Impact of treatment against Hepatitis C virus on the overall survival in naive patients with advanced liver disease

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Abstract:260 words

Keywords: survival, HCV, sustained virological response, treatment
Background. The beneficial effect of achieving a sustained virologic response (SVR) after antiviral treatment against hepatitis C virus is well established. However it remains unclear whether unsuccessful treatment (non-SVR) also improves patient’s survival, especially in patients with advanced liver fibrosis.

Methods. We retrospectively evaluated the incidence of death or liver transplantation in the 427 naïve Child A patients with advanced fibrosis newly admitted in our hospital between 2000 and 2010. Patients were followed for a median time of 5.5 years.

Results. Baseline characteristics of untreated (N=102) and treated (N=325) patients were largely similar and there was no evidence of a bias of indication. Treated patients received a combination of interferon and ribavirin with a SVR rate of 32%. The incidence of death or liver transplantation per 100 person-years was 1.00, 3.20 and 5.44 in SVR, non-SVR and untreated patients, respectively. After adjusting on baseline characteristics the risk of death or liver transplantation was significantly lower in SVR than in non-SVR patients and in non-SVR than in untreated patients (hazard ratio equal to 0.35 and 0.51, respectively; p=0.019 and 0.038, respectively). The effect of treatment in non-SVR patients was higher in patients who had a virological or a biochemical response than in those who did not have a virological or a biochemical response.

Conclusions. The risk of death or liver transplantation was significantly lower in treated than in untreated patients. Moreover there was a gradient of mortality between SVR, virological or biochemical responders and untreated patients, suggesting that treatment, even in absence of viral eradication, has a beneficial effect on survival.
Introduction

Chronic infection with hepatitis C virus (HCV) affects approximately 160 million people worldwide and is the leading cause of cirrhosis, hepatocellular carcinoma (HCC) and liver transplantation (1) (2) (3). The goal of treatment is to achieve a sustained virological response (SVR) defined by the absence HCV RNA 6 months after the end of treatment. Although viral eradication is thought to delay or even reverse the course of the disease (4), the evaluation of SVR effect is mostly based on retrospective cohorts whose results are often hampered by a large rate of loss to follow up and population or treatment heterogeneity. In particular most studies which showed a beneficial effect of SVR on clinical outcome were obtained on heterogeneous population (5)(6)(7)(8)(9) and did not stratify on the stage of liver fibrosis, which is yet a major determinant of survival in HCV infected patients (10)(11)(12)(13). Recently two studies have been published showing that SVR was associated with a lower incidence of HCC and all-cause mortality in patients with advanced liver diseases (14)(15). However the number of patients remained limited and more data are still needed to confirm these findings.

Until recently the reference therapy was pegylated-interferon and ribavirin (Peg-IFN+RBV). In spite of the emergence of direct acting antivirals that are rapidly changing the landscape of HCV treatment, a large proportion of patients with advanced liver disease still do not achieve SVR. For those non-SVR patients it remains unclear whether treatment has any benefit on overall survival. In a population of 345 Japanese cirrhotic patients only SVR but not non-SVR were found to significantly reduce the risk of overall deaths (16). Alternatively in a recent study cirrhotic non-SVR patients had an improved survival compared to untreated patients. However the number of untreated patients was small (N=48 patients) and 35% of both untreated and treated patients had received a treatment before inclusion in the study, making it difficult to evaluate the intrinsic effect of treatment on survival (15).
Overall the amount of data looking specifically to the effect of treatment in non-SVR patients remains very limited.

Here we used the HEPALIST database, a large repertoire of patients admitted for care at Beaujon Hospital (Paris area, France) to evaluate the benefit of treatment with or without SVR on overall survival.

Methods and Materials

Patients

HEPALIST is a prospective cohort initiated in 1992 that records all patients admitted for care in the hepatology department of Paris-Beaujon hospital (France).

We included in our analysis all patients enrolled from 2000 to 2010 meeting the following criteria: metavi r score F3 (pre-cirrhosis) or F4 (cirrhosis) assessed by liver biopsy in the first 6 months following enrollment, HCV treatment naïve and positive HCV RNA (by quantitative polymerase chain reaction assay test and qualitative Bayer VERSANT).

Exclusion criteria included presence of HCC at baseline, absence of liver biopsy, history of Child Pugh B-C or decompensation. Moreover we also defined as exclusion criteria the presence of HIV infection and of any of the following active hepatitis diseases: HBV (defined by positive HBsAg), autoimmune hepatitis, Wilson’s disease, hemochromatosis, Budd-Chiari syndrome, primary biliary cirrhosis and primary sclerosing cholangitis.

The cohort was conducted in accordance with the ethical guidelines of the Declaration of Helsinki revised at 2013, actual French legislation and the protocol was approved by our institutional review board.

Baseline collected data

A large number of baseline characteristics were collected upon enrollment. This included socio-demographic information, clinical and blood parameters (Table 1). Patients
were considered with history of alcohol intake if their daily intake was ≥30 g/day (males) or ≥20 g/day (females).

**Anti-HCV treatment**

Anti-HCV therapy was interferon (standard or pegylated, alfa-2a or alfa-2b) in combination with ribavirin. Reasons for non-treatment were recorded and classified into medical contraindication, anticipated lack of compliance or refusal by patient. Further patients receiving less than half the treatment duration by the standard of care (i.e., less than 24 and 12 weeks for patients infected with HCV Genotype 1, G1, and non-G1, respectively) were also considered as untreated.

SVR was defined as undetectable HCV-RNA in serum 24 weeks after the end of treatment; otherwise the patient was considered as non-SVR. Non-SVR patients were further categorized according to the virological and the biochemical response. Patients with undetectable HCV RNA at the end of treatment were considered as transient virological responders (TVR) and those with detectable HCV RNA were considered as non-virological responders (NVR). Patients with normal ALT levels at the end of treatment and 6 months after were considered as sustained biochemical responder (SBR), while patients not meeting this criterion were considered as non-sustained biochemical responder (non-SBR).

**Study follow-up and endpoint**

Patient’s date of enrollment was the first visit at the hospital and the follow-up ended at the latest for all patients on 31 December 2011.

The endpoint was the time to death (liver or non-liver-related) or liver transplantation. We considered without loss of generality (see results) that the date of enrollment corresponded to the initiation of treatment and this was considered as the time origin (t=0) in our analysis.
Information on the living status at the end of the study period and the date of death if relevant were obtained by contacting the patient himself or his primary care physician. Because French law makes it mandatory for local administration to send a copy of the death certificate of every French-born citizen to his municipality of birth, a request was sent to the vital statistic department of each municipality for which information on vital status of a patient was missing. Causes of death were classified as liver-related (defined by hepatic failure, end-stage liver disease, or complications of portal hypertension, HCC, and liver transplantation), not liver-related (other causes of death) or unknown. Information on liver transplantation was obtained by contacting the French biomedicine agency which manages the national list of patients awaiting liver transplant.

Statistical analysis
Results were reported as medians and interquartile ranges for continuous variables and as percentages for categorical variables. Differences were assessed using the Mann–Whitney U for continuous variables and the Chi-square or Fisher exact tests for categorical variables.

The incidence of the event was stratified on treatment outcome (classified as SVR, non-SVR and untreated) and reported per 100 person-years. Survival analysis was performed using Kaplan-Meier estimates and differences were assessed using log-rank tests. In a second step, non-SVR group was stratified according to the occurrence of a virological or a biochemical response.

The effects of the following baseline characteristics on survival were assessed using Cox univariate models: gender, alcohol intake, diabetes, hypertension, anti-HBc antigen, HCV genotype 1, Metavir score (categorical variables); age, BMI, ratio AST/ALT, albumin, AFP, bilirubin serum, creatinine, prothrombin, platelet counts, HCV-RNA (continuous variables). Finally the effect of treatment outcome on survival was analyzed using a
multivariate Cox model that incorporated all covariates having P<0.05 in univariate analysis. As suggested in Yoshida (7), age and gender were incorporated in the multivariate model regardless of their p-value in univariate analysis because these covariates are strongly associated with life expectancy. Missing data were imputed at the mean of distribution.

In complement, a propensity score (PS) analysis was performed (17), in order to estimate the effect of treatment adjusted on the probability to be treated (18) (19) (Supplementary information, method section) and therefore correct for a possible bias of indication (Supplementary information, Table S1)

All statistical tests were 2-sided, and p<0.05 was considered statistically significant. SAS software version 9.3 (SAS Institute, Cary, North Carolina), was used for all statistical analyses.

Results

Population characteristics

From 2000 to 2010, 685 patients with advanced fibrosis were enrolled in the HEPALIST cohort. Among them, 258 were diagnosed at baseline with HCC (N=119), child pugh B-C or a liver-related disease (N=39), HIV coinfection (N=16) or did not have a liver biopsy (N=84) (Fig 1). Overall 427 patients met the inclusion criteria and were included; median age (inter-quartile range) was 50 (IQR: 43-58), 286 patients (67%) were men, 94 (28%) had alcohol intake history, 238 (56%) were HCV genotype 1 and 212 (50%) were F4. The overall median time between enrollment and treatment initiation was 5 months (IQR: 3-9) in both SVR and non-SVR patients (Table 1).

Further 325 patients (76%) received at least one course of treatment and 102 (24%) patients were classified as untreated: 43 patients had medical contraindication (psychiatric disorders, significant coronary heart disease, untreated thyroid diseases), 5 patients had
anticipated compliance issues, 19 patients refused treatment, 30 patients did not receive more than half the treatment duration and in 5 patients, the cause of non-treatment was not known. Importantly information on liver transplantation, death and date of death, if relevant, were obtained for all patients and there were no missing data related to survival.

**Response to anti-HCV treatment**

Among the 325 treated patients, 241 (74%) did not achieve SVR during their first course of treatment; of these 43 (18%) subsequently received at least one additional course of treatment and 21 (9%) eventually achieved SVR. Finally, 104 patients were SVR (after the first or the second course of treatment), 221 were non-SVR and 102 patients remained untreated. Among non-SVR patients, 61 (28%) were transient virological responders and 160 (72%) were non-virological responders. Further 62 (28%) were sustained biochemical responder and 159 (72%) were non-sustained biochemical responder.

The proportion of G1 patients was significantly lower in SVR than in non-SVR group (41% vs 61%, respectively; p=0.001). Although the difference was not statistically significant, the proportion of cirrhotic patients (F4) was also lower in SVR than in non-SVR group (43% vs 55%, respectively; p=0.054). Regarding the untreated group, the proportions of cirrhotic or G1 patients were comparable to those observed in non-SVR group (45% vs 55% and 58% vs 61%, p=0.11 and 0.53, respectively). Beside cirrhosis and HCV genotype, baseline characteristics and comorbidities were largely similar between SVR, non-SVR and untreated patients (Table 1).

**Survival analysis according to treatment outcome**

The overall median follow-up period was equal to 5.5 years (IQR: 3-8) and was equal to 5.6 years (IQR: 2.8-8.2), 6 years (IQR: 3.4-8.4) and 3 years (IQR: 2-5.2) in SVR, non-SVR and untreated patients, respectively. Forty nine of the 427 enrolled patients died during the follow-up period: 3 in SVR group, 27 in non-SVR group and 19 in untreated group. Moreover 19
patients underwent liver transplantation: 3 in SVR group, 15 in non-SVR group and 1 in untreated group (Table 2). This led to a total of 68 events (death or liver transplantation): 6 in SVR group, 42 in non-SVR group and 20 in untreated group. Cause of death/LT was liver-related in 3 (50%), 30 (71%) and 17 patients (85%) in SVR, non-SVR and untreated group, respectively (Figure 1).

Incidence of death/liver transplantation per 100 person-years was 1.00, 3.20 and 5.44 in SVR, non-SVR and untreated patients, respectively (p=0.005 and 0.001 for comparing SVR vs non-SVR and non-SVR vs untreated, respectively). Further the cumulative Kaplan Meier showed that the estimation of occurrence of the event was significantly different in SVR, non-SVR and untreated group, respectively (p=0.005 and 0.001 for comparing SVR vs non-SVR and non-SVR vs untreated, respectively). In a second step, the survival analysis was done by including only non-SVR and untreated patients. We found that there was a gradient in survival along both the virological and the biochemical response (Figures 2B and 2C), and the survival was significantly higher in transient virological responders (TVR) and in sustained biochemical responders (SBR) than in non-virological responders (NVR) and non-sustained biochemical responders (NSBR), respectively (p=0.003 and p=0.001, respectively).

**Determinants of death or liver transplantation**

Univariate analysis using Cox proportional hazards regression showed that the risk of death or liver transplantation was lower in SVR than in Non-SVR patients (Hazard ratio (HR) 0.31, CI95%= [0.13;0.45], p=0.008) and in Non-SVR than in untreated patients (HR= 0.41, CI95%= [0.24;0.71], p= 0.001) (Table 2).

Baseline factors significantly associated with the death or liver transplantation in multivariate Cox analysis were alcohol intake (HR=2.28, CI95%= [1.23;4.22], p=0.008), ratio AST/ALT (HR=1.96, CI95%= [1.10-3.46], p=0.020), alpha-fetoprotein (HR=1.05, CI95%= [1.02;1.07], p=0.006) and prothrombin (HR=1.03, CI95%= [1.00;1.05], p=0.035) (Table 2).
3). After adjusting on these baseline characteristics, the risk of death or liver transplantation was lower in SVR than in non-SVR patients (HR = 0.35, CI95% = [0.15; 0.84], p = 0.019) and in non-SVR than in untreated patients (HR = 0.51, CI95% = [0.27; 0.96], p = 0.038).

When stratification on propensity scores (PS) was used the treatment effect was slightly lower than without using PS but remained highly significant (HR = 0.28 vs 0.34, CI95% = [0.16; 0.49] vs [0.18, 0.65], respectively, p = 0.001 in both cases). Similar results were found in restricted analysis including non-SVR and untreated only (HR = 0.48 and 0.36, CI95% = [0.25; 0.93]) and [0.20; 0.63], respectively, p = 0.029 and p = 0.004, respectively). Results of the PS analysis are given in the supplementary information (Table S2).

Discussion

The objective of this study was to evaluate the effect of anti-HCV treatment, either successful or unsuccessful, on the survival of patients with advanced liver disease compared to untreated patients. For that purpose, we retrospectively analyzed the overall survival reported in the Hepalist database, a large repertoire of patients admitted for care at Beaujon Hospital (Paris area, France). We limited the heterogeneity of the population by including only HCV treatment naïve patients, enrolled between 2000 and 2010, having F3/F4 metavi score assessed by biopsy and without presence or history of Child-Pugh B/C. We found on this population a pronounced gradient for the cumulative overall death/liver transplantation between SVR, non-SVR and untreated patients (Figure 2).

The fact that SVR patients with advanced liver disease had a better overall survival than non-SVR or untreated patients has been reported in some studies (20) (21). However only a small number of patients with advanced fibrosis was included in these studies, making it difficult to evaluate the effect of treatment in this specific population, which is characterized by both a smaller SVR rate and a higher mortality rate. In a recent study by Van der Meer et al. where only F3/F4 patients were included, the incidence rate of all-cause mortality per 100
Person-Years was about three times lower in SVR than non-SVR patients (1.01 vs 2.93) consistent with our findings (1.00 vs 3.20). However all patients included in this study were treated and thus the effect of unsuccessful treatment over the absence of treatment could not be investigated. To our knowledge, only one study by Aleman et al. specifically compared the incidence of death in non-SVR and untreated cirrhotic patients and concluded to a significant lower mortality in non-SVR patients compared to untreated patients (15). Our sample size was comparable to that in Aleman et al. both in terms of number of patients (427 and 351, respectively) and of follow-up time (mean 5.5 and 5.3 years, respectively) but the number of untreated patients was larger in our study (102 and 48, respectively). The fact that the incidence rate for overall death in non-SVR was higher in Aleman et al. than in our study (4.1 vs 3.20 per 100 person-years, respectively) might be due to the fact that only F4 cirrhotic patients were included in their study whereas both F3 and F4 were included in our study. Consistent with the hypothesis that the effect of treatment might depend on the fibrosis stage, the incidence rate of overall death in SVR patients was also larger in Aleman et al. was equal to 1.8, i.e., substantially larger than found in our study and in Van der Meer et al (1.0 and 1.01, respectively). However the incidence rates for untreated patients were largely similar in both studies (5.4 vs 5.1, respectively).

Overall the difference in incidence rates between non-SVR and untreated patients was more pronounced in our study (3.20 vs 5.4, respectively, p=0.038) than in Aleman et al (4.1 vs 5.11, p=0.11).

The estimation of the effect of treatment on survival is subject to various sources of bias. The most problematic one is the bias of indication, i.e., the fact that patients who did receive a treatment may have different characteristics than those who did not receive a treatment. Because peg-IFN treatment leads to a modest SVR rate, especially in patients with advanced liver disease, but may cause severe side effects, it is possible that patients who were...
not treated were also the one with the less favorable clinical profile. In order to control this bias, we first limited the heterogeneity of the population by excluding all patients with Child Pugh classes B/C. Secondly, we examined retrospectively the medical files of all untreated patients and we found that contraindication due to liver diseases were reported in only a small subset of untreated patients as a cause of non-treatment (n=9 patients). Thirdly the survival analyses were adjusted on baseline factors, and our conclusions remained unchanged. Lastly we verified that our results remained unchanged when using propensity scores (Supplementary information, Table S2). A second source of bias is the bias of survival, i.e., the fact that survival may be higher in treated patients because the effect of treatment can be estimated only in patients who survived until the time of treatment’s initiation. This bias could be corrected by including treatment as a time-dependent covariate in the analysis, as done for instance in Aleman et al (15). However, here, this bias was minimal, since all patients received a treatment within the first five month of their inclusion in the cohort and only 21 patients achieved SVR after a second course of treatment. Lastly the heterogeneity of treatment was controlled because all patients received dual therapy with IFN and RBV. This is an important difference with previous studies, where cohorts included several different therapeutic options.

In this study, we purposely focused on overall survival because this information can be obtained even if patients dropped out of the study. In fact the living status and the occurrence of liver transplantation were obtained for all patients and therefore there were no censored data. This would not have been the case if we had considered HCC or decompensation that may be subject to interval censoring and, in addition, to a bias of diagnosis. More, a previous analysis of the same cohort found that SVR patients had significantly lower chances of HCC and liver complications than non-SVR patients (22). Consistent with this finding results from the HALT-C trial showed a lower incidence of HCC in patients randomized to long-term low-dose peg-interferon; however the difference only emerged after 5–7 years of follow-up (23).
The mechanism by which IFN/RBV may improve the overall survival even though viral eradication is not achieved is unclear. One possibility is that IFN may act by ways that are not directly related to its antiviral efficacy, in particular through its immuno-modulatory activity (24). Another possibility is that treatment leads to a reduction of liver inflammation and delays the natural course of the infection. This is supported by the fact that in our study treated patients with a virological or a biochemical response had a better overall survival than treated patients without a virological or a biochemical response. This result, consistent with previous similar reports in the literature (25)(21)(26), reinforces the hypothesis that survival is causally related to effect of treatment, and that the better survival observed in non-SVR over untreated patients is not due to a bias of indication.

Here we observed that, after a delay of approximately around 50 months where no death occurred in the non-SVR patients, the overall survival between non-SVR and untreated patients tended to parallel afterwards (Fig. 1). This may suggest that a 3-4 years interval between two treatment courses may be relevant in order to maintain its protective effect.

In conclusion, IFN/RBV treatment, even if does not lead to SVR, was found to improve the overall survival in naïve patients with advanced fibrosis. Further studies will be needed to evaluate whether this effect is IFN-specific or also exists in the new era of IFN-free treatment.
References


among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA: the journal of the American Medical Association 308:2584-2593.


Figure 1. Flow chart

685 HCV advanced fibrosis
At presentation

268 Patients excluded

119 HCC at presentation
55 Child B-C and/or other hepatitis or HIV
84 without biopsy

427 advanced fibrosis patients

Treated patients

104 SVR (52%)

6 Event (6%)
3 Died (3%)
3 LT (3%)

98 No Event (94%)

221 Non-SVR (69%)

42 Event (19%)
27 Died (12%)
15 LT (7%)

179 No event (81%)

19 Died (19%)

1 LT (1%)

Untreated patients

20 Event (19%)

82 No event (81%)

1 LT (1%)
Figure 2: Survival analysis (death or liver transplantation):

A) Kaplan-Meier curves of time to death or liver transplantation in the 427 patients with advanced fibrosis. Log-rank test was used to compare survival in SVR vs non-SVR and non-SVR vs untreated patients.

B) Kaplan-Meier curve of time to death or liver transplantation in untreated and non-SVR patients according to the virological response. Log rank test was used to compare survival in transient virological responders vs non virological responders (NVR) and NVR vs untreated.

C) Kaplan-Meier curve of time to death or liver transplantation in untreated and non-SVR patients according to the biochemical response. Log rank test was used to compare survival in sustained biochemical responders (SBR) vs non-SBR.
Table 1. Baseline characteristics of 427 patients with advanced fibrosis according to antiviral therapy and response to therapy

<table>
<thead>
<tr>
<th></th>
<th>OVERALL (N=427)</th>
<th>SVR 1 (n=104)</th>
<th>non-SVR 2 (n=221)</th>
<th>Untreated 3 (n=102)</th>
<th>P value (1 vs 2)</th>
<th>P value (2 vs 3)</th>
<th>P value (1+2 vs 3)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>286 (67%)</td>
<td>74 (71%)</td>
<td>144 (65%)</td>
<td>66 (65%)</td>
<td>0.360</td>
<td>0.811</td>
<td>0.573</td>
</tr>
<tr>
<td>Age, median [IQR]</td>
<td>50 [43-58]</td>
<td>50 [43-57]</td>
<td>49 [43-57]</td>
<td>51 [45-63]</td>
<td>0.790</td>
<td>0.020</td>
<td>0.016</td>
</tr>
<tr>
<td>BMI</td>
<td>25 (23-28)</td>
<td>24 (23-28)</td>
<td>25 (23-27)</td>
<td>24 (22-27)</td>
<td>0.082</td>
<td>0.320</td>
<td>0.117</td>
</tr>
<tr>
<td>Alcohol intake</td>
<td>21 (20%)</td>
<td>21 (20%)</td>
<td>51 (24%)</td>
<td>22 (23%)</td>
<td>0.677</td>
<td>0.375</td>
<td>0.883</td>
</tr>
<tr>
<td>Diabetes</td>
<td>69 (16%)</td>
<td>17 (16%)</td>
<td>50 (23%)</td>
<td>12 (12%)</td>
<td>0.698</td>
<td>0.149</td>
<td>0.166</td>
</tr>
<tr>
<td>Arterial hypertension</td>
<td>85 (20%)</td>
<td>20 (20%)</td>
<td>47 (22%)</td>
<td>18 (20%)</td>
<td>0.872</td>
<td>0.450</td>
<td>0.512</td>
</tr>
<tr>
<td>AST/ALT ratio</td>
<td>0.88 [0.69-1.15]</td>
<td>0.80 [0.62-1.10]</td>
<td>0.88 [0.70-1.13]</td>
<td>0.96 [0.77-1.22]</td>
<td>0.008</td>
<td>0.546</td>
<td>0.005</td>
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<tr>
<td>Anti-HBc positivity</td>
<td>116 (28%)</td>
<td>32 (33%)</td>
<td>55 (26%)</td>
<td>29 (27%)</td>
<td>0.395</td>
<td>0.819</td>
<td>0.962</td>
</tr>
<tr>
<td>Albumin (g/l)</td>
<td>42 [39-46]</td>
<td>43 [39-45]</td>
<td>42 [38-46]</td>
<td>42 [40-46]</td>
<td>0.224</td>
<td>0.297</td>
<td>0.490</td>
</tr>
<tr>
<td>Alpha-fetoprotein (ng)</td>
<td>7 [4-12]</td>
<td>6 [4-9]</td>
<td>8 [5-12]</td>
<td>8 [4-12]</td>
<td>0.014</td>
<td>0.984</td>
<td>0.468</td>
</tr>
<tr>
<td>Creatinine (µmol/l)</td>
<td>74 [68-79]</td>
<td>75 [70-82]</td>
<td>74 [68-80]</td>
<td>74 [65-75]</td>
<td>0.248</td>
<td>0.094</td>
<td>0.050</td>
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<tr>
<td>Platelets count (10⁹/L)</td>
<td>151 [131-183]</td>
<td>154 [134-187]</td>
<td>150 [128-181]</td>
<td>151 [112-176]</td>
<td>0.177</td>
<td>0.530</td>
<td>0.865</td>
</tr>
<tr>
<td>Prothrombin (%)</td>
<td>83 [77-92]</td>
<td>84 [78-92]</td>
<td>83 [74-91]</td>
<td>83 [77-92]</td>
<td>0.686</td>
<td>0.174</td>
<td>0.193</td>
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<tr>
<td>HCV RNA (log10 IU/mL)</td>
<td>6 [5.7-6.3]</td>
<td>5.9 [5.6-6.2]</td>
<td>6 [5.7-6.2]</td>
<td>6 [5.7-6.3]</td>
<td>0.424</td>
<td>0.662</td>
<td>0.496</td>
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<td>Genotype</td>
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<tr>
<td>Genotype 1</td>
<td>238 (56%)</td>
<td>64 (62%)</td>
<td>164 (74%)</td>
<td>56 (55%)</td>
<td>0.053</td>
<td>0.106</td>
<td>0.292</td>
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<tr>
<td>Genotype non-G1</td>
<td>189 (44%)</td>
<td>40 (38%)</td>
<td>149 (66%)</td>
<td>40 (40%)</td>
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<td>Metavir Score</td>
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<td></td>
<td></td>
<td>0.001</td>
<td>0.527</td>
<td>0.623</td>
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</tbody>
</table>

Abbreviations: ALT, alanine aminotransferase; anti-HBc, anti-hepatitis B core antigen; AST, aspartate aminotransferase; BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; IQR, interquartile range; SVR, sustained virological response; non-SVR, non-sustained virological response.

Data are presented as (%) or median [IQR], unless otherwise noted. See “Methods” section for definition of Metavir score. Baseline characteristics were compared between patients (1 vs 2), (2 vs 3) and (1+2 vs 3) using the Mann-Whitney test for continuous variables and the χ² test or Fisher Exact for categorical variables.
Table 2. Incidence Rates of Death and Liver transplantation per 100 Person-Years for Sustained Virologic Response (SVR), non-SVR, and Untreated Person-Time

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Events</th>
<th>PY</th>
<th>Rate</th>
<th>CI95%</th>
</tr>
</thead>
<tbody>
<tr>
<td>SVR</td>
<td>104</td>
<td>6</td>
<td>600</td>
<td>1.00</td>
<td>0.44 – 2.22</td>
</tr>
<tr>
<td>Death</td>
<td>3</td>
<td>0.05</td>
<td>0.04 – 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LT</td>
<td>3</td>
<td>0.05</td>
<td>0.04 – 0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-SVR</td>
<td>221</td>
<td>42</td>
<td>1310</td>
<td>3.20</td>
<td>2.36 – 4.33</td>
</tr>
<tr>
<td>Death</td>
<td>27</td>
<td>2.06</td>
<td>1.98 – 2.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LT</td>
<td>15</td>
<td>1.14</td>
<td>0.57 – 1.71</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>102</td>
<td>20</td>
<td>367</td>
<td>5.44</td>
<td>3.51 – 8.44</td>
</tr>
<tr>
<td>Death</td>
<td>19</td>
<td>5.17</td>
<td>4.93 – 5.40</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LT</td>
<td>1</td>
<td>0.27</td>
<td>0.22 – 0.32</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PY: person-year, LT: liver transplantation and CI95%: confidence intervals
Table 3. Univariate and Multivariate analysis of factors associated with all-cause mortality or Liver transplantation in 427 patients with advanced fibrosis according to antiviral therapy and response

<table>
<thead>
<tr>
<th></th>
<th>Univariate HR (95%CI)</th>
<th>p value¹</th>
<th>Multivariate HR (95%CI)</th>
<th>p value²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.03 [1.01-1.05]</td>
<td>0.004</td>
<td>1.00 [0.98-1.03]</td>
<td>0.545</td>
</tr>
<tr>
<td>Gender (M vs F)</td>
<td>1.06 [0.66-1.74]</td>
<td>0.802</td>
<td>1.17 [0.67-2.04]</td>
<td>0.579</td>
</tr>
<tr>
<td>BMI (kg/m2)</td>
<td>0.97 [0.91-1.02]</td>
<td>0.298</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol intake (+ vs −)</td>
<td>2.00 [1.22-3.27]</td>
<td>0.005</td>
<td>2.28 [1.23-4.22]</td>
<td>0.008</td>
</tr>
<tr>
<td>Diabetes (+ vs −)</td>
<td>1.25 [0.71-2.20]</td>
<td>0.424</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension (+ vs −)</td>
<td>1.54 [0.91-2.63]</td>
<td>0.105</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ratio AST/ALT</td>
<td>3.09 [1.91-4.99]</td>
<td>&lt;.001</td>
<td>1.96 [1.10-3.46]</td>
<td>0.020</td>
</tr>
<tr>
<td>Anti-HBc (+ vs −)</td>
<td>1.28 [0.73-2.21]</td>
<td>0.378</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum albumine</td>
<td>0.85 [0.80-0.90]</td>
<td>&lt;.001</td>
<td>0.89 [0.82-0.96]</td>
<td>0.002</td>
</tr>
<tr>
<td>Alpha-fetoprotein</td>
<td>1.05 [1.03-1.08]</td>
<td>&lt;.001</td>
<td>1.05 [1.02-1.07]</td>
<td>0.006</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>1.02 [1.00-1.05]</td>
<td>0.048</td>
<td>0.97 [0.93-1.00]</td>
<td>0.124</td>
</tr>
<tr>
<td>Creatinine</td>
<td>0.99 [0.99-1.01]</td>
<td>0.509</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets account</td>
<td>1.00 [1.00-1.00]</td>
<td>&lt;.001</td>
<td>1.00 [1.00-1.01]</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Prothrombin</td>
<td>0.96 [0.94-0.98]</td>
<td>&lt;.006</td>
<td>1.03 [1.00-1.05]</td>
<td>0.035</td>
</tr>
<tr>
<td>HCV RNA</td>
<td>0.99 [0.73-1.34]</td>
<td>0.954</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genotype (1 vs others)</td>
<td>0.77 [0.47-1.27]</td>
<td>0.318</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metavir score (F3 vs F4)</td>
<td>2.45 [1.46-4.13]</td>
<td>&lt;.008</td>
<td>1.55 [0.86-2.78]</td>
<td>0.138</td>
</tr>
<tr>
<td>SVR vs non-SVR</td>
<td>0.31 [0.13-0.74]</td>
<td>0.008</td>
<td>0.35 [0.15-0.84]</td>
<td>0.019</td>
</tr>
<tr>
<td>non-SVR vs Untreated</td>
<td>0.41 [0.24-0.71]</td>
<td>0.001</td>
<td>0.51 [0.27-0.96]</td>
<td>0.038</td>
</tr>
</tbody>
</table>

Abbreviation: Cont., continuous variable; HR, hazard ratio; 95%CI= 95% of confidence interval.

¹Univariate Cox proportional hazards regression analyses with P statistically significant (P < .05).
²Multivariate Cox proportional hazards regression analyses to adjust the HR of SVR, non-SVR and untreated for all-cause mortality or Liver transplantation.