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ORIGINAL RESEARCH

# Effectiveness and Safety of Sofosbuvir-Velpatasvir in Patients with Cirrhosis Associated with Genotype 3 Hepatitis C Infection in Xinjiang, China

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**Purpose:** Patients with cirrhosis from genotype 3 (GT3) hepatitis C virus (HCV) infection are difficult to cure. This study investigated the effectiveness and safety of sofosbuvir-velpatasvir (SOF/VEL) with and without ribavirin (RBV) in patients with GT3 HCV-infection-related cirrhosis from Xinjiang, China.

**Patients and Methods:** This study included 33 patients with GT3 HCV infected cirrhosis, who were treated with either SOF/VEL +RBV for 12 weeks (n = 27) or SOF/VEL alone for 24 weeks (n = 6) between January 2019 and June 2021. The primary endpoint was a sustained virological response at 12 weeks (SVR12), post-treatment. Secondary endpoints included changes from baseline in Child-Pugh-Turcotte scores, clinical results, hepatic-encephalopathy status, ascites, and gastrointestinal bleeding at 12 weeks, post-treatment.

**Results:** Out of the 33 patients, 18 (54.6%) were diagnosed with GT3a, 15 (45.4%) with GT3b, 16 (48.5%) with compensated cirrhosis, and 17 (51.5%) with decompensated cirrhosis. SVR12 was 87.9% (compensated cirrhosis: 93.8%, decompensated cirrhosis: 82.4%). The Child-Pugh-Turcotte scores improved at 12 weeks ($p < 0.05$). Total bilirubin, albumin, and alanine transaminase levels, as well as hepatic-encephalopathy were significantly improved among patients with compensated and decompensated cirrhosis ($p < 0.05$). The blood cell count and serum creatinine levels did not deteriorate.

**Conclusion:** SOF/VEL, with and without RBV, was effective, safe, and well-tolerated as a treatment for GT3 HCV associated cirrhosis.

**Keywords:** hepatitis C, genotype 3, cirrhosis, sofosbuvir-velpatasvir, ribavirin

## Introduction

Chronic hepatitis C virus (HCV) infection is a major global health problem. Approximately 58 million people are infected with HCV worldwide, with about 1.5 million new infections occurring per year, and the mortality rate is approximately 290,000 per year, mostly from cirrhosis and hepatocellular carcinoma.[1] In mainland China, HCV prevalence in the general population was 1.0%.[2] Infected individuals are at risk of progressive liver disease, liver cirrhosis, and hepatocellular carcinoma. Genotype data are widely collected because HCV genotype is important for predicting disease progression. In China, the most prevalent genotypes and subtypes are 1b (52.18%), 2a (28.69%), 3b (7.06%), 6a (6.41%), and 3a (4.62%), accounting for 98.84% of the tested patient samples.[3] In Xinjiang, China, the most prevalent genotypes and subtypes are 1b (53.1%), 2a (24.1%), 3a (14.3%), 3b (7.9%), and 6a (0.6%).[4] Genotype 3 (GT3) HCV is associated with a higher risk of liver fibrosis, cirrhosis, and cancer, compared with other HCV genotypes.[5–7] Although the recent discovery of direct-acting antivirals (DAAs) has revolutionized treatment, that results in most

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patients achieving a sustained virologic response (SVR) greater than 95%.[8,9] Despite these advances, GT3 HCV infected individuals, particularly those with cirrhosis, still exhibit an impaired SVR rate.[10] Therefore, real-world data are crucial for a better understanding of treatment outcomes.

Various international guidelines recommend two pan-genotypic DAA regimens, glecaprevir/pibrentasvir (GLE/PIB) and sofosbuvir/velpatasvir (SOF/VEL), as first-line treatments for GT3 HCV patients. In China, SOF/VEL and sofosbuvir/ledipasvir are DAAs approved by the National Health Insurance Agency for treating these patients,[11–13] and GLE/PIB is not eligible for insurance reimbursements. Hence, SOF/VEL administration is dependent on physician decisions in accordance with drug availability and price. Previous real-world data from Western cohorts reported high SVR (80–100%) among GT3 HCV-infected cirrhotic patients treated with SOF/VEL ± RBV.[14–17] A recent real-world study from Singapore showed that the SVR12 was 99.3% and 88.2% for GT3 HCV-related compensated cirrhosis and decompensated cirrhosis, respectively, when treated with SOF/VEL ± RBV.[18] In China, treatment strategies for GT3a-infected patients can be formulated based on recommendations in international guidelines and current clinical data, but there are insufficient data to make recommendations for GT3b-infected patients, especially patients with GT3b HCV-related cirrhosis as a difficult-to-treat population.[19] More clinical trials needed to evaluate various regimens and then to determine the optimal ones in this group. To address the relative lack of real-world studies that assess the effectiveness and safety of SOF/VEL, with or without RBV, in these patients, particularly from non-Western populations, we investigated this question in a cohort from Xinjiang.

# Materials and Methods

## Patients and Treatment

The study enrolled patients older than 18 years of age with GT3 HCV infected cirrhosis, who received either SOF/VEL alone (Epclusa®, fixed-dose combination 400/100 mg per tablet; Gilead Sciences, Carrigtohill, Ireland) or including ribavirin (1000 mg/day if weight <75 kg, 1200 mg/day if weight ≥75 kg) for 24 and 12 weeks, respectively. Participants were admitted to the People's Hospital of Xinjiang Uygur Autonomous Region between January 2019 and June 2021. Treatment regimens were in accordance with the guidelines from the European Association for the Study of the Liver, 2020, AASLD-IDSA Hepatitis C Guidance, 2020, and Chinese Society of Hepatology and Chinese Society of Infectious Diseases.[11–13] Patients who met one of the following criteria were excluded: <18 years old, diagnosed with chronic hepatitis C without cirrhosis, coinfection with hepatitis A/B/E or human immunodeficiency virus, autoimmune hepatitis, primary biliary cholangitis or primary sclerosing cholangitis, non-alcoholic fatty liver cirrhosis, alcoholic fatty liver cirrhosis, drug-induced cirrhosis, and genetic liver diseases.

The study was approved by the Ethics Committee of the People's Hospital of the Xinjiang Uygur Autonomous Region and performed in accordance with the Declaration of Helsinki. The requirement for written informed consent was waived because of the retrospective design, anonymous data use, and elimination of patient-identifying information.

## Measurements

Detailed medical history was recorded for each patient. All patients underwent a clinical examination, and baseline laboratory values were collected at the beginning of treatment. The following data were recorded at baseline, end of treatment, and during week 12 post-treatment: baseline demographics (age, sex, and nationality), leukocytes, hemoglobin (lower limit of normal [LLN], 130 g/L for men and 115 g/L for women), platelets, serum albumin, total bilirubin (upper limit of normal [ULN], 26 μmol/L for men and 21 μmol/L for women), alanine transaminase (ALT) (ULN, 60 U/L for men and 45 U/L for women), creatinine (ULN, 97 μmol/L for men and 73 μmol/L for women), plasma prothrombin time, and HCV RNA. Serum HCV RNA was quantified using reverse transcription-polymerase chain reaction (RT-PCR) using the Cobas AmpliPrep/COBAS TaqMan HCV Test (Roche Diagnostics, Branchburg, NJ, USA), which has a lower limit of quantitation at 15 IU/mL. The HCV genotype was determined using RT-PCR with genotype-specific primers from the five noncoding regions of the virus. The presence of cirrhosis was confirmed with liver biopsy showing cirrhosis, transient elastography (FibroScan) higher than 12.5kPa or FibroTest higher than 0.75 and an aspartate aminotransaminase to platelet ratio index (APRI) higher than 2 or Fibrosis-4 (FIB-4) higher than 3.25. Hepatic imaging examinations which included ultrasonography, computed tomography or magnetic resonance imaging were also used for diagnosis of cirrhosis. Ascites was confirmed with clinical features or hepatic imaging. Hepatic-encephalopathy (HE)

was diagnosed following Chinese guidelines on HE management in cirrhosis.[20] Esophageal and gastric variceal bleeding (EGVB) was diagnosed using gastroscopy. Child-Pugh-Turcotte (CPT) scores were calculated for all patients.

## Efficacy Assessments

The primary endpoint was SVR12. The secondary endpoint was a change in CPT scores at week 12 post-treatment from baseline, along with undetectable levels of HCV RNA, defined as <15 IU/mL at the end of treatment (SVR0) and post-treatment week 12 (SVR12).

## Safety Assessments

Adverse events associated with SOF/VEL with or without RBV in real-world settings were examined, and adverse hematological reactions including neutropenia, anemia, etc. were recorded. Changes of HE, ascites, and gastrointestinal bleeding before and after treatment were recorded.

## Statistical Analysis

Categorical (nominal or ordinal) data were expressed as percentages, and continuous data as means ± standard deviation (SD). Continuous variables were analyzed using Student's paired or unpaired t-tests. Nominal variables were analyzed using the $\chi^2$ test or McNemar's test. Ordinal variables were analyzed using the Wilcoxon signed-rank test. All statistical tests were two-tailed. Significance was set at $p < 0.05$. Analyses were performed in SPSS Statistics version 23.0 (IBM Corp., Armonk, NY, USA). Graphs were constructed in GraphPad Prism 5.1 (GraphPad Software, Inc., La Jolla, CA, USA).

# Results

## Patient Characteristics

The mean age of the enrolled patients (n = 33) was 45.64 ± 4.75 years, and 72.7% (n = 24) were Male (Table 1). Out of the 33 patients, seven (21.2%) were Han, 16 (48.5%) were Uygur, nine (27.3%) were Hui, and one (3.0%) was Kazakh. Among the enrolled patients (n = 33), 18 (54.6%) had GT3a, 15 (45.4%) had GT3b, 16 (48.5%) had compensated

**Table 1** Baseline Characteristics of GT3 HCV Infected Cirrhosis

| Parameter | GT3 HCV Cirrhosis (n=33) |
|---|---|
| Age (years) M ± SD | 45.64±4.75 |
| Male, n (%) | 24 (72.7%) |
| Race, n (%) | |
| Han | 7 (21.2%) |
| Uygur | 16 (48.5%) |
| Hui | 9 (27.3%) |
| Kazakh | 1 (3.0%) |
| HCV genotype, n (%) | |
| 3a | 18 (54.6%) |
| 3b | 15 (45.4%) |
| Cirrhosis, n (%) | |
| Compensated cirrhosis | 16 (48.5%) |
| Decompensated cirrhosis | 17 (51.5%) |
| Treatment regimen, n (%) | |
| SOF/VEL | 6 (18.2%) |
| SOF/VEL+RBV | 27 (81.8%) |
| Course, n (%) | |
| 12 weeks | 27 (81.8%) |
| 24 weeks | 6 (18.2%) |
| HCV RNA (log10 IU/mL) M ± SD | 5.20±1.36 |

**Abbreviations**: GT, genotype; SOF/VEL, sofosbuvir/velpatasvir; RBV, ribavirin.

cirrhosis, and 17 (51.5%) had decompensated cirrhosis. Six patients (18.2%) received SOF/VEL for 24 weeks and the remaining patients received SOF/VEL+RBV for 12 weeks (Table 1).

## Treatment Effectiveness

### Virologic Response

The SVR0 was 93.9% (31/33) and overall SVR12 was 87.9% (29/33). For compensated and decompensated cirrhosis, SVR12 was 93.8% (15/16) and 82.4% (14/17), respectively. The SVR12 for GT3a and GT3b patients was 94.4% (17/18) and 80.0% (12/15), respectively. Among patients treated with SOF/VEL, SVR12 was 83.3% (5/6); among patients treated with SOF/VEL+RBV, SVR12 was 88.9% (24/27) (Figure 1). Four patients experienced virological failure; one had GT3a and decompensated cirrhosis treated with SOF/VEL, while another had GT3b and decompensated cirrhosis treated with SOF/VEL+RBV, in both these cases, HCV RNA remained detectable at the end of treatment. The remaining two were GT3b patients, one with compensated cirrhosis and the other with decompensated. Both were treated with SOF/VEL+RBV for 12 weeks and achieved SVR0 but relapsed at week 12 post-treatment (Table 2).

## Changes in Liver Function

The proportion of CPT class A patients increased from 51.5% to 75.8%, whereas proportions of class B and C patients decreased from 30.3% to 18.2% and from 18.2% to 6.1%, respectively (Table 3). Among the 17 decompensated cirrhotic patients, six individuals, who were class B at baseline, improved to class A, and four baseline class C individuals improved to class B or A (Table 4). Mean CPT score significantly improved, from 7.12 ± 2.40 points at baseline to 5.85 ± 1.50 points at 12 weeks, post-treatment (Table 5). No patient regressed in their CPT class.

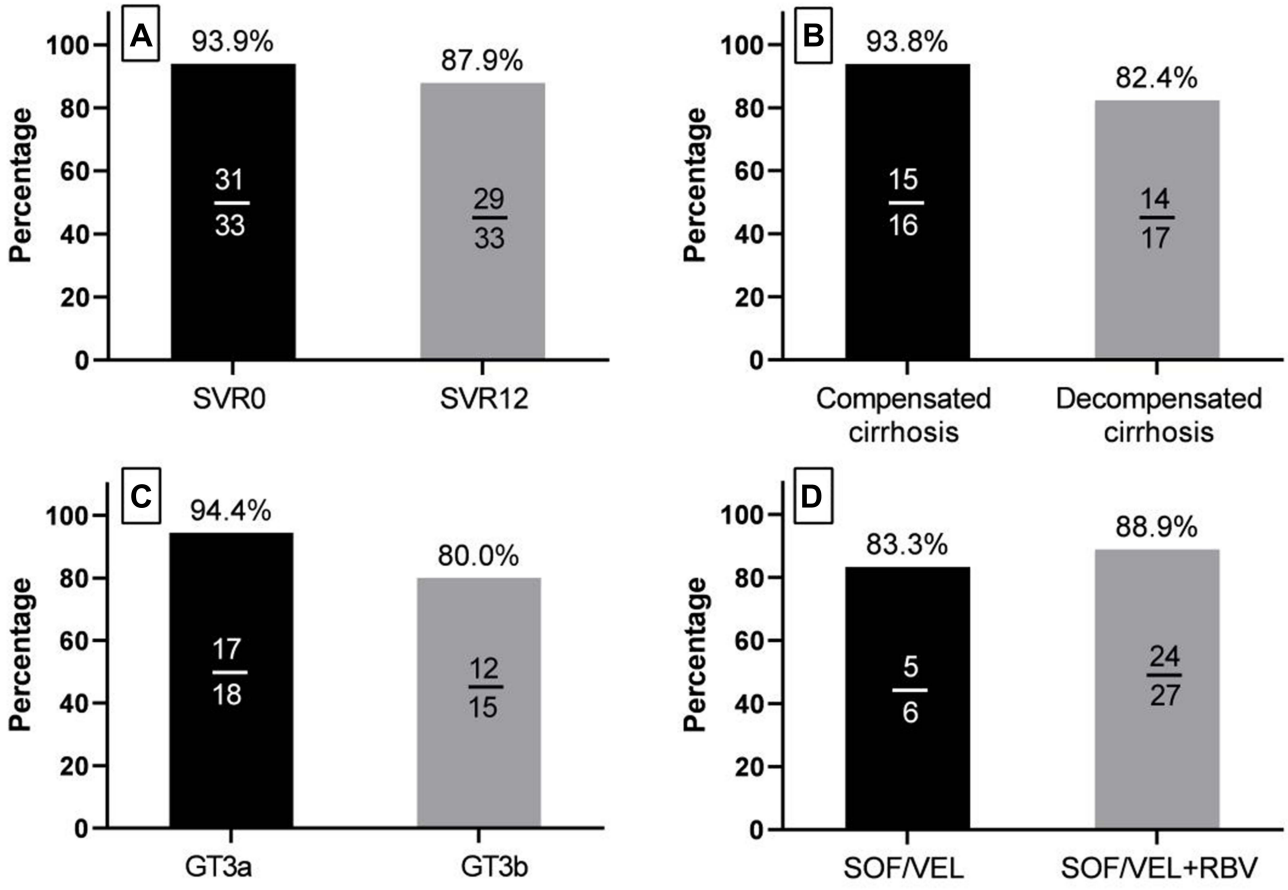


**Figure 1** (**A**) The SVR0 and SVR12 of GT3 HCV cirrhosis treated with SOF/VEL ± RBV. (**B**) The SVR12 of GT3 HCV compensated cirrhosis and decompensated cirrhosis treated with SOF/VEL ± RBV. (**C**) The SVR12 of GT3a HCV cirrhosis and GT3b HCV cirrhosis treated with SOF/VEL ± RBV. (**D**) The SVR12 of GT3 HCV cirrhosis treated with SOF/VEL ± RBV.

**Table 2** Characteristics of 4 Virologic Failure Patients

| Patient | | Male1 | Male2 | Male3 | Male4 |
|---|---|---|---|---|---|
| HCV genotype | | 3b | 3b | 3b | 3a |
| Regimen | | SOF/VEL+RBV | SOF/VEL+RBV | SOF/VEL+RBV | SOF/VEL |
| Course (weeks) | | 12 | 12 | 12 | 24 |
| SVR0 | | NO | YES | YES | NO |
| ALT (U/L) | Before treatment | 87 | 66 | 45 | 53 |
| | After treatment | 45 | 46 | 34 | 39 |
| CPT scores | Before treatment | 8 | 14 | 5 | 8 |
| | After treatment | 7 | 8 | 5 | 7 |

**Abbreviations**: SOF/VEL, sofosbuvir/velpatasvir; RBV, ribavirin; SVR0, sustained virological response at the end of treatment; ALT, alanine transaminase; CPT, Child-Pugh-Turcotte.

**Table 3** Comparison of GT3 HCV Infected Cirrhosis Before and After Treatment

| | | After treatment | | | | *p* |
|---|---|---|---|---|---|---|
| | | CPT A | CPT B | CPT C | n | |
| Before treatment | CPT A | 17 | 0 | 0 | 17 | 0.003 |
| | CPT B | 6 | 4 | 0 | 10 | |
| | CPT C | 2 | 2 | 2 | 6 | |

**Abbreviation**: CPT, Child-Pugh-Turcotte.

**Table 4** Comparison of GT3 HCV Decompensated Cirrhosis Before and After Treatment

| | | After Treatment | | | | *p* |
|---|---|---|---|---|---|---|
| | | CPT A | CPT B | CPT C | n | |
| Before treatment | CPT A | 1 | 0 | 0 | 1 | 0.003 |
| | CPT B | 6 | 4 | 0 | 10 | |
| | CPT C | 2 | 2 | 2 | 6 | |

**Abbreviation**: CPT, Child-Pugh-Turcotte.

**Table 5** Comparison of GT3 HCV Cirrhosis and Decompensated Cirrhosis Before and After Treatment

| Parameter | GT3 HCV Cirrhosis (n=33) | | GT3 HCV Decompensated Cirrhosis (n=17) | |
|---|---|---|---|---|
| | Before Treatment | After Treatment | Before Treatment | After Treatment |
| CPT scores M ± SD | 7.12±2.40 | 5.85±1.50* | 8.76±2.31 | 6.65±1.77** |
| Leukocytes ($\times 10^9$/L) M ± SD | 4.83±1.68 | 4.92±1.65 | 4.58±2.01 | 4.36±1.80 |
| Hemoglobins (g/L) M ± SD | 130.03±32.18 | 154.03±117.77 | 111.53±33.37 | 160.94±165.76 |
| Platelets ($\times 10^9$/L) M ± SD | 96.51±44.78 | 100.67±43.87 | 89.65±47.78 | 89.82±46.93 |
| Total bilirrubin (μmol/L) M ± SD | 34.54±15.91 | 25.60±11.17** | 41.99±17.03 | 30.45±12.88** |
| Albumin (g/L) M ± SD | 34.30±7.01 | 36.17±6.03** | 28.81±5.05 | 32.5±5.62** |
| ALT (U/L) M ± SD | 86.12±72.56 | 31.13±13.33** | 61.47±46.06 | 35.8±16.10* |
| PT (S) M ± SD | 14.85±2.40 | 13.51±1.20** | 16.08±2.57 | 14.76±1.88 |
| Creatinine (μmol/L) M ± SD | 62.79±10.86 | 62.77±10.32 | 62.95±11.84 | 61.44±12.12 |
| Ascites, n (%) | 8(24.2%) | 3(9.1%) | 8(47.1%) | 3(17.6%) |
| HE, n (%) | 8(24.2%) | 1(3.0%)* | 8(47.1%) | 1(5.9%)* |
| EGVB, n (%) | 3(9.09%) | 1(3.0%) | 3(17.7%) | 1(5.9%) |

**Note**: *P < 0.05, **P < 0.01.
**Abbreviations**: CPT, Child-Pugh-Turcotte; ALT, alanine transaminase; PT, plasma prothrombin time; HE, hepatic encephalopathy; EGVB, esophageal and gastric variceal bleeding.

## Safety

Patient groups did not differ significantly in pre- and post-treatment values of leukocytes, hemoglobin, platelets, creatinine, ascites, and EGVB. At 12 weeks post-treatment, total bilirubin, albumin, ALT levels, and HE improved significantly from baseline for cirrhotic patients, including those with decompensated cirrhosis ($P < 0.05$) (Table 5). No deaths, hepatocellular carcinoma, severe adverse events, drug-related adverse events, or drug-related discontinuation were recorded.

# Discussion

In this study, SOF/VEL ± RBV was highly effective, generally safe, and well-tolerated in Chinese patients with GT3 HCV-related cirrhosis. Out of a total of 33 patients, 27 (81.8%) were treated with SOF/VEL+RBV for 12 weeks, and six (18.2%) received SOF/VEL only for 24 weeks because of RBV intolerance. The decision to add RBV or extend treatment duration was at the physician's discretion, with consideration of cirrhotic status. We found that RBV addition resulted in an SVR12 of 88.9%, whereas the lack of RBV led to an SVR12 of 83.3%; therefore, RBV seems to improve the treatment effectiveness of SOF/VEL for GT3 HCV-infected cirrhotic patients. Our findings indicated that SOF/VEL +RBV 12 weeks should be the first choice for these patients, SOF/VEL+RBV 24 weeks are worth exploring further.

The presence of cirrhosis seems to influence the effectiveness of SOF/VEL. Previous study revealed that despite the availability of pan genotypic, strong therapeutic options, GT3 infected patients with cirrhosis still remain difficult to treat.[21] Though GLE/PIB could be a good option in HCV GT3 patients including HCV GT3 with compensated cirrhosis patients,[21,22] it is clearly forbidden to be administered in decompensated cirrhosis patients due to the presence of protease inhibitor, hence, SOF/VEL remains the only option. To achieve a high SVR rate for those relatively difficult to treat population, extending the duration of treatment to 24 weeks or adding ribavirin are worth confirming. Esteban et al reported that a higher rate of patients with GT3 HCV infection and compensated cirrhosis achieved SVR12 with SOF/VEL+RBV 12 weeks than SOF/VEL monotherapy (96% vs 91%) 12 weeks, and RBV addition could ameliorate the negative influence of baseline NS5A RASs.[23] A recent Phase III study, testing SOF/VEL in Chinese patients with GT3, showed that the SVR12 was 90% and 100% for GT3a patients with and without compensated cirrhosis, respectively. The percentages dropped to 50% and 96%, respectively, for GT3b patients with and without compensated cirrhosis.[24] Our SVR12 rates were much higher, at 94.4% and 80.0% for GT3a HCV cirrhosis and GT3b HCV cirrhosis, respectively, suggesting that RBV might be needed to improve SVR among GT3 HCV cirrhotic patients. To date, only two-phase III studies are available regarding the administration of SOV/VEL with or without RBV for patients with decompensated cirrhosis: ASTRAL-4 for CPT B patients and another from Japan. The ASTRAL-4 study found that overall SVR12 was 94% for those treated with 12 weeks of SOF/VEL+RBV, and 86% for those treated with 24 weeks of SOF/VEL; these rates dropped to 85% and 50% among GT3 patients.[25] Our results were similar with an SVR12 of 82.4% for GT3 HCV-decompensated cirrhosis, indicating that SOF/VEL with or without RBV is highly effective in patients with this condition. In the Japanese phase III study, overall SVR12 was 92% for 12 weeks of SOF/VEL with or without RBV.[26] However, the previous study focused on patients with GT1b or GT2 HCV, our study only focused on GT3 HCV patients. A recent real-world study from Singapore[18] showed that 163 HCV GT3 cirrhosis patients (10% decompensated cirrhosis) were treated with SOF/VEL ± RBV, the SVR12 was 88.2% (15/17) for GT3 HCV-decompensated cirrhosis, interestingly, this study comprised a low percentage of GT3b (0.4%). Although the total sample size in our study was relatively small, the number of patients with GT3 HCV-decompensated cirrhosis was 17 (51.5%) in our study, consistently with the prior Singapore study, and the number of HCV GT3b in our study was 15 contributed to 45.4% of all the patients, which were much higher than that of the above study. With the approval of Sofosbuvir/Velpatasvir/Voxilaprevir (SOF/VEL/VOX) in China, SOF/VEL/VOX has become accessible and affordable, providing more options for the treatment of HCV GT3 patients. POLARIS-3 study had also shown that SOF/VEL/VOX 8 weeks treatment could achieve 96% SVR12 in patients with HCV GT3 with compensated cirrhosis,[27] but physicians should note that SOF/VEL/VOX contains protease inhibitor (VOX) and is contraindicated in patients with decompensated disease or a history of prior decompensation. In addition, the approved indication of SOF/VEL/VOX in China is for the patients who have experienced DAA treatment failure.

Interferon-free DAA-based regimens have only recently become available for treating HCV infection. Thus, their clinical benefits in patients with decompensated cirrhosis are still being characterized. In our study overall mean CPT score significantly improved post-treatment, including 4 patients with virological failure; these findings are consistent with previous research.[28] Achieving SVR in patients with decompensated cirrhosis should have long-term benefits, with several studies reporting a decrease in mortality after comparing the survival rates of patients treated with sofosbuvir-based regimens to matched controls from transplant waitlists.[29]

Considering that the safety of the treatment is important due to the advanced nature of liver disease with high morbidity and mortality, we found no significant difference in leukocyte, hemoglobin, platelet, and creatinine levels from baseline to week 12. Furthermore, these patients exhibited a significant improvement in the levels of total bilirubin, albumin, and ALT, along with a significant improvement in HE. The antiviral treatment can restore liver function; therefore, cirrhosis-related complications may also be ameliorated.

Our study has several limitations. First, inherent bias could not be excluded owing to the retrospective nature of the study, which was limited by the sample size. Therefore, these results should be verified by conducting a prospective clinical study with a larger cohort. Second, although we observed early improvements in liver function, the mid- and long-term clinical benefits of achieving SVR12 in patients with cirrhosis remain unclear and need to be further explored.

## Conclusion

In conclusion, GT3 HCV patients with cirrhosis, including decompensated cirrhosis, achieved high SVR12 when subjected to 12 or 24 weeks of SOF/VEL with or without RBV, respectively. These treatment regimens also improved liver function while being safe and well-tolerated.

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## Disclosure

The authors report no conflicts of interest in this work.

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