Slow regression of liver fibrosis presumed by repeated biomarkers after virological cure in patients with chronic hepatitis C

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Background & Aims: Chronic hepatitis C is both a virologic and fibrotic disease and complications can occur in patients with sustained virologic response (SVR) with residual fibrosis. Due to the limitations of repeated biopsies, no studies have assessed the dynamic of fibrosis before and after treatment. Using biopsy as reference, FibroTest™ has been validated as a biomarker of fibrosis progression and regression, with similar prognostic values. The aim was to estimate the impact of SVR on the dynamic of fibrosis presumed by FibroTest™.

Methods: In a prospective cohort, the main end point was the 10-year regression rate of fibrosis, defined as a minimum 0.20 decrease in FibroTest™, equivalent to one METAVIR stage.

Results: A total of 933 patients with both repeated FibroTest™ and transient elastography were included. At 10 years, among the 415 patients with baseline advanced fibrosis, 49% (95% CI 33–64%) of the 108 SVR had a regression, which was greater than in the 219 non-responders [23% (14–33%; p <0.001 vs. SVR)] and not lower than in the 88 non-treated [45% (10–80%; p = 0.39 vs. SVR)] patients. In all 171 SVR, cirrhosis regressed in 24/43 patients, but 15 new cirrhosis cases occurred out of 128 patients, that is only a net reduction of 5.3% [(24–15) = 9/171); (2.4–9.8%)].

Four cases of primary liver cancer occurred in SVR [4.6% (0–9.8%)] and 13 in non-responders [5.6% (1.5–9.8%); p = 0.07]

Conclusions: In patients with chronic hepatitis C, and as presumed by FibroTest™, virological cure was associated with slow regression of fibrosis 10 years later, a disappointing 5% decrease in cirrhosis cases, and a remaining 5% risk of primary liver cancer. © 2013 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Introduction

Chronic hepatitis C (CHC) is both a virologic and fibrotic disease [1], with mortality resulting mainly from the complications of cirrhosis [2]. Therefore, a sustained virologic response (SVR) is considered the first step toward reducing future HCV mortality [3]. However, complications, such as primary liver cancer (PLC), can occur in patients who have recovered from the hepatitis C virus but continue to have residual fibrosis [4], even 13 years after SVR [5].

Due to the limitations of repeated biopsies, few studies have been done on the long-term outcomes of fibrosis using repeated biopsies in SVR [6-10] (Supplementary File 1). In 2002, we analyzed the larger study, including 1094 SVR with a 2-year interval between biopsies and discussed the need of non-invasive biomarkers for longer follow-up [8]. The study with longer mean interval between biopsies (4-year) included only 60 SVR with 12 advanced fibrosis [9].

Assessment of fibrosis dynamics can now be achieved through the validation of biomarkers such as FibroTest™ (FT) approved in France by health authorities in CHC as an alternative to liver biopsy for staging fibrosis [11,12]. Furthermore, FT was also validated vs. biopsy for assessing fibrosis progression rate (FPR) [7,13], fibrosis regression rate (FRR) [7,14], predicting mortality [15,16] and cost-effectiveness [17].

Since 1997, we have proposed the use of FT in all CHC patients followed in our hospital [17], including co-infected patients with HIV [19], and we set up a cohort (FIBROFRANCE-DOSVIRC) to estimate the dynamic of fibrosis. The specific goal of the present analysis was to estimate the impact of SVR on 10-year FR in comparison with non-responders (NR) and non-treated patients (NT).

Materials and methods

Cohort design

The details of this cohort were already published for first analyses on a subpopulation of 537 cases with baseline FT-biopsy permitting analyses of discordances [20] and validation of FT prognostic value [15]; details are described in Supplementary File 2.
Patients with cirrhosis (stage F4) at baseline were included as well as patients at risk of liver steatosis due to alcohol consumption or metabolic disorder.

Patients were excluded if they had other chronic liver diseases, including HBV-DNA PCR positive, a liver transplantation before the period of follow-up, spontaneous clearance of HCV-RNA, non-reliable or missing FT or TE, or less than a 6-month interval between 2 estimates. Patients with HIV co-infection were included as well as patients at risk of liver steatosis due to alcohol consumption or metabolic disorder.

All patients were followed in our clinic; we scheduled follow-up visits and non-invasive biomarker assessment at least every 2 years. Liver stiffness measurement by FibroScan™ (TE) was introduced in 2005. Patients analyzed in the present study had a minimum of 2 interpretable estimates of liver fibrosis (biopsy, FT or TE) done at least 6 months apart. For cirrhotic patients, ultrasonography was scheduled every 6 months and endoscopy every 2 years.

Estimates of fibrosis

FT includes serum γ-glutamyl-transpeptidase, adjusted for age and gender. FT scores range from 0 to 1.00. The FT components were analyzed according to published recommendations using the M probe of FibroScan® and results were expressed in kilopascals (kPa) [22].

Patients had liver biopsies done, mainly before 2007, and then after 2007 in case of discordance between FT and TE [11]. One experienced pathologist (FC), unaware of the biomarkers, evaluated the stage of fibrosis according to the METAVIR scoring system [24].

HCV-RNA was assessed by sensitive PCR methods with gradually improving sensitivities over time and ranging from 50 to 12 IU/ml.

Statistical analysis

FRR, the main end point, was defined as the percentage of patients who had achieved a significant decrease of fibrosis during follow-up. A significant FRR was defined as a minimum 0.20 FT decrease between the first and last FT measurement, equivalent to 1 METAVIR stage (or 1.53% area of fibrosis) [25]. FRR was assessed among patients with at least an advanced fibrosis (AdF) (stage F2, F3 or F4) at baseline, predetermined as an FT >0.48 [18].

The secondary end points focus on cirrhosis, the major source of complications. In patients without cirrhosis at baseline, we assessed the progression rate from non-cirrhotic stages to cirrhosis [F4PR (FT ≥0.74)] during follow-up. In patients with cirrhosis at inclusion, we assessed the rate of significant decrease of fibrosis (0.20 FT), which could be a significant surrogate marker of mortality and morbidity [15,16] and the cirrhosis regression rate [F4PR (FT <0.74 FT)].

The F4PR was also assessed from birth (or from date of infection when known) to baseline, which enabled to quantify the impact of SVR on the natural history of FP [13,26].

The following clinical end points were assessed to associate the FRR to morbidity and mortality: the 10-year overall survival (no death or liver transplantation) and survival without PLC and liver-related complications, using hospital and national mortality files (Supplementary File 2).

FRR was calculated from the date of the first FT to the date of the last FT. Clinical survival was calculated from the first FT to the date of death, transplantation or complications according to the circumstances. We used time-dependent methods to estimate the liver FR. The cumulative FRR at 10 years used the Kaplan Meir method and cumulative hazard function. Hazard function (HR) is the probability that a subject experiences the event of interest (in this case, regression or progression of fibrosis from one stage to a lower or higher stage) during a small time interval given that the individual has survived up to the beginning of the interval. Comparison used log-rank test, and proportional hazard regression multivariate analysis [13,26]. To avoid overestimation of patient’s effect, all cases contributed only to one group; NT were patients never treated during the whole follow-up, NR were patients who never achieved SVR. To take into account the timing of FT and dates of treatments, the interval between first FT and first treatment as well as between last treatment and last FT was included in multivariate analyses. The prognostic value of FT, TE and biopsy was assessed using the AUROC.

The main difference between included and non-included subjects was the prevalence of HIV-co-infection (25% vs. 9%; p <0.0001) (Table 1 and Supplementary File 3).

The median follow-up was 6.3 years for any pairs of fibrosis estimates (range 0.5–18.2 years), 5.3 for FT, 3.0 for TE, and 1.0 for biopsies. A mean of 4 HCV-RNA detections, all-negative, were performed per patient in the SVR group.

Results

Between September 1997 and June 2012, 1271 CHC were pre-included in the paired fibrosis estimates population. A total of 338 patients were excluded, mainly due to non-reliable or missing repeated FT/TE (Fig. 1). A total of 933 patients with paired FT and paired TE were included in the analysis; 171 (18%) were SVR, 424 (45%) NR, and 338 (36%) NT; 59% were male, 49 years of age, 68% Caucasians, and infected by genotype 1 in 62% of the cases. As presumed by FT, 415 (45%) patients had baseline AdF and 170 (18%) cirrhosis.

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Regression and progression

The main end point was assessed in the 415 patients with AdF; 49% of the 108 SVR (95% CI, 33–64) had regression at 10 years, which was higher than in the 219 NR [23% (14–33; p <0.001 vs. SVR)] and not different than in the 88 NT [45% (10–80%; p = 0.39 vs. SVR)] (Fig. 2).

Dynamics of fibrosis (hazard function plots) according to baseline stage and virologic response to treatment are given in Fig. 3. As expected, the FRR (p <0.001) in all SVR (Fig. 3E) was only due to the regression in SVR patients with AdF (Fig. 3A). The progression in all patients (Fig. 3F) was mostly due to the progression in SVR patients with AdF (Fig. 3A) AdF. There was no significant difference between progression of SVR and NR (p = 0.07).

Factors associated with FR

The SVR status was associated with FRR in multivariate analysis, [Hazard rate (HR) = 4.94 (2.59–9.44), p = 0.0001]. All other factors [body mass index (BMI), metabolic factors, the severity of immunosuppression if HIV co-infection (NADIR CD4), and the maximum declared consumption during follow-up of alcohol, cannabis and tobacco] were not significantly associated with FR in univariate analysis or in multivariate analyses when the following factors were taken into account: age, gender, baseline FT value, and timing between FT and treatments (Table 2 and Supplementary File 4).

Progression to cirrhosis and regression in cirrhosis (Table 3)

In the 171 SVR, before baseline 43(25%) patients progressed to cirrhosis and this rate (HR = 0.19; 0.11–0.26) was not reduced
during follow-up (HR = 0.24; 0.10–0.39), with occurrence of 15 (12%) new cirrhosis among 128 non-cirrhotic patients; cirrhosis regressed in 24 (56%) out of 43 patients (HR = 1.22; 0.35 to 2.09). The “net reduction” in 10 years was 9 cases out of 171 (5.3%; 2.4–9.8). Details are given in Supplementary File 5.

In SVR, the F4PR before baseline was lower than in NT (HR = 0.10; p < 0.001), and the F4RR greater than in NR (HR = 0.43; p < 0.001). In NT, F4PR (33/338) was tripled during the ten-year follow-up (HR = 0.35) in comparison with the 50-year period before baseline (28/338; HR = 0.10; p < 0.001).

Transient elastography (Supplementary File 6)

Using TE, FRR was higher in SVR [0.31 (0.16–0.47)] than in NR [0.18 (0.12–0.24); Log-Rank = 7.0; p = 0.008] and NT [0.10 (0.05–0.16); Log-Rank = 14.0; p < 0.001].

FPR was not significantly lower in SVR [0.19 (0.06–0.08)] than in NR [0.19 (0.12–0.27); Log-Rank = 0.3; p = 0.60] and not lower than in NT [0.16 (0.08–0.23); Log-Rank = 0.5; p = 0.46].

Using FT at 5 years, FRR also was higher in SVR [0.12 (0.06–0.18)] than in NR [0.04 (0.02–0.06); Log-Rank = 19.2; p < 0.0001] and NT [0.02 (0.00–0.04); Log-Rank = 22.9; p < 0.0001]. In contrast to TE, FPR using FT was lower than in NT [0.14 (0.09–0.20); Log-Rank = 19.5; p < 0.0001].

Mortality and morbidity

The 10-year overall survival in the SVR group was 98.7% (97.0–100) vs. 95.2% (92.4–98.0) in NR (p = 0.28 vs. SVR) and 96.2% (93.7–98.7) in NT (p = 0.30 vs. SVR) (Table 3). These survivals were not different than the survivals expected in the matched controls of the French population: 96.8% (96.1–97.5; p = 0.17), 97.0% (96.7–97.4; p = 0.52), 97.7% (97.2–98.1; p = 0.51), respectively (Table 4).

In patients with SVR, PLC occurred in 4 cases [incidence at 10 year 4.6% (0–9.8)], three HCC and one cholangiocarcinoma; two of these patients died. All these four patients had cirrhosis presumed by FT, TE or biopsy before inclusion; PLC occurred despite regression of cirrhosis to stage F2 as presumed by the last FT in two patients (Supplementary File 7). This survival without cancer in SVR [95.4% (90.1–1.00)] was lower than in NT [99.7% (99.1–1.00); p = 0.04] but not different than in NR [94.4% (90.2–98.5)].

The survival rate without transplantation was 98.7% (97.0–100) higher than in NR [92.3% (89.1–95.4); p = 0.02 vs. SVR) and not different than in NT [96.2% (93.7–100) (p = 0.27 vs. SVR)]

The 10-year survival rate without liver complications was 95.4% (90.1–100% vs. 90.5% (86.0–95.1) in NR (p = 0.09 vs. SVR) and 98.5% (96.5–1.00) in NT (p = 0.12 vs. NR).

FT and TE had significant prognostic value for all clinical end points. The AUROC for FT [0.78 (0.65–0.86)] was greater than that of biopsy [0.70 (0.54–0.81); p = 0.02] (Supplementary File 8).

HIV population

All estimates of FPR were higher in HIV than in non-HIV patients, before and during the follow-up period, in both SVR and NT. The “natural” F4PR from birth to baseline was dramatically higher in the 107 NT HIV [HR = 0.41 (0.17–0.64)] vs. 231 NT mono-infected patients [HR = 0.01 (0.00–0.03); p < 0.001]. Two independent factors were associated with F4PR: lymphocytes CD4 NADIR count [Risk Ratio = 0.995 (0.992–0.998) p = 0.001] and male gender [Risk Ratio = 2.55 (1.07–6.07) p = 0.03]. The same results were observed in patients with known date of infection, during
follow-up, and according to the use of atazanavir and nevirapine (Supplementary File 9).

**Sensitivity analysis**

After exclusion of HIV patients, results were similar than those in the overall population. The main end point was assessed in the 292 patients with baseline fibrosis; 47% of the 76 SVR (29–75) regressed at 10 years, which was higher than in the 173 NR [23% (13–34; \( p = 0.01 \) vs. SVR)] and not different than in the 88 NT [40% (29–91; \( p = 0.44 \) vs. SVR)].

**Discussion**

In comparison with previous studies, this retrospective analysis of a prospective cohort using repeated biomarkers has permitted to better quantify the dynamic of fibrosis according to the virological response to treatment and its relationships with severe complications.

Since 1996 [4], the remaining risk of hepatocellular carcinoma in SVR is already well established but no previous study had specifically estimated the remaining risk of persistent cirrhosis or AdF. An unseen threat is the persistence of liver injury despite viral clearance.

**Impact of SVR on fibrosis dynamic**

The main original result is the disappointing long-term impact of virological cure on fibrosis dynamic presumed by FT; 10 years after virologic cure, only 49% of SVR with advanced baseline fibrosis had a significant improvement and the net reduction of cirrhosis prevalence was only 5%.

When compared with previous studies of fibrosis dynamics in SVR using repeated estimates (Supplementary File 1) [6–10], more patients were analyzed, with repeat fibrosis estimates performed over a longer follow-up period, with the use of two control groups and appropriate time dependent methods.

The methodology used had several advantages. First, fibrosis regression could be quantified. SVR patients had significantly higher FRR compared with NR. This regression was very slow,
(50% in 10 years) as a mirror of the “natural” slow progression after infection [1]. An earlier analysis, i.e., before 5 years, would not have identified significant differences. These results reinforced the need for large cohorts followed for more than 5 years to assess treatment impact on fibrosis [6]. From these quantitative estimates, the published trials on maintenance therapy using regression of fibrosis as end points, with less than 5 years of follow-up, seem underpowered.

Second, cirrhosis regression was better assessed. D’Ambrosio et al. study is a landmark study describing for the first time the persistence of liver injury, such as capillarization, 5 years after HCV cure observed in 33 out of 38 cirrhotic patients, that is a 61% F4RR [10]. However, such study was not designed to assess accurately an F4RR as not including all the fibrosis spectrum of SVR patients. This F4RR was biased because two main factors of variability were not taken into account: first, biopsy staging has false positive/negative, even for cirrhosis stage; and second, among SVR without cirrhosis at baseline, “new” cirrhosis can occur several years later. In our study, in SVR patients with presumed cirrhosis at baseline, we found similar results with 24/43 (56%) F4RR; but if we included all the fibrosis spectrum of 171 SVR, 15 new cirrhosis occurred out of 128 SVR patients, leading to a much lower impact of SVR on the cirrhosis prevalence. The net reduction was only 9 cases out of 171 SVR that is a 5% cirrhosis reduction in 10 years. The pragmatic message for clinicians is to continue to estimate fibrosis dynamic despite viral cure, as fibrosis can progress in more than 10% of patients.

These results support the finding of Innes et al. who observed a disproportionate burden of liver-related morbidity in non-cirrhotic SVR who were discharged from care [28]. In our study population, we identified only SVR and young age as strong predictors of FR, after taking into account gender, baseline fibrosis and both timing of FT and treatments. We were unable to identify any significant impact from alcohol, metabolic factors, tobacco, or cannabis consumption. These negative results, however, did not enable the role of these factors to be ruled out. The prevalence of drinkers was low at baseline (8%) without significant variability during follow-up.

Third, it was possible to compare the F4PR before, during, and after treatment. Reflecting the standard of care recommendation to treat CHC with AdF, patients who had been treated had higher rates than NT patients. During the follow-up period, the F4PR in NT was worrisome, as it rose dramatically (doubled in 10 years) and reached similar rates as treated patients. This was even worse in patients co-infected with HIV. In these patients, despite the younger age and low number of metabolic risk factors, F4PR whatever the groups (SVR, NR, and NT), were significantly higher than in mono-infected patients. One case of HCC occurred out of 41 SVR and this is another argument for starting HCV treatment as soon as possible in these very high-risk patients [17].

Fourth, it was possible according to the factors associated with persistence of fibrosis and the characteristics of complicated cases, to identify SVR patients with a high-risk profile. No complications occurred in patients with presumed stage F0 or F1 at baseline. Males over the age of 45 years should be closely followed as well as HIV patients with previous history of low NADIR-CD4.

Impact of SVR on PLC incidence

We identified a 2.1% (0–4.5) 10-year incidence of HCC in 171 SVR, which was in accordance with other estimates [2,3,6,29], and a 4.6% incidence of PLC was similar to the 5.1% observed in a multicenter study of 192 SVR [29]. Our observed case of cholangiocarcinoma is the second case to have been described in SVR [30], but it was not unexpected, as the association between HCV and cholangiocarcinoma has been well-established [31]. All four PLC occurred in patients who had cirrhosis previously and despite a significant improvement of fibrosis in two, as already described once [32]. These observations offer a major argument for treating patients before they develop AdF.

The lack of a significant difference in PLC incidence between SVR and NR in our study could not be explained by the increase of PLC in SVR, but by a relatively lower incidence among NR. This could be due to the high percentage (34%) of NR receiving reinforced regimen.

Impact of SVR on mortality

As expected according to the PLC incidence, our mortality rates were also not significantly different than previous prognostic studies in SVR [2,3,6,15,16,29]. In a multicenter study, the 10-year cumulative incidence rate of liver-related mortality or transplantation was 1.9% (95% CI, 0.0–4.1%) in SVR and 27.4% (95% CI, 22.0–32.8%) in NR (p <0.001) [29], similar to our results: 1.3% (0.0–3%) in SVR and 7.7% (4.6–10.9%) in NR (p = 0.02). As for PLC rate, the mortality rate was possibly lower among NR in our study, because of the frequent reinforced regimen in NR.

Biomarkers could be used as surrogate markers of morbidity and mortality. As previously observed at 5 years, FT [15] and TE [16] had a significant prognostic value at 10 years, at least similar to that of biopsy. The ten-year mortality curve [29] was similar to our FPR curve using FT and not TE, which seemed less sensitive at least for the first 5 years [7,33] (Supplementary File 6). The 0.20 FT decrease obtained in 49% of SVR could be a real benefit in later survival. In patients with cirrhosis, if FT decreased from 0.95 to
Fig. 3. Regression (FR) or progression (FP) during follow-up. (A) AdF at baseline. FR was higher in SVR than in NR (Log-Rank = 11.5; $p = 0.001$) and not different than in NT (Log-Rank = 1.0; $p = 0.31$). (B) AdF at baseline. FP was not different in SVR compared to NR (Log-Rank = 0.8; $p = 0.39$) and lower than in NT (Log-Rank = 12.0; $p = 0.001$).

(C) No-AdF at baseline. FR was not different in SVR compared to NR (Log-Rank = 0.2; $p = 0.67$) and NT (Log-Rank = 0.18; $p = 0.001$) and NT (Log-Rank = 22.9; $p < 0.001$). (E) All patients. FR was higher in SVR than in NR (Log-Rank = 19.2; $p < 0.001$) and NT (Log-Rank = 22.9; $p < 0.001$). (F) All patients. FP was not significantly lower in SVR than in NR (Log-Rank = 3.3; $p = 0.07$) and lower than in NT (Log-Rank = 19.5; $p < 0.001$).

(This figure appears in colour on the web.)
0.75, a 40% decrease in the 5-year mortality could be expected [15]. In HIV co-infected patients, the use of atazanavir or nevirapine, rarely associated with false positive of FT, did not impact the results [19,34].

**Limitations**

Despite the prospective inclusion of patients, the predetermined hypothesis, and the unchanged biomarkers cut-offs since their first validation, this cohort design has multiple limitations.

The impact of SVR should have ideally been evaluated in a large trial vs. a control group with long-term follow-up and repeat biopsies (not-fragmented and length >25 mm), but this was not possible due to ethical and practical reasons. Biopsy is the classical reference but has 25% of false positive/negative for staging fibrosis [20,25,35], FT is not a perfect reference for staging but has been extensively validated with similar performance than biopsy in CHC [11,12,35] for FP [7,13], regression [7,14], even for discriminating intermediate stages [25], and for prognosis [15,16]. These evidence-based validations were mandatory for using such non-invasive design.

Biopsy is the only “direct” estimate of liver injury. Therefore, FT could not assess the impact of SVR on the whole spectrum of histopathological features associated with HCV-cirrhosis. Despite fibrosis regression, ductular proliferation vanishing and lobular zonation restoration, other features such as portal inflammation

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**Table 2. Factors associated with fibrosis regression among 415 patients with baseline AdF presumed by FibroTest™.**

<table>
<thead>
<tr>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>% Without regression</td>
</tr>
<tr>
<td>Final model</td>
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<tr>
<td>Treatment response</td>
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<tr>
<td>SVR</td>
<td>108</td>
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<tr>
<td>NT</td>
<td>88</td>
</tr>
<tr>
<td>NR</td>
<td>219</td>
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<tr>
<td>Baseline presumed stages using FibroTest™</td>
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<tr>
<td>F2F3</td>
<td>245</td>
</tr>
<tr>
<td>F4</td>
<td>170</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;50 yr</td>
<td>211</td>
</tr>
<tr>
<td>≥50 yr</td>
<td>204</td>
</tr>
</tbody>
</table>

Other data are available in Supplementary File 4.
²Comparison between each group.

**Table 3. Progression to cirrhosis and regression from cirrhosis, presumed by FibroTest™.**

<table>
<thead>
<tr>
<th>Fibrosis dynamic assessed</th>
<th>Progression to cirrhosis</th>
<th>Progression to cirrhosis</th>
<th>Regression of fibrosis in patients with cirrhosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage at first estimate</td>
<td>Birth to inclusion No fibrosis</td>
<td>Follow-up No cirrhosis</td>
<td>Follow-up Cirrhosis</td>
</tr>
<tr>
<td>Patients included</td>
<td>All (n = 933) F0-F3 only (n = 763) F4 only (n = 170)</td>
<td></td>
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</tr>
<tr>
<td>Time exposure in yr, mean (95% CI)</td>
<td>49.1 (18.0-86.8) 5.3 (0.5-14.4) 5.2 (0.5-13.4)</td>
<td></td>
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<tr>
<td>Cumulative time of analysis (yr)</td>
<td>50 10 10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hazard rates (95% CI), n</td>
<td>To cirrhosis To cirrhosis Decrease of fibrosis</td>
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<tr>
<td>SVR</td>
<td>0.185 (0.106-0.264), 171</td>
<td>0.244 (0.095-0.394), 128</td>
<td>-1.222 (-0.348-2.094), 43</td>
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<tr>
<td>NR</td>
<td>0.173 (0.123-0.224), 424</td>
<td>0.394 (0.233-0.555), 325</td>
<td>-0.429 (-0.155-0.703), 99</td>
</tr>
<tr>
<td>NT</td>
<td>0.100 (0.053-0.147), 338</td>
<td>0.348 (0.171-0.525), 310</td>
<td>-0.650 (-0.000-1.477), 28</td>
</tr>
<tr>
<td>Significance</td>
<td>p = 0.97</td>
<td>p = 0.68</td>
<td>p = 0.005</td>
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<td>SVR vs. NR</td>
<td>p = 0.001</td>
<td>p = 0.56</td>
<td>p = 0.93</td>
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<td>NR vs. NT</td>
<td>p &lt;0.001</td>
<td>p = 0.27</td>
<td>p = 0.09</td>
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<tr>
<td>Number of cirrhosis</td>
<td>New cirrhosis New cirrhosis Cirrhosis disappearance</td>
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<tr>
<td>SVR</td>
<td>43/171 (25%) 15/128 (12%) 24/43 (56%)</td>
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<tr>
<td>NR</td>
<td>99/424 (23%) 47/325 (14%) 28/99 (28%)</td>
<td></td>
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</tr>
<tr>
<td>NT</td>
<td>28/338 (8%) 33/310 (11%) 8/28 (29%)</td>
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</table>
and sinusoidal capillarization did not regress after SVR [10]. The persistence of these features could explain the late onset of complications [32,36]. Aging patients could also develop hepatic insufficiency and portal hypertension, particularly if capillarization is associated with metabolic factors or heavy alcohol consumption.

We acknowledge that this type of cohort is not representative of the general population. Patients who were enrolled in a tertiary center had selection bias with a high prevalence of HIV co-infected patients; however, multiple possible factors were taken into account in the multivariate analyses. An improvement might be a nationwide follow-up of SVR.

We acknowledge that an observational cohort has obvious limitations, as the standard of monitoring is not at the level of phase 3 randomized trials. However, we focused on compliant patients who accepted paired FT and TE, we used time-dependent methods, and the multivariate analyses always take into account the different timing of biomarkers and treatment. “The reduced number of NT after the first 5 years reflects only shorter follow-up as no NT patients were analyzed twice and switched in treated groups.”

Further bias could be related to the significant proportion of patients with missing paired FT data. However, there were no major differences between the characteristics of patients who accepted or not to have repeated fibrosis estimates. Finally, the impact of SVR was adjusted on the main factors associated with FP.

We acknowledge the absence of genetic assays; we only declare: VT, HM, FC, FIB, DT, PL, MAV, YB, MR, VR, and CK. The following authors have no possible conflict of interest to declare; TP, HM, FC, FIB, DT, PL, MAV, YB, MR, VR, and CK.

In conclusion, non-invasive biomarkers such as FT could be useful for identifying SVR patients with persistent AdF and remaining risk of other cirrhosis complications. These should at least be followed with ultrasound for cancer detection.

The second implication involves revisiting the pharmaco-economic models and the present controversies about HCV screening. The prevalence of patients with virological cure will increase dramatically with the improvement of new therapies. Treating patients before advanced fibrosis seems more rational. The new models will need to take into account the burden of this “post-HCV disease” and dynamics of liver fibrosis [17].

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Conflict of interest

TP has a possible conflict of interest as the inventor of FibroTest™ (FibroSure in USA) with a capital interest in BioPredictive the company marketing the tests. The patents belong to the public organization “Assistance Publique Hôpitaux de Paris”. MM, YN, and OD are full employee of BioPredictive.

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Authors’ contributions

TP: Study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; statistical analysis; study supervision; obtained funding.
MM, DT, PL, VR, CK, MAV, YB, MR: acquisition of data; analysis and revision of the manuscript critical; drafting of the manuscript critical; acquisition of data; technical and material support.

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Supplementary data

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