

Sofosbuvir-based therapies achieved satisfactory virological response in Chinese with genotypes 3 and 6 infection: a real-world experience from a centre

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Research

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Abstract

Background

As previously shown by others, sofosbuvir-based regimens yield high sustained virological response rates in patients with HCV infection except for genotype 3b complicating with cirrhosis. The real-world study aims to explore efficacy and safety of sofosbuvir-based regimens in genotypes 3 and 6 infected patients, especially the impact of ribavirin co-administration on sustained virological response in cirrhotic patients with genotype 3b infection.

Methods

A retrospective cohort study included 173 patients initiated on sofosbuvir-based regimens. Main endpoint of treatment was sustained virological response at post-treatment week 12 (SVR12).

Results

92 patients with sufficient follow-up were included. Overall, SVR12 rate was 96.7% (89/92), including 62 patients treated with addition of ribavirin to sofosbuvir-based regimens, given superior SVR12 rate (98.4%) than ribavirin free regimens (93.3%). SVR12 rates were 96.3% and 96.7% in patients infected with genotype 3 (54) and genotype 6 (38). Among patients with genotype 3b infection, SVR12 was achieved in 97.1%, and 100% when complicating with cirrhosis. SVR12 rate was achieved in 96.6% among patients with cirrhosis (28/29), 100% with ribavirin co-administration regimens and 87.5% without ribavirin. Totally, three patients failed to achieve SVR12, including 2 non-cirrhotic patients with genotype 3b and 6a infection treated with sofosbuvir+ribavirin and sofosbuvir/velpatasvir regimen, one cirrhotic patient with genotype 3k infection treated with SOF/VEL regimen. No severe adverse events occurred.

Conclusions

Real-world data show that sofosbuvir-based regimens are highly effective and safe for patients with HCV genotypes 3 and 6 infection. Addition of ribavirin to sofosbuvir-based regimens may improve efficacy, especially in patients with genotype 3 infection and cirrhosis.

Trial registration

Not applicable.

Background

It was estimated that hepatitis C virus (HCV) genotype 3 was the next most common genotype around the world, only second to genotype 1, accounting for 30.1%, about 54.3 million patients. In East Asia, genotype 1 was still dominant, followed by genotype 6 (16.3%), higher than genotype 3 (10.4%), which was ranked fourth, respectively.¹ In China, genotype 1b and genotype 2a were two main genotypes more prevalent than genotypes 3 and 6. And the prevalence increased in population with genotypes 3 and 6 infection significantly in south China, where the patients were younger than patients infected with other genotypes.²⁻⁴ It's well-known that HCV infection increased the risk of hepatocellular carcinoma (HCC), end-stage liver disease and hepatic related death, especially in patients with serum detectable HCV-RNA.^{5,6} Moreover, patients with genotypes 3 and 6 infection are more closely associated with the occurrence of HCC than other genotypes.⁷⁻⁹

Previous studies have shown that sofosbuvir (SOF) -based treatment yield high sustained virological response (SVR) rates in patients with HCV infection.¹⁰⁻¹⁴ However, it is recognized that population infected with genotype 3, especially sub-type 3b complicated with liver cirrhosis are characterized by a lower SVR rate in the time of direct antiviral agents (DAAs) therapy.¹⁵⁻¹⁷ And there always exists debate about whether the addition of RBV have impact on SVR in HCV infected patients.¹⁸⁻²⁰ Unfortunately, mostly data on efficacy and safety of SOF-based therapy in patients infected with genotypes 3 and 6 were from

Europe but limited in China, especially regimens of SOF/VEL with or without ribavirin (RBV) .^{19,21-23} Therefore, there is an urgent need for more real-world research from China to be conducted.

The purpose of present real-world study was aimed to explore the efficacy and safety of SOF ± RBV, SOF + daclatasvir (DCV) ± RBV and SOF/velpatasvir (VEL) ± RBV regimens in Chinese patients with genotypes 3 and 6 infection, especially whether RBV co-administration have impact on SVR in patients with GT3b infection and cirrhosis.

Methods

study design and participants selection

This is a retrospective cohort study revolving a total of 173 patients initiated on SOF-based regimens in routine practice from the Second Affiliated Hospital of Chongqing Medical University between July 2017 and January 2020. Patients infected with genotypes 3 and 6 were initiated on 6 kind of SOF-based regimens, including SOF, SOF+DCV and SOF/VEL regimens with RBV or not for regular duration according to the guideline, availability of DAAs and the physician. Inclusion criteria for screening participants was 18 years or older with hepatitis C virus infection, regardless of hepatitis B virus (HBV) co-infection, cirrhosis status and treatment experience.

Data collection

The following information were collected at baseline: general demographic feature (gender, age), viral related data (HCV-genotype and level of serum HCV-RNA), clinical laboratory examinations (the level of aspartate aminotransferase (AST), alanine aminotransaminase (ALT), total bilirubin, total bile-acid, albumin, hemoglobin, platelet count and AFP), assessment of cirrhosis status and comorbidity (diabetes, chronic renal diseases, fatty liver) and co-infection with HBV. The serum HCV-RNA was determined by Roche Cobas Ampliprep/ Cobas TaqMan or Kehua. The liver cirrhosis was diagnosed by APRI index over 2 or FIB-4 index over 3.25 or liver stiffness over 14.6 kPa, or ultrasonography imaging and examination indicated.

Outcome

The efficacy of treatment was determined by the sustained virological response at post-treatment week 12 (SVR12) defined as the main endpoint of treatment, the improvement of fibrosis evaluated by FIB-4 ($(\text{Age} \times \text{AST}) / (\text{PLT} \times (\text{square root of ALT}))$), and APRI ($\text{AST}/\text{PLT} \times 100$). The clinical symptoms and adverse events were monitored during the treatment and follow-up for safety and tolerance assessment.

Statistic analysis

The deference of continuous variables between pre-treatment and post-treatment were compared by paired t-test. The Chi-square test was performed in comparison of categorical data. Variables that were associated with liver fibrosis progression with a p-value < 0.1 were included in multivariate logistic regression models. Two sided P values were calculated for all tests. And P value < 0.05 was considered statistically significant. Data were analyzed via SPSS version 24.0 (IBM Corp., Armonk, NY, USA).

Results

Baseline characteristics

A total of 173 patients infected with genotypes 3 (n=93) and 6 (n=80) received SOF-based regimens were enrolled at initiation, whose baseline demographic and clinical characteristics were shown in Table1. 24.9% patients with cirrhosis, 7.7% were treatment experienced. The percentage of patients received the SOF±RBV, SOF+DCV±RBV and SOF/VEL±RBV regimens for regular duration accounting for 22.5%, 13.9% and 63.6%. There was no statistic difference in age, gender, level of ALT, total bilirubin, total bile-acid, albumin, hemoglobin, AFP, serum RNA, HBV co-infection and treatment experience except for higher level of AST, lower level of platelet, higher proportion of cirrhosis and RBV co-administration in patients with genotype 3 infection.

High virologic response [RVR and SVR12]

rapid viral response (RVR) rate was achieved in 84.0% (68/81), similar in genotypes 3 and 6 (79.6% versus 90.6%, $P=0.229$). Fig.1 showed the RVR rate in patients treated with SOF/VEL+RBV regimens was significantly lower than SOF and SOF+DCV+RBV regimens (58.3% versus 100%, 93.3%). A number of 92 patients completed a follow-up more than 12 weeks after the end of treatment (Fig.2). Overall, SVR12 rate was achieved in 96.7% (89/92), 96.3% in genotype 3 (52/54) and 97.4% in genotype 6 (37/38), respectively.

Among patients infected with genotype 3, SVR12 rates were achieved in 88.9%, 100% and 100% among patients treated with SOF+RBV, SOF+DCV+RBV and SOF/VEL+RBV, comparing to 100%, 100% and 83.3% without RBV regimens. The similar results were found in patients infected with genotype 6, where SVR12 rates were achieved in 100%, 100% and 100% among patients treated with SOF+RBV, SOF+DCV+RBV and SOF/VEL+RBV, comparing to 100%, 100% and 88.9% without RBV regimens. The SVR12 rate of SOF/VEL regimen was numerically lower than other regimens, but no significant difference was found (Fig.3).

We further analyzed the impact of factors such as, gender, age, cirrhotic status, viral load, treatment history, HBV co-infection and level of baseline ALT on SVR12 in patients with genotypes 3 and 6 infection. Data on Fig.4 show above-mentioned factors had no impact on SVR12 in both genotypes 3 and 6.

High SVR12 rate in sub-type 3b

Data on Fig.5 showed that patients infected with 3b sub-type achieved a SVR12 rate of 97.1% (34/35), accounting for similar and high SVR12 rates irrespective of gender, age, cirrhosis status, treatment history, viral load, HBV co-infection and level of baseline ALT. Moreover, there was no significant difference in SVR12 rates between 3b and non-3b genotype, which was 96.5% (55/57). Among cirrhotic patients infected with 3b sub-type, the SVR12 rate was 100% (13/13), 85% of these patients were treated with RBV to SOF-based regimens. The detailed clinical process of those patients ($n=12$) were described in Fig.6. One patient treated with SOF/VEL+RBV for 12 weeks was not presented because the time of undetectable HCV-RNA was not sure.

Patients failed to achieve SVR12

Totally, three patients with good compliance failed to achieve SVR12, all of whom are treated naive and with elevated level of AST at baseline, including 2 non-cirrhotic patients with genotypes 3b and 6a infection treated with SOF+RBV regimen for 24 weeks and SOF/VEL regimen for 12 weeks, one cirrhotic patient with genotype 3k infection treated with SOF/VEL regimen for 12 weeks with alcohol intake during the period of medication. Unfortunately, we didn't take further action, such as testing for drug resistance or occult HCV infection, to identify the cause of treatment failure.

Higher SVR12 rate in RBV co-administration regimen

The baseline characteristics in patients treated with RBV or not were presented in Table 2. Patients treated with RBV co-administration to SOF-based regimens achieved the SVR12 rate of 98.4% (61/62), numerically higher than 93.3% (28/30) in RBV free regimen. We compared the SVR12 rates in patients treated with or without RBV in diverse characteristics such as genotype, viral load, cirrhosis status HBV co-infection and treatment history, finally RBV co-administration mildly increase SVR12 rate but no statistic difference was found. (Fig.7)

Of note, SVR12 rate was achieved in 96.6% among patients with cirrhosis (28/29), 100% with RBV co-administration regimens and 87.5% without RBV, comparing to 97.6% and 95.5% in patients without cirrhosis (61/63), respectively.

Antiviral treatment contributes to fibrosis improvement

The data on Fig.8 showed the APRI was significantly reduced after treatment as compared to that at baseline (2.04 versus 0.56, $p<0.0001$) and the similar result was found in FIB-4(3.43 versus 2.15, $p<0.0001$). We further compared the scores of APRI and FIB-4 between pre-treatment and post-treatment among patients with different characteristics, which indicated that patients with HBV co-infection, treatment experienced and normal ALT level at baseline gained no significant decrease in APRI or FIB-4

scores (Table 3 and 4). Also we found that APRI or FIB-4 scores were increased in some patients (n=15). The multivariate logistic regression (Table 5) showed that patients with normal ALT level at baseline was identified as a negative predictor of fibrosis improvement (p=0.01, OR=6.668).

SOF-based regimens were well-tolerated

SOF-based treatment was well-tolerated by patients. Adverse events (AEs) occurred in 13.29% of patients, and no severe AEs, death occurred and no discontinuation due to AEs. And there were no significant differences in 6 treatment regimens (Table 6).

Discussion

In present study, we assessed that SOF-based regimens achieved satisfactory virological response and were well-tolerated in Chinese patients infected with genotypes 3 and 6 in real-world practice. Although higher proportion of cirrhosis, higher level of AST and lower platelet count at baseline were found in patients infected with genotype 3 comparing to genotype 6, similar and high SVR rates were estimated in two genotypes. The SVR12 rates are similar and high in diverse SOF-based regimens. And the addition of RBV treatments yield numerically superior SVR12 rates than RBV free regimens irrespective of genotype, cirrhosis status and treatment experience.

SOF (an NS5B nucleotide polymerase inhibitor), DCV (an NS5A replication complex inhibitor, which is not FDA-approved but has been studied widely), and SOF/VEL (a new pangenotypic drug, which is the combination of NS5A and NS5B nucleotide polymerase inhibitor), highly effective in HCV infection and approved in treatment among patients with genotypes 3 and 6 infection according to the guideline and clinical trials.^{15,24} However, it's reported that SVR12 rates in real-world practice were not same satisfactory as comparing to clinical trials.²⁵ And a phase III clinical trial from Asia showed unsatisfactory SVR12 rate of SOF/VEL treatment on patients infected with genotype 3b, significant inferior than other genotypes, especially in cirrhotic patients.²⁶ In China, to our knowledge, only a few studies in real-world practice explored the efficacy of SOF-based regimens particularly SOF/VEL in patients with genotype 3 and 6 infection. One study conducted by Tang H provided the data on the efficacy of SOF-based regimens in Chinese patients infected with genotype 3 (n = 60), the SVR24 rate was over 90% in SOF + DCV + RBV and SOF /VEL regimens except of SOF + DCV regimens. Neither sub-genotype information was provided nor the effect of ribavirin on SVR12 was analyzed.²⁷ Another real-world study from China showed that genotype 3a infected patients yield high and similar SVR12 rate in SOF/VEL and SOF + DCV ± RBV regimens.²⁸ However, the number of patients enrolled were small and the SVR12 rate on 3b sub-type with cirrhosis wasn't shown. In present study, patients with genotype 3 infection achieved SVR12 rates over 90% even high to 100% except for SOF + RBV and SOF/VEL regimens. Among cirrhotic patients infected with genotype 3b (n = 13), 84.6% was treated with RBV co-administration regimens, and nobody failed to achieve SVR12.

RBV, has been shown to improvement in efficacy of pegylated interferon, which was recommended in patients with decompensated cirrhosis in the time of DAA therapy according to guideline.^{24,29} It's still controversial about the role of RBV on antiviral efficacy in DAA therapy. Data from a systematic review showed that the addition of RBV to SOF/VEL and SOF + DCV significantly increased the efficacy and side effect meanwhile.¹⁰ And another data from several studies reported that RBV co-administration had no impact on antiviral efficacy.^{18,19} In present study, RBV were more frequently used in patients with genotype 3 infection than genotype 6, which obtained similar and high SVR12 rates and side effects. Additionally, RBV co-administration to three SOF-based regimens achieved numerically superior SVR12 rate in genotype 3 and 6 infected patients with cirrhotic or non-cirrhotic, comparing to RBV free regimens. Moreover, there was evidence for increased occurrence of HCC in patients treated with RBV free SOF-based regimens.³⁰ Accordingly, this may provide some of evidence for the treatment for genotype 3 and 6 in China, that is RBV co-administration to SOF-based regimens should be applied for more satisfactory SVR12 and lower incidence of HCC. Likewise, it's contributes to achieving the ambitious goal of eliminating HCV by 2030.

It's well known that antiviral treatment contributes to fibrosis improvement. And data from a long-term follow-up study showed that high ALT at baseline predicts the fibrosis progress.³¹ A real-world study from China first reported that liver fibrosis

evaluated by APRI and FIB-4 were significantly improved in patients with genotype 3 infection.²⁷ In present study, we also found that fibrosis improvement evaluated by APRI and FIB-4 occurred in most of patients, including patients with cirrhotic or high viral load but not patients with HBV co-infection, treatment experienced or normal level of ALT at baseline, which was diametrically opposed to that in above study has been mentioned. In our opinion, it's an issue of great concern to monitoring of cirrhotic status for patients with following characteristics, treatment experienced, HBV co-infection or normal level of ALT at baseline. And more research should be conducted to identify the predictors like baseline ALT of fibrosis progress.

Although the analysis on the percentage of RVR suggest that patients treated with SOF/VEL + RBV regimens achieved significantly lower RVR rate. The SVR12 rate wasn't significantly different in diverse regimens. which indicated that the RVR had no impact on SVR12. This may provide some implications for the surveillance during treatment, that is there is no necessary to detect the viral load in serum during early stage of antiviral therapy. Maybe twice tests are feasible, before antiviral treatment and post-treatment 12 weeks, when multiple detection of viral load is unavailable and can't be affordable.

There are some other insufficiency in present retrospective study. Only 82% patients detected serum viral load with Roche Cobas Ampliprep/ Cobas TaqMan, whose lowest limit of quantification

(LLOQ) is 15 IU/mL at post-treatment 12 weeks or with Kehua detection whose LLOQ is 1000 IU/mL at post-treatment 24 weeks. And for patients who failed to achieve SVR12, we didn't take further action to confirm the reasons, such as alcohol intake, drug resistance, and others. We didn't use the liver biopsy to assess the degree of liver fibrosis improvement, which may affect the results in some way.

Conclusion

Real-world data show that SOF-based regimens are highly effective and safe for patients with HCV genotypes 3 and 6 infection. Addition of RBV to SOF-based regimens may improve antiviral efficacy, especially in patients with genotype 3 infection and cirrhosis.

Abbreviations

HCV, hepatitis C virus; SOF, sofosbuvir; SVR, sustained virological response; DAA, direct antiviral agents; RBV, ribavirin; DCV, daclatasvir; VEL, velpatasvir; HBV, hepatitis B virus; AST, aspartate aminotransferase; ALT, alanine aminotransaminase; APRI, aspartate aminotransferase to platelet ratio index; FIB-4, Fibrosis-4; RVR, rapid viral response; AE, adverse event; LLOQ, lower limit of quantification.

Declarations

Ethical Approval :

This study was approved by the Institutional Review Board of the Second Affiliated Hospital of Chongqing Medical University.

Consent for publication:

Not applicable.

Availability of data and materials:

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests:

The authors report no conflicts of interest in this work.

Funding:

This work was prepared independently without financial support.

Authors' contributions:

PH conceived the study, LW and XQL retrieved and analyzed the data, and all authors contributed to the writing of the manuscript.

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Tables

Table 1 Baseline characteristics of patients received SOF-based regimens in genotypes 3 and 6

	Total(n=173)	Genotype3(93)	Genotype6(80)	P value
Age(y)	44.4±9.9	43.8±8.0	45.1±11.7	0.415
Gender(males/female)	110/63	63/30	47/33	0.211
ALT(U/L) ^a	106.5±80.5	117.6±71.1	93.6±88.9	0.073
AST(U/L) ^b	76.4±57.4	86.7±54.1	64.4±59.2	0.019
Total bilirubin(mmol/L)	18.4±29.5	16.2±11.5	21.0±41.9	0.345
Total bile-acid(mmol/L)	16.9±29.2	19.9±31.4	13.5±26.3	0.250
Albumin(g/L)	42.1±5.2	42.0±5.0	42.2±5.5	0.791
Hemoglobin(g/L)	143.2±23.4	145.3±22.6	140.6±24.4	0.270
Platelets(10 ⁹ /L)	154.9±72.0	136.4±62.2	178.3±77.1	0.001
PLR ^c	94.62±47.2	83.38±40.6	108.92±51.3	0.003
NLR ^d	1.97±1.3	1.84±1.1	2.14±1.6	0.211
AFP(ng/mL)	13.3±19.6	14.7±23.9	11.3±11.1	0.446
HCV ^e -RNA(Ig IU/mL)	6.22±1.0	6.18±0.9	6.27±1.1	0.597
Cirrhosis,n(%)	43(24.9%)	30(32.2%)	13(16.3%)	0.015
Treatment experienced,n(%)	13(7.7%)	10(11.0%)	3(3.8%)	0.082
HBV ^f co-infection,n(%)	14(8.1%)	7(7.6%)	7(8.8%)	1.000
Treatment regimens				
SOF ^g ,n(%)	14(8.1%)	7(7.5%)	7(8.8%)	0.796
SOF+RBV ^h ,n(%)	25(14.5)	11(11.8%)	14(17.5%)	0.290
SOF+DCV ⁱ ,n(%)	5(2.9%)	3(3.2%)	2(2.5%)	1.000
SOF+DCV+RBV,n(%)	19(11.0%)	13(14.0%)	6(7.5%)	0.174
SOF/VEL ^j ,n(%)	53(30.6%)	17(18.3%)	36(45.0%)	<0.001
SOF/VEL+RBV,n(%)	57(29.5%)	42(45.2%)	15(18.8%)	<0.001

Notes: Continuous variable are expressed as mean and SD (standard deviation), and categorical variables as n and percentage.

a: alanine aminotransaminase; b: aspartate aminotransferase; c: platelete lymphocyte ratio; d: neutrophil lymphocyte ratio; e: hepatitis C virus; f: hepatitis B virus; g: sofosbuvir; h: ribavirin; i: daclatasvir; j: velpatasvir.

Table 2 Baseline characteristics of patients received SOF-based regimens with or without RBV

	Total(n=173)	With RBV (n=101)	Without RBV (n=72)	P value
Age(y)	44.4±9.9	44.3±9.3	44.5±10.7	0.907
Gender(males/female)	109/63	72/29	38/34	0.013
ALT(U/L)	106.5±80.5	110.5±75.3	100.6±87.8	0.465
AST(U/L)	76.4±57.4	78.1±50.7	73.8±66.4	0.662
Total bilirubin(mmol/L)	18.4±29.5	21.2±37.4	14.2±8.2	0.170
Total bile-acid(mmol/L)	16.9±29.2	20.9±35.5	11.5±16.2	0.063
Albumin(g/L)	42.1±5.2	41.7±5.4	42.8±4.8	0.246
Hemoglobin(g/L)	143.2±23.4	144.1±24.1	141.6±22.5	0.569
Platelets(10 ⁹ /L)	154.9±72.0	154.9±77.0	155.0±63.1	0.995
PLR	94.62±47.2	92.97±47.9	97.46±46.2	0.609
NLR	1.97±1.3	1.97±1.3	1.98±1.3	0.940
AFP(ng/mL)	13.3±19.6	12.68±14.9	14.2±25.9	0.736
HCV-RNA(Ig IU/mL)	6.22±1.0	6.28±0.9	6.13±1.0	0.363
Cirrhosis,n(%)	43(24.9%)	30(29.7%)	13(18.1%)	0.081
Treatment experienced,n(%)	13(7.7%)	9(8.9%)	4(5.5%)	0.409
HBV co-infection,n(%)	14(8.1%)	9(8.9%)	5(6.9%)	0.640
Treatment regimens				
SOF,n(%)	39(22.5%)	25(24.8%)	14(19.4%)	0.917
SOF+DCV,n(%)	24(13.9%)	19(18.8%)	5(6.9%)	0.001
SOF/VEL,n(%)	110(63.6%)	57(56.4%)	53(73.6%)	0.021
Genotype				
GT3,n(%)	93(53.8%)	66(65.3%)	27(37.5%)	P<0.001
GT6,n(%)	80(46.2%)	35(34.7%)	45(62.5%)	P<0.001

Notes: Continuous variable are expressed as mean and SD (standard deviation), and categorical variables as n and percentage. The abbreviations appeared in this table were mentioned in the notes below table 1.

Table 3 The fibrosis improvement evaluated by FIB-4 in patients with different characteristics

	FIB-4	Before treatment	After treatment	P value
Gender	male	4.01±4.42	2.32±2.43	<0.0001
	female	2.38±3.12	1.83±2.14	0.010
Age	≤40y	2.20±2.94	1.2±1.04	0.005
	>40y	4.37±4.55	2.86±2.5	<0.0001
cirrhotic	yes	8.00±5.65	4.65±3.56	<0.0001
	no	2.02±1.89	1.37±0.86	<0.0001
Viral load	high	3.63±3.97	2.20±2.36	<0.0001
	low	3.00±4.31	2.02±2.28	0.025
Treatment experienced	yes	5.52±6.32	3.10±3.04	0.050
	no	3.18±3.69	2.03±2.22	<0.0001
HBV co-infection	yes	2.52±3.19	1.7±1.65	0.499
	no	3.47±4.11	2.16±2.36	<0.0001
ALT level	elevated	3.37±3.57	2.07±2.11	<0.0001
	normal	3.63±5.46	2.40±2.98	0.054
Genotype	3	3.97±4.54	2.37±2.54	<0.0001
	3b	3.96±4.44	2.33±2.65	<0.0001
	6	2.72±3.27	1.86±2.00	0.003
Treatment regimens	SOF±RBV	3.30±3.98	2.13±2.48	<0.0001
	SOF+DCV±RBV	3.92±4.35	2.41±2.68	<0.0001
	SOF/VEL±RBV	3.86±4.66	2.59±2.86	<0.0001
RBV addition	with	3.76±4.62	2.33±2.76	<0.0001
	without	2.87±2.84	1.84±1.26	0.006

Notes: Continuous variables are expressed as mean and SD. We compared the FIB4 ((Age × AST)/ (PLT × (square root of ALT))) in patients with diverse characteristics between pre-treatment and post-treatment.

Table 4 The fibrosis improvement evaluated by APRI in patients with different characteristics

	APRI	Before treatment	After treatment	P value
Gender	male	2.58±3.10	0.65±0.68	<0.0001
	female	1.06±1.01	0.43±0.39	<0.0001
Age	≤40y	1.80±2.67	0.40±0.34	0.001
	>40y	2.20±2.65	0.70±0.72	<0.0001
cirrhotic	yes	4.85±4.03	1.23±0.90	<0.0001
	no	1.16±1.06	0.37±0.24	<0.0001
Viral load	high	1.99±2.00	0.55±0.51	<0.0001
	low	2.13±3.76	0.61±0.77	0.017
Treatment experienced	yes	3.34±3.80	0.73±0.62	0.036
	no	1.88±2.46	0.55±0.6	<0.0001
HBV co-infection	yes	1.70±1.58	0.58±0.51	0.216
	no	2.05±2.70	0.57±0.61	<0.0001
ALT level	elevated	2.37±2.86	0.59±0.62	<0.0001
	normal	0.98±1.42	0.50±0.55	0.028
Genotype	3	2.63±3.25	0.67±0.72	<0.0001
	3b	2.72±3.40	0.63±0.69	<0.0001
	Non-3b	2.46±3.01	0.74±0.78	0.014
	6	1.25±1.18	0.44±0.36	<0.0001
Treatment regimens	SOF±RBV	1.34±1.26	0.35±0.21	<0.0001
	SOF+DCV±RBV	2.44±2.74	0.46±0.36	0.004
	SOF/VEL±RBV	2.28±3.12	0.73±0.76	<0.0001
RBV addition	with	2.22±2.93	0.58±0.63	0.001
	without	1.72±2.09	0.55±0.57	<0.0001

Notes: Continuous variables are expressed as mean and SD. We compared the APRI (AST/PLT*100) in patients with diverse characteristics between pre-treatment and post-treatment.

Table 5 Predictors model of fibrosis improvement analyzed for all patients treated with SOF-based regimens

characteristics		APRI or FIB-4		Univariate P value	Multivariate P value	OR
		Improvement (n=78)	No improvement (n=15)			
Gender	male	54	6	0.036	0.100	3.030
	female	24	9			
Age	≤40y	30	10	0.051	0.103	0.267
	>40y	48	5			
cirrhotic	yes	22	0	0.998		
	no	56	15			
Viral load	high	57	7	0.05	0.092	3.150
	low	21	8			
Treatment experienced	yes	8	2	0.725		
	no	70	13			
HBV co-infection	yes	3	1	0.626		
	no	75	14			
ALT level	elevated	64	7	0.006	0.010	6.668
	normal	14	8			
Genotype	3	45	8	0.755		
	6	33	7			
Treatment regimen ^{1s}	SOF±RBV	24	3	0.56		
	SOF+DCV±RBV	13	4			
	SOF/VEL±RBV	41	8			
RBV addition	with	51	8	0.378		
	without	27	7			
APRI ^a		0.59±0.63	0.35±0.26	0.137		
FIB-4 ^b		2.29±2.42	1.18±0.65	0.076	0.326	0.689

Notes: Continuous variables are expressed as mean and SD (standard deviation), and categorical variables as n. The variables that were associated with liver fibrosis progression with a p-value < 0.1 were included in multivariate logistic regression models. a: aspartate aminotransferase to platelet ratio index; b: fibrosis-4.

Table 6 The safety of patients received SOF-based regimens

	Total (n=173)	SOF (n=14)	SOF+RBV(n=25)	SOF+DCV (n=5)	SOF+DCV+RBV (n=19)	SOF/VEL (n=53)	SOF/VEL+RBV (n=57)
AEs ^a , n(%)	23(13.29)	3(21.43)	3(12.00)	2(40.00)	3(15.79)	4(7.55)	8(14.04)
Mild to moderate anemia	17(9.83)	3(21.43)	2(8.00)	0(0)	2(10.53)	3(5.66)	7(12.28)
Severe anemia	1(0.58)	0(0)	0(0)	0(0)	0(0)	0(0)	1(1.75)
Abdominal distention	2(1.16)	0(0)	1(4.00)	0(0)	1(5.26)	0(0)	0(0)
Fatigue, n(%)	1(0.58)	0(0)	0(0)	1(20.00)	0(0)	0(0)	0(0)
Headache, n(%)	1(0.58)	0(0)	0(0)	1(20.00)	0(0)	0(0)	0(0)
Diarrhoea, n(%)	1(0.58)	0(0)	0(0)	0(0)	0(0)	1(1.89)	0(0)
Serious AEs, n(%)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Discontinuation due to AEs, n(%)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)
Death, n(%)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)	0(0)

Notes: categorical variables as n and percentage. Difference in AEs rate between diverse treatment regimens: P >0.05.

a: adverse event

Figures

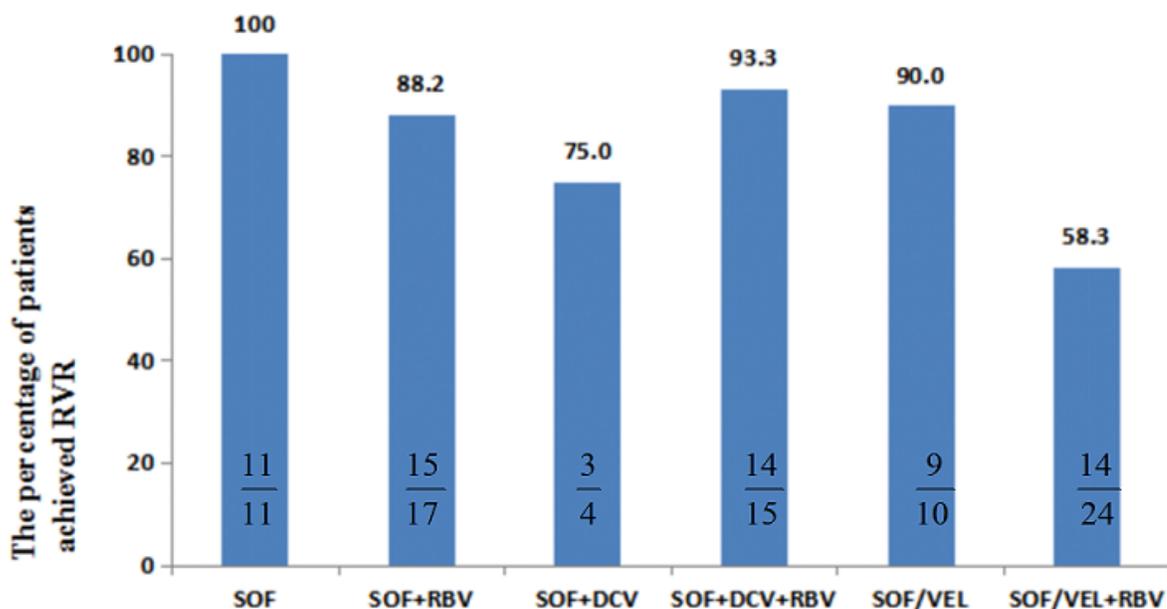


Figure 1

The RVR rates in patients treated with diverse regimens. We compared the rapid virological response (RVR) rates between 6 treatment regimens, including sofosbuvir (SOF), SOF+ribavirin (RBV), SOF+daclatasvir (DCV), SOF+DCV+RBV, SOF/velpatasvir

(VEL) and SOF/VEL +RBV regimens. Difference between SOF and SOF/VEL+RBV regimens: p=0.015. Difference between SOF+DCV+RBV and SOF/VEL+RBV regimens : p=0.028. Difference between other treatment regimens: P>0.05.

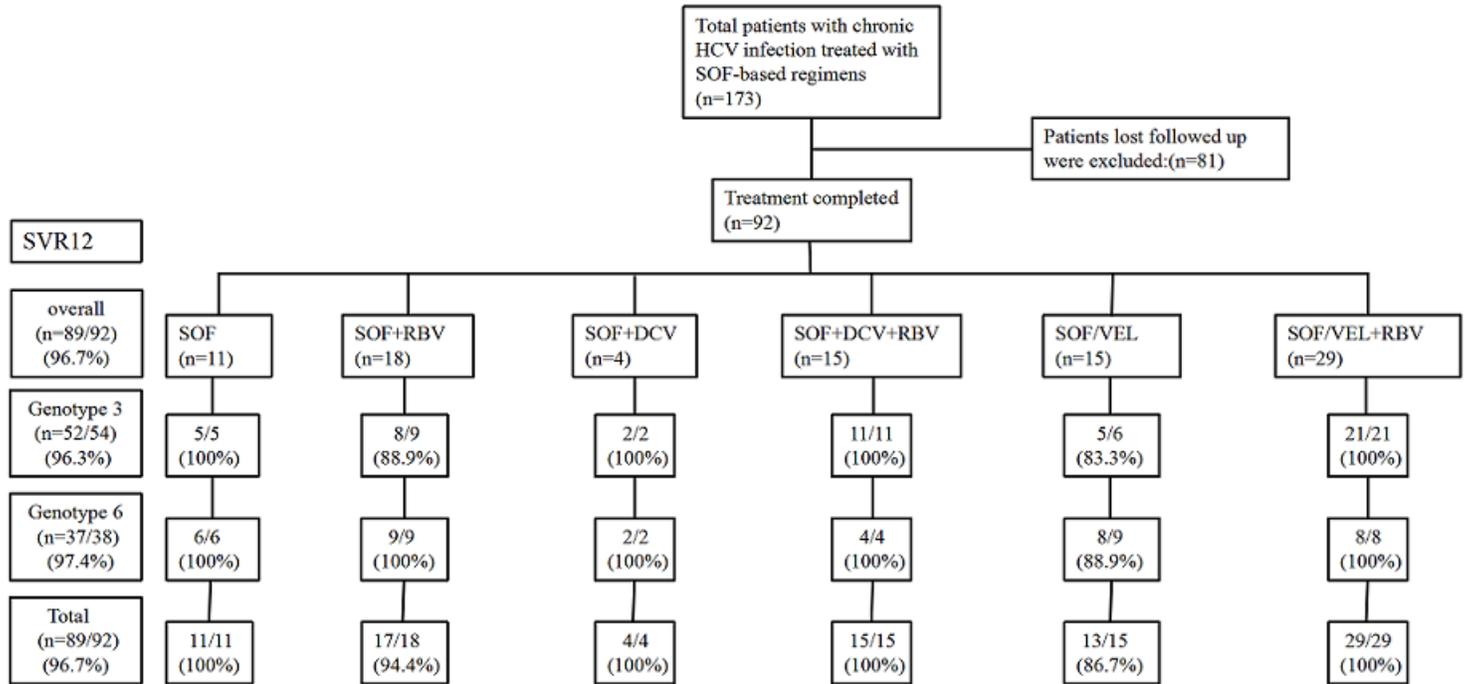


Figure 2

patients disposition and SVR12 in diverse treatment regimens. Study flow design. Distribution of patients into overall cohort, and sustained virological response at post-treatment week 12 (SVR12) rates in diverse genotypes and treatment regimens.

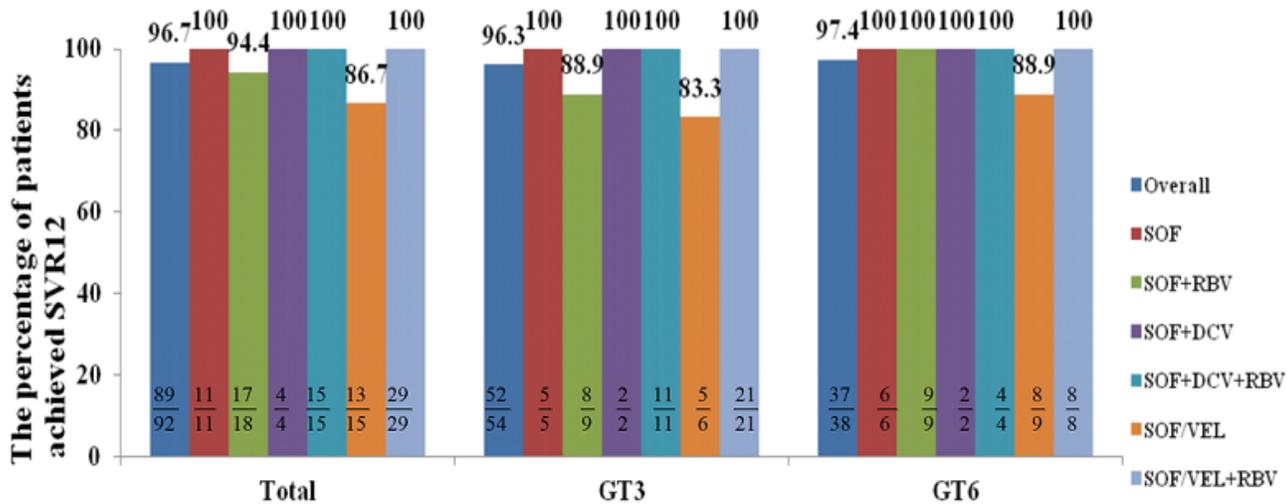


Figure 3

The SVR12 rates in patients infected with genotypes 3 and 6 in diverse regimens. Overall, the difference in SVR12 rate between six treatment regimens: P>0.05; For patients infected with genotype 3, the difference in SVR12 rate between six treatment regimens: P>0.05; For patients infected with genotype 6, the difference in SVR12 rate between six treatment regimens: P>0.05

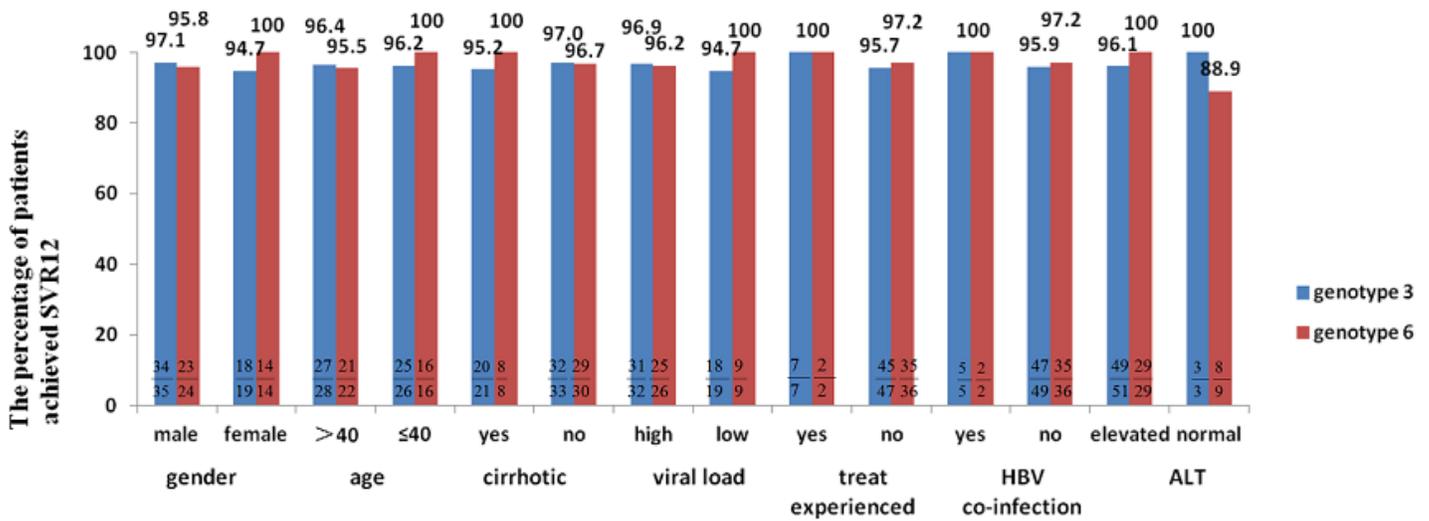


Figure 4

The SVR12 rates in patients infected with genotype 3 and 6 in different characteristics. We analyzed the impact of factors such as, gender, age, cirrhotic status, viral load, treatment history, HBV co-infection and level of baseline ALT on SVR12 in patients with genotypes 3 and 6 infection. For genotype 3, no statistic difference was found between above factors: $p>0.05$. The similar results were found in patients infected with genotype 6.

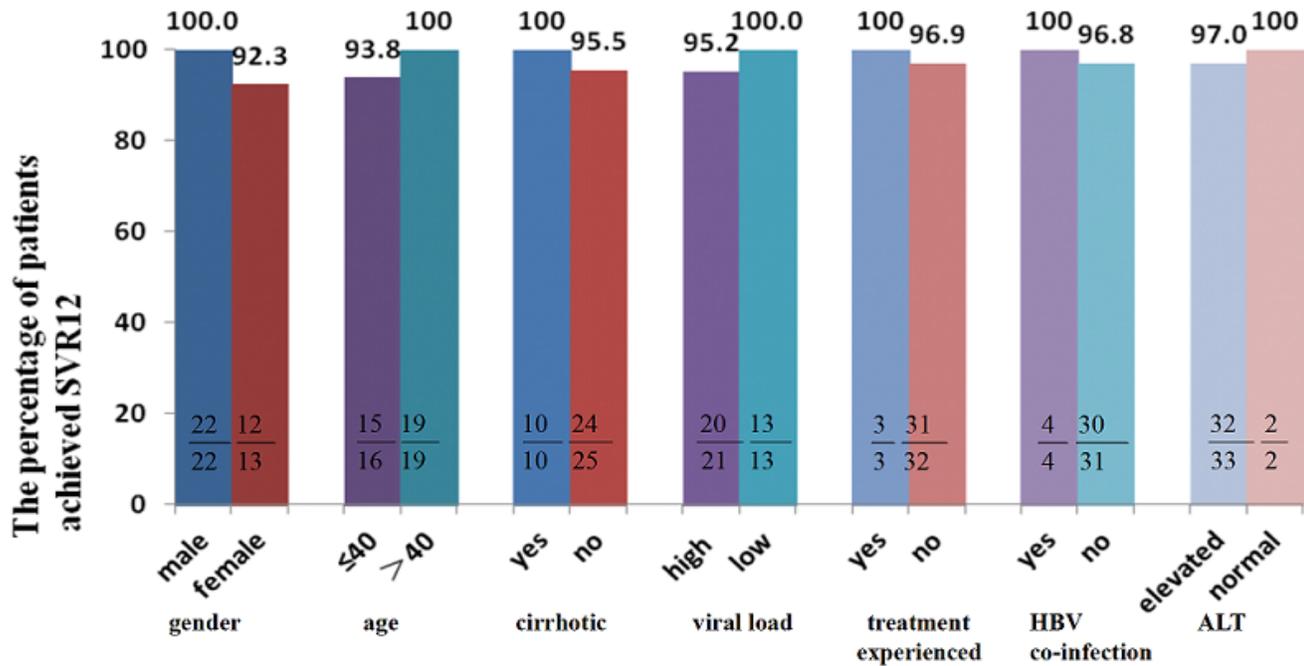
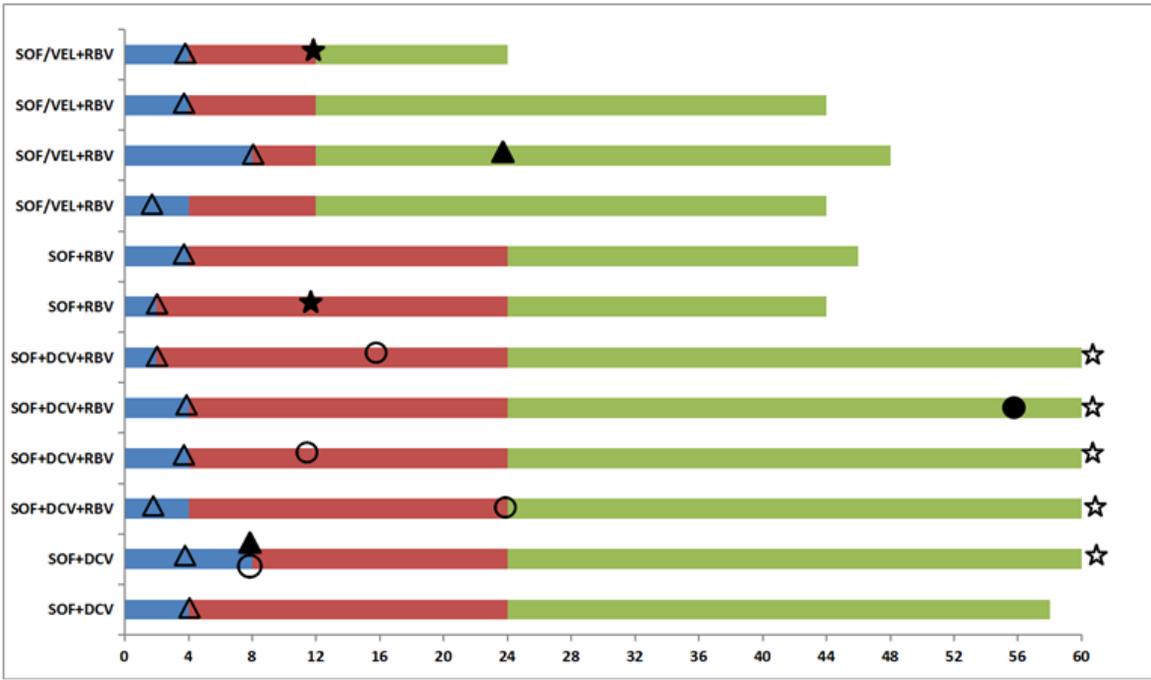


Figure 5

The SVR rates in patients infected with sub-type 3b with different characteristics. We analyzed the impact of factors such as, gender, age, cirrhotic status, viral load, treatment history, HBV co-infection and level of baseline ALT on SVR12 in patients with sub-type 3b infection, no statistic difference was found between above factors: $p>0.05$.



- Serum HCV-RNA detectable
- Time at serum HCV-RNA undetectable to end of treatment
- Follow up after end of treatment
- △ Time at occurrence of ALT normalization
- Time at occurrence of AFP normalization
- ▲ Time at occurrence of elevated ALT which was normal before
- Time at occurrence of elevated AFP which was normal before
- ★ Time at detectable serum HCV-RNA which was undetectable before
- ☆ Patient still on follow-up after 60 weeks

Figure 6

The detailed clinical process in cirrhotic patients with genotype 3b infection. The left side of the figure are the treatment regimens, and the horizontal axis represents the time (week), and week 0 means time at baseline. The number of cirrhotic patients infected with genotype 3b was 13, one patient treated with SOF/VEL+RBV for 12 weeks was not be presented because the time of undetectable HCV-RNA was not sure.

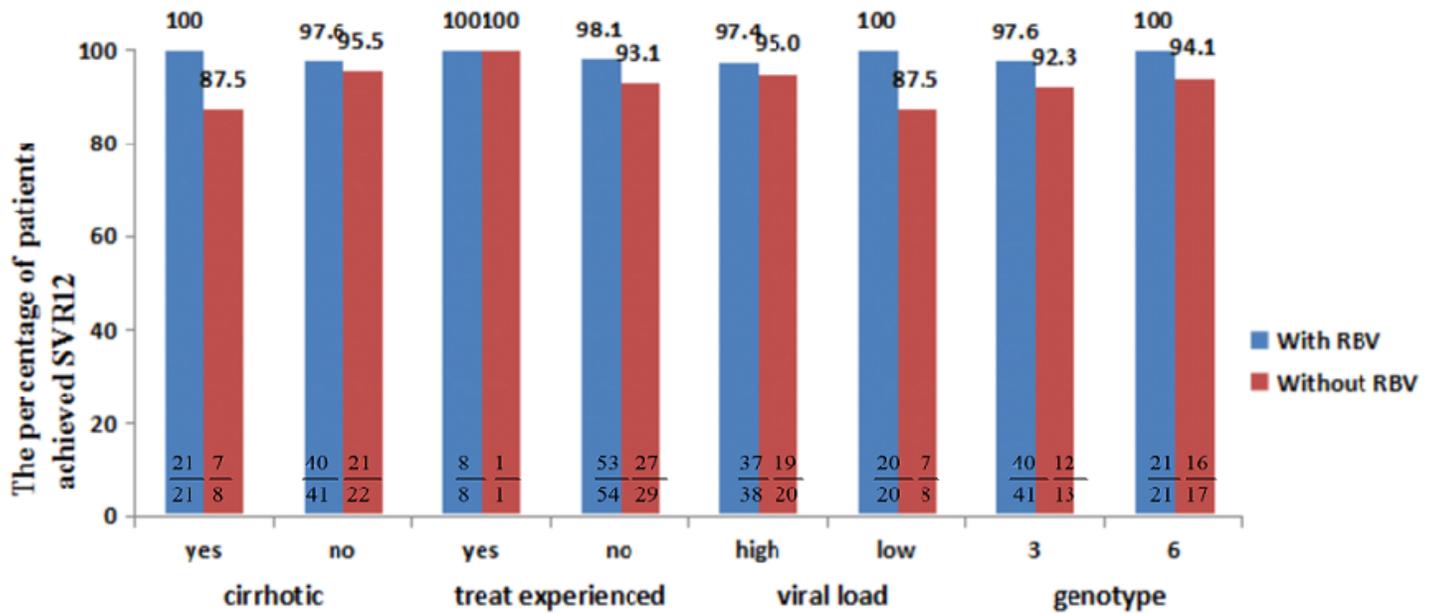


Figure 7

The SVR12 rates in patients treated with or without RBV in different characteristics. We compared the SVR12 rates in cirrhotic, non-cirrhotic, treatment-experienced (treated with DAAs or interferon and RBV regimens), treatment-naive, high viral load (level of serum HCV-RNA > 800000IU/mL), low viral load (HCV-RNA ≤ 800000IU/mL), and two genotypes. In patients with above characteristics, no statistic difference was found between groups with RBV and without RBV: p>0.05.

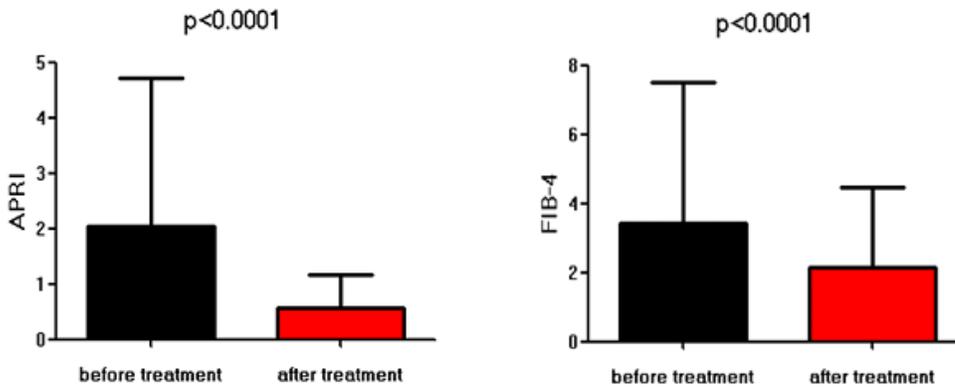


Figure 8

The improvement in fibrosis evaluated by APRI and FIB. We compared the APRI (AST/PLT*100) and FIB-4 ((Age × AST)/ (PLT × (square root of ALT))) between pre-treatment and post-treatment. Difference in APRI between pre-treatment and post-treatment: p<0.0001, similar result was found in FIB-4.