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## ORIGINAL ARTICLE

# HCV direct acting antiviral treatment leads to highly durable rates of ALT and AST lower than 30/19 criteria and improved APRI and FIB-4 scores

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**Abstract**

Direct acting antiviral treatment (DAA) has been the standard of care for hepatitis C virus (HCV) infection, but its long-term benefits in alanine aminotransferase (ALT) and aspartate aminotransferase (AST) improvement and hepatic fibrosis assessed by aspartate aminotransferase-to-platelet ratio index (APRI) and Fibrosis-4 index (FIB-4) scores remain unknown. The purpose of the present study was to assess DAA's long-term benefits, including frequencies of posttreatment week 96 ALT/AST <30 (males)/19 (females) (<30/19), improvement of APRI and FIB-4 scores, and the associated factors. This was a single-center, retrospective study on 157 patients with HCV with DAA-mediated sustained virological response (SVR) 12. At posttreatment week (post-Rx wk) 96, 75.4% had ALT <30/19; 62.7%, AST <30/19; and 60.1%, both ALT/AST <30/19. ALT/AST <30/19 at post-Rx wk 96 was associated with ALT/AST <30/19 at post-Rx wk 12 ( $p = 0.026$ ), independently of Child-Turcotte-Pugh <6 ( $p = 0.862$ ), platelets  $\leq 120 \times 10^9/L$  ( $p = 0.343$ ). Improvement rates of APRI <0.5 and FIB-4 <1.45 from baseline to post-Rx wk 96 were from 30.9% to 80.5%, and from 23% to 37.8%, respectively. Both APRI and FIB-4 improvement was associated with both ALT/AST <30 (males)/19 (females) at post-Rx wk 12 ( $p = 0.012$  and  $0.011$ , respectively). **Conclusion:** The present study showed that DAA-mediated SVR12 in patients with HCV resulted in (1) high and durable rates of ALT (75.4%), AST (62.7%), and both ALT/AST (60.1%) <30/19, and (2) high rates of APRI <0.5 (80.5%) and FIB-4 <1.45 (37.8%) at post-Rx wk 96, demonstrated clinical value of ALT/AST <30/19 and excellent long-term outcomes of DAA-mediated SVR12 in these patients.

**INTRODUCTION**

Hepatitis C virus (HCV) infection causes chronic hepatitis C (CHC) with an estimated 2.4 million infected

individuals in the United States,<sup>[1]</sup> and 70 million infected individuals worldwide.<sup>[2]</sup> When left untreated, CHC may progress to cirrhosis and hepatocellular carcinoma (HCC).<sup>[3]</sup> Several treatments have been

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developed for HCV infection, with direct-acting antivirals (DAAs) showing extremely high sustained virologic response (SVR), resulting in HCV elimination.<sup>[4]</sup> Several DAA regimens have become the standard of care, including two pangenotypic agents, sofosbuvir-velpatasvir and glecaprevir-pibrentasvir. HCV infection has now become a curable disease defined as the absence of detectable HCV RNA at posttreatment week 12, also known as SVR12.<sup>[5]</sup>

Both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been biochemical surrogates for liver injury, including HCV-mediated hepatocytic injury.<sup>[5,6]</sup> During chronic HCV infection, ALT and AST are frequently elevated. Although HCV-RNA monitoring during HCV treatment has been a standard practice, currently only ALT monitoring is used to assess improvement of liver injury, drug side effects or interactions, and treatment response.<sup>[7]</sup> Our previous and other studies have demonstrated an extremely high rate of rapid ALT normalization during DAA treatment and SVR12,<sup>[5–7]</sup> but no study thus far has reported long-term follow-up on changes of ALT and AST after achieved SVR12. We conduct this study to assess the dynamic changes of ALT and AST during and after DAA-mediated SVR, posttreatment week (post-Rx wk) 48 and 96.

While modified ALT criteria, such as ALT lower than 30 IU/L in males and 19 IU/L in females (<30/19), has been used to track the progress of patients with hepatitis B virus (HBV),<sup>[8]</sup> there has been no study to assess the value of the same criteria for patients with HCV, especially its long-term outcomes after achieving SVR12. Because DAAs have become the standard of care for HCV treatment, we have the unique opportunity to assess the rates and long-term outcomes of post-DAA-treatment ALT and AST levels <30/19 IU/L in patients infected with HCV.

Noninvasive models have been developed and clinically used to stage hepatic fibrosis. Among them, both AST-to-platelet ratio index (APRI) and fibrosis-4 (FIB-4) are most commonly used.<sup>[9,10]</sup> APRI is calculated using the following formula:  $APRI = (AST [IU/L]/upper\ limit\ of\ normal [IU/L]) \times 100/platelets (10^9/L)$ . APRI at a threshold value <0.5 rules out cirrhosis; at a threshold >1.5, APRI rules in significant fibrosis. Meta-analysis studies showed that APRI test had 68.1%–77.0% sensitivity and 72%–72.3% specificity in diagnosing fibrosis, and 76%–84% sensitivity and 72%–83% specificity in diagnosing cirrhosis.<sup>[11,12]</sup> FIB-4 can be calculated using the following formula:  $age \times AST (IU/L)/platelets (10^9/L) \times ALT^{1/2} (IU/L)$ . The FIB-4 index at a threshold <1.45 excludes advanced fibrosis, and a threshold >3.25 to diagnose advanced fibrosis.<sup>[13]</sup> Vallet-Pichard et al. reported that in patients infected with HCV, a FIB-4 index <1.45 had 94.7% negative predictive value to exclude severe fibrosis, whereas a FIB-4 index >3.25 had 82.1% positive predictive value to confirm severe

fibrosis.<sup>[14]</sup> Recent studies indicated that there is a significant drop in mean APRI and FIB-4 score from baseline after achieving SVR12.<sup>[15,16]</sup> However, data remain lacking on whether and how a successful DAA treatment (i.e., SVR12) affects APRI and FIB-4 score in a long-term follow-up.

The present study retrospectively assessed the long-term impact after a successful DAA-mediated SVR12 on frequencies of post-Rx wk 96 ALT/AST <30/19 IU/L, improvement of APRI and FIB-4 scores, and the associated factors in 157 patients infected with HCV.

## METHODS

### Study design and patient enrollment

This was a single-center study. Institutional review board approval was obtained, and informed consent was waived. Patients with CHC who received DAA treatment with 12 different DAA regimens from September 1, 2014 to July 17, 2020 in the Liver Clinic at the University of California Irvine Medical Center were assessed and enrolled if they met the inclusion criteria. Inclusion criteria included patients with CHC treated with a full course of a DAA regimen with or without ribavirin, and had SVR12 and a minimum 48-week post-treatment follow-up. Exclusion criteria included patients with incomplete treatment or missing lab data during the treatment and follow-up.

Of the 202 patient charts that were reviewed, 45 were excluded from the study due to incomplete treatment or missing lab data during or after completed DAA treatment, lack of SVR12 data, or lack of 48-week post-treatment follow-up. Consequently, 157 patients met the inclusion criteria and were included in the present study.

### Data collection

Baseline data collection included age, gender, ethnicity, comorbidities, diagnosis of cirrhosis, Child-Turcotte-Pugh (CTP) class, Model for End-Stage Liver Disease (MELD) score, body mass index (BMI), and history of prior HCV treatment. The diagnosis of clinical cirrhosis was made based on radiographic, histologic findings, or endoscopic finding of esophageal/gastric varices. Radiographic findings included presence of nodular liver, splenomegaly (>12.5 cm), and/or ascites. Histologic findings included presence of stage 3–4 fibrosis, using a modified Knodell system.<sup>[17,18]</sup> Baseline and follow-up lab data included HCV genotype (polymerase chain reaction [PCR]/sequencing method; Abbott Molecular Inc.), international normalized ratio, levels of creatinine, complete blood count (white blood cells, hemoglobin, and platelets). The sensitivity of HCV-RNA test was 12 IU/ml (RealTime

HCV; Abbott Molecular Inc.). ALT, AST, platelet count (PLTs), and HCV-RNA PCR results were collected at the time points of treatment week 2, end of treatment (EOT), and post-Rx wk 12, 48, and 96. ALT and AST were quantified using the UV/NADH-Rate method with reference range 7–40 IU/L on the Beckman Coulter AU analyzer. Both APRI and FIB-4 scores were calculated at baseline, post-Rx wk 48, and post-Rx wk 96.

## Statistical analysis

Statistical analyses were performed using the Statistical Package for the Social Science software (SPSS, version 25). Categorical variables were reported as number

and percentages or mean with range and compared using Pearson chi-square ( $\chi^2$ ) test. The analysis of variance was used to compare means. Both univariate and multivariate analyses were performed to evaluate the association among different variables of biochemical, virologic, and clinical response during the HCV treatment (Rx) with rates of ALT/AST < 30 IU/L (males) and 19 IU/L (females), APRI, and FIB-4 at post-Rx wk 96 after DAA-mediated SVR. All tests of significance were two-tailed and  $p < 0.05$  was considered statistically significant. Pair sample  $t$  test was performed to compare the differences of APRI < 0.5 and FIB-4 < 1.45 at baseline, post-Rx Wk 48 and 96.

## RESULTS

### Pretreatment demographics, laboratory values, and APRI and FIB-4 scores

The demographic characteristics of the study population are summarized in Table 1. The mean age of the cohort was 60 (20–90) years; 82 (52.2%) were male; 59 (37.6%) were >65 years old, 41 (26.1%) with BMI  $\geq 30$  kg/m<sup>2</sup>. Among the 157 patients, 86 (54.8%), 26 (16.6%), 28 (17.8%), 8 (5.1%), and 9 (5.7%) were Caucasian, Asian, Hispanic, African American, and other races, respectively. Four patients also had human immunodeficiency virus–HCV coinfection. Clinical cirrhosis was diagnosed in 74 (47.1%) patients. In 107 patients with liver biopsy, 43 (40.2%) had histological stage 3–4 fibrosis; 71 patients had calculated MELD scores (mean 9.3, range 6.4–32.5) and 47 (66.2%) had CTP < 6.

Baseline laboratory variables are given in Table 1. Mean serum ALT and AST were 66 (4–496) and 60.2 (10–244) IU/L, respectively; mean MELD score was 9.3 (6.4–32.5). Mean APRI score was 1.39 (0.14–18.5). Mean FIB-4 score was 3.84 (0.52–27.1). Forty of 152 (26.3%) patients had platelets  $\leq 120 \times 10^9$ /L. As indicated in Table 2, at baseline, 38.8% of patients had ALT < 40; 11.5% had ALT < 30 (males)/19 (females);

**TABLE 1** Baseline characteristics in 157 study subjects

| Characteristics                     | n (% or range)    |
|-------------------------------------|-------------------|
| Mean age (years)                    | 60 (20–90)        |
| Age > 65 years old                  | 59 (37.6)         |
| Male-to-female ratio                | 82:75 (52.2:47.8) |
| Ethnicity                           |                   |
| Caucasian                           | 86 (54.8)         |
| Asian                               | 26 (16.6)         |
| Hispanic                            | 28 (17.8)         |
| African American                    | 8 (5.1)           |
| Other                               | 9 (5.7)           |
| BMI $\geq 30$ kg/m <sup>2</sup>     | 41 (26.1)         |
| Clinical cirrhosis                  | 74 (47.1)         |
| Stage 3–4 fibrosis                  | 43/107 (40.2)     |
| Mean MELD score                     | 9.3 (6.4–32.5)    |
| Mean baseline ALT (IU/L)            | 66 (4–496)        |
| Mean baseline AST (IU/L)            | 60.2 (10–244)     |
| Mean baseline APRI                  | 1.39 (0.14–18.5)  |
| Mean baseline FIB-4                 | 3.84 (0.52–27.1)  |
| Platelets $\leq 120 \times 10^9$ /L | 40/152 (26.3)     |

Abbreviations: BMI, body mass index; MELD, Model for End-Stage Liver Disease.

**TABLE 2** Summary of improvement rates (%) of ALT, AST, both ALT and AST to < 40 and < 30 (males)/19 (females) IU/L from baseline to posttreatment week 96

| Time course | ALT changes    |                | AST changes    |               | ALT/AST changes |                 |
|-------------|----------------|----------------|----------------|---------------|-----------------|-----------------|
|             | ALT < 40       | ALT < 30/19    | AST < 40       | AST < 30/19   | ALT/AST < 40    | ALT/AST < 30/19 |
| Baseline    | 61/157 (38.8)  | 18/157 (11.5)  | 67/157 (42.7)  | 14/157 (8.9)  | 23/157 (14.6)   | 10/157 (6.3)    |
| Rx2         | 77/87 (88.5)   | 54/87 (62)     | 75/87 (86.2)   | 36/87 (41.3)  | 47/87 (54)      | 31/87 (35.6)    |
| EOT         | 130/141 (92.2) | 102/141 (72.3) | 130/141 (92.2) | 75/141 (53.2) | 100/141 (70.9)  | 72/141 (51)     |
| PRx12       | 132/136 (97)   | 104/136 (76.5) | 127/136 (93.4) | 75/136 (55.1) | 98/136 (72.1)   | 74/136 (54.4)   |
| PRx48       | 146/153 (95.4) | 121/153 (79)   | 151/153 (98.7) | 95/153 (62.1) | 127/153 (83)    | 93/153 (60)     |
| PRx96       | 113/118 (95.8) | 89/118 (75.4)  | 116/118 (98.3) | 74/118 (62.7) | 89/118 (75.4)   | 71/118 (60.1)   |

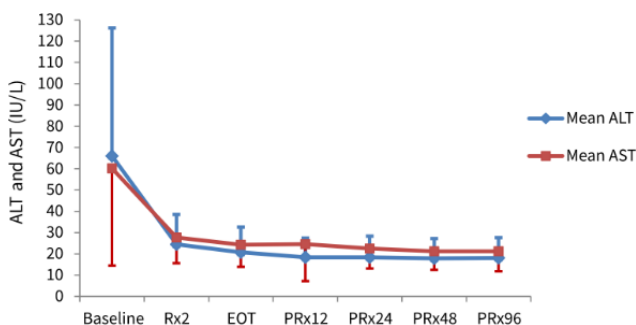
Abbreviation: Rx, treatment week.

42.7% had AST <40; 8.9% had AST <30 (males)/19 (females); 14.6% had both ALT/AST <40; and 6.3% had both ALT/AST <30 (males)/19 (females).

The following 12 different DAA treatment regimens were used in the study: 73 (46.5%) patients treated with ledipasvir-sofosbuvir; 11 (7%) patients treated with ledipasvir-sofosbuvir + ribavirin; 14 (8.9%) patients treated with sofosbuvir + ribavirin; 1 (0.6%) patient treated with ombitasvir-paritaprevir-ritonavir/dasabuvir (3D); 3 (1.9%) patients treated with ombitasvir-paritaprevir-ritonavir/dasabuvir (3D)+ribavirin; 10 (6.3%) patients treated with sofosbuvir and simeprevir; 14 (8.9%) patients treated with elbasvir-grazoprevir; 13 (8.3%) patients treated with sofosbuvir-velpatasvir; 1 (0.6%) patient treated with sofosbuvir-velpatasvir-voxilaprevir; 8 (5.1%) patients treated with glecaprevir-pibrentasvir; 4 (2.5%) patients treated with sofosbuvir and daclatasvir; and 5 (3.2%) patients treated with other regimens. Sixty (38.2%) patients were treatment-experienced. In this study, 131 (83.4%) patients were treated with sofosbuvir-based treatment.

### Frequency and variables associated with ALT/AST < 40 IU/L at post-Rx wk 96

Our previous study demonstrated that DAA-mediated SVR resulted in ALT and AST normalization at post-Rx wk 24.<sup>[5]</sup> Figure 1 shows the dynamics of mean ALT and AST improvement during and after DAA treatment. The mean of ALT and AST (IU/L) improvement was from baseline 66/60.2 to 24.5/27.7, 20.7/24.3, 18.4/24.6, 18.4/22.5, 17.9/21.2, and 18.1/21.2 at treatment week 2, EOT, post-Rx wk 12, 24, 48, and 96, respectively. As indicated in Table 2,



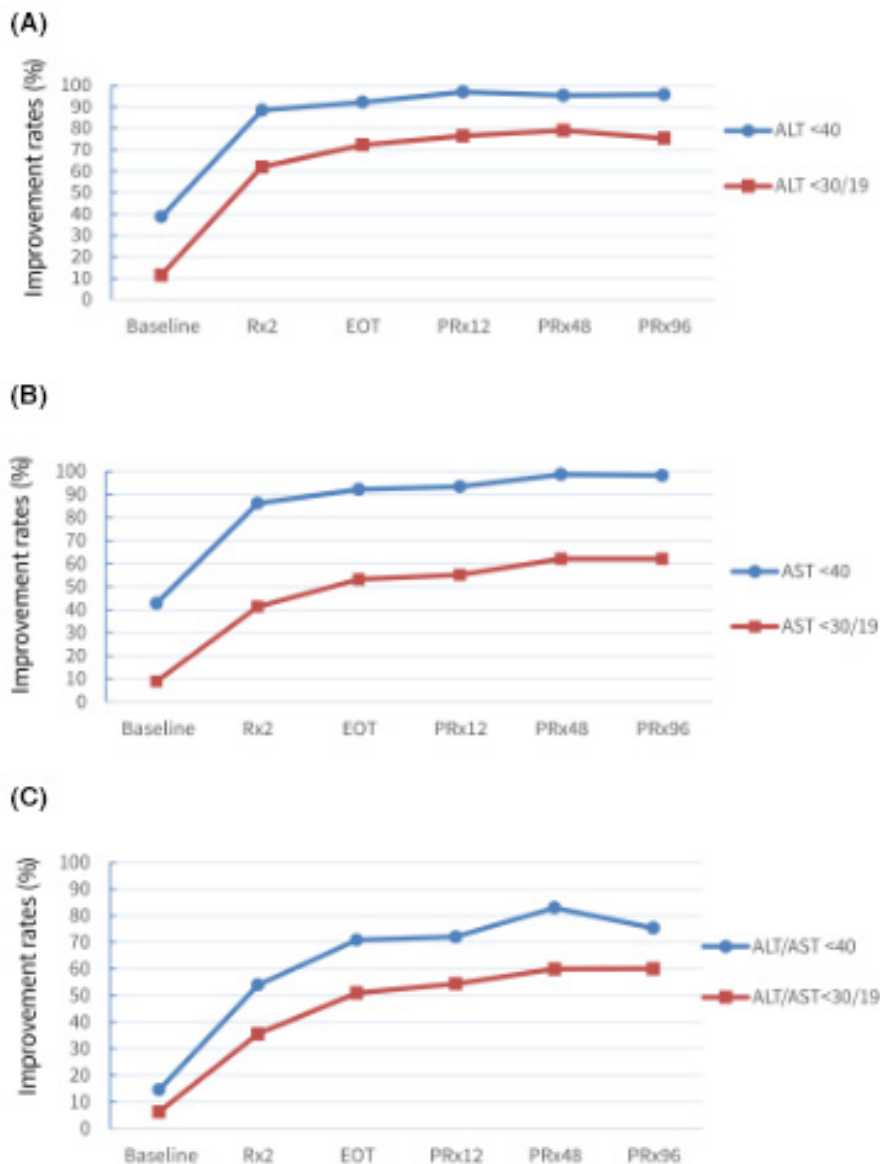
**FIGURE 1** Dynamics of the mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) reduction during and after DAA-mediated sustained virological response (SVR) 12. The dynamic changes of mean ALT and AST (IU/L) including SDs are shown on the y-axis. Time course of direct-acting antiviral (DAA) treatment and posttreatment follow-up are shown on the x-axis. Both mean ALT and AST reduction occurred rapidly as early as DAA treatment week 2 and continued until posttreatment follow-up. ALT and AST remained normal (<40 IU/L) until posttreatment (pRx) week 96

DAA-mediated SVR 12 resulted in not only significant and rapid ALT and AST <40 IU/L as we reported before with 96.1% and 94.8% improvement at post-Rx wk 24,<sup>[5]</sup> but also remaining significantly high rates of ALT and AST <40 IU/L at post-Rx wk 48 and 96 (95.4% and 95.8% for ALT [Figure 2A], and 98.7% and 98.3% for AST [Figure 2B] at post-Rx wk 48 and 96, respectively). The corresponding rates for both ALT/AST <40 IU/L were lower (83.0% and 75.4%; Figure 2C) than ALT or AST <40 IU/L alone, but higher than that (72.1%) at post-Rx wk 12. These indicated that DAA-mediated SVR12 resulted in high and durable rates of ALT and/or AST <40 IU/L.

### Dynamics and frequency of ALT and AST < 30 (males)/19 (females) IU/L and the variables associated with these criteria at post-Rx wk 96

Studies have confirmed the value of modified ALT upper limit of normal criteria from 40 IU/L to 30 IU/L in men and 19 IU/L in women (30/19) in patients infected with HBV.<sup>[19–20]</sup> We then assessed how DAA-mediated SVR12 impacts the rates and durability of ALT and/or AST <30/19 in patients infected with HCV. As indicated in Table 2 and Figure 2, the rates of ALT <30/19 were 11.5%, 62%, 72.3%, 76.5%, 79%, and 75.4% (Figure 2A); the rates of AST <30/19 were 8.9%, 41.3%, 53.2%, 55.1%, 62.1%, and 62.7% (Figure 2B) at baseline, treatment week 2, EOT, and post-Rx wk 12, 48, and 96, respectively. The rates of AST improvement to <30/19 were lower than those with ALT <30/19. The rates of both ALT/AST <30/19 were 6.3%, 35.6%, 51%, 54.4%, 60%, and 60.1% (Figure 2C) at baseline, treatment week 2, EOT, and post-Rx wk 12, 48 and 96, respectively, and lower than that for ALT or AST <30/19. Thus, effective DAA-mediated SVR12 was associated with early, rapid, and durable rates of ALT and/or AST improvement to <30/19, as early as treatment week 2 and until post-Rx wk 96. We also analyzed conversion in AST/ALT ratio during the follow-up and found that in 54 cases with baseline AST >ALT, 14.8% of them (8 of 54) were converted to ALT >AST at post-Rx wk 96.

We then assessed variables associated with both ALT/AST <30/19 at post-Rx wk 96. As summarized in Table 3, univariate analysis showed that both ALT/AST <30/19 at post-Rx wk 96 was significantly associated with CTP <6 ( $p = 0.031$ ), absence of platelets  $\leq 120 \times 10^9/L$  ( $p = 0.035$ ), and both ALT/AST <30/19 at post-Rx wk 12 ( $p = 0.001$ ), but not associated with stage 3–4 fibrosis ( $p = 0.632$ ), clinical cirrhosis ( $p = 0.751$ ), and baseline ALT >40 IU/L ( $p = 0.398$ ). Multivariate analysis showed that both ALT/AST <30/19 at post-Rx Wk 96 was significantly associated with ALT/AST <30/19 at post-Rx wk 12 (95% confidence interval [CI], 1.27–41.87;  $p = 0.026$ ),



**FIGURE 2** Improvement rates of ALT, AST, and both ALT/AST < 40 and < 30 (males)/19 (females) IU/L during and after DAA-mediated SVR12. The improvement rates of ALT (A), AST (B), and both ALT/AST (C) are shown on the y-axis. Time course of DAA treatment and posttreatment follow-up are shown on the x-axis. There were persistent improvement rates of all biochemical markers starting at treatment week 2 and continued to posttreatment week 48 and week 96. Abbreviation: EOT, end of treatment

independent of CTP < 6 (95% CI, 0.25–5.15;  $p = 0.862$ ) and absence of platelets  $\leq 120 \times 10^9/L$  (95% CI, 0.09–2.32;  $p = 0.343$ ).

Compared to 116 cases with both ALT/AST < 30/19 at post-Rx wk 96, PLTs  $< 120 \times 10^9/L$  (as given in Table 3) and male gender in 49 of 58 (84.5%,  $p = 0.001$ ), but not presence of hepatic steatosis in 37 of 59 (62.7%,  $p = 0.738$ ) nor BMI  $> 30 \text{ kg/m}^2$  in 16 of 27 (59.3%,  $p = 0.806$ ) were significantly associated with both ALT/AST  $> 30/19$  at post-Rx wk 96.

We then assessed how DAA-induced SVR affects PLTs. In 50 cases with baseline PLTs  $< 150 \times 10^9/L$ , 30% (15 of 50) of them had PLTs improve to  $> 150 \times 10^9/L$  at post-Rx wk 96.

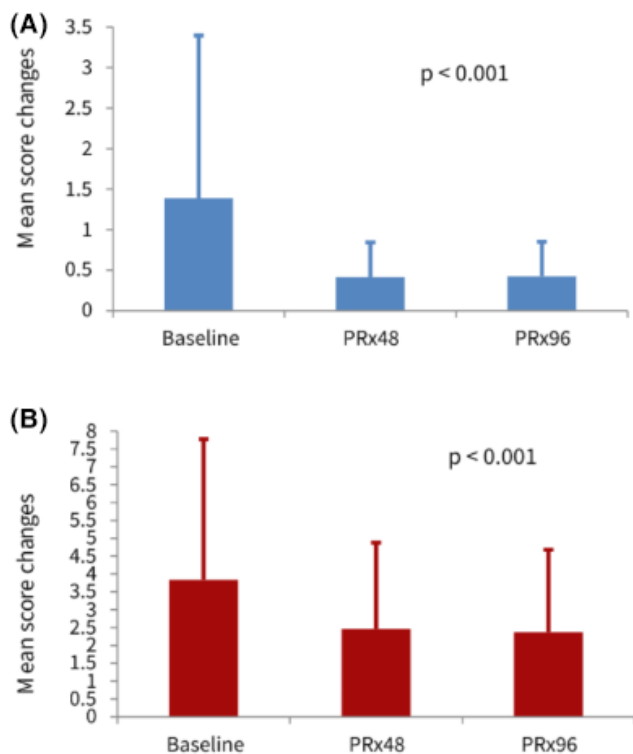
### Frequency of APRI score < 0.5 at post-Rx wk 48 and 96 and the associated variables

Having demonstrated a successful DAA-mediated SVR12 results in rapid, significant, and durable ALT and/or AST improvement, we then assessed whether these would translate to improvement of hepatic fibrosis. APRI score has been well correlated to fibrosis stage in patients with CHC.<sup>[9]</sup> As shown in Figure 3A, the mean APRI score was improved from 1.39 at baseline to 0.41 and 0.42 at post-Rx wk 48 and 96 ( $p < 0.001$ ), respectively. As shown in Figure 4A, the rates of APRI score < 0.5 was improved from 30.9% at pretreatment baseline to 77.8%, and 80.5% at post-Rx wk 48 and

**TABLE 3** Univariate and multivariate analysis of baseline variables and association with post-Rx week 96 ALT/AST <30 IU/L (males)/19 IU/L (females)

| Variables                                   | Univariate analysis |              |          | Multivariate analysis |          |
|---|---------------------|--------------|----------|-----------------------|----------|
|   | Yes                 | No           | <i>p</i> | 95% CI                | <i>p</i> |
| Age >65 years old                           | 25/71 (35.2)        | 22/47 (46.8) | 0.294    |                       |          |
| CTP <6                                      | 23/31 (74.2)        | 14/23 (60.1) | 0.031    | 0.25–5.15             | 0.862    |
| Baseline platelets $\leq 120 \times 10^9/L$ | 31/88 (35.2)        | 22/40 (55)   | 0.035    | 0.09–2.32             | 0.343    |
| Stage 3–4 fibrosis                          | 22/52 (42.3)        | 13/30 (43.3) | 0.632    |                       |          |
| Clinical cirrhosis                          | 35/71 (49.3)        | 23/47 (48.9) | 0.751    |                       |          |
| Baseline ALT >40 (IU/L)                     | 44/79 (55.7)        | 31/49 (63.6) | 0.398    |                       |          |
| ALT/AST <30/19 at PRx week 12               | 40/45 (88.9)        | 19/59 (32.2) | 0.001    | 1.27–41.87            | 0.026    |

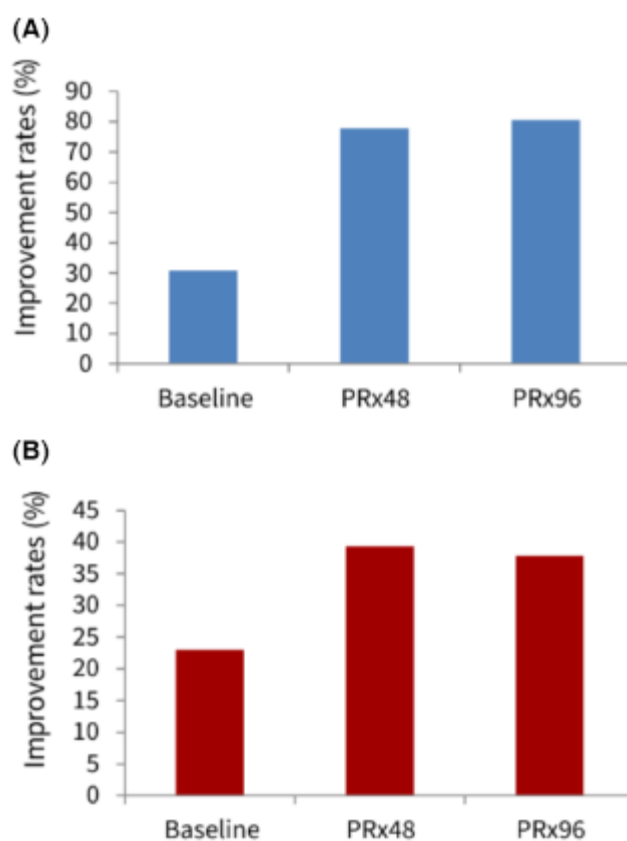
Abbreviations: CI, confidence interval; CTP, Child-Turcotte-Pugh.



**FIGURE 3** Mean score changes of AST-to-platelet ratio index (APRI) and Fibrosis-4 index (FIB-4) at baseline and posttreatment week 48 and 96. The mean score changes of APRI (A) and FIB-4 (B) with SDs are shown on the y-axis. The mean scores of both APRI and FIB-4 were significantly declined at posttreatment week 48 and 96 ( $p < 0.001$ ), compared with the respective baseline scores

96, equal to 46.9% and 49.6% of the net improvement, respectively.

As summarized in Table 4, univariate analyses indicated APRI <0.5 at post-Rx wk 96 was associated with the absence of stage 3–4 fibrosis ( $p = 0.026$ ), clinical cirrhosis ( $p = 0.0001$ ), and occurrence of both ALT/AST <30/19 at post-Rx wk 12 ( $p = 0.0001$ ). Multivariate analysis showed that APRI <0.5 at post-Rx wk 96 was significantly associated with absence of clinical cirrhosis (95% CI, 0.01–0.99;  $p = 0.049$ ) and both ALT/AST <30/19 at post-Rx wk 12 (95% CI, 1.60–45.98;  $p = 0.012$ ), independent of absence of stage 3–4 fibrosis (95% CI, 0.09–3.66;  $p = 0.549$ ).



**FIGURE 4** Changes in rates of APRI <0.5 and FIB-4 <1.45 at baseline and posttreatment week 48 and 96. The rates (%) of APRI <0.5 (A) and FIB-4 <1.45 (B) are shown on the y-axis. There was a significant increase in improvement rate of APRI score <0.5 and FIB-4 score <1.45 at posttreatment week 48 and 96 ( $p < 0.001$ ), compared with the respective baseline rates

### Frequency of FIB-4 < 1.45 during and at post-Rx wk 96 and the associated variables

Likewise, as shown in Figure 3B, the mean value of FIB-4 score was improved from 3.84 at baseline to 2.46 and 2.37 at post-Rx wk 48 and 96 ( $p < 0.001$ ), respectively. As shown in Figure 4B, the rates of FIB-4 score improvement to <1.45 was from 23% at baseline

**TABLE 4** Univariate and multivariate analysis of variables and association with post-Rx week 96 APRI < 0.5

| Variables             | Univariate analysis |              |          | Multivariate analysis |          |
|-----------------------|---------------------|--------------|----------|-----------------------|----------|
|                       | Yes                 | No           | <i>p</i> | 95% CI                | <i>p</i> |
| Stage 3–4 fibrosis    | 28/72 (38.9)        | 7/9 (77.8)   | 0.026    | 0.09–3.66             | 0.549    |
| Clinical cirrhosis    | 38/94 (40.4)        | 21/22 (95.5) | 0.0001   | 0.01–0.99             | 0.049    |
| ALT/AST PRx12 < 30/19 | 49/80 (61.3)        | 3/21 (14.3)  | 0.0001   | 1.60–45.98            | 0.012    |

**TABLE 5** Univariate and multivariate analysis of variables and association with posttreatment week 96 FIB-4 < 1.45

| Variables             | Univariate analysis |              |          | Multivariate analysis |          |
|-----------------------|---------------------|--------------|----------|-----------------------|----------|
|                       | Yes                 | No           | <i>p</i> | 95% CI                | <i>p</i> |
| Stage 3–4 fibrosis    | 10/34 (29.4)        | 25/47 (53.2) | 0.033    | 0.24–2.81             | 0.744    |
| Clinical cirrhosis    | 14/43 (32.6)        | 45/73 (61.6) | 0.002    | 0.09–1.14             | 0.080    |
| ALT/AST PRx12 < 30/19 | 27/36 (75)          | 25/65 (38.5) | 0.0001   | 1.56–28.99            | 0.011    |

to 39.3% and 37.8% at post-Rx wk 48 and 96, equal to 16.3% and 14.8% of the net improvement, respectively.

As summarized in [Table 5](#), univariate analyses indicated FIB-4 < 1.45 at post-Rx wk 96 was associated with the absence of stage 3–4 fibrosis ( $p = 0.033$ ), clinical cirrhosis ( $p = 0.002$ ), and occurrence of both ALT/AST < 30/19 at post-Rx wk 12 ( $p = 0.0001$ ). Multivariate analysis showed that FIB-4 < 1.45 at post-Rx wk 96 was significantly associated with both ALT/AST < 30/19 at post-Rx wk 12 (95% CI, 1.56–28.99;  $p = 0.011$ ), independent of absence of stage 3–4 fibrosis (95% CI, 0.24–2.81;  $p = 0.744$ ) and clinical cirrhosis (95% CI, 0.09–1.14;  $p = 0.080$ ).

During posttreatment follow-up, 2 cases developed hepatic decompensation by ascites and hepatic encephalopathy (HE), and both cases were under control. Two other cases had newly diagnosed HCC at post-Rx wk 24. One case received transarterial chemoembolization treatment; another case was treated with ablation, then sorafenib; and both cases were stable at post-Rx wk 96.

## DISCUSSION

Our previous and several other studies demonstrated that HCV clearance mediated by DAA-induced SVR12 resulted in rapid resolution of hepatocytic injury indicated by both ALT and AST normalization at treatment week 2 and at post-Rx wk 24,<sup>[5,21,22]</sup> which may have resulted from the rapid decrease of ongoing inflammation that is paralleled with the removal of HCV.<sup>[23,24]</sup> In the present study, we redemonstrated that together with ALT improvement, there was also a rapid AST improvement as early as in treatment week 2, and thereafter. Furthermore, we demonstrated that ALT and AST normalization (<40 IU/L) are durable, and lasted to post-Rx wk 96 in most patients. Indeed, further increased rate of AST normalization also occurred at post-Rx wk

96, and 75.4% had both ALT/AST < 40 IU/L, which was a 60.8% increase from baseline. These data indicate that in addition to ALT, AST could also be a reliable surrogate of DAA treatment response.

Studies have shown that the normal range for serum ALT level has fallen between 30 and 40 IU/L,<sup>[19,25–28]</sup> and modified ALT criteria lower than 30 IU/L in males and 19 IU/L in females, has been used for managing patients with HBV.<sup>[8]</sup> In the present study, we found that the improvement of ALT to <30/19 occurred rapidly at DAA treatment week 2, which was further increased from the EOT to post-Rx wk 96 as high as 75.4%. Additionally, the improvement of AST to <30/19 IU/L also occurred rapidly at the treatment week 2, which was further increased from the EOT to post-Rx wk 96 as high as 62.7%. Indeed, both ALT/AST < 30/19 occurred in 35.6% and 60.1% at the treatment week 2 and post-Rx wk 96, respectively. Our data demonstrated that ALT and AST normalization by DAA-induced SVR12 is not only very durable, but also could be commonly as low as both ALT/AST < 30/19, consistent with the modified upper limit of normal level recommended for patients with HBV. Based on our data, it is reasonable to advocate extending the modified ALT and even AST cutoff value to <30/19 for patients with HCV. Likewise, our findings also support that further studies are needed to assess the cutoff value of ALT and AST to <30/19 for other types of chronic liver diseases or liver injury.

Both univariate and multivariate analysis indicated that the patients with both ALT/AST < 30/19 after DAA-mediated SVR12 have a significantly higher chance to achieve ALT/AST < 30/19 at post-Rx wk 96. On the other hand, PLTs < 120 × 10<sup>9</sup>/L and male gender, but not presence of hepatic steatosis nor BMI > 30 kg/m<sup>2</sup>, were significantly associated with both ALT/AST > 30/19 at post-Rx wk 96. As our sample size was small, further studies are needed to address this important issue.



This study has shown that AST>ALT has been associated with advanced hepatic fibrosis.<sup>[29]</sup> We found that in 54 cases with baseline AST>ALT, 14.8% of them were converted to ALT>AST at post-Rx wk 96, indicating that DAA-induced SVR may result in improvement of AST/ALT ratio in some of these patients. Due to small sample size and uncertain clinical value of this change when both ALT and AST have returned to normal range, further studies are needed to assess the clinical value of conversion in AST/ALT ratio.

Thrombocytopenia is associated with portal hypertension and cirrhosis.<sup>[30]</sup> We found in 50 cases with baseline PLTs < 150 × 10<sup>9</sup>/L, 30% of them had PLTs improved to >150 × 10<sup>9</sup>/L at post-Rx wk 96, indicating that DAA-induced SVR can result in PLT improvement in some patients with baseline low PLTs.

Noninvasive models, such as APRI and FIB-4, are used widely to stage hepatic fibrosis in place of liver biopsy because they are easy to use, cost-effective, and absent of biopsy-related risks.<sup>[9,10]</sup> Recent studies showed that there was a significant reduction in APRI from baseline to 2 weeks after DAA and to post-Rx wk 12.<sup>[15,31,32]</sup> Our study demonstrated that the mean APRI was significantly reduced from 1.39 to 0.42 ( $p < 0.001$ ) and the improvement rate of APRI to <0.5 was increased from 30.9% at baseline to 80.5% post-Rx wk 96, equal to 70% reduction in mean APRI and doubled improvement rate of APRI <0.5. Along with APRI, Lee and Ghoneim's study has shown that the FIB-4 was reduced from baseline to post-Rx wk 12 and to 1 year following SVR.<sup>[15,16]</sup> In our study, we found that the mean FIB-4 was significantly reduced from 3.84 to 2.37 ( $p < 0.001$ ), and the improvement rate of FIB-4 < 1.45 was increased from 23% at baseline to 37.8% post-Rx wk 96, equal to 35% reduction in mean FIB-4 and 1.6-times improvement rate of FIB-4 < 1.45. Our study not only reconfirmed the improvement of both APRI and FIB-4, but also demonstrated that these improvements are durable, lasting to post-Rx wk 96.

Both univariate and multivariate analysis indicated the importance of both ALT/AST at post-Rx wk 12 to <30/19, and perhaps the absence of clinical cirrhosis, in achieving fibrosis regression assessed by APRI and FIB-4 scores after DAA-mediated SVR12. These data further support the advocacy to extend the modified ALT and even AST cutoff value to <30/19 for patients with HCV, and possible value of APRI and FIB-4 scores in post-DAA treatment follow-up.

During posttreatment follow-up, 2 cases developed hepatic decompensation by ascites and HE, and two other cases had newly diagnosed HCC. Our data support the current American Association for the Study of Liver Diseases guidance that all patients with HCV cirrhosis should be followed regularly and continue HCC screening after achieving DAA-induced SVR.<sup>[33]</sup>

## CONCLUSIONS

This study assessed the long-term benefits of DAA-mediated SVR12, including ALT/AST dynamic changes, the rates of ALT/AST normalization, or <30/19 IU/L, improvement of APRI and FIB-4 scores at post-Rx wk 48 and 96, and the related factors. We demonstrated high and durable rates of ALT/AST <30/19 IU/L as early as treatment week 2 and lasted to post-Rx wk 96, and ALT/AST <30/19 IU/L at post-Rx wk 12 is independently associated with APRI and FIB-4 improvement. Our data support the clinical value and application of ALT/AST <30/19 IU/L in managing patients with HCV, as it has been used for patients with HBV. In addition, APRI and FIB-4 models can be used to assess the long-term benefits of DAA-mediated SVR12. The limitations of our study included a single-center retrospective study with a small sample size, and inability to assess whether and how DAA-induced SVR impacts hepatic fibrosis by elastography test. Thus, further studies will be needed to confirm these findings.

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None.

## CONFLICT OF INTEREST

Dr. Hu is on the Speaker Bureau for Gilead.

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