

Adverse impact of metabolic dysfunction on fibrosis regression following direct-acting antiviral therapy: A multicenter study for chronic hepatitis C

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List of Abbreviations

aHR, adjusted hazard ratio; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CHC, chronic hepatitis C; CI, confidence interval; DAA, direct-acting antiviral; DM, diabetes mellitus; FIB-4, fibrosis-4; INR, international normalized ratio; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; h-TC, hypercholesterolemia; LS, liver stiffness; SVR, sustained virological response; VCTE, vibration-controlled transient elastography.

Abstract

Background/Aims: Direct-acting antivirals (DAAs) effectively eradicate hepatitis C virus (HCV). This study investigated whether metabolic dysfunction influences the likelihood of fibrosis regression after DAA treatment in patients with chronic hepatitis C (CHC).

Methods: This multicenter, retrospective study included 8,819 patients diagnosed with CHC who were treated with DAAs and achieved a sustained virological response (SVR) between January 2014 and December 2022. Fibrosis regression was defined as a 20% reduction in noninvasive surrogates for liver fibrosis, such as liver stiffness (LS) measured by vibration-controlled transient elastography (VCTE) and the fibrosis-4 (FIB-4) score. Hypercholesterolemia (h-TC) were defined as >200 mg/dL.

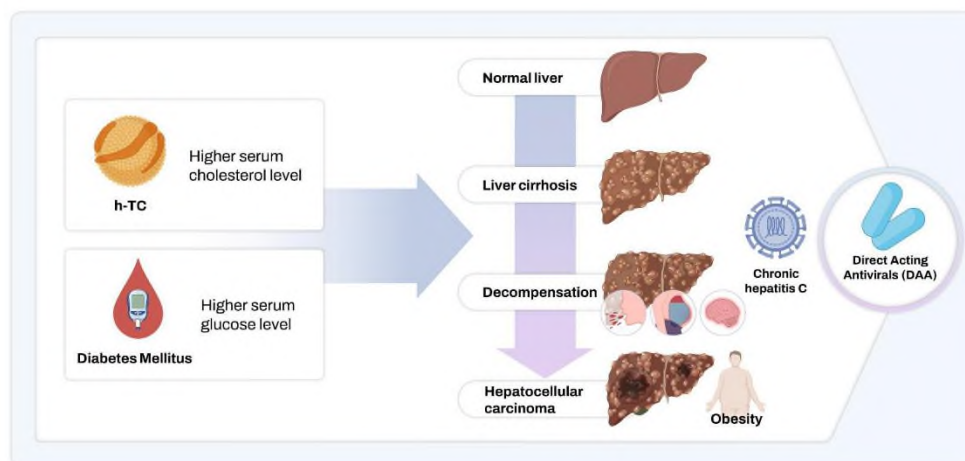
Results: The median age of the study population was 59.6 years, with a predominance of male patients (n = 4,713, 57.3%). Genotypes 1, 2, and others were confirmed in 3,872 (46.2%), 3,487 (41.6%), and 1,024 (12.2%) patients, respectively. Diabetes mellitus (DM) was present in 1,442 (17.2%) patients and the median LS was 7.50 kPa (interquartile range, 5.30–12.50). Multivariate analysis revealed that the presence of DM and pre-DAA h-TC were independently associated with a decreased probability of fibrosis regression by VCTE. Additionally, pre-DAA h-TC was independently associated with a decreased probability of fibrosis regression by the FIB-4.

Conclusions: Metabolic dysfunction has an unfavorable influence on fibrosis regression in patients with CHC who achieve SVR after DAA treatment.

Keywords: direct-acting antivirals, liver fibrosis, regression, dyslipidemia, diabetes mellitus

Highlights

- In this multicenter, retrospective study, a high serum levels of total cholesterol level (h-TC) reduced the likelihood of fibrosis regression after a sustained virological response (SVR) following direct-acting antiviral (DAA) treatment in patients with chronic hepatitis C.
- The presence of diabetes mellitus also reduced the likelihood of fibrosis regression after achieving SVR with DAA treatment, as measured by liver stiffness using vibration-controlled transient elastography.
- Pre-DAA h-TC independently reduced the likelihood of fibrosis regression as assessed via fibrosis-4 index.



Introduction

Hepatitis C virus (HCV) infection is a significant global health issue, with 58 million people chronically infected and 1.5 million newly diagnosed cases each year. In 2019, the World Health Organization reported 290,000 deaths related to HCV, primarily due to advanced liver cirrhosis and hepatocellular carcinoma (HCC).¹ Chronic HCV infection often progresses slowly, leading to liver fibrosis that advances from stage 0 to stage 4.^{2,3}

Real-world data suggest that pan-genotypic direct-acting antivirals (DAAs), such as glecaprevir/pibrentasvir and sofosbuvir/velpatasvir, are well-tolerated and effective, achieving a sustained virological response (SVR) in 12 weeks for patients with chronic hepatitis C (CHC).⁴ The high SVR rate (>97%) with DAA treatment is also associated with regression of the fibrotic burden, which has been well documented.^{5,6} Several studies have demonstrated the effectiveness of DAAs in reducing liver fibrosis related to HCV infection. Such studies have used various noninvasive tools to measure fibrosis, including liver stiffness (LS) via vibration-controlled transient elastography (VCTE) and the fibrosis-4 (FIB-4) score.⁷⁻⁹ Additionally, a recent study showed that SVR induced by DAA treatment not only resulted in fibrosis regression but also reduced the occurrence of HCC compared to treatment with pegylated interferon plus ribavirin at 144 weeks.¹⁰

Recent studies have highlighted a close association between HCV infection and metabolic factors. HCV is known to induce *de novo* lipogenesis by impairing beta-oxidation, generating reactive oxygen species, and activating nuclear factor kappa B and peroxisome proliferator-activated receptor alpha.¹¹⁻¹³ Additionally, it increases phospholipid synthesis, which plays a crucial role in viral replication and assembly by upregulating fatty acid synthase.¹⁴ While the relationship between HCV infection and lipogenesis is well established, the link between SVR and metabolic factors remains controversial. During the interferon treatment era, obesity was a significant risk factor for decreased SVR rates.¹⁵ However, with

the advent of DAAs, patients who achieved SVR were observed to gain weight, while those who did not achieve SVR experienced significant weight loss.¹⁶

To the best of our knowledge, no study has specifically analyzed the impact of metabolic factors on the efficacy of DAAs in fibrosis regression. This study investigated whether metabolic dysfunction influences the likelihood of fibrosis regression after DAA treatment in patients with CHC.

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Materials and Methods

Patient selection

This multicenter, retrospective study included 8,819 patients diagnosed with CHC who were treated with DAAs and achieved a SVR between January 2014 and December 2022. Data were extracted from the patients' electronic medical records. Patients were excluded if they met any of the following criteria: alanine aminotransferase (ALT) concentration > 400 mg/dL,¹⁷ serum concentrations of total bilirubin > 10 mg/dL,¹⁸⁻²⁰ serum concentrations of total cholesterol $> 1,000$ mg/dL, body mass index (BMI) > 50 kg/m², or failure to achieve SVR. Patients with a 6-month LS/baseline LS ratio > 5 , or a 6-month FIB-4/baseline FIB-4 ratio > 30 also excluded. Additionally, patients without follow-up measurements of LS, FIB-4 at 6 months post-DAA treatment were excluded from the analysis of liver fibrosis regression rates (**Figure 1**). To investigate the impact of medication for hypertension, diabetes mellitus (DM), and hypercholesterolemia (h-TC), we collected the medical record for patients with the chronic diseases and prescription for the medication for limited cohort, additionally.

Assessment of fibrosis index based on LS by VCTE and serological findings

The fibrotic burden was assessed using LS by VCTE (FibroScan[®]; EchoSens, Paris, France) and the FIB-4 index. Reliable VCTE results were defined as those with 10 successful measurements and an interquartile range to median ratio $< 30\%$. Patients without follow-up measurements were excluded from the analysis of changes in LS values from baseline to 6 months post-DAA treatment.

Noninvasive surrogates for liver fibrosis, such as the FIB-4 index, were also used. The FIB-4 index, which incorporates the platelet count, ALT concentration, and AST concentration, is a cost-effective and accurate screening tool for diagnosing liver fibrosis in patients with CHC. A FIB-4 value > 3.25 has demonstrated a positive predictive value of 82.1% for the presence

of significant fibrosis.²¹ FIB-4 were calculated using the following formula:

$$\text{FIB-4 score}^{22} = [\text{age (years)} \times \text{AST level (IU/L)}] / [\text{platelet count (10}^9\text{/L)} \times \text{ALT level (IU/L)}^{1/2}]$$

Study outcome measures and definitions

We assessed changes in LS as measured by VCTE and FIB-4 at 6 months post-DAA treatment in patients with CHC who achieved SVR and identified predictors of fibrosis regression. Additionally, we compared the occurrence of decompensation events and newly diagnosed HCC cases during the 96-month follow-up period post-DAA treatment in patients achieving SVR and identified predictors of decompensation or HCC.

To assess clinically significant portal hypertension (CSPH), we adopted the Baveno VII criteria. CSPH-included was defined as patients with LS ≥ 25 kPa, while CSPH-excluded was defined as LS < 15 kPa and platelet count $\geq 150 \times 10^9\text{/L}$. Patients who did not meet the criteria for CSPH-included or CSPH-excluded were categorized as being in a grey zone. Using the ANTICIPATE model for CSPH, patients in the grey zone were further stratified into two subgroups: high probability of CSPH (LS between 20–25 kPa and platelet $< 150 \times 10^9\text{/L}$, or LS between 15–20 kPa and platelet $< 110 \times 10^9\text{/L}$) and low probability of CSPH with remaining patients within the grey zone.²³

Data were extracted by reviewing the patients' electronic medical records, which included information on demographic data, laboratory findings, VCTE measurements, history of DAA treatment and response, as well as alcohol consumption patterns. Hypertension and DM was diagnosed based on medical records, use of antihypertensive or antidiabetic medications. Significant alcohol consumption was defined as greater than 210 g/week for men and greater than >140 g/week for women.²⁴ Obesity was defined as BMI over 25 kg/m^2 .²⁵ Higher viral load was defined as above 167,000 IU/mL.^{26,27} Genotype 2 was classified as sole

risk factor for patients.²⁸ In addition, h-TC was defined as total cholesterol level > 200 mg/dL.²⁹ Combined metabolic dysfunction was defined as the presence of at least two out of three conditions: hypertension, DM, and h-TC.

Decompensation was defined as the occurrence of any of the following conditions: upper gastrointestinal bleeding, ascites, hepatic encephalopathy, spontaneous bacterial peritonitis, or hepatorenal syndrome. To assess changes in fibrotic burden between baseline and SVR, we compared the ratios of the LS and FIB-4 values at 6 months post-DAA treatment to the baseline values. Improvement in liver fibrosis was defined as a >20% decrease in LS as shown by the LS by VCTE and FIB-4 values.³⁰⁻³²

Statistical analysis

Data were analyzed using Student's t-test and the Kaplan–Meier survival estimate. Univariate and multivariate logistic regression analyses were conducted to estimate the unadjusted or adjusted hazard ratios (HRs) for fibrosis regression, considering various factors such as sex, presence of hypertension, DM, significant alcohol consumption, obesity, old age, hemoglobin, platelet count, AST, ALT, total bilirubin, creatinine, serum albumin, INR, higher viral load, genotype 2, h-TC, and steatosis by CAP. Multiple linear regression analysis was conducted for independent variables with continuous numerical values. Pearson's correlation analysis was used to examine the correlation between fibrosis feature ratios, including LS by both VCTE and FIB-4, and baseline characteristics such as the BMI and blood lipid concentration. The statistical analysis was conducted using IBM SPSS for Windows, version 24.0 (IBM Corp., Armonk, NY, USA).

Ethical consideration

This study was conducted in accordance with the ethical guidelines of the World Medical

Association's Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the 29 tertiary academic institutes where the medical records were collected, including Soonchunhyang University Hospital, Seoul (IRB No. SCHUH 2023-04-015). The requirement for informed consent was waived because of the retrospective nature of the study.

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Results

Baseline characteristics of the study population

The baseline characteristics of the study population, which included 8,383 patients who were initially diagnosed with CHC and completed 6 months of DAA treatment, are summarized in **Table 1**. The median age of the study population was 59.6 years (interquartile range, 51–68 years), and 57.3% were male. The HCV genotype distribution was predominantly composed of genotypes 1 and 2, which together accounted for the majority of CHC cases in the study. Genotypes 1, 2, and others were confirmed in 3,872 (46.2%), 3,487 (41.6%), and 1,024 (12.2%) patients, respectively. The median BMI was 23.75 kg/m² (interquartile range, 21.63–26.03 kg/m²). DM was present in 1,442 (17.2%) patients, and hypertension was observed in 2,968 (35.4%). The median follow-up period was 26 months (range, 1–96 months).

Comparison between baseline and post-DAA SVR values

When comparing baseline (pre-DAA) and post-DAA SVR values, significant changes were observed in several laboratory parameters. Platelet counts, serum levels of albumin and total cholesterol, and the controlled attenuation parameter significantly increased from a median of 176 to 180 × 10³/μL, 4.2 to 4.3 g/dL, 161 to 175 mg/dL, and 222 to 229 dB/m, respectively. Hemoglobin levels remained unchanged at a median of 13.6 g/dL as did the INR. Significant decreases were observed in serum levels of total bilirubin, AST, ALT. LS values, and FIB-4 scores

Prior to DAA treatment, the proportions of patients with CSPH-excluded, low probability of CSPH, high probability of CSPH, and CSPH-included were 60.7%, 26.0%, 5.3%, and 8.0%, respectively. Following DAA therapy, there was a significant increase in the proportion of patients categorized as CSPH-excluded, accompanied by a decrease in the proportions of patients in the low probability, high probability, and CSPH-included groups.

These changes were statistically significant ($P < 0.001$).

When analyzing the proportion of individuals by steatosis grades based on CAP scores before and after DAA treatment, a decrease in the proportion of S0 (from 66.2% to 59.3%) and an increase in the proportions of S1–3 were observed post-treatment, which had a significance in proportional difference ($P < 0.001$). While the overall steatosis grade showed an increasing trend, changes occurred in both directions, with 7.8% of the study population developing mild hepatic steatosis, 23.7% experiencing aggravation, 62.1% showing no change, and 14.2% achieving improvement. (**Table 2**)

Effect of DM and h-TC on fibrosis regression in patients treated with DAA

In assessments of hepatic fibrosis using the FIB-4 index, univariate analysis revealed several factors influencing a 20% improvement in the FIB-4 score after DAA treatment. Multivariate analysis confirmed that male sex (adjusted HR [aHR], 1.305; 95% confidence interval [CI], 1.122–1.518; $P = 0.001$), obesity (aHR, 1.263; 95% CI, 1.102–1.448; $P = 0.001$), and AST (aHR, 1.052; 95% CI, 1.048–1.057; $P < 0.001$) were favorable factors, while higher platelet count (aHR, 0.996; 95% CI, 0.995–0.997; $P < 0.001$), higher ALT (aHR, 0.987; 95% CI, 0.984–0.989; $P < 0.001$), higher total bilirubin (aHR, 0.752; 95% CI, 0.651–0.869; $P < 0.001$), and h-TC (aHR, 0.802; 95% CI, 0.677–0.951; $P = 0.011$) were inhibitory factors (**Table 3**). In linear regression analyses, BMI ($\beta = -0.043$) was significantly negatively correlated while the albumin levels ($\beta = 0.043$) and total cholesterol levels ($\beta = 0.050$) were significantly positively correlated with the FIB-4 difference ratio (6 months/baseline) (**Supplementary Table 1**).

A 20% improvement in LS at 6 months post-DAA treatment was also influenced by several factors. Multivariate analyses revealed that higher AST significantly induced fibrosis regression (aHR, 1.004; 95% CI, 1.000–1.008; $P = 0.029$), and presence of DM and h-TC significantly inhibited LS improvement (aHR, 0.612; 95% CI, 0.486–0.772; $P < 0.001$ and aHR,

0.781; 95% CI, 0.617–0.988; $P = 0.039$, respectively). (**Supplementary Table 2**). Linear regression analysis showed a positive correlation between the serum level of total cholesterol and the LS ratio (post-DAA/baseline) ($\beta = 0.115$), suggesting that higher cholesterol levels were associated with less fibrosis regression after DAA treatment (**Supplementary Table 3**).

When analyzing the impact of hepatic steatosis on fibrosis regression, baseline hepatic steatosis was not significantly associated with fibrosis regression, as measured by both FIB-4 (HR, 0.952; 95% CI, 0.831–1.089; $P = 0.473$) and LS by VTCE (HR, 0.921; 95% CI, 0.756–1.122; $P = 0.413$) (**Table 3 and Supplementary Table 2**). Changes in CAP, whether increased or decreased, also showed no significant impact on fibrosis regression, as measured by both FIB-4 (HR, 1.068; 95% CI, 0.828–1.378; $P = 0.610$), and LS by VCTE (HR, 1.148; 95% CI, 0.890–1.480; $P = 0.289$).

For the comprehensive analysis, we conducted a risk assessment of combined metabolic dysfunction for fibrosis regression. In terms of a 20% improvement of LS by VCTE, combined metabolic dysfunction was associated with poorer regression (HR, 0.661; 95% CI, 0.523–0.834; $P < 0.001$).

Comparison of fibrosis regression between patients with or without medication use for metabolic diseases

To evaluate the impact of specific medication use on fibrosis regression, we analyzed subsets of patients diagnosed with hypertension, DM, and h-TC in a specific cohort. 19.8%, 54.9%, and 7.0% of patients were on medication of hypertension, DM, and h-TC, among the patients diagnosed with each metabolic disease. Patients receiving hypertension treatment showed significantly improved fibrosis regression with LS by VCTE (HR, 11.96; 95% CI, 3.980–35.92; $P < 0.001$). Similarly, DM treatment was associated with better LS improvement (HR, 4.503; 95% CI, 1.961–10.34; $P < 0.001$).

Alternative cutoffs of FIB-4 and LS improvements

In addition to the 20% improvement criteria, we analyzed alternative cutoffs of 10% and 30% improvement in FIB-4 and LS to assess fibrosis regression further.

For a 10% improvement in FIB-4, male sex (aHR, 1.330; 95% CI, 1.102–1.605; $P = 0.003$), obesity (aHR, 1.294; 95% CI, 1.096–1.527; $P = 0.002$), and higher AST (aHR, 1.048; 95% CI, 1.042–1.054; $P < 0.001$) were significantly associated with greater fibrosis regression. Conversely, higher platelet count (aHR, 0.995; 95% CI, 0.994–0.996; $P < 0.001$), higher ALT (aHR, 0.989; 95% CI, 0.986–0.992; $P < 0.001$), higher creatinine (aHR, 0.935; 95% CI, 0.875–1.000; $P = 0.048$) and h-TC (aHR, 0.831; 95% CI, 0.694–0.995; $P = 0.044$) were linked to less fibrosis regression (**Supplementary Table 4**).

For a 10% improvement in LS by VCTE, while higher AST (aHR, 1.005; 95% CI, 1.001–1.009; $P = 0.013$) was linked to more fibrosis regression, DM (aHR, 0.665; 95% CI, 0.516–0.857; $P = 0.002$) was significantly associated with reduced fibrosis regression (**Supplementary Table 5**).

For a 30% improvement in FIB-4, male sex (aHR, 1.420; 95% CI, 1.229–1.640; $P < 0.001$), obesity (aHR, 1.195; 95% CI, 1.152–1.357; $P = 0.006$), and higher AST (aHR, 1.048; 95% CI, 1.044–1.052; $P < 0.001$) were associated with greater fibrosis regression, while higher platelet count (aHR, 0.998; 95% CI, 0.997–0.999; $P < 0.001$), higher ALT (aHR, 0.986; 95% CI, 0.984–0.988; $P < 0.001$), and higher total bilirubin (aHR, 0.859; 95% CI, 0.757–0.974; $P = 0.018$) were linked to less fibrosis regression (**Supplementary Table 6**). For a 30% improvement in LS, higher AST (aHR, 1.003; 95% CI, 1.000–1.005; $P = 0.032$) was associated with more fibrosis regression (**Supplementary Table 7**).

Serum levels of cholesterol and BMI are significantly correlated with changes in fibrosis

severity

The LS ratio (post-DAA/baseline) exhibited a significant positive correlation with the baseline total cholesterol level ($r^2 = 0.007$, $P = 0.046$); however, the baseline BMI did not show a significant correlation with this ratio ($r^2 = 0.002$, $P = 0.145$) (**Supplementary Figure 1**).

Similarly, the FIB-4 ratio (post-DAA/baseline) showed a significant positive correlation with the baseline total cholesterol level ($r^2 = 0.005$, $P < 0.001$), while the baseline BMI showed a negative correlation ($r^2 = 0.002$, $P < 0.001$) in patients treated with DAAs (**Figure 2**). These findings suggest that h-TC prior to DAA treatment may impact the antifibrotic efficacy of DAAs as evidenced by significant correlations in LS and FIB-4.

Metabolic components are key prognostic factors for decompensation and HCC occurrence

When analyzing the impact of various metabolic components on decompensation and HCC occurrence, we observed that decompensation events and HCC occurrence were significantly higher among patients with a prior diagnosis of DM (**Figure 3**). While h-TC appeared to be a favorable factor for reducing decompensation events, it was associated with an increased occurrence of HCC in patients who achieved SVR with DAAs ($P = 0.019$ and $P = 0.004$, respectively) (**Supplementary Figure 2**). Additionally, obesity did not significantly affect decompensation events ($P = 0.876$) whereas HCC occurred more frequently in obese patients ($P = 0.034$) (**Supplementary Figure 3**).

The clinical outcomes of decompensation and HCC occurrence were analyzed based on 20% improvement in FIB-4 and LS. There was no significant difference in decompensation rates between patients with and without a 20% improvement in FIB-4 ($P = 0.106$). However, patients with a 20% improvement in FIB-4 showed a significantly higher incidence of HCC compared to those without improvement ($P < 0.001$) (**Supplementary Figure 4**). In contrast, 20% improvement in LS was not significantly associated with differences in decompensation

or HCC occurrence ($P = 0.557$ and $P = 0.977$, respectively). These findings suggest potential discrepancies in the prognostic implications of fibrosis improvement as measured by different noninvasive markers (**Supplementary Figure 5**).

Risk analyses were conducted to identify variables associated with liver decompensation, HCC occurrence, and mortality at 6 months post-DAA therapy. For liver decompensation, male sex (aHR, 1.419; 95% CI, 1.054–1.910; $P = 0.021$) and higher total bilirubin (aHR, 1.085; 95% CI, 1.001–1.176; $P = 0.048$) were associated with an increased risk, while higher hemoglobin (aHR, 0.878; 95% CI, 0.803–0.959; $P = 0.004$), higher platelet count (aHR, 0.993; 95% CI, 0.991–0.996; $P < 0.001$), higher serum albumin (aHR, 0.308; 95% CI, 0.227–0.418; $P < 0.001$), and genotype 2 (aHR, 0.725; 95% CI, 0.539–0.975; $P = 0.033$) were associated with a reduced risk (**Supplementary Table 8**). For HCC occurrence, male sex (aHR, 1.981; 95% CI, 1.446–2.714; $P < 0.001$), hypertension (aHR, 1.633; 95% CI, 1.271–2.190; $P = 0.001$), older age (aHR, 1.788; 95% CI, 1.319–2.425; $P < 0.001$), obesity (aHR, 1.506; 95% CI, 1.095–2.071; $P = 0.012$), and older age (aHR, 1.904; 95% CI, 1.342–2.700; $P < 0.001$) were significant risk factors. Conversely, higher platelet count (aHR, 0.987; 95% CI, 0.985–0.990; $P < 0.001$), higher serum albumin (aHR, 0.517; 95% CI, 0.373–0.716; $P < 0.001$), higher viral load (aHR, 0.654; 95% CI, 0.484–0.883; $P = 0.006$) and genotype 2 (aHR, 0.637; 95% CI, 0.474–0.855; $P = 0.003$) were associated with a lower risk of HCC (**Supplementary Table 9**). In terms of mortality, male sex (aHR, 1.436; 95% CI, 1.058–1.949; $P = 0.020$) and higher INR (aHR, 1.525; 95% CI, 1.008–2.309; $P = 0.046$) were identified as significant risk factors, whereas hypertension (aHR, 0.704; 95% CI, 0.499–0.994; $P = 0.046$), higher hemoglobin (aHR, 0.902; 95% CI, 0.823–0.988; $P = 0.026$), higher platelet count (aHR, 0.997; 95% CI, 0.995–0.999; $P = 0.007$) and higher ALT (aHR, 0.997; 95% CI, 0.994–1.000; $P = 0.027$) were associated with a reduced risk of mortality (**Supplementary Table 10**).

Discussion

This study evaluated the impact of metabolic dysfunction on likelihood of fibrosis regression in patients with CHC who achieved a SVR following DAA treatment. Our results demonstrated that metabolic dysfunction, particularly DM and h-TC, significantly reduces the likelihood of fibrosis regression. In multivariate analysis, DM and h-TC were both associated with a lower probability of fibrosis improvement, as assessed by LS by VCTE and FIB-4. However, obesity was an unfavorable factor for HCC occurrence, and DM worsened both decompensation and HCC occurrence. Although higher cholesterol levels were associated with favorable outcomes regarding decompensation events, they were also linked to an increased risk of HCC occurrence during the follow-up period.

In this study, changes in CAP values, which reflect hepatic steatosis, were not significantly associated with fibrosis regression in this study. This suggests that steatosis alone would not be a primary determinant of fibrosis improvement, highlighting the requirement to consider other metabolic or inflammatory factors influencing liver fibrosis. Furthermore, significant improvements in CSPH status were observed following DAA therapy, with a higher proportion of patients being categorized as CSPH-excluded and reductions observed in the low probability, high probability, and confirmed CSPH groups. These results suggest that achieving SVR through DAA therapy not only reduces liver inflammation but also improve portal hypertension, reflecting potential structural and functional recovery of the liver.

Our findings highlight distinct factors influencing fibrosis regression as assessed by FIB-4 and LS following DAA therapy. For FIB-4 improvement, male sex, obesity, and AST were favorable predictors, while higher platelet count, higher ALT, higher total bilirubin, and h-TC were inhibitory factors. These results suggest that FIB-4 reflects a combination of metabolic and hematologic factors that influence fibrosis regression. In contrast, LS improvement was significantly inhibited by DM and h-TC. The positive correlation between

total cholesterol levels and the LS ratio further shows the impact of dyslipidemia on liver stiffness. These findings suggest that LS would detect structural changes in fibrosis, while FIB-4 might be influenced by broader systemic factors.

h-TC was found to significantly reduce the likelihood of fibrosis regression following DAA therapy, as demonstrated by both LS measured by VCTE and FIB-4 scores. This finding aligns with previous studies that have identified elevated cholesterol levels as a negative factor in liver disease progression, possibly due to the close interaction between lipid metabolism and liver fibrosis.³³⁻³⁵ For instance, it is well established that HCV infection modulates lipid metabolism, promoting lipogenesis and impairing lipid oxidation, which in turn contributes to liver inflammation and fibrosis.^{36,37} The negative association between h-TC and fibrosis regression observed in our study suggests that persistent dyslipidemia, even after viral eradication, might drive fibrogenic pathways. Further investigation is required to determine whether targeted lipid-lowering interventions could enhance fibrosis regression in this patient population.

Our clinical findings explaining the inhibitory effect of DM on fibrosis regression following DAA treatment in patients with CHC support these ideas. This inhibitory effect of DM on liver fibrosis recovery would be explained by the broader impact of insulin resistance and chronic hyperglycemia on hepatic stellate cell activation and fibrogenesis. Insulin resistance, which is central to the pathophysiology of DM, contributes to ongoing liver inflammation and fibrosis by promoting hepatic steatosis, oxidative stress, and the release of pro-inflammatory cytokines, even in the context of viral eradication.³⁸⁻⁴⁰ Persistent insulin resistance also drives hepatic steatosis and microvascular changes that exacerbate liver fibrosis.⁴¹ Studies have shown that hyperinsulinemia and increased circulating levels of free fatty acids in diabetic patients exacerbate liver injury through the activation of transforming growth factor-beta and other profibrotic mediators.^{42,43} This is also affected by microvascular

changes in the liver that are characteristic of long-standing diabetes, contributing to a fibrotic environment, even after the resolution of HCV infection.⁴⁴ h-TC might contribute to impaired fibrosis regression through lipid-driven hepatocellular stress and inflammation, with increased lipotoxicity activating fibrogenic pathways.⁴⁵

In addition, both lipotoxicity and glucotoxicity may contribute fibrosis progression by modulating several processes involved in fibrogenesis, including hepatic stellate cell activation, inflammation, apoptosis, angiogenesis, and hepatic sinusoidal capillarization.⁴⁶ Excess flow of free fatty acid to the liver, muscle, and other tissues promotes mitochondrial dysfunction, and activate inflammatory pathways. Adipose tissue also tends to release pro-inflammatory cytokines such as tumor necrosis factor- α , transforming growth factor- β , and interleukin-6, while showing a deficiency in anti-inflammatory adipokines such as adiponectin in insulin resistant state.⁴⁷⁻⁴⁹ The activation of inflammatory pathways indirectly damages the liver by increasing oxidative stress, inducing hepatocellular damage, and promoting the activation of hepatic stellate cells, while also directly contributing to liver damage.⁵⁰

The analysis of alternative cutoffs for FIB-4 and LS improvements demonstrated variability in predictive factors, emphasizing the importance of cutoff selection in assessing fibrosis regression. At the 10% threshold, male sex, obesity, and AST remained significant for FIB-4 improvement, while creatinine and h-TC also emerged as inhibitory factors, potentially reflecting sensitivity to metabolic and renal influences. DM had a more pronounced negative impact on LS improvement at this level. At the 30% threshold, the predictive role of male sex, obesity, and AST persisted for FIB-4 improvement. However, total bilirubin became an additional inhibitory factor, likely indicating advanced liver dysfunction in patients achieving more pronounced fibrosis regression. For LS improvement, AST remained significant, but the influence of other variables diminished, potentially due to the smaller subset of patients with greater fibrosis improvement.

The discrepancy between the results of LS and FIB-4 analyses in this study, particularly regarding the effects of metabolic diseases such as hypertension, DM, h-TC, and combined metabolic dysfunction, shows the need for careful interpretation of fibrosis regression using different noninvasive methods. FIB-4, as a composite index, incorporates platelet count, AST, ALT, and age, all of which can be influenced by factors unrelated to fibrosis regression, such as splenic sequestration or other hematologic conditions.⁵¹ These factors may obscure the direct relationship between metabolic dysfunction, including combined metabolic dysfunction, and fibrosis regression when assessed using FIB-4. In contrast, LS by VCTE directly measures liver stiffness and structural changes, making it more sensitive to the adverse effects of DM and combined metabolic dysfunction on fibrosis improvement.⁵² This methodological difference would account for the divergence in findings between these two noninvasive markers.

The findings of this study suggest that effective management of metabolic comorbidities, such as hypertension and diabetes, through medication might play a crucial role in promoting fibrosis regression in patients for LS by VCTE. However, the significant association requires cautious interpretation. For instance, patients receiving hypertension treatment might have had better overall access to healthcare or adherence to treatment regimens. Additionally, antihypertensive medications, particularly angiotensin II receptor blockers have been reported to exert anti-fibrotic effects through mechanisms such as reducing hepatic stellate cell activation and attenuating inflammation.^{53,54}

In this study, the CAP score of study population showed tended to increase after 6 months post-DAA treatment. These findings align with previous studies reporting an increase in CAP following successful DAA treatment suggesting that post-SVR de novo steatosis is associated with metabolic comorbidities.⁵⁵⁻⁵⁷ As genotype 3 HCV is strongly associated with hepatic steatosis, which is considered a direct cytopathic effect of the virus, studies have

demonstrated that hepatic steatosis in chronic hepatitis C caused by genotype 3 HCV correlates with HCV replication levels and often improves with successful antiviral therapy. However, in non-genotype 3 infections, steatosis is more commonly linked to metabolic factors rather than viral replication.⁵⁸ While fibrosis regression could be achieved through the anti-inflammatory effects of viral clearance, the persistence of metabolic dysfunction might continue to maintain steatosis despite successful DAA treatment.⁵⁹ Given that our study population predominantly consisted of non-genotype 3 patients, the lack of improvement in steatosis could be attributed to the persistence of underlying metabolic dysfunction. Although hepatic steatosis itself might influence changes of fibrosis, changes in CAP score, as well as baseline CAP score, were not significantly associated with fibrosis regression in our study. This suggests that baseline metabolic factors, specifically h-TC and DM, regardless of the presence of hepatic steatosis, were among the important determinants of post-DAA fibrosis improvement in HCV patients.

The contrasting associations of hypercholesterolemia with lower risk of liver decompensation and higher risk of HCC reflect the dual roles of cholesterol in liver disease. In patients with advanced liver disease, lower cholesterol levels are often observed due to impaired hepatic synthesis and metabolic dysfunction, which are hallmarks of cirrhosis progression.⁶⁰ Consequently, patients with higher cholesterol levels might have better preserved liver function, reducing the likelihood of liver decompensation.⁶¹ This is consistent with evidence suggesting that serum cholesterol decreases with the severity of liver cirrhosis, as reported in prior study.⁶²

The finding that patients with a 20% improvement in FIB-4 had a higher incidence of HCC, while LS improvement showed no significant association, highlights the distinct mechanisms underlying these markers. FIB-4 may be influenced by factors unrelated to fibrosis regression, such as independent risk factors for HCC, potentially skewing its association with HCC risk. Improved FIB-4 scores might also lead to heightened surveillance and earlier HCC

detection. In contrast, LS improvement, which reflects structural changes in fibrosis, showed no significant link to HCC risk, suggesting it would be less confounded by non-fibrotic factors. These findings present the need for caution in interpreting changes in noninvasive fibrosis markers and the importance of understanding their unique characteristics.

Our risk analysis highlights the impact of metabolic components on clinical outcomes, including liver decompensation, HCC, and mortality, following DAA therapy. DM was associated with increased risks of both decompensation and HCC, reflecting its role in driving fibrosis progression. In contrast, h-TC reduced the risk of decompensation, possibly due to better preserved liver function, but was linked to higher HCC incidence, suggesting complex interactions with lipid metabolism. Regarding mortality, male sex and elevated INR were significant risk factors, while hypertension, higher hemoglobin, platelet count, and ALT were associated with reduced mortality risk. These findings present the requirement to address metabolic risk factors and optimize patient management strategies to improve survival and reduce liver-related complications after DAA therapy.

Moreover, several large cohort studies have identified DM as an independent risk factor for the development of liver cirrhosis and HCC in patients with CHC. Studies revealed that patients with both CHC and DM have been shown to have higher rates of liver-related complications, including decompensation and HCC, compared to their non-diabetic control group.^{63,64} These evidences emphasize the importance of addressing metabolic comorbidities, such as DM, in the management of CHC. Effective glycemic control might play a critical role in enhancing the liver's capacity for fibrosis regression post-SVR.

While our study provides several evidences into the differences metabolic dysfunctions on fibrosis regression in patients with CHC treated with DAAs, it is important to acknowledge its limitations. As a retrospective study, there were inherent limitations regarding to the reviewed medical records. Specifically, detailed metrics such as waist circumference and

high density lipoprotein levels, which are essential for the classical definition of metabolic syndrome, were unavailable in our dataset. Instead, we used a surrogate definition of combined metabolic dysfunction, which while not fully encompassing the criteria of metabolic syndrome, allows for a more comprehensive evaluation of metabolic factors compared to a single variable approach, given the limitations of the available retrospective data. The exclusion criteria for patient enrollment were based on certain thresholds that might not fully align with peer-reviewed studies. In addition, the follow-up period varied among patients, which would minimize the consistency of the observed outcomes. The lack of a significant association between significant alcohol use and fibrosis regression in our study might reflect behavioral changes during treatment, as patients receiving HCV therapy often reduce or abstain from alcohol consumption. However, it is not fully explained due to the retrospective design of the study. In addition, the number of study participants who underwent LS measurement by VCTE after 6 months of DAA treatment was relatively small compared to population evaluated using FIB-4. The observed differences between factors influencing LS and FIB-4 improvement might partly result from the smaller sample size for LS measurements compared to FIB-4 analyses, potentially limiting the statistical power to detect significant associations and contributing to this mismatch. Another limitation is the reliance on noninvasive methods, such as LS by VCTE and the FIB-4, to evaluate fibrosis regression. Although these methods are widely utilized and practical for the physician, they would be less precise than histological evaluation. The absence of liver biopsy data limits the ability to directly evaluate histopathological changes in liver fibrosis. Additionally, the absence of a control group of patients without HCV infection limits our ability to distinguish the direct effects of metabolic factors from those associated with HCV clearance. Furthermore, as our study population was predominantly Asian, the generalizability of these findings to other ethnic groups would be limited.

Future studies should utilize prospective designs to minimize biases presented in

retrospective analyses and the use of liver biopsy or advanced imaging techniques alongside noninvasive markers might provide a more accurate assessment of fibrosis regression. Furthermore, investigating the impact of metabolic interventions, such as lipid- and glucose-lowering agents, on fibrosis outcomes in CHC patients treated with DAA could offer additional insights for optimizing treatment strategies

In conclusion, we found that metabolic dysfunction has an unfavorable influence on fibrosis regression in patients with CHC who achieve SVR after DAA treatment. Addressing these metabolic factors may enhance treatment outcomes and reduce the risk of adverse liver-related events.

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Author's contributions

Conception: Tom Ryu, Jae Young Jang; Study design: Young Chang, Soung Won Jeong, Seung Up Kim; Data analysis and interpretation: Jeong-Ju Yoo, Sang Gyune Kim; Review of the results: Young Seok Kim, Hong Soo Kim, Seung Up Kim, Jae Young Jang; Drafting of manuscript: Tom Ryu, Young Chang; Critical revision of the article: Seung Up Kim, Jae Young Jang. All authors approved the final version of the manuscript.

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Table 1. Baseline characteristics of the study population (n = 8,383)

Variables	Values
<i>Demographic variables</i>	
Age, years	60 (51–68)
Male sex	4,713 (57.3)
Diabetes mellitus	1,442 (17.2)
Significant alcohol consumption	1211 (14.4)
Hypertension	29,689 (53.4)
Body mass index, kg/m ²	23.75 (21.63–26.03)
<i>Laboratory variables</i>	
Hemoglobin, g/dL	13.6 (12.5–14.6)
Platelet count, ×10 ³ /μL	176 (130–222)
Total bilirubin, mg/dL	0.70 (0.52–0.97)
Serum albumin, g/dL	4.2 (4.0–4.5)
AST, IU/L	44 (28–73)
ALT, IU/L	37 (22–70)
INR	1.02 (0.97–1.09)
Total cholesterol, mg/mL	161 (139–186)
<i>Genotypes of hepatitis C virus</i>	
Genotype 1	3,872 (46.2)
Genotype 2	3,487 (41.6)
Others	1,024 (12.2)
<i>Severity of liver fibrosis</i>	
LS, kPa	7.50 (5.30–12.50)
FIB-4 score	2.46 (1.50–4.52)
<i>Severity of liver steatosis</i>	
CAP, dB/m	222 (197–252)

Values are presented as n (%) or median (interquartile range). AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; LS, liver stiffness; FIB-4, fibrosis-4; CAP, controlled attenuation parameter.

Table 2. Changes in baseline characteristics after 6 months of DAA treatment (n = 8,383)

Variables	At the time of diagnosis of CHC	At 6 months of DAA treatment	P value
<i>Laboratory variables</i>			
Hemoglobin, g/dL	13.6 (12.5–14.6)	13.6 (12.6–14.7)	0.122
Platelet count, $\times 10^3/\mu\text{L}$	176 (130–222)	180 (135–224)	<0.001
Total bilirubin, mg/dL	0.70 (0.52–0.97)	0.70 (0.50–0.91)	<0.001
Serum albumin, g/dL	4.2 (4.0–4.5)	4.3 (4.1–4.6)	<0.001
AST, IU/L	44 (28–73)	24 (19–30)	<0.001
ALT, IU/L	37 (22–70)	17 (13–24)	<0.001
INR	1.02 (0.97–1.09)	1.02 (0.97–1.08)	0.809
Total cholesterol, mg/mL	161 (139–186)	175 (151–201)	<0.001
<i>Severity of liver fibrosis</i>			
LS, kPa	7.50 (5.30–12.50)	6.25 (4.60–10.20)	<0.001
FIB-4 score	2.46 (1.50–4.52)	1.96 (1.32–3.06)	<0.001
CSPH by Baveno VII			<0.001
CSPH-excluded	2984 (60.7)	1037 (65.5)	
Low probability of CSPH	1275 (26.0)	402 (25.4)	
High probability of CSPH	260 (5.3)	58 (3.7)	
CSPH-included	390 (8.0)	85 (5.4)	
<i>Severity of liver steatosis</i>			

CAP, dB/m	222 (197–252)	229 (203–260)	<0.001
Steatosis by grade			<0.001
No steatosis (S0)	2,542 (66.2)	936 (59.3)	
Mild steatosis (S1)	508 (13.2)	243 (15.4)	
Moderate steatosis (S2)	519 (13.5)	248 (15.7)	
Severe steatosis (S3)	270 (7.0)	151 (9.6)	
Increased steatosis grade		374 (23.7)	
Steatosis change from S0 to S1		123 (7.8)	
Unchanged steatosis grade		980 (62.1)	
Decreased steatosis grade		224 (14.2)	

Values are presented as n (%) or median (interquartile range).

CHC, chronic hepatitis C; DAA, direct-acting antivirals; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; LS, liver stiffness; FIB-4, fibrosis-4; CAP, controlled attenuation parameter.

Table 3. Factors related to improvement in FIB-4 value at 6 months after DAA treatment completion compared with index FIB-4 value (n = 7,148)

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Male sex	1.227 (1.126–1.337)	<0.001	1.305 (1.122–1.518)	0.001
Hypertension	1.253 (1.135–1.383)	<0.001	1.102 (0.944–1.286)	0.220
Diabetes mellitus	1.307 (1.166–1.465)	<0.001	1.082 (0.911–1.286)	0.370
Significant alcohol consumption	1.054 (0.980–1.094)	0.060		
Obesity	1.281 (1.154–1.421)	<0.001	1.263 (1.102–1.448)	0.001
Age $\geq$ 65 years	1.214 (1.109–1.330)	<0.001	1.005 (0.868–1.163)	0.949
Hemoglobin, g/dL	1.033 (1.007–1.059)	0.013	1.018 (0.969–1.070)	0.469
Platelet count, $\times 10^3/\mu\text{L}$	0.993 (0.993–0.994)	<0.001	0.996 (0.995–0.997)	<0.001
AST, IU/L	1.035 (1.032–1.037)	<0.001	1.052 (1.048–1.057)	<0.001
ALT, IU/L	1.010 (1.009–1.012)	<0.001	0.987 (0.984–0.989)	<0.001
Total bilirubin, mg/dL	1.125 (1.044–1.212)	0.002	0.752 (0.651–0.869)	<0.001
Creatinine, mg/dL	0.913 (0.876–0.951)	<0.001	0.960 (0.906–1.017)	0.165
Serum albumin, g/dL	0.555 (0.500–0.615)	<0.001	1.174 (0.979–1.408)	0.084
INR	1.206 (0.961–1.514)	0.106		
Higher viral load	1.001 (0.908–1.104)	0.980		
Genotype 2	0.916 (0.838–1.001)	0.051		
h-TC	0.501 (0.377–0.666)	<0.001	0.802 (0.677–0.951)	0.011

Steatosis by CAP

0.952 (0.831–1.089)

0.473

FIB-4, fibrosis-4; DAA, direct-acting antiviral; HR, hazard ratio; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; HCV, hepatitis C virus, h-TC, hypercholesterolemia; CAP, controlled attenuation parameter.

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Figure Legends

Figure 1. Algorithm for patient exclusion and enrollment. CHC, chronic hepatitis C; ALT, alanine aminotransferase; IU, international units; BMI, body mass index; SVR, sustained virological response; DAA, direct-acting antiviral; LS, liver stiffness; FIB-4, fibrosis-4.

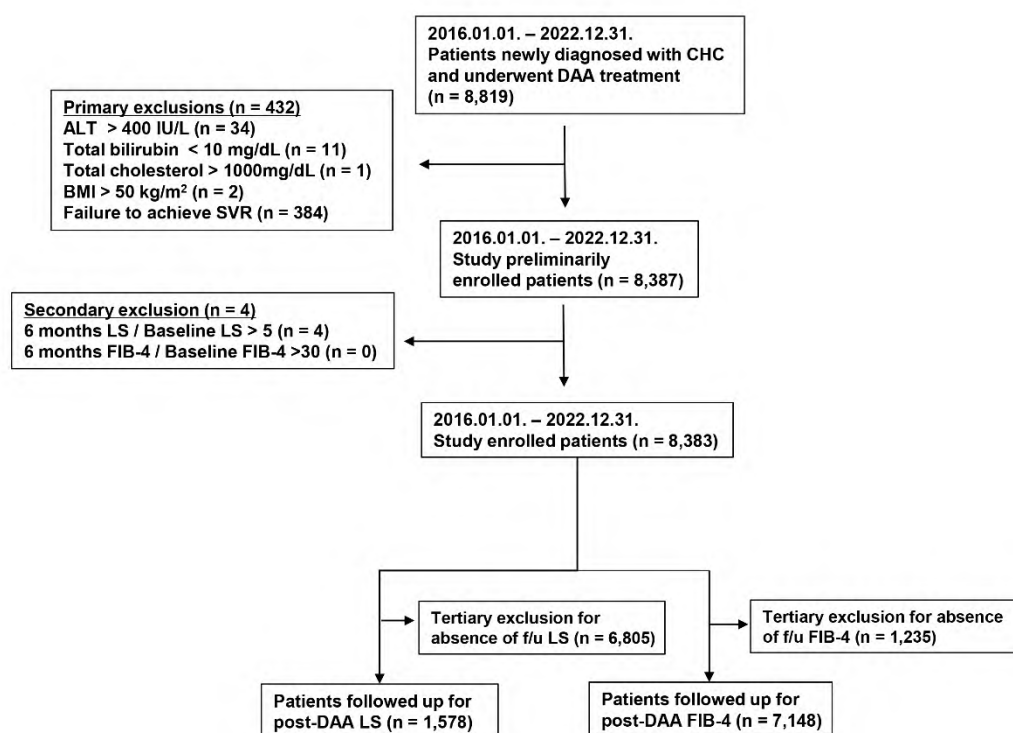


Figure 2. h-TC interfering with and obesity promoting FIB-4 improvement 6 months after the completion of DAA treatment. Correlation graphs presenting r^2 and P -value between the (A) serum concentration of total cholesterol and (B) BMI, and the FIB-4 difference ratio at the 6-month time point (6 months/baseline). h-TC, hypercholesterolemia; FIB-4, fibrosis-4; DAA, direct-acting antiviral; BMI, body mass index.

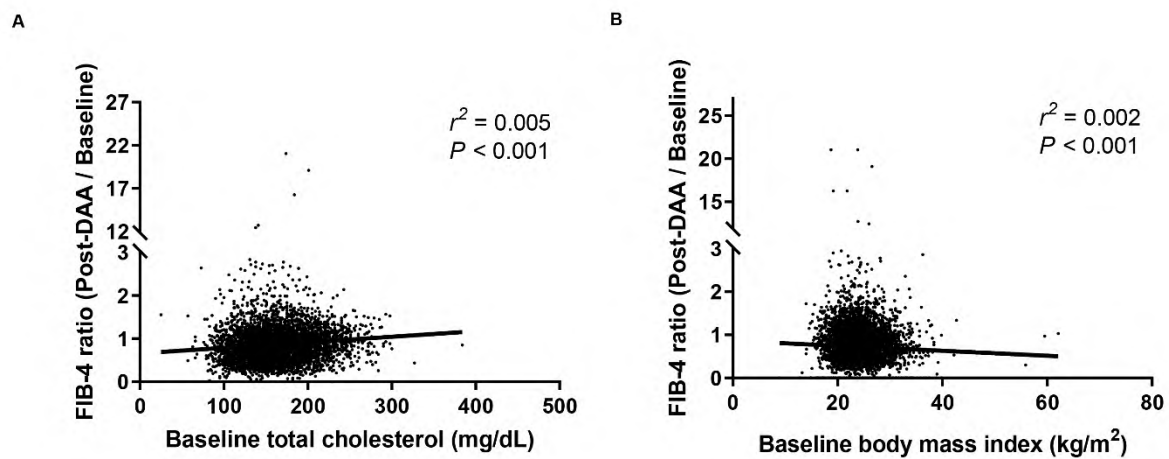
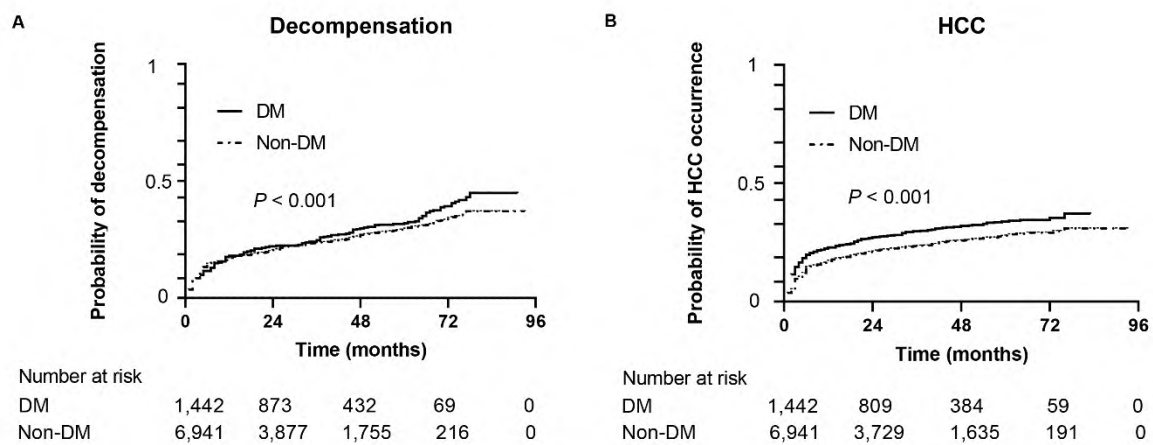
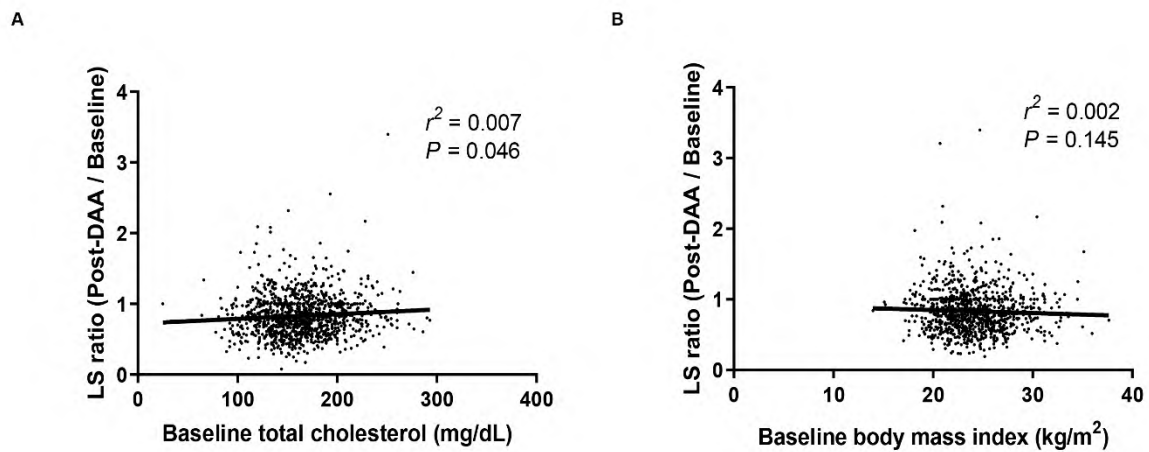


Figure 3. Decompensation events and HCC occurrence within the follow-up period after DAA treatment with or without DM. Kaplan–Meier curves expressing the (A) decompensation event rate and (B) HCC occurrence rate among patients with CHC, with or without DM. HCC, hepatocellular carcinoma; DAA, direct-acting antiviral; DM, diabetes mellitus; CHC, chronic hepatitis C.

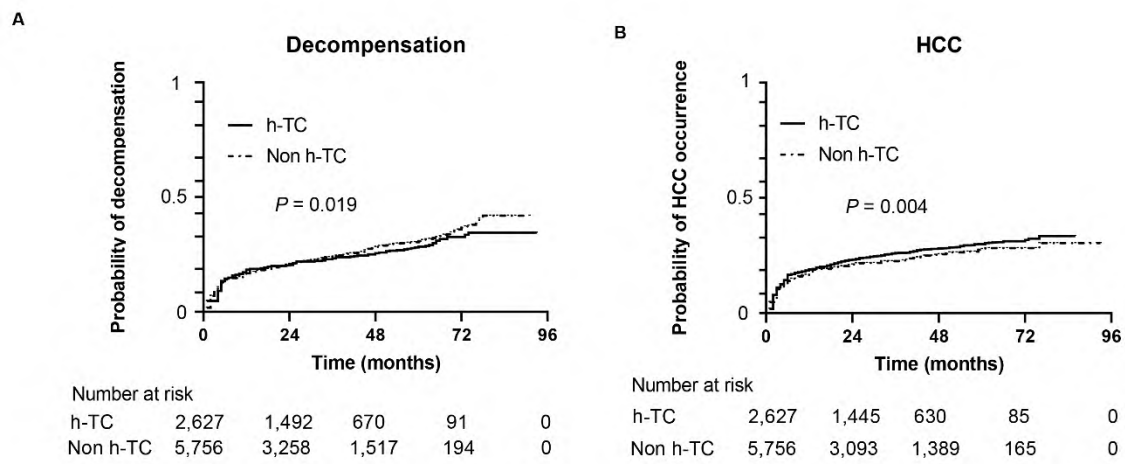


Supplementary Figures

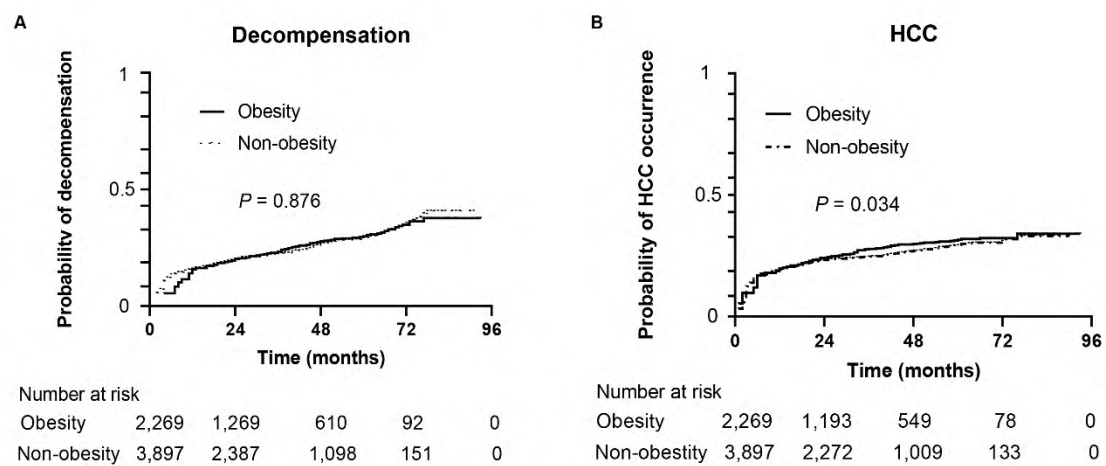
Supplementary Figure 1. h-TC interfering with LS improvement 6 months after the completion of DAA treatment. Correlation graphs presenting r^2 and P-value between the (A) serum concentration of total cholesterol and (B) BMI, and the LS difference ratio at the 6-month time point (6 months/baseline). h-TC, hypercholesterolemia; LS, liver stiffness; DAA, direct-acting antiviral; BMI, body mass index.



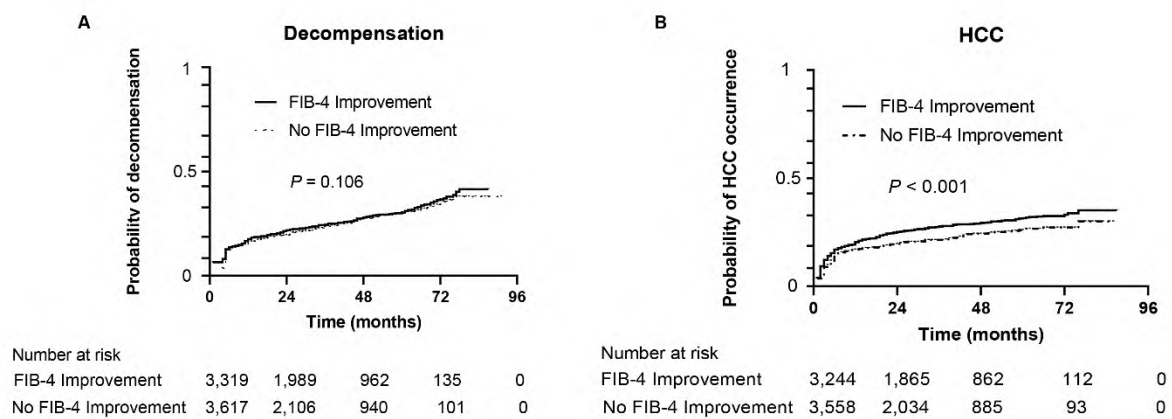
Supplementary Figure 2. Decompensation events and HCC occurrence within the follow-up period after DAA treatment with or without h-TC. Kaplan–Meier curves expressing the (A) decompensation event rate and (B) HCC occurrence rate among patients with CHC, with or without h-TC. HCC, hepatocellular carcinoma; DAA, direct-acting antiviral; h-TC, hypercholesterolemia; CHC, chronic hepatitis C.



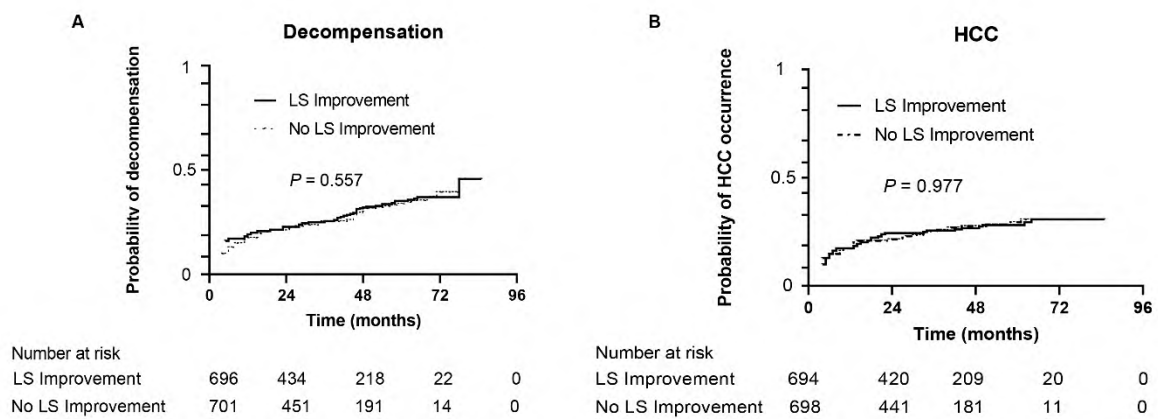
Supplementary Figure 3. Decompensation events and HCC occurrence within the follow-up period after DAA treatment with or without obesity. Kaplan–Meier curves expressing the (A) decompensation event rate and (B) HCC occurrence rate among patients with CHC, with or without obesity. HCC, hepatocellular carcinoma; DAA, direct-acting antiviral; CHC, chronic hepatitis C.



Supplementary Figure 4. Decompensation events and HCC occurrence within the follow-up period after DAA treatment with or without FIB-4 improvement. Kaplan–Meier curves expressing the (A) decompensation event rate and (B) HCC occurrence rate among patients with CHC, with or without FIB-4 improvement. HCC, hepatocellular carcinoma; DAA, direct-acting antiviral; CHC, chronic hepatitis C; FIB-4, fibrosis-4.



Supplementary Figure 5. Decompensation events and HCC occurrence within the follow-up period after DAA treatment with or without LS improvement. Kaplan–Meier curves expressing the (A) decompensation event rate and (B) HCC occurrence rate among patients with CHC, with or without LS improvement. HCC, hepatocellular carcinoma; DAA, direct-acting antiviral; CHC, chronic hepatitis C; LS, liver stiffness.



Supplementary Tables

Supplementary Table 1. Linear regression analysis table for FIB-4 change with continuous variables

Dependent variable	Independent variables	Non-standardized coefficient		Standardization factor	t	P
		B	Standard error	β		
FIB-4 ratio (Post-DAA/baseline)	Constants	0.635	0.138		4.614	
	Body mass index, kg/m ²	−0.009	0.003	−0.043	−2.856	<0.001
	Serum albumin, mg/dL	0.075	0.027	0.043	2.800	<0.001
	Serum total cholesterol, mg/dL	0.001	0.000	0.050	3.276	<0.001

FIB-4, fibrosis-4; DAA, direct-acting antiviral.

Supplementary Table 2. Factors related to 20% improvement in LS value using VCTE at 6 months after DAA treatment completion compared with index LS value (n = 1,578)

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Male sex	1.137 (0.967–1.337)	0.121		
Hypertension	0.907 (0.755–1.090)	0.299		
Diabetes mellitus	0.738 (0.604–0.902)	<0.001	0.612 (0.486–0.772)	<0.001
Significant alcohol consumption	0.985 (0.753–1.125)	0.325		
Obesity	1.070 (0.878–1.304)	0.501		
Age ≥ 65 years	0.910 (0.765–1.082)	0.284		
Hemoglobin, g/dL	1.007 (0.960–1.056)	0.788		
Platelet count, ×10 ³ /μL	1.000 (0.998–1.001)	0.492		
AST, IU/L	1.004 (1.002–1.006)	<0.001	1.004 (1.000–1.008)	0.029
ALT, IU/L	1.002 (1.001–1.004)	0.003	1.000 (0.997–1.002)	0.799
Total bilirubin, mg/dL	1.009 (0.926–1.098)	0.842		
Creatinine, mg/dL	0.992 (0.914–1.077)	0.850		
Serum albumin, g/dL	0.863 (0.706–1.054)	0.149		
INR	3.482 (1.450–8.361)	0.005		
Higher viral load	0.975 (0.809–1.175)	0.787		
Genotype 2	0.927 (0.788–1.090)	0.360		

h-TC	0.796 (0.656–0.930)	0.013	0.781 (0.617–0.988)	0.039
Steatosis by CAP	0.921 (0.756–1.122)	0.413		

LS, liver stiffness; VCTE, vibration-controlled transient elastography; DAA, direct-acting antiviral, HR, hazard ratio; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; h-TC, hypercholesterolemia; CAP, controlled attenuation parameter.

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Supplementary Table 3. Linear regression analysis table for LS change with continuous variables

Dependent variable	Independent variables	Non-standardized coefficient		Standardization factor	t	P
		B	Standard error			
LS ratio (Post-DAA/baseline)	Constants	0.632	0.213		2.964	0.003
	Body mass index, kg/m ²	−0.001	0.005	−0.0010	−0.282	0.778
	Serum albumin, mg/dL	−0.001	0.044	−0.001	−0.023	0.982
	Serum total cholesterol, mg/dL	0.002	0.000	0.115	3.251	<0.001

LS, liver stiffness; DAA, direct-acting antiviral.

Supplementary Table 4. Factors related to 10% improvement in FIB-4 value at 6 months after DAA treatment completion compared with index FIB-4 value

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Male sex	1.164 (1.063–1.273)	0.001	1.330 (1.102–1.605)	0.003
Hypertension	1.198 (1.079–1.329)	0.001	1.131 (0.938–1.364)	0.198
Diabetes mellitus	1.307 (1.158–1.476)	<0.001	1.089 (0.882–1.344)	0.429
Significant alcohol consumption	1.161 (1.014–1.328)	0.030	0.848 (0.677–1.061)	0.148
Obesity	1.316 (1.178–1.469)	<0.001	1.294 (1.096–1.527)	0.002
Age ≥ 65 years	1.157 (1.052–1.273)	0.003	0.923 (0.770–1.107)	0.388
Hemoglobin, g/dL	1.018 (1.074–1.018)	0.001	1.018 (0.960–1.081)	0.548
Platelet count, ×10 ³ /μL	0.993 (0.992–0.994)	<0.001	0.995 (0.994–0.996)	<0.001
AST, IU/L	1.038 (1.035–1.040)	<0.001	1.048 (1.042–1.054)	<0.001
ALT, IU/L	1.012 (1.011–1.013)	<0.001	0.989 (0.986–0.992)	<0.001
Total bilirubin, mg/dL	1.201 (1.097–1.315)	<0.001	0.900 (0.771–1.050)	0.181
Creatinine, mg/dL	0.906 (0.870–0.943)	<0.001	0.935 (0.875–1.000)	0.048
Serum albumin, g/dL	0.627 (0.563–0.699)	<0.001	1.169 (0.940–1.454)	0.160
INR	1.082 (0.892–1.313)	0.422		
Higher viral load	0.984 (0.888–1.091)	0.766		
Genotype 2	0.856 (0.779–0.940)	0.001	0.856 (0.733–1.000)	0.050
h-TC	0.636 (0.559–0.725)	<0.001	0.831 (0.694–0.995)	0.044

Steatosis by CAP

0.990 (0.858–1.142)

0.887

FIB-4, fibrosis-4; DAA; direct-acting antiviral, HR, hazard ratio; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; h-TC, hypercholesterolemia; CAP, controlled attenuation parameter.

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Supplementary Table 5. Factors related to 10% improvement in LS value using VCTE at 6 months after DAA treatment completion compared with index LS value

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Male sex	1.103 (0.911–1.335)	0.316		
Hypertension	0.805 (0.651–0.995)	0.044	0.883 (0.698–1.117)	0.300
Diabetes mellitus	0.697 (0.552–0.878)	0.002	0.665 (0.516–0.857)	0.002
Significant alcohol consumption	1.359 (1.020–1.811)	0.036	1.310 (0.980–1.751)	0.069
Obesity	1.216 (0.961–1.540)	0.103		
Age ≥ 65 years	0.924 (0.754–1.133)	0.448		
Hemoglobin, g/dL	1.013 (0.958–1.072)	0.643		
Platelet count, ×10 ³ /μL	1.000 (0.998–1.001)	0.665		
AST, IU/L	1.005 (1.003–1.008)	<0.001	1.005 (1.001–1.009)	0.013
ALT, IU/L	1.003 (1.001–1.005)	0.001	1.000 (0.997–1.003)	0.823
Total bilirubin, mg/dL	1.066 (0.898–1.265)	0.464		
Creatinine, mg/dL	0.954 (0.875–1.040)	0.288		
Serum albumin, g/dL	0.886 (0.699–1.123)	0.318		
INR	2.386 (0.890–6.399)	0.084		
Higher viral load	0.986 (0.791–1.229)	0.900		
Genotype 2	0.976 (0.805–1.183)	0.805		

h-TC	0.786 (0.604–1.023)	0.072
Steatosis by CAP	0.963 (0.763–1.216)	0.753

LS, liver stiffness; VCTE, vibration-controlled transient elastography; DAA, direct-acting antiviral, HR, hazard ratio; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; h-TC, hypercholesterolemia; CAP, controlled attenuation parameter.

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Supplementary Table 6. Factors related to 30% improvement in FIB-4 value at 6 months after DAA treatment completion compared with index FIB-4 value

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Male sex	1.288 (1.184–1.402)	<0.001	1.420 (1.229–1.640)	<0.001
Hypertension	1.182 (1.073–1.301)	0.001	1.026 (0.889–1.183)	0.728
Diabetes mellitus	1.244 (1.114–1.389)	<0.001	1.069 (0.911–1.254)	0.822
Significant alcohol consumption	1.348 (1.192–1.525)	<0.001	1.094 (0.921–1.299)	0.308
Obesity	1.201 (1.085–1.329)	<0.001	1.195 (1.052–1.357)	0.006
Age ≥ 65 years	1.127 (1.031–1.232)	0.008	0.928 (0.807–1.066)	0.289
Hemoglobin, g/dL	1.029 (1.004–1.055)	0.024	1.014 (0.969–1.061)	0.554
Platelet count, ×10 ³ /μL	0.994 (0.994–0.995)	<0.001	0.998 (0.997–0.999)	<0.001
AST, IU/L	1.028 (1.027–1.030)	<0.001	1.048 (1.044–1.052)	<0.001
ALT, IU/L	1.008 (1.007–1.009)	<0.001	0.986 (0.984–0.988)	<0.001
Total bilirubin, mg/dL	1.135 (1.057–1.219)	0.001	0.859 (0.757–0.974)	0.018
Creatinine, mg/dL	0.934 (0.895–0.974)	0.001	0.987 (0.932–1.045)	0.645
Serum Albumin, g/dL	0.569 (0.515–0.629)	<0.001	1.080 (0.914–1.276)	0.368
INR	1.224 (0.987–1.518)	0.065		
Higher viral load	0.994 (0.902–1.094)	0.897		
Genotype 2	0.916 (0.839–1.000)	0.051		
h-TC	0.679 (0.597–0.772)	<0.001	0.860 (0.723–1.023)	0.089

Steatosis by CAP

0.956 (0.836–1.093)

0.506

FIB-4, fibrosis-4; DAA; direct-acting antiviral, HR, hazard ratio; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; h-TC, hypercholesterolemia; CAP, controlled attenuation parameter.

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Supplementary Table 7. Factors related to 30% improvement in LS value using VCTE at 6 months after DAA treatment completion compared with index LS value

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Male sex	1.138 (0.984–1.317)	0.080		
Hypertension	0.908 (0.769–1.071)	0.252		
Diabetes mellitus	0.841 (0.698–1.013)	0.067		
Significant alcohol consumption	1.068 (0.872–1.308)	0.522		
Obesity	1.026 (0.861–1.223)	0.774		
Age $\geq$ 65 years	0.893 (0.765–1.043)	0.448		
Hemoglobin, g/dL	1.009 (0.967–1.054)	0.668		
Platelet count, $\times 10^3/\mu\text{L}$	1.000 (0.999–1.001)	0.665		
AST, IU/L	1.003 (1.001–1.004)	0.002	1.003 (1.000–1.005)	0.032
ALT, IU/L	1.001 (1.000–1.003)	0.022	1.000 (0.998–1.002)	0.831
Total bilirubin, mg/dL	1.459 (0.808–2.637)	0.208		
Creatinine, mg/dL	1.020 (0.937–1.112)	0.645		
Serum albumin, g/dL	0.860 (0.718–1.031)	0.103		
INR	1.496 (0.516–4.339)	0.184		
Higher viral load	1.011 (0.856–1.195)	0.894		
Genotype 2	0.921 (0.796–1.066)	0.270		

h-TC	0.868 (0.704–1.070)	0.186
Steatosis by CAP	0.929 (0.777–1.110)	0.415

LS, liver stiffness; VCTE, vibration-controlled transient elastography; DAA, direct-acting antiviral, HR, hazard ratio; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; h-TC, hypercholesterolemia; CAP, controlled attenuation parameter.

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Supplementary Table 8. Factors related to decompensation events in DAA treated patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Male sex	1.340 (1.063–1.688)	0.013	1.419 (1.054–1.910)	0.021
Hypertension	1.753 (0.379–0.230)	<0.001	1.155 (0.843–1.583)	0.369
Diabetes mellitus	1.986 (1.536–2.568)	<0.001	1.192 (0.852–1.668)	0.305
Significant alcohol consumption	1.336 (0.951–1.876)	0.093		
Obesity	1.050 (0.791–1.394)	0.736		
Age ≥ 65 years	1.388 (1.095–1.759)	0.006	0.837 (0.618–1.134)	0.250
Hemoglobin, g/dL	0.719 (0.675–0.765)	<0.001	0.878 (0.803–0.959)	0.004
Platelet count, ×10 ³ /μL	0.987 (0.985–0.989)	<0.001	0.993 (0.991–0.996)	<0.001
AST, IU/L	1.001 (1.000–1.002)	0.072		
ALT, IU/L	0.998 (0.996–1.000)	0.049	0.998 (0.995–1.000)	0.081
Total bilirubin, mg/dL	1.153 (1.057–1.257)	0.001	1.085 (1.001–1.176)	0.048
Creatinine, mg/dL	1.081 (0.996–1.174)	0.061		
Serum albumin, g/dL	0.162 (0.131–0.200)	<0.001	0.308 (0.227–0.418)	<0.001
INR	1.409 (1.179–1.683)	<0.001	1.124 (0.872–1.448)	0.366
Higher viral load	0.691 (0.539–0.885)	0.003	0.835 (0.610–1.143)	0.259
Genotype 2	0.699 (0.544–0.898)	0.005	0.725 (0.539–0.975)	0.033
h-TC	0.379 (0.227–0.633)	<0.001	0.663 (0.359–1.222)	0.188

Steatosis by CAP

1.086 (0.740–1.593)

0.673

DAA; direct-acting antiviral, HR, hazard ratio; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; h-TC, hypercholesterolemia; CAP, controlled attenuation parameter.

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Supplementary Table 9. Factors related to HCC occurrence in DAA treated patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Male sex	1.919 (1.571–2.345)	<0.001	1.981 (1.446–2.714)	<0.001
Hypertension	2.381 (1.949–2.908)	<0.001	1.633 (1.271–2.190)	0.001
Diabetes mellitus	2.172 (1.748–2.698)	<0.001	1.276 (0.937–1.738)	0.122
Significant alcohol consumption	1.500 (1.153–1.952)	0.002	1.226 (0.854–1.761)	0.270
Obesity	1.293 (1.044–1.603)	0.019	1.283 (0.966–1.703)	0.085
Age $\geq$ 65 years	2.387 (1.953–2.918)	<0.001	1.788 (1.319–2.425)	<0.001
Hemoglobin, g/dL	0.836 (0.790–0.884)	<0.001	0.987 (0.899–1.084)	0.784
Platelet count, $\times 10^3/\mu\text{L}$	0.984 (0.982–0.985)	<0.001	0.987 (0.985–0.990)	<0.001
AST, IU/L	1.001 (1.000–1.002)	0.010	1.001 (0.999–1.003)	0.497
ALT, IU/L	1.000 (0.998–1.001)	0.617		
Total bilirubin, mg/dL	1.172 (1.072–1.281)	0.001	1.092 (0.966–1.235)	0.159
Creatinine, mg/dL	0.933 (0.829–1.050)	0.248		
Serum albumin, g/dL	0.208 (0.172–0.251)	<0.001	0.517 (0.373–0.716)	<0.001
INR	1.389 (1.160–1.663)	<0.001	1.051 (0.783–1.410)	0.743
Higher viral load	0.523 (0.426–0.641)	<0.001	0.654 (0.484–0.883)	0.006
Genotype 2	0.656 (0.524–0.820)	<0.001	0.637 (0.474–0.855)	0.003
h-TC	3.621 (2.214–5.923)	<0.001	1.258 (0.661–2.395)	0.484

Steatosis by CAP

0.905 (0.613–1.338)

0.618

DAA; direct-acting antiviral, HCC, hepatocellular carcinoma; HR, hazard ratio; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; h-TC, hypercholesterolemia; CAP, controlled attenuation parameter.

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Supplementary Table 10. Factors related to mortality in DAA treated patients

Characteristics	Univariate analysis		Multivariate analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Male sex	1.138 (0.984–1.317)	0.001	1.436 (1.058–1.949)	0.020
Hypertension	0.414 (0.341–0.502)	<0.001	0.704 (0.499–0.994)	0.046
Diabetes mellitus	0.449 (0.698–1.013)	<0.001	0.708 (0.476–1.052)	0.708
Significant alcohol consumption	0.941 (0.736–1.204)	0.630		
Obesity	0.729 (0.583–0.911)	0.005	0.804 (0.588–1.100)	0.172
Age $\geq$ 65 years	1.312 (1.142–1.508)	<0.001	1.246 (0.917–1.691)	0.159
Hemoglobin, g/dL	0.958 (0.921–0.996)	0.031	0.902 (0.823–0.988)	0.026
Platelet count, $\times 10^3/\mu\text{L}$	0.998 (0.997–0.999)	0.001	0.997 (0.995–0.999)	0.007
AST, IU/L	1.000 (0.999–1.001)	0.602		
ALT, IU/L	0.998 (0.997–1.000)	0.007	0.997 (0.994–1.000)	0.027
Total bilirubin, mg/dL	1.046 (0.991–1.104)	0.104		
Creatinine, mg/dL	1.019 (0.957–1.085)	0.559		
Serum albumin, g/dL	1.126 (0.961–1.320)	0.142		
INR	1.251 (1.062–1.475)	0.008	1.525 (1.008–2.309)	0.046
Higher viral load	1.272 (1.080–1.497)	0.004	1.009 (0.733–1.390)	0.956
Genotype 2	0.914 (0.797–1.049)	0.202		
h-TC	0.729 (0.570–0.932)	0.011	0.744 (0.463–1.196)	0.221

Steatosis by CAP

0.907 (0.711–1.156)

0.429

DAA; direct-acting antiviral, HR, hazard ratio; CI, confidence interval; AST, aspartate aminotransferase; ALT, alanine aminotransferase; INR, international normalized ratio; h-TC, hypercholesterolemia; CAP, controlled attenuation parameter.

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