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Reply to "Establishing the independence and clinical importance of non-alcoholic fatty liver disease as a risk factor for cardiovascular disease"

To the Editor:

We kindly thank Drs. Chimakurthi and Rowe for their thoughtful comments. Waist circumference, an anthropometric measure of abdominal obesity, is known to be associated with cardiovascular (CV) risk, independent of classical risk factors, as suggested by a recent analysis of the Emerging Risk Factors Collaboration [1], but do not significantly add to the prediction accuracy of CV risk models. As waist circumference is a surrogate of hepatic steatosis, the authors suggest that the association between steatosis and increased CV risk only reflects the impact of visceral adiposity on the CV risk.

Overall, we agree that it is difficult to determine the specific contribution of NAFLD to the increase in CV risk because NAFLD patients have cardiometabolic risk factors that confound this association. Waist circumference is an imperfect clinical marker of visceral adiposity, as it can be influenced by sex, race [2,3] and subcutaneous fat. It correlates poorly with visceral fat, when measured by CT-scan, in different ethnic groups [4,5]. Interestingly, in our cohort, waist circumference was an independent predictor of CV risk in patients without steatosis, but not in patients with steatosis (Table 1A, transversal cohort). When adjusting for classical CV risk factors, steatosis was still an independent predictor of CV risk in patients with BMI $\leqslant$25 kg/m^2 (beta = 0.051, p = 0.035) or with normal waist (beta = 0.067, p = 0.003). Moreover, in our longitudinal cohort, steatosis, but not waist circumference, predicted the occurrence of carotid plaques during follow-up (Table 1B, longitudinal cohort).

An argument in favor of NAFLD as an independent contributor to accelerated atherosclerosis, is the recent demonstration that resolution of NAFLD resulted in regression or a lower progression rate of atherosclerosis. In a sub-analysis of the Welcome trial, Bhatia *et al.*, demonstrated that regression of steatosis (assessed by magnetic resonance spectroscopy) and steatohepatitis (as assessed by serum CK18 fragments) were independently associated with lower carotid intima-media thickness (C-IMT) progression rate, even after adjustment for confounders, including standard CV risk factors, weight changes and specific medication use [6]. Conversely, a recent study of 8020 healthy Korean men has shown that persistent NAFLD (defined by ultrasound) during follow-up was associated with a higher risk of developing carotid plaques even after adjustment for smoking, alcohol, BMI and weight change [7].

Our results favor screening for CV disease in patients with NAFLD, a recommendation made by the recent European Association for the Study of the Liver (EASL) clinical practice guidelines. Whether adding NAFLD to existent CV risk scores will improve prediction remains to be proven by long-term, prospective, follow-up studies. A relevant question will then be to determine which of the histological lesions defining NAFLD (steatosis, steatohepatitis or fibrosis) adds significantly to the prediction value of established CV risk models. While hepatic steatosis seems to be associated with early atherosclerosis but not with clinical CV events [8], liver fibrosis impacts long-term CV outcomes [9,10]. Since current guidelines do not recommend that patients at risk of CV disease should be screened for NAFLD, these issues deserve to be explored thoroughly in future studies.

Table 1. Cardiovascular risk factors. (A) Transversal cohort: Independent predictors of C-IMT in patients with and without steatosis. (B) Longitudinal cohort: Independent predictors of the occurrence of carotid plaques in Cox multivariate models.

	A Transversal cohort (N = 5671)				**B** Longitudinal cohort (N = 1872)			
	C-IMT				Occurrence of carotid plaques during follow-up			
	With steatosis		Without steatosis		Model 1		Model 2*	
Variable	Beta	*p* value	Beta	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age	0.368	<0.001	0.418	<0.001	1.01 (0.98-1.03)	0.35	1.007 (0.98-1.02)	0.51
Male sex	0.114	<0.001	0.094	<0.001	0.61 (0.43-0.88)	0.008	0.56 (0.36-0.87)	0.011
Tobacco	0.001	0.97	0.021	0.236	1.10 (0.78-1.55)	0.57	1.14 (0.80-1.62)	0.45
High blood pressure	0.092	<0.001	0.049	0.005	1.04 (0.73-1.47)	0.81	1.03 (0.72-1.47)	0.85
Type 2 diabetes	-0.026	0.296	0.032	0.062	0.84 (0.54-1.33)	0.47	0.81 (0.51-1.29)	0.38
hsCRP	0.039	0.127	0.021	0.235	0.95 (0.89-1.01)	0.14	0.94 (0.88-1.01)	0.12
Baseline C-IMT	-	-	-	-	2.21 (0.67-7.25)	0.18	2.51 (0.76-8.31)	0.13
Steatosis at baseline	-	-	-	-	1.63 (1.10-2.41)	0.014	-	-
BMI	-0.002	0.967	0.047	0.073			0.99 (0.92-1.08)	0.97
Waist circumference	0.036	0.351	0.076	0.009			1.008 (0.97-1.03)	0.61
Triglycerides	0.005	0.853	-0.026	0.133			1.04 (0.98-1.09)	0.12
GGT	-0.010	0.678	-0.003	0.863			1.001 (0.99-1.004)	0.62

Model 2* – FLI was replaced by its components.

Conflict of interest

The authors declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

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A strong message is needed to address the issue of HCC recurrence after DAA therapy

To the Editor:

We read the article from the ANRS collaborative study group on hepatocellular carcinoma (HCC) [1] with great interest, as it provides data that support the notion that patients with a history of treated HCC do not have an increased risk for recurrence when treated with direct-acting antivirals (DAAs). This article follows the investigations from Reig *et al.* and Buonfiglioli *et al.*, who reported an unexpected early HCC recurrence in patients treated with DAAs [2,3]. Reig *et al.* noted this trend to be increased when the DAA treatment was taken in the 4 months following HCC treatment, which makes this particular time frame of most interest. These analyses have limitations as acknowledged by the authors themselves and as reported by others [4,5]. Among these are the small number of patients and the absence of comparison arms. However, it was important to publish these findings to alert other centers to investigate this issue.

In the current state of knowledge, this important issue remains unclear and well-designed studies with proper comparison arms are required to determine the effect of DAAs on HCC recurrence. For this purpose, the ANRS collaborative study group on HCC used three French cohorts to investigate the effect of DAAs on HCC recurrence. The HEPATHER cohort provided the opportunity to study a significantly larger group of patients who were HCV-infected with a history for treated HCC (n = 267) than previously published; of whom, 189 had been treated with a DAA. The author found no difference in HCC recurrence rates between treated and untreated patients with DAAs. In our opinion, some points merit further comment.

Almost two-thirds of the cohort were diagnosed with HCC more than 1 year before inclusion in the cohort (65.5% [n = 175] >1 year; 34.8% [n = 93] >3 years). As the analysis only began at the time of inclusion in the cohort, the study misses – for most of the patients – the particular time frame, identified by Reig *et al.*, at which patients seem to be at risk for HCC recurrence. This may lead to potential underestimation of recurrences in the treated group. Furthermore, it has the potential to lower the rate of HCC recurrence by ignoring patients who had HCC recurrence and died before inclusion, since these patients were specifically excluded from the cohort.

In the survival analysis (Fig. 1 of the article), it seems that the whole cohort is included in the untreated group, and that patients were censored as they received DAA treatment. This methodology may artificially decrease the rate of HCC recurrence that arises in patients not receiving DAA therapy.

Finally, the information given about the radiological assessment of the liver is limited. It would be very interesting to know what the delay was between the last radiological assessment and the beginning of DAA treatment.

We congratulate the ANRS collaborative study group on HCC for providing further information about the important issue of