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ORIGINAL ARTICLE

Analysis of the albumin-bilirubin score as an indicator of improved liver function among hepatitis C virus patients with sustained viral response after direct-acting antiviral therapy

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Abstract

Background and Aim: To investigate the performance of the albumin-bilirubin (ALBI) score as an indicator of improved hepatic function using a cohort of hepatitis C virus (HCV) patients with sustained viral response (SVR) after direct-acting antiviral therapy (DAA).

Methods: HCV patients who achieved SVR after DAAs between 2015 and 2016 were followed for at least 24 months. Changes in ALBI were evaluated in the entire cohort and according to liver function and liver stiffness status at baseline.

Results: Four hundred ninety-seven patients were enrolled. Exactly 96.92% were in Child–Pugh (CTP) class A, and 42% had grade 2 fibrosis. Median ALBI was −3.02, while 87.7 and 11.3% of patients were in ALBI grades 1 and 2, respectively. ALBI improved significantly over time, particularly in patients who had a worse ALBI at baseline. Exactly 77% of patients initially in ALBI grade 1 and 93.9% of those in ALBI grades 2–3 improved their ALBI score in different amounts. Improved ALBI was observed irrespective of CTP score at baseline. Median ALBI at baseline and after 24 months were −3.03 and −3.27 for CTP 5, 2.02 and −2.88 for CTP 6, and −1.59 and −2.84 for CTP >6. Similarly, a significant improvement in ALBI was observed within each stage of fibrosis at baseline.

Conclusion: ALBI was a good indicator of improved hepatic function in HCV patients with SVR after DAA therapy, able to identify changes even in those patients who started DAA therapy with well-preserved function and mild fibrosis. This simple, objective, and noninvasive test should be evaluated in other clinical scenarios where liver function is relevant.

Introduction

The different and complex functions of the liver make it difficult to evaluate this organ function in a comprehensive way. Single tests, from serum bilirubin levels to indocyanine green clearance, provide valuable albeit limited information. The Child–Pugh (CTP) score combines laboratory and clinical variables in a tool that was designed to establish the prognosis of cirrhotic patients after variceal bleeding and is currently the most widely used tool to estimate liver function.[1] Variables include serum levels of bilirubin and albumin, international normalized ratio (INR), ascites, and hepatic encephalopathy, the last two being based on subjective assessment. In 2015, the albumin-bilirubin (ALBI) score was designed as a less subjective method to estimate liver function status and prognosis in patients with hepatocellular carcinoma (HCC).[2] The ability of ALBI to predict overall survival has been validated in a large cohort of HCC patients treated with resection, transarterial chemoembolization, or sorafenib,[3] and ALBI was shown as a prognostic factor in non-malignant hepatic conditions. Since ALBI combines the assessment of two important liver functions, that is, albumin synthesis and bilirubin excretion, we hypothesized that ALBI could identify subtle changes in liver function and therefore improve in patients with chronic viral hepatitis when eventually the infection is eradicated.

Chronic hepatitis C virus (HCV) infection is a global health problem. The World Health Organization (WHO) estimated in 2015 a worldwide prevalence of 0.5–2.3% across regions.[4–6] In Spain, between 2017 and 2018, the prevalence of antibodies against HCV and active infection in the general population was 0.85%, with the highest prevalence in men over 50 years old and in women over 70 years of age.[7] Interferon-free regimens using new direct-acting antivirals (DAAs) represent a

turning point in the treatment of patients with chronic hepatitis C.[8] The main advantages of DAAs are their availability, pangenotypic activity, simplicity, good tolerability, and high effectiveness, with sustained virological response (SVR) in more than 95% of patients. In Spain, the National Health System launched a National Strategic Approach for Hepatitis C in 2015 that allowed treatment of all patients in a stepwise manner, starting from those with the most advanced disease. In the following years, eradication of HCV infection in patients with less advanced fibrosis has provided a unique opportunity to study the improvement of liver function when liver function is not severely compromised. To understand whether ALBI could capture subtle changes in liver function, we have studied a cohort of patients with chronic HCV infection who achieved SVR after DAA therapy.

Methods

Patients. The study includes all patients with HCV infection treated with the new DAAs at San Pedro Hospital in Logroño, Spain, between April 2015 and December 2016, who were on SVR 12 weeks after the end of antiviral treatment. SVR was assessed by quantitative HCV-RNA determination, using real-time polymerase chain reaction with a threshold for detection of 15 IU/mL. Patients were excluded if they (i) were on the waiting list for liver transplantation, (ii) had evidence of hepatocellular or cholangiocellular carcinoma before DAA treatment, (iii) were under 18 years of age, (iv) were coinfected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV), (v) had any other coexisting etiology of liver disease such as autoimmune hepatitis, hemochromatosis, or others.

Clinical data collection and follow-up. Clinical data were obtained from electronic medical records of the regional Health Service of La Rioja. The use of these data followed the rules to guarantee the privacy and the anonymity of patients by creating a dissociated database. Variables were collected before and 24 months after the beginning of DAAs, and included age, gender, nationality, serology, viral genotype, previous antiviral treatment, grade of fibrosis (assessed by transient elastography), transaminases, total bilirubin, albumin, INR, and platelet count. Patients were followed until December 2018 to ensure a minimum follow-up of 24 months after DAA therapy with SVR. This study was conducted according to the ethical principles of the Declaration of Helsinki and approved by our Ethical Committee for Clinical Research of La Rioja (Ref. CEICLAR P.I. 276).

The CTP score was calculated according to albumin, total bilirubin, prothrombin time, ascites, and encephalopathy.[9] CTP was divided into three categories, and 1–3 points were given by category so that the minimum score is 5 and the maximum is 15. The values for ascites and encephalopathy were derived from the information available in the medical record. ALBI was calculated as $-0.085\cdot \times$ albumin (g/L) $+ 0.66 \times$ log total bilirubin (mmol/L). ALBI was further classified into three grades, grade 1 for ALBI ≤ -2.6; grade 2 for ALBI > -2.6 and ≤ -1.39; and grade 3 for ALBI > -1.39.

Statistical analysis. Statistical analysis was performed using SPSS version 21.0 software (SPSS Inc., Chicago, IL, USA). Continuous variables were expressed as median (interquartile range [IQR]), and categorical data were presented as frequency or percentage. Differences between two unpaired groups were evaluated with Mann–Whitney *U* test, whereas Wilcoxon signed-rank test was used to compare repeated measurements before and after treatment. The correlation between two variables was assessed using the Spearman rank correlation test. A two-tailed *P*-value below 0.05 was considered statistically significant.

Table 1 Patient characteristics before direct-acting antiviral therapy

Number of patients	497
Age, years, median (IQR)	56 (49–66)
Gender: Male, *n* (%)	304 (61.2)
Nationality: Spanish, *n* (%)	463 (93.2)
Previous HCV treatment: Yes, *n* (%)	295 (59.4%)
Genotype, *n* (%)	
1a	135 (27.2)
1b	240 (48.3)
2	14 (2.8)
3	65 (13.1)
4	42 (8.5)
Unknown	1 (0.2)
Fibrosis, *n* (%)	
F0–1	56 (11.3)
F2	208 (42.1)
F3	102 (20.6)
F4	128 (25.9)
CTP, median (IQR)	5.0 (5.0–5.0)
MELD score, median (IQR)	7.0 (7.0–8.0)
ALBI, median (IQR)	−3.02 (−3.21 to −2.78)

ALBI, albumin-bilirubin; CTP: Child–Pugh; HCV, hepatitis C virus; IQR, interquartile range; MELD, model for end-stage liver disease.

Results

Study population. In total, 513 patients met the inclusion and exclusion criteria. Sixteen had no further visits recorded during follow-up, making a final sample size of 497 patients. Their baseline characteristics are shown in Table 1. Median follow-up time was 30 months (IQR 27–34 months). The majority (61.2%) were males, and the median age was 56 years. Genotype 1 was predominant (75.5%) and most patients (59.4%) had been previously treated for HCV infection. The vast majority of patients had well-preserved liver function, with a median CTP score of 5 (IQR 5–5) and 96.92% being in class A. Median ALBI was −3.02 (IQR −3.21 to −2.78), and most patients were in ALBI grade 1 (436, 87.7%) or 2 (56, 11.3%). Regarding the degree of fibrosis at the start of treatment, most patients (42.1%) had grade 2 fibrosis.

Changes in liver tests and ALBI score. As shown in Table 2, laboratory tests at 2 years showed a significant improvement in transaminases and liver function tests together with an increase in platelet count.

An improvement in ALBI was observed over time (Fig. 1), which was already significant at 12 months and remained significant up to 24 months from baseline. Median ALBI scores were −3.02 at baseline, −3.24 at 12 months, and

Table 2 Changes in laboratory parameters after direct-acting antiviral therapy with sustained viral response

	Median (IQR)	*P*-value[†]
AST (UI/L)		
Baseline	43 (30–69.5)	<0.001
At 24 months	20 (17–25)	
ALT (UI/L)		
Baseline	53 (36–82.5)	<0.001
At 24 months	17 (13–22)	
Total bilirubin (mg/dL)		
Baseline	0.6 (0.4-0.8)	<0.001
At 24 months	0.5 (0.4–0.7)	
Albumin (g/dL)		
Baseline	4.3 (4–4.5)	<0.001
At 24 months	4.5 (4.3-4.7)	
INR		
Baseline	1.02 (1–1.08)	0.036
At 24 months	1.01 (0.99-1.08)	
Platelets ($\times 10^9$/L)		
Baseline	181 (138–228)	<0.001
At 24 months	196 (148–250)	
Cr (mg/dL)		
Baseline	0.8 (0.7-0.9)	<0.001
At 24 months	0.84 (0.73-0.96)	

[†]Wilcoxon test.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio; IQR, interquartile range.

−3.27 at 24 months. The fundamental improvement in ALBI occurred among patients who started with a worse ALBI (Fig. 2). Most patients (89.1%) who were in ALBI grade 2 before DAA improved to ALBI grade 1, and the three patients who were in ALBI grade 3 before treatment improved to ALBI grade 2. Thus, the proportion of the population that was ALBI grade 1 increased from 87.7 to 96.3% at 12 months, and remained at 95.3% at 24 months.

Changes in liver function scores over time were also analyzed at an individual patient level (Fig. 3). Comparing ALBI scores at baseline and after 24 months, 77% of patients who were initially in ALBI grade 1 and 93.9% of those in ALBI grades 2–3 improved their score to a different extent (Panels a and b).

A significant improvement in ALBI was also observed within each CTP score group at baseline (5, 6 or >6), as shown in Figure 4. Median ALBI scores at baseline and after 24 months were −3.03 and −3.27 for CTP 5 patients, −2.02 and −2.88 for CTP 6 patients, and −1.59 and −2.84 for CTP >6 patients. Similarly, a significant improvement in ALBI was observed within each stage of fibrosis at baseline (F1–2 and F3–4), as shown in Figure 5. Median ALBI at baseline and after 24 months were −3.11 and −3.23 for F1–2 stage ($P < 0.001$), and −2.86 and −3.27 for F3–4 stage ($P < 0.001$). Finally, a significant improvement in ALBI was also observed from baseline to 24 months in patients with model for end-stage liver disease (MELD) score <7 (median ALBI −3.09 to −3.32), 7–9 (median ALBI −3.07 to −3.21), and >9 (median ALBI −2.24 to −2.88) ($P < 0.001$ for all three comparisons).

Discussion

Individual parameters are commonly used to measure an organ function. This is the case of serum creatinine for renal function, thyroid-stimulating hormone for thyroid function, or left ventricular ejection fraction for heart function. The liver has multiple functions including protein synthesis, bile production, energy storage, detoxification, or immune surveillance. Different

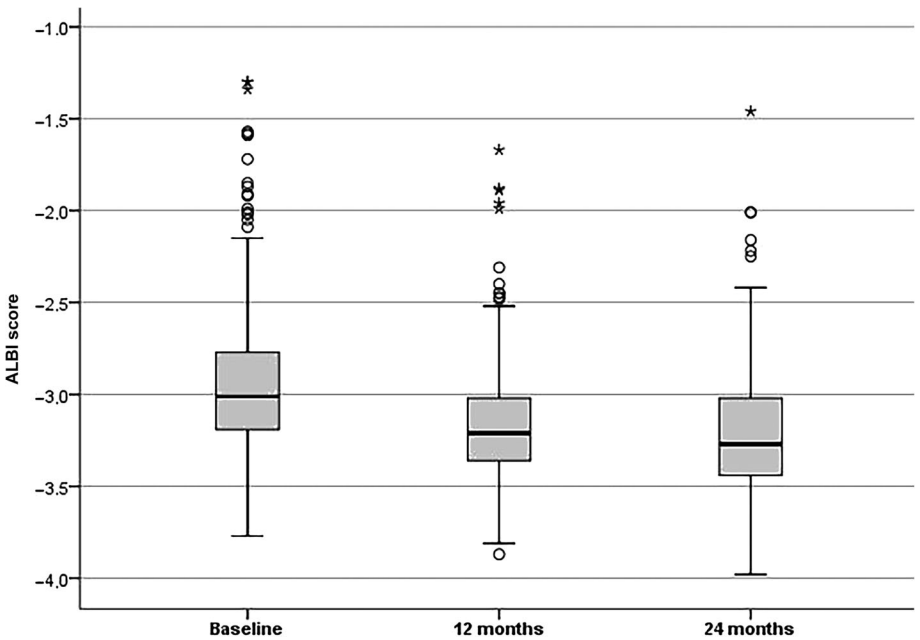

Figure 1 Changes in albumin-bilirubin (ALBI) score over time after direct-acting antiviral therapy with sustained viral response

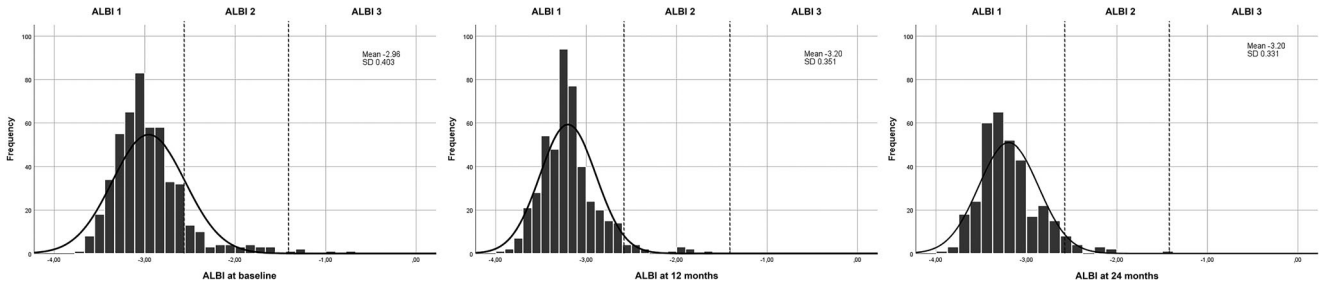

Figure 2 Distribution of albumin-bilirubin (ALBI) values in the population over time

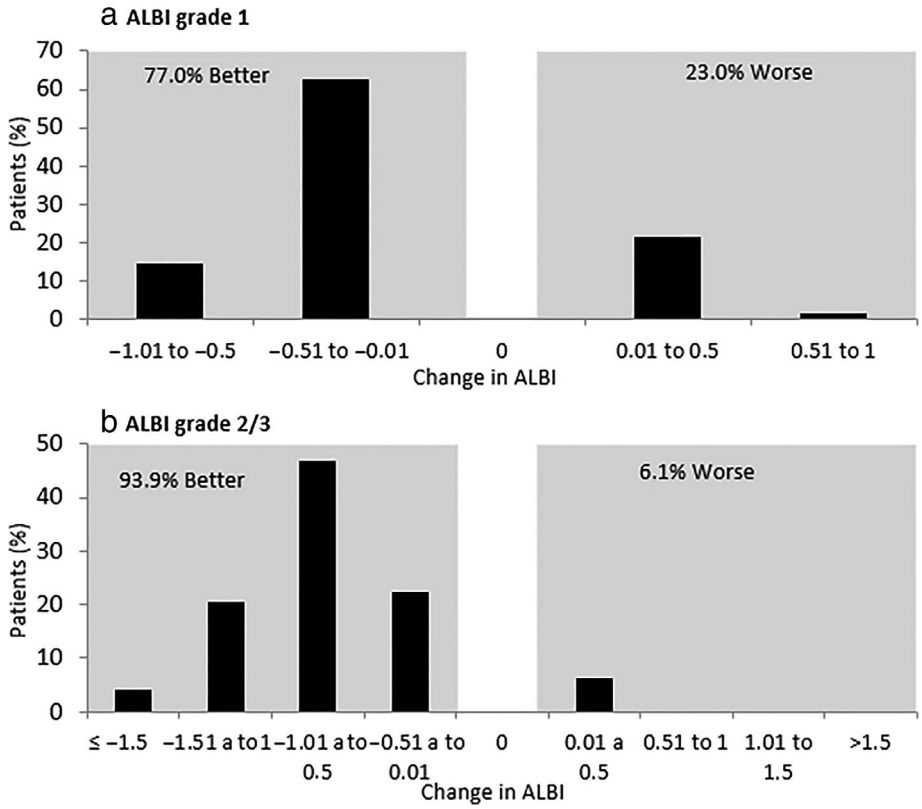

Figure 3 Magnitude of change in albumin-bilirubin (ALBI) score 24 months after direct-acting antiviral therapy with sustained viral response according to baseline ALBI grade

diseases or conditions may alter individual functions in a different way. Composite scores are therefore preferred to individual parameters to evaluate liver overall performance. In diseases involving vital systems, organ dysfunction usually impairs prognosis. Hence, individual or composite scores may help estimate the individual chances of patients getting worse outcomes, from complications to the use of health resources or death, and are therefore useful tools in medical decision-making to guide patient care. CTP is by and large the score that is used most frequently to assess liver function.[9] However, it is not a continuous variable; it includes items that can only be assessed subjectively such as ascites and hepatic encephalopathy; uses arbitrary cutoff values for bilirubin, albumin, and prothrombin time; gives the same importance to each variable; and has a floor and ceiling effect. In addition, prothrombin time cannot be evaluated in patients under oral anticoagulants. The MELD score is a continuous scale that lacks floor or ceiling effects but includes creatinine (which does not assess liver function) and INR (which is altered in patients under oral anticoagulation).

On the other hand, ALBI requires only laboratory parameters and is therefore devoid of subjectivism. Originally was reported as a robust determinant of survival in patients with HCC

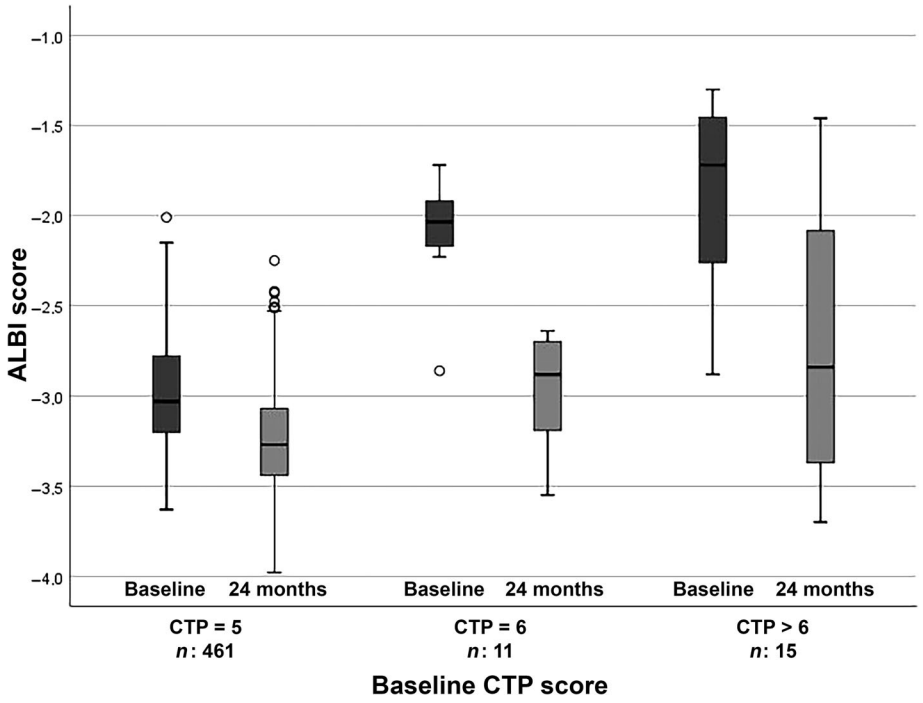

Figure 4 Albumin-bilirubin (ALBI) score at baseline and 24 months after direct-acting antiviral therapy with sustained viral response by initial Child–Pugh (CTP) class

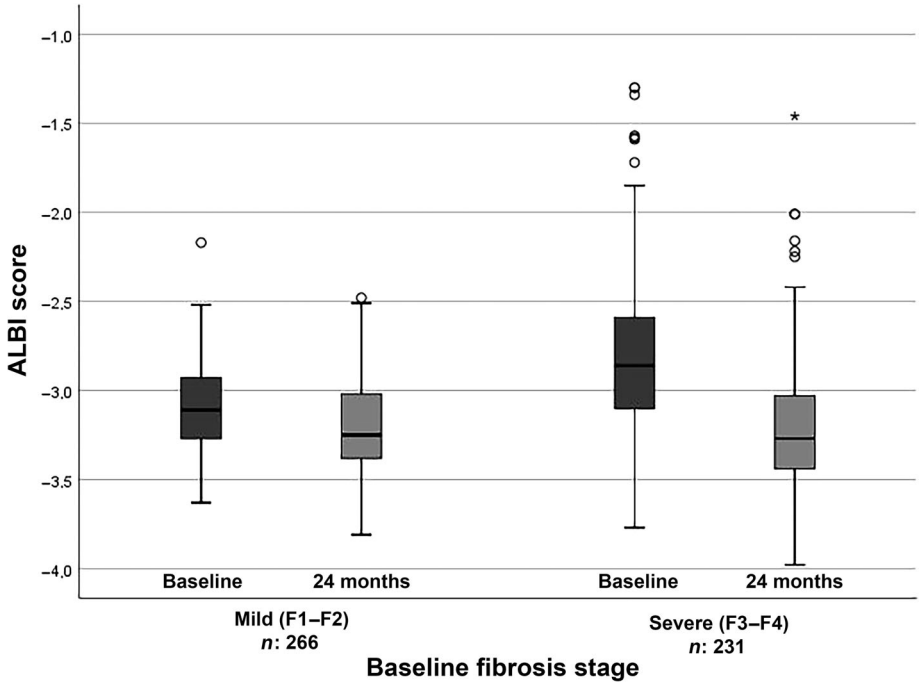

Figure 5 Changes in albumin-bilirubin (ALBI) score at baseline and 24 months after direct-acting antiviral therapy with sustained viral response by initial degree of fibrosis

receiving a variety of therapies.[2,3] Accumulating evidence indicated that the ALBI score predicted prognosis of patients with HCC who underwent oral chemotherapy using sorafenib, radioembolization, and drug-eluting embolic chemoembolization.[10–13] ALBI has more recently been considered as a good indicator of liver function. Indeed, it shows a good correlation with indocyanine green clearance[14]: an invasive test that is used to estimate liver function before liver resection in non-malignant hepatic conditions. ALBI was shown as a prognostic factor in patients with primary biliary cholangitis,[15] HBV-related acute-on-chronic liver failure,[16] and HBV cirrhosis,[17] suggesting its capacity to assess liver dysfunction in the absence of liver cancer. Finally, ALBI has been used as an indicator of deterioration in liver function comparable to MELD, being a good predictor of mortality and postoperative complications.[18–20] Even more importantly, there is no minimum score for ALBI as there is for CTP, and this lack of "floor effect" may provide ALBI with a better ability to discriminate liver function between patients with a fairly preserved liver function. In other words, if ALBI echoes accurately liver function, it should be able to capture slight improvements in function when liver damage subsides after therapy in conditions where there is little liver dysfunction.

To analyze this hypothesis, we studied to what extent HCV eradication results in an ALBI improvement as a result of an improved hepatic function. And indeed, our results confirm that SVR after DAA therapy is followed by a progressive improvement in ALBI that is already present after 12 months and further increases at 24 months. This is in line with recent observations.[21,22] ALBI score improved after SVR even among patients in CTP A class and with a CTP score of 5, a group where the CTP score can never capture any improvement in liver function due to its floor effect. Similar findings were observed among patients with mild degrees of fibrosis. As could be somehow expected, the magnitude of the improvement was higher in patients with a CTP score of 6 or > 6 compared with 5, and in patients with higher degrees of fibrosis compared with lower degrees. This ability of ALBI to discriminate liver function in patients without cirrhosis could be useful in clinical practice (and should be assessed prospectively) in several scenarios such as the baseline evaluation and later monitoring of liver function in non-cirrhotic patients submitted to liver resection, under therapies with potential impact on liver function (for instance, oxaliplatin or irinotecan chemotherapy for cancer patients), with liver metastasis from any cancer, and others.[24–26] Moreover, our results also support the possibility that ALBI could be used to estimate non-invasively the degree of fibrosis and differentiate cirrhosis from non-cirrhotic stages, as recently suggested.[23]

This study has some limitations. The first one is its retrospective nature. Completeness of clinical, biochemical, and pathological data and long duration of follow-up (up to 24 months) can partly compensate for this limitation. Also, most of our study population had a compensated cirrhosis, and it would have been interesting to analyze also patients with decompensated cirrhosis in CTP classes B and C. This is a difficult task nowadays for a good reason, because in Spain the vast majority of cirrhotics with chronic HCV infection have already been identified and treated with DAAs.

In conclusion, the ALBI score is a simple, objective, accessible, and noninvasive test that can be used in clinical practice to estimate overall liver function in patients with HCV-related chronic liver disease that are free from HCC. Future studies should confirm if ALBI has a similar performance in other prevalent etiologies of chronic liver disease such as HBV or metabolic syndrome-associated liver disease. Furthermore, ALBI could be evaluated as a tool to detect subclinical derangements of hepatic function in situations where this may be clinically relevant.

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