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Subclinical and clinical atherosclerosis in non-alcoholic fatty liver disease is associated with the presence of hypertension

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Abstract *Background and aims:* Non-alcoholic fatty liver disease (NAFLD) is associated with increased cardiovascular (CV) risk. However, it is unclear whether NAFLD contributes independently to the development of CV disease. Our study aimed at assessing the differences in several indices of atherosclerosis, arterial stiffness and cardiac morphology among patients with isolated NAFLD, isolated hypertension (HT) or a combination of the two conditions.
Methods and results: A total of 169 participants (mean age = 50.4 ± 10.2 yrs; males = 73.6%) were divided according to the presence of NAFLD and HT into three groups: only NAFLD (55 patients), only HT (49 patients), and NAFLD + HT (65 patients). Exclusion criteria were a BMI≥35 kg/m^2 and a diagnosis of diabetes mellitus. Carotid ultrasonography was performed to measure markers of atherosclerosis and arterial stiffness. Cardiac remodeling was analyzed using echocardiography. The prevalence of subclinical and overt atherosclerosis was significantly higher in the NAFLD + HT patients as compared to the other two groups (atherosclerotic plaques: 43.1%, 10.9%, and 22.4% ($p < 0.001$) in NAFLD + HT, NAFLD, and HT groups, respectively). No differences were found among indices of arterial stiffening and cardiac remodeling across the three groups. In multivariate regression analysis, the coexistence of NAFLD and HT was an independent risk factor for overt atherosclerosis (OR = 4.88, CI 95% 1.14–20.93), while no association was found when either NAFLD or HT was considered alone.
Conclusion: Overt atherosclerosis was significantly present only in NAFLD + HT patients, but not in patients with isolated NAFLD. This implies that the impact of NAFLD on vascular structure and function could depend on the coexistence of other major CV risk factors, such as HT.

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1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common hepatic disease in Western countries, and it encompasses a wide range of liver diseases from simple steatosis to steatohepatitis (NASH), fibrosis, and cirrhosis [1,2]. Despite the high risk of hepatic complications, such as liver decompensation and hepatocellular carcinoma, cardiovascular (CV) disease is the leading cause of morbidity and mortality in NAFLD patients [3].

In fact, NAFLD is characterized by a higher prevalence of clinical and subclinical atherosclerosis [4–7], coronary artery disease [7,8], increased arterial stiffness [9,10], cardiac dysfunction and arrhythmia [11], increased epicardial adipose tissue (EAT) [11,12], and higher incidence of CV events, compared to the general population [4,13]. The association between NAFLD and CV disease could be partly explained by the higher prevalence of several metabolic alterations in NAFLD patients, such as obesity, hypertension (HT), dyslipidemia, insulin resistance, and type 2 diabetes mellitus (T2DM) [14,15]. Beyond this, NAFLD may foster CV damage by other mechanisms, namely hyperuricemia [16], hypoadiponectinemia [17], and pro-inflammatory and pro-coagulant state [18]. Therefore, questioning about the impact of NAFLD *itself* on CV damage, independently of the coexistence of metabolic comorbidities, is attracting interest in the literature.

A study population involving 334,280 healthy Korean subjects demonstrated that the incidence of CV events over a 5-year period was associated with the presence of NAFLD, diagnosed by the fatty liver index, independently of the presence of T2DM or HT [19]. Similarly, in a small study including 78 non-diabetic and non-hypertensive patients attending the CV department for a coronagraphic assessment, NAFLD diagnosed by US was associated with a 12-fold increased risk of having a coronary artery disease compared to non-NAFLD subjects [20]. An Italian study involving 173 T2DM patients and 183 healthy controls showed that NAFLD diagnosed by the controlled attenuation parameter at Fibroscan was associated with cardiac dysfunction irrespective of the presence of T2DM [21]. Finally, dyslipidemia treatment by lipid-lowering agents did not reduce the occurrence of CV events and CV mortality in a NAFLD population of 2566 patients over a period of 18 years [22].

Although data on the alleged role of NAFLD in CV disease development and progression are accumulating, whether NAFLD could confer an additional, and independent CV risk remains a matter of intense debate. Therefore, this study aimed to evaluate the association between NAFLD and HT, either considered alone or combined, with several CV parameters, trying to shed light on the impact of NAFLD itself on CV damage.

2. Methods

2.1. Study design and patients

This is a three centers cross-sectional study conducted from February 2018 to October 2021. A total of 169 consecutive patients referred to the outpatient hepatology clinics of the General Medicine and Liver Unit of the University Hospital of Verona (Verona, Italy), the Metabolic and Liver Disease Centre of the Policlinico Hospital of Milan (Milan, Italy), the Royal Free London NHS Foundation Trust, and Sheila Sherlock Liver Centre (London, UK) were enrolled. The study protocol was approved by the Institutional Ethics Committee of Verona and Milan (Italy) and London (UK). All patients provided written informed consent to be included in the study.

The inclusion criteria were an age between 18 and 75 years and a diagnosis of NAFLD, and/or essential HT. HT was defined as office systolic blood pressure (BP) values at least of 140 mmHg and/or diastolic BP values at least of 90 mmHg or the use of antihypertensive medications according to the last ESH/ESC guidelines [23]. BP was measured at rest, in supine position, with an oscillometric device (TM-2501, A&D instruments Ltd., Abingdon Oxford, UK). The average of 3 BP measurements performed 5 min apart was used for the analysis.

Patients with a previous diagnosis of T2DM or a body mass index (BMI) $\geq$35 kg/m^2 were excluded as well as subjects with a history of secondary HT or CV events (i.e., myocardial infarction, angina, stroke, symptomatic peripheral artery disease, or CV revascularization); likewise, patients with cirrhosis or other causes of liver disease, namely viral or autoimmune hepatitis, genetic hemochromatosis, Wilson's disease, and a1-antitrypsin deficiency, and those using drugs that potentially induced hepatic steatosis were not enrolled.

Enrolled patients were subdivided according to the presence of NAFLD and/or HT in three groups: the only NAFLD group: 55 patients; the only HT group: 49 patients; and the NAFLD + HT group: 65 patients.

At the time of study enrolment, for each participant, anthropometric measurement (height, weight, BMI, waist circumference [WC], and hip circumference), medical history, smoke habits, and use of current therapy (including antihypertensive agents and statins) were recorded.

2.2. Abdominal ultrasound (US)

For all patients, abdominal US was performed at enrolment by three (one for each center) experienced sonographers (LOGIQ P5 pro, GE, Indianapolis, USA) using a 3.5 MHz convex-array probe. Hepatic steatosis was classified as absent, mild, moderate, or severe according to the following accepted criteria: hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring [24].

In a subset of patients, visceral adipose tissue was measured by using 3.5 MHz convex-array probe as the distance between the posterior surface of the rectus abdominis muscle and the anterior wall of the aorta just above the origin of common iliac arteries [25].

2.3. Transient elastography and non-invasive fibrosis score

Hepatic fibrosis was assessed using transient elastography (FibroScan, Echosens, Paris, France) asliver stiffness

measurement (LSM) and calculating the Fibrosis-4 (FIB-4) index. Transient elastography was performed in fasting condition with the patients lying flat on the back. The probe was placed at the right upper abdominal quadrant in correspondence with the right lobe of the liver. The results were considered valid if the interquartile range did not exceed 30% of the median value, and the final LSM value was the mean of ten valid measurements [26]. The M probe was used by default, using the XL one in case of unsuccessful measurement with the former. An LSM value $\geq$ 8 kPa defined the presence of advanced fibrosis.

The FIB-4 was calculated through the following formula: age (years) $\times$ AST [U/l]/(platelets [109/l] $\times$ (ALT [U/l])1/2), and according to the literature values of $<$1.3 and $>$2.67 were considered to rule out and rule in advanced fibrosis, respectively [27].

2.4. Magnetic resonance imaging

In HT patients without steatosis at US, NAFLD was excluded by abdominal magnetic resonance imaging (MRI). Hepatic fat content was quantified by a 2D magnitude-based gradient-recalled/echo technique which estimates proton density fat fraction (PDFF), an MRI-based biomarker of liver fat content, using low fractional anisotropy (10°), relative to repetition time (125 ms). Other acquisition parameters include receiver bandwidth 6142 kHz, base matrix 224 3 124, one-signal average, rectangular field of view (FOV) adjusted to body habitus and breath-hold capacity, and a parallel imaging factor of 1.25. Cross-sectional maps depicting the PDFF of tissue are computed pixel-by-pixel from source images using custom-developed software that models observed signal as a function of time of echo (TE), considering the multiple frequency components of triglyceride (TG).

2.5. Carotid ultrasonography and pulse wave analysis

For all the patients, carotid Doppler-US was performed by the same experienced sonographers who performed steatosis assessment (LOGIQ P5 pro, GE, Indianapolis, USA) in each center. The Carotid Intima-Media Thickness (cIMT, mm) was measured with a 5–13 MHz linear-array probe at the far wall of the distal common carotid artery within 1 cm from the carotid bulb. The acquired images of both the right and left carotid arteries were processed automatically using a dedicated software (Cardiovascular Suite, Quipu, Pisa, Italy), and the final mean cIMT value was used for the analysis. Arterial plaques were defined as a focal thickening of cIMT higher than 1.5 mm or $>$50% of the surrounding values. The carotid distensibility coefficient (CD, $\times 10^{-3}$/kPa) was assessed contemporarily to the measurement of the brachial BP using an oscillometric device (TM-2501, A&D instruments Ltd., Abingdon Oxford, UK) and calculated using the following formula: CD = (ΔA/A)/PPa, where ΔA is the stroke change (i.e., distension) in common carotid artery cross-sectional area, normalized for the total diastolic common carotid artery cross-sectional luminal area (A), and PPa is the differential pressure, assuming that the artery cross-section is circular. To assess changes in the carotid diameters, several ultrasound B-mode image sequences were collected at both the right and left common carotid arteries and processed automatically using the above-mentioned software [28]. The mean CD value was used for the analysis. The carotid-femoral pulse wave velocity (cf-PWV, m/s) was measured by placing a cuff around the right femoral artery, and a tonometer at the right common carotid artery to capture both the femoral and the carotid waveforms. The length of the arteries was measured using a measuring tape. The waveform velocity was automatically computed through a dedicated device (SphygmoCor XCEL) by dividing the gap between the carotid and femoral arteries with the pulse transit time. An average of 3 measurements was used for the analysis. A value greater than 10 m/s was considered as an index of increased arterial stiffening, and thus the predictive of CV risk, according to the last ESH/ESC guidelines [23]. To derive the central systolic BP (cSBP, mmHg) using the SphygmoCor XCEL device, the cuff pulsations were recorded at the brachial artery level, and a general transfer function was applied to compute the aortic waveform. An average of 3 measurements was used for the analysis.

2.6. Echocardiography

A two-dimensional transthoracic echocardiography was performed in all participants by the same three (one for each center) experienced cardiac sonographers using a 2.5–3.5-MHz annular-array transducer. In the parasternal long axis view, B-mode images were acquired to measure diastolic interventricular septum thickness (IVS) and posterior wall thickness (PWT) as well as left ventricular end-diastolic and end-systolic diameters. Parasternal long- and short-axis views at the free wall of the right ventricle during the end of systole were measured as the maximum EAT thickness, as previously defined [29]. The mean of at least three measures was used for the analysis. A threshold value of 7.5 mm for females and 9.5 mm for males was considered as a marker of increased cardiometabolic risk according to Lacobellis et al. definition [30]. Relative wall thickness (RWT) was calculated through the following formula (PWT*2)/end-diastolic diameter and considered as a marker of left ventricular concentric remodeling if $>$0.42 [31]. Devereux equation was used to calculate left ventricular mass (LVM) (LVM = 0.80*1.04 [(end-diastolic diameter+PWT+ IVS)3–end-diastolic diameter3] + 0.6 g) [32], then indexed (LVMi) to body surface area (obtained with the Mosteller formula). A LVMi greater than 95 g/m^2 in females or 115 g/m^2 in men in the presence of a RWT $>$ 0.42 was considered diagnostic of concentric cardiac hypertrophy [33].

2.7. Statistical analysis

Continuous variables are presented as mean $\pm$ standard deviation or median (interquartile range) based on data

Table 1 Anamnestic and demographic data of the 169 enrolled patients divided according to the presence of NAFLD and/or hypertension.

	NAFLD (n° 55)	HT (n° 49)	NAFLD + HT (n° 65)	ANOVA p-value
Age (years)	46.9 ± 10.8	48.4 ± 12.1	55.9 ± 7.8	**<0.001**^^
Males, n (%)	48 (87.3)	30 (61.2)	47 (72.3)	**0.01***
Smoke, n (%)	12 (21.8)	9 (18.4)	8 (12.3)	0.374
Dyslipidemia, n (%)	26 (47.3)	6 (12.2)	31 (47.7)	**<0.001**°
Use of statins, n (%)	3 (5.5)	5 (10.2)	12 (18.5)	0.084
IFG, n (%)	4 (7.3)	4 (8.2)	9 (13.8)	0.428
Metabolic syndrome, n (%)	6 (10.9)	1 (2.0)	28 (43.1)	**<0.001**^^

NAFLD, non-alcoholic fatty liver disease; HT, hypertension; IFG, impaired fasting glucose.
Tukey post-hoc test at one-way ANOVA: ^^, NAFLD + HT significantly different compared to NAFLD and HT; *, NAFLD significantly different compared to both NALFD+HT and HT; °, HT significantly different compared to both NAFLD and NAFLD + HT.

Table 2 Anthropometric variables and indices of visceral adiposity of the 169 enrolled patients divided according to the presence of NAFLD and/or hypertension.

	NAFLD (n° 55)	HT (n° 49)	NAFLD + HT (n° 65)	ANOVA p-value
Body mass index (kg/m^2)	26.3 ± 2.5	23.5 ± 2.8	28.3 ± 3.4	**<0.001**^^,*,°
30 kg/m^2 ≥ BMI < 35 kg/m^2, n (%)	4 (7.3)	1 (2.0)	19 (29.2)	**<0.001**^
Waist circumference (cm)	97.0 ± 8.4	85.1 ± 10.6	102.4 ± 10.1	**<0.001**^^,*,°
>80 cm in females or >94 cm in males, n (%)	37 (67.3)	14 (28.6)	56 (86.2)	**<0.001**°
Visceral adipose tissue (mm)	56.7 ± 19.8	35.3 ± 17.1	55.3 ± 21.8	**<0.001**°
Epicardial adipose tissue (mm)	5.1 (4.0–6.6)	5.0 (4.0–5.8)	6.0 (5.0–8.0)	**<0.001**^^
>7.5 mm in females or >9.5 mm in males, n (%)[a]	6 (10.9)	1 (2.0)	11 (16.9)	**0.03**°

Legend: NAFLD, non-alcoholic fatty liver disease; HT, hypertension.
Tukey post-hoc test at one-way ANOVA: ^^, NAFLD + HT significantly different compared to NAFLD and HT; *, NAFLD significantly different compared to both NALFD + HT and HT; °, HT significantly different compared to both NAFLD and NAFLD + HT.
[a] Epicardial adipose tissue thickness measured according to Iacobellis definition https://doi.org/10.1016/j.echo.2009.10.013.

distribution. Categorical variables are expressed as percentages. Either one-way ANOVA or Kruskal–Wallis one-way ANOVA was used to compare continuous variables according to the data distribution pattern (normal or not). Categorical variables were compared using the chi-square test. Logistic multivariate regression analyses were performed to determine if any anamnestic or clinical variables (a diagnosis of NAFLD or HT, either alone or combined; age; sex; smoke habits; statins usage; BMI; LSM, either as continuous or categorical variable [greater than 8.0 kPa]; and cSBP or peripheral SBP) could be independently associated with any markers of subclinical or clinical atherosclerosis (cIMT ≥ 0.9 mm, presence of carotid plaques), arterial stiffness (cf-PWV ≥ 10 m/s), cardiac remodeling (RWT > 0.42, concentric hypertrophy), or increased EAT (greater than 7.5 mm in females or 9.5 mm in men). The variable selection was done through sequential replacement (a stepwise method) which consists of a combination of backward and forward techniques. If the p-value was less than 0.05 or above 0.1 the covariates were, respectively, included and excluded from the regression model. No fixed variables were considered [34]. Statistical package for social science (SPSS) version 22 was used for all data analysis. All tests were 2-sided, and p-values <0.05 were considered statistically significant.

3. Results

The demographic and anamnestic characteristics of the study population are shown in Table 1. Patients with NAFLD + HT were significantly older than the others, while in the group with only NAFLD, the percentage of males was higher as compared with the other two groups. No differences were found in smoke habit and statin use between the three groups, despite a lower prevalence of dyslipidemia in the only HT group.

Regarding anthropometric variables and indexes of visceral adiposity (Table 2), only HT patients presented lower BMI, WC, visceral adipose tissue, as well as lower frequency of increased EAT compared to the other two groups. In stepwise multivariate logistic regression analysis, none of the above-mentioned variables was significantly associated with an increase in EAT above 7.5 mm in females or 9.5 mm in men (data not shown).

Regarding liver disease, as expected the NAFLD + HT group and the only NAFLD group presented higher values of LSM compared to the only HT group, whereas the NAFLD + HT group presented significantly higher FIB-4-index values as compared with the only NAFLD and only HT groups (Table 3). Nevertheless, the prevalence of advanced hepatic fibrosis was overall low as only 7 patients in the NAFLD + HT group, and 1 in the only NAFLD

Table 3 Hepatic fibrosis assessment of the 169 enrolled patients divided according to the presence of NAFLD and/or hypertension.

	NAFLD (n° 55)	HT (n° 49)	NAFLD + HT (n° 65)	ANOVA p-value
Liver stiffness measurement (kPa)	5.2 ± 1.6	4.4 ± 0.9	5.7 ± 1.9	**0.01**[#]
> 8 kPa, n (%)	1 (1.8)	0	7 (10.8)	**0.02**[^]
FIB 4 − index	0.99 ± 0.33	0.96 ± 0.55	1.28 ± 0.48	**0.001**[^^]
≤1.3, n (%)	45 (81.8)	40 (81.6)	35 (53.8)	**0.002**[^^]
≥2.67, n (%)	0	0	1 (1.5)	0.562

NAFLD, non-alcoholic fatty liver disease; HT, hypertension; kPa, kilopascal; FIB4, Fibrosis 4.
Tukey post-hoc test at one-way ANOVA: #, NAFLD + HT significantly different compared to HT; ^^, NAFLD + HT significantly different compared to NAFLD and HT.

Table 4 Cardiovascular parameters of the 169 enrolled patients divided according to the presence of NAFLD and/or hypertension.

	NAFLD (n° 55)	HT (n° 49)	NAFLD + HT (n° 65)	ANOVA p-value
Blood pressure				
Systolic BP (mmHg)	125 ± 11	137 ± 14	135 ± 14	**< 0.001**[*]
Diastolic BP (mmHg)	78 ± 7	85 ± 10	83 ± 8	**< 0.001**[*]
Central systolic BP (mmHg)	119 ± 12	130 ± 13	130 ± 16	**< 0.001**[*]
cCD (kPa^{-1} 10^{-3})	22.9 ± 6.6	21.4 ± 6.5	20.1 ± 6.5	0.094
Vascular parameters				
PWV (m/s)	7.4±1.0	7.8±1.5	8.3±2.3	**0.03**[^]
> 10 m/s, n (%)[a]	0	3 (6.1)	6 (9.2)	0.085
cIMT (mm)	0.68±0.12	0.65±0.14	0.79±0.18	**< 0.001**[^^]
> 0.9 mm, n (%)	2 (3.6)	3 (6.1)	13 (20)	**< 0.007**[^]
Carotid plaques (%)	6 (10.9)	11 (22.4)	28 (43.1)	**< 0.001**[^^]
Cardiac parameters				
LVMi (g/m^2)	74.7 (62.7–90.6)	89.6 (70.6–104.9)	73.9 (58.8–89.5)	**0.03**[#]
RWT > 0.42	17 (30.9)	17 (34.7)	22 (33.8)	0.216
Concentric hypertrophy, n (%)	2 (3.7)	1 (2.0)	6 (9.2)	0.711
E/A	1.2 (0.9–1.4)	1.0 (0.8–1.4)	0.9 (0.8–1.2)	**0.01**[^]
TAPSE (mm)	23.0 (20.0–26.5)	22.9 (21.0–26.0)	22.0 (20.0–24.5)	0.378

NAFLD, non-alcoholic fatty liver disease; HT, hypertension; BP, blood pressure; cCD, carotid distensibility coefficient; cIMT, carotid intima media thickness; PWV, pulse wave velocity; LVMi, left ventricular mass index; RWT, relative wall thickness; TAPSE, tricuspid annular plane systolic excursion.
Tukey post-hoc test at one-way ANOVA: *, NAFLD significantly different compared to both NAFLD + HT and HT; ^, NAFLD + HT significantly different compared to NAFLD; ^^, NAFLD + HT significantly different compared to NAFLD and HT.
[a] PWV > 10 m/s according to 2018 ESC/ESH Clinical Practice Guidelines for the Management of Arterial Hypertension.

Table 5 Determinants of clinical atherosclerosis (carotid plaques) in stepwise multivariate logistic regression analysis in the overall population.

		Odds ratio	CI 95%	p-value	R^2
Age (years)	**Carotid plaques**	1.066	1.007–1.129	**0.03**	**0.44**
Use of statins (%)		0.100	0.022–0.485	**0.004**	
Systolic blood pressure (mmHg)		1.050	1.013–1.089	**0.008**	
Group membership					
HT		-	-	-	
NAFLD		0.859	0.178–4.136	**0.85**	
NAFLD + HT		4.882	1.139–20.932	**0.03**	

NAFLD, non-alcoholic fatty liver disease; HT, hypertension; CI, confidence interval.
After adjustment for: age, sex, body mass index, group membership, use of statins, smoke, liver stiffness measurement, central systolic blood pressure, epicardial adipose tissue.

group showed LSM values greater than 8 kPa. Similarly, a FIB4 index above 2.67 was found only in 1 patient in the NAFLD + HT group.

Considering CV variables (Table 4), in the NAFLD + HT group, the prevalence of both subclinical and overt atherosclerosis was higher with respect to the other two groups, as confirmed by greater percentage of patients with a cIMT above 0.9 mm and carrying carotid plaques. No significant differences were found among indices of conduit arteries stiffening (either cf-PWV greater than 10 m/s or CD) as well as cardiac remodeling (prevalence of concentric hypertrophy or RWT > 0.42) across groups. However, it is noteworthy to stress that alterations in very early markers of subclinical atherosclerosis, namely carotid

distensibility and cf-PWV, did not differ between the only NAFLD group and the only HT groups.

In stepwise multivariate logistic regression analysis, the coexistence of NAFLD + HT was independently associated with the presence of atherosclerotic plaques (OR = 4.88, 95% CI 1.14–20.93), while no association was found when NAFLD or HT were considered alone (Table 5). Other variables independently associated with overt atherosclerosis were age and cSBP, whereas the use of statins resulted in a protective factor. Conversely, when considering subclinical atherosclerosis as represented by cIMT greater than 0.9 mm, the association of NAFLD and HT (either alone or combined) was no longer significant in multivariate analysis, being age the only independent risk factor (data not shown). Similarly, none of the indices of arterial stiffness and cardiac remodeling was associated with neither NAFLD and HT (either alone or combined) nor with any other anamnestic or clinical variable (data not shown).

4. Discussion

Our study shows that NAFLD is associated with subclinical and clinical atherosclerosis, especially when coexisting with HT. Most interestingly, the association of NAFLD and HT seems to amplify the CV damage, with a nearly 5-fold increased risk of carotid plaques compared to NAFLD patients without HT and hypertensive patients without NAFLD.

HT or even high-normal BP is an important component of the metabolic syndrome, and it is also a well-established CV risk factor, usually strictly associated with NAFLD. About 55% of hypertensive patients are affected by NAFLD [35], while HT prevalence is higher in NAFLD patients than in the general population [36]. Moreover, prospective studies showed that NAFLD is associated with an increased risk of developing HT [37–39] and that HT is an independent predictor of NAFLD itself [40–46]. Given the strict association between NAFLD and MS, including HT, it is difficult to dissect how much NAFLD can affect CV damage, irrespective of the other MS components. Thus, we carefully selected three different groups of patients: one with only HT (NAFLD was excluded with MRI), one with only NAFLD, and one in which both HT and NAFLD were present. Moreover, we excluded two major CV risk factors that might act as confounders selecting only non-diabetic and non-severely obese patients.

We found that indices of subclinical and overt atherosclerosis were more pronounced in the NAFLD + HT group, where the prevalence of cIMT $\geq$ 0.9 mm and carotid plaques were significantly higher compared to those patients presenting with only NAFLD or HT. In multivariate analysis, the coexistence of NAFLD and HT, but not the presence of isolated NAFLD or HT, was an independent risk factor for carotid plaques. On the other hand, we did not notice a difference in the prevalence of subclinical and overt atherosclerosis as well as in increased conduit artery stiffening between NAFLD and hypertensive patients. Anyhow, the relatively young age of both groups may justify the absence of a significant CV burden, whereas the small sample size of both groups may have blurred some differences. Therefore, our results may hypothesize on the fact that while isolated, NAFLD and HT may promote the onset of very early vascular alterations they are able to create an evident vascular damage only when coexist, speculating on their synergistic effect. The association between NAFLD and both atherosclerosis and arterial stiffness is well established as depicted by the Multi-Ethnic Study of Atherosclerosis cohort, where the presence of NAFLD was associated with a higher CD and cIMT [47] or by a more recent study, where NAFLD was significantly associated with overt carotid atherosclerosis and arterial stiffness [48]. Furthermore, other observational studies reported that NAFLD led to an increased risk of endothelial dysfunction and atherosclerosis in adult male patients, independently of MS [49,50]. However, conversely to our study design, those studies were not specifically designed to investigate the impact of NAFLD on CV damage irrespective of other cardiometabolic comorbidities, and in particular, of HT. Indeed, since our results show no association between isolated NAFLD and carotid plaques, they seem apparently in contrast with those of a recent retrospective study of 14,288 adults reporting a higher risk of carotid plaques in NAFLD subjects compared to patients without NAFLD. However, also in that study, after adjustment for other potential confounders, HT was the only significant independent risk factor for atherosclerosis in NAFLD participants with hepatic fibrosis [51]. Moreover, Perticone and colleagues [52] demonstrated that in hypertensive patients with MS and NAFLD, the endothelium-dependent vasodilation was worse than in patients without HT. On the other hand, our data are in line with those reported by Styczyński et al., who explored the independent role of NAFLD in determining CV damage and concluded that in biopsy-proven NAFLD patients arterial stiffness was driven by cardiometabolic comorbidities, including HT, rather than liver disease itself [53]. Similarly, in a sample of patients affected by essential HT, the presence of NAFLD was not associated with increased arterial stiffness [54]. Indeed, the higher atherosclerotic burden of our population seems to be associated with the coexistence of NAFLD and HT in line with the hypothesis that NAFLD could amplify rather than provoke the vascular damage leading to CV disease. However, it is worth underlying that several studies pointed out that also the degree of liver fibrosis is a strong predictor of CV disease severity in NAFLD patients [6,55–57]. Unfortunately, in our study, the number of patients with a high value of hepatic fibrosis (LSM $\geq$ 8 kPa) was low (10%), and all patients had coexisting HT, thus making impossible a direct evaluation of the deleterious independent effect of liver fibrosis on CV structure and function. However, the young age of selected patients and the exclusion of risk factors for advanced fibrosis, such as diabetes and obesity, may explain this data. Finally, despite the supposed independent role of NAFLD on cardiac dysfunction and remodeling [58–60], in our sample, the echocardiographic measures obtained were mostly in the normal range, and no huge differences in heart geometry or function were documented across groups. We hypothesize that the absence of significant hepatic fibrosis and the fact that

CV risk factors, including HT, were efficaciously treated, as represented by mean BP values only slightly increased, can explain these findings. Interestingly enough, EAT seems to be strongly associated with NAFLD and other CV risk factors [61], and as described by Fracanzani et al., EAT was independently associated with both NASH ($p = 0.04$) and fibrosis ($p = 0.02$) [12]. Similarly, in our sample, EAT seems mostly related to NAFLD presence regardless of the presence of HT. These associations were not confirmed in multivariate analysis, possibly because of the low prevalence of increased EAT in our cohort.

To the best of our knowledge, this is the first time that an extensive evaluation of CV damage in carefully selected NAFLD subjects, with the exclusion of severely obese and diabetic patients, has been performed, since the independent role of NAFLD, either considered alone or combined with other HT, on CV disease has never been confirmed [36]. Indeed, the main strengths of our study are the accuracy of cases selection, since NAFLD was excluded by abdominal MRI, considered the gold standard approach, the use of non-invasive, largely applicable and accurate techniques to evaluate vascular and cardiac damage and the wide and complete CV characterization of our sample. Anyhow, our study has limitations, such as the relatively low sample size, the cross-sectional design, the relatively young age of the enrolled patients, and the low prevalence of liver fibrosis that could have contributed to the relatively low burden of CV damage, especially in NAFLD patients without HT. Nevertheless, age is a known risk factor for the development of metabolic alterations, the progression of liver disease to fibrosis and the onset of established CV damage, so that a young age in our carefully selected cohort could be justified. Moreover, the use of not widely available devices, such as transient elastography or MRI, in order to evaluate NAFLD patients, may limit the application of results to small centers. However, our first aim is to obtain information about the possible pathophysiological mechanisms underpinning the CV damage in this category of patients.

In conclusion, our study shows that when NAFLD and HT are not combined, they are seldom associated with CV organ damage, whereas when the two factors coexist, the CV damage becomes glaring. This implies that the impact of NAFLD on the vascular structure could depend on the coexistence of other major CV risk factors, such as HT, and for sure, further studies are warranted to confirm our results in prospective wider cohort and explore the role of NAFLD in combination also with other metabolic alterations. If, on the one hand, our study should encourage clinicians to search for CV damage, especially when NAFLD and HT are associated, on the other, our results would imply a change in the management of the CV risk in NAFLD patients. Indeed, applying prevention strategies aimed at controlling comorbidities may avert the development of an established CV damage in this category of patients.

Author contributions

Conceptualization, FC, RL, AD; methodology, FC, AD; validation, RL, AF, ET; formal analysis, FC, MB; investigation, FC, MB, MZ, LIP, LF, AC; data curation, LIP, LF, FC, AC; writing—original draft preparation, FC, RL, AM, AD; writing—review and editing, FC, RL, CF, AD; visualization, DS, AF, ET; supervision, ET, DS, CF; project administration, CF, AD. All authors have read and agreed to the published version of the manuscript".

Informed consent statement

Informed consent was obtained from all subjects involved in the study.

Declaration of competing interest

None.

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