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Speckle tracking Echocardiography in Metabolic associated fatty liver disease patients

Authors

Yehia Mohammed Sameh 1.MD, Dina Attia 1.Proffesor, Dina Said* 1.MSC, Talaat Saeed Badr 2.MD, Asmaa S. Sieddek 1.MD.

1Tropical Medicine Department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt; 2Cardiology Department, Faculty of Medicine, Beni-Suef University, Beni-Suef, Egypt.

- Corresponding author: Dina Said

Kornish el Nile ,Beni suef, Egypt.

Dinasaid1990@yahoo.com

PHONE NUMBER: 01152154327

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Abstract

Metabolic associated fatty liver disease (MAFLD) is a global health problem associated with extrahepatic manifestations and comorbidities. The main cause of mortality for those with MAFLD is cardiovascular diseases (CVD). Objective: The aim of this study was to evaluate silent cardiac dysfunction in MAFLD patients.

Material and Methods: This study was carried out on 1500 subjects from Beni-Suef population. All patients subjected to pelvi–abdominal ultra-sound as a screening tool, transient elastography to determine degree of steatosis/fibrosis, speckle tracking echocardiography and calculation of ASCVD (atherosclerotic cardiovascular disease risk score). Results: Our findings demonstrated a substantial correlation between MAFLD and higher E/e`, LA diameter, diastolic dysfunction grade II. There was a significant positive linear correlation between the Elastography with global longitudinal strain. The study showed a significant difference between non MAFLD, lean MAFLD and obese MAFLD regarding Atherosclerotic Cardiovascular Disease risk score (ASCVD). Conclusion: There was higher prevalence of subclinical cardiac dysfunction in MAFLD patients. So MAFLD patients should be evaluated for CVD and referred to a cardiologist, if needed.

Keywords: Metabolic associated fatty liver disease, Speckle tracking Echocardiography, Steatosis, Cardiovascular diseases.

1. Introduction:

About one-fourth of adults worldwide are affected by nonalcoholic fatty liver disease (NAFLD), which places a significant financial and health problem on all societies**1**.

A group of worldwide experts has advocated transforming the name of this widespread metabolic liver illness from Nonalcoholic fatty liver disease (NAFLD) to Metabolic dysfunction-associated fatty liver disease (MAFLD), which is now under consideration**2.**

The fact that diagnosis of MAFLD may commonly coexist with other disorders (such as heavy alcohol intake, viral hepatitis, or other well-known chronic liver diseases) is crucial to emphasize**3**.

Additionally, there is strong evidence that, in this patient population, the coexistence of these metabolic risk abnormalities is a major risk factor for extra-hepatic morbideties, primarily cardiovascular disease, chronic kidney disease, and certain types of extra-hepatic cancers like colorectal cancers**4.**

NAFLD often exhibits clinical silence, and its significance has probably been overestimated. If symptoms do exist, they are mild and non-specific, such as tiredness, dyspepsia, and pain in the right upper quadrant. Most physical examination results are likewise normal. The majority of individuals seek medical attention as a result of incidentally discovering increased aminotransferase levels or radiographic findings that the liver is fatty**5**.

In addition to having a high BMI, showing signs of the metabolic syndrome, and having normal or slightly raised liver enzyme values, obese persons with NAFLD often do not exhibit any other particular symptoms. Every six months, these individuals should be monitored for the emergence of diabetes and HCC using ultrasonography and alpha-fetoprotein. Weight reduction, exercise, food, and lifestyle modifications should be the main focuses of treatment, which should also be assessed every six months. Blood and platelet counts, liver biochemistry testing, prothrombin time, and screening for cardiovascular risk should all be performed twice a year. Every three to five years, staging of liver deterioration using non-invasive techniques like Fibroscan should be done**6**.

2. Materials and methods:

This was a cross- sectional analytical study, carried out on 1500 patients in the duration from February 2021 to June 2022, all subjects aged ≥18 years, working as office workers at Beni-Suef University.

Diagnostic Criteria of MAFLD:

MAFLD is considered when the pelvi–abdominal ultra-sound or transient elastography showed hepatic steatosis and associated with one of the following three criteria (namely overweight/obesity, presence of established type 2 diabetes mellitus, or evidence of metabolic dysregulation), regardless of daily alcohol consumption and other concomitant liver diseases. The criteria for diagnosing of metabolic dysregulation among lean/normal weight individuals is presence of at least two metabolic risk factors abnormalities: waist circumference ≥ 102/88 cm in Caucasian men and women, blood pressure ≥130 /85 mmHg or drug treatment, plasma triglycerides ≥150 mg/dl or drug treatment, plasma HDL- cholesterol <40 mg /dl for men and <50 mg/dl for women or drug treatment, prediabetics ,homeostasis model assessment – insulin resistance score≥ 2.5 or plasma highly specific C reactive protein level >2 mg/dl**3**.

2.1. Inclusion criteria: All patients aged ≥18 years, both genders were included.

2.2. Exclusion criteria: Exclusion criteria include subjects with current cancer, decompensated liver cirrhosis, alternative causes of fatty liver (such as amiodarone and tamoxifen usage), congestive hepatopathy, any missing data, and those who declined to participate in the research. We excluded patients with history of ischemic heart disease, significant Valvular heart disease, cardiomyopathy (with clinical cardiac dysfunction and no benefit) and arrhythmias (as it requires the use of multi-beat 3D acquisitions of the LV).

2.3. Methods:

2.3.1. Standard history:

Detailed history taking of age, sex, smoking, drug intake, history of diabetes mellitus or hypertension, history of concomitant hepatic and cardiovascular disorders.

2.3.2. Clinical examination:

Vital signs andbaseline anthropometric measurements, including the height and weight for calculating the body mass index (BMI) were measured and waist circumference (using a measuring tap placed in a horizontal plane around the abdomen at the level of the iliac crest. The measurement was made at the end of expiration).

2.3.3. Laboratory Work:

Including, liver function tests (ALT, AST, serum Albumin , serum bilirubin and prothrombin Time), serum creatinine, complete blood count, HbA1c, serum cholesterol , triglycerides, HDL and LDL. Finally, calculations of ASCVD score.

2.3.4. ASCVD was calculated by special equation using (age, sex, race, systolic, diastolic blood pressure, total cholesterol, HDL, LDL, history of diabetes, hypertension, smoking and history of aspirin and statin intake). Interpretation**7**:

- **Borderline 10-year ASCVD risk** (5% to <7.5%): are considered to be at risk and may be considered for drug therapy with a statin under certain circumstances.

- **Intermediate 10-year risk** (7.5% to <20%) should be considered for initiation of moderate- to high-intensity statin therapy.

- **High 10-year risk** (≥20%) should be considered for initiation of high-intensity statin therapy.

2.3.5. Pelvi –Abdominal Ultra-Sound: The examination was done by a multifrequency (2–5 MHz) convex transducer by a single experienced sonologist who was blinded to the transient elastography results of the patients

2.3.6. Transient Elastography (TE): TE using FibroScan® was performed by an experienced hepatologist using M and XL probe. Liver stiffness (LS) values were regarded as valid if the following criteria were met: number of valid measurements at least 10, a success rate above 60%and an interquartile range (IQR, reflecting the variability of measurements) less than 30% of the median LS measurements (M) value (IQR/M ≥30%).

CAP cut-off values indicating liver steatosis (S) were adapted as follows: (1) <237 dB/m (S0, no steatosis), (2) 237.0-259.0 dB/m (S1, mild steatosis), (3) 259.0-291.0 dB/m (S2, moderate steatosis), and (4) 291.0-400.0 dB/m (S3, severe steatosis). The cut-off values for fibrosis (F) were also adopted from the same study as follows: (1) <5.5 kPa (F0, no fibrosis), (2) 5.5-8.0 kPa (F1, mild fibrosis), (3) 8.0-10.0 kPa (F2, moderate fibrosis), (4) 11.0-16.0 kPa (F3, severe fibrosis), and (5) >16.0 kPa (F4, cirrhosis) **8**.

2.3.7. Echocardiography: The speckle tracking echocardiography including Doppler and tissue Doppler imaging was performed by trained sonographers who made measurements. It had evolved to be the imaging modality of choice for the detection of subclinical cardiac dysfunction. We measured global longitudinal strain (GLS) (normal range is −20.7±2 for males and −22.1±1.8 for females, with lower limits of normality (2 SD below the mean) were −16.7% in men, and −18.5% in women), reduced GLS may reflect abnormal systolic function before loss of ejection fraction becomes apparent, E/e` (the ratio between early mitral inflow velocity and mitral annular early diastolic velocity) (normal is <8) is used as a marker to diagnose diastolic heart failure, ejection fraction and diastolic dysfunction**9**.

3. Results and Discussion:

Based on the new diagnostic criteria of MAFLD, the studied subjects were classified into three groups; group (1) included 654 subjects who are not diagnosed with MAFLD, group (2) included 825 subjects who are diagnosed as overweight and obese MAFLD, group (3) included 21 subjects who are diagnosed as lean MAFLD.

Table (1) Association between MAFLD and different risk factors of baseline data of the studied patients:

Items	non MAFLD (no=654)	lean MAFLD (no=21)	Overweight and obese MAFLD (no=825)	P-value
Age (mean±SD) (years)	**47.8±14.1**	**51.76±16.7**	**50.8±11**	**<.001***
Sex(no-%)				
Male	**393(60.1%)**	15(71.4%)	**435(52.7%)**	**0.004***
Female	**261(39.9%)**	6(28.6%)	390(47.3%)	
BMI(mean±SD)	**28.3±5.4**	22.79±1.4	**33.7±5.82**	**<0.001***
Waist Circumference(mean±SD) (Cm)	**94.1±18.8**	85.66±13.42	**105.56±13.55**	**<0.001***
Residence (no-%)				
Rural	389(59.5%)	9(42.9%)	318(38.5%)	.218
Urban	265(40.5%)	12(57.1%)	507(61.5%)	

Table (2) Association between MAFLD and different Laboratory parameters of the studied patients:

Items	non MAFLD (no=654) (mean±SD)	lean MAFLD (no=21) (mean±SD)	Overweight and obese MAFLD (no=825) (mean±SD)	P-value
Hb	**12.9±1.5**	12.47±1.77	**12.78±1.47**	**0.011***
TLCX10^3	**6.8±1.9**	6.37±1.89	**6.78±2.02**	**0.020***
PLTX 10^3	**244.2±70.7**	220.66±51.8	**264.82±85.53**	**<0.001***
AST	**27.2±21.4**	25.04±7.8	**27.13±10.38**	**0.003***
ALT	27.1±32.9	23±6.41	25.74±11.8	0.240
Albumin	4.1±.47	4.16±.28	4.07±.53	0.307
T.bil	0.9±1.9	0.84±.29	.86±.34	0.118
D.bil	0.2±0.1	0.22±.14	.19±.13	0.304
ALP	78.7±44.4	68.85±34.31	80.92±45.37	0.283
INR	1.05±0.13	1.05±.08	1.06±.11	0.228
Creatinine	**0.95±0.18**	0.97±.17	**.99±.23**	**<0.001***
HbA1c	**5.2±1.3**	5.69±1.4	**5.46±1.5**	**0.001***
TGs	**131.9±46.4**	157.66±39.49	**151.36±66.2**	**<0.001***
Total Cholesterol	**178±31.3**	196.47±28.51	**187.4±38.92**	**0.009***
LDL	105.9±35.6	106.71±33.96	108.45±43.8	0.288
HDL	47.1±14.9	51.23±18.93	48.09±16.27	0.367
VLDL	**21.6±6.7**	25.4±9.8	**22.9±8.9**	**0.011***

ASCVD	**8.2±2.3**	**8.8±1.5**	**15.2±2.1**	**<0.001***

TLC: total leukocytic count, Hb: hemoglobin, PLT: platelets, AST: aspartate aminotransferase. ALT: alanine aminotransferase. INR: international normalization ratio, TGs: triglyceride, LDL: low density lipoprotein. HDL: high density lipoprotein, HbA1c: glycated hemoglobin, ALP: Alkaline phosphatase, D.bil: Direct bilirubin, T bil: Total bilirubin**.** ASCVD: atherosclerosis risk score for cardiovascular disease.

Table (3) Association between MAFLD and different cardiac parameters of the studied patients:

Items	**non MAFLD (no=634)**	**lean MAFLD (no=20)**	**Overweight and obese MAFLD (no=820)**	**P-value**
E/e` (mean±SD)	6.5±1.5	6.36±.49	**7.22±2.12**	**<0.001***
LA(mean±SD)	3.29±0.27	3.4±.29	**3.32±.29**	**0.034***
GLS(mean±SD)	-18.5±1.7	18.68±2	18.3±2.19	0.177
EF% (mean±SD)	63.2±5.9	62.23±6.33	63.57±5.31	0.458
DD grade (no-%)				
0.00	373(60.8%)	10(52.6%)	**468(60.3%)**	
1.00	235(38.3%)	9(47.4%)	**268(34.5%)**	**0.004***
2.00	5(0.8%)	0(0%)	**40(5.2%)**	

Table (4) Association between MAFLD and sonographic findings parameters of the studied patients:

Items	non MAFLD (no=654) no %	non obese MAFLD (lean) (no=21) no %	obese MAFLD (no=825) no %	P-value
Fatty liver (U/S)	**351(53.7%)**	21(100%)	**825(100%)**	**<0.001***
Grade of fatty liver(U/S) **0** **I** **II** **III**	**303(46.4%)** **258(39.8%)** **65(10.0%)** **25(3.9%)**	0(0%) 15(71.4%) 4(19%) 2(9.5%)	**0(0%)** **476(53.6%)** **238(29%)** **149(14.6%)**	**<0.001***
TE-KpA	**5.9±4.2**	1.62±1.38	**2.1±1.04**	**<.001***
Stage of fibrosis by transient elastography **0-1** **2** **3** **4**	**552(84.4%)** 28(4.3%) 34(5.2%) 40(6.1%)	17(81%) 1(4.8%) 0(0%) 3(14.3%)	**603(75.9%)** **122(11.8%)** **60(5.8%)** **66(6.4%)**	**<.001***
CAP	**202.3±39.3**	**281.5±40.8**	**299.77±39.07**	**<.001***
Grade of				

steatosis(CAP)	**618(94.5%)**	**0(0%)**	**0(0%)**	
0	**17(2.6%)**	**11(52.4%)**	**181(21.9%)**	**<0.001***
1	**4(0.6%)**	**2(9.5%)**	**92(11.2%)**	
2	**15(2.3%)**	**8(38.1%)**	**552(66.9%)**	
3				

CAP: controlled attenuation parameter.TE-KPA: Transient elastography measurements in kilo Pascals

Table (5) Correlation between Liver elastography and different cardiological parameters:

		Elastography
E/e`	Correlation Coefficient (r)	-0.001
	P-value	0.977
LA	Correlation Coefficient (r)	-0.011
	P-value	0.677
global long strain	Correlation Coefficient (r)	0.056*
	P-value	0.035
EF%	Correlation Coefficient (r)	0.012
	P-value	0.648

There is a broad spectrum of extrahepatic and hepatic symptomatology and comorbidities that are present with the multisystem disease MAFLD**2**.

MAFLD is linked to an increased risk of many extrahepatic malignancies in addition to liver cancer. The commonest causes of mortality in MAFLD patients are cardiovascular disease (CVD) and cancer, and the stage of liver fibrosis is the best

predictor. So, as part of a comprehensive approach to patient treatment, doctors caring for people with MAFLD should be urged to assess and start managing risk factors and comorbidities**10**.

According to the research, 56.4% of the participants had been diagnosed with MAFLD, and 96.8% of them had a BMI under 25 (mean: 33.46). This was almost in line with the (Tomah S, et al.2021) study's finding that 95 percent of MAFLD patients had a BMI of less than 25**11**.

The MAFLD group had a mean age of 50.8 11.1, a mean waist circumference of 105.1 13.8 cm, and a male predominance of 53.2%. These results were consistent with the (Hongbin L, et al.2020) study's findings that the majority of MAFLD patients were men with increasing waist circumference and were around the age of 50**12**.

The current study showed a significant correlation between MAFLD and lower hemoglobin mean ±SD (12.8±1.5), higher platelets mean ±SD (263.7±89.3), higher creatinine mean ±SD (0.98±0.23), These results are close to Hongbin L, et al. study as their participants with MAFLD also had significant higher platelets count, creatinine level, But their study showed significant association between MAFLD and higher hemoglobin levels (p- value <0.001), that disagreed with our results. This difference may be due to higher prevalence of smokers in their study causing secondary polycythemia**12**.

Our study reported that MAFLD patients had higher levels of cholesterol mean ±SD (187.6±38.7), triglycerides level (TGs) mean ±SD (151.5±65.7) and (very low density lipoprotein) VLDL mean ±SD (23±8.9) (p- value <0.001). That matched with Mansour R, et al. study, which reported a significant correlation between MAFLD and high lipid profile (total cholesterol and triglycerides (P < 0.001)**13**.

We found a significant association between MAFLD and higher E/e`(p-value=<0.001**)**, LA diameter (p-value=<0.039**)**, diastolic dysfunction grade II (p-value=<0.001**)** measured by 2 Dimentional echocardiography and tissue Doppler imaging. In Zamirian M, et al. study, significant correlation between NAFLD and higher E/e` ratio (8.4±0.8 vs. 7.4±1.2) was detected (P<0.001) but no significant

association between NAFLD and diastolic dysfunction was found. This difference may be due to higher prevalence of hypertensive patients in our MAFLD group which may be related to diastolic dysfunction**14**.

Our research found no clinical relevance between GLS and the MAFLD group (p-value=0.253), however the (Dong Y, et al.2020) study found a significant connection between GLS (p-value 0.001) evaluated by speckle tracking echocardiography and patients with moderate to severe MAFLD**15**.

Transient elastography was performed to all the studied patients and showed a significant association between MAFLD and higher liver stiffness (LSM) (p-value<0.001), that matched Chan A, et al. study results of significant LSM with MAFLD (p-value<0.001)**16**.

In our study stage 2, 3 of steatosis measured by CAP was higher in both MAFLD groups (78.1%) (P-value<0.001) which is close to the findings of Chan W, et al. study which showed 97% of NAFLD group were ≥ stage 1 steatosis**17**.

This study reported significant increase in stages of steatosis measured by transient elastography in lean MAFLD group compared to non MAFLD group but no significant differences in the liver fibrosis stages (p- value < .05). That disagreed with Kumar R and Mohan S study which reported a significant increase in fibrosis stages in lean MAFLD compared to non MAFLD group. This disagreement may be due to fewer number of lean MAFLD patients than non MAFLD patients**18**.

5. Conclusion: There was higher prevalence of subclinical cardiac dysfunction in MAFLD patients compared to non–MAFLD subjects, so MAFLD patients should be evaluated for CVD and referred to a cardiologist, if needed.

Conflict of interest:

There are no potential conflicts of interest to declare.

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