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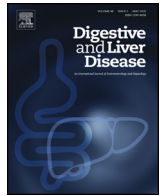
Hepatocellular carcinoma risk assessment by the measurement of liver stiffness variations in HCV cirrhotics treated with direct acting antivirals / Ravaoli, Federico; Conti, Fabio; Brillanti, Stefano; Andreone, Pietro; Mazzella, Giuseppe; Buonfiglioli, Federica; Serio, Ilaria; Verucchi, Gabriella; Bacchi Reggiani, Maria Letizia; Colli, Agostino; Marasco, Giovanni; Colecchia, Antonio; Festi, Davide. - In: DIGESTIVE AND LIVER DISEASE. - ISSN 1590-8658. - 50:6(2018), pp. 573-579. [10.1016/j.dld.2018.02.010]

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Liver, Pancreas and Biliary Tract

Hepatocellular carcinoma risk assessment by the measurement of liver stiffness variations in HCV cirrhotics treated with direct acting antivirals

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ABSTRACT

Background: Direct-acting antivirals (DAA) are an effective treatment for hepatitis C virus infection. However, sustained virologic response (SVR) after DAA treatment does not seem to reduce the risk of hepatocellular carcinoma (HCC) development in these patients. Liver stiffness measurement (LSM) may predict the risk of developing HCC in liver cirrhosis patients.

Aims: The aim of our study was to evaluate the role of LSM variation as predictor of HCC development in patients treated with DAA.

Methods: In 139 HCV-related cirrhotic patients, LSM and laboratory tests were carried out at baseline (BL) and at the end of DAA treatment (EOT). Patients were followed for at least 6 months after the EOT. LSM reduction was expressed as Delta LS (Δ LS). Cox regression analysis was used to identify prognostic factors for HCC development after DAA.

Results: Median LSM values were significantly reduced from BL to EOT (from 18.6 to 13.8 kPa; $p < 0.001$). The median Δ LS was -26.7% (IQR: -38.4% – -13.6%). During a median follow-up of 15 months after DAA treatment, 20 (14.4%) patients developed HCC. Significant LSM reduction was observed both in patients who developed HCC and in those who did not, but this was significantly lower in the patients who developed HCC (-18.0% vs -28.9% $p=0.005$). At multivariate analysis, Δ LS lower than -30% , Child-Turcotte-Pugh-B and history of HCC were independently associated with HCC development.

Conclusion: Our results indicate that Δ LS is a useful non-invasive marker for predicting HCC development after DAA treatment.

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1. Introduction

Hepatitis C Virus (HCV) is the most prevalent cause of chronic hepatitis, liver cirrhosis and hepatocellular carcinoma (HCC) in Europe [1].

In December 2014, direct-acting antiviral agents (DAAs) were introduced into Italian clinical practice for the treatment of chronic HCV infection, replacing interferon (IFN)-based regimens [2]. These

drugs, directly targeting HCV replication, have been shown to achieve sustained virologic response (SVR) rates in more than 90% of treated patients, regardless of the viral genotype, liver fibrosis stage and cirrhosis compensation [3].

HCV eradication with DAAs treatment in cirrhotic patients also reduces extrahepatic liver manifestations [4], liver-related morbidity and overall mortality [5], confirming previous studies carried out in HCV patients treated with IFN-based regimens [6].

Of all the complications of liver cirrhosis, HCC development is one of the most important factors affecting liver-related mortality [7], achieving SVR after IFN, reduces HCC development, however the risk remains [8].

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Liver stiffness measurement (LSM), using transient elastography (TE), is a non-invasive marker for assessing liver fibrosis stage [9] and correlates with portal hypertension [10]. LSM has also been proposed in order to evaluate the effect of antiviral treatments on liver inflammation and fibrosis, representing a possible alternative method to liver histology [11]. Studies have also found a correlation between LSM values and the risk of clinically relevant outcomes and HCC development in patients with chronic liver diseases [12,13].

To date, the rate of HCC development after DAA treatment in cirrhotic patients appears to vary considerably, some authors have shown unexpectedly high rates of HCC recurrence and occurrence [14–17], while others have indicated that patients treated with DAAs have similar HCC development rates as those obtained after IFN-based regimens [18–20].

We thus decided to evaluate the role of LSM, in conjunction with other clinical liver function scores, in predicting HCC development in HCV cirrhotic patients treated with DAA-based regimens.

2. Materials and methods

2.1. Patients

This retrospective analysis included all patients with HCV-cirrhosis treated with DAAs between January 2015 and June 2016 at our center, with a valid measurement of LSM by TE at baseline (BL) and at the end of DAA treatment (EOT). We excluded patients without a complete response to surgical resection or loco-regional ablation of previous HCC (i), who developed HCC during antiviral treatment (ii) and/or with follow-up duration less than six months after EOT (iii).

2.2. Antiviral treatment

Eligibility for treatment of HCV patients with DAAs was assessed following the priority criteria established in the protocol approved by the Italian Medicines Agency committee. The choice of DAA and treatment duration (12 or 24 weeks) was based on viral genotype and stage of disease, according to the guidelines available at the time of enrollment [22].

Diagnosis of cirrhosis was assessed by TE (stiffness values ≥ 12.5 kPa according to Castera et al. [21]), abdominal ultrasound and/or histology, if available. At baseline, anthropometric measures included body weight (kg) and height (m). In addition, Model for End stage Liver Disease (MELD) and Child-Turcotte-Pugh (CTP) scores were also calculated for each patient. Aspartate aminotransferase to platelet ratio index (APRI) and fibrosis-4 score (FIB4) [23] were calculated from BL laboratory values. SVR was defined as undetectable HCV-RNA, using real-time PCR, with a detection limit of 15 IU/mL, at 12-week post-treatment follow-up visit.

2.3. Surveillance and HCC assessment

Before starting antiviral treatment, all patients underwent abdomen ultrasound (US). If a possible focal lesion was detected in the liver, the diagnostic work up was completed with contrast-enhanced ultrasonography (CEUS), and subsequent computerized tomography (CT) scan or magnetic resonance imaging (MRI) was performed to exclude the presence of HCC. All patients with a history of HCC underwent CT scan or MRI, in addition to US, to exclude recurrent HCC.

All patients were followed up for a period of at least six months after EOT or until HCC development. During the follow-up period, patients repeated US evaluation as recommended by the surveillance programme guidelines [24]. In the case of suspected HCC

development, CEUS/CT/MRI were carried out to confirm or exclude the presence of HCC.

2.4. Liver stiffness measurements

LSMs were performed using TE (FibroScan, Echosens, Paris France) with a 3.5-MHz transducer (M-probe). The details of the technical background and examination procedure have been previously defined [25]. LSMs were performed by one experienced clinician (who had performed at least 500 examinations) after at least six hours of fasting and after a complete abdominal US examination. Results were recorded in kilopascal (kPa) ranging from 3 kPa to a maximum value of 75 kPa. Briefly, for each patient, the examination was considered complete when at least 10 valid measurements or a maximum of 20 attempts at measurement were carried out. LS values were accepted if the success rate was $>60\%$ and the interquartile range (IQR) was $<30\%$ of the median value [26]. LSM was performed at BL and EOT. The Delta LS (Δ LS) was calculated as the difference between LSM at BL and EOT and divided by LSM at BL. The predefined limit to consider Δ LS significant was $\geq 30\%$ decrease from baseline, since the 30% threshold of LS change corresponds to the accepted variability of the TE assay.

2.5. Statistical analysis

Categorical data were expressed as numbers (percentages) and continuous variables as medians (IQR or range). For group comparison, the Mann-Whitney U test was used for continuous variables and the Chi² test for categorical variables. The Δ LS was also evaluated as a binary variable according to the median value of the entire population. Group comparisons among LSM at BL and EOT were evaluated with Friedman's non-parametric test, and Bonferroni-corrected alphas were used for post-hoc pairwise comparison. The Kaplan-Meier method was used to estimate HCC development after DAA treatment. A log-rank test was used to assess the differences in term of survival. An overall event-free survival plot for HCC development after DAA treatment was constructed for descriptive purposes.

Demographic, clinical, functional and elastometric variables were evaluated with univariate and multivariate Cox regression models in order to assess the risk factors associated with the primary outcome. After evaluation of multicollinearity, variables with a p-value of <0.10 at univariate analysis were included in several multivariate Cox regression models with stepwise backward procedures. The estimated hazard ratios (HRs) with their 95% confidence intervals (CIs), LR chi² and Harrell's C were presented. Only p-values of less than 0.05 were considered statistically significant. The statistical analysis was conducted using Stata/SE (Version 14.0; Stata Corp, Texas, U.S.A.).

2.6. Ethics

The DAA-treatment protocol was approved by the National Institutional Review Board (IRB) of the Italian Medicines Agency committee. Local IRB [Institutional Ethics Committee of Sant'Orsola-Malpighi University Hospital (Bologna, Italy)] approval for subsequent anonymous retrospective analyses was authorized.

3. Results

A total of 139 (36.6%) patients undergoing DAA treatment met inclusion/exclusion criteria and were enrolled in the study (Fig. 1).

The major clinical and biochemical parameters of patients included in the study are listed in Table 1. A total of 65% of the patients were males, median age was 62 (IQR: 38–83) years, with

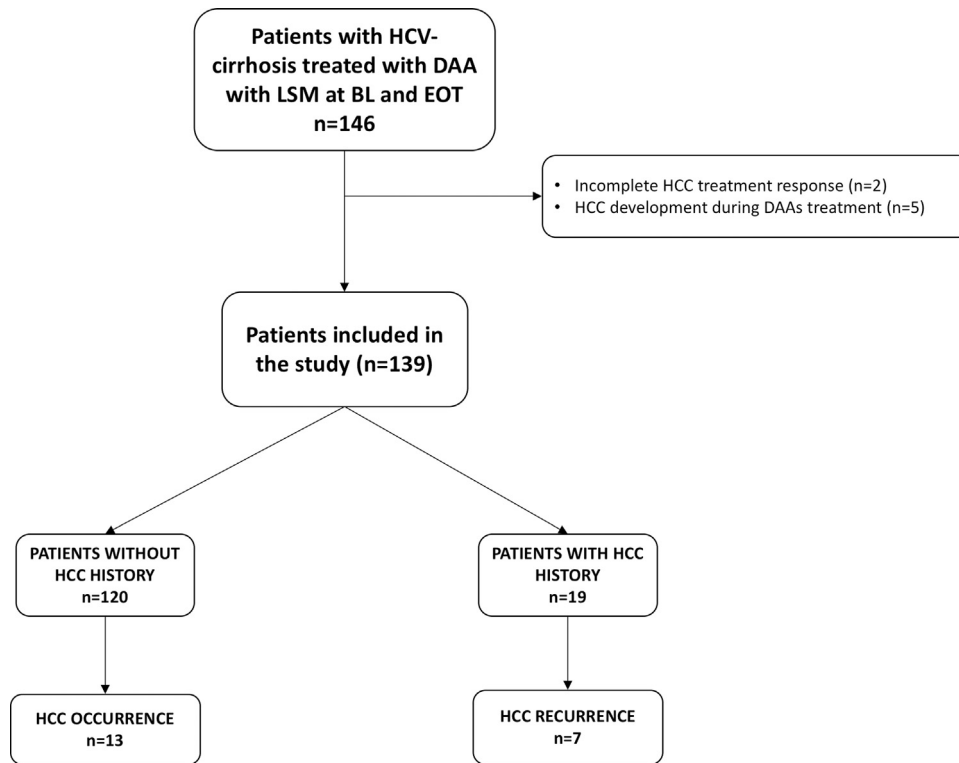


Fig. 1. The study design flow chart of the patients studied and the study time points.

Table 1

Baseline features of 139 patients without HCC development (n = 119) or with HCC development (n = 20) after DAA treatment.

	Entire cohort (n = 139)	Without HCC after DAA (n = 119)	With HCC after DAA (n = 20)	p-value*
Male, n (%)	91 (65.5%)	79 (66.4%)	12 (60%)	0.578
Age (years), median (IQR)	63 (52–73)	62 (52–73)	66 (58–77)	0.229
HCV genotype, n (%):				0.810
■ 1a	21 (15.1%)	19 (16%)	2 (10%)	
■ 1b	81 (58.3%)	69 (58%)	12 (60%)	
■ 2	16 (11.5%)	14 (11.8%)	2 (10%)	
■ 3	13 (9.4%)	10 (8.4%)	3 (15%)	
■ 4	8 (5.7%)	7 (5.8%)	1 (5%)	
CTP score, median (IQR)	5 (5–6)	5 (5–6)	6 (5–7)	0.022
CTP class, n (%):				0.009
■ A	123 (88.5%)	108 (90.8%)	14 (70%)	
■ B	16 (11.5%)	11 (9.2%)	6 (30%)	
MELD score, median (IQR)	8 (7–9)	8 (7–9)	10 (8–11)	0.060
HBsAg positive, n (%)	3 (2.2%)	2 (1.7%)	1 (5%)	0.345
DAA schedule, n (%):				0.925
■ SOF	17 (12.2%)	15 (12.6%)	2 (10%)	
■ SOF + DCV	28 (20.1%)	23 (19.3%)	5 (25%)	
■ SOF + SMV	54 (38.8%)	46 (38.7%)	8 (40%)	
■ SOF + LDV	18 (13%)	16 (13.4%)	2 (10%)	
■ PAR/r/OBV + DAS	19 (13.7%)	17 (4.3%)	2 (10%)	
■ PAR/r/OBV	3 (2.2%)	2 (1.7%)	1 (5%)	
Treatment duration, n (%):				0.696
■ 12 weeks	82 (59%)	71 (59.7%)	11 (55%)	
■ 24 weeks	57 (41%)	48 (40.3%)	9 (45%)	
History of previous HCC, n. (%)	19 (13.7%)	12 (10.1%)	7 (35%)	0.007
PLT (cells × 10 ⁹ /L), median (IQR)	119 (82–165)	118 (82–169)	120 (102–143)	0.680
INR, median (IQR)	1.12 (1.04–1.18)	1.12 (1.03–1.2)	1.1 (1.07–1.13)	0.583
ALT (U/L), median (IQR)	56 (35–101)	55 (34–101)	58 (37–78)	1
AST (U/L), median (IQR)	59 (35–85)	65 (35–8)	51 (39–80)	0.807
Bilirubin (mg/dL), median (IQR)	0.90 (0.67–1.23)	0.85 (0.65–1.21)	0.98 (0.68–1.23)	0.523
APRI at BL	1.667 (0.865–2.630)	1.587 (0.859–2.537)	2.064 (1.047–3.871)	0.124
FIB4 at BL	4.743 (3.000–6.826)	4.688 (2.905–6.774)	5.848 (3.869–12.485)	0.056
LSM at BL	18.6 (15–26)	18.5 (14.8–26)	20.1 (15.7–27.9)	0.540

* p-value for comparison of patients with HCC after DAA and patients without HCC after DAA.

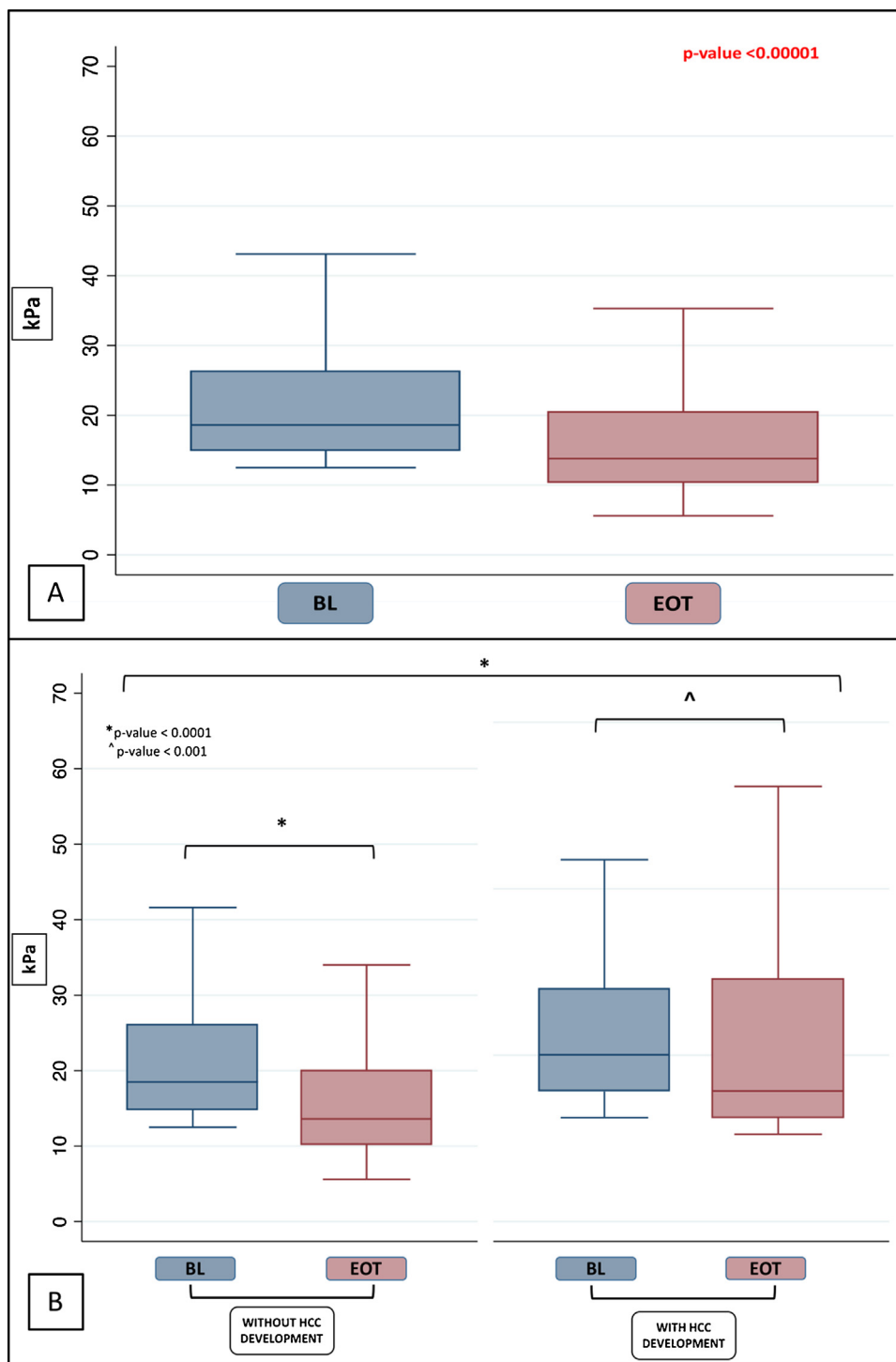


Fig. 2. (A) Whole population assessment of dynamic changes of LSM by TE between BL and EOT. (B) Dynamic changes of LSM by TE in group with or without HCC development after DAA-treatment.

prevalent HCV genotype 1 (51%). Most patients had a functional status CTP class A (88%) and a median MELD score of 8 (IQR: 7–9). Nineteen (13.7%) patients had a history of previous HCC with a median follow-up interval of 13 (IQR: 5–62) months between the previous HCC treatment and the beginning of antiviral therapy with DAA.

In our cohort 3 (2.1%) patients had a hepatitis B (HBV) infection (all with long-term suppressive therapy with antiviral nucleo-

side/nucleotide analogue (NUC)) and no patient was co-infected by HIV.

Most patients (84.1%) were treated with SOF-based schedules. DAA-treatment duration was 12 weeks in 82 patients (59%), and 24 weeks in 57 patients (41%). An SVR was achieved in 131 (94.2%) patients. Patients were followed up for a median time of 15 (IQR: 12–19) months after EOT.

Table 2
Cox proportional hazard analyses for hepatocellular carcinoma development after DAA treatment.

Variables	Univariate model			Multivariate model LR chi2 = 21.78 AIC = 171.61 Harrell's c = 0.7716		
	HR	95%CI	p-value	HR	95%CI	p-value
Age	1.233	0.983–1.065	0.259			
Gender (M vs F)	1.211	0.495–2.964	0.675			
MELD score	1.138	1.001–1.294	0.049			
Child-Pugh (B vs A)	3.974	1.521–10.381	0.005	4.046	1.542–10.618	0.005
HBsAg (positive vs negative)	3.850	0.509–29.172	0.192			
APRI at BL	1.147	0.995–1.322	0.06			
APRI at EOT	2.935	1.275–6.757	0.011			
FIB4 score at BL	1.077	1.018–1.139	0.010			
FIB4 score at EOT	1.143	1.033–1.264	0.009			
History of previous HCC (yes vs no)	3.299	1.207–4.378	0.011	2.758	1.350–5.635	0.005
LSM at BL	1.019	0.975–1.064	0.4			
LSM at EOT	1.043	1.005–1.082	0.027			
DLSM (<30% vs ≥30%)	5.034	1.475–17.189	0.010	5.36	1.561–18.405	0.008

3.1. HCC development

During the follow-up period, 20 out of 139 (14.4%) patients developed HCC.

Patients who developed HCC after DAA treatment had a significantly higher Child Pugh Score, the majority of whom had a history of previous HCC (Table 1). Three patients had a virological relapse after antiviral treatment. The median interval between EOT and HCC diagnosis was 7 (IQR: 4–10) months. Thirteen out of 120 (10.8%) patients developed de novo HCC, with a median time from EOT of 6 (IQR: 4–8) months. HCC recurrence was reported in 7 out of 19 patients (36.8%) with a median time of 10 (IQR: 6–15) months between EOT and HCC diagnosis. In this subgroup, the median interval between previous HCC treatment and neoplastic recurrence was 24 (IQR: 22–49) months.

3.2. Changes in liver stiffness measurement in patients treated with DAA

As shown in Fig. 2A, a significant reduction in LSM after DAA treatment was observed in the majority of patients. Overall, median LSM values decreased from 18.6 kPa (15–26.3) at BL to 13.8 kPa (10.4–20.4) at EOT ($p < 0.001$). A similar trend was observed (Fig. 2B), both in patients who developed HCC after DAA [from 20.1 kPa (15.7–27.9) at BL to 15.7 kPa (12.8–29.1) at EOT; and in those who did not [from 18.5 kPa (14.8–26) at BL to 13.6 kPa (10.2–20.0) at EOT; $p < 0.00001$]. The same trend was observed comparing patients with de novo occurrence and recurrence of HCC after DAA. In 122 (87.8%) of the patients, Δ LS confirmed an LS reduction from BL to EOT. Δ LS did not correlate with Δ AST/ALT ratio ($R = 0.188$ $p = ns$).

The median Δ LS was -26.7% (IQR: -38.4% to -13.6%). Patients who developed HCC after DAA had a significantly lower Δ LS than those who did not (-18.0% and -28.9% , respectively; $p = 0.005$) (Fig. 3). An LSM reduction of $>30\%$ was observed in 62 (44.6%) patients, of whom 59 (95.1%) did not develop HCC during follow-up (Supplemental Material Fig. S1).

Examining only patients without a history of HCC, the median Δ LS was -26.7% (IQR: -40.6% to -14.5%). Also in this cohort, patients who developed de novo HCC after DAA had a significantly lower Δ LS than those who did not (-18.7% and -28.9% , respectively; $p = 0.022$). Similarly, in patients with a history of HCC, the median Δ LS was -21.8% (IQR: -34.1% to -10.5%). No statistically significant difference in Δ LS was observed in patients who developed HCC recurrence in comparison with those who did not (-13.6% and -29.6% , respectively; $p = 0.205$).

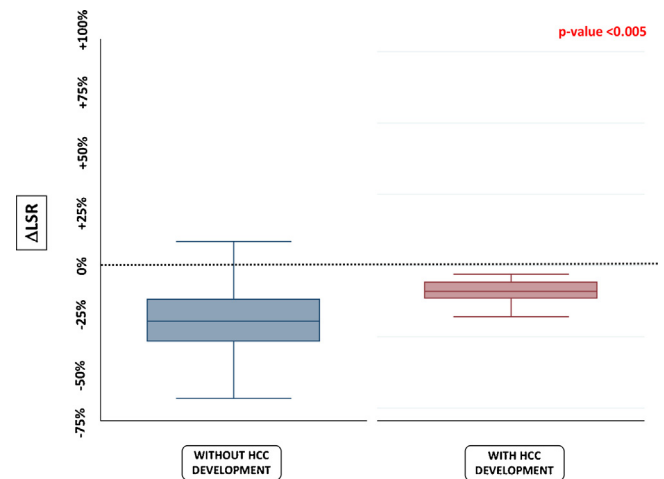


Fig. 3. Delta liver stiffness (Δ LS) [between LSM at baseline (BL) and end of treatment (EOT)] according HCC development groups.

3.3. Risk factors for HCC development after DAA treatment

At univariate Cox regression analysis, Δ LS of -30% , MELD score, CTP score, history of previous HCC, LSM at EOT were significantly associated with HCC development after DAA treatment (Table 2).

Table 2 shows the results of Cox multivariate models, Δ LS less than -30% (HR: 5.360, 95%CI: 1.561–18.405; $p = 0.008$), history of previous HCC (HR: 2.758, 95%CI: 1.350–5.635; $p = 0.005$) and CTP-B (HR: 4.046, 95%CI: 1.542–10.618; $p = 0.005$) were independent predictors of HCC development after DAA treatment with good predictive power (LR chi2 = 21.78, Harrell's C = 0.7716).

Fig. 4 shows Kaplan–Meier estimated curves of survival from HCC development as a function of the Δ LS value. Patients whose Δ LS was lower than -30% had shorter HCC-free survival than those with Δ LS higher than -30% ($p < 0.001$).

A multivariate sub-analysis in patients without history of HCC confirmed Δ LS less than -30% (HR: 11.623, 95%CI: 1.508–89.606; $p = 0.019$) and CTP-B (HR: 4.200, 95%CI: 1.289–13.678; $p = 0.017$) as an independent predictor of de novo occurrence of HCC development after DAA treatment (Supplemental Material Table S1 and Supplemental Material Fig. S2). The above analysis was not performed in patients with a history of HCC due to the small sample size.

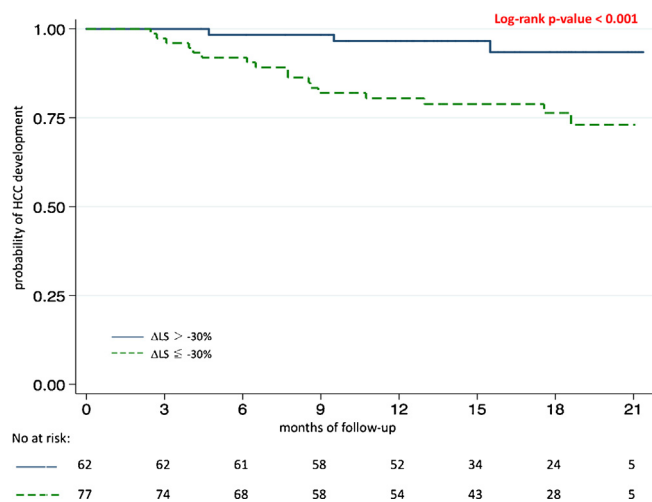


Fig. 4. Kaplan–Meier estimated curve of HCC-free survival for HCC development after DAA treatment using Δ LS.

4. Discussion

The development of DAA-based antiviral treatment has offered the possibility to cure HCV infection even in patients with liver cirrhosis, thus to obtaining an improvement in CPT and MELD scores after HCV-eradication in patients with advanced liver disease [27,28]. Similarly, LS reduction measured by TE has been observed in patients undergoing DAA treatment [29–32]. However, despite clinical improvement and achievement of SVR, patients seem to maintain the risk of HCC development, especially in the short term [14,15], although the role of DAA is still an open issue [33].

In this study, we evaluated the LSM variation and its possible role in patient surveillance during a long-term follow-up after treatment with DAA-based regimens. Firstly, our study confirmed a significant improvement in LSM immediately after the EOT in cirrhotic patients, finding a median reduction of LSM equal to about a quarter of its value at BL (Δ LS = -26.7%), both in patients with and without a previous history of HCC. Our data confirm recent studies which showed a regression of LSM and biochemical fibrosis markers (FIB4 and APRI index) after DAA treatment [32,31]. These findings have also been observed in patients treated with IFN-based regimens [34,35]. While LSM has been considered an accurate, although surrogate, marker for fibrosis staging in different chronic liver diseases, there are preliminary and conflicting results when LSM is used to identify histologically documented fibrosis regression [36–38]. In addition, a significant decrease in portal hypertension as recorded by repeated hepatic venous pressure gradient (HVPG) measurements has been reported after IFN-free therapy [39], correlated with LSM variations [40].

It is thus possible that the improvement in LSM after DAA treatment observed in our study could be the result of two time-related events: a reduction in necro-inflammatory and in fibrosis activities, the latter possibly being influenced by the reduction in portal pressure.

Our key result of the present study was finding that LSM variation could be a tool to indicate the most at-risk patients for HCC development after viral clearance with DAAs. This is particularly important since it is known that the achievement of an SVR in cirrhotic patients reduces, but does not completely abolish, the risk of HCC occurrence/recurrence. In fact, in patients treated with IFN, HCV-clearance has been associated with an improvement in the natural history of patients, but the risk of HCC did not disappear [6,41]. In addition, in cirrhotic patients treated with DAAs, the risk

of HCC recurrence and occurrence is not eliminated and might even increase [33,42,43].

LSM may also be a reliable prognostic tool for HCC development [13,44,45]. A retrospective study using an LSM-based score reported the risk of HCC development in a cohort of SVR HCV patients treated with IFN [46]. Similar results were obtained in HBV patients, showing that early LSM changes predicted liver-related events and HCC development in patients chronically treated with NUC [47].

However, no data have been reported on the role of LSM variation in predicting HCC development/recurrence in patient treated with DAAs. We believe that this is the first study to show that patients with HCC development after antiviral treatment had a significantly lower LSM reduction compared to those without HCC occurrence, although non-invasive markers of fibrosis (LSM, APRI and FIB4 scores) were not significantly different in the two groups ($p > 0.05$) before the antiviral treatment. In our study Δ LS was more representative of this trend (-18% in HCC patients vs 28.9% in non-HCC patients). This finding was additionally confirmed by a Kaplan–Meier estimated curve of event-free survival which showed significantly better disease-free survival in the population of patients who had a reduction percentage $> -30\%$. In addition, only a reduction of LSM lower than -30% , as well as the CTP B and history of previous HCC, were confirmed as independent factors associated with HCC development at multivariate analysis. Due to the different risk of HCC development in patients previously treated for HCC, we conducted a separate analysis that confirmed the same results in patients without a history of HCC which was then in turn confirmed by a Kaplan–Meier estimated curve of event-free survival in patients without a history of HCC. Due to the small number of patients with HCC in the subgroup analysis, the significance of the estimate of LSM reduction of -30% could be a limiting factor, although the clinical impact of lower delta LS reduction in terms of HCC development remains relevant.

A possible explanation of our results could be the persistence of greater fibrosis and portal hypertension after DAA treatment in patients who developed HCC compared to those who did not, in whom the reduction of LS might mainly be due to an improvement in inflammation.

The main limitations of our study include its retrospective nature and the small sample size of patients who developed HCC after DAA. However, no other concomitant causes of liver disease or HIV-coinfection were observed in our cohort as possible confounding factors for LSM variations and/or HCC development. A key strength of this study is the homogeneity of the two groups at baseline (those with and without HCC development after DAA), in particular regarding the non-invasive marker values of fibrosis ($p > 0.05$). Another strength is that HCC development after DAA-treatment was assessed during a long-term follow-up (median 15 months).

In conclusion, our results confirm a significant improvement in LSM in patients with HCV-related advanced liver disease after DAA treatment, probably due to reduced necro-inflammatory activity or improvement in portal hypertension. LSM variation, expressed as Δ LS, was correlated with HCC development after antiviral treatment. Monitoring HCV patients with LSM at EOT and subsequently calculating the Δ LS may improve the ultrasound-based screening for HCC identification after DAA treatment. However, even in patients with high decrease in LSM, this does not remove the need for US screening in patients with baseline cirrhosis of F3 fibrosis. These conclusions need to be confirmed by external validation and longitudinal studies. What is clear, however, is that the persistent risk of HCC development after HCV-eradication justifies the need for additional tools for surveillance in patients with HCV-related cirrhosis, and LSM variation could be useful in this context.

Conflict of interest statement

FR, FC, BF, IS, MLBR, AC, GM, AC, DF declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript. PA: Consultant: Roche, MSD, Janssen Cilag, AbbVie, Boehringer, Ingelheim, Gilead Sciences, Intercept, BMS; SB: Grant: Novartis, Gilead, Other: Gilead, Janssen, MSD; GV: Consultant: AbbVie, Gilead Sciences, BMS., Sponsored Lectures (National or International): AbbVie, Gilead Sciences, BMS, MSD.

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.2018.02.010>.

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