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Prediction of hepatic decompensation and hepatocellular carcinoma after direct-acting antiviral therapy in patients with hepatitis C-related liver cirrhosis: a cohort study

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Abstract

Aim This study aimed to evaluate the rate of hepatic decompensation and de novo HCC and identify their independent factors in HCV genotype 4-infected patients with compensated liver cirrhosis following successful direct-acting antiviral (DAA) therapy.

Methods This prospective cohort study included 1789 patients with HCV genotype 4-related compensated liver cirrhosis who achieved viral eradication after DAAs. Baseline and follow-up clinical, laboratory, albumin-bilirubin score (ALBI), and abdominal ultrasound were recorded to detect hepatic decompensation and de novo HCC. Logistic regression was performed to evaluate the variables associated with decompensation and HCC.

Results During the 24-month period of follow-up, 184 (10.28%) patients developed hepatic decompensation. Ascites was the commonest presentation. Baseline serum albumin, bilirubin, and platelet count were the independent factors associated with hepatic decompensation (*P*-values 0.022, 0.03, and < 0.001, respectively). A formula was developed for the prediction of decompensation using these 3 factors (AUC: 0.641 at cutoff 0.1098969 with a sensitivity of 59.9% and specificity of 61.7%). Pre-treatment ALBI score could predict decompensation at cutoff value − 2.5184, AUC 0.609, sensitivity 58.3%, and specificity 59.7%. Post-treatment ALBI score could predict hepatic decompensation after DAA therapy at cutoff value − 2.9521, AUC 0.597, sensitivity 48.1%, and specificity 75.5%. Sixteen (0.9%) patients developed de novo HCC. Age (odds ratio: 1.061, 95%, confidence interval: 1–1.126) and male gender (OR 3.450, 95% CI 1.105–10.769) were the independent factors associated with the development of de novo HCC but not the ALBI score.

Conclusion Baseline demographic and laboratory data could predict hepatic decompensation and HCC in patients with compensated liver cirrhosis after successful DAA therapy

Keywords Direct-acting antivirals, ALBI score, De novo hepatocellular carcinoma, Liver cirrhosis, Decompensation

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Introduction

Hepatic decompensation and hepatocellular carcinoma (HCC) are serious complications during the natural history of hepatitis C virus (HCV)-related chronic liver injury. Although direct-acting antiviral therapies (DAAs) are associated with high rates of sustained virological response (SVR), the risk of hepatic decompensation and HCC is not entirely eradicated after viral clearance [1–3].

The episodes of hepatic decompensation occurred at various times during and after all types of DAA therapy [4]. The proposed underlying mechanisms are that this decompensation is part of the natural history of the HCV-related established liver cirrhosis and consequently portal hypertension [3, 4]. Few studies have evaluated the outcome of patients with liver cirrhosis successfully treated with DAAs and with no previous history of hepatic decompensation [5]. Thus, new data are warranted to support the use of costlier DAAs, particularly in developing countries [3].

In 2006, the National Committee for Control of Viral Hepatitis (NCCVH) was established in Egypt. Their main objectives were the assessment of disease burden, establishment of an infrastructure for a national treatment program, and development of a national strategy for the control of viral hepatitis and management of advanced liver disease, while continuing to perform clinical and epidemiological research activities [6, 7]. Egypt is now on the road to the elimination of HCV infections. It is one of only ten countries where patients achieving SVR are 5 times more than patients with new infections [8].

HCV is a major risk factor for HCC with underlying both direct and indirect oncogenic factors [9]. Many recent studies showed surprising rates of de novo and recurrent HCC after DAA treatment whether SVR was achieved or not [10, 11]. This study aimed to assess the incidence and independent factors associated with hepatic decompensation and the occurrence of HCC after successful DAA therapy in patients with HCV genotype 4-related liver cirrhosis.

Patients and methods

This prospective cohort study included adult patients, older than 18 years of age, with HCV genotype 4-related liver cirrhosis. They had compensated liver cirrhosis (Child-Pugh class A) and were eligible for direct-acting antiviral (DAA) therapy according to the National Committee for Control of Viral Hepatitis (NCCVH) protocol. Patients received DAAs at the centers of the National Committee for Control of Viral Hepatitis (NCCVH) established within the Ministry of Health and Population (MOHP) healthcare facilities according to the patients' geographic distribution [7]. Patients received treatment according to the chronological treatment regimens of the NCCVH [6]. Only patients who achieved SVR were included in this study.

This work is funded by the authors. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The study was performed in compliance with the ethical principles of the 1975 Declaration of Helsinki and its later amendments (as revised in Brazil 2013) with Good Clinical Practice (GCP) guidelines. Patients were recruited from Damanhur Viral Hepatitis Center (Boheira Governorate) affiliated to NCCVH in the period between June 2016 and May 2018 with follow-up for 24 months. The study protocol was approved by the ethics committee of NCCVH. Patients signed written informed consent for inclusion in research.

Baseline demographic and laboratory data were collected in the form of full history taking, clinical examination, laboratory investigations, electrocardiography (ECG), and abdominal ultrasound. Laboratory investigations including complete blood picture, alanine transaminase (ALT), aspartate transaminase (AST), total serum bilirubin, international normalized ratio (INR), alfa-fetoprotein (AFP), antinuclear antibodies, thyroid-stimulating hormone (TSH), and quantitative real-time polymerase chain reaction (PCR) for HCV RNA were performed (Cobas Amplicor, HCV Roche, Branchburg, NJ, USA, v 2.0, detection limit 15 IU/mL). An established diagnosis of cirrhosis was obtained by at least 1 of the following criteria: histology, radiological or endoscopic evidence of portal hypertension, and transient elastography > 14 kPa.

Albumin-bilirubin (ALBI) score was calculated [12]. The equation for the linear predictor is (log10 bilirubin $\times$ 0.66) + (albumin $\times$ −0.085), where bilirubin is in mcmol/L and albumin is in g/L.

The exclusion criteria are previous or current liver decompensation (ascites, bleeding esophageal varices, encephalopathy, or other portal hypertension-related complications), calculated creatinine clearance $\leq$ 30 mL/min, previously treated or current diagnosis with hepatocellular carcinoma, patients with extra-hepatic malignancy (except after 2 years of a disease-free interval), pregnancy and refusal to comply with adequate contraception, and hepatitis B virus (HBV) or human immunodeficiency virus (HIV) co-infection.

Follow-up

Routine follow-up was performed monthly during treatment according to the protocol of the NCCVH. Sustained virological response (SVR) was detected as negative HCV RT-PCR 12 weeks after the end of treatment. Patients with liver cirrhosis were advised for regular follow-up for physical, laboratory assessment, and abdominal

ultrasound every 6 months until the end of the study duration.

Decompensation was recorded in the form of jaundice, portal hypertension-related complications, ascites, bleeding esophageal varices, and hepatic encephalopathy. Hepatocellular carcinoma was detected as a hepatic focal lesion during routine abdominal ultrasound follow-up and confirmed by triphasic CT scan and/or MRI with or without AFP.

Statistical analysis

Data were summarized using descriptive statistics (mean and standard deviation). Number and percentage were used for qualitative data. Statistical differences between the groups were done using the chi-square test for qualitative data, independent *t*-test for quantitative normally distributed data, and Mann-Whitney for quantitative non-normally distributed data. The value 0.05 was selected as a significant level for the test. Those factors demonstrating significant association in bivariate analysis and any others believed to be important regardless of these results were included in a multivariate logistic regression model. Analyses were performed using SPSS version 21.

Results

This prospective cohort study included 1789 patients with HCV genotype 4-related liver cirrhosis, and 184 (10.28%) patients developed hepatic decompensation after the end of DAA therapy during the follow-up period of the study. Baseline and follow-up data of patients who developed hepatic decompensation and those who did not develop decompensation are shown in Table 1. The most common form of decompensation was ascites (Table 2).

Male gender, AST, baseline levels of serum albumin, total bilirubin, total leukocyte count, hemoglobin, and platelet count as well as on-treatment levels of total bilirubin, albumin, prothrombin concentration, platelets, and leukocyte count are factors associated with decompensation in univariate analysis (Table 1).

According to multivariate logistic regression, baseline serum albumin, bilirubin, and platelet count were the independent parameters related to hepatic decompensation following DAA therapy with *P* values of 0.022, 0.03, and 0.001,

Table 1 Demographic and laboratory features of the studied patients according to the occurrence of hepatic decompensation

Variables		Hepatic decompensation				*P*-value
		Yes, number = 184		No, number = 1605		
		Mean	SD	Mean	SD	
Age		54.21	7.29	54.89	8.58	0.201
Gender, number (%)	**Male**	105 (57.1%)		438 (47.5%)		**0.017**
	Female	79 (42.9%)		485 (52.5%)		
Treatment status	**Past interferon treatment**	1	0.6%	4	0.5%	1
	Naïve	172	97.7%	863	97.5%	
	Experienced	3	1.7%	18	2.0%	
ALT		64.24	39.47	63.33	42.97	0.499
AST		73.88	40.94	68.28	42.19	**0.033**
Alpha-fetoprotein		12.02	14.16	11.95	20.61	0.209
Serum albumin		3.79	0.57	3.97	0.67	**< 0.001**
Total bilirubin		1.10	0.70	0.96	0.47	**0.008**
Total leukocytes count × 10^3		5.56	3.73	6.14	4.68	**0.001**
Hemoglobin		13.16	1.64	13.57	4.41	**0.029**
Platelets count × 10^3		124.46	60.97	152.71	69.25	**< 0.001**
Serum creatinine		0.85	0.19	1.01	3.42	0.556
Total bilirubin (during treatment)		1.22	0.59	1.07	0.57	**< 0.001**
Albumin (during treatment)		3.70	0.50	3.84	0.53	**0.002**
PC (during treatment)		78.78	15.86	84.18	11.89	**0.001**
INR (during treatment)		1.98	8.22	1.15	0.16	0.122
Total leukocytes count × 10^3 (during treatment)		5.14	1.87	5.53	2.02	**0.042**
Platelets count × 10^3 (during treatment)		121.26	60.53	153.55	67.12	**< 0.001**
Pre-treatment ALBI score		− 2.42	0.52	− 2.61	0.59	**< 0.001**
Post-treatment ALBI score		− 2.54	0.60	− 2.77	1.57	**< 0.001**

Table 2 Timing and description of hepatic decompensation

	Count	Percent
Within the first 1 year		
Bleeding esophageal varices	14	0.8%
Hepatic encephalopathy	6	0.3%
Ascites	185	10.3%
Jaundice	33	1.8%
Within the second year		
Bleeding esophageal varices	1	0.1%
Hepatic encephalopathy	1	0.1%
Ascites	12	0.6%
Jaundice	2	0.1%

Table 3 Multivariate regression analysis for prediction of hepatic decompensation after DAAs

	P-value	Odds ratio	95% confidence interval	
			Lower	Upper
Albumin	0.022	0.728	0.555	0.956
Total bilirubin	0.030	1.337	1.029	1.736
Platelets x 10^3	< 0.001	0.993	0.990	0.996

respectively (Table 3). ROC curves were plotted to detect the cutoff values of the three parameters (Fig. 1).

The three independent factors revealed by the multivariate analysis were used to develop a formula to predict hepatic decompensation after DAA therapy (Table 4) = 0.29 × total bilirubin − 0.317 × serum albumin − 0.007 × platelet count.

The ROC curve of the formula for prediction of decompensation using predicted probability from multivariate logistic regression model revealed an area under the ROC curve of 0.641 at cutoff 0.1098969 with sensitivity 59.9% and specificity 61.7% (Fig. 2).

We calculated the ALBI score for patients who developed hepatic decompensation and those who did not and found a significant difference between them in both pre-treatment and post-treatment ALBI scores (Table 1). We also used the ALBI score to predict hepatic decompensation in our cohort. Pre-treatment ALBI score could predict hepatic decompensation after DAA therapy at a cutoff value −2.5184; AUC was 0.609 with a sensitivity of 58.3% and a specificity of 59.7%. Post-treatment ALBI score could predict hepatic decompensation after DAA therapy at a cutoff value −2.9521; AUC was 0.597 with a sensitivity of 48.1% and a specificity of 75.5% (Fig. 3).

Regarding the development of de novo HCC, it was detected in 16 patients (0.999%) during a mean duration of 14.6 months after the end of DAA therapy. Most of the HCC lesions were single lesions 10 (62.5%), in the right lobe 13 (81.25%), with a mean focal lesion size of 3.95 ± 2.12 cm. Univariate analysis

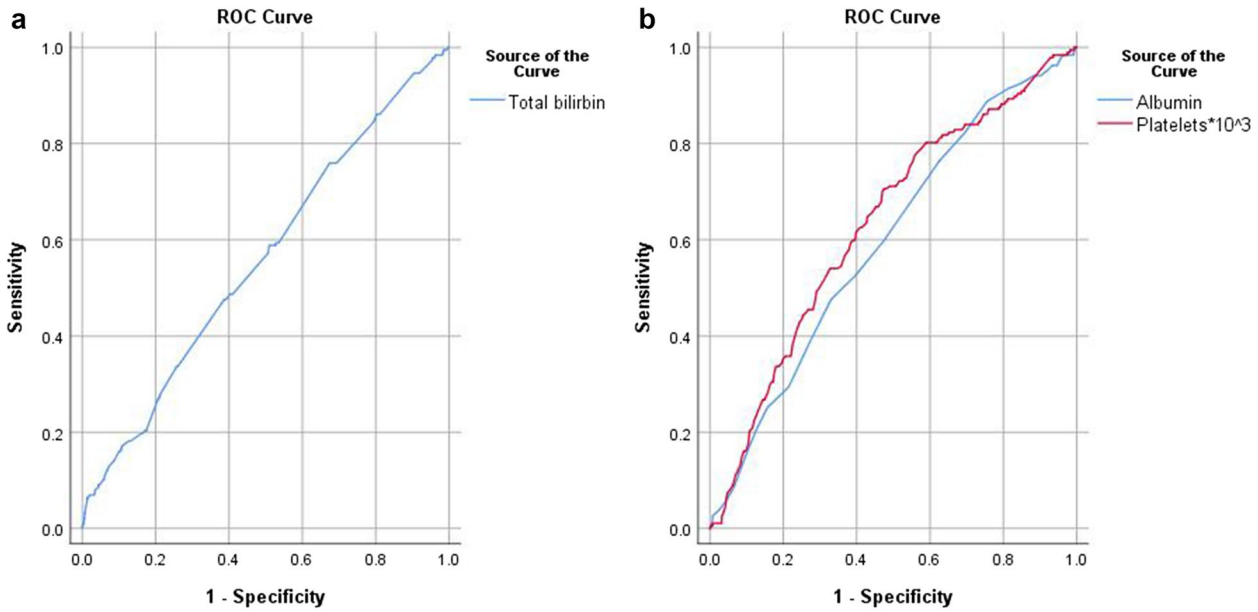

Fig. 1 ROC curve for prediction of hepatic decompensation after DAA therapy. **a** ROC curve for the prediction of hepatic decompensation after DAA therapy using total bilirubin. **b** ROC curve for the prediction of hepatic decompensation after DAA therapy using serum albumin and platelet count

Table 4 Prediction of hepatic decompensation using predicted probability from the multivariate logistic regression model

	B	S.E.	Wald	df	*P*-value	Odds ratio	95% confidence interval	
							Lower	Upper
Albumin	−0.317	0.139	5.228	1	0.022	0.728	0.555	0.956
Total bilirubin	0.290	0.133	4.734	1	0.030	1.337	1.029	1.736
Platelets × 10^3	−0.007	0.002	20.404	1	0.000	0.993	0.990	0.996
Constant	−0.300	0.564	0.284	1	0.594	0.741		

PROBIT (p) = 0.29 × total bilirubin − 0.317 × albumin − 0.007 × platelets

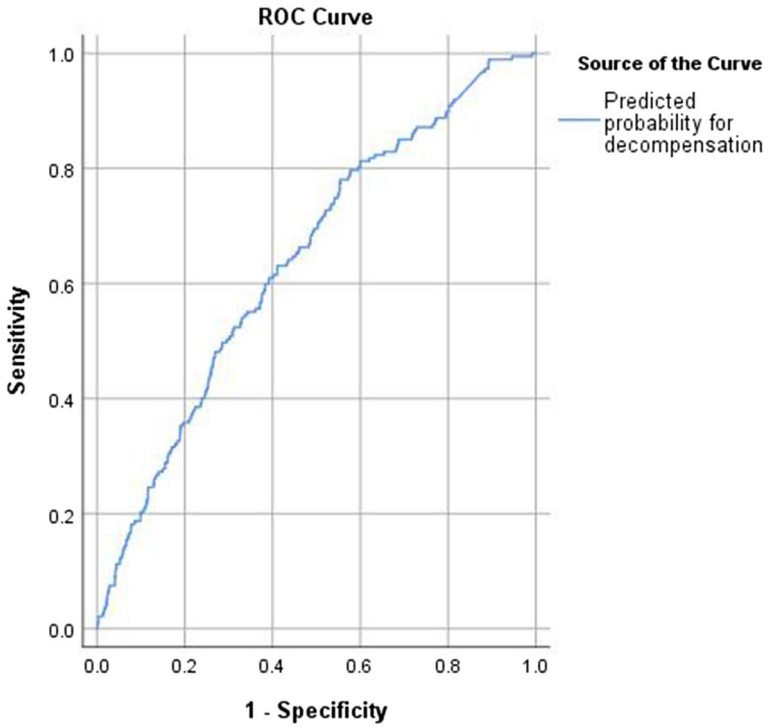

Fig. 2 ROC curve for the prediction of decompensation using predicted probability from the multivariate logistic regression model

was performed to detect the factors associated with the occurrence of de novo HCC after DAA therapy in patients with advanced fibrosis and liver cirrhosis and revealed age, male gender, previous antiviral therapy, and INR value during treatment. ALBI score was not associated with the occurrence of de novo HCC (Table 5). Multivariate logistic regression analysis revealed that age and male gender were the only independent factors associated with the development of de novo HCC. As age increases, HCC risk increases (odds ratio: 1.061, 95% confidence interval: 1–1.126). Males are more predisposed to HCC risk (odds ratio: 3.450, 95% confidence interval: 1.105–10.769) (Table 6).

Discussion

The natural history of patients with hepatitis C-related liver cirrhosis includes 2 stages. First, a prolonged asymptomatic phase of compensated cirrhosis followed by a significantly shorter phase of decompensated cirrhosis. Decompensated liver cirrhosis is diagnosed by the presence of one or more complications of portal hypertension (portal hypertensive bleeding, ascites, and/or hepatic encephalopathy) and is a determinant of poor survival [13]. The rate of decompensation may differ according to the etiology of liver cirrhosis, with evidence that NASH cirrhosis may progress more rapidly than cirrhosis from other etiologies [14]. Thus, a simple noninvasive tool to

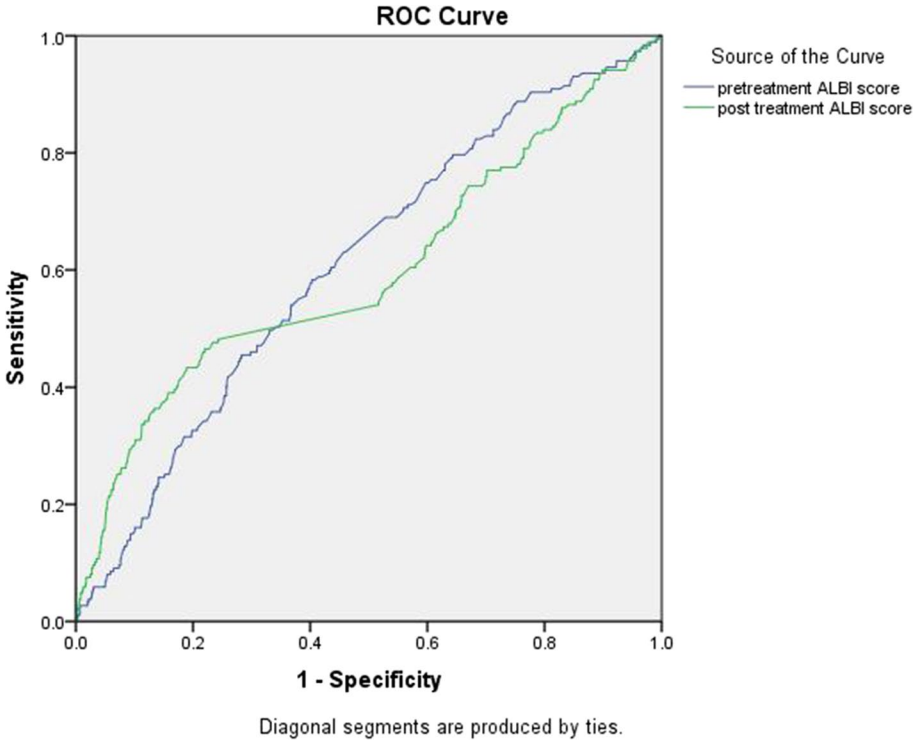

Fig. 3 ROC curve for prediction of hepatic decompensation after DAAs using ALBI score

predict hepatic decompensation in cirrhosis is a great need in clinical practice. This tool would likely need to be etiology-specific, incorporating specific predictive elements for the specific etiology [15].

This prospective cohort study was performed to detect the incidence and independent factors associated with hepatic decompensation and de novo HCC after successful viral eradication in patients with HCV genotype 4-related liver cirrhosis. Although all our patients achieved SVR without any previous decompensation episodes, according to our inclusion criteria, some of them reported hepatic decompensation during follow-up after the end of treatment. The most common presentation of hepatic decompensation in our study was ascites similar to previous studies [16–18]. The annual incidence of hepatic decompensation was similar to previous studies [3, 18] lower than previously reported as the natural history of HCV-related liver cirrhosis [19].

A previous study by Elnadry and colleagues found that patients with HCV-related liver cirrhosis who received DAAs showed significantly lower incidences of early decompensation than patients who did not receive DAAs [20]. Nahon et al. found that DAA therapy was associated with a decrease in all-cause mortality and HCC and was not associated with the occurrence of hepatic decompensation. They included patients with liver cirrhosis of different etiologies, e.g., alcoholic, HCV, HBV, and patients with HIV co-infection [16]. A prospective study by Carrat et al. [17] found that exposure to direct-acting antivirals was not associated with an improvement in the incidence of hepatic decompensation but was associated with a decrease in all-cause mortality and hepatocellular carcinoma. About 31% of patients of Carrat et al. [17] reported excessive alcohol use during or before DAA intake, but none of our patients had a history of alcohol intake or any other liver-injurious agent than HCV. Direct-acting antivirals induce a sustained virological response, reducing liver damage and inflammation. This effect causes liver regeneration, decreasing the risk of progression to liver-related complications or hepatocellular carcinoma.

We report a low incidence of liver-related complications after DAA therapy in patients with no previous history of hepatic decompensation. In contrast, other cohorts published with patients with more advanced liver disease showed that they are still at high risk of developing liver-related complications after viral eradication. Thus, treating physicians should evaluate baseline variables at the time of initiation of DAA therapy to ensure patient retention for clinical monitoring and HCC surveillance after the achievement of SVR.

We found that baseline serum albumin, bilirubin, and platelet count were the independent factors associated with hepatic decompensation after DAA therapy.

Table 5 Demographic and laboratory features of the studied patients according to the occurrence of de novo HCC (total 1789)

Variables		Hepatocellular carcinoma				*P*-value
		Yes, number = 16 (0.9%)		No, number = 1773 (99.1%)		
		Mean	SD	Mean	SD	
Age		58.69	5.59	54.79	8.47	**0.041**
Gender, number (%)	**Male**	12 (75.0%)		845 (47.9%)		**0.031**
	Female	4 (25.0%)		919 (52.1%)		
Treatment status	**Past interferon treatment**	0	0.0%	9	0.5%	**0.0378**
	Naïve	15	93.8%	1652	97.1%	
	DAA-experienced	1	6.3%	40	2.4%	
Fibrosis stage	**F3**	1	100.0%	88	72.1%	–
	F4	0	0.0%	32	26.2%	
ALT		62.44	26.69	64.74	43.85	0.552
AST		68.50	26.20	69.30	42.43	0.492
Alpha-fetoprotein		26.52	30.93	12.96	25.05	0.075
Serum albumin		3.99	0.62	3.95	0.68	0.842
Total bilirubin		1.11	0.55	0.97	0.51	0.267
Total leukocytes count × 10^3		6.08	2.08	6.08	4.61	0.524
Hemoglobin		13.77	2.07	13.57	4.38	0.554
Platelets count × 10^3		124.75	53.13	142.85	65.91	0.319
Serum creatinine		0.88	0.19	1.00	3.36	0.268
Total bilirubin (during treatment)		1.22	0.42	1.09	0.58	0.060
Albumin (during treatment)		3.75	0.50	3.83	0.64	0.591
PC (during treatment)		77.39	10.07	83.35	12.76	0.091
INR (during treatment)		1.28	0.15	1.25	2.73	**0.008**
Total leukocytes count × 10^3 (during treatment)		5.48	2.30	5.64	3.29	0.748
Platelets count × 10^3 (during treatment)		131.57	60.24	149.20	68.21	0.405
Pre-treatment ALBI score		− 2.59	0.53	− 2.59	0.59	0.879
Post-treatment ALBI score		− 2.55	0.56	− 2.75	1.50	0.172

Table 6 Multivariate logistic regression to detect independent predictors of de novo HCC

		P-value	Odds ratio	95% confidence interval	
				Lower	Upper
HCC	**Age**	0.049	1.061	1.000	1.126
	Gender (male)	0.033	3.450	1.105	10.769

Mendizabal et al. reported that clinically significant portal hypertension, low serum albumin, and significant liver fibrosis were associated with hepatic decompensation and HCC after achieving SVR, but they did not assess independent factors for HCC separately [3]. A Portuguese study by Pereira Guedes and colleagues [18] found that previous history of pre-treatment decompensation and baseline platelet and serum albumin levels were significantly associated with the occurrence of hepatic decompensation after the end of DAAs.

The ALBI score was validated as a measure of hepatic dysfunction in patients with liver cirrhosis of different etiologies [21]. The ALBI score was previously used to predict the outcome of patients with stable decompensated cirrhosis on the list of liver transplantation [22], but it was not used to predict hepatic decompensation after DAA therapy. In this study, it was found that pre-treatment and 6 months post-treatment ALBI score could predict the occurrence of hepatic decompensation.

In this study, 0.9% of our patients developed de novo HCC during the follow-up period of the study which is a low incidence similar to previous studies that reported a low incidence of de novo HCC after DAA therapy [16, 17, 23]. The annual risk of HCC in HCV-related cirrhotic patients is approximately 2–8% [24].

We found that age and male gender were the only independent factors associated with the development of de novo HCC. As age increases, HCC risk increases, and males are more predisposed to HCC risk. Carrat et al [17]. found that older age; male gender; HCV

genotypes 3, 5, 6, or 7; advanced fibrosis; systemic hypertension; serum albumin; platelets; and AFP were independently associated with HCC. This difference from our study may be related to the small number of patients who developed HCC in our study (only 16 patients). Also, according to Carrat et al [17]. study, HCV genotype 4 was not associated with the occurrence of de novo HCC in multivariate analysis while all our patients carry genotype 4. Nahon et al [16]. reported that among SVR patients, HCC occurrence was associated with lower prothrombin time less than 80%, lower platelet count less than 100.103/mm^3, a higher g-glutamyltransferase level greater than the upper limit of normal, higher AST greater than the upper limit of normal, and features of metabolic syndrome (defined by body mass index 25 kg/m^2 and/or diabetes and/or dyslipidemia).

In conclusion, DAA therapy is associated with a lower incidence of hepatic decompensation and HCC in patients with HCV genotype 4-related liver cirrhosis with no previous history of decompensation. Baseline serum albumin, bilirubin, and platelet count were the independent factors associated with hepatic decompensation. Our proposed formula and pre- and post-treatment ALBI score could predict hepatic decompensation but not de novo HCC. Age and male gender were the only independent factors associated with the development of de novo HCC. As age increases, HCC risk increases, and males are more predisposed to HCC risk.

Abbreviations

HCC	Hepatocellular carcinoma
HCV	Hepatitis C virus
DAA	Direct antivirals
ALBI	Albumin-bilirubin score
SVR	Sustained virological response
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus
AFP	Alpha-fetoprotein
INR	International normalized ratio
ALT	Alanine transaminase
AST	Aspartate aminotransferase
TSH	Thyroid-stimulating hormone
PCR	Polymerase chain reaction
NASH	Non-alcoholic steatohepatitis
NCCVH	National Committee for Control of Viral Hepatitis

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Authors' contributions
All authors have contributed significantly to finish this work; all authors are in agreement with the content of the article. M. S and H.I.S designed the study. M.S.M., R.A., and H.D. contributed to the performance of management. R.A., W.A., and M.H. contributed to the acquisition of the data. M.S. and W.M.A. analyzed the data. H.I.S. and M.S.M. interpreted the data and drafted the article. M.S., M.S.M., H.I.S., M.H., W.M.A., and M.H. revised the article. M.S. approved the final version of the article. M.S.M. submitted the article.

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Availability of data and materials
Please contact the authors for data requests.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the ethics committee of NCCVH. Patients signed written informed consent for inclusion in research.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

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