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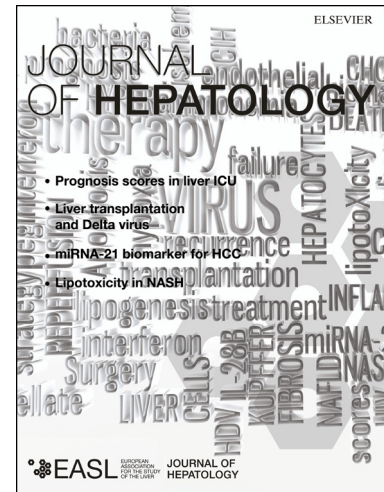
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TITLE: **Epicardial Fat, Cardiac Geometry and Cardiac Function in Patients with Nonalcoholic Fatty Liver Disease: Association with the Severity of Liver Disease**

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ABBREVIATIONS: NAFLD : nonalcoholic fatty liver disease; NASH: nonalcoholic steatohepatitis.

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Abstract

Background and Aims: Nonalcoholic fatty liver disease (NAFLD) has been associated with increased cardiovascular risk, including coronary artery disease and cardiac dysfunction. In addition, recent evidence highlighted the possible role of epicardial fat as a new cardiometabolic risk factor. We tested the correlation between epicardial fat, alterations in cardiac geometry and function and the severity of liver damage in patients with biopsy-proven NAFLD.

Methods: The anthropometric, biochemical and metabolic features were recorded in 147 consecutive biopsy-proven NAFLD cases (Kleiner score). Epicardial fat thickness was measured by echocardiography.

Results: Epicardial fat was higher in patients with severe vs. milder fibrosis (8.5±3.0 vs. 7.2±2.3 mm; p=0.006); this association was maintained at multivariate logistic regression analysis (OR 1.22, 95%C.I. 1.01-1.47; p=0.04) after correction for gender, age>50 years, visceral obesity, IFG/diabetes, non-alcoholic steatohepatitis and severe steatosis. Of note 37.1% of patients with epicardial fat >7mm (median value) had severe liver fibrosis, compared to 18.3% of cases with lower epicardial fat (p=0.01). As for echocardiographic indices, after adjusting for cardiometabolic confounders, diastolic posterior-wall thickness (p=0.01), left ventricular mass (p=0.03), relative wall thickness (p=0.02), and left atrial volume (0.04), as well as ejection fraction (p=0.004), lower lateral TDI e' (p=0.009), E/A ratio (0.04) (cardiac geometry alterations and diastolic dysfunction) were linked to severe liver fibrosis.

Conclusions: In patients with NAFLD, a higher epicardial fat thickness is associated with the severity of liver fibrosis, in keeping with a possible pathogenic role of ectopic fat depots in whole body organ damage. In addition, morphological and functional cardiac alterations are more pronounced according to the severity of fibrosis. Further studies are needed to validate our results.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) is increasing worldwide, affecting roughly 20%-30% of the general population [1]. In addition to an expected risk for disease progression from non-alcoholic steatohepatitis (NASH) to bridging fibrosis, cirrhosis and its complications [1], NAFLD patients are also at higher risk of early asymptomatic cardiovascular alterations and/or frank cardiovascular disease [2]. Specifically, NAFLD, diagnosed either by ultrasonography or by liver biopsy, has been associated with a higher prevalence of low coronary flow reserve [3], coronary calcification [4], and carotid atherosclerosis [5-7] well-before the occurrence of cardiovascular events. These alterations have been partly associated with the severity of liver damage, measured by both lobular inflammation and fibrosis. Accordingly, cross sectional studies showed an association between NAFLD and the presence/extent of coronary, cerebral and peripheral cardiovascular involvement [8], whereas longitudinal studies identified NAFLD as a risk factor for incident cardiovascular events after adjustment for cardiometabolic confounders [9].

In the last few years a number of studies also assessed the association between cardiac morphology or function, and the presence of NAFLD. Specifically, studies in small cohorts of subjects at high [10,11] or low [12] cardiometabolic risk highlighted the association of an ultrasonographic diagnosis of NAFLD, after adjustment for metabolic confounders, with a significant impairment in echocardiographic diastolic function compared to non-NAFLD cases. Along this line, a recent study on a small cohort of NAFLD patients reported significant changes in cardiac structure and function as assessed by MRI, in the absence of metabolic changes or overt cardiac disease [13]. No data were however available on the impact of the severity of liver damage on these cardiac alterations. The complex interplay between liver fat and heart function has been further demonstrated by studies reporting an association between NAFLD and epicardial fat

thickness. Epicardial fat thickness, assessed by either magnetic resonance imaging (MRI) [14] or echocardiography [15,16] was higher in NAFLD subjects compared to non-NAFLD, and a correlation was reported between epicardial fat thickness and ALT levels [17], the severity of ultrasonographic (US) [15] or MR spectroscopy [18] steatosis, and the Nonalcoholic Activity Score (NAS) in un-adjusted analyses [16].

In a consecutive cohort of patients with biopsy-proven NAFLD, we assessed whether epicardial fat is correlated to the severity of liver damage, and whether liver damage is linked to cardiac alterations in morphology and function.

Patients and Methods

Patients

The study involved 147 consecutive patients with NAFLD, recruited at the Gastrointestinal & Liver Unit of Palermo University Hospital, and fulfilling all the inclusion and exclusion criteria detailed below. Inclusion criteria were: 1) a histological diagnosis of NAFLD on a liver biopsy done less than 6 months before enrollment, showing steatosis (>5% of hepatocytes) with or without necroinflammation and/or fibrosis including cirrhosis. The pre-biopsy assessment of NAFLD was based on chronically elevated ALT for at least 6 months and alcohol consumption of <20 g/day in the year before (also confirmed by a questionnaire). Exclusion criteria were: (1) decompensated cirrhosis (jaundice, presence of ascites or encephalopathy); (2) hepatocellular carcinoma; (3) liver disease of different or mixed etiology (excessive alcohol consumption, hepatitis C, hepatitis B, autoimmune liver disease, Wilson's disease, hemochromatosis, α1-antitrypsin deficiency); (4) human immunodeficiency virus infection; (5) previous treatment with antiviral therapy, immunosuppressive drugs and/or regular use of steatosis-inducing drugs (steroid, amiodarone, tamoxifen, etc.), as assessed at interview; (6) history of heart diseases (both coronary or cardiac disease); (7) active intravenous drug addiction.

The study was carried out in accordance with the principles of the Helsinki Declaration and its appendices, and with local and national laws. Approval was obtained from the hospital's Internal Review Board and its Ethics Committee, and written informed consent was obtained from all patients.

Clinical and Laboratory Assessment

Clinical and anthropometric data were collected at the time of liver biopsy. Patients were classified as normal weight (BMI 18.5-24.9 kg/m^2), overweight (BMI 25-29.9), obese (BMI ≥30). Waist circumference (WC) was measured at the midpoint between the lower border of the rib cage and the iliac crest. Visceral obesity was diagnosed in the presence of WC ≥96 cm in males and ≥ 80 cm in females, these thresholds being well applicable to Mediterranean/European population [19]. The diagnosis of arterial hypertension was based on the following criteria: systolic blood pressure ≥140 mm Hg and/or diastolic blood pressure ≥90 mm Hg (measured three times within 30 minutes, in the sitting position and using a brachial sphygmomanometer), or use of blood-pressure-lowering agents. The diagnosis of impaired fasting glucose (IFG) and of type 2 diabetes was based on the revised criteria of the American Diabetes Association, using a value of fasting blood glucose ≥100 to <126, and ≥126 mg/dl, respectively [20]. In patients with a previous diagnosis of type 2 diabetes, current therapy with insulin or oral hypoglycemic agents was documented.

A 12-hour overnight fasting blood sample was drawn at the time of biopsy to determine the serum levels of ALT, total cholesterol, HDL-cholesterol, triglycerides, plasma glucose, insulin, and platelet count. Insulin resistance (IR) was determined according to the homeostasis model assessment (HOMA) method [21], as: Insulin resistance (HOMA-IR)= Fasting insulin (µU/mL) x Fasting glucose (mmol/L)/22.5.

Assessment of Histology

Slides were coded and read by one pathologist (D.C.), who was unaware of the patient's identity and history. A minimum length of 15 mm of biopsy specimen or the presence of at least 10 complete portal tracts was required [22]. Steatosis was assessed as the percentage of hepatocytes containing fat droplets (minimum 5%), and evaluated as continuous variable. The Kleiner classification [23] was used to grade steatosis, lobular inflammation, and hepatocellular ballooning, and to stage fibrosis from 0 to 4. NASH was considered to be present when steatosis, ballooning, and lobular inflammation were all present.

Echocardiographic assessment

Within three months from liver biopsy and before starting educational programs, all patients underwent an echocardiography examination by a single experienced observer, using a GE VIVID 7 interfaced with a 1.7/2.4 MHz phased-array probe. All recordings were digitally stored for off-line analyses by dedicated software, and were later interpreted by the same experienced cardiologist who performed the test.

M-mode echocardiograms of the left ventricle were recorded from the parasternal long-axis view guided by two-dimensional image. According to the American Society of Echocardiography (ASE) guidelines [24] the following parameters were determined: left ventricular telediastolic internal diameter (LVIDd), interventricular septum (IVSTd), and posterior wall thickness (PWTd). The relative wall thickness (RWT) was also calculated by a formula [(2XPWTd)/LVIDd)], as an index of left ventricular geometry pattern. When optimal orientation of LV M-mode ultrasound beam could not be obtained, correctly orientated linear dimension measurements were performed using two-dimensional imaging [24].

The ejection fraction (EF) was calculated at the apical four chamber views. In our laboratory the ejection fraction calculated over five consecutive beats shows optimal

reproducibility and accuracy [25]. Left atrial maximal volume was measured at the end of left ventricular systole from the apical four chamber views (by the modified Simpson rule) [24]. To quantify right ventricle size the basal right ventricle diameter was measured in the apical four-chamber view at end-diastole time.

LV mass was calculated in grams using the following formula: $0.8 \times (1.04[(LVID + IVS + PWT)^3 - LVID3]) + 0.6$. (1) LVM was normalized for height to the 2.7 power $(LVM/H^{2.7})$ [26].

The tricuspidal annular plane systolic excursion (TAPSE) was assessed in four-chamber view, placing the M-mode cursor on the lateral tricuspid annulus. The maximum plane systolic excursion of the lateral annulus was measured.

Pulsed-wave Doppler images at the level of the mitral valve tips from apical four-chambers two-dimensional views were obtained to measure flow velocities in the peak early diastolic (E-wave) and peak late diastolic (A-wave) phase, and to calculate their ratio (E/A) and the E-wave deceleration time (DTE), as measurement of diastolic filling. Each value was obtained as the average of three measurements.

Tissue Doppler Imaging (TDI) was used to measure the early peak (e') of septal and lateral mitral annulus velocities. The E/e' ratio was also calculated using the mean values of septal and lateral annulus measurements.

According to ASE Recommendations for the Evaluation of Left Ventricular Diastolic Function [27], the final assessment of diastolic dysfunction considered mitral E, E/A ratio, e' and E/e' ratio.

According to the validated Iacobellis' procedure [28], epicardial fat was measured in the parasternal long- and short-axis views that allow the most accurate measurement of epicardial adipose tissue of the right ventricle, with optimal cursor beam orientation in each view. Because it is compressed during diastole, maximum epicardial fat thickness was measured during end systole [28].

Statistics

Continuous variables were summarized as mean ± standard deviation, and categorical variables as percentage. The t-test, the chi-square test, and the ANOVA test were used when appropriate. Two multiple logistic regression models were used to assess the factors independently associated with both NASH (dependent variable, coded as 0=absent or 1=present) and severe fibrosis (coded as 0= no severe fibrosis (F0-F2) or 1=severe fibrosis (F3-F4)). The covariates for the multivariate regression analysis were gender, age ≥50 years (median value in the population), visceral obesity, impaired fasting glucose/diabetes, epicardial fat thickness, NASH (for F3-F4 fibrosis only) and grade 3 steatosis (for F3-F4 fibrosis only). They were chosen as potential confounders, based on their significance in univariate analysis and/or their biological plausibility.

Multiple linear regression models were used to assess the factors independently associated with echocardiographic features among patients stratified by NASH or F3-F4 fibrosis status. Regression analyses were performed using PROC LOGISTIC, PROC REG, and subroutines in SAS [29].

Patients

Mean age was 47 years, with a higher prevalence of males (64%). Eighty-five percent of patients fitted the criteria for visceral obesity, while IFG/diabetes, diabetes and hypertension were observed in 30%, 25% and 35% of subjects. All subjects with diabetes or hypertension were drug-treated. Mean values for total, HDL-cholesterol, and triglycerides were within the normal range, and 6% of patients were on statins.

At liver biopsy, two thirds of patients had grade 2-3 steatosis; NASH was diagnosed in 76% of cases, and finally one fourth of patients had F3-F4 fibrosis.

Epicardial fat thickness and severity of liver damage

Mean epicardial fat thickness was 7.5±2.6 mm, and significantly higher in subjects aged 50 or more (8.1±2.7 vs. 6.9±2.3 in cases less than 50, p=0.006), viscerally obese (7.8±2.5 vs. 6.2±2.4, p=0.01), hypertensive (8.2±2.5 vs 7.2±2.6, p=0.03), and statin user (9.2±2.2 vs 7.4±2.6, p=0.04) patients.

At multivariate logistic regression analysis, NASH was associated with age >50 years (OR 3.18, 95%C.I. 1.30-7.74; p=0.01) and visceral obesity (OR 5.27, 95%C.I. 1.76-15.7; p=0.003). Epicardial fat thickness did not differ according to the presence of NASH (7.6±2.5 for NASH vs. 7.4±2.7 for non-NASH, p=0.62), and the severity of steatosis (7.5±2.4 for grade 1 vs. 7.2±2.8 for grade 2, 8.0±2.6 for grade 3, p=0.43 by ANOVA).

Patients with F3-F4 fibrosis had higher epicardial fat thickness compared to their counterparts with F0-F2 fibrosis (8.5±3.0 vs. 7.2±2.3, p=0.006) (Figure 1). Of note after correction for confounders, including NASH (all patients with F3-F4 fibrosis had NASH) and severe steatosis, the association between severe fibrosis and epicardial fat was maintained (OR 1.22, 95%C.I. 1.04-1.44; p=0.01) (Table 2). Similar results were obtained when HOMA was included in the model instead of IFG/diabetes (data not shown). Of note, 37.1% of patients with epicardial fat >7 mm had severe liver fibrosis, compared to 18.3% of those with epicardial fat ≤7 mm (p=0.01). Along this line, when epicardial fat as continuous variable was replaced in the model with epicardial fat as categorical variable this last remained significantly associated with F3-F4 fibrosis (OR 2.46, 95%C.I. 1.06-5.71; p=0.03) by multivariate logistic regression analysis.

When considering statin treatment, patients taking statin had no differences in the prevalence of NASH or F2-F4 fibrosis (data not shown), but had lower ALT levels (46.6 ±20.1 vs 76.3±46.9, p=0.002)

Morphological and functional cardiac alterations in NAFLD

Several morphological and functional cardiac alterations were demonstrated in patients with NASH, compared with non-NASH. Notably, after adjustment for well-known

cardiometabolic risk factors none of the above quoted associations was maintained (Table 3).

Similarly, patients with F3-F4 fibrosis, when compared to F0-F2 fibrosis, presented a number of both morphological and functional cardiac alterations (Table 3). After correction for cardiometabolic risk factors, F3-F4 fibrosis remained associated not only with morphological alterations, like PWTd (p=0.01), LVM/H$^{2.7}$ (p=0.03), RWT (p=0.02), and left atrial volume (p=0.04), but also with functional alterations like EF (p=0.004), lower lateral TDI e' (p=0.009), lower E/A ratio (P=0.04) and marginally with E/e' (p=0.07) (Table 3). Similar results were obtained when HOMA was included in the model instead of IFG/diabetes (data not shown).

As for steatosis severity (grade 1 vs. grade 2 vs. grade 3), an association was found with LVM (p=0.04) and DTE (p=0.02), but it was not maintained after correction for cardiometabolic risk factors (p>0.10 for both).

DISCUSSION

In a western cohort of biopsy-proven NAFLD patients with a high prevalence of NASH and severe liver fibrosis, we observed that epicardial fat thickness is significantly associated with the severity of liver fibrosis, and that morphological and functional cardiac alterations by echocardiography are inversely related with the severity of liver damage. Of note, these associations were maintained after correction for both cardiometabolic and hepatic confounders.

Different lines of clinical studies showed that visceral fat [30], as well as other ectopic fat depots like the dorso-cervical fat [31], have a key role in the pathogenesis of NAFLD and especially in its histological severity. In the last years growing evidence also suggests that the increase in epicardial fat can be considered a cardiometabolic risk factor [32], being associated with the metabolic syndrome [33], with a diagnosis of NAFLD both

by US or MR spectroscopy [14-18], with carotid atherosclerosis [34] and coronary artery disease [35]. Accordingly, we confirmed the association of epicardial fat thickness with older age, visceral obesity, hypertension and statin use, well-known factors associated with an increased cardiovascular risk. To the best of our knowledge this is the first study showing an independent association between higher epicardial fat thickness and the severity of liver fibrosis in NAFLD. Of note this link was maintained after adjustment for well-known clinical and metabolic risk factors - including age, blood glucose alterations and visceral fat -, as well as histological features, like the presence of NASH and the severity of steatosis. Our findings agree with recent data from Iacobellis et al showing a direct link between epicardial fat thickness and ALT levels in a cohort of subjects with/without HIV infection and with/without metabolic syndrome [36]. However the overlap in epicardial fat thickness between our NAFLD patients with high or low hepatic fibrosis indicates that this feature is a general risk factor for NAFLD severity more than a measure to identify severe fibrosis.

This study shows that statin users had lower ALT levels compared with their counterpart, even if no differences were observed in terms of histological liver damage. Our data might suggest a protective effect of statins in NAFLD, as reported in other studies on patients taking statins for cardiometabolc disorders [37,38].

Another relevant finding of our study is the association of several indices of cardiac morphology and function with the severity of liver damage in terms of both NASH and severe liver fibrosis. Interestingly, after correction for well-known cardiometabolic risk factors (gender, age, visceral obesity, IFG/diabetes and hypertension) severe fibrosis maintained its link not only with the parameters of cardiac geometry (left atrial volume, LVM/H$^{2.7}$, PWT and RWT), but also with the indices of diastolic (lateral TDI e', E/e', E/A ratio) and systolic (EF) function. These results expand previous reports in small cohorts of NAFLD patients [10-13], reporting a significant impairment in cardiac structure and

function, as assessed by echocardiography or MRI, in clinically diagnosed NAFLD patients compared with subjects without fatty liver. Along this line, our results fit with the evidence for an association between liver injury and intima-media thickness [2], another early cardiovascular alteration, also present in NAFLD patients.

Our study is merely observational and not designed to explore the reasons for the association of epicardial fat thickness with liver fibrosis, as well as the link between cardiac alterations and the severity of liver damage in NAFLD. However, we may put forward a few hypotheses, leaving the demonstration of pathophysiological mechanisms to experimental studies. First, increased epicardial fat is able to act as a paracrince/endocrine organ and to secrete proatherogenic and proinflammatory adipokines, as tumor necrosis factor alfa, interleukin 6, interleukin 1beta and angiotensin [32]. In turn, these chemokines may activate stellate cells, leading to liver fibrogenesis. Second, the independent association between liver damage and both morphological and functional cardiac alterations might stem from the proinflammatory, proatherogenic and profibrogenic environment characterizing patients with NASH and/or advanced fibrosis. This inflammatory state might be able to act systemically, affecting the homeostasis of different organs, including the heart [2], as already demonstrated for systemic atherosclerosis and kidney damage [6,39].

From a clinical point of view and provided our data receive external validation in independent NAFLD cohorts, the present results suggest that ecocardiography might be useful in patients with steatosis for a global cardiovascular risk assessment and to detect cases needing a more intensive diagnostic and therapeutic follow-up. The reported functional and morphologic cardiac alterations observed in NAFLD patients with advanced fibrosis might have clinical relevance and impact on the future development of heart failure, arrhythmias, or other hard cardiovascular outcomes. In turn, the presence of increased epicardial fat or other cardiac alterations might identify subgroups of NAFLD patients not only at higher cardiovascular risk but also at probably higher risk of severe

liver fibrosis, where a careful assessment of liver disease might be worthy. Finally, the link between epicardial fat, cardiometabolic risk factors and severity of liver damage in NAFLD further identify in epicardial fat, together with other the well known risk factors another potential therapeutic target in NAFLD patients, these data being intriguing due to preliminary evidence showing that weight loss is able also to reduce this ectopic fat depot [40].

The study has both strengths and limits. The strength of our study lies in the availability of histological data and their correlation with epicardial fat and cardiac alterations. The main limitation is its cross-sectional nature, unable to prove the underlying pathogenic mechanisms(s) linking epicardial fat thickness and liver fibrosis, as well as cardiac alterations with the severity of liver damage. A further methodological question is the potentially limited external validity of the results for different populations and settings. Our study included a cohort of Italian NAFLD patients, largely obese, at high prevalence of NASH and severe fibrosis, who might be different, in terms of both metabolic features and of liver disease severity, from the majority of prevalent NAFLD cases in the general population. The lack of data on a control Sicilian population might further limit the strength of our results; however literature data already showed a higher epicardial fat thickness and a higher prevalence of cardiac alterations in NAFLD compared to subjects without fatty liver. The absence of an independent validation cohort further limits the significance of our results, which should be replicated in similar cohorts well characterized for both liver and cardiac damage. Finally, we also need data on serum levels and on the hepatic expression of proinflammatory and profibrogenic cytokines potentially involved in the cardiovascular alterations of NAFLD patients.

In conclusion, in a cohort of Southern-Italy NAFLD patients, we showed that epicardial fat thickness is an independent indicator of the severity of liver fibrosis, and that the presence of asymptomatic alterations in cardiac geometry and function are inversely

related to the severity of liver damage. The mechanisms underlying these associations and their long-term clinical meaning need to be further investigated.

Legend

Figure 1. Epicardial fat thickness in patients with F3-F4 liver fibrosis compared to patients with F0-F2 fibrosis.

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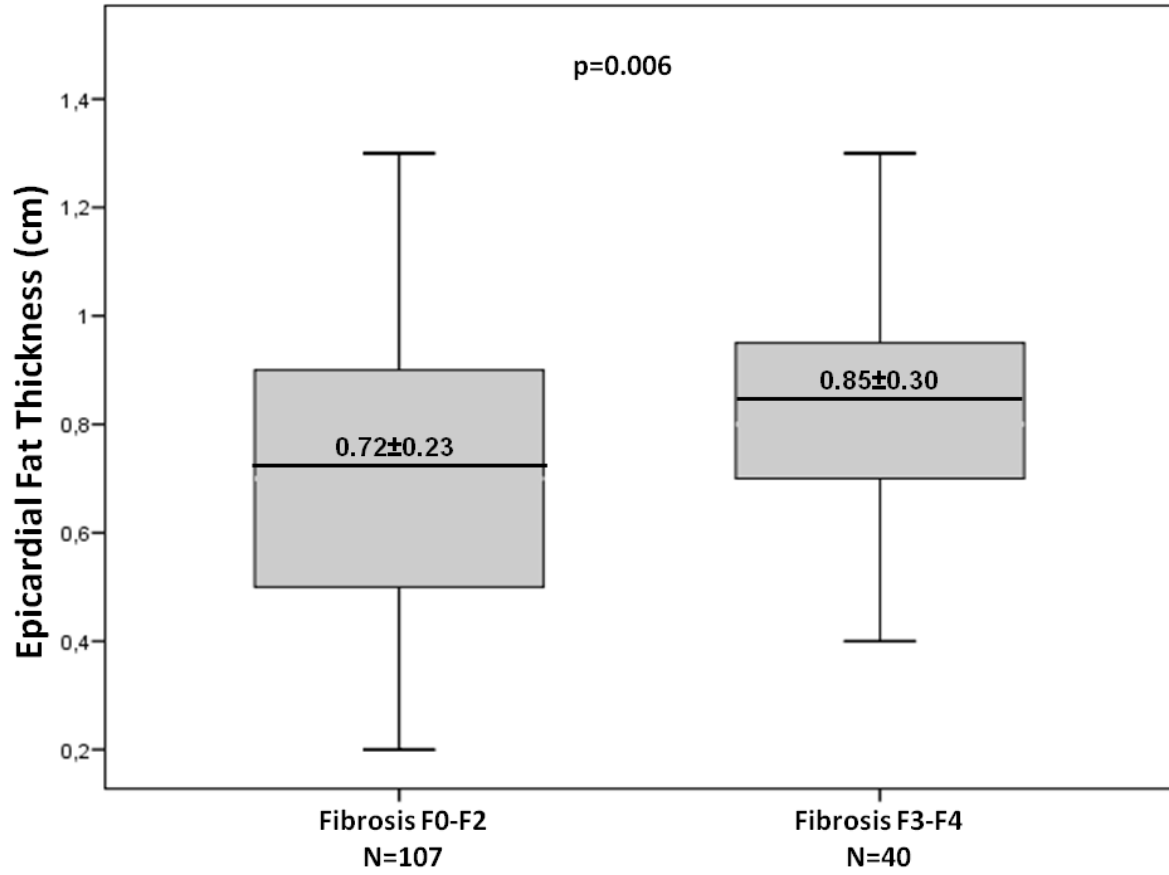
Table 1. Demographic, Laboratory, Metabolic and Histological Features of 147 Consecutive Patients with Non-alcoholic Fatty Liver Disease.

Variable	Non-alcoholic Fatty Liver Disease (n=147)
Mean age – **years**	48 ± 12
Male Gender (%)	64
Mean body mass index – **kg/m^2**	29 ± 4
Body mass index ≥30 – **kg/m^2 (%)**	43
Visceral Obesity (%)	85
Alanine aminotransferase – **IU/L**	74 ± 46
Platelet count – **10^{3}X mu/L**	231 ± 69
Cholesterol – **mg/dL**	202 ± 45
HDL cholesterol – **mg/dL**	52 ± 17
Triglycerides – **mg/dL**	136 ± 78
Blood glucose – **mg/dL**	101 ± 33
Insulin – **μU/mL**	15 ± 8
HOMA-score	3.73 ± 2.29
IFG/Type 2 diabetes (%)	30
Arterial hypertension (%)	35
Smoking (%)	24
Statin use (%)	6
Histology (%)	
Steatosis grade	
1 (5%-33%)	38
2 (>33%-66%)	37
3 (>66%)	25
Lobular inflammation	
0	7
1	52
2	34
3	7
Hepatocellular ballooning	
0	18
1	47
2	30
NASH	76
Stage of Fibrosis	
0	21
1	31
2	20
3	18
4	10

Data are given as mean ± SD or as PERCENTAGE.
HDL: high-density lipoprotein; HOMA: homeostasis model assessment; IFG: impaired fasting glucose; NASH: non-alcoholic steatohepatitis.

Table 2. Multivariate Analysis of Risk Factors Associated with Severe Liver Fibrosis (F3-F4) in 147 Patients with Non-alcoholic Fatty Liver Disease.

Variable	Multivariate Analysis	
	OR (95% CI)	*p* value
Female gender	0.59 (0.25 – 1.37)	0.22
Age >50 yrs	7.38 (2.51 – 21.6)	<0.001
Visceral Obesity	6.77 (0.80 – 57.0)	0.07
IFG/Diabetes	2.97 (1.29 – 6.80)	0.01
Epicardial fat – mm	1.22 (1.04 – 1.44)	0.01
Steatosis grade 3	1.90 (0.80 – 4.49)	0.14

IFG: impaired fasting glucose.

Table 3. Echocardiographic characteristics of NAFLD patients according to NASH and severity of fibrosis in unadjusted and adjusted models.

Variable	No NASH n=35	NASH n=112	Univariate Analysis *p* value	*p* value corrected for gender, age>50 yrs, visceral obesity, hypertension, IFG/diabetes, statin use, epicardial fat		F0-F2 Fibrosis n=107	F3-F4 Fibrosis n=40	Univariate Analysis *p* value	*p* value corrected for gender, age>50 yrs, visceral obesity, hypertension, IFG/diabetes, statin use, epicardial fat
Cardiac Morphology and Systolic Function Parameters (Indexes)									
LVIDd (cm)	4.37 ± 0.34	4.38 ± 0.39	0.84	0.32		4.39 ± 0.39	4.34 ± 0.38	0.44	0.96
IVSTd (cm)	0.85± 0.10	0.91 ± 0.15	0.02	0.11		0.88 ± 0.12	0.97 ± 0.17	0.001	0.16
PWTd (cm)	0.84 ± 0.10	0.90 ± 0.12	0.01	0.21		0.86 ± 0.10	0.96 ± 0.14	0.0001	0.01 [a]
LVM (g)	118.3 ± 28.8	131.1 ± 33.6	0.04	0.07		123.8 ± 30	139.5 ± 37.8	0.01	0.13
LVM/h^2.7 (g/m$^{2.7}$)	29.2 ± 6.9	32.7 ± 7.4	0.01	0.21		30.5 ± 6.2	35.5 ± 9.0	0.0001	0.03 [b]
RWT	0.38 ± 0.04	0.41 ± 0.06	0.02	0.25		0.39 ± 0.05	0.44 ± 0.08	0.0001	0.02 [c]
Basal RVd (cm)	2.93 ± 0.4	3.0 ± 0.3	0.27	0.68		2.96 ± 0.3	3.05 ± 0.3	0.15	0.56
Left Atrial Volume (ml)	50.3 ± 12.4	55.0 ± 13.5	0.01	0.66		51.1 ± 11.5	61.2 ± 15.2	<0.001	0.04 [d]
EF (%)	64.5 ± 3.1	63.5 ± 4.5	0.20	0.06		64.2 ± 3.4	62.4 ± 5.7	0.02	0.004 [e]
TAPSE (cm)	2.2 ± 0.2	2.2 ± 0.2	0.69	0.55		2.2 ± 0.2	2.1 ± 0.2	0.03	0.28
Cardiac Diastolic Function Parameters (Indexes)									
E vel (m/sec)	0.71 ± 0.13	0.67 ± 0.14	0.17	0.54		0.69 ± 0.13	0.64 ± 0.13	0.02	0.28
DTE (ms)	199.8 ± 41.8	220.2 ± 57.2	0.05	0.48		207.8 ± 48.1	235.4 ± 65.4	0.006	0.79
A vel (m/sec)	0.60 ± 0.15	0.67 ± 0.15	0.03	0.51		0.63 ± 0.15	0.72 ± 0.15	0.001	0.70
E/A	1.24 ± 0.38	1.06 ± 0.36	0.01	0.34		1.17 ± 0.38	0.91 ± 0.27	0.0001	0.04 [f]
Septal TDI E'	0.08 ± 0.02	0.07 ± 0.02	0.02	0.63		0.08 ± 0.02	0.06 ± 0.01	0.0001	0.11
Lateral TDI E'	0.14 ± 0.04	0.12 ± 0.03	0.004	0.13		0.13 ± 0.03	0.10 ± 0.02	0.0001	0.009 [g]
E/e'	4.8 ± 1.3	5.2 ± 1.2	0.08	0.78		4.9 ± 1.2	5.8 ± 1.4	0.002	0.07 [h]

[a] together with male gender, hypertension, IGF/diabetes; [b] together with hypertension; [c] together with hypertension, IGF/diabetes; [d] together with male gender, obesity, hypertension; [e] together with no statin use; [f] together with age>50 yrs, IGF/diabetes; [g] together with with age>50 yrs, hypertension, IGF/diabetes; [h] together with age>50 yrs, obesity.

LVIDd: left ventricular internal diameter diastolic; IVSTd: interventricular septum thickness diastolic; PWTd: posterior wall thickness diastolic; LVM: left ventricular mass; LVM/h$^{2.7}$: left ventricular mass indexed for height to the 2.7 power; RWT: relative wall thickness; Basal RVd: Basal right ventricular diameter; EF: ejection fraction; TAPSE: tricuspidal annular plane systolic excursion; E vel: peak early transmitral flow velocity; A vel: peak late transmitral flow velocity; DTE: deceleration time of E velocity; E/A: E to A ratio; TDI E': early annular diastolic tissue velocity by Tissue Doppler Imaging; E/e': E to e' ratio . IFG: impaired fasting glucose; NASH: non-alcoholic steatohepatitis.