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MINIREVIEWS

Elastography as a predictor of liver cirrhosis complications after hepatitis C virus eradication in the era of direct-acting antivirals

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Abstract

Chronic inflammation due to hepatitis C virus (HCV) infection leads to liver fibrosis and rearrangement of liver tissue, which is responsible for the development of portal hypertension (PH) and hepatocellular carcinoma (HCC). The advent of direct-acting antiviral drugs has revolutionized the natural history of HCV infection, providing an overall eradication rate of over 90%. Despite a significant decrease after sustained virological response (SVR), the rate of HCC and liver-related complications is not completely eliminated in patients with advanced liver disease. Although the reasons are still unclear, cirrhosis itself has a residual risk for the development of HCC and other PH-related complications. Ultrasound elastography is a recently developed non-invasive technique for the assessment of liver fibrosis. Following the achievement of SVR, liver stiffness (LS) usually decreases, as a consequence of reduced inflammation and, possibly, fibrosis. Recent studies emphasized the application of LS assessment in the management of patients with SVR in order to define the risk for developing the complications of chronic liver disease (functional decompensation, gastrointestinal bleeding, HCC) and to optimize long-term prognostic outcomes in clinical practice.

Key Words: Direct-acting antiviral agents; Liver stiffness; Portal hypertension; Hepatocellular carcinoma

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Core Tip: Direct-acting antiviral agents lead to hepatitis C virus eradication and to the regression of liver inflammation. However, they do not eliminate the risk of possible portal hypertension-related complications and hepatocellular carcinoma (HCC), increasing the necessity for post-sustained virological response surveillance and the development of non-invasive predictive models to detect the categories of patients requiring more intensive follow-up. Many studies reported a significant reduction in liver fibrosis markers after treatment with direct-acting antiviral drugs. Ultrasound elastography is gaining growing importance as a predictive element in the assessment of the risk of developing esophageal varices or gastrointestinal bleeding, liver functional decompensation and HCC.

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INTRODUCTION

Hepatitis C virus (HCV) infection is one of the major causes of chronic liver disease and a significant cause of morbidity and mortality worldwide[1]. In 2015, it was estimated that over 70 million people were affected, most of whom were unaware of the infection[2]. Chronic inflammation due to HCV infection leads to liver fibrosis and rearrangement of liver tissue, which is responsible for the development of portal hypertension (PH) and other complications. Moreover, inflammation and microenvironmental changes are known risk factors for the occurrence of hepatocellular carcinoma (HCC)[3].

The advent of direct-acting antiviral drugs (DAAs) has revolutionized the natural history of HCV infection, providing an overall eradication rate of over 90% associated with a remarkable safety profile in all stages of chronic liver disease[1].

The achievement of sustained virological response (SVR) prevents the development of cirrhosis in the early stages of the disease and significantly reduces the risk of HCC and PH-related events, such as ascites, hepatic encephalopathy, hepatorenal syndrome, infections and gastrointestinal bleeding, in patients with advanced liver disease[4-6]. However, initial reports have warned of an increased risk of HCC in patients who achieved SVR after treatments with DAAs[7,8]. On the other hand, other studies have shown a protective effect on the development of HCC[9,10]. More recently, a meta-analysis analyzing 41 studies concluded that there is no evidence for increased occurrence or recurrence of HCC in patients treated with DAAs compared with interferon-based therapies[11].

Despite a significant decrease after SVR, the rate of HCC and liver-related complications is not completely eliminated in patients with advanced liver disease. Although the reasons are still unclear, cirrhosis itself has a residual risk for the development of HCC and other PH-related complications[12]. At present, there are no validated predictors to estimate the risk of HCC and PH-related events after HCV eradication.

Ultrasound elastography is a recently developed non-invasive technique for the assessment of liver fibrosis. Vibration controlled transient elastography (VCTE), is the oldest share-wave-based method and the reference standard in this field. The device is equipped with a one-dimensional probe, where a vibrator sends low frequency shear waves through the liver. Wave propagation, evaluated by an ultrasound receiver inside the probe, is directly related to liver tissue elasticity. Since its emergence, this technique has provided a fast point-of-care estimate of liver fibrosis in daily clinical practice, avoiding the complications of liver biopsy[13]. Indeed, several studies using histology as the reference standard defined accurate thresholds that are able to distinguish the different stages of liver fibrosis[14]. In the last few years, new ultrasound based elastographic techniques have been developed. They are embedded into conventional ultrasound devices, allowing visualization of the sampling area. The two main categories are the point shear wave elastography (pSWE) and bidimensional SWE (2D-SWE)[13]. All these devices are able to evaluate the elastic properties of the

liver during real-time B mode imaging. In particular, the ultrasound probe generates short-duration acoustic impulses in a small region of interest that causes soft tissue displacement and shear waves running in the perpendicular plane. Shear wave travelling speed can then be quantified and interpreted as a measurement for liver stiffness (LS)[13].

To date, LS measurement (LSM) is recommended by the European Association for the Study of Liver Disease (EASL) and the American Association for the Study of Liver Disease (AASLD) guidelines for the assessment of liver disease severity in patients with HCV infection eligible for DAAs[1,15]. Following the achievement of SVR, LS usually decreases, as a consequence of reduced inflammation and, possibly, fibrosis [16-19]. Recent studies evaluated the usefulness of LS assessment after HCV eradication and the prediction of HCC and other PH-related complications in patients with advanced liver disease.

In this review, we summarize the current evidence on the role of ultrasound elastography in the prediction of liver-related outcomes of patients with HCV infection treated with DAAs.

DIRECT-ACTING ANTIVIRAL AGENTS AND LIVER FIBROSIS

Despite DAAs being pharmacologically designed only for the eradication of HCV infection and since HCV is directly responsible for liver injury and consequent parenchymal fibrosis, the achievement of both SVR and anti-fibrotic effect results in advantages in terms of prevention of chronic liver disease complications (Table 1).

Different non-invasive methods traditionally used to assess liver fibrosis such as VCTE and the Fibrosis-4 (FIB-4) score (based on patient's age, transaminases levels and platelet count) and aspartate aminotransferase to platelet ratio index (APRI score) have been evaluated for staging chronic liver disease and predicting hepatic fibrosis in patients with HCV infection.

It has been demonstrated that baseline LSM by VCTE together with FIB-4 and APRI score have an important role in the prediction of treatment outcome in the new era of DAAs and could be integrated in pre-treatment assessment as a guide for treatment decisions and optimization of patient management[20,21].

Many authors have documented the improvement of VCTE, FIB-4 and APRI score after DAAs treatment. However, it is not clear if this finding is a true recovery of liver fibrosis or represents only an epiphenomenon of the reduction in liver inflammation resulting in the normalization of blood tests and decrease of LS values[22-25]. The retrospective study by Elsharkawy *et al*[26] analyzed a group of 337 Egyptian patients with chronic genotype 4 HCV infection who underwent sofosbuvir-based treatments. Among the patients evaluated, 29.1% had non-relevant fibrosis (F0-1; VCTE < 7.1 kPa), 17.2% were included in the F2 group (7.1 kPa ≤ VCTE < 9.5 kPa), 8.6% in the F3 group (VCTE ≥ 9.5 kPa) and 45.1% were classified as cirrhotic (F4; ≥ 12.5 kPa). One year after treatment, 77% of responders (with any stage fibrosis) and 81.8% of cirrhotic patients had a valuable recovery in liver fibrosis parameters (measured with FIB-4 and APRI score), due to the increase in platelet count and decrease in transaminase levels together with a reduction in LS values (11.8 ± 8.8 kPa *vs* 14.8 ± 10.7 kPa, $P = 0.000$). A higher number of patients with poor LS improvement after DAAs-therapy was observed in cases with low baseline LS values and infection relapse.

In a group of 42 patients treated with DAAs, Chekuri *et al*[27] demonstrated a significant decrease in LS values at SVR 24 wk after the end of treatment (median values: 10.40 kPa *vs* 7.60 kPa, $P < 0.01$), without significant improvement in the follow-up.

Abdel Alem *et al*[28] used pre-treatment liver fibrosis (measured by VCTE and FIB-4 score) as a predictor of treatment outcome after sofosbuvir-based regimens in 7256 HCV patients (46.6% cirrhotic, 91.4% with SVR12). Both, baseline FIB-4 and VCTE were significantly lower in the group with SVR (2.66 ± 1.98 kPa and 17.8 ± 11.5 kPa, respectively) compared to relapsers (4.02 ± 3.3 kPa and 24.5 ± 13.9 kPa, respectively). Based on these results, the authors concluded that fibrosis stage is a crucial element in the evaluation of treatment outcome and disease prognosis. In particular, a LS value higher than 16.7 kPa resulted as an unfavorable prognostic factor for treatment response (relapse rate 13%), probably related to an impaired immune-mediated HCV clearance that is worsened in advanced liver fibrosis. Similar considerations were drawn by Neukam *et al*[29] in patients treated with pegylated interferon/ribavirin-based therapy associated with NS3/4A protease inhibitor (PR-PI) and patients under DAAs therapy. In the PR-PI group, SVR12 was obtained in 59.6% of patients with LS < 21 kPa and in 46.5% of subjects with LS ≥ 21 kPa ($P = 0.064$); in the DAAs group,

Table 1 Liver stiffness improvement after treatment with direct acting antivirals

Ref.	Study design	Number of Patients	Drugs	Patients with LS improvement (%)	Pre-treatment LS	Post-treatment LS	*P* value	Measurement
Elsharkawy *et al*[26], 2017	Retrospective	337	DAA	81.8% (cirrhotic) 71.7% (non-cirrhotic)	14.8 ± 10.7 kPa	11.8 ± 8.8 kPa	0.000	Fibroscan
Chekuri *et al* [27], 2016	Observational	100	IFN-based and DAA	NA	10.40 kPa	7.60 kPa	< 0.01	Fibroscan
Bachofner *et al* [30], 2017	Multicenter, observational	392	DAA	93%	12.65 kPa	8.55 kPa	< 0.001	Fibroscan
Afdhal *et al* [39], 2017	Prospective	52	DAA	59.6%	15.2 kPa	9.3 kPa (6.7–16.8 kPa)	< 0.0001	Fibroscan
Ravaioli *et al* [68], 2018	Retrospective	139	DAA	44.6% (LS reduction > 30%)	18.6 kPa (15-26.3 kPa)	13.8 kPa (10.4-20.4 kPa)	< 0.001	Fibroscan
Pan *et al*[70], 2018	Retrospective	84	DAA	62%	Fibrosis regression by at least two stages: Cirrhosis group (48%); F3 fibrosis group (39%)		-	Fibroscan

DAA: Direct acting antivirals; IFN: Interferon; LS: Liver stiffness; NA: Not applicable.

SVR12 was reached by 95.3% of patients with LS < 21 kPa and 87.4% of patients with ≥ 21 kPa. Relapse rates after an apparent end-of-treatment response were 4.8% *vs* 17.9% in patients treated with PR-PI and 2.4% *vs* 8.2% in the DAAs group, respectively, for LS < 21 kPa and ≥ 21 kPa. These results suggest that LS evaluation might be useful to avoid HCV-relapse in cirrhotic patients by choosing both the appropriate composition and duration of DAAs-therapy.

Many studies reported a significant reduction in liver fibrosis markers after treatment with DAAs. In particular, Bachofner *et al*[30] highlighted a 32.4% drop in VCTE values from 12.65 kPa to 8.55 kPa ($P < 0.001$), a reduction of FIB-4 from 2.54 to 1.80 ($P < 0.001$) and a decrease of APRI from 1.10 to 0.43 ($P < 0.001$).

DIRECT-ACTING ANTIVIRAL AGENTS AND LIVER CIRRHOSIS RELATED EVENTS

Even though DAA-therapy leads to HCV eradication and to the regression of liver inflammation, it does not eliminate the risk of possible PH-related complications and HCC, increasing the necessity for post-SVR surveillance and the development of non-invasive predictive models to detect the categories of patients requiring more intensive follow-up (Table 2).

To this purpose, Trivedi *et al*[31] suggested a VCTE-based algorithm in order to schedule the controls of patients with SVR after HCV eradication: In the case of mild fibrosis (F1) without liver-related comorbidities, regular monitoring with the primary care physician is indicated; for advanced fibrosis/cirrhosis (F3-4), routine HCC and variceal surveillance is prescribed (six-monthly ultrasound, upper endoscopy every 2-3 years, annual non-invasive fibrosis assessment); for moderate fibrosis (F2) or in the case of concomitant liver-related comorbidities an annual non-invasive fibrosis measurement should be performed.

The importance of liver fibrosis stage in the development of liver-related complications was confirmed by Kozbial *et al*[32], who analyzed 551 patients treated with DAAs for a median period of 65.6 wk: No complications were registered in patients with severe fibrosis, whereas 9.1% of subjects with compensated cirrhosis developed liver-associated complications including HCC (4.1%). Furthermore, the presence of decompensated cirrhosis was markedly associated with the development of complications and mortality.

Even though histology remains the gold standard in evaluating fibrosis, liver biopsy presents some potential obstacles such as patient compliance, severe post-procedural complications, and sampling errors. For this reason, elastography has been proposed as a possible non-invasive alternative to biopsy for patient surveillance after SVR[33-35].

Table 2 Direct-acting antiviral agents and liver cirrhosis related events

Ref.	Study design	Number of patients	Drugs	HCC	Portal hypertension-related complications
Kozbial *et al* [32], 2018	Prospective	551	DAA	16 (4.1%)	Ascites: 3.1%; variceal hemorrhage: 1%; hepatic encephalopathy: 0%
Masuzaki *et al* [36], 2009	Prospective	984	DAA	77 (2.9% *per* 1 person-year); HCC risk: 45.5 times higher in LS > 25 kPa	NA
Afdhal *et al* [39], 2017	Prospective	50	DAA	LS improvement in patients who did not develop HCC during follow-up (42.6% reduction in patients without HCC *vs* 13.6% in HCC group)	24% patients had ≥ 20% decreases in HVPG during treatment (89% subjects with baseline HVPG ≥ 12 mmHg had a ≥ 20% reduction in HVPG after SVR)
Giannini *et al* [51], 2019	Prospective	52	DAA	4 (7.7%)	Clinical decompensation: 0%
Tachi *et al*[58], 2017	Prospective	263	DAA	19 (7.2%)	NA
Foster *et al* [60], 2016	Retrospective, observational	467	DAA	NA	MELD improvement (0.85, SD 2.54); composite adverse outcome in 52.0% (treated) *vs* 61.7% (untreated)
Rinaldi *et al* [63], 2019	Multicenter, prospective	258	DAA	35 (13.6%)	NA
Ravaioli *et al* [68], 2018	Retrospective	139	DAA	20 (14.4%)	NA
Pan *et al*[70], 2018	Retrospective	84	DAA	4 (4.8%)	NA
Toyoda *et al* [75], 2015	Retrospective/prospective	522	IFN-based	18 (1.2% after five yr; 4.3% after ten yr)	NA
D'Ambrosio *et al*[77], 2018	Prospective	38	DAA	5 (13%)	Clinical decompensation: 0%
Lleo *et al*[78], 2019	Prospective	1927	DAA	Previous HCC: 38/161 (recurrence rate: 24.8 *per* 100-yr); No previous HCC: 50/1766 (incidence rate: 2.4 *per* 100-yr)	NA
Hamada *et al* [79], 2018	Retrospective	196	DAA	8 (4.1%)	NA

DAA: Direct acting antivirals; HCC: Hepatocellular carcinoma; HVPG: Hepatic venous pressure gradient; IFN: Interferon; LS: Liver stiffness; MELD: Model for end-stage liver disease; NA: Not applicable; SD: Standard deviation; SVR: Sustained virological response.

VCTE is gaining growing importance as a predictive element in the assessment of the risk of developing esophageal varices or gastrointestinal bleeding, liver functional decompensation and HCC[36]. The retrospective study by Mandorfer *et al*[37] was the first to compare Hepatic Venous Pressure Gradient (HVPG) measurement with VCTE for the assessment of PH and showed a good agreement between the techniques. The authors also observed that a PH decrease after SVR was less likely in subjects with baseline HVPG higher than 16 mmHg and severe liver function impairment.

The review by Garbuzenko *et al*[38] confirmed that staging the severity of PH in cirrhotic subjects and personalized preventive therapy could lead to an increase in both patient survival and treatment effectiveness; particularly, DAAs achieve the amelioration of subclinical PH. In a recent study by Afdhal *et al*[39] of 50 patients with clinically significant PH (presence of esophageal varices, HVPG > 6 mmHg) from different international centers, 89% obtained a HVPG reduction of > 20% and only 3 patients obtained a reduction of portal pressure to less than 12 mmHg.

Paternostro *et al*[40] endorsed spleen stiffness measurement (SSM) through elastography (especially pSWE and 2D-SWE) as an effective tool for high-risk varices assessment in chronic liver disease, especially in distinguishing between small and large varices as confirmed by Sharma *et al*[41]. Previously, both Colecchia *et al*[42] and Fraquelli *et al*[43] had underlined the efficacy of LSM and SSM association in the assessment of HVPG and prediction of gastroesophageal varices in cirrhotic patients, showing a very high sensitivity (98% and 100% in the two studies, respectively), and economic advantages following the implementation of endoscopic screening progr-

ams. However, there are some important limitations related to SSM: It is an operator-dependent measurement and the upper limit of VCTE is fixed to a fibrosis value of 75 kPa that, in the case of severe PH, could be widely exceeded by SSM unlike LSM. Concerning the latter issue, Calvaruso *et al*[44] demonstrated the superior predictive value of SSM for high-risk varices, adopting a modified VCTE unit with a maximum stiffness value of 150 kPa (AUC: 0.80 for SSM *vs* 0.71 for LSM).

It has been demonstrated that the association of LSM with other non-invasive items (*e.g.* platelets, SSM) has a powerful positive predictive value in the detection of esophageal varices: Stefanescu *et al*[45] created a simple diagnostic algorithm with the combination of LSM and SSM (cut-off: 19 kPa and 55 kPa, respectively), thus reaching a 93% sensibility and a 95% positive predictive value.

Wang *et al*[46] observed that the combination of Baveno VI criteria with SSM (with 46 kPa cut-off) might help to avoid 61.6% of esophagogastroduodenoscopies in HBV-related cirrhosis with persistent viral suppression due to antiviral therapy, missing less than 5% high-risk varices.

An interesting analysis by Fofiu *et al*[47] evaluated a score based on the combination of LSM, SSM and spleen size as non-invasive predictors of high-risk varices in compensated cirrhosis, proving a better performance of the association of the three elements compared to each parameter alone. However, a meta-analysis by Ma *et al*[48] found that SSM alone is superior to LSM in predicting any grade esophageal varices, thus turning out to be useful in clinical practice, especially in the case of non-measurable LSM (multifocal HCC, biliary obstruction or liver metastasis).

Semmler *et al*[49] underlined the predictive value of LSM by VCTE included in a non-invasive algorithm together with von Willebrand factor-platelet count ratio as a useful method to define PH, stratify risk categories and predict liver decompensation and HCC development in patients with HCV-related advanced chronic liver disease treated with DAAs. These results could be very interesting in introducing the concept of a tailored follow-up strategy.

It is still not clear if the improvement in non-invasive markers after SVR could be associated to a decline in PH itself. However, in a recent study, Thabut *et al*[50] noted that subjects with previous unfavorable Baveno VI status (LS > 20 kPa, platelets < 150000/mm^3) who experienced platelets increase and/or LS reduction after SVR reached a favorable Baveno VI class, with a subsequent reduction in the probability of PH progression and development of esophageal varices. A decrease of PH has also been demonstrated by Giannini *et al*[51] in a group of 52 patients with advanced fibrosis/cirrhosis at baseline followed for approximately 60 wk after SVR with DAAs. A significant improvement in HVPG was detected, together with a decrease in LS values (from 15.2 kPa at baseline to 9.3 kPa at the end of follow-up), APRI and FIB-4 score, spleen bipolar diameter and an increase in platelet count[37].

As the role of these indices is quite limited, other non-invasive methods have been proposed to detect varices at high risk of bleeding: Considering the worldwide low availability of TE, Jangouk *et al*[52] demonstrated the effectiveness of Baveno VI consensus criteria as a non-invasive method to identify patients with compensated liver cirrhosis and low-risk of varices requiring endoscopic treatment. In particular, the authors highlight the uppermost role of both platelet count (> 150000/mm^3) and MELD score (< 6) in defining a low probability of high-risk varices.

Chen *et al*[53] demonstrated the efficacy and extremely high negative predictive value (97.1% in the study group and 98.1% in the validation cohort) of the association of albumin-bilirubin grade with platelet count (ALBI-PLT score) in the screening of high-risk esophageal varices in subjects with HCC: The 5-year variceal hemorrhage rate was 9.7% in patients with ALBI-PLT score > 2 (decompensated liver disease) as compared to 1.7% in those with a score of 2 (P = 0.007).

Baveno VI guidelines indicate platelet count and VCTE as effective elements in the identification of cirrhotic patients who are at high-risk of developing esophageal varices: Due to the not-always easy access to VCTE (for example, in the case of inmates) or to the unavailability of adequate instrumentation in all hepatological centers, Calvaruso *et al*[54] proposed the "Rete Sicilia Selezione Terapia–HCV" algorithm as an effective and simple tool (based only on blood tests: Platelet count and serum albumin level) that could substitute Baveno VI criteria in the identification of HCV-cirrhotic patients with medium/large varices, thus simplifying the diagnosis of the complications of PH, with a reduction of more than 30% of useless endoscopic exams and diminishing the risk of false-negative results.

The implications of HCV eradication on HCC development are even more complex. Despite the widely demonstrated efficacy of DAAs in both achieving SVR and a reduction in liver fibrosis, there is no corresponding decrease in HCC development risk. These data led to an initial alert claiming the possibility of a DAAs-driven

oncogenic mechanism[7], even if this theory was subsequently proved wrong by other studies[11]. The mechanism of HCC development post SVR is probably sustained by a "point of no-return" in HCV pathogenesis that determines the loss of the potential benefits brought by viral eradication[55]. This evidence highlights the necessity for optimizing regular HCC surveillance with a particular focus on patients with advanced fibrosis or cirrhosis[56]. In fact, even though a decrease in LS values from cirrhosis to advanced fibrosis was observed in some cases after DAAs therapy, patients with SVR maintained an elevated HCC risk[57,58].

Whether the HCC risk of patients with SVR coincides with that of viremic subjects is still a matter of debate. In the case of precariously compensated or decompensated liver function, the achievement of SVR could be useful to reduce the risk of HCC because of the decrease in intrahepatic inflammatory processes, despite the persistence of PH and decompensated liver function (that increase the risk of liver cancer in cirrhotic patients)[59,60].

Both EASL and AASLD guidelines recommend continuing ultrasound surveillance in subjects with advanced fibrosis/cirrhosis despite histological response to treatment and suggest accurate definition of the additional baseline risk-factors profile[61,62].

Rinaldi *et al*[63] assessed the importance of both baseline LS evaluation and ultrasound liver surveillance for the risk of HCC in patients with HCV-related cirrhosis, treated with DAAs: Among 258 subjects enrolled, divided into three groups according to liver fibrosis stage (< 20 kPa, from 20 kPa to 30 kPa, > 30 kPa), 35 developed HCC during follow-up. The group with LS higher than 30 kPa had a statistically significant increase in HCC risk [HR (95%CI): 0.329 (0.131-0.830); $P = 0.019$].

Even though the mechanisms directly involving HCV in both fibrogenesis and oncogenesis have not yet been completely explained, it seems crucial to define the degree of liver fibrosis through VCTE and FIB-4, in order to set appropriate HCC screening and the subsequent therapeutic strategy[64,65].

Many attempts have been made to create prognostic scores to evaluate the risk of HCC development in chronic liver diseases, considering other criteria than PH alone [66]. An interesting example is represented by the King score that includes laboratory parameters (platelet count and bilirubin levels) and gene signature, and classifies cirrhotic patients with HCV infection into three risk categories for functional decompensation, HCC and death. However, it is not clear if this score maintains its predictive efficacy in patients with SVR[67].

Ravaioli *et al*[68] studied 139 cirrhotic patients treated with DAAs, analyzing the difference between LS at baseline and at the end of treatment: They found a lower reduction of LS in patients who developed HCC compared to patients who did not (-18.0% *vs* -28.9%, $P = 0.005$).

Recent studies demonstrated that LS assessment after SVR could be an inaccurate method to define the grade of fibrosis in patients treated with DAAs. In fact, the fast modifications in LS could be determined by both the reduction of liver inflammatory activity and the narrowing of fibrotic septa, without real histological improvement in fibrosis grading as demonstrated by liver biopsy[69-71]. Notwithstanding, LS evaluation by VCTE remains a cornerstone in the assessment of HCC risk after SVR, especially due to its non-invasiveness.

Masuzaki *et al*[36] demonstrated that HCC risk was 45.5 times higher in patients with LS values higher than 25 kPa.

However, it becomes important in the association to other elements in a more complete non-invasive score. Among them, we can include: Age, alcohol abuse, pre-treatment advanced fibrosis/cirrhosis, platelet count, steatosis, diabetes, alfa fetoprotein (AFP), baseline gamma-glutamyltransferase (GGT) levels together with ethnic and environmental factors. All these factors have been studied in patients treated with interferon-based therapies with interesting results[72-76]. During the pre-DAAs era, studies on the complications of liver cirrhosis after HCV-treatment showed that SVR and fibrosis regression did not prevent hepatic carcinogenesis. D'Ambrosio *et al*[77] found that 13% of patients who responded to interferon-based treatments, developed HCC during an 8-year follow-up (17% cumulative probability and 1.2% annual incidence rate) whereas neither variceal-bleeding nor liver-function decompensation occurred. Higher baseline levels of GGT and glycemia were identified as risk factors for HCC development. Similarly, Toyoda *et al*[75] demonstrated that diabetes mellitus and FIB-4 index increase represent risk factors for HCC after SVR with interferon-based regimens, thus suggesting continuing active surveillance in these groups of patients.

In a prospective analysis of 1927 patients with HCV-related cirrhosis, receiving DAAs in ten tertiary Italian liver centers, Lleo *et al*[78] observed a recurrence rate of HCC of 24.8 *per* 100 patients/year and a *de novo* occurrence rate of 2.4 *per* 100

patients/year. They found that treatment failure and high AFP levels represent independent predictors of HCC development, while SVR and absence of PH are associated with a lower HCC incidence, suggesting that HCC risk stratification should rely on the presence of PH and elevated baseline AFP levels.

It has been suggested that PH as a complication of liver fibrosis (more than fibrosis itself) may represent an independent risk factor for HCC[66]. Afdhal *et al*[39] analyzed 50 patients with HCV-related liver cirrhosis treated with DAAs and observed a significant reduction in HVPG values during long-term follow-up after SVR: 24% of all patients and 89% of subjects with baseline HVPG ≥ 12 mmHg who reached SVR had a ≥ 20% reduction in HVPG. With regard to LS, a more evident improvement was observed in patients who did not develop HCC during follow-up (42.6% reduction in patients without HCC *vs* 13.6% in the HCC group), thus proposing a protective role of HVPG and LS against HCC development.

In a recent retrospective study performed in patients with SVR after DAAs, Hamada *et al*[79], identified six variables that could be included in the HCC prediction model: Age, body mass index, platelet count, albumin, AFP, LS and FIB-4 index. Following multivariate analysis they found that age ≥ 75 years, AFP ≥ 6 ng/mL, and LS ≥ 11 kPa were independent risk factors for hepatocarcinogenesis (risk ratio: 35.16, 43.30 and 28.71, respectively; P = 0.001, 0.003 and 0.006, respectively). In particular, patients with LS < 11 kPa had a cumulative HCC incidence of 1.3% at 12 mo, 24 mo, 36 mo and 48 mo, while in the group with LS > 11 kPa the HCC incidence rate was 4.6% at 12 mo and 24 mo, 24.8% at 36 mo and 62.4% at 48 mo.

The role of LSM in the development of a prediction model for HCC has also been emphasized by Feier *et al*[80]. They confirmed that high levels of AFP, transaminases and LS are excellent predictors of HCC but underlined the importance of interquartile range (IQR) in LSMs. This led to the hypothesis of "stiffness shadow" that indicated an inhomogeneous shear stress due to the chaotic tumoral growth in the already hard cirrhotic tissue, with relevant diagnostic repercussions[81,82]. The overall prognostic model combining the four variables demonstrated relevant results both in the training and validation phase with a positive relation with tumor size. The four parameters together showed a 64.5% HCC prediction, with LS alone reaching the highest predictive power. The authors concluded that an elevation in LS values and IQR during follow-up could enhance the diagnostic skill towards early HCC[80].

It is interesting to note that some genetic factors also seem to be involved in hepatocarcinogenesis, despite the lack of clear evidence and the need for further prospective studies.

In their cohort of 200 patients with HCV-related cirrhosis with SVR after DAAs, Simili *et al*[83] noted a strong association of the single-nucleotide polymorphism of interleukin 28 (IL28B–rs12979860) with HCC development (both *de novo* and disease recurrence); furthermore, they observed a relation of HCC with lower levels of serum retinol and the presence of another two polymorphisms: Major histocompatibility complex class I polypeptide-related sequence A gene (*MICA*) and tolloid-like 1. The latter has proven particularly controversial since its oncogenic role was stated by Matsuura *et al*[84] but denied by Degasperi *et al*[85]: The difference between these studies could be ascribed to the different allele frequency or the presence of still unknown cofactors in the two ethnic groups (Japanese and Caucasian) or to discrepancies in the length of the follow-up period.

CONCLUSION

DAAs-therapy has brought about an effective revolution in hepatology resulting in HCV eradication in a wide range of patients and eventually reducing liver fibrosis after SVR. However, these benefits have not erased the risk of developing liver disease-related complications and in particular HCC and PH associated events. For this reason, it is crucial to continue long-term systematic surveillance after HCV eradication focusing on the subjects with a high-risk score.

Due to its accuracy, cost-effectiveness and non-invasiveness, together with specific clinical and laboratory parameters, LSM is gaining a relevant role in the construction of algorithms assessing both liver fibrosis and PH. The potential application of this non-invasive and simple method has been emphasized especially in the management of patients with SVR in order to define the risk to develop the complications of chronic liver disease (functional decompensation, gastrointestinal bleeding, HCC) and optimize long-term prognostic outcomes in clinical practice.

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