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Simplified follow-up of patients with mild chronic hepatitis C in areas with limited access to antiviral therapy

Sabela Lens[a,*], Ferran Torres[b,c], Martin Bonacci[a], Concepció Bartres[a], Anna Pocurull[a], Zoe Mariño[a], María-Carlota Londoño[a], Sergio Rodríguez-Tajes[a], Xavier Forns[a]

[a] Liver Unit, Hospital Clinic, IDIBAPS, CIBEREHD, University of Barcelona, Barcelona, Spain
[b] Biostatistics and Data Management Platform, IDIBAPS, Hospital Clinic, Barcelona, Spain
[c] Biostatistics Unit, Autonomous University of Barcelona, Barcelona, Spain

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ABSTRACT

Background and aims: In some areas of the world, antiviral therapy for chronic hepatitis C (CHC) is not available for all patients. The optimal interval for liver stiffness measures (LSM) and noninvasive scores to assess fibrosis progression has not been studied. We evaluated the usefulness of consecutive LSM, APRI, FIB-4 and Forns scores to predict disease progression.
Methods: Patients with CHC and at least two annual LSM within 3 years were followed for a minimum of 5 years. Noninvasive scores were assessed. Evolution of LSM and scores were expressed as change/year (Delta).
Results: 623 non-cirrhotic patients were included. Median baseline LSM was 6.6 kPa (IQR 5.4–8.4). During a median follow-up of 6 years, 61(9.7%) patients developed cirrhosis. Baseline LSM ≥ F2 and Forns ≥ 6.9 were the main predictors of cirrhosis (C-index 0.97). The addition of Delta variables did not improve its prediction. In patients with mild fibrosis (F0-1), progression to ≥F2 occurred in 80 (23%) within the first 3 years. Baseline BMI ≥ 24 kg/m^2 and LSM ≥ 5.9 kPa were associated to progression.
Conclusions: Baseline LSM and Forns are highly predictive of cirrhosis development. In patients with mild CHC, BMI < 24 and LSM < 5.9, the likelihood of progression is very low, allowing for a significant spacing of noninvasive assessments over time.

1. Introduction

Hepatitis C virus (HCV) infection is the leading cause of end-stage liver disease worldwide and represents a major burden for national health systems. The prognosis and management of chronic HCV infection (CHC) relies on the progression of liver fibrosis. Twenty years after HCV infection, the cumulative probability of cirrhosis approximates 20% and may increase up to 45% 30 years after infection [1,2]. Due to the slow progression of CHC, large cohorts and long follow-up periods are necessary to assess accurately the natural history of the disease in patients with mild hepatitis C.

Several studies have proved that noninvasive methods are precise in the diagnosis of mild and advanced liver fibrosis, thus, reducing the need for liver biopsy. Liver stiffness measurement (LSM) by transient elastography [3,4] has been extensively studied and validated as a reliable surrogate marker for grading the severity of liver fibrosis in patients with CHC. Other well-known noninvasive scores are panels of clinical and biochemical parameters. The AST-to-platelet ratio index (APRI) [5], Forns [6], and FIB-4 [7] have demonstrated a satisfactory diagnostic accuracy for the detection of significant fibrosis and cirrhosis. The practical advantages of using these methods to measure fibrosis include their high applicability and reproducibility, as well as their potential widespread availability [8].

One of the questions that remains unanswered is how often do patients need to undergo a noninvasive assessment of liver fibrosis during follow-up. The question may appear irrelevant due to the efficacy of current antiviral therapy for CHC. Nevertheless, direct acting antivirals (DAAs) are not available for all patients in large parts of the world. To our knowledge, no study has evaluated and compared the prognostic value and clinical usefulness of consecutive measurements of LSM, APRI, FIB4 and Forns Index

* Corresponding author at: Liver Unit, Hospital Clinic, IDIBAPS and CIBERehd, Villarroel 170, Barcelona 08036, Spain.
E-mail address: slens@clinic.ub.es (S. Lens).

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in non-cirrhotic CHC patients, to predict disease progression and development of cirrhosis in routine clinical practice.

2. Patients and methods

2.1. Patients

Retrospective analysis of patients with CHC visited at the Hospital Clinic (2004–2011). Exclusion criteria were HIV or HBV coinfection, other causes of liver disease, previous sustained virological response (SVR), liver transplantation, hepatocellular carcinoma or cirrhosis (defined as detailed below or by LSM > 12.5 kPa) [3].

Yearly LSM were recorded. In patients with more than 1 LSM within the same year, the measure with the date closer to the annual interval was selected. A "valid LSM" assessment was defined if at least 10 valid measurements and a success rate (SR) >60%. Measurements that fulfilled these criteria and an IQR/M lower or equal than 0.3 were considered "quality LSM" [9].

In order to assess the prognostic value of consecutive LSM assessments, those patients with a minimum of 2 LSM within the first 3 years (as to calculate dynamic variables) and at least 5 years of follow-up, constituted the final cohort. Those patients treated and cured within the first 3 years were excluded. Patients cured after this period were censored at the time of SVR.

The study protocol conformed to the ethical guidelines of the updated 1975 Declaration of Helsinki and was approved by the local ethics committee. Due to the retrospective nature of the study, no specific informed consent was required.

2.2. LSM assessment

LSM was performed using FibroScan® (Echosens, Paris-France) with the patient lying in dorsal decubitus and the right arm in maximal abduction. The same specialized nurse (CB) at the outpatient clinic performed all the examinations, and the machine model remained the same during all the study period. The used cut-offs to stratify patients according to fibrosis stage were 7.6 kPa for F2, 9.5 kPa for F3 and 12.5 kPa for F4/cirrhosis [3,10].

2.3. Definitions and follow-up

The date of the first LSM was the baseline time-point.

Following our clinical protocol, patients with chronic HCV infection underwent yearly laboratory tests and LSM assessment, with abdominal ultrasound (US) performed every 2-3 years. Noninvasive serological markers of fibrosis such as APRI, FIB-4 and the Forns score were retrospectively calculated according to published formulas [5–7]. In case of antiviral therapy, the date, type, duration and virological response were recorded. Antiviral therapy regimens varied overtime and were indicated according to EASL guidelines [11,12]. SVR was defined as undetectable serum HCV-RNA 24 weeks after discontinuation of antiviral treatment.

Clinical events such as cirrhosis development, liver decompensation, liver transplant or death were assessed. The diagnosis of liver cirrhosis during follow-up was based on the presence of at least one of the following criteria: (1) F4 fibrosis stage in a liver biopsy; (2) portal hypertension, defined as a hepatic venous pressure gradient ≥6 mmHg or presence of gastroesophageal varices in an upper endoscopic study; (3) presence of at least 2 signs of cirrhosis (nodular liver surface, portal vein diameter >12 mm, spleen size >12 cm) in 2 consecutive ultrasound studies [13]. The date of cirrhosis was established as the earliest date at which any of the previous criteria was present.

In patients with F3 fibrosis or in those who developed cirrhosis during follow-up, laboratory tests and ultrasonographic studies were performed every six months.

Fibrosis progression was defined as an increase in at least one fibrosis category assessed by LSM.

Follow-up evaluation ended in February 2015, at death or at the last follow-up visit. For assessing the development of cirrhosis and fibrosis progression, patients were censored at the time of SVR or the diagnosis of the event.

2.4. Statistical analysis

Categorical variables are described as frequencies and percentages, continuous variables as median and percentiles 25 and 75 (P25–P75) or as otherwise specified. Time to event data was estimated by means of the Kaplan–Meier method. To define the predictors of overall survival we used extended Cox models with time-dependent covariates, considering statistically significant clinical variables ($p < 0.05$) in the univariate for the multivariate analyses. Changes from previous LSM measurement were also modelled to estimate risk for Delta changes in key variables. The discriminative ability of the models was assessed by the Harrell's C statistic for survival data [14]. The Fisher's exact test was used to compare categorical variables and the Mann-Whitney method was used to compare ordinal and continuous variables. The analysis was performed using SAS version 9.3 software (SAS Institute Inc., Cary, NC, USA), SPSS v18 (SPSS, Inc., Chicago IL) and significance was established at the 0.05 level (two-sided).

3. Results

3.1. Patients characteristics

In all, 2122 CHC patients underwent a valid LSM between 2004 and 2011. Finally, 623 patients with 2 valid LSM within the first 3 years and at least 5 years of follow-up constituted our study cohort. Of these, 526 patients fulfilled criteria for quality LSM (Fig. 1). Baseline characteristics of the final cohort are depicted in Table 1. Median LSM at baseline was 6.6 kPa [IQR: 5–8]. At baseline, 71%, 17% and 12% of patients were F0-F1, F2 and F3, respectively. The median number of LSM assessments per patient during the observation period was 5; the median value of the last follow-up LSM was 6.2 kPa [4.8–8.8]. When assessing the dynamic evolution of repeated LSM and noninvasive fibrosis scores, we observed that these values remained remarkably stable during follow-up. Indeed, estimated median delta LSM was 0 kPa/year [IQR −0.65–0.7]. Changes of other noninvasive scores based on serum markers also remained stable during the follow-up (Table 1).

Regarding antiviral therapy, 350 (56%) patients underwent at least one antiviral treatment. Patients achieving SVR within the first 3 years (n = 66) were excluded from the analysis (Fig. 1). After this time point, 45 additional patients achieved SVR and were censored at the time of SVR.

3.2. Clinical events and prediction of cirrhosis development

After a median follow-up of 6 years (IQR 5–7), cirrhosis was diagnosed in 61 (9.6%) patients. In most patients (42, 68%) diagnosis was based on ultrasonographic criteria, in 15 (24%) on the presence of portal hypertension (varices or HVPG ≥ 6 mmHg) and in 4 (6.5%) on histological findings. Three patients developed liver decompensation and 7 hepatocellular carcinoma (all of them had liver cirrhosis). One patient underwent liver transplantation and 2 patients died during follow-up.

Median time from baseline to cirrhosis diagnosis was 5 years. Overall, the cumulative probability of cirrhosis development at 3

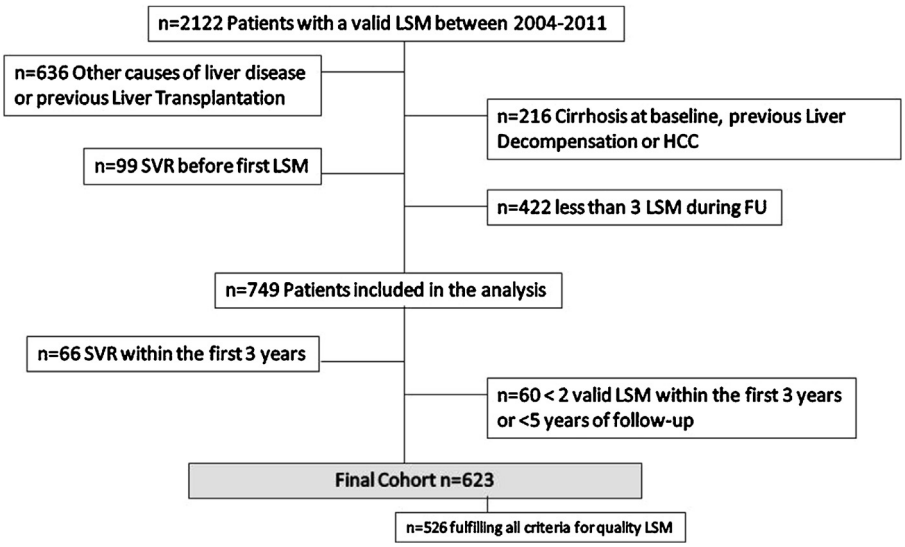

Fig. 1. Flowchart of patients.

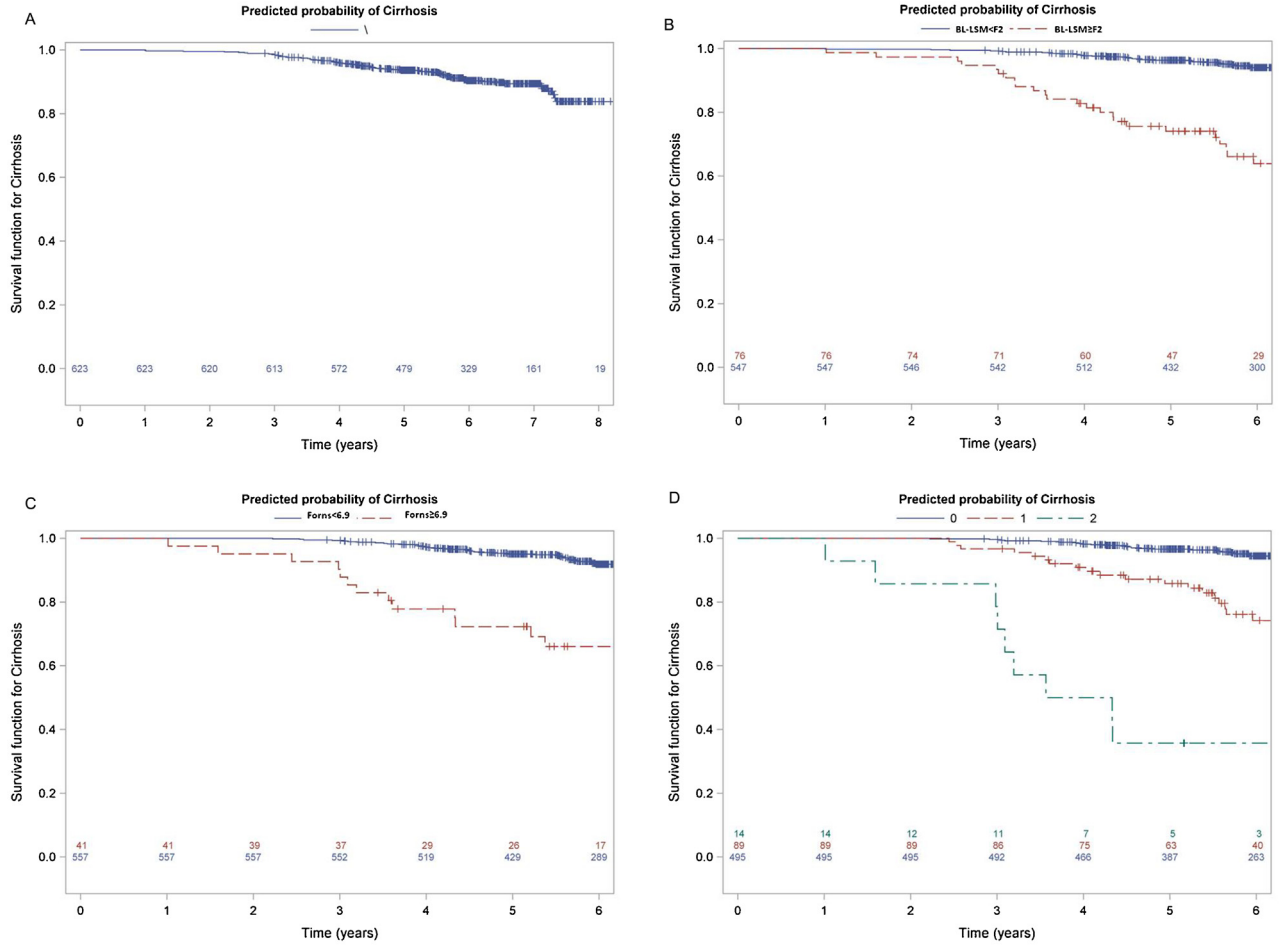

Fig. 2. Survival function for cirrhosis development overall (2A) (n = 623) and according to baseline liver stiffness (LSM) and Forns. 2B represents cirrhosis development according to the presence of baseline LSM ≥ F2 (623 patients) and 2C if Forns ≥ 6.9 (598 patients). 2D stratifies patients in three groups: (0) if absence of both risks factors (F < 2 and Forns < 6.9); (1) if presence of at least one (LSM ≥ F2 or Forns ≥ 6.9) and (2), those patients who present both factors at baseline (LSM ≥ F2 and Forns ≥ 6.9).

and 5 years was 1.6% and 5.5%, respectively. The survival curve for cirrhosis is represented in Fig. 2A.

Patients who developed cirrhosis had significantly different baseline characteristics: they were older (56 vs 47 years), had a higher BMI, higher BL-noninvasive scores, higher BL-LSM (9.4 vs 6.3 kPa) and a greater annual delta change within the first 3 years for LSM, APRI, FIB-4 and Forns (Table 1). The longer follow-up among

Table 1
Baseline characteristics of the cohort and differences between patients who developed cirrhosis or not.

Variable	All patients (n = 623)	Cirrhosis development during follow-up		P Value*
		No (n = 562)	Yes (n = 61)	
Sex (male)	306 (49%)	277 (49%)	29 (48%)	0.79
Age (years)	48 (42–57)	47 (41–55)	56 (49–64)	<0.0001
BMI (kg/m2)	24 (22–27)	24 (22–27)	25 (24–28)	0.002
Diabetes	32 (5.1%)	29 (5%)	4 (7%)	0.09
Excessive alcohol	20 (3.2%)	18 (3.2%)	2 (3%)	1
Genotype				
1a	108 (17%)	106 (18%)	10 (17%)	
1b	418 (67%)	405 (72%)	46 (75%)	0.30
3	31 (5%)	36 (7%)	2 (3%)	
Others	66 (10%)	15 (3%)	3 (5%)	
IL28 (CC)[a]	143 (32%)	133 (29%)	10 (17%)	0.031
Viral Load (Log)	5.8 (5.3–6.3)	5.83 (5.3–6.2)	6.0 (5.7–6.4)	<0.001
Treatment-experienced	234 (36%)	204 (36%)	30 (49%)	0.008
AST UI/L	44 (34–63)	43 (33–61)	61(41–85)	<0.0001
ALT UI/L	60 (42–90)	59 (40–89)	73 (54–114)	0.002
GGT UI/L	36 (20–63)	34 (19–60)	58 (35–82)	<0.0001
Platelets (x10^9)	225 (190–269)	230 (193–272)	199 (163–222)	<0.0001
Cholesterol g/dl	175 (153–199)	176 (154–199)	167 (147–202)	0.18
LSM- Baseline (kPa)	6.6 (5.4–8.1)	6.3 (5.3–7.9)	9.4 (7.6–10.9)	<0.0001
LSM- baseline				
<7.6 kPa	440 (71%)	424 (75%)	16 (26%)	
≥7.6 and <9.5 kPa	107 (17%)	99 (17%)	18 (29%)	<0.0001
≥9.5 kPa	76 (12%)	49 (8%)	27 (44%)	
LSM-3 yr	6.7 (5.3–8.4)	6.5 (5.1–8)	10.7 (8–13.6)	<0.0001
LSM-delta3 yr (unit/year)	0 (−0.65–0.7)	−0.003 (−0.65–0.65)	0.70 (−0.32–2.13)	<0.0001
APRI-baseline	0.44 (0.30–0.68)	0.42 (0.29–0.62)	0.72 (0.43–1.02)	<0.0001
APRI-3 yr	0.42 (0.29–0.46)	0.40 (0.28–0.61)	0.78 (0.55–1.41)	<0.0001
APRI-delta3 yr (unit/year)	−0.002(−0.05–0.05)	−0.005 (−0.05–0.04)	0.05 (−0.05–0.20)	<0.0001
Forns-baseline[b]	4.59 (3.52–5.58)	4.46 (3.43–5.38)	5.93 (5.16–6.99)	<0.0001
Forns ≥ 6.9	39 (6.4%)	22 (4.2%)	17 (28%)	<0.0001
Forns-3 yr	4.78 (3.67–5.91)	4.68 (3.55–5.67)	6.74 (5.85–7.70)	<0.0001
Forns-delta3 yr (unit/year)	0.08(−0.16–0.35)	0.07 (−0.17–032)	0.22 (−0.02–0.59)	<0.0001
FIB-4-baseline	1.20 (0.88–1.73)	1.16 (0.86–1.67)	1.91 (1.30–2.60)	<0.0001
FIB-4-3 yr	1.27 (0.91–1.90)	1.19 (0.87–1.80)	2.43 (1.67–3.29)	<0.0001
FIB-4-delta3 yr (unit/year)	0.01 (−0.07–0.14)	0.011 (−0.07–0.32)	0.18 (0.01–0.39)	<0.0001
Baseline US features				
Irregular liver surface	89 (14%)	73 (13%)	16 (26%)	<0.0001
Heterogeneity of liver echo-texture	42 (7%)	34 (6%)	8 (13%)	0.03
Mild steatosis	22 (3%)	17 (3%)	5 (8%)	0.04
Mild splenomegaly	24 (4%)	22 (4%)	2 (3%)	0.81
2 features or more	44 (7%)	39 (7%)	5 (9%)	0.71
Follow-up (years)	6.2 (5–7)	6.1 (5–7)	7 (6.1–7.5)	<0.001

Descriptive statistics are frequencies and percentages or median (interquartile range: P25–P75). BMI: Body mass index. LSM: liver stiffness measurement.
* p-Values from the Cox-regression analysis.
[a] Available in 448 patients.
[b] Available in 598 patients.

patients with cirrhosis is in keeping with the continuous monitoring despite achievement of virological cure.

Baseline LSM and Forns index along with their dynamic evaluation were the variables that remained significantly associated to cirrhosis development in multivariate analysis. Other potential relevant variables, such as previous antiviral therapy, did not show a significant association with progression to cirrhosis (the latter most likely reflecting the potential bias due to treatment of more advanced disease). Models to accurately predict the development of cirrhosis were calculated combining different baseline and dynamic variables: liver stiffness (as a continuous variable or categorized by fibrosis ≥F2), annual change in LSM during the first 3 years (kPa/year or categorized by 1 kPa/year), baseline Forns index (continuous or greater than significant fibrosis 6.9) and change in Forns (units/year or categorized by the annual median change in the overall cohort).

The results of the most accurate models with the specific Hazard Ratio (HR) for each factor are summarized in Table 2. When applying the constructed logistic models, the Harrell-C index to estimate the 5-year cirrhosis probability were: 0.93 for BL-LSM ≥ F2; 0.96 for the combination BL-LSM ≥ F2 and DeltaLSM; 0.97 for the model including both baseline BL-LSM ≥ F2 and Forns ≥ 6.9, and finally, 0.98 for the model combining all four baseline and dynamic variables. The addition of dynamic variables (model V) did not improve the prognostic value of the combination of BL-LSM ≥ F2 and Forns ≥ 6.9 (model III). Survival function for cirrhosis based on the presence of BL-LSM ≥ F2 and Forns ≥ 6.9 separately or combined is represented in Figs. 2B–D.

From a practical point of view, the combination of baseline LSM ≥ F2 and Forns score ≥ 6.9 with the specified cut-off values obtained specificity (SP) of 99% and a negative predictive value (NPV) of 95% for cirrhosis development at 5 years. Sensitivity (SE) was 32% and the positive predictive value (PPV) was 78%.

3.3. Fibrosis progression in patients with mild hepatitis C (F0-F1)

We were interested in assessing disease progression in patients with mild hepatitis C. For this purpose, we selected only indi-

Table 2
Harrell C-Index for the prediction of cirrhosis after 5 years by prognostic models based on baseline variables and the influence of the addition of dynamic (delta) variables.

Models	Variables	HR [CI 95%]	P Value	Harrell C-index
I	BL-LSM ≥ F2 (kPa)	6.30 [3.81–10.4]	<0.001	0.93 [0.92 to 0.95]
II	Forns ≥ 6.9	5.68 [3.23–9.98]	<0.001	0.90 [0.75 to >0.99]
III	BL-LSM ≥ F2 (kPa) Forns ≥ 6.9	4.88 [2.85–8.37] 3.42 [1.88–6.19]	<0.001	0.97 [0.94 to >0.99]
IV	BL-LSM ≥ F2 (kPa) DeltaLSM (kPa/year)	6.38 [3.80–10.7] 1.41 [1.23–1.62]	<0.001	0.96 [0.92 to >0.99]
V	BL-LSM ≥ F2 (kPa) DeltaLSM ≥ 1 kPa/year Forns ≥ 6.9 DeltaForns ≥ 0.08/year (Md)	4.69 [2.70–8.14] 2.33 [1.35–4.02] 2.92 [1.56–5.43] 1.83 [1.06–3.19]	<0.001 0.002 0.001 0.031	0.98 [0.96 to >0.99]

HR: hazard ratio; Md: median value; LSM: liver stiffness measurement.

Table 3
Baseline characteristics of the mild fibrosis cohort (F0-1) and differences between patients who presented fibrosis progression or not at 3 years.

Variable	Baseline	Fibrosis progression (F ≥ 2)		P Value*
	F0-1 patients (n = 350)	No (n = 270)	Yes (n = 80)	
Sex (male)	164 (47%)	124 (46%)	40 (50%)	0.14
Age (years)	47 (41–54)	46 (41–54)	48 (40–58)	0.10
BMI (kg/m2)	24 (21–26)	23 (21–26)	25 (23–28)	0.02
BMI ≥ 24	142 (41%)	103 (38%)	39 (49%)	0.02
Diabetes	10 (3%)	7 (2.6%)	3 (3.7%)	0.72
Excessive alcohol	14 (4%)	12 (4.4%)	2 (2.5%)	0.53
Genotype				
1a	59 (17%)	45 (17%)	11 (14%)	
1b	234 (67%)	180 (67%)	64 (80%)	0.29
3	21 (6%)	18 (6%)	3 (4%)	
Others	36 (10%)	27 (10%)	2 (2%)	
IL28 (CC)[a]	115 (43%)	85 (31%)	30 (37%)	0.27
Viral load (Log)	5.6 (5.2–6.1)	5.8 (5.4–6.2)	5.8 (5.4–6.2)	0.98
Treatment-experienced	116 (34%)	86 (32%)	30 (37%)	0.29
AST UI/L	41 (32–58)	40 (31–55)	46(34–64)	0.08
ALT UI/L	56 (39–83)	56 (37–80)	58 (40–85)	0.18
GGT UI/L	32 (19–54)	31 (18–52)	35 (20–65)	0.04
Platelets ($\times 10^9$/L)	236 (205–280)	240 (208–281)	222 (195–258)	0.05
Cholesterol g/dl	178 (156–200)	180 (157–200)	174 (151–199)	0.17
LSM-baseline (kPa)	5.9 (4.9–6.7)	5.8 (4.7–6.5)	6.5 (5.7–6.9)	<.001
LSM-baseline ≥ 5.9	188 (54%)	128 (47%)	60 (75%)	<.001
APRI	0.38 (0.27–0.58)	0.37 (0.27–0.55)	0.42 (0.32–0.63)	0.017
Forns	4.17 (3.18–5.07)	4.10 (3.2-4.9)	4.6 (3.6–5.7)	0.009
FIB-4	1.10 (0.80–1.56)	1.10 (0.80–1.50)	1.16 (0.88–1.78)	0.03

Descriptive statistics are frequencies and percentages or median (interquartile range: P25–P75). BMI: Body mass index; LSM: Liver stiffness measurement.
* p Values obtained with Fisher's exact test (categorical variables) and the Mann–Whitney method (continuous variables).
[a] available in 264 patients.

viduals with strict quality LSM (10 valid measures, SR > 60% and IQR/M ≤ 0.3). Among 526 patients who met these criteria, 350 had a LSM below 7.6 kPa at baseline (F0-F1).

It is important to notice that the baseline characteristics of the "quality cohort" and the entire study group were similar (Supplementary Table 1). Indeed, cirrhosis developed in 51 patients, HCC in 4 patients, and the variables independently associated to cirrhosis development were the same as those identified in the entire cohort. The Harrell-C index to estimate the 5-year cirrhosis probability when applying the constructed logistic models were 0.97 (0.94–>0.99) for the combination of BL-LSM ≥ F2 and Forns ≥ 6.9 and 0.98 (0.96- > 0.99) for the model including both baseline and dynamic variables (Supplementary Table 2).

As stated above, we aimed to assess the variables associated to fibrosis progression within the first three years of follow-up in those patients with mild fibrosis at baseline (F0-1). All patients (n = 350) had a minimum follow-up of 5 years. Fibrosis stage was re-assessed on follow-up, and categories were defined as F0-1 if LSM < 7.6 kPa, F2 if 7.6-9.4 kPa, F3 if ≥9.5 kPa and F4 (cirrhosis) by previously defined criteria. After three years of follow-up, 80 (22.8%) patients had progressed to F2 fibrosis stage or greater: 54 to F2 (15.7%), 25 to F3 (7%) and only 1 to F4 (0.3%).

Table 3 summarizes baseline characteristics of F0-1 patients and differences between those with fibrosis progression or not. In the univariate analysis, a higher BMI, LSM and noninvasive markers were associated to fibrosis progression after 3 years (Table 4). In multivariate analysis, the best predictive model was based on LSM and BMI, although only LSM remained statistically significant (OR 1.7 [1.3–2.3]; p< 0.01 and OR 1.08 [0.9–1.2]; p = .08; respectively).

When including baseline LSM ≥ 5.9 kPa and BMI ≥ 24 (median value in our cohort) in the multivariate analysis, again only LSM remained as a statistically associated to fibrosis progression (OR 3.56 [1.88-5.36]; p< 0.001 for LSM ≥ 5.9 kPa and 1.76 [0.95–3.25]; p = .07 for BMI ≥ 24 kg/m^2) (Table 4). However, the combination of both factors was superior to LSM alone, obtaining a SE of 84%, SP of 56%, PPV of 38% and a NPV for fibrosis progression of 92% at 3 years. If only considering the presence of LSM< or ≥5.9, the numbers were 79% (SE), 38% (SP), 27% (PPV) and 87% (NPV).

Table 4
Uni- and multivariate analysis for fibrosis progression at 3 years in patients with mild fibrosis at baseline (F0-1).

Variables	Univariate analysis		Multivariate analysis	
	OR [CI 95%]	P value	OR [CI 95%]	P Value
BMI (kg/m2)	1.09 [1.00–1.19]	0.04	–	–
BMI ≥ 24	2.01 [1.14–3.74]	0.016	1.76 [0.95–3.25]	0.07
LSM- Baseline (kPa)	1.73 [1.35–2.23]	<0.001	–	–
LSM-Baseline ≥ 5.9	3.19 [1.89–5.36]	<0.001	3.56 [1.88–6.75]	<0.001
APRI	2.14 [1.01–4.54]	0.012		
Forns	1.23 [1.0.3–1.46]	0.02		
FIB-4	1.60 [1.11–2.30]	0.02		

OR: odds ratio; BMI: Body mass index. LSM: Liver stiffness measurement.

These results suggest that rate of fibrosis progression among patients with mild fibrosis with a baseline LSM < 5.9 kPa and BMI < 24 kg/m^2 is very low. Therefore, spacing intervals between LSM assessments to every 3 years appears to be a feasible and practical policy for patient surveillance.

4. Discussion

Disease-based restrictions are common worldwide and also across Europe, with nearly half of countries/jurisdictions (46%) restricting DAAs to people with moderate and advanced liver disease [15]. In these setting, the optimal identification of patients at risk of disease progression is very relevant [12].

Elastography has become the most used noninvasive technique to monitor patients and dynamically assess fibrosis stage due to its reproducibility and acceptable cost [9,16]. However, the optimal interval for LSM monitoring remains to be defined. In a previous study a higher LSM at baseline, non-SVR and an increase of LSM ≥1 kPa/year within the first 3 years, were associated to a worse prognosis [17]. However, patients in this study presented more advanced liver disease (baseline LSM 9.0 ± 7.9 kPa) and a significant proportion of patients even had cirrhosis at baseline.

In our cohort of 623 patients, most had mild fibrosis (71% F0-1) and at least five years of follow-up. Since several reports have already proven that the achievement of virological cure prevents fibrosis progression [18], patients achieving SVR were excluded (before dynamic assessment) or censored (during follow-up) for the analysis. Our results show that the majority of patients remained stable as assessed by minimal progression of LSM and noninvasive scores. Median LSM at baseline was 6.6 kPa and LSM change was insignificant (0 [−0.65–0.7] kPa/year) within the first three years. After a median follow-up of 6 years, only 9.7% developed cirrhosis. Baseline US features were slightly different between groups. However, we believe that these data are not unexpected taking into account the higher baseline prevalence of F2/F3 fibrosis among patients who developed cirrhosis. It is important to notice, however, that these US features are more subjective than those used to define cirrhosis by ultrasound [13].

The presence of a LSM value ≥7.6 kPa at baseline was significantly associated to the development of cirrhosis at 5 years. A Forns score ≥ 6.9 appeared almost as accurate as LSM for the prediction of cirrhosis [6]. Indeed, in our study, the survival function for cirrhosis among the prognostic subgroups identified by BL-LSM ≥ F2 and Forns ≥ 6.9 showed a similar pattern (Figs. 2B-C), and global evaluation using Harrell C- indexes showed that the 2 models derived from baseline LSM or Forns were not significantly different (0.93 and 0.90, respectively) (Table 2).

Compared to Forns, LSM is more expensive and may be less accessible to some practitioners, but has some particular advantages for diagnosis and prognostic assessment in CHC as the provision of immediate results and the possibility of intermediate classifications. Surprisingly, our study did not demonstrate a major impact of adding dynamic changes within the first 3 years to baseline assessments in predicting cirrhosis development. The combination of both, baseline LSM and Forns for significant fibrosis (≥F2: 7.6 kPa for LSM and 6.9 for Forns) was as good as the combination of these factors and their estimated annual changes (delta) to predict cirrhosis development in 5 years (Harrell C-Index 0.97 and 0.98, respectively).

Our data have relevant implications for clinical practice. As shown in Fig. 2D, those patients with both BL-LSM ≥ F2 and Forns ≥ 6.9 at baseline had the highest risk of developing cirrhosis, as compared to those non accomplishing any of the criteria, and therefore, should be monitored by non-invasive methods at least annually and promptly receive antiviral treatment. On the contrary, the negative predictive value (NPV) of cirrhosis development at 5 years in the absence of both factors is 95%, which may be highly convincing for patients (and treating physicians).

Importantly, we also aimed to assess the variables associated to fibrosis progression in patients with mild hepatitis C (F0-F1), which comprised the vast majority of our cohort. As stated above, and despite the differences in health-care budgets among countries compromising drug availability and treatment decisions, it is common to base the indication or prioritization of HCV treatment on fibrosis stage [15]. In this setting, the identification of those patients at higher risk of fibrosis progression in the mid-term is essential. In order to base fibrosis stage on reliable measures, only those patients with mild fibrosis (F0-1) and fulfilling all criteria for quality LSM were analyzed. In the multivariate analysis, the variables associated to fibrosis progression were baseline LSM ≥ 5.9 and BMI ≥ 24. Previous reports have also associated BMI and obesity to a higher rate of fibrosis progression, indeed those patients with a LSM < 5.9 and a BMI < 24 have the lower probability of fibrosis progression at 3 and 5 years with a NPV of 92% and 89%, respectively (data at 5 years not shown). Thus in these patients, it seems reasonable spacing the interval between LSM to, at least, every 3 years. The latter is very relevant from a practical point of view, since it allows reducing significantly the number of follow-up visits in the vast majority of patients with mild hepatitis C, decreasing health-care related costs.

Our study has several strengths such as homogeneous follow-up and the same elastography machine and nurse operator (CB) during all the study period. On the other hand, our study also has limitations such as the retrospective nature of the study, which implies missing assessments during follow-up in some patients. In addition, the technique was not performed under standardized fasting conditions until the publication of the influence of meal on LSM assessment, which may have had an influence on the results [19].

In summary, widely available noninvasive methods at baseline (LSM, Forns score) are highly predictive of long-term cirrhosis development in patients with CHC. The addition of dynamic variables does not significantly improve the predictive power of the model. Regarding follow-up of patients with mild hepatitis C (F0-

F1), the presence of low LSM and a normal BMI identifies individuals with an extremely low risk of disease progression. The latter allows extending the follow-up intervals up to 3 years, with the consequent savings of costs and time and simplifies the management of patients with CHC and restricted access to therapy.

Conflict of interest statement

XF: advisor for Abbvie and Gilead and unrestricted grant support from Abbvie. SL: advisor for Abbvie and Gilead. ZM: advisor for BMS. MCL: advisor for Janssen, MSD and BMS.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.dld.2018.11.019.

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