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Treatment with direct-acting antivirals for HCV decreases but does not eliminate the risk of hepatocellular carcinoma

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Abbreviations: AFP, alpha-foetoprotein; BCLC, barcelona clinic liver cancer; CI, confidence interval; CT, computerized tomography; DAA, direct-acting antivirals; HCC, hepatocellular carcinoma; HR, hazard ratio; IQR, interquartile range; MRI, magnetic resonance imaging; SHR, subhazard ratio; SVR, sustained virologic response.

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Abstract

Background & Aims: Data from Europe and North America have been published regarding the risk of developing hepatocellular carcinoma (HCC) after treatment with direct antiviral agents (DAA). We proposed to evaluate cumulative incidence and associated risk factors for de novo HCC.

Methods: This was a prospective multicentre cohort study from Latin America including 1400 F1-F4-treated patients with DAAs (F3-F4 n = 1017). Cox proportional regression models (hazard ratios, HR and 95% CI) were used to evaluate independent associated variables with HCC. Further adjustment with competing risk regression and propensity score matching was carried out.

Results: During a median follow-up of 16 months (IQR 8.9-23.4 months) since DAAs initiation, overall cumulative incidence of HCC was 0.02 (CI 0.01; 0.03) at 12 months and 0.04 (CI 0.03; 0.06) at 24 months. Cumulative incidence of HCC in cirrhotic patients (n = 784) was 0.03 (CI 0.02-0.05) at 12 months and 0.06 (CI 0.04-0.08) at 24 months of follow-up. Failure to achieve SVR was independently associated with de novo HCC with a HR of 4.9 (CI 1.44; 17.32), after adjusting for diabetes mellitus, previous interferon non-responder, Child-Pugh and clinically significant portal hypertension. SVR presented an overall relative risk reduction for de novo HCC of 73% (CI 15%-91%), 17 patients were needed to be treated to prevent one case of de novo HCC in this cohort.

Conclusions: Achieving SVR with DAA regimens was associated with a significant risk reduction in HCC. However, this risk remained high in patients with advanced fibrosis, thus demanding continuous surveillance strategies in this population.

KEYWORDS
direct-acting antivirals, eradication, hepatitis C, liver cancer, treatment

1 | INTRODUCTION

The annual incidence risk of hepatocellular carcinoma (HCC) among patients with chronic hepatitis C virus (HCV) and cirrhosis has been reported between 1.5% and 8%.[1,2] Sustained virologic response (SVR) has been associated with a reduced risk of liver-related and overall mortality rates,[3,4] and in patients with interferon (IFN)-based antiviral treatments a 76% relative risk reduction of developing HCC was observed in this population.[4] High SVR rates with the new direct-acting antiviral (DAA) combinations raised the hope that there would be a significant reduction in HCC incidence, particularly in patients with severe fibrosis.[5]

However, recently published studies from Europe and North America suggested that there is little or no impact of DAA-based regimens on the occurrence of de novo HCC and on the contrary, some authors even described a potential increased risk.[6-8] Following these preliminary reports, larger cohorts and meta-analysis did not describe robust evidence associating DAAs regimens with an increased risk of de novo HCC when compared to IFN-based therapies.[9-15] No evidence has come from other regions of the world, in particular Latin America. Thus, we sought to prospectively evaluate the cumulative incidence of de novo HCC after therapy with DAAs in a large prospective cohort from the Latin

LAY SUMMARY

European and North American data regarding the risk of developing liver cancer (HCC) in hepatitis C patients who received treatment with all-oral antiviral agents has already been published. However, there are no data published yet in Latin American patients. We conducted a regional prospective study in which we found that although the risk for developing HCC was significantly reduced in those who eliminate hepatitis C virus infection, it could still occur in the subgroup of patients with advanced liver disease. Therefore, surveillance among them is still recommended.

American Liver Research, Educational and Awareness Network (LALREAN).

2 | MATERIALS AND METHODS

This was a prospective cohort study performed between 1 May 2016 and 1 June 2018 in different regional Liver Units from Argentina, Uruguay, Chile, Colombia and Brazil. Sites were instructed to enrol all eligible patients on a prospectively consecutive basis. Study data were registered into a web-based electronic system. Central revision and resubmission was requested in cases of missing data.

Consecutive adult patients (>18 years of age) with chronic HCV infection were included in the study. HCV infection was confirmed with quantitative real chain polymerase reaction and genotyping/subgenotyping was carried out. Subjects were included after they signed an informed consent. Patients with any degree of liver fibrosis treated with all-oral DAA were eligible. All patients who received at least one pill of DAAs were included in the study as part of an intention to treat analysis. In addition, we included a small group of patients from a registry supported by LALREAN who received DAA therapies as part of different compassionate use programs during 2015. Patients with prior solid organ transplantation or previous diagnosis of HCC were excluded. All patients were under strict HCC surveillance in order to exclude HCC diagnosis prior to DAA initiation, according to international guidelines.[16,17]

Baseline variables recorded in included subjects were demographic data, relevant past medical history and co-infection with chronic hepatitis B virus (HBV) or human immunodeficiency virus (HIV). Evaluation of liver disease stage included: liver fibrosis stage assessed by liver biopsy or non-invasive methods including transient elastography or serum biomarkers (Fibrotest®) or by clinical diagnosis of cirrhosis (the presence of gastro-esophageal varices or ascites). Liver stiffness measurement (LSM) recorded as a continuous variable in kPa, was performed using liver elastography[18] and were categorized according to international recommendations in all patients[19]; kPa values more than 9.5 and more than 12.5 were categorized as F3 and F4 respectively.[18,19] Severity of liver disease was evaluated according to Child-Turcotte Pugh (CTP) classification. Clinically significant portal hypertension (CSPH) was defined as either the presence of ascites or portosystemic encephalopathy or gastro-esophageal varices on endoscopy.

Evaluation prior to DAA treatment included: year of HCV diagnosis, infection route and prior treatment with IFN-based therapies. The particular DAA regimen used was based on physicians' criteria according to available regimens in each country following international guidelines.[5] Laboratory values prior and following DAA therapy including HCV viral loads (IU/mL) and other laboratory values were registered. We assessed response to DAA therapy documenting SVR, defined as an undetectable HCV RNA (HCV viral load <15 UI/mL) 12 weeks after completion of therapy. Treatment failure was defined as the presence of detectable HCV RNA after discontinuation of antiviral regimen. Laboratory operators were blinded from baseline patient characteristics, treatment regimens and main events or outcomes.

2.1 | Main event: definition and diagnosis of hepatocellular carcinoma

The primary end-point analysed was cumulative incidence of de novo HCC. All patients with fibrosis stage 3 or 4 underwent HCC surveillance with abdominal ultrasound (US) with or without serum alpha-foetoprotein (AFP) before and every 6 months during and after DAAs, as recommended by international guidelines.[16,17] In order to avoid potential selection bias, all patients had at least two consecutive previous US with a negative test for HCC screening. Although surveillance for HCC is not recommended in patients with F1-2 fibrosis grades, an abdominal US every 6 months was recommended in the study protocol in this group of patients. Operators who performed abdominal ultrasounds at each centre were blinded from treatment regimens and achievement of SVR. Time of follow-up was recorded since DAA initiation until death or end of study. Patients were followed at least every 4 weeks during and until 12 weeks after treatment and every 6 months thereafter.

If during the semi-annual screening with an abdominal US a liver nodule ≥10 mm was identified, an abdominal triphasic-contrast image was performed either with computed axial tomography scan (CT) or magnetic resonance imaging (MRI). HCC diagnosis was defined as arterial enhancement (not rim-like lesion) and venous washout with or without capsule appearance on triphasic CT or MRI.[16,17] Tumour burden at diagnosis was classified according to Barcelona Clinic Liver Cancer criteria (BCLC).[20]

Secondary end-points analysed were patients' survival and adverse events related to DAAs and were classified according to common toxicity criteria.[21] Causes of death were recorded and categorized as complications of portal hypertension, cancer-related (HCC related), sepsis, cardiovascular events and other causes.

Procedures were conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[22] The Austral University Ethics Committee and each Ethical Committee (CIE) from all the participating centres approved the study protocol. All procedures followed ethical standards (institutional and national) as well as the Helsinki Declaration of 1975, as revised in 2008. The study protocol was recorded and registered in the CIE 16-023, had a public access database for all the co-investigators on a web link (https://temasis.com.ar/temasis-com-ar/lalrean-org) and received a Research National Grant from Argentina from the National Institute of Cancer (INC).

2.2 | Statistical analysis

A total sample size to enrol a minimum of 420 patients under DAAs was calculated to include a cohort with an annual risk of HCC 1%-6% as previously mentioned (α type I error of 5%, type II error or β of 0.20). Categorical data were compared using Fisher's exact test (2-tailed) or Chi-square (χ^2) test as appropriate. Continuous variables are

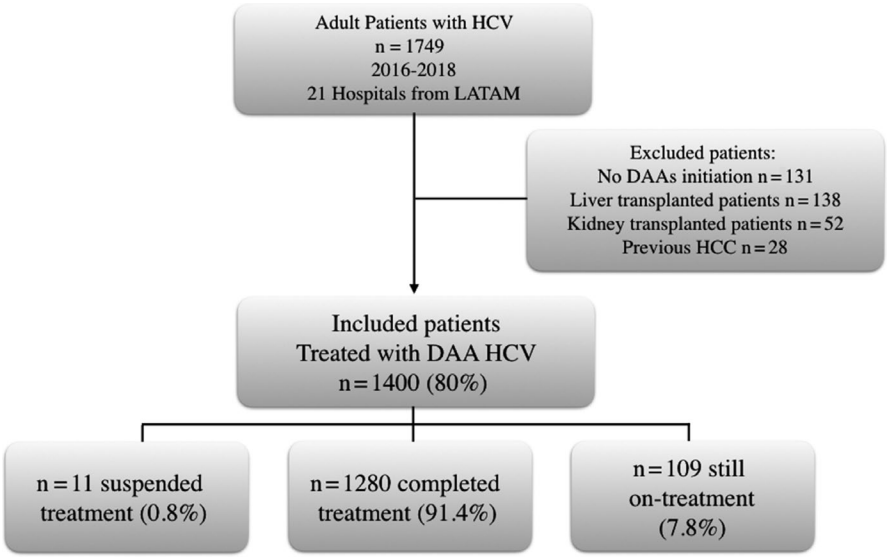

FIGURE 1 Flow chart describing the study population

shown with mean (±standard deviation, SD) or median (Interquartile ranges 25%-75%, IQR) and were compared with Student's *T* or Mann-Whitney *U* tests according to their distributions.

Kaplan-Meier survival and cumulative incidence curves were compared using the log-rank test. Among patients with or without SVR, the absolute and relative risks for de novo HCC and the number needed to treat (NNT) to prevent one case of HCC were calculated. A multivariable Cox regression analysis with hazard ratios (HR) and 95% confidence intervals (CI) was performed to evaluate independent variables associated with HCC development. Proportional hazards assumption was assessed through graphic and statistical evaluation (Schoenfeld residuals test) and calibration of the model by comparison of observed and predicted curves and by Harrell's c-statistic index. To further re-adjust the effect of SVR on the risk for de novo HCC, a competing risk regression analysis was carried out (subhazard ratios, SHR) considering death before HCC occurrence as a competing event. Finally, since the exposure of interest was an intervention not randomly assigned, we also used a propensity score matching from a logistic regression analysis, to reduce confounding bias. Therefore, we estimated the probability of achieving SVR as a function of different variables and used that score as a single matching covariate.[23] Collected data were analysed using STATA 13.0.

3 | RESULTS

From a total of 1749 HCV patients prospectively followed and enrolled in LALREAN´s registry, 1400 received at least one pill of DAA and were therefore included in the analysis (Figure 1). Baseline characteristics of the study population are shown on Table 1.

Overall, 91.4% (n = 1280) completed DAA regimen (Figure 1). SVR outcomes were available in 1,149 patients with a SVR rate of 96.9% (CI 95.8%-97.9%). The most frequently used antiviral regimen was sofosbuvir (SOF) + daclatasvir (DCV) in 80.5% of the patients (n = 1127), followed by paritaprevir-r/ombitasvir/dasabuvir (PrOD) 13.4% (n = 188), SOF/ledipasvir 2.3% (n = 32), Grazoprevir/Elbasvir 1.6% (n = 22), DCV +Asunaprevir (ASV) 1.6% (n = 21), SOF/Simeprevir 0.4% (n = 6), SOF/Velpatasvir and paritaprevir-r/ombitasvir in two patients each respectively. Sixty-three patients initiated DAAs during 2015 as part of different compassionate use programmes during 2015 and were also prospectively followed. Median treatment duration was 12 weeks (IQR 11-23 weeks). Adverse events were described in 370 patients (28.3%); mostly mild. The most common DAA regimen was SOF+DCV across all genotypes: genotype 1a (85.4%), genotype 1b (59.6%), genotype 2 (98.4%), genotype 3 (98.8%) and genotype 4 (82.3%). Ribavirin was frequently associated in genotype 3 (74.9%) and less frequently in genotype 1b (33.1%). SVR rates were not significantly different among genotypes (Table S1).

3.1 | Cumulative incidence of HCC in the overall population

Median follow-up since DAAs initiation was 16 months (IQR 8.9-23.4 months). During follow-up, 30 de novo HCC cases were diagnosed within a median time of 7.9 months (IQR 5.1-15.4 months) since DAA initiation (2 patients had F3 fibrosis and 28 patients fibrosis grade 4). None of the patients with grades 1-2 fibrosis developed HCC. Figure 2 shows the cumulative incidence of HCC at 12 months (0.02 [CI 0.01; 0.03]) and at 24 months (0.04 [CI 0.03; 0.06]) since DAA initiation. At HCC diagnosis, median largest tumour diameter was 25.5 mm (IQR 18-40 mm), 78% had only 1 HCC nodule and median serum AFP at diagnosis was 6.4 ng/mL (IQR 4.2-10 ng/mL). According to BCLC staging, 63.3% were within BCLC 0-A (n = 19), 20% were BCLC-B (n = 6) and 16.7% were BCLC C-D stages (n = 5). Three patients presented tumour macrovascular invasion, two patients had extrahepatic metastasis and one patient had both extrahepatic metastasis and vascular invasion. There was no association between the type of tumour burden and SVR.

TABLE 1 Patients' baseline characteristics

Variable	Values
Age, y (mean ± SD)	58 ± 12
Male gender, n (%)	668 (47.7)
Median years of known HCV infection, y (IQR)	7 (2-13)
HCV genotype, n (%)	
1a	356 (25.4)
1b	555 (39.6)
1 (without subgenotype)	88 (6.3)
2	127 (9.1)
3	245 (17.5)
4	17 (1.2)
Other	12 (0.1)
Comorbidities, n (%)	
Diabetes mellitus	214 (15.3)
Ischaemic heart disease	46 (3.3)
COPD	19 (1.4)
RRT	18 (1.3)
Kidney failure without RRT	8 (0.6)
Peripheral vascular disease	13 (0.9)
HIV co-infection, n (%)	165 (11.8)
HBV co-infection, n (%)	5 (0.4)
Liver fibrosis grade, n (%)	
F0	24 (1.8)
F1	188 (13.9)
F2	124 (9.2)
F3	233 (17.2)
F4	784 (57.9)
CSPH[a], n (%)	399 (28.5)
Listed for liver transplantation, n (%)	58 (4.1)
Previous INF-based regimens, n (%)	529 (37.8)
Previous Telaprevir or Boceprevir, n (%)	111 (7.9)

COPD, chronic obstructive pulmonary disease; CSPH, clinically significant portal hypertension; HBV, hepatitis B virus; HCV, hepatitis C virus; HIV, human immunodeficiency virus; IQR, interquartile range 25%-75%; RRT, renal replacement therapy; SD, standard deviation.

[a]Clinically significant portal hypertension defined as the presence of at least one of the following: ascites, gastroaesophaguel varices or hepatic encephalopathy.

3.2 | Baseline risk factors for de novo hepatocellular carcinoma

In univariate analysis, a higher risk of de novo HCC was observed in individuals with CSPH with a HR of 13.5 (CI 4.72; 38.81) (Figure 3A), cirrhosis HR 8.9 (CI 2.11; 37.4) (Figure 3B), platelets count ≤100 000 per mm^3 HR 4.1 (CI 1.88; 9.14) and in patients with AFP >20 ng/mL HR 3.2 (CI 1.20; 8.35). A stratified analysis among patients with advanced fibrosis grades with or without CSPH showed that the highest risk of HCC development was observed in patients with F4 and CSPH with a HR of 13.3 (1.81; 98.7) (Figure 3C). None of the DAA regimens were associated with a higher risk of HCC development (Table 2).

Although genotypes 1b and 3 had the highest incidence of de novo HCC (2.5% and 2.4% respectively), genotype 2 and 4 had the lowest incidence of HCC (0.79% and 0% respectively), these differences did not reach statistical significance (Table S2).

Not achieving SVR was also significantly associated with a higher risk of de novo HCC (HR of 5.7 [CI 1.71; 18.80]). Overall cumulative incidence of HCC for patients with and without SVR at 12 months was 0.02 (CI 0.01-0.03) and 0.04 (CI 0.02-0.06) respectively (Figure 4). Achieving SVR presented a relative risk reduction for de novo HCC of 73% (CI 15%-91%), with an absolute risk difference of −0.06 (CI −0.15; 0.0.03) when compared with antiviral failure. This represented a number needed to treat (NNT) of 17 patients to prevent one case of de novo HCC.

A multivariable model describing the adjusted effect of SVR is shown on Table 2. Non-SRV patients presented a HR of 4.9 (CI 1.44; 17.32; $P = 0.011$) for developing HCC after DAAs initiation, adjusted for the presence of diabetes mellitus, previous non-responders to PegIFN-based regimens, CTP class and the presence of CSPH. The presence of CSPH was the strongest predictor of HCC development with a HR of 9.1 (CI 2.69; 30.89; $P < 0.0001$). Not achieving SVR was independently associated with HCC development, adjusted for other covariates including diabetes mellitus, non-responders to PegIFN-based regimens, CTP class and the presence of CSPH (Figure S1) in the competing risk regression analysis (Table 3) and in the propensity score matching, assessing the probability of SVR (Table S2 and Figure S2).

3.3 | Sensitivity analysis: Risk of HCC among cirrhotic patients

A sensitivity analysis including only patients with F4 or cirrhosis (n = 784) showed that cumulative incidence of HCC at 12 months was 0.03 (CI 0.02-0.05) and 0.06 (CI 0.04-0.08) at 24 months of follow-up respectively. As expected, a higher incidence of de novo HCC was observed with increasing Child-Pugh score (Table 4). From a multivariable Cox regression analysis, non-SVR and the presence of CSPH were independently associated variables with HCC development among patients with cirrhosis (Table 4).

4 | DISCUSSION

In our cohort, we found a cumulative incidence of de novo HCC of 2% and 4% at 12 and 24 months of follow-up in patients who received all-oral direct-acting antiviral therapies for HCV. This cumulative incidence of HCC was higher among cirrhotic patients even after SVR achievement, particularly in those presenting with CSPH. Moreover, CSPH was the strongest independent predictor associated with HCC development. After controlling for confounding variables, patients not achieving SVR presented a five-fold increased

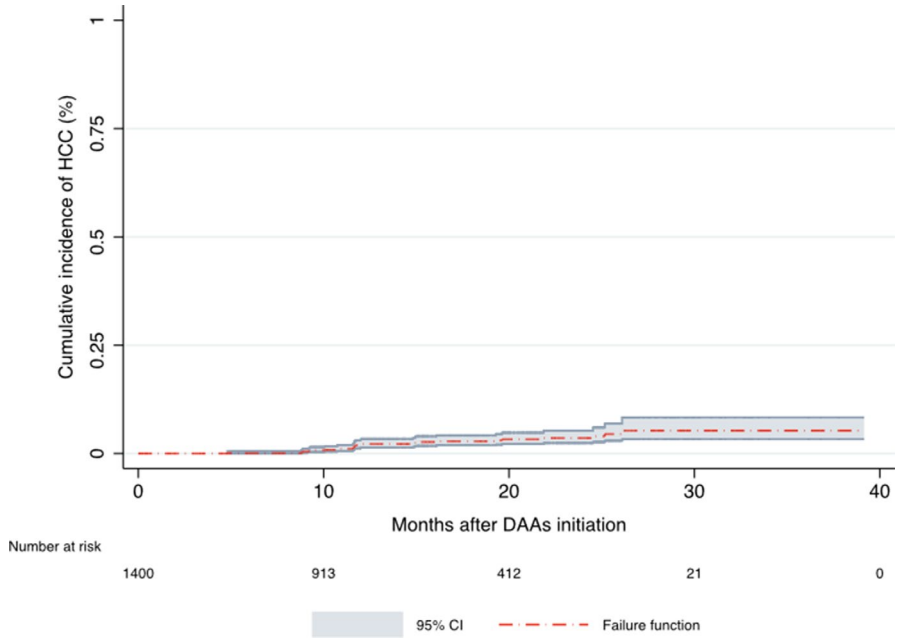

FIGURE 2 Kaplan-Meier cumulative incidence curve of hepatocellular carcinoma in the overall population

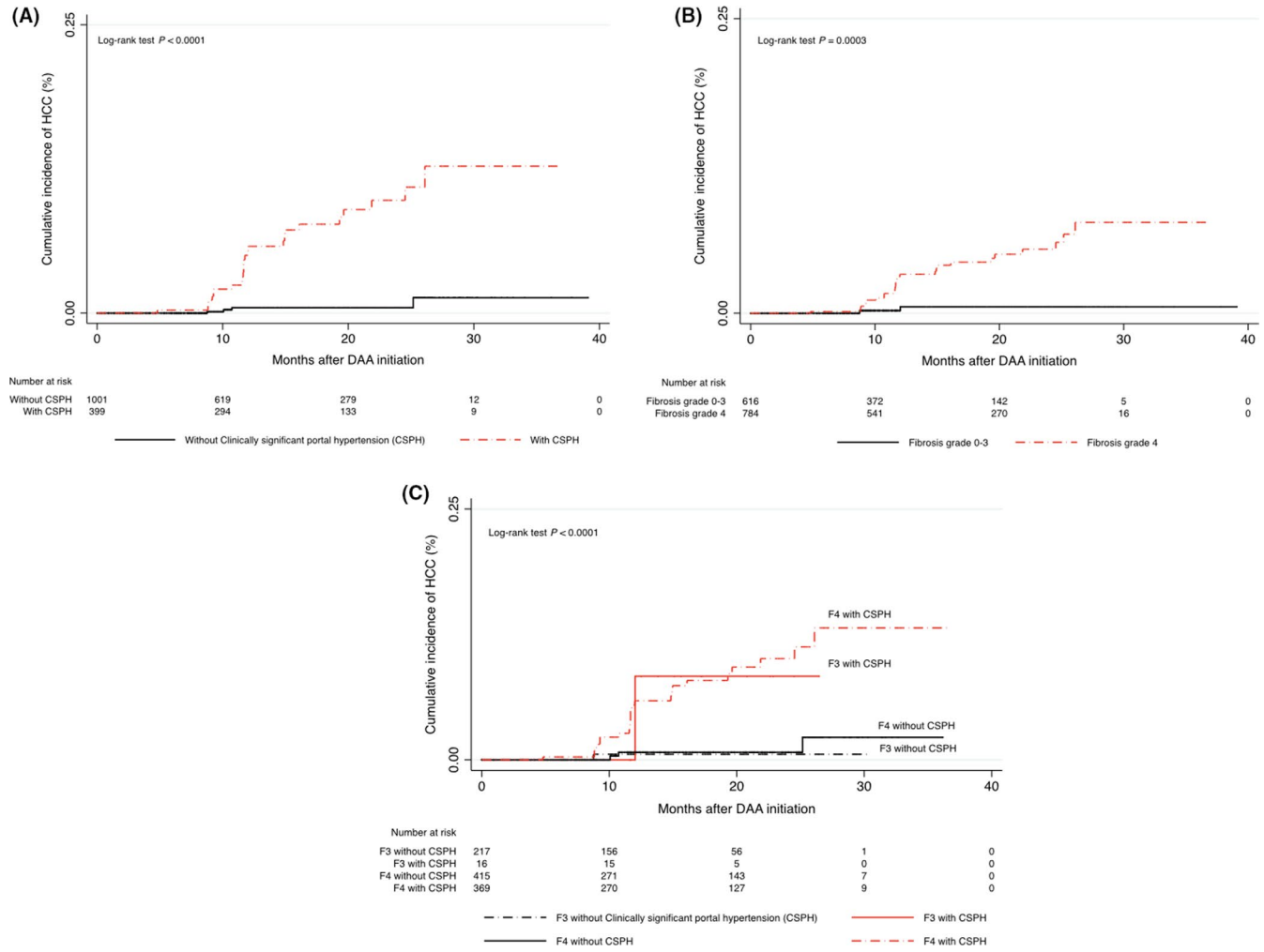

FIGURE 3 Univariate Cox regression analysis and Kaplan-Meier cumulative incidence curves showing the effect of different covariates and the incidence of de novo HCC: Panel A, clinically significant portal hypertension; Panel B, Fibrosis grade; Panel C, fibrosis grade stratified by the presence of portal hypertension

TABLE 2 Baseline variables associated with de novo HCC development. Cox regression analysis, hazard ratios (HR)

Variable	HCC (%)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age (y)		1.0 (0.96; 1.08)	0.53	–	
Gender					
Male (n = 732)	1.9				
Female (n = 668)	2.4	1.3 (0.64; 2.68)	0.46	–	
Diabetes mellitus					
Yes (n = 214)	3.7	1.9 (0.85; 4.29)	0.12	1.0 (0.44; 2.49)	0.92
No (n = 1186)	1.8				
HIV co-infection					
Yes (n = 165)	1.8	1.1 (0.32; 3.52)	0.92	–	
No (n = 1235)	2.2				
HBV co-infection					
Yes (n = 5)	0	–		–	
No (n = 1395)	2.1				
Previous INF-based regimens					
Yes (n = 529)	3.6	2.1 (0.96; 4.26)	0.06	1.04 (0.98; 5.24)	0.053
No (n = 871)	1.3				
Years of HCV infection		1.02 (0.97; 1.08)	0.43	–	
Fibrosis grade					
F0-F1 (n = 212)	0	–			
F2 (n = 124)	0	–			
F3 (n = 233)	0.8	0.3 (0.08; 1.42)		-	
F4 (n = 784)	3.6	8.9 (2.11; 37.4)	0.003	–	
LSM, kPa					
<19 (n = 600)	0.7	-			
19-23 (n = 82)	0	-			
>23 (n = 104)	4.8	6.8 (1.83; 25.64)	0.009	–	
Child-Turcotte Pugh					
A (n = 717)	2.7	-			
B (n = 113)	5.3	2.0 (0.82; 5.07)	0.13	1.35 (0.53;3.45)	0.53
C (n = 14)	21.4	6.1 (1.79; 20.63)	0.004	2.7 (0.57; 12.49)	0.21
CSPH[a]		13.5 (4.72; 38.81)	<0.0001	9.1 (2.69;30.89)	<0.0001
Yes (n = 399)	6.5				
No (n = 1001)	0.4				
Platelets <100 000/mm^3					
Yes (n = 294)	5.4	4.1 (1.88; 9.14)	<0.0001	–	
No (n = 1106)	1.1				
AFP >20 ng/mL					
Yes (n = 65)	9.2	3.2 (1.20; 8.35)	0.02	–	
No (n = 506)	2.6				
SVR					
Yes (n = 1114)	2.3				
No (n = 35)	8.6	5.7 (1.71; 18.80)	0.005	4.9 (1.44; 17.32)	0.011

CI, confidence interval; CSPH, clinically significant portal hypertension; HCC, Hepatocellular carcinoma; HR, hazard ratio; SVR, sustained virological response.

[a]Clinically significant portal hypertension defined as presence of at least one of the following: ascites, gastro-esophageal varices or hepatic encephalopathy. Harrell's c-statistic index 0.78.

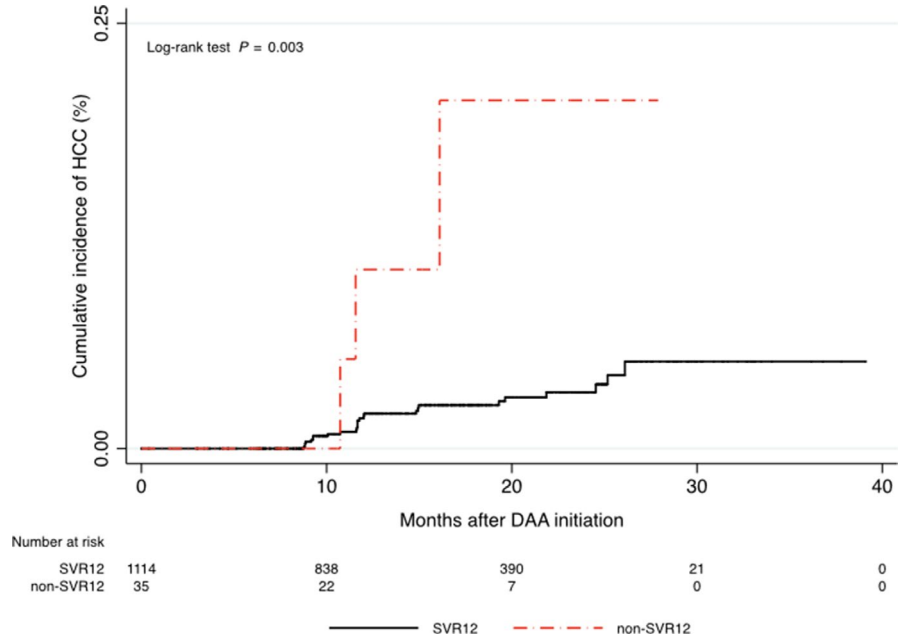

FIGURE 4 Kaplan-Meier cumulative incidence curve of hepatocellular carcinoma (HCC) according to achievement of SVR12

TABLE 3 Competing risk regression analysis regarding cumulative incidence of HCC, subhazard ratios (SHR)

Variable	Adjusted SHR	Standard error	95% confidence intervals	*P*
SVR				
Yes (n = 1114)	4.9	3.181	1.43; 17.41	0.012
No (n = 35)				
Diabetes mellitus				
Yes (n = 214)	1.0	0.488	0.41; 2.61	0.93
No (n = 1186)				
Previous INF-based regimens				
Yes (n = 529)	2.3	0.972	1.00; 5.27	0.050
No (n = 871)				
Child Pugh				
A (n = 717)	–			
B (n = 113)	1.4	0.685	0.51; 3.65	0.54
C (n = 14)	2.7	1.726	0.77; 9.46	0.12
CSPH[a]				
Yes (n = 399)	9.1	5.92	2.53; 32.60	0.001
No (n = 1001)				

CI, confidence interval; CSPH, clinically significant portal hypertension; HCC, Hepatocellular carcinoma; SHR, subhazard ratio; SVR, sustained virological response.
[a]Clinically significant portal hypertension defined as presence of at least one of the following: ascites, gastro-esophageal varices or hepatic encephalopathy.

risk of HCC. This fold increase in non-responders implies a 73% relative risk reduction for de novo HCC incidence in SVR, with 17 patients requiring treatment to prevent one case of de novo HCC. This effect was specific when evaluated among cirrhotic patients.

Since the introduction of all-oral IFN-free regimens, high cure rates of these new therapies raised the hope that natural history of HCV-related cirrhosis could be modified, including a reduced incidence of HCC. However, several studies suggested an increased risk of HCC after DAA therapy.[8-14] This initial alarm was postulated prior to the full introduction of DAAs in Latin America.[6,7] Approval of DAA regimens in Latin America occurred 18 to 24 months after their approval in Europe and the USA. This allowed us to prospectively evaluate the incidence of de novo HCC following DAAs regimens. To our knowledge, this is the largest to-date prospective cohort study

TABLE 4 Baseline variables associated with de novo HCC development among patients with cirrhosis (n = 784). Cox regression analysis, hazard ratios (HR)

Variable	HCC (%)	Unadjusted HR (95% CI)	*P*	Adjusted HR (95% CI)	*P*
Age (y)		1.02 (0.96; 1.08)	0.53		
Gender					
Male (n = 424)	3.3				
Female (n = 360)	3.9	1.16 (0.55; 2.44)	0.69		
DBT mellitus					
Yes (n = 159)	4.4				
No (n = 625)	3.4	1.26 (0.54; 2.98)	0.58		
Previous INF-based regimens					
Yes (n = 326)	5.5	1.79 (0.82; 3.89)	0.14		
No (n = 458)	2.2				
Child Pugh					
A (n = 666)	2.9	—	—	—	—
B (n = 107)	5.6	2.03 (0.80; 12)	0.13	1.17 (0.46; 2.98)	0.33
C (n = 14)	21.4	5.75 (1.68; 9.65)	0.005	1.91 (0.44; 8.39)	0.86
CSPH[a]					
Yes (n = 369)	6.8	8.61 (2.59; 28.49)	<0.0001	8.35 (2.51; 27.79)	0.001
No (n = 415)	0.7				
Platelets <100 000/mm^3					
Yes (n = 255)	6.3	2.61 (1.16; 5.92)	0.021	—	
No (n = 529)	2.2				
AFP >20 ng/mL					
Yes (n = 57)	8.8	2.05 (0.72; 5.85)	0.18		
No (n = 727)	4.0				
SVR 12					
Yes (n = 653)	3.7				
No (n = 19)	15.8	5.96 (1.78; 19.92)	0.004	6.41 (1.90; 21.59)	0.003

CI, confidence interval; CSPH, clinically significant portal hypertension; DBT, diabetes; HCC, Hepatocellular carcinoma; HR, hazard ratio.

[a]Clinically significant portal hypertension defined as presence of at least one of the following: ascites, gastro-esophageal varices or hepatic encephalopathy. Harrell's c-statistic index 0.74. Cox proportional hazard assumption, *P* = NS.

evaluating de novo HCC in Latin America, a region with wide sociocultural and racial heterogeneity and different spectrum of barriers to access DAA therapies.

Several studies including patients treated with IFN-based therapies described that the risk of HCC was markedly lower in patients achieving SVR.[3] This has been postulated to be the consequence of IFN´s immune modulating and antitumour properties rather than its antiviral activity alone. This issue has been a matter of debate. The biological plausibility that sustained this hypothesis is the loss of the anti-oncologic surveillance after the accelerated viral eradication obtained with DAA treatment.[24] Small studies with heterogeneous populations reported a high incidence of HCC following DAA therapy, whereas larger retrospective studies described a HCC risk reduction on achieving SVR.[25] Their retrospective nature and comparison with IFN-treated historical cohorts with less advanced liver disease than DAA cohorts led to important selection biases.

More recently, two large prospective Italian studies reported interesting results that are in line with ours.[26,27] Authors described a similar HCC incidence following DAA therapy and risk factors for HCC development such as diabetes, HBV co-infection,[26] low platelet count and serum albumin.[27] Although SVR was associated with a lower risk of de novo HCC, a persistent risk of HCC development after SVR was observed in cirrhotic patients in both studies. Thus, maintenance of cancer surveillance is still recommended.[26,28] Similar to what was reported by other groups, in our study, the risk of de novo HCC was inversely associated with antiviral therapy response.[8,26-30] In addition, we did not find any association with more aggressive tumour presentation at HCC diagnosis and SVR, in line with other groups' findings.[26,27]

A significant strength of our study is the prospective and multicentre design that allowed us to analyse well-documented variables associated with de novo HCC. However, we faced some limitations.

First, our study has a relatively short follow-up time, as a consequence of the recent introduction of DAAs in Latin America. Nevertheless, in most published series, the diagnosis of de novo HCC was done during the first year of initiating DAA therapy. Second, neither do we include a historical nor a control group without antiviral therapy due to ethical restraints. Third, a potential selection bias could have been avoided if HCC had been excluded with contrast-enhanced imaging methods prior to DAAs initiation, differentiating de novo from pre-existing HCC. However, this would be very costly. Nevertheless, in our cohort, six monthly abdominal ultrasound examinations were rigorously indicated before, during and after DAA treatment. This issue has not been correctly assessed in previous studies using ICD codes, in that misclassification of patients might have led to a risk of bias.

In conclusion, our study demonstrates that achieving SVR with DAA regimens was associated with a significant risk reduction in HCC. However, this risk remains high in patients with advanced fibrosis even after achieving viral eradication, thus demanding proper and continuous surveillance strategies in this population.[31,32] Early treatment to prevent cirrhosis is the preferred strategy to avoid liver cancer development. Consequently, in our region we should implement strong public health strategies to provide treatment of HCV infection in early stages of liver disease if our goal is to further diminish de novo incidence of HCC. A lot still needs to be done in our region to overcome barriers to access treatment. On the other hand, health providers should maintain close surveillance of HCC development even in patients achieving viral clearance, with particular focus in those with CSPH.

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CONFLICT OF INTEREST

The authors do not have any disclosures to report.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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