INTRODUCTION

Hepatitis C virus (HCV) infection causes chronic hepatitis C (CHC) with an estimated 2.4 million infected individuals in the United States,\textsuperscript{[1]} and 70 million infected individuals worldwide.\textsuperscript{[2]} When left untreated, CHC may progress to cirrhosis and hepatocellular carcinoma (HCC).\textsuperscript{[3]} Several treatments have been...
developed for HCV infection, with direct-acting antivirals (DAAs) showing extremely high sustained virologic response (SVR), resulting in HCV elimination. 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.

Both alanine aminotransferase (ALT) and aspartate aminotransferase (AST) have been biochemical surrogates for liver injury, including HCV-mediated hepatocytic injury. 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. Our previous and other studies have demonstrated an extremely high rate of rapid ALT normalization during DAA treatment and SVR12, 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), 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. APRI is calculated using the following formula: APRI = (AST [IU/L]/upper limit of normal [IU/L]) × 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 81.1%–77.0% sensitivity and 72%–72.3% specificity in diagnosing fibrosis, and 76%–84% sensitivity and 72%–83% specificity in diagnosing cirrhosis. FIB-4 index can be calculated using the following formula: age × AST (IU/L)/platelets (10^9/L) × 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. 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. Recent studies indicated that there is a significant drop in mean APRI and FIB-4 score from baseline after achieving SVR12. 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. Baseline and follow-up lab data included HCV genotype (polymerase chain reaction/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 ≥30 kg/m$^2$. 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 confection. 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 ≤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).

| 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 ≥30 kg/m$^2$ | 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 ≤120 $\times$ 10$^9$/L | 40/152 (26.3) |

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

| 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 experienced. In this study, 131 (83.4%) patients were treated with ledipasvir-sofosbuvir-based treatment.

**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,[5] 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.

**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.[5] 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, 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,[5] 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 30 IU/L in women (30/19) in patients infected with HBV.[19–20] 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.

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 ≤ 120 × 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),
independent of CTP < 6 (95% CI, 0.25–5.15; \(p = 0.862\)) and absence of platelets ≤ 120 × 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 × 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 kg/m² 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 × 10^9/L, 30% (15 of 50) of them had PLTs improve to >150 × 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.\(^{[9]}\) 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
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 \((p = 0.0001)\), 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 \((95\% \text{ CI}, 0.01–0.99; \ p = 0.049)\) and both ALT/AST < 30/19 at post-Rx wk 12 \((95\% \text{ CI}, 1.60–45.98; \ p = 0.012)\), independent of absence of stage 3–4 fibrosis \((95\% \text{ CI}, 0.09–3.66; \ p = 0.549)\).

**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                    | \(p\)       | 95% CI      | \(p\)      |
| 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 ≤ 120 × 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      |

**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.

**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
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, which may have resulted from the rapid decrease of ongoing inflammation that is paralleled with the removal of HCV. 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 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. 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 x 10^9/L and male gender, but not presence of hepatic steatosis nor BMI > 30 kg/m², 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. 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. We found in 50 cases with AST > ALT, 14.8% of them had ALT < AST at post-Rx wk 96, indicating that DAA-induced SVR can result in ALT improvement in some patients with baseline low ALT.

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. Recent studies showed that there was a significant reduction in APRI from baseline to 2 weeks after DAA and to post-Rx wk 12. 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. 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.

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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CONFLICT OF INTEREST
Dr. Hu is on the Speaker Bureau for Gilead.

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REFERENCES
1. CDC Viral Hepatitis. Hepatitis C questions and answers for health professionals. 2018. [cited 2020 July 7]. Available from: https://www.cdc.gov/hepatitis/hcv/hcvfaq.htm#section1
2. Zappulo E, Scotto R, Buonomo A, Maraolo AE, Pinchera B, Gentile I. Efficacy and safety of a fixed dose combination tablet of asunaprevir + beclabuvir + daclatasvir for the treatment for Hepatitis C. Expert Opin Pharmacol. 2020;21:261–73.
3. Health and Human Services. Hepatitis C. 2019 Mar 29. [cited 2020 July 7]. Available from: https://www.hhs.gov/opa/productive-health/fact-sheets/sexually-transmitted-diseases/hepatitis-c
4. Jakobsen JC, Nielsen EE, Feinberg J, Katakam KK, Fobian K, Hauser G, et al. Direct-acting antivirals for chronic hepatitis C. Cochrane Database Syst Rev. 2017;9:CD012143.
5. Huynh T, Zhang J, Hu KQ. Hepatitis C virus clearance by direct acting antiviral results in rapid resolution of hepatocytic injury as indicated by both alanine aminotransferase and aspartate aminotransferase normalization. J Clin Transl Hepatol. 2018;6:258–63.
6. Ribeiro RM, Layden-Almer J, Powers KA, Layden TJ, Perelson AS. Dynamics of alanine aminotransferase during hepatitis C treatment. Hepatology. 2003;38:509–17.
7. Botros M, Sikaris KA. The deritis ratio: the test of time. Clin Biochem Rev. 2013;34:117–30.
8. Shim JJ, Kim JW, Oh CH, Lee YR, Lee JS, Park SY, et al. Serum alanine aminotransferase level and liver-related mortality in patients with chronic hepatitis B: a large national cohort study. Liver Int. 2018;38:1751–9.
9. Wai CT, Greenon JK, Fontana RJ, Kalbfleisch JD, Marrero JA, Conjeevaram HS, et al. A simple non-invasive index can predict both significant fibrosis and cirrhosis in patients with chronic hepatitis C. Hepatology. 2003;38:518–26.

10. Bedossa P, Dargere D, Paradis V. Sampling variability of liver fibrosis in chronic hepatitis C. Hepatology. 2003;38:1449–57.

11. Serafy MA, Kassem AM, Omar H, Mahfouz MS, Raziky ME. APRI test and hyaluronic acid as non-invasive diagnostic tools for post HCV liver fibrosis: systematic review and meta-analysis. Arab J Gastroenterol. 2017;18:51–7.

12. Lin ZH, Xin YN, Dong QJ, Wang Q, Jiang XJ, Zhan SH, et al. Performance of the aspartate aminotransferase-to-platelet ratio index for the staging of hepatitis C-related fibrosis: an updated meta-analysis. Hepatology. 2011;53:726–36.

13. Saviano A, Tripoli S, Baumert TF. FIB-4 score and hepatocellular carcinoma risk after hepatitis C virus cure time to revise surveillance? Hepatobiliary Surg Nutr. 2020;9:661–4.

14. Vallet-Pichard A, Mallet V, Nalpas B, Verkarre V, Nalpas A, Dhalluin-Venier V, et al. FIB-4: an expensive and accurate marker of fibrosis in HCV infection. Comparison with liver biopsy and fibrotest. Hepatology. 2007;46:32–6.

15. Lee SH, Shin HP, Lee JI. Real-world single center experience with direct acting antivirals for improvement of the liver fibrosis after chronic hepatitis C treatment. Antiviral Chem Chemother. 2020;28:1–8.

16. Ghoneim S, Butt MU, Trujillo S, Asaad I. FIB-4 regression with direct-acting antiviral therapy in patients with hepatitis C infection: a safety-net hospital experience. Front Med. 2020;7:359.

17. Knodell RG, Ishak KG, Black WC, Chen TS, Craig R, Kaplowitz N, et al. Formulation and application of a numerical scoring system for assessing histological activity in asymptomatic chronic active hepatitis. Hepatology. 1981;1:431–5.

18. Desmet VJ, Gerber M, Hoofnagle JH, Manns M, Scheuer PJ. Classification of chronic hepatitis: diagnosis, grading and staging. Hepatology. 1994;19:1513–20.

19. Prati D, Taioli E, Zanella A, Torre ED, Butelli S, Vecchio ED, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med. 2002;137:1–10.

20. Kim BK, Kim SA, Park YN, Cheong JY, Kim HS, Park JY, et al. Noninvasive models to predict liver cirrhosis in patients with chronic hepatitis B. Liver Int. 2007;27:969–76.

21. Turbide C, Soullellis C, Deschenes M, Hilzenrat N. Does a rapid decline in the hematological and biochemical parameters induced by interferon and ribavirin combination therapy for the hepatitis C virus predict a sustained viral response? Can J Gastroenterol. 2008;22:149–52.

22. Ribeiro RM, Layden-Almer J, Powers KA, Layden TJ, Perelson AS. Dynamics of alanine aminotransferase during hepatitis C virus treatment. Hepatology. 2003;38:509–17.

23. Dogan UB, Akin MS, Yalaki S. Alanine aminotransferase normalization at week 8 predicts viral response during hepatitis C treatment. World J Gastroenterol. 2013;19:8678–86.

24. Huynh T, Hu KQ. Excellent safety and sustained virologic response to direct-acting antivirals treatment in HCV-infected geriatric patients: a real-world data. Dig Dis Sci. 2021;66:1327–34.

25. Pratt DS, Kaplan MM. Evaluation of abnormal liver enzyme results in asymptomatic patients. N Engl J Med. 2000;342:1266–71.

26. Prati D, Capelli C, Zanella A, Mozzì F, Bosoni P, Pappalettere M, et al. Influence of different hepatitis C virus genotypes on the course of asymptomatic hepatitis C virus infection. Gastroenterology. 1996;110:176–83.

27. Angulo P, Keach JC, Batts KP, Lindor KD. Independent predictors of liver fibrosis in patients with nonalcoholic steatohepatitis. Hepatology. 1999;30:1356–62.

28. Yagura M, Tanaka A, Kamitsukasa H, Otsuka H, Kanno S, Aoyama T. Re-evaluation of the serum alanine aminotransferase upper normal limit in chronic hepatitis C patients. Intern Med. 2010;49:525–8.

29. Williams AL, Hoofnagle JH. Ratio of serum aspartate to alanine aminotransferase in chronic hepatitis. Relationship to cirrhosis. Gastroenterology. 1988;95:734–9.

30. Afshal A, McHutchison J, Brown R, Jacobson I, Manns M, Poodad F, et al. Thrombocytopenia associated with chronic liver disease. J Hepatol. 2008;48:1000–7.

31. Paunovic K, Stojanovic M, Dimitrijevic Z, Paunovic G, Djordjevic U, Konstantinovic L, et al. Indirect serum fibrosis markers in hepatitis C virus (HCV) infection. Med Arh. 2012;66:222–5.

32. Hsu WF, Lai HC, Su WP, Lin CH, Chuang PH, Chen SH, et al. Rapid decline of noninvasive fibrosis index values in patients with hepatitis C receiving treatment with direct-acting antiviral agents. BMC Gastroenterol. 2019;19:63.

33. American Association for the Study of Liver Disease–Infectious Disease Society of America (AASLD-IDSA). HCV guidance: recommendations for testing, managing, and treating hepatitis C. [cited 2022 April 24]. Available from: https://www.hcvguidelines.org/