circumference was 110.98 ±9.4 cm. Only 3 cases out of 84 patients have NFS >0.675 (3.6%), mean ± SD of FIBS score was 1.27 ± 0.67 with 69% had FIB4 score less than 1.45 that indicates no fibrosis, none of our patients has FIB4score >3.25. In this study, the mean ± SD of fatty liver index was 85.34 ± 12.55 with (80 patients) 95.2% had FLI more than 60 that indicates fatty liver ruled in . AST, ALT and LDL were independent risk factors for advanced fibrosis assessed by FIB-4. AST, ALT, uric acid and triglycerides were independent risk factors for advanced fibrosis assessed by NFS .By using fibroscan ; the majority of MAFLD patients had no or mild fibrosis (F0-F1 69%), while,16.9% had moderate fibrosis, and only 12 patients had advanced fibrosis (F3 9.5%, F4 4.8%). Most patients had marked hepatic steatosis as demonstrated by CAP (S2, 31% at cutoff value 260-290 Db/m and S3 58.3% a cut off value >290 dB/m). While 8,3% showed mild steatosis (S1 at cut off value 238-260 dB/m) **(Table 1)**.

The present study showed a significant difference between the two studied groups regarding sex (p=0.014) as females were more in group 1, compared to group 2. Age was significantly higher in group 2 compared to group 1. Group 2 showed significant prevalence of smoking compared to group 1.Abdominal distension was significant in group 1 (P<0.001) ,while most patients in group 2 were asymptomatic (P<0.001). There was no significant difference between the two studied groups regarding hypertension and DM (P>0.05). Waist circumference was significantly higher in group 2 compared to group 1 (P=0.005). There was no significant difference between the two studied groups regarding weight, height and BMI (P>0.05) **(Table 2)**.

Regarding biochemical analysis, Group 1 showed significant increase in platelets count compared to group 2 (P=0.002). Group 2 showed significant increase in INR compared to group 1 (P=0.005) .Group 2 showed significant increase in fasting blood sugar, postprandial blood sugar and HbA1c compared to group 1 (p=0.015, 0.004 & 0.013 respectively). There was no significant difference between the two studied groups regarding urea, creatinine and uric acid (P>0.05). **(Table 3)**.

Both NFS and FIB4 were significantly higher in group2 compared to group 1, however there was no significant difference between the two studied groups regarding FLI **(Table 4)**.

Regarding fibrosis reading and CAP, fibrosis score reading was significantly higher in group 2 compared to group 1 (P<0.001). There was no statistically significant difference between steatosis in the two studied groups regarding CAP (P>0.05) **(Table 5)**.

There was significant negative correlation between CAP with total bilirubin, direct bilirubin and HDL and positive correlation with triglyceride(r=0.348,p=0.001) .Also, there was significant positive correlation between CAP with waist circumference (r= 0.270, p=0.013) and BMI (r= 0.246, p=0.024) (Data not shown). However the results of multivariate analysis showed that steatosis had no significant association between the parameters mentioned **(Table 6)**.

There was no significant correlation between fibrosis and steatosis detected by fibroscan (r= 0.130,p= o.238). The results of multivariate analysis showed that AST, ALT, platelets, cholesterol and LDL were independent risk factors for fibrosis detected by fibroscan **(Table7)**.

At cut off value of 6.3 Kpa TE has the highest sensitivity, specificity and accuracy to detect fibrosis (80.8%%, 81%,83% respectively) in MAFLD patients .The diagnostic accuracy of FLI in disease staging in MAFLD patients was 87% at cut off value >88.29 with sensitivity and specificity of 88.5%, 80.7% respectively .The diagnostic accuracy of CAP in disease staging in MAFLD patients was 88% at cut off value of >297 dB/m with sensitivity 88.5% and specificity 82.8. The diagnostic accuracy of combined CAP and FLI for diagnosis of liver steatosis was 95%. with sensitivity 96.2% and specificity 87.7% % **(Table 8)**.

**Table (1):** Distribution of the studied cases as FIB4,NFS, Fatty liver index (FLI) , fibrosis and CAP reading by fibroscan.

| Test | **No** |
|---|---|
| FIB4 | |
| <1.45 | 58 |
| (1.45-3.25) | 26 |
| >3.25 | 0 |
| NFS | |
| <-1.455 | 38 |
| (-1.455-0.675) | 43 |
| >(0.675) | 3 |
| FLI | |
| (<30) | 0 |
| (30-60) | 4 |
| (>60) | 80 |
| Fibrosis | |
| F0-F1(2-7) | 58 |
| F2(7.5-10) | 14 |
| F3(10-14) | 8 |
| F4>14 | 4 |
| CAP | |
| S0(<238) | 2 |
| SI(238-260) | 7 |
| S2(260-290) | 26 |
| S3(>290) | 49 |

**Table (2):** Comparison between the two studied groups regarding demographic characteristics & Clinical data.

| | | Group (1) (No. = 58) | | Group (2) (No. = 26) | | Test value | P-value |
|---|---|---|---|---|---|---|---|
| | | N | % | n | % | | |
| **Sex** | **Male** | 39 | 67.2% | 24 | 92.3% | $X^2$= 6.02 | **0.014** |
| | **Female** | 19 | 32.8% | 2 | 7.7% | | |
| **Age (years)** | **Mean± SD** | 44.26± 11.89 | | 50.42± 6.96 | | T = 2.97 | **0.004** |
| | **Median** | 42.50 | | 51.5 | | | |
| | **Range** | 23.0 – 69.0 | | 37.0 - 68.0 | | | |
| **Smoking** | **No** | 37 | 63.8% | 9 | 34.6% | $X^2$= 6.17 | **0.013** |
| | **Yes** | 21 | 36.2% | 17 | 65.4% | | |
| **Alcohol intake** | **No** | 58 | 100.0% | 26 | 100.0% | NA | NA |
| | **Yes** | 0 | 0.0% | 0 | 0.0% | | |
| **Clinical symptoms** | **Asymptomatic** | **9** | 15.5% | 14 | 53.8% | | |
| | **Fatigue** | **32** | 55.2% | 15 | 57.7% | | |
| | **Heart burn** | **28** | 48.3% | 13 | 50.0% | | |
| | **Abdominal distension** | **49** | 84.5% | 12 | 46.2% | | |
| | **Cardiac symptoms** | **5** | 8.6% | 2 | 7.7% | | |
| **Hypertension** | **No** | **38** | 65.5% | 16 | 61.5% | | |
| | **Yes** | **20** | 34.5% | 10 | 38.5% | | |
| **DM** | **No** | **36** | 62.1% | 6 | 23.1% | | |
| | **Prediabetic** | **10** | 17.2% | 11 | 42.3% | | |
| | **Diabetic** | **12** | 20.7% | 9 | 34.6% | | |
| **HBsAg** | **Negative** | **58** | 100.0% | 20 | 76.9% | | |
| | **Positive** | **0** | 0.0% | 6 | 23.1% | | |
| **HCV Ab.** | **Negative** | **58** | 100.0% | 6 | 23.1% | | |
| | **Positive** | **0** | 0.0% | 20 | 76.9% | | |

**Other clinical numerical parameters**

| | Group (1) (No. = 58) | | | Group (2) (No. = 26) | | | Test value | P-value |
|---|---|---|---|---|---|---|---|---|
| | Mean | ± SD | Median | Mean | ± SD | Median | | |
| **Weight (Kg)** | 92.78 | 8.83 | 92.50 | 97.04 | 9.98 | 99.00 | T= 1.96 | 0.053 |
| **Height (cm)** | 170.81 | 7.40 | 171.00 | 171.85 | 5.81 | 171.50 | T= 0.631 | 0.530 |
| **BMI (Kg/m$^2$)** | 31.85 | 2.72 | 31.80 | 32.85 | 2.61 | 33.90 | Z MWU= 1.61 | 0.108 |
| **Waist circumference (cm)** | 109.07 | 9.52 | 108.00 | 115.25 | 7.75 | 118.00 | Z MWU=2.799 | 0.005 |

P≤0.05 is considered statistically significant, p≤0.01 is considered high statistically significant, SD= standard deviation, comparison between groups done by Student T test, Mann-Whitney U test and Chi- Square test

**Table (3):** Comparison between the two studied groups regarding renal function tests and other laboratory tests.

| | Group (1) (No. = 58) | | | Group (2) (No. = 26) | | | Test value | P-value |
|---|---|---|---|---|---|---|---|---|
| | Mean | ± SD | Median | Mean | ± SD | Median | | |
| **Urea (mg/dL)** | 39.50 | 10.52 | 37.00 | 39.88 | 11.15 | 37.50 | ZMWU= 0.272 | 0.786 |
| **Creatinine(mg/dL)** | .98 | .17 | .90 | 1.06 | .23 | .95 | ZMWU= 1.442 | 0.149 |
| **Uric Acid (mg/dL)** | 5.07 | 1.01 | 5.10 | 5.40 | 1.08 | 5.60 | T= 1.360 | 0.177 |
| **F.B.S(mg/dL)** | 106.09 | 30.52 | 92.00 | 131.08 | 44.09 | 121.50 | ZMWU= 2.432 | **0.015** |
| **PostPrandial BS(mg/dL)** | 158.28 | 63.27 | 129.00 | 211.31 | 90.13 | 188.00 | ZMWU= 2.89 | **0.004** |
| **HBA1C** | 5.64 | 0.81 | 5.40 | 6.19 | 0.81 | 6.10 | ZMWU= 2.484 | **0.013** |

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant Z: Mann-Whitnney U Test , T: Student T Test. SD: standard deviation.

**Table (4):** Comparison between the two studied groups regarding FIB4, NFS and fatty liver index.

| | Group (1) No. = 58 | | Group (2) No. = 26 | | Test value | P value |
|---|---|---|---|---|---|---|
| **FIB4** | | | | | | |
| | **Mean ± SD** | **Median** | **Mean ± SD** | **Median** | **Test value** | **P value** |
| | 1.10 ± 0.52 | 0.98 | 1.64 ± 0.81 | 1.44 | ZMWU= 2.94 | 0.003 |
| | **No.** | **%** | **No.** | **%** | | |
| **FIB4 (<1.45)** | 45 | 77.6 | 13 | 50.0 | $X^2$= 5.167 | 0.023 |
| **FIB4 (1.45-3.25)** | 13 | 22.4 | 13 | 50.0 | | |
| **FIB4 (>3.25)** | 0 | 0.0 | 0 | 0.0 | | |
| **NFS** | | | | | | |
| | **Mean ± SD** | **Median** | **Mean ± SD** | **Median** | **Test value** | **P value** |
| | -1.58 ± 1.28 | -1.94 | -0.47± 1.18 | -0.33 | T= 4.66 | <0.001 |
| | **No.** | **%** | **No.** | **%** | | |
| **NFS (<-1.455)** | 33 | 56.9 | 5 | 19.2 | $X^2$= 14.716 | 0.001 |
| **NFS (-1.455-0.675)** | 25 | 43.1 | 18 | 69.2 | | |
| **NFS (>0.675)** | 0 | 0.0 | 3 | 11.5 | | |
| **Fatty liver index** | | | | | | |
| | **Mean ± SD** | **Median** | **Mean ± SD** | **Median** | **Test value** | **P value** |
| | 83.91 ± 13.42 | 89.89 | 88.55 ± 9.83 | 91.94 | ZMWU= 1.113 | 0.266 |

**Table (5):** Comparison between the two studied groups regarding fibrosis reading and CAP.

| | Group (1) (No. = 58) | | Group (2) (No. = 26) | | Test value | P-value |
|---|---|---|---|---|---|---|
| **Fibrosis reading** | | | | | | |
| | **Mean ± SD** | **Median** | **Mean ± SD** | **Median** | **Test value** | **P-value** |
| | 5.31± 2.21 | 4.60 | 9.11± 3.97 | 8.45 | ZMWU= 4.875 | <0.001 |
| | **No.** | **%** | **No.** | **%** | | |
| **F0-F1 (2-7)** | 49 | 84.5% | 9 | 34.6% | X2= 24.44 | <0.001 |
| **F2 (7.5-10)** | 7 | 12.1% | 7 | 26.9% | | |
| **F3(10-14)** | 1 | 1.7% | 7 | 26.9% | | |
| **F4 (>14)** | 1 | 1.7% | 3 | 11.5% | | |
| **CAP** | | | | | | |
| | **Mean ± SD** | **Median** | **Mean ± SD** | **Median** | **Test value** | **P-value** |
| | 307.79± 49.96 | 295.5 | 290.69± 53.47 | 301.5 | ZMWU= 0.561 | 0.575 |
| | **No.** | **%** | **No.** | **%** | | |
| **S0 (<238 )** | 0 | 6.9% | 2 | 7.7% | X2= 6.473 | 0.091 |
| **S1 (238-260)** | 5 | 8.6% | 2 | 7.7% | | |
| **S2 (260-290)** | 21 | 36.2% | 5 | 19.2% | | |
| **S3 (>290 )** | 32 | 55.2% | 17 | 65.4% | | |

p≤0.05 is considered statistically significant, p≤0.01 is considered highly statistically significant Z Mann-Whitney U Test, T: Student T Test. X2:Chi- Square test, SD: standard deviation

**Table (6):** Multivariate regression analysis for steatosis.

| Parameters | B | S.E | Wald | P-value | Odds ratio (OR) | 95% CI | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower limit | Upper limit |
| ALT | .010 | .026 | .142 | .707 | 1.010 | .959 | 1.064 |
| AST | .016 | .037 | .193 | .660 | 1.016 | .946 | 1.092 |
| T. bilirubin | -4.368- | 2.899 | 2.270 | .132 | .013 | .000 | 3.719 |
| D. bilirubin | -1.363- | 4.886 | .078 | .780 | .256 | .000 | 3688.663 |
| GGT | .000 | .030 | .000 | .996 | 1.000 | .944 | 1.060 |
| Albumin | 1.836 | 1.308 | 1.970 | 0.160 | 6.274 | .483 | 81.516 |
| INR | -.857- | 3.059 | .079 | .79 | .424 | .001 | 170.385 |
| Urea | -.049- | .033 | 2.154 | .142 | .952 | .892 | 1.016 |
| Creatinine | -1.466- | 1.896 | .598 | .439 | .231 | .006 | 9.481 |
| Uric acid | -.474- | .326 | 2.113 | .146 | .622 | .328 | 1.180 |
| HB | -.007- | .228 | .001 | .976 | .993 | .636 | 1.552 |
| TLC | -.126- | .141 | .794 | .373 | .882 | .669 | 1.163 |
| Platelets | -.004- | .005 | .534 | .465 | .996 | .985 | 1.007 |
| Cholesterol | -.012- | .013 | .963 | .326 | .988 | .963 | 1.013 |
| Triglycerides | -.007- | .006 | 1.157 | .282 | .993 | .981 | 1.006 |
| LDL | .022 | .013 | 3.005 | .083 | 1.022 | .997 | 1.048 |
| HDL | -.087- | .047 | 3.389 | .066 | .917 | .836 | 1.006 |
| SBP | -.017- | .027 | .399 | .527 | .983 | .933 | 1.036 |
| DBP | .007 | .031 | .053 | .817 | 1.007 | .948 | 1.070 |
| F.B.S | .081 | .046 | 3.125 | .077 | 1.085 | .991 | 1.187 |
| P.P.B.S | -.006- | .021 | .082 | .775 | .994 | .955 | 1.035 |
| HBA1C | -1.712- | 1.101 | 2.417 | .120 | .180 | .021 | 1.563 |
| Waist circumference | .015 | .061 | .058 | .810 | 1.015 | .901 | 1.142 |
| BMI | .224 | .184 | 1.490 | .222 | 1.251 | .873 | 1.793 |

**Table (7):** Multivariate regression analysis for fibrosis detected by fibroscan in MAFLD patients.

| Parameters | B | S.E | Wald | P-value | Odds ratio (OR) | 95% CI | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower limit | Upper limit |
| ALT | -.82- | .037 | 4.939 | .026 | .921 | .857 | .990 |
| AST | .093 | .041 | 5.322 | .021 | 1.098 | 1.014 | 1.189 |
| T. bilirubin | .538 | 3.156 | .029 | .865 | 1.713 | .004 | 831.577 |
| D. bilirubin | -2.191- | 5.949 | .136 | .70. | .112 | .000 | 12960.143 |
| GGT | .041 | .028 | 2.105 | .147 | 1.042 | .986 | 1.101 |
| Albumin | 1.240 | 1.244 | .993 | .319 | 3.454 | .302 | 39.547 |
| INR | 1.631 | 1.895 | .741 | .389 | 5.108 | .125 | 209.436 |
| Urea | .009 | .032 | .086 | .769 | 1.009 | .948 | 1.075 |
| Creatinine | 2.612 | 1.879 | 1.932 | .165 | 13.626 | .343 | 541.793 |
| Uric acid | -.133- | .307 | .188 | .665 | .875 | .479 | 1.599 |
| HB | -.028- | .239 | .014 | .905 | .972 | .608 | 1.553 |
| TLC | .125 | .147 | .729 | .393 | 1.134 | .850 | 1.512 |
| Platelets | .031 | .010 | 10.428 | .001 | .969 | .951 | .988 |
| Cholesterol | .178 | .068 | 6.903 | .009 | .837 | .732 | .956 |
| Triglycerides | .022 | .012 | 3.315 | .069 | 1.002 | .998 | 1.046 |
| LDL | .155 | .072 | 4.648 | .031 | .856 | .744 | .986 |
| HDL | -.017- | .032 | .266 | .606 | .983 | .923 | 1.048 |
| Systolic pressure | -.001- | .028 | .002 | .965 | .999 | .946 | 1.055 |
| Diastolic pressure | -.042- | .039 | 1.158 | .282 | .959 | .889 | 1.035 |
| F.B.S | -.007- | .036 | .033 | .855 | .993 | .925 | 1.067 |
| P.P.B.S | .006 | .016 | .129 | .720 | 1.006 | .974 | 1.039 |
| HBA1C | .381 | .891 | .182 | .669 | 1.463 | .255 | 8.393 |
| Waist circumference | .062 | .067 | .867 | .352 | 1.064 | .934 | 1.212 |
| BMI | -.025 | .243 | .011 | .917 | .975 | .605 | 1.571 |

B: Regression coefficient; S.E.: Standard error,, CI: Confidence interval

**Table (8):** Diagnostic accuracy of FLI & CAP in disease staging in MAFLD patients

| Parameter | Cutoff value | AUC | Sensitivity | Specificity | PPV | NPV | Accuracy | P value |
|---|---|---|---|---|---|---|---|---|
| *FLI* | *>88.29* | 0.866 | 88.5% | 80.7% | 82.1% | 87.5% | 87% | <0.001 |
| *CAP* | >297 | 0.878 | 88.5% | 82.8% | 83.7% | 87.8% | 88% | <0.001 |
| *CAP+ FLI* | | 0.947 | 96.2% | 87.7% | 88.7% | 95.8% | 95.0% | <0.001 |

PPV= Positive Predictive Value, NPV= Negative Predictive Value, AUC= Area Under Curve

## DISCUSSION

NAFLD is one of the world's most frequent chronic liver illnesses. MAFLD is a new concept that may help clinicians identify patients who are more likely to have a negative result **[3,11]**.

The reference standard for the detection of NAFLD and the assessment of NAFLD-related pathological abnormalities such as the degree of steatosis and liver fibrosis is often liver biopsy **[5]**. However, there are well-known disadvantages to liver biopsy. Noninvasive laboratory and radiographic assessment methods for hepatic steatosis and fibrosis in NAFLD have evolved, which may help overcome the limitations of liver biopsy, such as the FIB4, APRI score, FLI, and NFS, as well as radiological methods such as Transient elastography **[6]**.

In this study, the mean ± SD of age was 46.17± 10.95 years. Age was significantly higher in group 2 compared to group 1 (P=0.004). 63 (75%) cases were males and 21 (25%) were females. There was significant difference between the two studied groups regarding sex (P=0.014) as females was significantly more in group 1 compared to group 2. These findings are in agreement with **Taheri et al. [12]** as the mean ± SD of the patients age was 43.5 ± 12.7 years. Also, **Yuan et al. [13]** reported that ,there was significant difference between males and females (36.80% vs. 28.65%, P<0.001). The prevalence of MAFLD in males and females both increased with age (P<0.001) also, NAFLD is prevalent among male gender.

In the current study, the average weight, BMI were 94.10 ± 9.36 Kg, and 32.16 ± 2.71 Kg/m$^2$ respectively. There was no significant difference between the two studied groups regarding weight, and BMI (P>0.05). Waist circumference were 110.98 ± 9.41 cm and was significantly higher in group 2 compared to group 1 (P=0.005**). De ledinghen and Vergniol [14]** revealed that high BMI and WC are the main obesity indices and risk factor for NAFLD. In addition, WC had the greatest power to predict fatty liver and correlated with the severity of fatty liver **[15]**.

Also, **Mansour et al**. **[16]** showed that the mean ± SD of BMI of MAFLD patients was 35.59 ± 5.77 Kg/m$^2$ and waist circumference (cm) 109.44 ± 11.54 as, MAFLD is tightly linked to the weight and metabolic syndrome, in addition, there was a statistically significant positive correlation between hepatic steatosis and, fibrosis with BMI, WC. In addition**, Hu et al**. **[17]** showed that BMI was higher in the NAFLD group than in the non-NAFLD group.

On the other hand **Yuan et al. [13]** found that, in the general population, 3.72% had non obese MAFLD. The lean/normal weight MAFLD group had a female predominance than the non-MAFLD group.

Abdominal distension was significantly higher in group 1 (P<0.001), while most patients in group 2 were asymptomatic (P<0.001), while there was no significant difference between the two studied groups regarding fatigue, heart burn and cardiac symptoms (P>0.05).

NAFLD seems frequently asymptomatic at diagnosis, feeling of fullness, discomfort in right upper abdomen and malaise are reported in many cases, NAFLD is detected on doing ultrasonography or performing investigation for other aliments **[18]**.

Regarding comorbidities, 35.7% were hypertensive, 25% were prediabetics and 25% were diabetics. There was no significant difference between the two studied groups regarding hypertension and DM (P>0.05). Group 2 showed significant increase in fasting blood sugar, postprandial blood and HbA1c compared to group 1 (p=0.015, 0.004 & 0.013 respectively) as hepatitis C virus and hepatitis B virus are associated with insulin resistance and more diabetes prevalence **[19]**.

Also**, Taheri et al., (2021) [12]**, reported that the incidence of diabetes, hypertension, and cardiovascular disease was higher in the NAFLD group than in the non-NAFLD group, and the

differences were statistically significant (P<0 .05). Similarly, also, **Yuan et al. (2022) [13]** reported that the prevalence of hypertension and DM in lean/normal weight MAFLD participants was higher than that in non-MAFLD participants.

In addition**, Jiaofeng et al. 2021 [20]** recorded that, 28.65% of MAFLD patients had diabetes, and 35.8% had hypertension and this is in line with this study as MAFLD patients may have one or more metabolic conditions.

In this study MAFLD with HCV patients were 20 patients (23.8%) and MAFLD with HBV were 6 patients (7.1%) . Those patients were classified before as viral hepatitis rather than MAFLD; it was found that steatosis occur more frequently with chronic hepatitis C (55%) than in general population (20-30%). This may be due to insulin resistance associated with HCV or viral factor like core antigen. Also HBV commonly associated with steatosis (41%) due to insulin resistance and viral factor like x antigen and poly morphism in interleukin 28B which may affect lipid metabolism **[21]**.

**Huang et al. 2021 [20]** reported that in between 4087 patients with MAFLD there was ninety patients with HCV and, 17 with HBV, this may be due to geographic difference and prevalence of HCV, HBV.

In the present study, the mean ± SD ALT was 46.48± 33.65 U/L.Normal levels of liver enzymes have been demonstrated in 80% NAFLD patients **[22]**.

In the present study, Group 1 showed significant increase in platelets count compared to group 2(p=0.002), but still within normal range as majority of our patients has no or mild fibrosis as the prevalence and degree of thrombocytopenia increase with severity of chronic liver disease and fibrosis. It may be due to extrahepatic manifestation to HBV, HCV, antiplatelet antibodies, bone marrow suppression or hypersplenism **[23].**

This study revealed that the mean ± SD FIBS score was 1.27± 0.67 with 69% had FIB4 score less than 1.45 that indicates no fibrosis, none of our patients has FIB4score >3.25 . Mean ± SD FIBS score was significantly higher in group 2 compared to group 1 (p=0.003).

As regards NFS, in this study only 3 cases out of 84 patients have NFS > 0.675 (3.6%). NFS Mean ± SD was significantly higher in group 2 compared to group 1 (p<0.001) with increasing score level in group 2 (P=0.001). As MAFLD patients associated with chronic HCV, HBV liver disease had higher grade of fibrosis ; those patients have multiple risk factors for fibrosis **[24]**.

In this study, the mean ± SD of fatty liver index was 85.34± 12.55 with(80 patients) 95.2% had FLI more than 60 that indicates fatty liver ruled in. There was no significant difference between the two studied groups regarding fatty liver index (p>0.05). This finding is consistent with **Motamed et al. 2016 [25]** who revealed a significant positive high correlation between serum FLI and NAFLD, which was also confirmed by binary regression, to the point where a one-unit increase in FLI resulted in a 5.8% increase in the risk of developing NAFLD and showed good predictive performance in the diagnosis of NAFLD.

The present study revealed that, Fibrosis reading using fibroscan ;the majority of MAFLD patients had no or mild fibrosis (F0-F1 69%),while,16.9% had moderate fibrosis,and only 12 patients had advanced fibrosis (F39.5%, F4 4.8%) and these results agreed with **Mansour et al. (2020) [16]** who found that most of NAFLD patients had mild liver fibrosis [F0: 52 (57.78%), F1: 20 (22.22%)], while 16 patients had moderate fibrosis [F2: 16 (17.78%)], and only 2 patients had advanced fibrosis [F4:2 (2.22%)].

While, **Fallatah et al.2016 [26]** who evaluated in 122 Saudi patients with NAFLD, the role of FibroScan vs. various non-invasive evaluation scores was investigated. In his study, FibroScan identified advanced liver fibrosis in a considerable number of people [F4: 40 (32.8 percent)]. This could be due to demographic variations between patients in two studies, where his patients have a high prevalence of metabolic syndrome and type 2 diabetes, which could explain progressive fibrosis. Fibroscan revealed AST, ALT, platelets, cholesterol, and LDL as independent risk factors for fibrosis**. Pathik et al .2015 [27]** reported the platelet count may be a biomarker of the severity of liver fibrosis in NAFLD patients, with a high statistical correlation between liver transaminases and increased LMS indicative of liver fibrosis **[28]**.

In the present study, there was no significant correlation between fibrosis detected by fibroscan and steatosis (r= 0.130, p=0.238), as

the association between steatosis and fibrosis invariably dependent on simultaneous association between steatosis, and hepatic inflammation as hepatic inflammation may mediate fibrogenesis **[29]**

In terms of CAP, in this study, 82 out of 84 patients exhibited steatosis, with the majority of patients having severe hepatic steatosis as seen by CAP (S2, 31 percent at 260-290 Db/m, and S3 58.3 percent at >290 dB/m). while 8.3% had moderate steatosis (S1 at 238-260 dB/m cut-off value)**. Ahn et al. 2016 [30]** reported that CAP can distinguish between the different grades of steatosis, however, **Chon et al. 2014** considered that it is less accurate and has greater diagnostic value for S1 and S2. However, this problem of CAP in obese individuals was overcome by using the X probe. **[33]**.

There was significant negative correlation between CAP with total bilirubin, and HDL .Also, there was significant positive correlation between CAP and waist circumference (r= 0.270, p=0.013), positive correlation with triglyceride(r=0.348,p=0.001) and BMI (r= 0.246, p=0.024) (Data not shown). However the results of multivariate analysis showed that steatosis had no significant association between the parameters mentioned.AS BMI,WC are the major obesity indices and strong risk factors for NAFLD, with a 66 percent rise in NAFLD in obese people **[33]**. This is in line with the findings of **Dehnavi et al. 2018 [31]** who reported that BMI, WC, and steatosis grades were demonstrated to have a highly significant association in between.

In this study the diagnostic accuracy of CAP in disease staging in MAFLD patients is 88% at cut off value of>297dB/m with sensitivity 88.5% and specificity 82.8%.This was in agreement with **Eddowes et al .2019 [32],** who assessed the diagnostic accuracy of CAP by TE for evaluating liver steatosis in NAFLD patients with AUROC of 0.87,sensitivity of 80% and specificity of 83%. While, **Chon et al.** [**33**] found that the sensitivity and specificity of CAP for S1 at cut off 250 dB/m were 73.1% and 95.2% respectively for detection of S2 at cut off 299 dB/m were82.4%,86.1 respectively and for S3 at cut off 327dB/m were 77.8%,84.1 respectively, difference may be due to variation in geographical region.

CAP has the ability to detect hepatic steatosis with >5% steatosis on histology **[34**]. Here the possibility to assess concomitant fibrosis and steatosis using CAP make TE a promising noninvasive tool for assessment and quantifying of both steatosis and fibrosis in MAFLD patients **[16,35]**

In this study, diagnostic accuracy of FLI in disease staging in MAFLD patients is 87% at cut off value >88.29 with sensitivity and specificity of 88.5%,80.7% respectively. Score of FLI varies from zero to 100 and at cut off value of >60,sensitivity and specifity were 86%, 87% respectively, FLI is also, independently associated with cardiovascular and cancer related mortality **[36]**.

In the present study the diagnostic accuracy of combined CAP and FLI for diagnosis of liver steatosis was 95%. with sensitivity 96.2% and specificity 87.7%,

So, combination of both noninvasive imaging technique and laboratory score may improve the diagnostic accuracy in assessing steatosis in MAFLD patients ,which may add to CAP, as FLI is independently associated with overall ,cardiovascular and cancer related mortality **[37].**

## CONCLUSION

CAP could be a promising noninvasive tool for assessing and quantifying steatosis in MAFLD patients. Combining noninvasive imaging with a laboratory score could increase diagnostic accuracy in assessing steatosis in MAFLD patients, which could be beneficial to CAP.

**No Conflict of interest.**

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**Ethical considerations :**Prior to the study's execution, the Ethical Committee of Zagazig University's Faculty of Medicine gave its approval (IRB no. 7092-7-9-2021 ). After a thorough description of the study's objectives and methodology, all participants were asked to sign a written informed consent form. The study conformed with the guidelines of the Helsinki Declaration.

**Research Highlights:**

- Metabolic associated fatty liver disease (MAFLD) is increasingly becoming a serious clinical concern owing to its severe morbidity and potential progression to end stage of liver disease .
- CAP may be used as a promising noninvasive

tool for assessment and quantifying of steatosis in MAFLD patients.

- Combination of both noninvasive imaging technique and laboratory score may improve the diagnostic accuracy in assessing steatosis in MAFLD patients, which may add to CAP.

## REFERENCES


1- Nassir F, Rector RS, Hammoud, GM and Ibdah, JA. Pathogenesis and prevention of hepatic steatosis. *Gastroenterology & Hepatology*; 2015, 11(3), 167.

2- Mitra S, De A, and Chowdhury A. Epidemiology of non-alcoholic and alcoholic fatty liver diseases. *Translational Gastroenterology and Hepatology*; 2020, 5;5:16

3- Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. New definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. *Journal of Hepatology*, 2020, 73(1), 202-209.

4- Lonardo A, Bellentani S, Argo CK, Ballestri S, Byrne CD, Caldwell SH, et al. Epidemiological modifiers of non-alcoholic fatty liver disease: Focus on high-risk groups. *Digestive and Liver Disease*, 2015. 47(12), 997-1006.

5- Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: Practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology, 2012, 55(6) : 2005-2023.

6- Noureddin M, Yates KP, Vaughn IA, Neuschwander-Tetri BA, Sanyal AJ, McCullough A, et al. Clinical and histological determinants of nonalcoholic steatohepatitis and advanced fibrosis in elderly patients. *Hepatology*, 2013, 58(5), 1644-1654.

7- Sasso M, Beaugrand M, De Ledinghen V, Douvin C, Marcellin P, Poupon R et al. Controlled attenuation parameter (CAP): a novel VCTE™ guided ultrasonic attenuation measurement for the evaluation of hepatic steatosis: preliminary study and validation in a cohort of patients with chronic liver disease from various causes. *Ultrasound in Medicine & Biology*, 2010, 36(11), 1825-1835.

8- Sasso M, Miette V, Sandrin L and Beaugrand M. The controlled attenuation parameter (CAP): A novel tool for the non-invasive evaluation of steatosis using Fibroscan®. *Clinics and Research in Hepatology and Gastroenterology*, 2012, 36(1), 13-20.

9- Hernaez R, Lazo M, Bonekamp S, Kamel I, Brancati FL, Guallar E, et al. Diagnostic accuracy and reliability of ultrasonography for the detection of fatty liver: a meta-analysis. Hepatology. 2011;54(3):1082-1090.

10- Li Y, Chen Y and Zhao Y. The diagnostic value of the FIB-4 index for staging hepatitis B-related fibrosis: a meta-analysis. *PloS One*, 2014, 9(8), e105728.

11- Kanwar P and Kowdley KV. The metabolic syndrome and its influence on nonalcoholic steatohepatitis. *Clinics In Liver Disease*, 2016, 20(2), 225- 243.

12- Taheri E, Moslem A, Mousavi-Jarrahi A, Hatami B, Pourhosseingholi MA and Reza Zali M. Predictors of Metabolic-Associated Fatty Liver Disease (MAFLD) in Adults: A Population-Based Study in Northeastern Iran. *Gastroenterology and Hepatology from Bed to Bench*, 2021.Fall;14(suppl1):S102-S111.

13- Yuan Q, Wang H, Gao P, Chen W, Lv M, Bai S, et al. Prevalence and Risk Factors of Metabolic-Associated Fatty Liver Disease among 73,566 Individuals in Beijing, China. *International Journal of Environmental Research and Public Health*, 2022, 19(4), 2096.

14- De Ledinghen V and Vergniol J. Transient elastography (fibroscan). *Gastroenterologie Clinique et Biologique*, 2008, 32(6), 58-67.

15- Chao HC and Lin HY. Comparison of Body Mass Index and Fat Indices in Predicting the Severity of Nonalcoholic Fatty Liver Disease Among Children Who Are Overweight and Obese. *Frontiers in Pediatrics*, 2021, 9:724426

16- Mansour AM, Bayoumy EM, El-Ghandour AM, El-Talkawy MD, Badr SM and Ahmed AEM. Assessment of hepatic fibrosis and steatosis by vibration-controlled transient elastography and controlled attenuation parameter versus non-invasive assessment scores in patients with non-alcoholic fatty liver disease. *Egyptian Liver Journal*, 2020, 10(1), 1-10.

17- Hu YY, Dong NL, Qu Q, Zhao XF and Yang HJ. The correlation between controlled attenuation parameter and metabolic syndrome and its components in middle-aged and elderly nonalcoholic fatty liver disease patients. *Medicine*, 2018, 97(43).

18- Pu K, Wang Y, Bai S, Wei H, Zhou Y, Fan J, et al. Diagnostic accuracy of controlled attenuation parameter (CAP) as a non-invasive test for steatosis in suspected non-alcoholic fatty liver disease: a systematic review and meta-analysis. *BMC Gastroenterol*. 2019;19(1):51.

**19-** Hong YS, Chang Y, Ryu S, Cainzos-Achirica M, Kwon MJ, Zhang Y, et al. Hepatitis B and C virus infection and diabetes mellitus: A cohort study. *Sci Rep*. 2017;7(1):4606.

**20-** Huang J, Ou W, Wang M, Singh M, Liu Y, Liu S, et al. MAFLD Criteria Guide the Subtyping of Patients with Fatty Liver Disease. *Risk Manag Healthc Policy*. 2021;14:491-501.

**21-** Chang E, Park CY, Park SW, et al. Role of thiazolidinediones, insulin sensitizers, in non-alcoholic fatty liver disease. *J Diabetes Investig*. 2013;4(6):517-24.

**22-** Paul, J. Recent advances in non-invasive diagnosis and medical management of non-alcoholic fatty liver disease in adult. *Egypt Liver Journal* 2020;10, 37 .

**23-** Mitchell O, Feldman DM, Diakow M and Sigal SH. The pathophysiology of thrombocytopenia in chronic liver disease. *Hepatic Medicine: Evidence and Research*, 2016, 8, 39.

**24-** Cai S, Ou Z, Liu D, Liu L, Liu Y, Wu X, et al. Risk factors associated with liver steatosis and fibrosis in chronic hepatitis B patient with component of metabolic syndrome. *United European Gastroenterology Journal*, 2018, 6(4), 558-566.

**25-** Motamed N, Sohrabi M, Ajdarkosh H, Hemmasi G, Maadi M, Sayeedian FS, et al. Fatty liver index vs waist circumference for predicting non-alcoholic fatty liver disease. *World J Gastroenterol*. 2016 ;22(10):3023-30.

**26-** Fallatah HI, Akbar HO, Fallatah AM. Fibroscan Compared to FIB-4, APRI, and AST/ALT Ratio for Assessment of Liver Fibrosis in Saudi Patients With Nonalcoholic Fatty Liver Disease. *Hepat Mon*. 2016 ;16(7):e38346.

**27-** Pathik P, Ravindra S, Ajay C, Prasad B, Jatin P, Prabha S. Fibroscan versus simple noninvasive screening tools in predicting fibrosis in high-risk nonalcoholic fatty liver disease patients from Western India. *Ann Gastroenterol*. 2015 ;28(2):281-286.

**28-** Yoneda M, Fujii H, Sumida Y, Hyogo H, Itoh Y, Ono M, et al. Japan Study Group of Nonalcoholic Fatty Liver Disease. Platelet count for predicting fibrosis in nonalcoholic fatty liver disease. *J Gastroenterol*. 2011;46(11):1300-6.

**29-** -Foucher J, Chanteloup E, Vergniol J, Castéra L, Le Bail B, Adhoute X, et al. Diagnosis of cirrhosis by transient elastography (FibroScan): a prospective study. *Gut*. 2006;55(3):403-8.

**30-** Ahn, J. M., Paik, Y. H., Min, S. Y., Cho, J. Y., Sohn, W., Sinn, D. H., et al (2016). Relationship between controlled attenuation parameter and hepatic steatosis as assessed by ultrasound in alcoholic or nonalcoholic fatty liver disease. *Gut and Liver*, 10(2), 295–302.

**31-** Dehnavi, Z., Razmpour, F., Naseri, M. B., Nematy, M., Alamdaran, S. A., Vatanparast, H. A., et al (2018). Fatty liver index (FLI) in predicting non-alcoholic fatty liver disease (NAFLD). *Hepatitis Monthly*, 18(2).

**32-** Eddowes PJ, Sasso M, Allison M, Tsochatzis E, Anstee QM, Sheridan D, et al. Accuracy of FibroScan Controlled Attenuation Parameter and Liver Stiffness Measurement in Assessing Steatosis and Fibrosis in Patients With Nonalcoholic Fatty Liver Disease. *Gastroenterology*. 2019;156(6):1717-1730.

**33-** Chon YE, Jung KS, Kim SU, Park JY, Park YN, Kim DY, et al. Controlled attenuation parameter (CAP) for detection of hepatic steatosis in patients with chronic liver diseases: a prospective study of a native Korean population. *Liver International*, 2014, 34(1), 102-109.

**34-** Bae JS, Lee DH, Lee JY, Kim H, Yu SJ, Lee JH, et al. Assessment of hepatic steatosis by using attenuation imaging: a quantitative, easy-to-perform ultrasound technique. *European Radiology*, 2019, 29(12), 6499-6507.

**35-** Castera, L., Friedrich-Rust, M and Loomba R. Noninvasive assessment of liver disease in patients with nonalcoholic fatty liver disease. *Gastroenterology*, 2019, 156(5), 1264-1281.

**36-** Bedogni G, Bellentani S, Miglioli L, Masutti F, Passalacqua M, Castiglione A, et al. The Fatty Liver Index: a simple and accurate predictor of hepatic steatosis in the general population. BMC Gastroenterol. 2006 2;6:33.

**37-** Unalp-Arida A, Ruhl CE. Liver fat scores predict liver disease mortality in the United States population. *Aliment Pharmacol Ther*. 2018; 48(9):1003-1016.