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Assessment of Left Atrial Phasic Functions in Type 2 Diabetes Mellitus patients Associated with Non-Alcoholic Fatty Liver Disease by 2D Speckle Tracking Echocardiography

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Abstract

Left atrium (LA) plays an important role in maintaining optimal cardiac output. Diabetes mellitus has been considered independent cardiovascular risk factors that can affect all cardiac chambers including the left atrium. Non-Alcoholic Fatty Liver Disease (NAFLD) is the most common chronic liver disease in T2DM and is considered as a risk factor for early subclinical cardiac abnormalities including left atrium. Assessment of LA phasic functions in type 2 Diabetes Mellitus patients associated with NAFLD using 2D Speckle tracking echocardiography. Sixty patients with type 2 DM associated with NAFLD and 30 healthy control subjects were included and subjected to full clinical assessment, full laboratory evaluation, abdominal ultrasound, and echo-Doppler examination measurements included LV dimensions, ejection fraction, trans-mitral Doppler flow and tissue Doppler velocities (E, A, E/A, E/Em), LA dimensions, volumes, phasic LA peak strain (2D-Peak LAS). Group I had higher values LA superior inferior dimension, mitral valve late diastolic velocity (A) and mitral valve early diastolic velocity to average early diastolic velocity of MV annulus by TDI (E/Em ratio) compared to the control group. On the other hand, they had lower values parameters of reservoir & contractile function (Peak atrial strain during ventricular systole & Late peak strain just before the active atrial contractile phase, compared to the control subjects. While LA conduit function tends to be reduced but did not reach statistically significant. HgA1c significantly had negative correlation with LA reservoir and contractile function ($r= -0.30$, $p<0.01$). Type 2 DM with NAFLD is associated with subclinical impairment of LA phasic functions using 2D speckle tracking echocardiography. Subclinical LA phasic functions are affected by patient's glycemic control. Moreover, the presence of NAFLD in diabetic patients double the risk of subclinical cardiovascular affection.

Keywords: Left atrium, Nonalcoholic fatty liver disease, Two-dimensional speckle-tracking, echocardiography.

1. Introduction

The left atrium is not only a passive transport chamber, but also a dynamic apparatus that plays an important role in cardiac function and adjusting LV filling with its reservoir, conduit and contractile function [1].

Non-Alcoholic Fatty Liver Disease (NAFLD) is increasingly diagnosed worldwide and is the most common chronic liver disease in type 2 diabetes mellitus (T2DM) (occurring in up to 70-75% of these patients) [2].

NAFLD is associated not only with liver – related morbidity and mortality, but also with an increased risk of developing cardiovascular disease, which is the most common cause of death among patients with type 2 diabetes mellitus [3].

NAFLD is considered as a risk factor for early subclinical abnormalities in myocardial metabolism as well as in myocardial structure and function including left atrium. There is close relationship between NAFLD and LA enlargement in patients with T2DM [4].

2D Speckle tracking echocardiography (2D-STE) is a novel technique for assessment of myocardial LA deformation and remolding. It enables early detection of LA dysfunction before LA morphological changes. Hence 2D-STE appears to be a promising technique for diagnosis and therapeutic making [5].

2. Patients and Methods

This study was a cross-sectional prospective study. It included 90 individuals divided into two groups: GI (type II DM with NAFLD patients), and GII (control group).

The study cases were selected from those coming for follow-up at Endocrinology and Cardiology Outpatient Clinics of Al-Zahraa University Hospital, Faculty of Medicine for Girls, from May to December 2021. All participants were informed of the purpose of the study, and written consent was obtained in adherence with the guidelines of the ethical committee of AL Azhar University, Cairo, Egypt. (IRB….)

2.1 Exclusion Criteria:

Patients with age > 65 yrs, known structural heart disease, Chronic liver diseases rather than NAFLD, chronic kidney diseases and ejection fraction (EF) <55% were excluded.

2.2 Methodology

All groups were subjected to the following:

2.2.1 History and physical examination:

Full history, with special emphasis on demographic data, including age and sex, history of alcohol intake, chest pain, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and palpitation; thorough clinical examination, including weight, height, waist circumference, body mass index (BMI) and body surface area (BSA); full clinical examination; blood pressure measurement; and 12 lead-ECG to detect resting heart rate, any rhythm rather than sinus rhythm, duration and amplitude of the P wave.

2.2.2 Laboratory investigation:

Complete blood count (CBC), Kidney Function Tests, liver function tests, fasting blood sugar (FBS), 2-hour post prandial sugar (PPBS) and HA1C, lipid profile were performed for all participants.

2.2.3 Pelvi-abdominal ultrasonography:

It was done by Toshiba SSA-340A machine with a3.5 MHZ curved convex probe, scanning procedure included liver examination: its size (RT, LT lobe) and

echogenicity were performed for all participants.

2.2.3 Echo-Doppler evaluation

Trans-thoracic echocardiographic examination was performed for all cases at the Cardiology Department, Al-Zahraa University Hospital, using GE- Vivid 6 system (GE- Ultrasound, Horten, Norway) with M3S (2.5MHz) matrix probe, having the capability of tissue Doppler imaging (TDI) and gray scale recording for speckle tracking study.

All measurements were done by a staff cardiologist over at least three cardiac cycles, and the average value for each parameter was calculated. Comprehensive transthoracic echocardiographic M-mode, 2D, Doppler (pulsed, continuous, color flow mapping, and TDI) and 2D Speckle tracking of the left atrium in the standard views from all accessible windows were obtained with displayed ECG physio signals. The loops of three cycles were recorded and digitally stored for later offline analysis automatically at GE Echo PAC, version 107

All echo-Doppler measures were obtained according to guidelines and standards recommended for cardiac chamber quantification by echo in adults [6].

I. **Conventional measurements** included LV end diastolic and systolic dimensions, end diastolic interventricular septal thickness, LV posterior wall thickness, LA diameters, LAVI, transmitral valve early and late diastolic velocity (MV-E vel and MV-A vel) and MV-E/A ratio.

II. **The TDI** was obtained from apical 4-chamber and 2chamber views. For data acquisition, three complete cardiac cycles were recorded and stored in a cine loop format. The image sector width was set as narrow as possible to allow a frame rate acquisition greater than 90 frames/s. TDI systolic andX, early and late diastolic velocities were obtained from four annular sites (inferoseptal, lateral, inferior, and anterior) and average values from these sites were calculated (Av-Sa, Av-Ea, and Av-Aa). Likewise average Av-Ea/Av-Aa ratio and MV-E/Av-Ea ratio were calculated.The TDI of the LA was assessed by placing sample volume at mid atrial segment of interest, usually about 2 mm for measuring velocity and preferably not more than 12 mm of length for strain because of its thin-walled structure**.** The velocity range was set at 20 to 30 cm/s with minimal gain and lower filter settings.

III. **2D-STE** was performed on gray scale images with good image quality to allow for good delineation of the endocardial border and for feasibility of frame-to-frame tracking. The frame rate was set between 60-80 f/sec. We used the QRS onset as the reference point, applying commercially LA strain software. The region of interest was adjusted to include the LA myocardium in the four-chamber, two-chamber views that included the left atrium. Figure 1

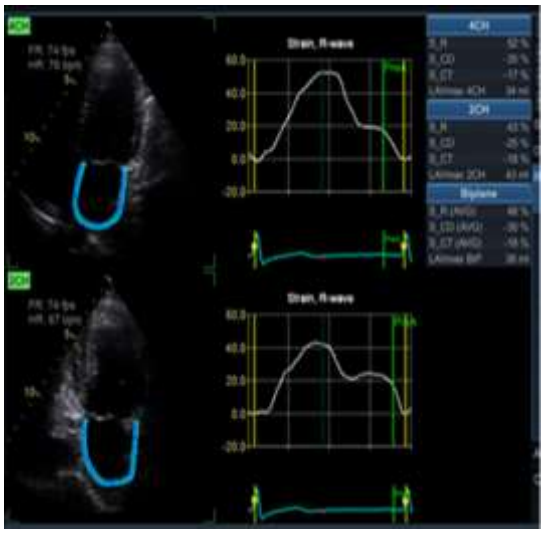

Figure1: 2D-speckle tracking of LA measuring reservoir, conduct and contractile functions:

2.3 Statistical analysis:

Data was collected, revised, tabulated and statistically analyzed. Quantitative data were expressed as mean ±SD and were

statistically analyzed to see the association of various variables using Microsoft excel, version 2010. The unpaired Student T-test was used for testing statistically significant difference between the means of two samples. The X^2–test was used to detect statistically significant relation between qualitative variables. The result was considered significant when P value was less than 0.05 and highly significant when less than 0.01.

3. Results

As show in table 1 basic demographic data of our study cases .Our study included 60 patients with type II DM associated with NAFLD diagnosed by pelvi-abdominal ultrasound (Group I) , in addition to 30 age and sex matched healthy individuals as a control group (Group II) .Our study revealed there were a statistical significance increase of body weight, body surface area (BSA) and body mass index (BMI) in group I compared to Group II with no significant differences between both groups as regard height and waist circumferences . Also, there were female sex predominance in our cases either group I or group II.

As show in table 2 there were a statistically significantly higher value of SGOT, SGPT, cholesterol, TG, LDL, HDL, FBS, PPBS, HbA1C and creatinine in group I compared to group II ($P<0.05$) .While there were a significantly lower value of platelet count, white blood cells, prothrombin time, INR and serum K in group I compared to group II($P<0.05$).There were no statistical significant differences were found between both groups in Hb, PC, Na, urea and albumin ($P>0.05$).

As shown in table 3 according to the echocardiographic data, Group I had statistically significantly lower value of ejection fraction (EF) measured by m-mode compared to group II. In the transmittal Doppler flow and tissue Doppler parameters, there were statistically significant higher difference between group I and group II in mitral valve late diastolic velocity (A) and mitral valve early diastolic velocity to average early diastolic velocity of MV annulus by TDI (E/Ea ratio).

Meanwhile, there were no statistically significant differences between both groups in mitral valve early diastolic velocity (E), E/A ratio (A: mitral valve late diastolic velocity) and the average early diastolic velocity of MV annulus by TDI (Ea).

Assessment of LA:

By the conventional echocardiographic parameters, there was only a statistically significant difference between both groups as regards left atrial superior-inferior diameters, whereas there was no statistically significant difference between both groups in (LA antero-posterior, medial-lateral diameters) and LA volume (maximum left atrial volume (LAV MAX) and maximum left atrial volume index).

TDI, there were a significant lower value in group I in the average left atrial strain derived TDI compared to group II.

2D speckle tracking echocardiography, LA phasic functions (Reservoir and contractile) had significant lower value in group I compared to group II, While LA conduit function tends to be reduced but didn't reach statistically significant.

As shown in table 4 there was a significant negative correlation between HbA1C and Av-LA-Strain (TDI), average reservoir and average conduit function ($r = -0.30$, p value <0.01).

Table 1: Baseline demographic data in studied groups with significant level of difference between each two groups:

Variables (mean± SD):	Group I N (60)	Group II N (30)	P value
Age (yrs):	50.8 ± 6.4	50.9 ± 6.9	0.4
Gender: Female Male	 37 (61.7%) 23(38.3%)	 18(60%) 12(40%)	0.44
Diabetic Duration (Yrs)	5.7 ±3.34	-	-
Smoking Yes No	 9 (15%) 51 (85%)	 6 (20%) 24 (80%)	-
Weight (Kg):	82±7.86	74.8±10.04	0.000(HS)
Height (Cm):	163±5.16	163.7±6.26	0.2(NS)
Waist circumference (cm):	91.86±8.64	90.37±9.45	0.3 (NS)
BMI (Kg/m2):	30.36 ±2.97	27.96±4.08	0.001(HS)
BSA (m2):	1.9± 0.1	1.8±0.1	0.004 (HS)

BMI: body mass index BSA: body surface area)

Table2: Biochemical characteristics data in the study populations with significant level of difference between each two groups:

Labs (mean ±SD):	Group I	Group II	P value
Hb(g/dl):	12.7 ± 1.28	12.7 ± 1.28	0.9 (NS)
WBC (x10^3/ul):	7.03 ± 1.2	8.3±1.7	0.000 (HS)
Platelet (x10^3/ul):	234.35 ± 41.7	285.5±41.07	0.01 (S)
PT (sec.):	11.5± 0.89	12.12±0.4	0.000 (HS)
PC (%):	99.82 ± 0.35	99.88±0.32	0.4(NS)
INR:	0.98 ± 0.05	1.04±0.097	0.004 (HS)
Na (mg/dl):	139.1 ± 2.27	139.1±2.17	0.8 (NS)
K (mg/dl):	4.07 ± 0.25	4.28 ± 0.4	0.01(S)
Urea(mg/dl):	26.4 ± 7.7	25.3 ± 5.7	0.6 (NS)
Creat. (mg/dl):	0.86 ± 0.2	0.7 ± 0.14	0.01 (S)
SGOT(U/L):	27.18±10.1	20 ± 6.8	0.000(HS)
SGPT(U/L):	33.4 ± 12.6	26.5 ± 6.6	0.001(HS)
Albumin(g/dl):	4.13 ± 0.3	4.2 ± 0.34	0.1(NS)
Cholesterol (mg/dl):	277 ± 58.8	175.1 ± 18.1	0.000(HS)
TG (mg/dl):	175.18 ± 101.1	110.27 ± 13.39	0.000(HS)
LDL (mg/dl):	117.8 ± 48.5	87.24 ± 8.8	0.000(HS)
HDL (mg/dl):	37.7 ± 7.6	31.6 ± 2.3	0.000(HS)
FBS (mg/dl):	166.8 ± 27.8	95.96 ± 9.37	0.000(HS)
PPBS (mg/dl):	272 ± 70.1	135.7 ± 5.03	0.000(HS)
HbA1C (%):	7.5 ± 1.36	5.7 ± 0.4	0.000(HS)

Hb: hemoglobin, WBC: white blood cell, PT: prothrombin time, PC: prothrombin concentration, INR: international normalization ratio, Na: sodium, K: potassium, SGOT: serum glutamic oxaloacetic transaminase, SGPT: serum glutamic pyruvate transaminase, TG: triglyceride, LDL: low density lipoprotein, HDL: high density lipoprotein, FBS: fasting blood sugar, PPBS: postprandial blood sugar).

Table 3: Baseline left atrial and ventricular echocardiographic parameters in studied groups with significant level of difference between both groups

Variable (mean ± SD)	Group I	Group II	P value
LVEDD (mm)	48.56 ± 6.05	49.9 ± 3.9	0.3(NS)
LVEDs (mm)	29.4 ± 5.2	29.5 ±3.36	0.8(NS)
IVSd (mm)	9.15 ± 1.28	8.79 ±1.18	0.19(NS)
LVPWd (cm)	9.9 ± 2.01	9.27±1.43	0.07(NS)
EF %(m-mode)	68.46±7.3	71.2±5.3	0.03(S)
EF %(2D)	63.2±5.8	63.8±5.2	0.6(NS)
LV-MPI	0.44±0.13	0.48±0.13	0.3(NS)
Av-Sa (cm/s)	6.48±1.24	6.83±1.32	0.2(NS)
Av-2D GLS %	19.38±2.97	22.58±2.96	2.9(NS)
M E vel (cm/sec)	70.7 ± 15	70 ± 13	0.9(NS)
M A vel (cm/sec)	72.9 ± 12	67.27 ± 14	0.04(S)
M E/A ratio	0.98 ± 0.25	1.19 ±0.8	0.1(NS)
Average LV Ea (cm/sec)	7.37 ± 1.8	8.15 ±1.5	0.05(NS)
LV E/Ea	9.98 ± 2.9	8.75 ±1.9	0.03(S)
LA sup-inf diam (mm)	37.18 ± 3.7	35.6 ± 3.8	0.03(S)
LA med-lat diam(mm)	32.8 ± 3.9	32.9±3.5	0.4(NS)
LA ant-post.diam(mm)	33.9± 3.9	33.4± 4.2	0.2(NS)
LAV Max (ml)	32.5 ± 8.5	31.2 ± 7.2	0.2(NS)
LAVI Max(ml/mm2)	17.3 ± 4.4	17.4± 3.7	0.4(NS)
Av-LA-Strain (TDI) %	37.2±11.17	46.6 ±10.27	0.000(HS)
Reservoir function %	38.5 ± 3.2	42.4 ± 3.7	0.000(HS)
Conduit function %	24.0 ± 3.4	25.0 ±1.7	0.2(NS)
Contractile function %	14.3±3.6	18.1±2.2	0.000(HS)

Av-2D-GLS%: Average 2-dimensional global longitudinal strain, Av-Sa(cm/s): mitral annular systolic velocity, Av- Ea (cm/sec): the average early diastolic velocity of MV annulus by TDI. E/Ea: mitral valve early diastolic velocity to average early diastolic velocity of MV annulus by TDI. Av-TDI strain, average tissue Doppler strain, EF%, ejection fraction, IVSD: interventricular septum dimension, LA: left atrium, LAVI: left atrium volume index, LVEDD: left ventricular end diastolic dimension, LVESD: left ventricular end systolic dimension, LVPWD: left ventricular posterior wall dimension; MV-A vel(m/s), mitral valve late diastolic filling velocity; MV-E vel(m/s): mitral valve early diastolic filling velocity)

Table 4: Correlation between Av-LA Strain (TDI) and HbA1C:

Variables	R (correlation coefficient)	P value
HbA1C	-0.30	<0.01

4. Discussion

Type 2 diabetes mellitus (T2DM) and nonalcoholic fatty liver disease (NAFLD) commonly exist together. Cardiovascular events in NAFLD are increased by 1.87-fold in the presence of T2DM [7]. NAFLD is considered as a risk factor for early subclinical abnormalities in myocardial metabolism as well as in myocardial structure and function including left atrium [4].

Our study included 60 patients with type II DM associated with NAFLD (Group I) In addition to age and sex matched 30 healthy individuals as a control group (Group II).

Most of our study groups were female with increased BMI and BSA of the diseased group, this may be attributed to Overweight/obesity and insulin resistance (IR) have been strongly linked with NAFLD. Our result in agreement with result of Maurice and his colleague [8], Body mass index was independently associated with NAFLD and type 2 diabetes, also The European Association for the Study of Diabetes (EASD) [9] concluded that NAFLD is closely linked to metabolic syndrome, it has been regarded as the hepatic manifestation of the syndrome. Evaluation of the risk for NAFLD is recommended in all patients with any component of metabolic syndrome as all components of the metabolic syndrome correlate with the degree of liver fat content and also vice versa.

Our study showed that serum creatinine was significantly higher in diabetic patients with NAFLD compared to normal subjects which were concordant with Singh,[10] who reported that plasma creatinine was observed to be significantly higher in type-2 DM subjects compared to non-diabetics' controls as it may indicate a pre-renal problem.

Also, our result in agreement with Nampoothiri et al. [11] who concluded that around one-third of patients with NAFLD have impaired renal functions. Prevalence of impaired renal function in patients with NAFLD is dependent on the severity of liver disease and presence of diabetes mellitus.

This result was in disagreement with Harita et al.[12] and Dabla,[13] who reported that lower serum creatinine is associated with an increased risk of type 2 diabetes.

Regarding lipid profile, our study showed significant differences between two groups in TG, LDL and total cholesterol, as triglyceride, LDL and total cholesterol were higher in diabetics than non-diabetics and these results were concordant with Elgohary results [14], who reported that there were statistically significant differences between the two groups as regard total cholesterol, LDL, HDL and triglycerides levels.

These results were discordant with Naidoo and Raal [15] who reported significantly low values of total cholesterol and LDL in diabetics. As Diabetic patient's treatment also included lipid lowering drugs (statins), thus explaining lower values of total cholesterol and LDL - cholesterol respective to control.

In our study, there were statistically significant increase in liver enzymes (AST and ALT) Particularly SGPT (ALT) in group I compared to group II (P-value <0.01) suggesting NAFLD being more common associated with elevated liver enzymes.

Our result agreed with Abdo,[16] who showed that, SGPT was significantly increased in T2DM with NAFLD when compared to the other group without NAFLD, while SGOT (AST) was not significantly increased (p-value 0.06).

Regarding LV conventional echocardiography, our study showed no significant differences between both groups in LV dimensions and systolic function by 2-D echo and this result concordant with Chang et al. [17] who concluded that the LV dimensions and systolic function don't differ among diabetic patients with or without NAFLD).

Also, our results were concordant to Kocaby et al. [18] who showed that there was no significant difference between NAFLD and healthy group as regard left ventricular dimensions and ejection fraction.

In current study, there were statistically significant higher differences between group I and group II in MV A velocity and E/Ea ratio by TDI.While, there were no significant difference between group I and group II as regards (E/A ratio and Ea). However, both groups showed impairment of diastolic function with more affection in the diseased group which explained by our control group were age matched to the diseased group with main age 50.9 ± 6.9.

It was found that with the progressing of age, the left ventricle becomes stiffer resulting in a reduction in early filling and a compensatory increase in flow due to atrial contraction. A progressive increase in LVMI, which accompanies aging may contribute to stiffening of the left ventricle and deterioration in diastolic function of the left ventricle [19]

These results were concordant with several studies like Cornelis et al.[20] who reported that MV A velocity was significantly higher in diabetics

Also, our results were concordant to Kocabay et al. [18] who showed that there was significant difference between NAFLD and healthy group as regard E/Ea ratio.

In a concordant with our result Chang et al. [17] reported higher E/Ea ratio in NAFLD patients compared with non NAFLD, with no significant difference in E/A ratio and Ea among NAFLD and non NAFLD groups.

Our result is disconcordant with the results of Naidoo and Raal, [15] and Elgohary, [14] they reported that there were no significant differences between two groups regarding LV diastolic function this explained by the younger patients with type I DM and with BMI<30 in their study while our patients were older with increased BMI.

Conventional echo-Doppler parameters of the LA dimensions and volumes (LA antero-posterior and medio-lateral diameter as well as max. LAV and LAVI), cannot differ in T2DM with NAFLD and control group. our results in agreement with results of Chang et al. [17]and Parvanescu et al. [21] they studied 150 adult patients with NAFLD and metabolic syndrome and 150 age and sex matched as a controlled group and revealed that there was no difference between both groups as regard conventional echocardiographic parameters of the left atrium.

In this study there were significant reductions in average left atrial strain derived TDI in diabetic patients with NAFLD compared with the control group.

Our study demonstrated a highly significant reduction in LA phasic functions (Reservoir and contractile) by 2D STE in group I compared with group II. While LA conduit function tends to be reduced but didn't reach statistically significant.

Our results agreed with Kocabay et al. [18] who showed that left atrial reservoir and contractile function significantly reduced in diabetic patients with NAFLD when compared with the healthy individuals (P value 0.007,0.006 respectively).

Also, our results agreed with Chang et al. [17] who showed that left atrial reservoir and contractile function were decreased in NAFLD group compared to the control group (p-value <0.05).

This finding supports the fact that the increased insulin resistance (IR) may have an additional impact on LV diastolic function in patients with NAFLD. Previously, it has been shown that elevated insulin levels in patients with IR stimulate myocyte growth and interstitial fibrosis [22] (Wong et al., 2004).

Prolonged exposure to hyperglycemia results in vascular damage. The association between chronic hyperglycemia and cardiovascular complications, however, is not fully understood [23] (Navarro-Pérez et al., 2018). The HbA1c level is an indicator

of the average blood glucose concentrations over the preceding 2–3 months and is used as a biomarker of diabetes control in clinical practice [24] (Camara et al., 2014). There is much evidence on the role of hyperglycemia as a cardiovascular disease (CVD) risk factor, sudden death, mortality in myocardial infarction and mortality in critically ill patients (Navarro-Pérez et al., 2018).

Despite the fact that elevated HbA1c has shown inconsistent risk stratification, according to different levels Observational studies and meta-analyses report that patients with uncontrolled diabetes, defined as HbA1c>6.5%, are at increased risk for CVD and mortality compared to patients with controlled diabetes [25] (Oh et al., 2011).

In our study there was a significant negative correlation between HbA1C and Av-LA-Strain (TDI), average reservoir and average conduit function ($r = -0.30$, p value <0.01), which indicate worsening of left atrial phasic function parameters and hence LV diastolic function with poor diabetic control.

Study limitations

This study is limited by relatively small sample size and lack of liver biopsy for grading fatty liver.

5. Conclusion

Type 2 DM with NAFLD is associated with subclinical impairment of LA phasic functions using 2D speckle tracking echocardiography. Subclinical LA phasic functions are affected by patient's glycemic control. The presence of NAFLD in diabetic patients double the risk of subclinical cardiovascular affection. Further studies on larger sample sizes with grading the degree of NAFLD based on liver biopsy for more accurate assessment.

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