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Kinetics of emergence of liver complications in HCV-infected patients and advanced fibrosis, with and without HIV-coinfection, after SVR

Running title: Kinetics of liver complications after SVR

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Abstract

Objective: There is scarce available evidence on the distribution over time of liver complications emergence in hepatitis C virus (HCV)-infected patients who achieve sustained virological response (SVR) with direct-acting antiviral (DAA)-based therapy. Therefore, we aimed at describing the kinetics of liver-related events appearance in this setting.

Design: Multicentric prospective cohort study.

Methods: HCV-monoinfected and HIV/HCV-coinfected patients from GEHEP-011 cohort, whose inclusion criteria were: 1) Had achieved SVR with DAA-based therapy; 2) Liver stiffness (LS) prior to starting treatment≥ 9.5 kPa; 3) Available LS measurement at SVR. SVR was considered as the baseline time-point.

Results: 1035 patients were included, 664 (64%) coinfected with HIV. Before DAA-based therapy, 63 (6.1%) individuals showed decompensated cirrhosis. After SVR, 51 (4.9%) patients developed liver complications. Median (Q1-Q3) time to the emergence of hepatic events was: hepatic encephalopathy 11 (7-24) months, ascites 14 (6-29) months, hepatocellular carcinoma (HCC) 17 (11-42) months and portal hypertension gastrointestinal bleeding (PHGB) 28 (22-38) months (p=0.152). We define two profiles of liver complications: those emerging earlier (encephalopathy and ascites) and, those occurring continuously during the follow-up (HCC, PHGB) [median (Q1-Q3) time to emergence 12.7 (6.6-28.2) months vs. 25.4 (12.5-41.53) months, respectively (p=0.026)].

Conclusions: The vast majority of HCV-infected patients who develop liver complications after reaching SVR with DAA do it within three years after SVR time-point. Specifically, hepatic encephalopathy and ascites do not usually emerge after this period. Conversely, HCC and PHGB may occur in longer term. It is critical to identify patients at risk of developing hepatic events to continue performing surveillance for them.

Keywords: hepatitis C virus, HIV/HCV-coinfection, sustained virological response, direct-acting antivirals, hepatocellular carcinoma, liver decompensation

Introduction

In patients with hepatitis C virus (HCV) chronic infection, the benefits of sustained virological response (SVR) achievement, in terms of global survival and survival free from liver-related complications, have been demonstrated in several studies. Thus, viral clearance is related to a decrease in the incidence of liver decompensations [1], hepatocellular carcinoma (HCC) [2–5] and all-cause mortality [5–9]. However, even after attaining SVR, the risk of developing HCC and other hepatic decompensations is not zero, mainly among patients with cirrhosis [2,10–13]. As a result, life-long surveillance for liver complications is recommended in individuals with pre-treatment cirrhosis [14]. Furthermore, according to some experts, after achieving virologic cure, patients with advanced fibrosis should be included in HCC surveillance programs as well [15,16].

In the last few years, research about the development of liver events after HCV cure with direct acting antivirals (DAA)-therapy has mostly focused on HCC emergence. In this sense, some studies have assessed the incidence of HCC after SVR [17,18]. Recently, the incidence of liver-related events after HCV cure has been assessed in compensated cirrhotic patients, both in HCV-monoinfected and HIV/HCV-coinfected individual [19,20]. However, there is little available evidence of the distribution of liver complications over time. Understanding the patterns of hepatic-related events appearance over time in HCV cured individuals is of best interest to accurately design surveillance programs and therapeutic strategies. Therefore, the aim of this study was to describe the kinetics of appearance of liver complications in HCV-infected patients, with advanced fibrosis, who attain SVR after DAA-based therapy.

Methods

Study design and patients

This was a prospective multicenter study which included patients from the GEHEP-011 cohort (clinicaltrials.gov ID: NCT04460157). In this cohort, patients infected with HCV who had received DAA-based regimens after October 2011, at units of infectious diseases of 18 hospitals throughout Spain, are enrolled. To be recruited at the cohort, subjects should fulfill the following criteria: 1) Had achieved SVR 12 weeks after DAA-based regimen; 2) Had a liver stiffness (LS) value ≥9.5 kPa prior to treatment, and; 3) Had LS measurement available at the SVR time-point. Patients seropositive for HBsAg are excluded.

Follow-up

After SVR, which was considered the baseline time-point, all participants were evaluated, under a common protocol, at least every six months until death, liver transplant, HCV reinfection or the censoring date (November 30th, 2019). Clinical examination focusing on the early detection of liver complications was carried out at every visit, and routine laboratory examinations were completed. LS was assessed by vibration-controlled transient elastography (FibroScan®, Echosens, Paris, France), according to a standardized procedure [21]. The

management of patients with cirrhosis was performed according to a specific protocol detailed elsewhere [22]. The screening of HCC was conducted based on both ultrasound examinations and plasma alpha-fetoprotein determinations every six months. At each participating center, ultrasound examinations were undertaken by an experienced operator. Gastroesophageal varices surveillance was performed with periodic upper gastrointestinal endoscopy in patients with LS ≥21 kPa [22].

Endpoint and other definitions

The primary endpoint of the study was the emergence of a first hepatic complication after SVR, either HCC or any hepatic decompensation, regardless of the occurrence of previous liver events. The following clinical events were classified as decompensations: portal hypertensive gastrointestinal bleeding (PHGB), ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, hepatorrenal syndrome and acute on chronic liver failure. HCC was diagnosed in accordance with the American Association for the Study of Liver Diseases criteria [14]. The diagnosis of hepatic decompensation was done as reported in previous studies [23]. The indication of liver transplant was established on the basis of the criteria currently in force in Spain [24]. In individuals lost to follow-up, the vital status was determined by contacting the patient or a next of kin and information on liver events was obtained from patients' electronic clinical records at each center. In line with other studies, patients with LS value ≥ 14.0 kPa before DAA therapy were considered as cirrhotic [25–28]. SVR was defined as undetectable HCV RNA 12 weeks after the end of HCV therapy.

Statistical Analysis

Continuous variables are expressed by median (quartile 1–quartile 3) and categorical data by frequencies (percentage). Cumulative and incidence rate of overall liver events, HCC and individual hepatic decompensations were estimated. The time-to-event was computed as the months elapsed from SVR time-point to the emergence of the outcome. When the median time to liver event was not reached, a value of more than the maximum time to the emergence of the specific hepatic complication was given. Estimated survival functions were calculated using the Kaplan– Meier method, and survival curves were compared by the log-rank test. All incidence rates and time estimates are provided along with 95% confidence intervals (95% CI). Statistical analyses were conducted using the SPSS statistical software package release 25.0 (IBM, Chicago, IL, USA) and Stata 16.0 Statistics/Data Analysis (StataCorp College Station, TX, USA) package

Ethics

This study was conducted according to the Helsinki declaration and was approved by the Ethics Committee of the Hospital Universitario de Valme. All patients gave written informed consent before being recruited in the cohorts.

Results

Characteristics of the study population

One thousand and thirty-five patients were included in this study. Six hundred and sixty-four (64.2%) individuals were coinfected with HIV. Five hundred and sixty-four (54.4%) patients showed compensated cirrhosis before starting DAA-based therapy. Prior to SVR, 63 (6.1%) patients had developed a liver complication; the most common one was ascites (3.8%) followed by PGHB (1.5%) and HCC (1.4%). Almost all patients had achieved SVR with interferon-free regimens (n=973; 94%). At SVR time point, 435 (42%) had a liver stiffness value equal to or above 14 kPa. The most relevant characteristics of the study population are depicted in table 1. Regarding HIV-coinfection, all participants living with HIV were receiving antiretroviral therapy at the time of SVR and 610 (92%) had an undetectable plasma HIV-RNA load. The median (Q1-Q3) CD4 cell count was 571 (353-793) cells/ml.

After a median (Q1-Q3) follow-up time of 43 (30-49) months, 49 (4.7%) patients had died: 16 (32.7%) were classified as liver-related deaths, 28 (57.1%) as non-liver related and 5 (10.2%) deaths were unclassified. Nine (0.9%) individuals underwent a liver transplant, 20 (1.9%) patients were lost to follow-up and 5 (0.5%) were reinfected with HCV after SVR.

Liver complications during follow-up

At the end of the study, 51 (4.9%) individuals had developed a liver complication after SVR. Liver event cumulative incidence after SVR, according to the severity of liver disease is depicted in supplementary table 1, http://links.lww.com/QAD/C161. When specifically evaluating the first hepatic complication emerging after SVR, globally, HCC was the most frequently observed one, with an incidence rate (95% CI) of 0.6 (0.4-1.0) per 100 person-years. Regarding to hepatic decompensations other than HCC, 32 [3.1% (2.1%-4.3%)] patients developed a liver decompensation, accounting for an incidence rate of 1.0 (0.7-1.4) per 100 person-years. Table 2 shows cumulative incidences and incidence rates of first liver complications after SVR, by type of event. Ascites was the most frequent first decompensation occurred after SVR, followed by PHGB, and hepatic encephalopathy. Only one patient presented with a hepatorenal syndrome (table 2). Forty- nine (96.1%) out of the 51 patients who developed a hepatic complication after SVR were cirrhotic before starting DAA-based therapy.

Considering patients with no prior liver complications, 38 (3.9%) of the 972 individuals developed a liver event after achieving SVR, with an incidence rate of 1.2 (0.9-1.2) per 100 person-years. Similarly, HCC and ascites were the most frequently observed complications (table 2). Among the 63 patients who had developed a liver event before SVR, 13 (20.6%) individuals also experienced complications related to their liver disease after HCV cure [incidence rate 7.5 (4.4-12.9) per 100 person-years]. Likewise, ascites was the most commonly first event developed in this setting, followed by HCC (table 2).

Kinetics of liver complications emergence

The overall median (Q1-Q3) time between SVR assessment and diagnosis of liver complication was 16.8 (10.2-37.1) months. Thirty eight out of 51 (74.5%) of the liver events observed during the study period emerged within the first 36 months after SVR (figure 1). The median time to HCC occurrence was 17 (11-42) months and 16.8 (9.8-35.1) months to the emergence of hepatic decompensation other than HCC (p=0.123). Concerning liver decompensations, ascites (range 0.6-58.1 months) and hepatic encephalopathy (range 5.6-35.8 months) were the earliest events to emerge after SVR. PHGB (range 12.8-48.4 months) was more prone to be developed throughout the entire follow-up. The median time to the emergence of specific liver events are shown in table 2. Additionally, no episode of hepatic encephalopathy was diagnosed after 36 months of follow-up. Likewise, the vast majority of ascites events (n=17; 89%) occurred within this period. Conversely, HCC, PHGB and hepatorenal syndrome appeared in the late follow-up as well. Thus, we could define two patterns of liver complications, those which tended to appear earlier (ascites and hepatic encephalopathy) and those also emerging continuously during the follow-up (HCC, PHGB and hepatorenal syndrome). Median (Q1-Q3) time to appearance of earlier complications was significantly shorter than that of continuous events [12.7 (6.6-28.2) months vs. 25.4 (12.5-41.53) months, respectively (p=0.026; figure 2)]. The distribution of liver complications is displayed in figure 1, altogether and by the kind of event.

When specifically evaluating individuals without episodes of hepatic complications prior to HCV cure, the pattern of liver events emergence after SVR was very similar (figure 3a). Twenty-six out of the 38 (68.4%) patients who developed liver complications did it within the first 36 months after SVR time-point. Again, complications of the earlier profile appeared sooner in the follow-up. HCC and PHGB emerged throughout the whole study period (table 2). Considering patients with liver complications before SVR, practically all individuals developed liver events in the first 36 months after achieving SVR (n=12; 92.3%). Only one individual showed an episode of HCC latter during the follow-up. The distribution of liver events appearance post-SVR among this subgroup is showed in figure 3b. The median time to liver complication in this subset is depicted in table 2.

Sensitivity analyses by HIV-coinfection were conducted. Again, ascites and hepatic encephalopathy were developed earlier than HCC and PHGB, regardless of HIV-coinfection [HIV/HCV-coinfected individuals: median (Q1-Q3) time 11.1 (6.1-27.4) months vs. 24.4 (12.8-39.4) months, respectively (p=0.057); HCV-monoinfected patients 15.2 (6.8-32.0) months vs. 26.5 (11.8-46.4) months, respectively (p=0.252)]. The kinetics of liver complications after SVR by HIV coinfection status are depicted in supplementary figures 1a and 1b, http://links.lww.com/QAD/C160.

Discussion

This study evidences that, in HCV-infected patients with advanced fibrosis who achieve HCV cure, liver complications emerge according to a specific pattern after SVR. Thus, the

vast majority of liver events tend to appear in the first three years of follow-up. However, we can find two different profiles of complications. In fact, ascites and hepatic encephalopathy (earlier complications) usually emerge in the first 3 years of follow-up, whereas PHGB and HCC (continuous complications) also frequently occur in a longer term. These findings underly the need of accurately identify patients at risk of developing continuous complications and maintaining long-term surveillance for them.

It is well known that HCV eradication, either with interferon or with DAA-based regimens, leads to a decline in the incidence of liver-related outcomes, even in patients with cirrhosis [1,4,5,29,30]. In the present study, the incidence of liver complications emergence after SVR was very low, including in individuals with prior liver events before HCV cure. However, a substantial risk of hepatic complication persists. As a result, surveillance and therapeutic measures are maintained in a considerable number of individuals. After SVR, it is expected that the proportion of patients at a high risk of developing liver-related complications substantially decrease and therefore, these strategies would no longer be cost-effective in this subset. Considering the notable proportion of patients achieving HCV eradication with DAA therapy and the health costs associated to monitoring after SVR, it is important to stratify them according to the risk of developing liver complications in order to optimize management. The distribution of liver complications over time, showing a well-defined chronology, helps us to identify individuals at low risk of liver events. Specifically, ascites and hepatic encephalopathy are rare in long-term follow-up. This particular distribution is more remarkable in patients with prior liver events, but tends to be similar in those who had not decompensated before SVR.

The underlying causes for these differences in liver events kinetic after SVR remain uncertain. Once HCV is eradicated, patients experience a rapid improvement of the synthetic (albumin level, prothrombin time) and purifying (bilirubin) liver functions [31–33]. This might justify the prompt decline in the incidence of hepatic encephalopathy. Ascites, hepatorenal syndrome and, more importantly, PHGB are closely related to portal hypertension. Even if SVR achievement is associated with a reduction of hepatic venous pressure gradient, clinical significant portal hypertension persists in long-tern among a considerable proportion of patients [34] and might explain latter PHGB episodes in the follow-up. Finally, HCV eradication reduces the risk of HCC [3–5,29]. However, the epigenetic alterations induced by HCV, which are maintained after SVR [35], might explain late carcinogenesis and the emergence of HCC in the medium-long term. The coexistence of additionally factors leading to liver injury, such as alcoholic or non-alcoholic fatty liver disease, might have an impact on the kinetic of hepatic complications occurrence. The effect of such factors on the latter appearance of liver complications cannot be entirely ruled out.

Since DAA therapy has shown high efficacy, even under the worst-case scenario, and is currently widespread used, the vast majority of HCV-infected individuals do achieve SVR, including patients with cirrhosis. Thus, as mentioned previously, it is imperative to develop predictive models for risk stratification of liver complications, once HCV is eradicated, to individualize the post-SVR management of these patients. With regards to this, LS has turned

out to be a reliable predictor of liver-related outcomes following HCV cure [36]. Similarly, LS measurement along with albumin or platelet count can stratify individuals according to their risk of developing HCC or PHGB, respectively, after HCV cure [37,38]. Noninvasive serum markers might be a useful tool as well. In this sense, FIB-4 score have demonstrated to accurately identify HCV-infected patients with low risk of HCC emergence, many years after SVR [12,13]. Combining these surrogate markers with data on the kinetics of liver events occurrence could be considered as a candidate to identify patients at risk of hepatic complications in whom specific surveillance and therapeutic measures would be cost-effective and should be maintain.

This study has some limitations. First, it is possible that some events have been missed, underestimating the incidence of liver complications. Particularly, in 5 cases for whom the cause of death could not be identified, liver-related factors might have been involved. Nevertheless, only 1 of them was cirrhotic before starting DAA-therapy. In addition, in a number of patients, HCC diagnosis might be delayed. However, due to the rapid progression of HCC to advanced and symptomatic stages [39], it seems very unlikely that an hypothetic failure in HCC surveillance would entirely modify the trends observed. Finally, the GEHEP-011 cohort includes mainly HIV/HCV-coinfected individuals. Nonetheless, HIV-coinfection is not associated with poorer liver outcomes, following viral clearance [20,25]. To date, as far as we know, data regarding the long-term distribution of liver-related complications appearance after SVR with DAA-based therapy, in HCV-infected patients with advanced fibrosis and cirrhosis, were lacking. In this sense, this study provides long-term prospective data on the kinetics of liver complications after SVR in a large and well-characterized cohort of HCV-infected patients, including the largest sample of HIV-coinfected individuals reported so far. Moreover, all patients included showed the same cause of liver disease and had attained HCV cure. Those are the strengths of this study.

In conclusion, even though the incidence of liver-related events after SVR in HCV-infected patients with advanced fibrosis treated with DAA-based therapy is low, they are still at risk of developing HCC or other hepatic decompensations, especially among individuals with cirrhosis. Two different patterns of liver complications emergence can be identified: those which tended to appear earlier after SVR and those developed continuously during the follow-up. Specifically, although the majority of liver complications appear in the first three years, HCC and PHGB may continue to emerge in the long-term. For this reason, it is critical to identify patients at a higher risk of developing liver-related events to continue performing screening and therapeutic measures for these complications.

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Figure 1. Distribution of first hepatic complication during follow-up, globally and by type of first liver event (n=51).

Abbreviations: HCC: hepatocellular carcinoma; PHGB: portal hypertensive gastrointestinal bleeding; HRS: hepatorenal syndrome

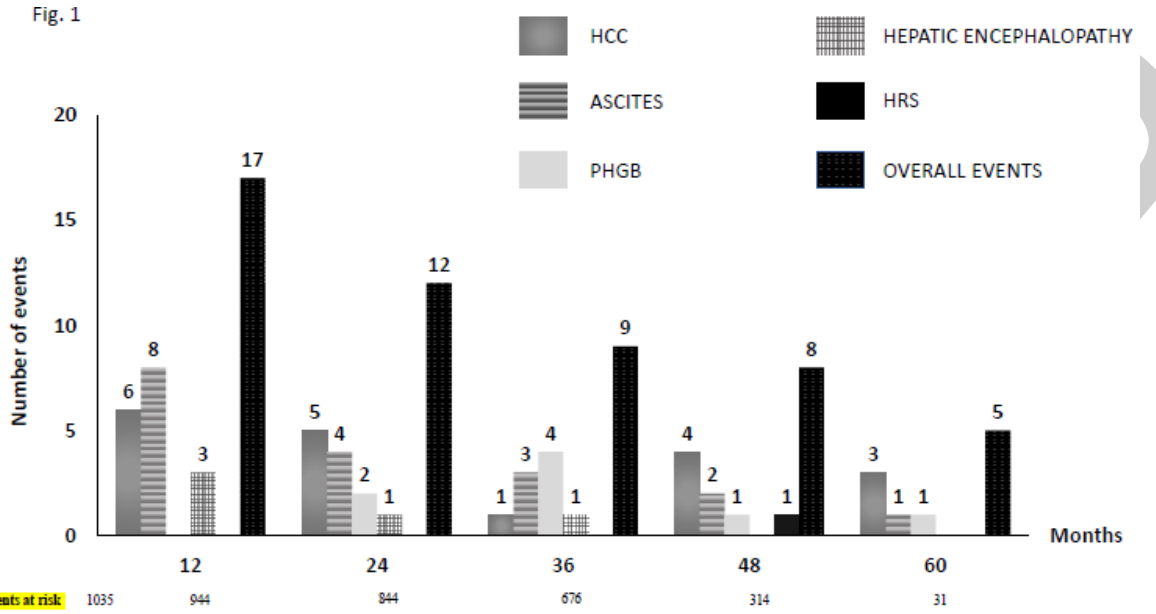
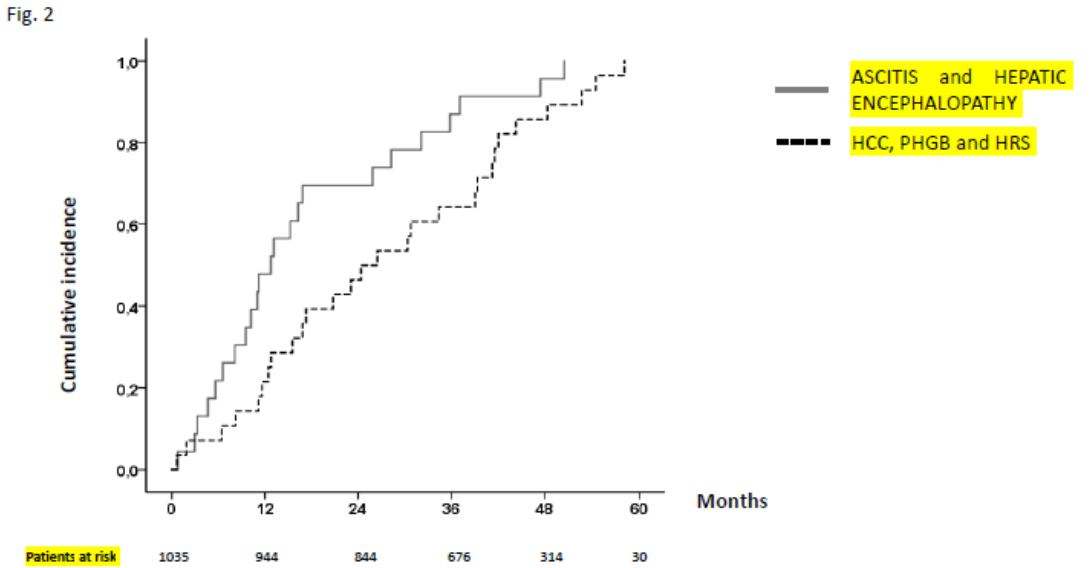


Figure 2. Time to appearance of a first episode of complications of the earlier profile (ascites and hepatic encephalopathy) versus that of the continuous profile (hepatocellular carcinoma, portal hypertensive gastrointestinal bleeding and hepatorenal syndrome) after SVR (p=0.026).

Abbreviations: HCC: hepatocellular carcinoma; PHGB: portal hypertensive gastrointestinal bleeding; HRS: hepatorenal syndrome



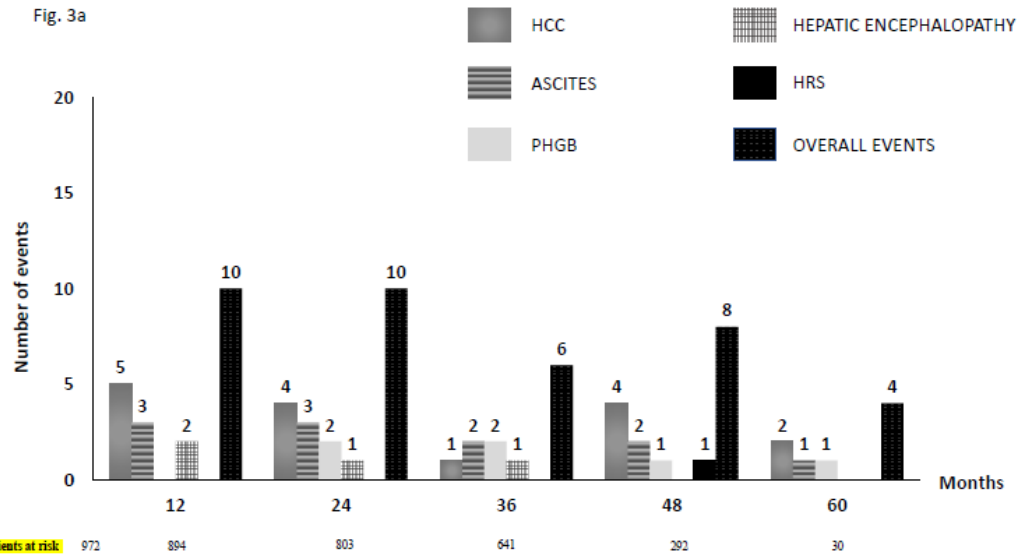
Figures 3.

(A) Distribution of first hepatic complication during follow-up, globally and by type of first liver event, among patients without liver complications prior to SVR (n=38).

Abbreviations: HCC: hepatocellular carcinoma; PHGB: portal hypertensive gastrointestinal bleeding; HRS: hepatorenal syndrome

(B) Distribution of first hepatic complication during follow-up, globally and by type of first liver event, among patients with liver complications prior to SVR (n=13).

Abbreviations: HCC: hepatocellular carcinoma; PHGB: portal hypertensive gastrointestinal bleeding; HRS: hepatorenal syndrome



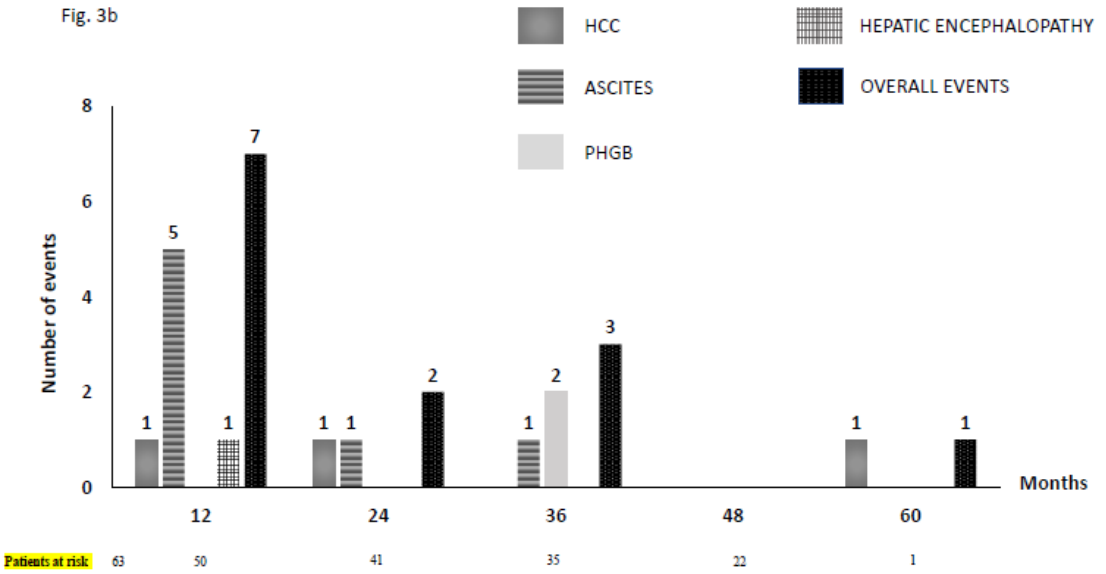


Table 1. Main characteristics of the study population (N=1035)

Parameter	**Value**
Pre-treatment	
Age (years)*	53 (49-57)
Male sex, n (%)	844 (81.5)
Injecting drug users, n (%)	697 (67.3)
HIV coinfection, n (%)	664 (64.2)
HCV genotype 3, n (%)	178 (17.2)
Cirrhosis, n (%)	627 (60.6)
CPT class[¥], n (%)	
-A5	451 (43.6)
-A6	91 (8.8)
-B7 or higher	44 (4.3)
MELD score *	6 (6-7)
Decompensation before SVR, n (%)	63 (6.1)
-Ascites only	26 (2.5)
-HCC only	12 (1.2)
-PHGB only	7 (0.7)
-HE only	3 (0.3)
-Acute failure on chronic disease only	2 (0.2)
-Ascites and PHGB	5 (0.5)
-Ascites and HE	3 (0.3)
-HCC and ascites	1 (0.1)
-HCC and acute failure on chronic disease	1 (0.1)
-HE, ascites and PHGB	2 (0.2)
-HCC, HE and PHGB	1 (0.1)

SVR	
Liver stiffness ≥14 (kPa), n (%)	435 (42.0)
CPT class, n (%)	
-A5	334 (32.3)
-A6	54 (5.2)
-B7 or higher	25 (2.4)
MELD score*	6 (6-7)
Platelets count (10^9/L)*	151 (108-200)

*Median (Q1-Q3)

Data are number (%) of participants. ¥Available at 586 patients. §Available at 413 patients.

Abbreviations: HIV: human immunodeficiency virus; HCV: hepatitis C virus; CPT: Child-Pugh-Turcotte; MELD: Model for End-Stage Liver Disease; SVR: Sustained virological response; HCC: hepatocellular carcinoma; PHGB: portal hypertensive gastrointestinal bleeding.

Table 2. Liver event cumulative incidence, incidence rate (per 100 person-years), and median time to occurrence of first liver complications after sustained virological response, by type of event (n=51), overall and according to previous liver complications

	Events No.	Cumulative incidence (95% CI)	Rate (per 100 person-years)	Median (Q1-Q3) time (months) to occurrence
Overall (N=1035)				
Hepatocellular carcinoma	19	1.8% (1.1%-2.9%)	0.6 (0.4-1.0)	17.3 (11.1-42.1)
Ascites	18	1.7% (1.0%-2.7%)	0.6 (0.4-0.9)	14.0 (6.1-29.2)
Portal hypertensive gastrointestinal bleeding	8	0.8% (0.3%-1.5%)	0.3 (0.1-0.5)	28.4 (21.7-37.9)
Hepatic encephalopathy	5	0.5% (0.2%-1.1%)	0.2 (0.07-0.4)	11 (7.5-24.5)
Hepatorenal syndrome	1	0.1% (0.02%-0.5%)	0.03 ($4x10^{-3}$-0.2)	39.4
Patients with no prior liver complications (n=972)				
Hepatocellular carcinoma	16	1.6% (0.9%-2.7%)	0.5 (0.3-0.8)	19.9 (11.3-42.0)
Ascites	11	1.1% (0.6%-2.0%)	0.4 (0.2-0.6)	16.8 (11.2-37.1)
Portal hypertensive gastrointestinal bleeding	6	0.6% (0.2%-1.3%)	0.2 (0.09-0.4)	28.4 (18.8-41.4)
Hepatic encephalopathy	4	0.4% (0.1%-1.1%)	0.1 (0.05-0.3)	11.3 (6.6-30.1)
Hepatorenal syndrome	1	0.1% (0.003%-0.6%)	0.03 ($5x10^{-}$-0.2)	39.4
Patients with liver events before SVR (n=63)				
Hepatocellular carcinoma	3	4.8% (1.0%-13.3%)	1.7 (0.5-5.3)	58.1
Ascites	7	11.1% (4.6%-22.6%)	4.0 (1.9-8.3)	8.1 (3.3-12.7)
Portal hypertensive gastrointestinal bleeding	2	3.2% (0.4%-11.0%)	1.1 (0.3-4.5)	34.4
Hepatic encephalopathy	1	1.6% (0.04%-8.5%)	0.6 (0.08-4.0)	11.0