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Original Article

Evaluation of subclinical LV systolic dysfunction by speckle tracking echocardiography in patients with Non-alcoholic fatty liver disease

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ABSTRACT

Background: Non-alcoholic fatty liver disease (NAFLD) is the most common kind of chronic liver disease, and it is associated with a high rate of liver-related morbidity and mortality in people affected. The purpose of this study was to use speckle tracking echocardiography to assess subclinical left ventricular systolic dysfunction in individuals with non-alcoholic fatty liver disease. **Methods**: This prospective cross-sectional study was conducted on 92 patients with NAFLD Which were divided according to Transabdominal ultrasound into three groups: GroupI (grade I fatty liver) included 27 patients, Group II (grade II fatty liver) included 29 patients and group III (grade III fatty liver) included 36 patients. All patients had transabdominal ultrasonography, transthoracic echocardiography, and LV end diastolic diameter measurements. LV End systolic diameter, Diastolic volume and LV function assessment by GLS. **Results:** Group III had significantly higher levels of total cholesterol, triglycerides, and LDL compared to the other groups, indicating an increase in disease severity. Group III had higher levels of ESD, EDD, ESV, and EDV on echocardiography compared to the other groups, indicating a substantial difference in cardiac affection. GLS was found to be adversely associated with NAFLD grades but favorably associated with HTN, regardless of other factors. HTN and NAFLD grades can be considered as independent predictors for systolic dysfunction between the examined groups. **Conclusions:** In asymptomatic patient there was a significant association between NAFLD and cardiac systolic dysfunction as NAFLD grades were associated with low GLS (systolic dysfunction).

Keywords: Non-alcoholic fatty liver disease; left ventricular; echocardiography

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD), which starts with simple liver steatosis and progresses to cirrhosis, non-alcoholic steatohepatitis, and finally hepatocellular carcinoma, is the most prevalent chronic hepatic illness. Heart disease and cerebrovascular disease are independently predicted by nonalcoholic fatty liver disease (NAFLD), which is often regarded as the characteristic of liver involvement in the metabolic syndrome. Furthermore, NAFLD has been linked to vascular and cardiac subclinical alterations that are known to occur prior to significant cardiovascular events [1,2].

On liver biopsies, NAFLD is detected when at least 5% of cells are filled with fat and there is less than 30 g of alcohol consumed daily by males and 20 g by women. As an alternative, liver steatosis can be identified via hepatic imaging, elastography, or biochemical scores with negligible reductions in specificity and sensitivity [3,4].

A sensitive method for identifying early myocardial dysfunction is 2D speckle-tracking echocardiography [5]. Real-time, cross-sectional pictures of the heart are provided by 2D echocardiography, which enables assessment of the global systolic function, wall thickness, and cardiac chamber size [6]. A more recent development, STE allows for angle-independent, multidirectional strain analysis by monitoring the migration of natural acoustic markers, or sparkles, in the myocardium during the course of the cardiac cycle. In many clinical contexts, left

ventricular global longitudinal strain (LVGLS), a promising prognostic indicator for HF, deteriorates before the LV ejection fraction decreases [5].

Even in the absence of conventional cardiovascular risk factors, 2D echocardiography and STE have shown promise in identifying modest changes in heart shape and in people with nonalcoholic fatty liver disease [7].

Aim of the work

This study aimed to evaluate of subclinical LV systolic dysfunction by speckle tracking echocardiography in patients with Non-alcoholic fatty liver disease.

METHODS:

Between September 2023 and October 2024, 92 patients with NAFLD who were present to the cardiology department of Zagazig University Hospitals and El Mabara Hospitals participated in this cross-sectional study. The Ethics Committee of Zagazig University's Faculty of Medicine in Egypt gave its approved the study (IRB # 10912). Every patient provided written, informed consent. The study followed the World Medical Association's Declaration of Helsinki, the organization's rule of ethics for human subjects research.

Inclusion criteria were both male and female patients, NAFLD patients were identified by ultrasonography as having fatty livers, which show enhanced echogenicity (also known as "bright liver") because of the increased interfaces that fat droplets within hepatocytes create, which causes more echoes to return to the transducer. Significant valvular lesions were excluding criteria. which include patients with cardiac muscle disease, or CAD, individuals with alcoholic liver disease, other liver disorders, end-organ liver cell failure, individuals suffering from end-organ renal failure, individuals with severe irregularities in their rhythm, inadequate myocardial delineation in the ECHO window TTE. signs of LV systolic dysfunction and heart failure. Patients were categorized into three main groups; Group I (n=27): grade I fatty liver by Transabdominal Ultrasound enrolled as a case group. Group II (n=29): grade II fatty liver by Transabdominal Ultrasound enrolled as a case group. Group III (n=36): grade III fatty liver by Transabdominal Ultrasound enrolled as a case group.

Every patient were subjected to a comprehensive clinical examination that included a pulse, blood pressure, chest, abdomen, and lower limb oedema, as well as a comprehensive history and demographic data collection. BMI evaluation. Check the local cardiac exam for signs of heart failure, such as lung rales, S3 gallop, and S4. Laboratory analysis After at least 12 hours of fasting, a lipid profile comprising low-density lipoprotein cholesterol (LDL-C), triglycerides (TG), and total cholesterol (TC) was assessed and AST, ALT with LVT to exclude liver cell failure. Renal function test to exclude renal failure.

Transabdominal ultrasonography was the primary imaging method used to image patients who are suspected of having nonalcoholic fatty liver disease. Because intracellular buildup of fat vacuoles reflects the ultrasound beam, the liver parenchyma is more echogenic than the right kidney's cortex, which is the fundamental indicator of steatosis. The following grading scheme was commonly used to classify steatosis: Grade 0: When compared to the right kidney's cortex, the right liver lobe's echogenicity is normal. Grade 1: the diaphragm and intrahepatic artery boundaries can be seen normally, and the liver parenchyma has a slight, diffuse rise in fine echoes. Grade 2: mildly compromised visibility of the diaphragm and intrahepatic arteries, along with a mildly widespread rise in fine echoes. Grade 3: a noticeable rise in fine echoes accompanied by inadequate or nonexistent visibility of the diaphragm, posterior right lobe of the liver, and intrahepatic vascular boundaries [8].

One skilled physician echocardiographer performed standard 2D transthoracic echocardiography on each participant, including STE utilizing a Vivid E9 machine (GE). The left lateral decubitus position was used to scan the patients. Using a 3.5-MHz transducer, standard pictures were acquired in the apical (four-, two-chamber, and long-axis) and parasternal (long and short-axis) perspectives. The obtained image frame rates ranged from 82 to 95 frames per second **[9].**

Left ventricular Size

Linear Measurements:

left ventricular End Diastolic Diameter (LVEDD); inner edge to inner edge at or just below the level of the mitral valve leaflet tips, perpendicular to the LV's long axis.

Execute at end-diastole, which is the frame with the biggest LV dimensions/volume or the first frame following mitral valve closure.

LV End Systolic Diameter (LVEDS); inner edge to inner edge at or just below the level of the mitral valve leaflet tips, perpendicular to the LV's long axis. Perform during end-systole, the smallest LV volume or dimension of the frame after the aortic valve closes.

LV Volume Measurement:

Simpson's method, which measures from the apical 4- and 2-chamber views, computed

automatically after tracing the endocardial-blood pool interface on pictures showing a distinct endocardial border at end-diastole and end-systole (ASE 2015 chamber quantification paper for the alternative area-length technique).

Left Ventricular Function Assessment:

The difference between the 2D parameter's end-diastolic and end-systolic values is divided by its end-diastolic value to calculate the global LV function. [10].

The formula LVEF = [(LVEDV – LVESV) / LVEDV] X 100 is used to compute EF from EDV and ESV estimates.

Myocardial deformation analysis:

GE Echo PAC software was used to analyze 2D speckle tracking imaging offline. End-systole, as determined by pulsed-wave Doppler tracing along the LV outflow tract, was defined for the purposes of speckle tracking imaging analysis as the instant the aortic valve closed. At a frame rate of 43 to 60 frames per second, GLS was measured in the three conventional apical views (long axis, apical 4 chamber, and 2 chamber) and the average GLS was reported [11,12].

In every LV segment and area, every study participant exhibited excellent segmental tracking. First, the endocardial border of the left ventricle was automatically drawn; if necessary, it was then manually outlined. The regions of interest's widths were modified to correspond with the real endocardial and epicardial borders. A measure of strain at every location within the myocardium was obtained by automatically recording speckle patterns frame by frame during the cardiac cycle. In each apical view, Six parts of the left ventricle were identified, and each section was examined separately. Global longitudinal strain, or "GLS," was computed automatically by averaging the strain values of entire left ventricular segments at rest; values below -20% were deemed abnormal [13].

Statistical analysis

IBM SPSS 23.0 for Windows, a database software tool, was used to code, input, and analyze the gathered data (SPSS Inc., Chicago, IL, USA). Fisher's exact test (f) is used when the assumption that "less than 20% of cells have expected count less than 5" is not met. To compare the continuous variables between the two groups, the independent samples t test was employed. Whitney-Mamann The U test was utilized in order to compare the outcomes between two separate groups. In order to investigate the differences in independent variable means between more than two groups, the One Way Analysis of Variance (ANOVA) test was utilized. Two or more independent, non-normally distributed samples with equal or different sample sizes were compared using the Kruskal-Wallis test. A quantitative variable's dependency on a group of independent factors was tested and estimated using multiple linear regression. A significant p-value was one that was less than 0.05.

RESULTS

This study included 92 patients with NAFLD, divided by Transabdominal ultrasound into three groups; **Group I** included 27 patients. Their ages ranged from 23 to 65 years, with a mean ± SD of 44.6 ± 8.18. (66.7%) were males and (33.3%) were females. Their BMI ranged from 21.3 to 26.4 kg/m^2 with a mean ± SD of 23.9 ± 1.41. **Group II** included 29 patients. Their ages ranged from 31 to 75 years, with a mean ± SD of 52.4 ± 11.97. (58.6%) were males and (41.4%) were females. Their BMI ranged from 23.1 to 28.1 kg/m^2 with a mean ± SD of 25.2 ± 1.47. **Group III** included 36 patients. Their ages ranged from 40 to 78 years, with a mean ± SD of 53.3 ± 10.49. (69.4%) were males and (30.6%) were females. Their BMI ranged from 23.4 to 31.2 kg/m^2 with a mean ± SD of 26.8 ± 2.28.

Table 1; showed a statistically significant difference between the NAFLD degrees as regards age and BMI, as group III patients were older than the other groups *(P<0.001)*. Also, group III patients had a higher BMI than the other groups *(P<0.001)* figure 1,2.

In terms of the lipid profile, Figures 3,4 and 5 demonstrated a statistically significant difference between the NAFLD degrees, with group III having greater levels of total cholesterol, triglycerides, and LDL than the other groups (P<0.001).

Table 2; showed a statistically significant difference between the NAFLD degrees as regards systolic indices, as ESD, EDD, ESV and EDV were higher among group III when compared with the other groups *(P<0.001)*. While LVEF and GLS levels were higher among group I when compared with the other groups *(P<0.001)*.

Table 3; showed that after applying logistic regression analysis for predictors of systolic dysfunction, HTN and NAFLD grades can be used as independent factors for predicting systolic dysfunction among the studied groups.

Table (1): Demographic data among the studied groups

Variables		**Group I (n=27)**	**Group II (n=29)**	**Group III (n=36)**	***P Value**	**Post-Hoc**
Age (years)	Mean ± SD	44.6 ± 8.18	52.9 ± 11.97	53.3 ± 10.49	**<0.001**[1]	P1=**0.01** P2=**0.004** P3=**0.99**
Sex (n. %)	Male	18 (66.7%)	17 (58.6%)	25 (69.4%)	0.65[2]	-
	Female	9 (33.3%)	12 (41.4%)	11 (30.6%)		
BMI (kg/m^2)	Mean ± SD	23.9 ± 1.41	25.2 ± 1.47	26.8 ± 2.28	**<0.001**[1]	P1=**0.03** P2<**0.001** P3=**0.001**

*[1]*One way ANOVA test,* [2]*Chi-square test, Non-significant: P >0.05, Significant: P ≤0.05*
**P value=Comparison between the three groups, P1=Comparison between Group I & Group II, P2=Comparison between Group I & Group III, P3= Comparison between Group II & Group III*
***BMI**=Body mass index*

Table (2): Echocardiographic findings among the studied groups (Systolic indices)

Variables		**Group I (n=27)**	**Group II (n=29)**	**Group III (n=36)**	**P Value**	**Post-Hoc**
ESD (mm)	Mean ± SD	32.7 ± 1.29	32.9 ± 1.31	34.7 ± 0.82	**<0.001**[2]	P1=0.924 P2<**0.001** P3<**0.001**
EDD (mm)	Mean ± SD	46.1 ± 1.83	47.9 ± 2.07	51.3 ± 2.42	**<0.001**[2]	P1=**0.005** P2<**0.001** P3<**0.001**
ESV (ml)	Mean ± SD	40 ± 1.6	44.6 ± 1.68	45.6 ± 2.07	**<0.001**[2]	P1<**0.001** P2<**0.001** P3=**0.02**
EDV (ml)	Mean ± SD	92.4 ± 3.2	98.7 ± 4.1	101 ± 2.41	**<0.001**[1]	P1<**0.001** P2<**0.001** P3=**0.02**
LVEF (%)	Mean ± SD	64.7 ± 2.92	62.4 ± 2.82	58.2 ± 2.33	**<0.001**[1]	P1=**0.005** P2<**0.001** P3<**0.001**
GLS (%)	Mean ± SD	-19.2 ± 1.46	-15.3 ± 0.95	-11.8 ± 1.08	**<0.001**[1]	P1<**0.001** P2<**0.001** P3<**0.001**

*[1]*One way ANOVA test,* [2]*Kruskal-Wallis test, Non-significant: P >0.05, Significant: P ≤0.05*
**P value=Comparison between the three groups, P1=Comparison between Group I & Group II, P2=Comparison between Group I & Group III, P3= Comparison between Group II & Group III*
***ESD**=End systolic diameter, **EDD**=End diastolic diameter, **ESV**=End systolic volume, **EDV**=End diastolic volume, **LVEF**=Left ventricular ejection fraction, **GLS**=Global longitudinal strain*

Table (3): Logistic regression analysis for predictors of GLS (Systolic indices)

Variables	Univariate analysis		Multivariate analysis	
	P value	**Odds (CI 95%)**	**P value**	**Odds (CI 95%)**
Age	**0.002**	1.08 (1.03 – 1.13)	0.56	0.91 (0.67 – 1.25)
Sex	0.83	0.91 (0.39 – 2.12)	-	-
BMI	**<0.001**	2.61 (1.71 – 3.94)	0.14	5.12 (0.58 – 4.54)
Smoking status	0.63	1.27 (0.49 – 3.32)	-	-
DM	0.37	0.66 (0.27 – 1.62)	-	-
HTN	**0.04**	1.06 (1.03 – 1.09)	0.02	1.43 (1.05 – 1.95)
NAFLD grades Mild Moderate Severe	 **<0.001** **<0.001** **<0.001**	 1.04 (1.02 – 1.06) 1.16 (1.15 – 1.29) 1.77 (1.39 – 2.22)	 0.004 0.001 <0.001	 1.11 (1.04 – 1.26) 1.81 (1.22 – 1.34) 1.99 (1.59 – 2.97)
TC	0.09	2.31 (0.87 – 6.15)	-	-
TG	**0.007**	1.68 (1.15 – 2.45)	0.39	1.05 (0.94 – 1.19)
LDL	**0.001**	1.54 (1.18 – 2.01)	0.11	2.56 (0.84 – 7.87)
ESD	0.83	1.03 (0.78 – 1.37)	-	-
EDD	**<0.001**	1.69 (1.33 – 2.14)	0.69	1.22 (0.44 – 3.38)
ESV	**<0.001**	1.31 (1.12 – 1.54)		
EDV	**0.006**	1.14 (1.04 – 1.25)	0.06	2.14 (0.97 – 4.69)
LVEF	**<0.001**	0.59 (0.48 – 0.73)	0.52	0.79 (0.39 – 1.61)

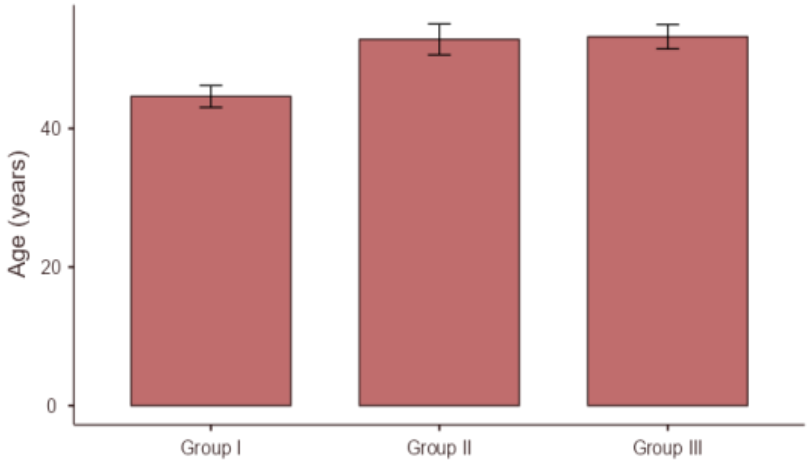

Figure (1): Bar plot showing age among the studied groups

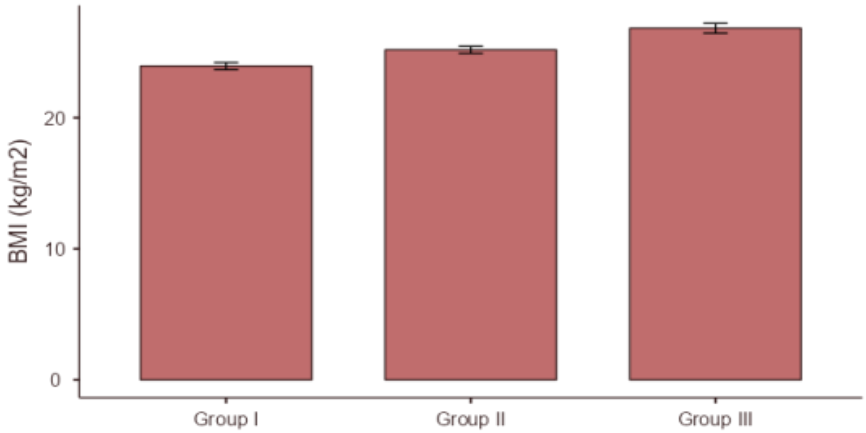

Figure (2): Bar plot showing BMI among the studied groups

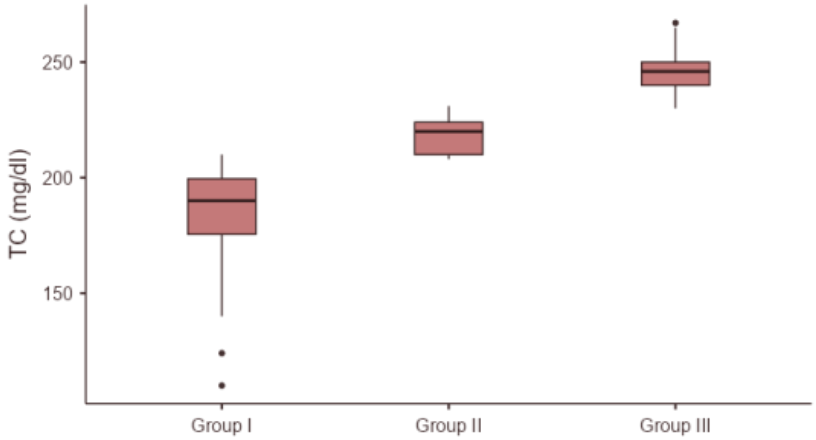

Figure (3): Box plot showing total cholesterol levels among the studied groups

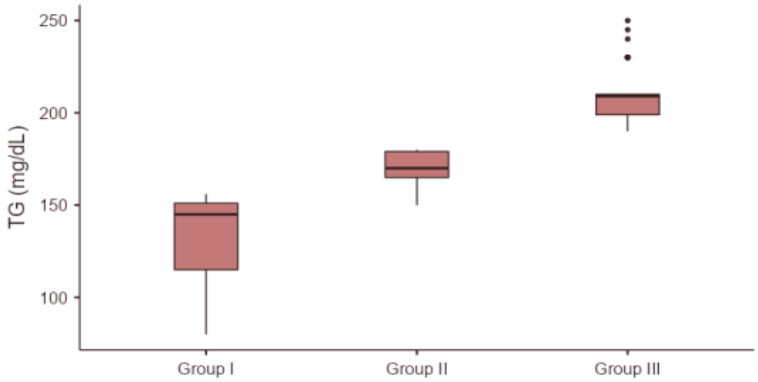

Figure (4): Box plot showing triglyceride levels among the studied groups

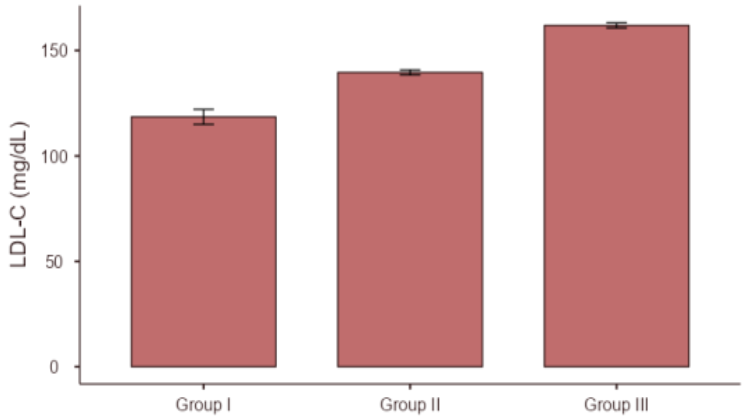

Figure (5): Bar plot showing LDL levels among the studied groups.

DISCUSSION

Groups II and III in the current study had significantly higher ages than group I, however there was no significant difference in sex.

This was consistent with a research conducted by **Borai et al. [14]** on 87 NAFLD patients (31 with grade, 26 with grade 2, and 30 with grade 3), along with 47 controls. According to their report, group II and III had significantly greater ages than group I.

Awad et al. [15] prospective case-control study of our results were confirmed by 80 children (20 obese without NAFLD, 40 with NAFLD, and 20 healthy controls). They demonstrated that, in comparison to controls, obese patients with NAFLD had considerably higher mean age values. Furthermore, when comparing obese children and adolescents with NAFLD to controls, there was a slight male predominance.

Since total cholesterol, triglycerides, and LDL levels rise with disease severity, our study showed a significant difference across NAFLD

degrees in terms of lipid profile, with group III having greater levels than the other groups.

Catena et al. [1] showed that steatosis patients had significantly higher levels of LDL cholesterol, triglycerides, and cholesterol than non-steatosis patients, which supported our findings.

This was in line with research by **Borai et al. [14],** who discovered that grade 3 pupils had higher levels of LDL, triacylglycerol, and total cholesterol than did grade 2 and 1.

DU et al. [16] conducted a study on 70 people with an ultrasound diagnosis of NAFLD, which supported our findings. Of 70 cases with an ultrasonography-diagnosed NAFLD, 47.15% had grade I NAFLD, 42.85% had grade II, and 10% had grade III. They discovered a strong correlation between rising LDL and total cholesterol levels and rising NAFLD grades.

ESD, EDD, ESV, and EDV were higher in group III than in the other groups, indicating a significant difference in NAFLD degrees with respect to echocardiographic functions in our investigation.

This was consistent with the findings of **Hegazy et al. [17],** who discovered that the NAFLD group's post-procedural LVEF was considerably lower than that of the non-NAFLD group. Additionally, NAFLD patients had a considerably poorer LVEF than the control group, according to **Yong et al. [18].**

Furthermore, group NAFLD, High Fibrosis Score (≥−1.455) had greater LVEDV, E/e', and LAstiff than group NAFLD, Low Fibrosis Score (<−1.455), according to **Lai et al. [19]**. NAFLD groups had lower LV GLS than controls.

ESD, EDD, E/A ratio, and left atrial volume were all considerably larger in steatosis patients than in non-steatosis patients, but e' velocity was significantly lower in steatosis patients than in non-steatosis patients, according to **Catena et al. [1].** LVEF and the E/e' ratio, however, did not differ significantly between the groups.

Independent of other variables, GLS was favorably correlated with HTN and negatively correlated with NAFLD grades in this investigation. Systolic dysfunction in the groups under study can be predicted using HTN and NAFLD grades as independent variables. Increased iron storage and impaired iron metabolism, which are commonly seen in NAFLD patients, may cause oxidative stress and negatively impact cardiovascular functioning [20]. Additionally, a prothrombotic state commonly found in fatty liver patients may play a role in the onset and advancement of heart injury associated with hypertension [21].

Skouloudi et al. [22] who studied 135 cirrhotic individuals, provided evidence for this. They demonstrated that individuals with a Model for End Stage Liver Disease (MELD) score of ≥15 had a greater LV-GLS than those with a MELD score of <15.

Similarly, a prospective analysis of 95 individuals with ultrasound-diagnosed NAFLD undergoing echocardiographic examination was carried out by **Armandi et al. [23].** They demonstrated that both diastolic and systolic dysfunction were associated with greater Fibrosis-4 score levels.

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CONCLUSION :

Since NAFLD grades were linked to poor GLS (systolic dysfunction), there was a substantial correlation between NAFLD and cardiac systolic dysfunction in asymptomatic patients.

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