ABSTRACT

**Background:** Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide. Metabolic associated fatty liver disease (MAFLD) is a novel concept proposed in 2020 aiming to replace the term NAFLD. The aim of the current study is to assess the impact of controlled attenuation parameter (CAP) in disease staging in MAFLD patients. 

**Patients and methods:** This study included 82 patients with fatty liver and classified into groups; MAFLD with other chronic liver disease (G2), and MAFLD without other chronic liver disease (G1). All patients were subjected to history taking, clinical examination, physical measurement of BMI, waist circumference, routine laboratory investigation, pelvic abdominal ultrasonography, and non-invasive assessment scores for hepatic fibrosis and steatosis (FIB4, NFS, FLI and Fibroscan for measuring liver stiffness and CAP).

**Results:** The mean age in our studied patients was 46.17± 10.95 years. FIB4 was significantly higher in group 2 compared to group 1. NFS was significantly higher in group 2 compared to group 1. A significant positive correlation was found between CAP with waist circumference. A significant positive correlation was found between fatty liver index with waist circumference. Fibrosis reading can significantly determine disease staging in MAFLD patients at cutoff 6.3 with sensitivity, specificity, PPV and NPV was 80.08%, 81%, 81% and 80.8% respectively. Using both CAP and FLI increases the sensitivity to 96.2% and increases the specificity to 87.7% with accuracy reached to 95%. The PPV and NPV were 88.7% and 95.8% respectively.

**Conclusion:** The diagnostic accuracy for assessing steatosis in MAFLD patients can be improved using noninvasive imaging technique with laboratory score.

**Keywords:** Hepatic fibrosis; MAFLD; NAFLD; CAP; BMI; Steatosis

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is a growing global health problem that affects about a quarter of the world’s adult population and poses a major health and economic burden to all societies. Non-alcoholic steatohepatitis (NASH) was introduced to describe an alcoholic-like hepatitis in patients without a history of alcohol abuse or hepatotropic viruses' infection, mainly in obese patients (1). Afterward, the term of non-alcoholic fatty liver disease (NAFLD) was firstly used to describe a less severe
Steatosis condition more than 5-10% of hepatocytes with fat droplet on liver biopsy and then to define the wide spectrum of liver conditions associated to steatosis, ranging from simple fatty liver to cirrhosis (2).

Both environmental and genetic factors are contributing to the development of NAFLD and its progression. First-degree relatives of patients with NAFLD are at higher risk than the general population (3). Also, excessive fatty acids in the liver make the liver more vulnerable to injury (4). NAFLD reflects a progressive condition in many instances and its prevalence parallels trends in obesity and diabetes. Several steatosis scores have been proposed for the detection of steatosis, including Fatty Liver Index, Hepatic Steatosis Index, lipid accumulation product and the Index of NAFLD Liver Fat Score (5).

Metabolic-dysfunction-associated fatty liver disease (MAFLD) is diagnosed in patients when they have both hepatic steatosis and any of the following three metabolic conditions: overweight/obesity, diabetes mellitus, or evidence of metabolic dysregulation (MD) (6). Fibroscan is a useful test in almost any patient in whom a clinician wishes to stage liver fibrosis. CAP can be commonly measured using FibroScan probes, and it has demonstrated a very good accuracy in assessing steatosis compared with liver biopsies (7).

Controlled attenuation parameter (CAP) is determined by measuring the degree to which the ultrasound signal is attenuated by hepatic fat at the central frequency of the transient elastography [FibroScan (Echosens, France)] M or XL probe while a liver stiffness measurement (LSM) is being obtained (8). CAP has been reported to perform well for mild steatosis on patients with NAFLD, but it performs poorly in patients with high BMI due to the thick layer of subcutaneous adipose tissue. The XL probe has been developed to overcome the issue of liver stiffness and CAP measurement in overweight patients (9).

The aim of the current study is to assess the impact of controlled attenuation parameter (CAP) in disease staging on MAFLD patients.

PATIENTS AND METHODS

This study included 82 patients with fatty liver and conducted at Tropical Medicine Department, Faculty of Medicine, Zagazig University. Patients were classified equally into:

Group (1): MAFLD without other chronic liver disease.

Group (2): MAFLD with other chronic liver disease

Inclusion and exclusion Criteria:

Patients with MAFLD who diagnosed based on ultrasonography with the presence of any one of the following: obesity, diabetes mellitus (DM), or metabolic dysregulation. While, patients who were stable not hepatic decompensated, morbid obesity (BMI>35) and hepatocellular carcinoma were excluded.

Clinical evaluation:

All patient were subjected to full history taking, clinical
examination, physical measurement of BMI, waist circumference, routine laboratory investigation including (CBC, liver and kidney functions, lipid profile and blood glucose level), pelvic abdominal ultrasonography, and non-invasive assessment scores for hepatic fibrosis and steatosis (FIB4,NFS and FLI respectively). Fibroscan for measuring liver stiffness and CAP was also done.

Complete Blood Count, Liver and kidney function tests, fasting blood glucose (FBG) and Lipid profile were estimated. Serum fibrosis markers include NAFLD fibrosis score (NFS) fibrosis 4 (FIB-4)

Controlled attenuation parameter (CAP) is based on FibroScan ultrasonic signals at the central frequency of the Vibration-controlled transient elastography (VCTE) at M or regular probe.

Statistical analysis:
Data analyzed using Microsoft Excel software. Data were then imported into Statistical Package for the Social Sciences (SPSS version 26.0) software for analysis. According to the type of data qualitative represent as number and percentage, quantitative continues group represent by mean ± SD. ANOVA or Kruskal Wallis, Chi square test and Spearman's method and ROC Curve were used. P value was set at <0.05 for significant results and <0.001 for high significant result.

RESULTS
The present study showed the mean age in our studied patients was 46.17±10.95 years and ranged from 23 to 69 years. 63 (75%) cases were males and 21 (25%) were females. Regarding smoking, 38 (45.2%) were smokers and 46 (54.8%) were non-smokers. None of patients were alcoholics (Table 1).

About 27.4% cases were asymptomatic, 46% had fatigue, 48.8% had heartburn, 72.6% had abdominal distension, 8.3% had cardiac symptoms. The average weight, height, BMI and waist circumference were 94.10±9.36 Kg, 171.13±6.93 cm, 32.16±2.71 Kg/m2 and 110.98±9.41 cm respectively. The average systolic and diastolic blood pressure measured were 122.26±15.39 mm/Hg and 80.0±12.32 mm/Hg respectively. Regarding comorbidities, 35.7% were hypertensive, 25% were prediabetics and 25% were diabetics. 7.1% patients had positive HBsAg and 23.8% had positive HCV Antibodies (Figure 1).

The mean FIBS score was 1.27±0.67 with 69% had FIB4 score less than 1.45 that indicates no fibrosis. The mean NFS was 90.0±10.21 with 45.2% had NFS score less than -1.455 that indicates no fibrosis. Meanwhile, the mean fatty liver index was 85.34±12.55 with 95.2% had FLI more than 60 that indicates fatty liver ruled in (Table 2).

Regarding biochemical analysis, Group 1 showed significant increase in platelets count compared to group 2 (p=0.002). There was no significant difference between the two groups regarding Hb and TLC (p>0.05). Group 1 showed significant increase in ALT level compared to
group 2 (p=0.026). Group 2 showed significant increase in INR compared to group 1 (p=0.005). There was no significant difference between the two studied groups regarding AST, direct and total bilirubin (p>0.05). There was no significant difference between the two studied groups regarding cholesterol, TG, LDL and HDL (p>0.05) (Table 3).

Comparison between the studied patients regarding pelviabdominal US showed hepatomegaly and coarse liver were significantly higher in group 2 (p<0.001) while there was no significant difference between the two studied groups regarding echogenicity (p>0.05). Splenomegaly was significantly higher in group 2 compared to group 1 (p<0.001) (Table 4).

FIBS4 was significantly higher in group 2 compared to group 1 (p=0.003). In addition, group 2 showed increased score of FIBS (p=0.023) (Figure 2). NFS was significantly higher in group 2 compared to group 1 (p<0.001) with increasing score level in group 2 (P=0.001) (Figure 3).

A significant positive correlation was found between CAP with waist circumference (r= 0.270, p=0.013) (Figure 4). In addition, significant positive correlation was found between fatty liver index with waist circumference (r= 0.818, p<0.001) (Figure 5).

By using ROC-curve analysis, fibrosis reading can significantly determine disease staging in MAFLD patients at cutoff 6.3 with sensitivity, specificity, PPV and NPV was 80.08%, 81%, 81% and 80.8% respectively (p<0.001) (Table 5). Using both CAP and FLI increases the sensitivity to 96.2% and increases the specificity to 87.7% with accuracy reached to 95%. The PPV and NPV was 88.7% and 95.8% respectively (p<0.001) (Figure 6).

Table (1): Distribution of the studied cases as per demographic characteristics

<table>
<thead>
<tr>
<th></th>
<th>Studied patients (No. = 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>63</td>
</tr>
<tr>
<td>Female</td>
<td>21</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Mean± SD</td>
<td>46.17± 10.95</td>
</tr>
<tr>
<td>Median</td>
<td>47.0</td>
</tr>
<tr>
<td>Range</td>
<td>23.0 – 69.0</td>
</tr>
<tr>
<td>Smoking</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>46</td>
</tr>
<tr>
<td>Yes</td>
<td>38</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>84</td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
</tbody>
</table>

No.= number, %= percentage
Figure (1): Distribution of the studied cases regarding comorbidities.

Table (2): Distribution of the studied cases as FIB4, NFS and fatty liver index

<table>
<thead>
<tr>
<th></th>
<th>Studied patients (n= 84)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FIB4</td>
</tr>
<tr>
<td>Range</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>0.29- 3.03</td>
<td>1.27± 0.67</td>
</tr>
<tr>
<td>FIB4 (&lt; 1.45)</td>
<td>58</td>
</tr>
<tr>
<td></td>
<td>No.</td>
</tr>
<tr>
<td>FIB4 (1.45-3.25)</td>
<td>26</td>
</tr>
<tr>
<td>FIB4 (&gt;3.25)</td>
<td>0</td>
</tr>
<tr>
<td>Range</td>
<td>Median</td>
</tr>
<tr>
<td>65.0- 125.0</td>
<td>90.0± 10.21</td>
</tr>
<tr>
<td>NFS (&lt; -1.455)</td>
<td>38</td>
</tr>
<tr>
<td>NFS (-1.455 - 0.675)</td>
<td>43</td>
</tr>
<tr>
<td>NFS (&gt;0.675)</td>
<td>3</td>
</tr>
</tbody>
</table>

- Hypertension: Yes 64.3%, No 35.7%
- DM: Yes 50.0%, No 25.0%
- Diabetic: Yes 25.0%, No 25.0%
- HBsAg: Negative 92.0%, Positive 7.1%
- HCV Ab: Negative 76.2%, Positive 23.8%
Table (3): Comparison between the two studied groups regarding biochemical analysis

<table>
<thead>
<tr>
<th>Test Value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MannWhitney U Test</td>
<td>T-test</td>
</tr>
</tbody>
</table>

Table (4): Comparison between the two studied groups regarding pelviabdominal US

<table>
<thead>
<tr>
<th>Test Value</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chi-square test</td>
<td>X² Test</td>
</tr>
</tbody>
</table>
Figure (2): Comparison between the study groups regarding FIBS.

Figure (3): Comparison between the study groups regarding NFS.

Figure (4): Scatter plot showing positive correlation between CAP and waist circumference.
DISCUSSION

Metabolic associated fatty liver disease (MAFLD) is a novel concept proposed in 2020 aiming to replace the term NAFLD. MAFLD is associated with hepatic steatosis and one of the following condition as obesity, diabetes mellitus or evidence of metabolic dysregulation with or without other chronic liver disease. MAFLD concept may enable clinicians to identify patients at more risk of adverse outcome (2).

Liver biopsy is the gold standard test for diagnosis, However, it is an invasive procedure and impractical to conduct this procedure for surveillance and progression monitoring. Non-invasive laboratory and radiological assessment method for hepatic steatosis and fibrosis in NAFLD have evolved NALFD (10). Transient elastography (FibroScan) is
a non-invasive method proposed for the assessment of hepatic fibrosis in patients with chronic liver disease by measuring liver stiffness (11). CAP uses the postulate that fat affects ultrasound propagation, and is a measure of ultrasound attenuation at the central frequency of the Fibroscan® M or regular probe (12).

This study was conducted on 82 patients, diagnosed as having fatty liver by abdominal ultrasonography and conducted in Tropical Medicine Department, Faculty of medicine, Zagazig University to assess the impact of controlled attenuation parameter (CAP) in disease staging on MAFLD patients.

The current study showed that the mean±SD of age was 46.17±10.95 years and 63 (75%) cases were males. The prevalence of MAFLD in male peaked at the 40—49 years, and then began to decline of age. However, Mansour et al. (13) found that in cross-sectional study included 90 adult patients with NAFLD, divided into 62 females (68.9 %) and 28 males (31.1 %) as NAFLD was more common in females than in males after the age of 50 years. Also, in Farrell et al. (14) study, those with MAFLD were older. This may be due difference in patients selection, criteria and different geographical distribution with different genetic predisposition.

This study revealed that there were 27.4% asymptomatic cases, 46% had fatigue, 48.8% had heartburn, 72.6% had abdominal distension, 8.3% had cardiac symptoms. 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, heartburn and cardiac symptoms (p>0.05). NAFLD seems frequently asymptomatic at diagnosis, Feeling of fullness, discomfort in right upper abdomen and malaise were reported in many cases, NAFLD is detected on doing ultrasonography or performing investigation for other ailments (15).

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 associated with insulin resistance and more diabetes prevalence. Taheri et al. (16) reported 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<.05). Similarly, Yuan et al. (17) reported the prevalence of hypertension and DM in lean/normal weight MAFLD participants was higher than that in non-MAFLD participants.

Our biochemical results are matched with those obtained by öztürk et al. (18) which showed that there was no significant difference among groups in terms of red blood cell, platelet, and neutrophil to lymphocyte ratio parameters. On the
The other hand, Chung et al. (19) analyzed the relationship between the risk of developing NAFLD and the serum WBC count. 25.5% subjects developed incidental NAFLD during the follow-up period. The prevalence of NAFLD increased steadily with increasing WBC counts after adjustment for age and BMI. Also, Farrell et al. (14) found participants with ALT elevation (≥ 40 IU/L in men and ≥ 30 IU/L in women), were over 3 times more likely to have MAFLD.

In this study, the mean GGT, albumin and INR were 46.36± 18.19 U/L, 4.48 ± 0.32 g/dl and 1.08± 0.13 respectively. The mean alfa fetoprotein was 10.20± 6.53 ng/mL. Group 2 showed significant increase in INR compared to group 1, but still within normal (p=0.005). There was no significant difference between the two studied groups regarding GGT and albumin (p>0.05). Similarly, Francque et al. (20) reported that the mean+SD GGT was 39.5± 38.3 U/L respectively.

In this study, there was no significant difference between the two studied groups regarding cholesterol, LDL, HDL and triglyceride (p>0.05). In agreement with this study, Hu et al. (21) who revealed the mean cholesterol and HDL which were 203.8± 40.8 mg/dl and 51.5± 14.9 mg/dl respectively. The mean triglyceride level was 148.5 ± 83.8 mg/dl. Similarly, Francque et al. (20) showed the mean cholesterol, HDL and triglyceride level were 203.8± 40.8 mg/dl and 51.5± 14.9 mg/dl 148.5 ± 83.8 mg/dl respectively. Also, there was a significant difference between NAFLD group and non-NAFLD group as regard LDL, HDL and TG. While, Taheri et al. (16) found MAFLD patients had higher serum levels of TG, TC and LDL-C, that were statistically significant and lower HDLC than the controls as MAFLD is closely associated with metabolic syndrome.

This study revealed that the mean 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 FIB4 score >3.25 . FIBS4 was significantly higher in group 2 compared to group 1 (p=0.003). In addition, group 2 showed increased score of FIBS (p=0.023). In addition, significant positive correlation was found between fatty liver index with waist circumference (r= 0.818, p<0.001) and BMI (r= 0.838, p<0.001). Mansour et al. (13) reported that, there was a statistically significant positive correlation with BMI, WC, FLI, and presence of diabetes mellitus.

In this study, both CAP and FLI increase the sensitivity to 96.2% and increases the specificity to 87.7% with accuracy reached to 95%. FLI can serve as surrogate markers for liver fat content and metabolic syndrome in type 1 diabetes (22). Also, Farrell et al. (14) revealed the diagnostic criteria for MAFLD correlated strongly with the presence of hepatic steatosis by FLI.
Motamed et al. (23) found 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 led to a 5.8% increase in the risk of developing NAFLD and showed good predictive performance in the diagnosis of NAFLD.

CONCLUSION

The diagnostic accuracy for assessing steatosis in MAFLD patients can be improved using noninvasive imaging technique with laboratory score.

No Conflict of interest.

REFERENCES


