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ORIGINAL ARTICLE

Sofosbuvir/velpatasvir/voxilaprevir for patients with chronic hepatitis C virus infection previously treated with NS5A direct-acting antivirals: a real-world multicenter cohort in Taiwan

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Abstract

Background Real-world data are scarce about the effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) for retreating East Asian patients with hepatitis C virus (HCV) infection who previously received NS5A direct-acting antivirals (DAAs). We conducted a multicenter study to assess the performance of SOF/VEL/VOX in patients who were not responsive to prior NS5A inhibitors in Taiwan.

Methods Between September 2021 and May 2022, 107 patients who failed NS5A inhibitor-containing DAAs with SOF/VEL/VOX salvage therapy for 12 weeks were included at 16 academic centers. The sustained virologic response at off-treatment week 12 (SVR_{12}) was assessed in the evaluable (EP) and per-protocol (PP) populations. The safety profiles were also reported.

Results All patients completed 12 weeks of treatment and achieved an end-of-treatment virologic response. The SVR_{12} rates were 97.2% (95% confidence interval (CI) 92.1–99.0%) and 100% (95% CI 96.4–100%) in EP and PP populations. Three (2.8%) patients were lost to off-treatment follow-up and did not meet SVR_{12} in the EP population. No baseline factors predicted SVR_{12}. Two (1.9%) not-fatal serious adverse events (AE) occurred but were unrelated to SOF/VEL/VOX. Sixteen (15.0%) had grade 2 total bilirubin elevation, and three (2.8%) had grade 2 alanine transaminase (ALT) elevation. Thirteen (81.3%) of the 16 patients with grade 2 total bilirubin elevation had unconjugated hyperbilirubinemia. The estimated glomerular filtration rates (eGFR) were comparable between baseline and SVR_{12}, regardless of baseline renal reserve.

Conclusions SOF/VEL/VOX is highly efficacious and well-tolerated for East Asian HCV patients previously treated with NS5A inhibitor-containing DAAs.

Clinical trials registration The study was not a drug trial. There was no need for clinical trial registration.

Keywords Hepatitis C virus · Direct-acting antiviral · Sofosbuvir · Velpatasvir · Voxilaprevir · Resistance-associated substitution · Pangenotypic · Sustained virologic response · Effectiveness · Safety

Abbreviations

HCV	Hepatitis C virus
DAA	Direct-acting antiviral
HCC	Hepatocellular carcinoma
SVR	Sustained virologic response
IFN	Interferon
RAS	Resistance-associated substitution
WHO	World Health Organization
SOF	Sofosbuvir
VEL	Velpatasvir
VOX	Voxilaprevir
FDC	Fixed-dose combination
GT	Genotype
RBV	Ribavirin
LLOQ	Lower limit of quantification
HBV	Hepatitis B virus
HIV	Human immunodeficiency virus

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RNA	Ribonucleic acid
DNA	Deoxyribonucleic acid
DDI	Drug-drug interaction
DM	Diabetes mellitus
HTN	Hypertension
ULN	Upper limit of normal
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
eGFR	Estimated glomerular filtration rate
FIB-4	Fibrosis index based on four parameters
AE	Adverse event
IQR	Interquartile range
CI	Confidence interval
MAFLD	Metabolic dysfunctional-associated fatty liver disease
DILI	Drug-induced liver injury
NUC	Nucleot(s)ide analogue
OATP	Organic anion transport protein
DCV	Daclatasvir
ASV	Asunaprevir
PrOD	Paritaprevir/ritonavir/ombitasvir plus dasabuvir
EBR	Elbasvir
GZR	Grazoprevir
GLE	Glecaprevir
PIB	Pibrentasvir
LDV	Ledipasvir
CKD-EPI	Chronic kidney disease epidemiology collaboration
CTCAE	Common terminology criteria for adverse events

Introduction

Although the global prevalence of chronic hepatitis C virus (HCV) infection has decreased from 0.9 to 0.7% between 2015 and 2020 following the widespread use of direct-acting antivirals (DAAs), it remains one of the major causes of cirrhosis, hepatocellular carcinoma (HCC), hepatic decompensation and liver transplantation [1–3]. Currently, the sustained virologic response (SVR) rates with DAAs for HCV are generally more than 95% in DAA-naïve patients, regardless of clinical trials or real-world studies [4–15]. While the treatment response for HCV in the era of interferon (IFN)-free DAAs is satisfactory, a small proportion of patients fail to respond to DAAs, resulting in the selection of resistance-associated substitutions (RASs) at the HCV non-structural (NS)3, NS5A, or NS5B regions that complicate the retreatment strategies. It is particularly relevant to patients exposed to NS5A inhibitors because (1) NS5A inhibitor is the backbone among most licensed DAA regimens; (2) the persistence of NS5A RASs is much longer than other classes of RASs following treatment failures [16]. Therefore, an effective means to eradicate HCV is needed in patients who are not responsive to previous NS5A inhibitors to meet the World Health Organization's (WHO) target for HCV elimination by 2030.

Sofosbuvir/velpatasvir/voxilaprevir (SOF/VEL/VOX) is a fixed-dose combination (FDC) of HCV NS5B, NS5A, and NS3 inhibitors, which exhibits pangenotypic potency against HCV by once-daily, oral administration [17]. SOF/VEL/VOX is indicated to retreat patients with compensated HCV disease previously treated with a DAA regimen containing an NS5A inhibitor (HCV genotype [GT] 1–6) or SOF without an NS5A inhibitor (HCV GT 1a or 3). To date, SOF/VEL/VOX has been recommended by international guidelines as the first-line salvage therapy for DAA-experienced patients with HCV. [18–20]

The phase 3 POLARIS-1 trial evaluated the performance of SOF/VEL/VOX for 12 weeks in patients with compensated HCV GT 1–6 infection previously treated with NS5A inhibitor-containing DAAs, demonstrating that the SVR_{12} rates were 96% [21]. Furthermore, the SVR_{12} rate of SOF/VEL/VOX for 12 weeks was 97% in patients allocated to the deferred arm in the POLARIS-1 trial, which corroborated the excellent response in managing such patients [22]. Baseline HCV GT, cirrhosis, and RAS distribution did not affect the treatment responses [21, 22]. The real-world studies from Western countries, including the U.S., Canada, Italy, Spain, and Australia, have reported the SVR_{12} rates of SOF/VEL/VOX for DAA-experienced patients with HCV ranged from 90 to 100%, and most patients tolerated treatment well [23–29]. In contrast, data regarding the performance of SOF/VEL/VOX in the Asian population are limited. Only two small-scaled studies from Taiwan and Singapore recruited two and twenty-five NA5A inhibitor-experienced patients with HCV, in which the SVR_{12} rates were 100% and 96%, respectively. [30, 31] Furthermore, both studies recruited a significant portion of patients treated outside the label recommendation, including coadministration of ribavirin (RBV) and decompensated cirrhosis, making the clinical performance of SOF/VEL/VOX elusive in NS5A-inhibitor experienced Asian patients with HCV. Based on the above-mentioned concerns, we conducted a multicenter prospective cohort study in Taiwan to confirm the effectiveness and tolerance of SOF/VEL/VOX for patients with HCV previously treated with NS5A inhibitor-containing DAAs.

Materials and methods

Patients

Between September 2021 and April 2022, patients with chronic HCV infection and compensated liver disease

aged ≥ 20 years who failed to respond to previous IFN-free DAAs containing an NS5A inhibitor were prospectively recruited at 16 academic centers in Taiwan. Chronic HCV infection was defined as the presence of HCV antibody (anti-HCV; Abbott HCV EIA 2.0, Abbott Laboratories, Abbott Park, Illinois, USA) and quantifiable serum HCV RNA level (Cobas TaqMan HCV Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, lower limit of quantification [LLOQ]: 15 IU/mL) for ≥ 6 months. Compensated liver disease was defined as patients without cirrhosis or with compensated cirrhosis (Child–Pugh A). Patients were excluded if they had active HCC or decompensated cirrhosis (Child–Pugh B or C).

Study design

We inquired about patient demographic data, including age, sex, previous anti-HCV treatment regimens, most recent virologic response to DAAs, history of HCC, diabetes mellitus (DM), and arterial hypertension (HTN). In addition, all participants underwent laboratory testing for hemogram, international normalized ratio (INR), serum albumin, total bilirubin (upper limit of normal [ULN]: 1.0 mg/dL), direct bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT) (ULN: 30 U/L for males and 19 U/L for females), estimated glomerular filtration rate (eGFR) as calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, anti-HCV, hepatitis B surface antigen (HBsAg) (Abbott Architect HBsAg qualitative assay, Abbott Laboratories, Abbott Park, Illinois, USA) to confirm hepatitis B virus (HBV) coinfection, anti-HIV (Abbott Architect HIV Ag/Ab Combo, Abbott Laboratories, Abbott Park, Illinois, USA), to confirm HIV coinfection HCV RNA, and HCV genotype (Roche Cobas HCV GT, Roche Diagnostics GmbH, Mannheim, Germany, or Abbott RealTi*me* HCV Genotype II, Abbott Laboratories, Abbott Park, Illinois, USA) [32–34]. The severity of hepatic fibrosis was graded by the fibrosis index based on four parameters (FIB-4) with cut-off values of < 1.45, 1.45–3.25, and > 3.25 [35]. Hepatic imaging studies, including ultrasonography, computed tomography or magnetic resonance imaging, were performed before treatment to detect active HCC or decompensated cirrhosis. Baseline HBV deoxyribonucleic acid (DNA) (Cobas AmpliPrep/Cobas Taqman HBV DNA test, v.2.0, LLOQ): 10 IU/mL) was checked in patients with HBV coinfection. Furthermore, HIV RNA (Cobas AmpliPrep TaqMan HIV-1 Test v2.0, Roche Diagnostics GmbH, Mannheim, Germany, LLOQ: 20 copies/mL) was checked in patients with HIV coinfection. Baseline RASs at the HCV NS3 and NS5A regions were analyzed by population sequencing with a cut-off detection level of 15% [36]. RAS analysis was performed at off-treatment week 12 if participants had virologic failures to SOF/VEL/VOX.

Patients received SOF/VEL/VOX (Vosevi®, FDC 400/100/100 mg per tablet, Gilead Sciences, Carrigtohill, County Cork, Ireland) 1 tablet once daily with food for 12 weeks. Coadministration of RBV was permitted based on physicians' discretion. Before initiating SOF/VEL/VOX, the investigators performed drug-drug interaction (DDI) assessment for all comedications through the pre-defined study checklist [37]. If the comedications were contraindicated for use during SOF/VEL/VOX treatment, the investigators stopped the comedications or switched to other non-contraindicated agents. All patients underwent outpatient visits at on-treatment weeks 4 and 12 and off-treatment week 12. Serum HCV RNA levels were assessed at on-treatment week 12 and off-treatment week 12. Total bilirubin, direct bilirubin, AST, and ALT were assessed at on-treatment weeks 4 and 12. Hemogram, INR, albumin, total bilirubin, direct bilirubin, AST, ALT, eGFR, and hepatic imaging studies were assessed at off-treatment week 12. In patients with HBV coinfection, the serum HBV DNA levels were determined at on-treatment week 12 and off-treatment week 12. Additional HBV DNA testing was allowed during SOF/VEL/VOX treatment when indicated.

Effectiveness

We assessed the end-of-treatment virologic response and SVR at on-treatment week 12 and off-treatment week 12. Patients with serum HCV RNA levels > LLOQ at off-treatment week 12 (virologic failure) or did not have SVR_{12} data (non-virologic failure) were considered failures to achieve SVR_{12}. We defined two SVR_{12} endpoints, which included the evaluable population (EP) in patients receiving at least one dose of SOF/VEL/VOX and the per-protocol population (PP) in patients undergoing virologic testing at off-treatment week 12 to confirm treatment responses.

Tolerance

At each outpatient visit, the investigators evaluated the constitutional adverse events (AEs), laboratory AEs, and serious AEs. Furthermore, they also assessed the causal relationship between SOF/VEL/VOX and various AEs, including early treatment discontinuation. We reported the proportion of patients with ≥ grade 2 total bilirubin or ALT elevation according to Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The changes in eGFR from baseline to the off-treatment week 12 were also assessed. HBV reactivation was defined as an on-treatment ≥ 2 $\log_{10}$ increase in HBV DNA level compared to the baseline level. HBV-associated hepatitis was defined as the presence of HBV reactivation in combination with ≥ grade 2 ALT elevation [38].

Statistical analysis

We used the Statistical Program for Social Sciences (SPSS Statistics Version 23.0, IBM Corp., Armonk, New York, USA) for all statistical analyses. Baseline characteristics were shown in median (interquartile range, IQR) and numbers (percentages) when appropriate. The virologic responses at on-treatment week 12 and off-treatment week 12 were shown in numbers (percentages) with a 95% confidence interval (CI). We demonstrated subgroup analyses of SVR_{12} in number (percentage) with 95% CI according to the EP population with forest plots. The constitutional, laboratory, and serious AEs were shown in numbers (percentages). The eGFR at baseline and off-treatment week 12 was shown with box plots. The changes in eGFR between baseline and off-treatment week 12 in the overall population, patients with an eGFR ≥ 60 mL/min/1.73m^2, and patients with an eGFR < 60 mL/min/1.73m^2 were compared with Wilcoxon signed-rank test. All statistical analyses were two-tailed, and a p-value of < 0.05 was considered statistically significant.

Results

Patient characteristics

Of 107 patients who received SOF/VEL/VOX because of a previously failed course of NS5A inhibitor-containing DAA regimen, all were eligible for the study. All patients completed 12 weeks of SOF/VEL/VOX treatment, and 104 (97.2%) completed 12 weeks of off-treatment follow-up (Fig. 1).

Table 1 shows the baseline characteristics. The median age was 62, and 61 (57.0%) were males. One hundred and five (98.1%) failed to respond to one course of DAAs, and the other two (1.9%) failed to respond to two courses of DAAs. The most recent failed DAA regimen included daclatasvir plus asunaprevir (DCV plus ASV) ($n = 14$; 13.1%), paritaprevir/ritonavir/ombitasvir plus dasabuvir (PrOD) ($n = 6$; 5.6%), elbasvir/grazoprevir (EBR/GZR) ($n = 14$; 13.1%), glecaprevir/pibrentasvir (GLE/PIB) ($n = 27$; 25.2%), SOF/ledipasvir (SOF/LDV) ($n = 23$; 21.5%), SOF plus DCV ($n = 1$; 0.9%), SOF/VEL ($n = 21$; 19.6%), and SOF/VEL plus RBV ($n = 1$; 0.9%). One hundred and one (94.4%) experienced viral relapse from a previous course of DAAs. The most common HCV GTs were GT1b ($n = 40$; 37.4%), GT2 ($n = 39$; 36.4%), and GT6 ($n = 18$; 16.8%).

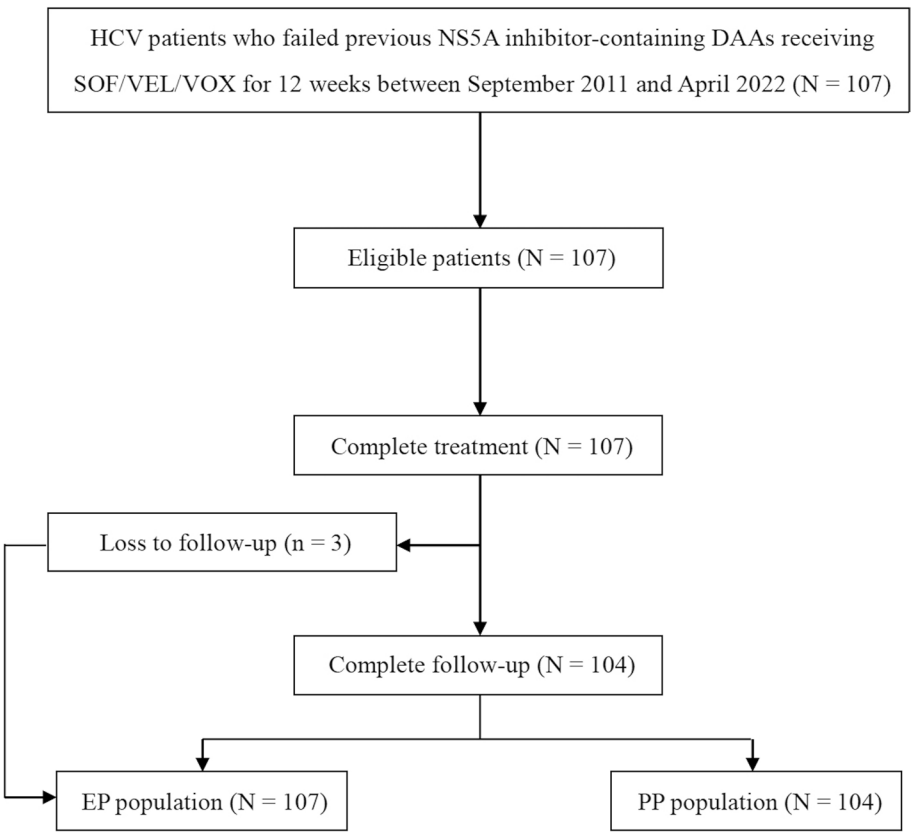

Fig. 1 Study flow. *HCV*, hepatitis C virus; *NS5A*, nonstructural protein 5A; *DAA*, direct-acting antiviral; *SOF*, sofosbuvir; *VEL*, velpatasvir; *VOX*, voxilaprevir; *EP*, evaluable population; *PP*, per-protocol population

Table 1 Baseline characteristics

Characteristics*	Patients ($N = 107$)
Age, year, median (IQR)	62 (52–71)
Age > 60 year	60 (56.1)
Male	61 (57.0)
No. of previous PR treatment	
0	90 (84.1)
1	15 (14.0)
2	2 (1.9)
No. of previous IFN-free DAA treatment	
1	105 (98.1)
2	2 (1.9)
Most recent failed DAA regimen	
DCV plus ASV	14 (13.1)
PrOD	6 (5.6)
EBR/GZR	14 (13.1)
GLE/PIB	27 (25.2)
SOF/LDV	23 (21.5)
SOF plus DCV	1 (0.9)
SOF/VEL	21 (19.6)
SOF/VEL plus RBV	1 (0.9)
Most recent failed virologic response to DAAs[†]	
Relapse	101 (94.4)
Null response	6 (5.6)
Rescue DAA regimen	
SOF/VEL/VOX	106 (99.1)
SOF/VEL/VOX plus RBV	1 (0.9)
Prior HCC	11 (10.3)
HBV coinfection	7 (6.5)
HIV coinfection	7 (6.5)
DM	21 (19.6)
Arterial HTN	31 (29.0)
HCV RNA, $\log_{10}$IU/mL, median (IQR)	6.7 (5.4-6.7)
HCV RNA > 2,000,000 IU/mL	71 (66.4)
HCV genotype	
1a	2 (1.9)
1b	40 (37.4)
2	39 (36.4)
3	7 (6.5)
6	18 (16.8)
Indeterminate	1 (0.9)
FIB-4 index	
< 1.45	29 (27.1)
1.45-3.25	43 (40.2)
> 3.25	35 (32.7)
RAS ($n = 99$)[‡]	
None	35 (35.4)
NS3 only	13 (13.1)
NS5A only	30 (30.3)
NS3 and NS5A	21 (21.2)
Hemoglobin, g/dL, median (IQR)	14.0 (12.8-15.0)
White blood cell count, 10^9cells/L, median (IQR)	5.5 (4.5-6.9)
Platelet count, 10^9 cells/L, median (IQR)	174 (130-230)
INR, median (IQR)	1.02 (0.98-1.07)
Albumin, g/dL, median (IQR)	4.2 (4.0-4.5)
Total bilirubin, ULN, median (IQR)[§]	0.8 (0.6-1.0)
ALT, ULN, median (IQR)[§]	1.5 (1.1-3.3)
eGFR, mL/min/1.73m^2, median (IQR)[¶]	87 (69-98)
CKD stage[¶]	
1 (≥ 90 mL/min/1.73m^2)	47 (43.9)
2 (60-89 mL/min/1.73m^2)	45 (42.1)
3 (30-59 mL/min/1.73m^2)	13 (12.1)
4 (15-29 mL/min/1.73m^2)	1 (0.9)
5 (< 15 mL/min/1.73m^2)	1 (0.9)

IQR, interquartile range; *PR*, peginterferon plus ribavirin; *IFN*, interferon; *DAA*, direct-acting antiviral; *DCV*, daclatasvir; *ASV*, asunaprevir; *PrOD*, paritaprevir/ritonavir/ombitasvir plus dasabuvir; *EBR/GZR*, elbasvir/grazoprevir; *GLE/PIB*, glecaprevir/pibrentasvir; *SOF/LDV*, sofosbuvir/ledipasvir; *SOF/VEL*, sofosbuvir/velpatasvir; *RBV*, ribavirin; *SOF/VEL/VOX*, sofosbuvir/velpatasvir/voxilaprevir; *HCC*, hepatocellular carcinoma; *HBV*, hepatitis B virus; *HIV*, human immunodeficiency virus; *DM*, diabetes mellitus; *HTN*, hypertension; *HCV*, hepatitis C virus; *RNA*, ribonucleic acid; *FIB-4*, fibrosis index based on four parameters; *RAS*, resistance-associated substitution; *INR*, international normalized ratio; *ALT*, alanine aminotransferase; *ULN*, upper limit of normal; *eGFR*, estimated glomerular filtration rate; CKD, chronic kidney disease

*Values are numbers (percentages) unless otherwise indicated

[†]Relapse was defined as undetectable serum HCV RNA levels at the end of treatment but detectable at off-treatment week 12. Null response was defined as persistently on-treatment detectable serum HCV RNA levels

[‡]Ninety-nine patients had available serum for RAS analysis

[§]The ULN of total bilirubin is 1.0 mg/dL. The ULN of ALT is 30 U/L for males and 19 U/L for females

[¶]Assessed by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation

Twenty-nine (27.1%), 43 (40.2%), and 35 (32.7%) patients had a FIB-4 index of < 1.45, 1.45–3.25, and > 3.25. Ninety-nine (92.5%) patients consented to perform RAS analysis at HCV NS3 and NS5A regions, which yielded no RAS in 35 (35.4%), NS3 RAS only in 13 (13.1%), NS5A RAS only in 30 (30.3%), and both NS3 and NS5A RAS in 21 (21.2%) patients. We showed the detailed RASs at NS3 and NS5A loci according to HCV genotype and the most recent failed DAA regimen (Supplementary Table 1). One hundred and six (99.1%) received SOF/VEL/VOX alone for 12 weeks, and the remaining one (0.9%), who was infected with HCV GT1b and had not responded to two courses of DAAs (EBR/GZR, followed by SOF/VEL plus RBV), received SOF/VEL/VOX plus weight-based RBV for 12 weeks. Before the third course of DAA treatment, this patient had a baseline RAS at the NS3 locus V170I, but did not have any

RAS at the NS5A region. Ninety-two (86.0%) had an eGFR of ≥ 60 mL/min/1.73m^2. Five (71.4%) of seven patients with HBV coinfection had undetectable HBV DNA levels, and all seven patients with HIV coinfection had undetectable HIV RNA levels.

Table 2 On-treatment and off-treatment virologic responses

HCV RNA < LLOQ*	Patients ($N = 107$)	
	n/N (%)	95% CI
During treatment		
Week 12	107/107 (100)	96.5–100
After treatment		
SVR_{12} (EP)†	104/107 (97.2)	92.1–99.0
SVR_{12} (PP)‡	104/104 (100)	96.4–100
Reason for failure to achieve SVR_{12}, *n*		
Off-treatment		
Loss to follow-up	3	

LLOQ, lower limit of quantification; *CI*, confidence interval; *SVR*, sustained virologic response

*HCV RNA LLOQ = 15 IU/mL

†Evaluable population (EP) included patients receiving at least one dose of SOF/VEL

‡Per-protocol population (PP) included patients with available SVR_{12} data

Effectiveness

At on-treatment week 12, all patients (95% CI 96.5–100%) had serum HCV RNA level < LLOQ. The SVR_{12} rate was 97.2% (95% CI 92.1–99.1%) in the EP population. Three (2.8%) completed 12 weeks of SOF/VEL/VOX but declined follow-up to assess treatment response at off-treatment week 12. Supplementary Table 2 shows the characteristics of the three patients with non-virologic failures. After excluding these patients with non-virologic failures, the SVR_{12} rate was 100% (95% CI 96.4–100%) in the PP population (Table 2).

Figures 2 and 3 show the stratified SVR_{12} rates in the EP population according to patient demographics and viral/treatment factors. No pre-treatment factors significantly affected the SVR_{12} rates. Most baseline factors had an SVR_{12} rate of > 90%, except for patients with the most recent null response to NS5A inhibitor-containing DAAs (83.3%; 95%

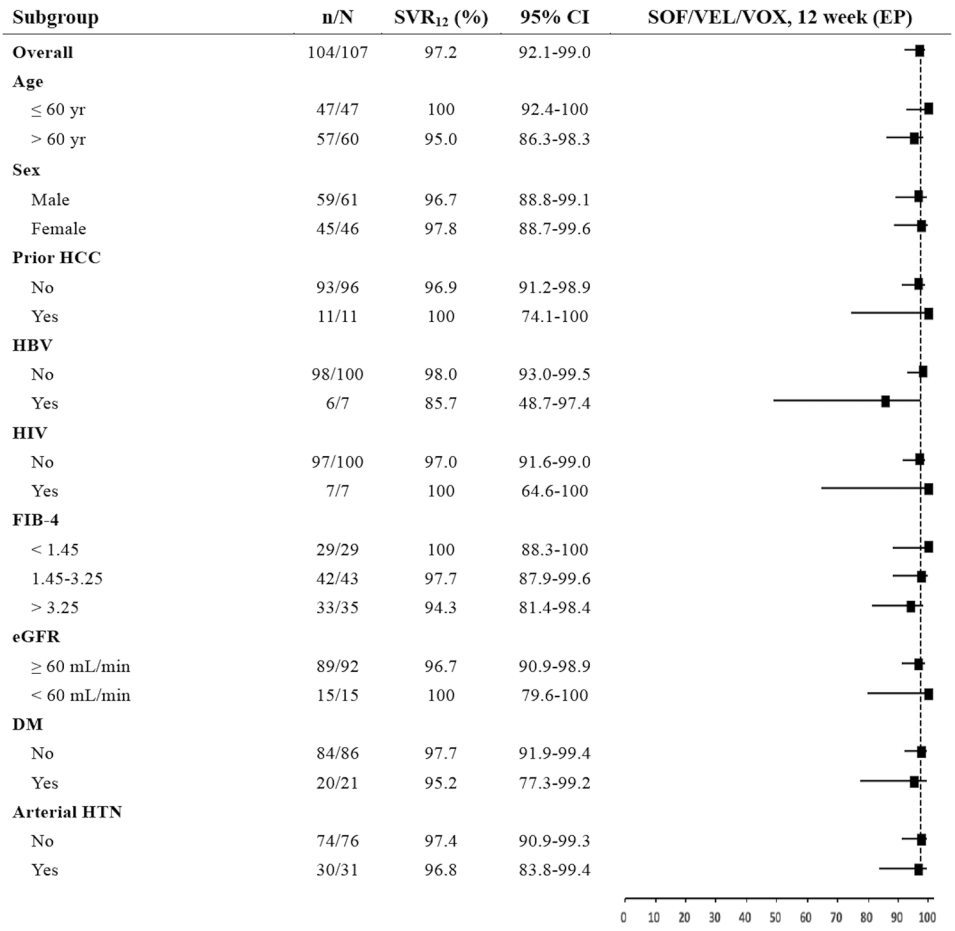

Fig. 2 Sustained virologic response (SVR) rates by evaluable population (EP) analysis according to patient factors. The position of the square indicates the sustained virologic response rate at off-treatment week 12 week (SVR_{12}) in each subgroup; the horizontal lines indicate 95% confidence intervals (*Cis*). The dotted vertical line represents the overall SVR_{12} rate. *SOF*, sofosbuvir; *VEL*, velpatasvir; *VOX*, voxilaprevir; *HCC*, hepatocellular carcinoma; *HBV*, hepatitis B virus; *HIV*, human immunodeficiency virus; *FIV-4*, fibrosis index based on four parameters; *eGFR*, estimated glomerular filtration rate; *DM*, diabetes mellitus; *HTN*, hypertension

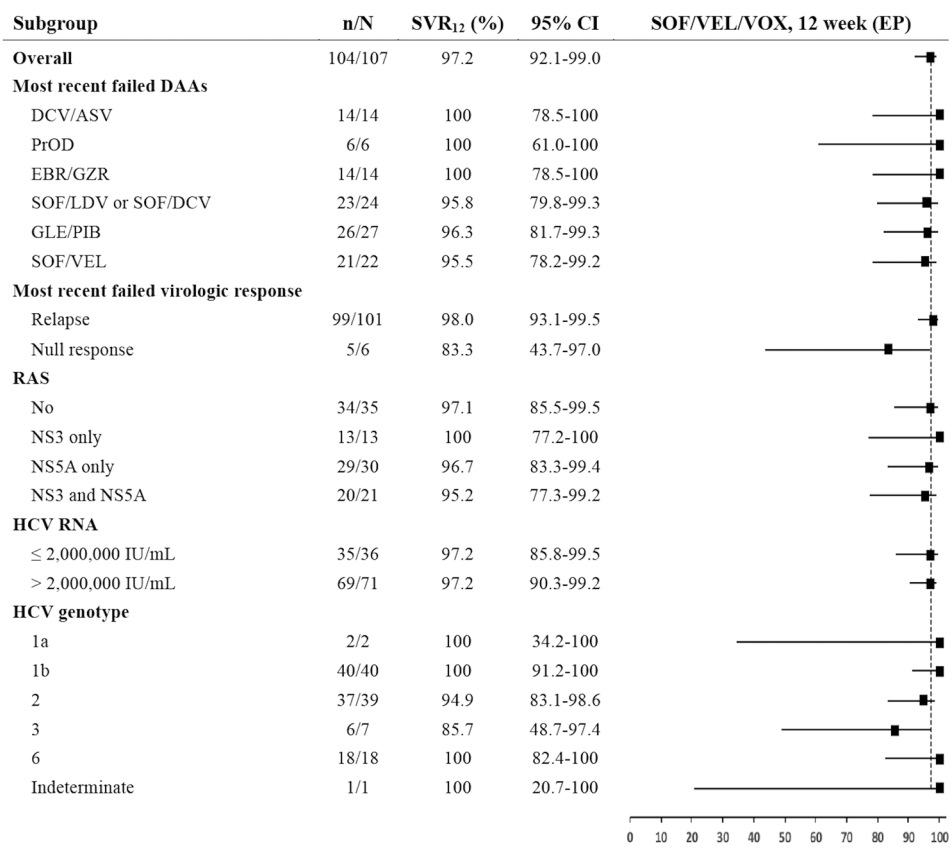

Fig. 3 Sustained virologic response (SVR) rates by evaluable population (EP) analysis according to viral and treatment factors. The position of the square indicates the sustained virologic response rate at off-treatment week 12 week (SVR_{12}) in each subgroup; the horizontal lines indicate 95% confidence intervals (Cis). The dotted vertical line represents the overall SVR_{12} rate. Patients previously treated with SOF/VEL plus RBV were categorized into the subgroup of SOF/VEL. *SOF*, sofosbuvir; *VEL*, velpatasvir; *VOX*, voxilaprevir; *DCV*, daclatasvir; *ASV*, asunaprevir; *PrOD*, paritaprevir/ritonavir/ombitasvir plus dasabuvir; *EBR*, elbasvir; *GZR*, grazoprevir; *LDV*, ledipasvir; *GLE*, glecaprevir; *PIB*, pibrentasvir; *RAS*, resistance-associated substitution; *NS*, non-structural protein; *HCV*, hepatitis C virus; *RNA*, ribonucleic acid

CI 43.7–97.0%), and patients with HCV GT3 infection (85.7%; 95% CI 48.7–97.4%).

Tolerance

Eighteen (16.8%) patients reported having at least one AE. Two (1.9%) had non-fatal serious AEs, but neither was related to SOF/VEL/VOX. None discontinued SOF/VEL/VOX due to treatment-emergent AEs. The constitutional AEs included fatigue in 9 (8.4%), headache in 5 (4.7%), diarrhea in 4 (3.7%), and insomnia in 3 (2.8%) (Table 3). Sixteen (15.0%) patients developed on-treatment grade 2 total bilirubin elevation, but none had ≥ grade 3 total bilirubin elevations. Supplementary Table 2 shows the clinical characteristics of patients with on-treatment grade 2 total bilirubin elevation. Thirteen (81.3%) patients had unconjugated hyperbilirubinemia. The remaining three patients with conjugated hyperbilirubinemia improved at off-treatment week 12. Three (2.8%) had grade 2 ALT elevation, but none had concurrent total bilirubin elevations. One patient had metabolic dysfunction-associated fatty liver disease (MAFLD), and the other two had a drug-induced liver injury (DILI) unrelated to SOF/VEL/VOX. Four (57.1%) of seven patients with HBV coinfection had taken oral nucleot(s)ide analogues (NUCs) before SOF/VEL/VOX, and none developed HBV reactivation or HBV-associated hepatitis. There were no significant changes in eGFR from baseline to off-treatment week 12 (87 versus 88 mL/min/1.73m^2; $p = 0.98$) (Fig. 4A). In addition, the eGFR had no significant changes in patients with a baseline eGFR ≥ 60 mL/min/1.73m^2 (90 versus 91 mL/min/1.73m^2; $p = 0.72$) (Fig. 4B), and a baseline eGFR < 60 mL/min/1.73m^2 (52 versus 50 mL/min/1.73m^2; $p = 0.28$) (Fig. 4C).

Discussion

Although the first-line DAA treatment is highly effective with an overall SVR_{12} rate of > 95%, a minority of patients with HCV are not responsive to such treatment, mandating the need for salvage therapy to manage these patients in whom multiple RASs may emerge. Our results revealed that the SVR_{12} rates were 97.2% and 100% in the EP and PP populations, comparable to the Western studies and meta-analyses reporting the SVR_{12} rates of 90% to 100% [21–29, 39]. Our results corroborated the SOF/VEL/VOX's excellent effectiveness in managing patients previously treated with NS5A inhibitors, regardless of ethnicity [30, 31].

Our study revealed that no specific patient, viral, or treatment factors predicted treatment responses. Although 65% of our patients had baseline RASs at various NS3 and NS5A loci, none developed virologic failures after

Table 3. Safety summary

Event, *n* (%)	Patients (*N* = 107)
Any AE	18 (16.8)
Discontinuation due to treatment-emergent AE	0 (0)
Serious AE *	2 (1.9)
Death	0 (0)
DAA-related serious AE or death	0 (0)
Constitutional AE	
Fatigue	9 (8.4)
Headache	5 (4.7)
Diarrhea	4 (3.7)
Insomnia	3 (2.8)
Laboratory abnormalities	
Total bilirubin	
Grade 2 (1.5-3.0 x ULN) †	16 (15.0)
Grade 3 (> 3.0 x ULN)	0 (0)
ALT	
Grade 2 (3.0-5.0 x ULN)‡	3 (2.8)
Grade 3 (> 5.0 x ULN)	0 (0)

AE, adverse event; *DAA*, direct-acting antiviral; *ULN*; upper limit of normal; *ALT*, alanine aminotransferase

*Humerus fracture at on-treatment week 12 (n = 1), and recurrent HCC at off-therapy week 12 (n = 1)

†Thirteen (81.3%) patients had unconjugated hyperbilirubinemia. All had on-treatment ALT levels of < 3 *x* ULN. None developed hepatic decompensation. Eight (50%) had baseline total bilirubin levels of ≥ 1.5 x ULN

‡One patient had metabolic-dysfunction-associated fatty liver disease (MAFLD). The baseline, on-treatment week 4, on-treatment week 12, and off-therapy week 12 ALT levels were 115, 88, 85, and 110 U/L, respectively. The other two patients had a drug-induced liver injury (DILI), and all had normalized ALT levels after discontinuing the offending drugs. None developed ≥ grade 2 total bilirubin level elevations

SOF/VEL/VOX, implying the combination of potent HCV NS3, NS5A, and NS5B agents can overcome complicated RAS profiles. However, HCV GT3 infection and previous null-response tended to have numerically lower response rates [36, 40–42]. Although some real-world studies indicated that patients with HCV GT3 infection, cirrhosis, previous SOF/VEL treatment, and multiple RASs might adversely affect the SVR_{12} rate, the POLARIS-1 trial and the other real-world studies, including ours, did not show such association [21–29, 42]. Onofrio et al. indicated that the SVR_{12} rate of SOF/VEL/VOX might be lower if patients presented at least two unfavorable factors, such as HCV GT3 infection, cirrhosis, multiple RASs, previous SOF/VEL treatment, and liver transplantation [26]. Because of unfavorable factors, the Italian and Canadian real-world studies reported that about 20% of patients received RBV in combination with SOF/VEL/VOX based on physicians' discretion. However, patients with combination therapy did not confer a better SVR_{12} rate than those with SOF/VEL/VOX alone [24, 26]. While the EASL guidelines recommend SOF/VEL/VOX plus RBV for "difficult-to-cure" patients to intensify the retreatment responses, the AASLD guidelines do not endorse the universal combination except for cirrhotic patients with HCV GT3 infection [18, 19]. Because the coadministration of RBV remains controversial for NS5A inhibitor-experienced patients, we herein propose to use SOF/VEL/VOX alone for 12 weeks to manage such patients based on the current label recommendation.

In line with the POLARIS-1 trial and real-world studies, we demonstrated that the tolerance of SOF/VEL/VOX was excellent, with the reported rates of AEs and serious AE of only 16.8% and 2.9%. There were no deaths or early SOF/VEL/VOX discontinuations due to AEs. Regarding

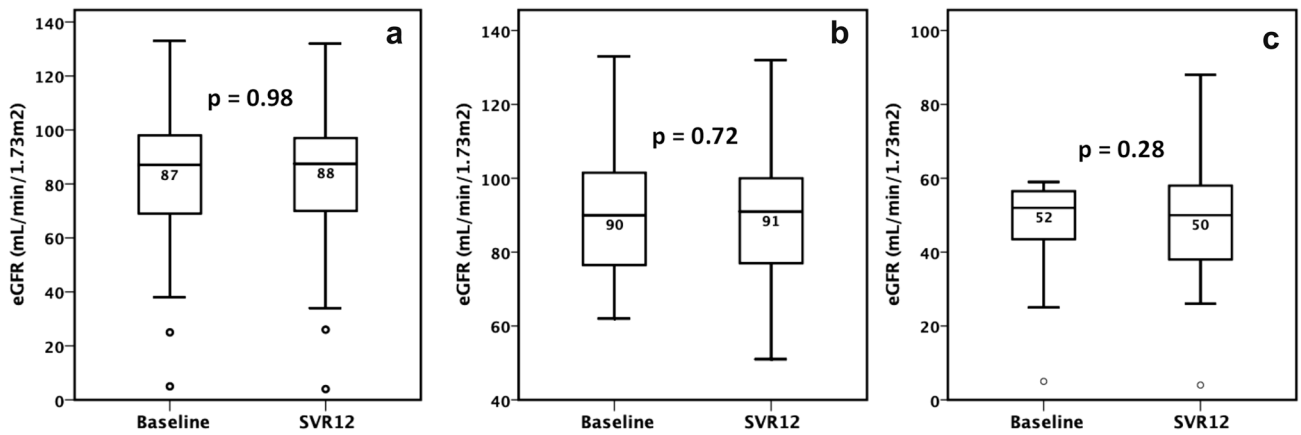

Fig. 4 Box plots of estimated glomerular filtration rate (eGFR) at baseline and at SVR12. **A** overall population, **B** patients with a baseline eGFR ≥ 60 mL/min/1.73m^2, and **C** patients with a baseline eGFR < 60 mL/min/1.73 m.^{2} The tops and bottoms of the boxes are the first and the third quartiles. The tops and bottoms of the horizontal lines are the upper and lower whiskers. The circles denote mild outliers. The changes of eGFR between baseline and SVR_{12} with Wilcoxon signed-rank tests were **A** p = 0.98, **B**, p = 0.72, and **C** p = 0.28, respectively

liver safety, none developed ≥ grade 3 total bilirubin elevations, ≥ grade 3 ALT elevations, or hepatic decompensation. Although 16 (15.0%) patients developed on-treatment grade 2 total bilirubin elevation, 81.3% of them had unconjugated hyperbilirubinemia, which was attributed to the use of VEL and VOX that inhibited the organic anion transporter protein (OATB) 1B1 and OATB1B3 [43, 44]. Among the 3 (2.8%) patients with on-treatment grade 2 ALT elevation, one had MAFLD, and the other two had DILI not related to SOF/VEL/VOX. Regarding renal safety, we demonstrated that the eGFR remained stable in patients receiving SOF/VEL/VOX regardless of baseline renal reserve [15, 45]. Furthermore, the APASL guidelines recommend the safe use of SOF-based DAAs without compromising efficacy in patients with renal impairment [46]. In patients with HBV coinfection, there was no HBV reactivation or HBV-related hepatitis during SOF/VEL/VOX. However, periodic surveillance of ALT and HBV DNA levels is needed to detect HBV reactivation/clinical hepatitis early and initiate NUC promptly [38]. Because more than half of our patients were aged more than 50 and may take comedications for comorbidities, careful DDI checks before SOF/VEL/VOX treatment are vital to secure on-treatment safety.

While a large proportion of patients with chronic HCV infection reside in Asian-Pacific regions, our study provides encouraging results of SOF/VEL/VOX as an excellent rescue regimen if patients fail to respond to the first-line NS5A-containing DAA regimens. By mass screening, efficient link-to-care, scale-up treatment uptake, and implementation of salvage treatment, most Asian-Pacific patients can speed up the cure to meet the WHO's HCV elimination goal by 2030.

The strengths of this study include the multicenter prospective cohort that recruited a sizable number of East Asian HCV patients previously treated with NS5A inhibitors and the clearly defined clinical as well as laboratory assessments to ensure outcome estimation. However, our study has several limitations. First, the number of patients with HCV GT3 infection, particularly those with cirrhosis, was relatively small. Therefore, we cannot assess the effects of these unfavorable factors on the effectiveness of SOF/VEL/VOX. Second, although several studies reported that SOF/VEL/VOX could be used in patients with Child–Pugh B or C cirrhosis, our study did not include patients with decompensated cirrhosis because SOF/VEL/VOX is not recommended for patients with decompensated cirrhosis [23, 27, 31, 47].

In conclusion, our multicenter, prospective, real-world study demonstrates that SOF/VEL/VOX for 12 weeks is highly efficacious and well-tolerated for East Asian HCV patients with compensated liver diseases previously treated with NS5A inhibitor-containing DAAs.

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Data availability All data collection was approved by the Research Ethics Committee of each participating center.

Declarations

Conflicts of interest Chen-Hua Liu: advisory board for Abbvie, Gilead Sciences, Merck Sharp & Dohme; speaker's bureau for Abbott, Abbvie, Gilead Sciences, Merck Sharp & Dohme; research grant from Abbvie, Gilead Science, Merck Sharp & Dohme. Sheng-Shun Yang: advisory board for Abbvie, Roche, Ipsen; speaker's bureau for Abbvie, Bristol-Myers Squibb, Gilead Sciences, Ipsen, Merck Sharp & Dohme. Jia- Horng Kao: advisory board for Abbott, Abbvie, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Roche; speaker's bureau for Abbott, Abbvie, Bayer, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Merck Sharp & Dohme, Novartis, Roche. All other authors declare no competing interests.

Animal research This study was not an animal research.

Ethical approval The study was approved by the Research Ethics Committee of each participating center (ID: 202109016RIND) and was conducted in accordance with the principles of the Declaration of Helsinki in 1975.

Consent to participate Each participant consented to this work and provided informed consent.

Consent to publish All the authors consented the publish the work.

References

1. Polaris Observatory HCV Collaborators. Global change in hepatitis C virus prevalence and cascade of care between 2015 and 2020: a modelling study. Lancet Gastroenterol Hepatol. 2022;7:396–415
2. Lauer GM, Walker BD. Hepatitis C virus infection. N Engl J Med. 2001;345:41–52
3. Liu CH, Kao JH. Nanomedicines in the treatment of hepatitis C virus infection in Asian patients: optimizing use of peginterferon alfa. Int J Nanomedicine. 2014;9:2051–2067

4. Feld JJ, Kowdley KV, Coakley E, Sigal S, Nelson DR, Crawford D, et al. Treatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370:1594–1603
5. Zeuzem S, Ghalib R, Reddy KR, Pockros PJ, Ben Ari Z, Zhao Y, et al. Grazoprevir-elbasvir combination therapy for treatment-naive cirrhotic and noncirrhotic patients with chronic hepatitis C virus genotype 1, 4, or 6 infection: a randomized trial. Ann Intern Med. 2015;163:1–13
6. Afdhal N, Zeuzem S, Kwo P, Chojkier M, Gitlin N, Puoti M, et al; ION-1 Investigators. Ledipasvir and sofosbuvir for untreated HCV genotype 1 infection. N Engl J Med. 2014;370:1889–98.
7. Feld JJ, Jacobson IM, Hézode C, Asselah T, Ruane PJ, Gruener N, et al; ASTRAL-1 Investigators. Sofosbuvir and velpatasvir for HCV genotype 1, 2, 4, 5, and 6 infection. N Engl J Med. 2015;373:2599–607.
8. Zeuzem S, Foster GR, Wang S, Asatryan A, Gane E, Feld JJ, et al. Glecaprevir-pibrentasvir for 8 or 12 weeks in HCV genotype 1 or 3 infection. N Engl J Med. 2018;378:354–369
9. Ioannou GN, Beste LA, Chang MF, Green PK, Lowy E, Tsui JI, et al. Effectiveness of sofosbuvir, ledipasvir/sofosbuvir, or paritaprevir/ritonavir/ombitasvir and dasabuvir regimens for treatment of patients with hepatitis C in the Veterans Affairs National Health Care System. Gastroenterology. 2016;151:457–71.e5
10. Liu CH, Liu CJ, Su TH, Yang HC, Hong CM, Tseng TC, et al. Real-world effectiveness and safety of paritaprevir/ritonavir, ombitasvir, and dasabuvir with or without ribavirin for patients with chronic hepatitis C virus genotype 1b infection in Taiwan. J Gastroenterol Hepatol. 2018;33:710–717
11. Liu CH, Liu CJ, Su TH, Yang HC, Hong CM, Tseng TC, et al. Real-world effectiveness and safety of sofosbuvir and ledipasvir with or without ribavirin for patients with hepatitis C virus genotype 1 infection in Taiwan. PLoS ONE. 2018;13: e0209299
12. Lampertico P, Carrión JA, Curry M, Turnes J, Cornberg M, Negro F, et al. Real-world effectiveness and safety of glecaprevir/pibrentasvir for the treatment of patients with chronic HCV infection: a meta-analysis. J Hepatol. 2020;72:1112–1121
13. Liu CH, Liu CJ, Hung CC, Hsieh SM, Su TH, Sun HY, et al. Glecaprevir/pibrentasvir for patients with chronic hepatitis C virus infection: real-world effectiveness and safety in Taiwan. Liver Int. 2020;40:758–768
14. Mangia A, Milligan S, Khalili M, Fagiuoli S, Shafran SD, Carrat F, et al. Global real-world evidence of sofosbuvir/velpatasvir as simple, effective HCV treatment: analysis of 5552 patients from 12 cohorts. Liver Int. 2020;40:1841–1852
15. Liu CH, Chen PY, Chen JJ, Lo CC, Su WW, Tseng KC, et al. Sofosbuvir/velpatasvir for patients with chronic hepatitis C virus infection and compensated liver disease: real-world data in Taiwan. Hepatol Int. 2021;15:338–349
16. Benítez-Gutiérrez L, Barreiro P, Labarga P, de Mendoza C, Fernandez-Montero JV, Arias A, et al. Prevention and management of treatment failure to new oral hepatitis C drugs. Expert Opin Pharmacother. 2016;17:1215–1223
17. Heo YA, Deeks ED. Sofosbuvir/velpatasvir/voxilaprevir: a review in chronic hepatitis C. Drugs. 2018;78:577–587
18. AASLD-IDSA HCV Guidance Panel. Hepatitis C Guidance 2018 Update: AASLD-IDSA recommendations for testing, managing, and treating hepatitis C virus infection. Clin Infect Dis. 2018;67:1477–1492
19. European Association for the Study of the Liver. EASL recommendations on treatment of hepatitis C: final update of the series. J Hepatol. 2020;73:1170–1218
20. Omata M, Kanda T, Wei L, Yu ML, Chuang WL, Ibrahim A, et al. APASL consensus statements and recommendation on treatment of hepatitis C. Hepatol Int. 2016;10:702–726
21. Bourlière M, Gordon SC, Flamm SL, Cooper CL, Ramji A, Tong M, et al; POLARIS-1 and POLARIS-4 Investigators. Sofosbuvir, velpatasvir, and voxilaprevir for previously treated HCV infection. N Engl J Med. 2017;376:2134–46.
22. Bourlière M, Gordon SC, Schiff ER, Tran TT, Ravendhran N, Landis CS, et al. Deferred treatment with sofosbuvir-velpatasvir-voxilaprevir for patients with chronic hepatitis C virus who were previously treated with an NS5A inhibitor: an open-label substudy of POLARIS-1. Lancet Gastroenterol Hepatol. 2018;3:559–565
23. Llaneras J, Riveiro-Barciela M, Lens S, Diago M, Cachero A, García-Samaniego J, et al. Effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in patients with chronic hepatitis C previously treated with DAAs. J Hepatol. 2019;71:666–672
24. Degasperi E, Spinetti A, Lombardi A, Landonio S, Rossi MC, Pasulo L, et al; NAVIGATORE-Lombardia and Veneto Study Groups. Real-life effectiveness and safety of sofosbuvir/velpatasvir/voxilaprevir in hepatitis C patients with previous DAA failure. J Hepatol. 2019;71:1106–15.
25. Belperio PS, Shahoumian TA, Loomis TP, Backus LI. Real-world effectiveness of sofosbuvir/velpatasvir/voxilaprevir in 573 direct-acting antiviral experienced hepatitis C patients. J Viral Hepat. 2019;26:980–990
26. Onofrio FQ, Cooper C, Borgia SM, Vachon ML, Ramji A, Lilly LB, et al. Salvage therapy with sofosbuvir/velpatasvir/voxilaprevir in DAA-experienced patients: results from a prospective Canadian registry. Clin Infect Dis. 2021;72:e799-805
27. Papaluca T, Roberts SK, Strasser SI, Stuart KA, Farrell G, MacQuillan G, et al. Efficacy and safety of sofosbuvir/velpatasvir/voxilaprevir for hepatitis C virus (HCV) NS5A-inhibitor experienced patients with difficult to cure characteristics. Clin Infect Dis. 2021;73:e3288–e3295
28. Da BL, Lourdusamy V, Kushner T, Dieterich D, Saberi B. Efficacy of sofosbuvir/velpatasvir/voxilaprevir in direct-acting antiviral experienced patients with hepatitis C virus. Eur J Gastroenterol Hepatol. 2021;33:859–861
29. Carson JM, Hajarizadeh B, Hanson J, O'Beirne J, Iser D, Read P, et al; REACH-C Study Group. Retreatment for hepatitis C virus direct acting antiviral therapy virological failure in primary and tertiary settings: the REACH-C cohort. J Viral Hepat. 2022;29:661–7.
30. Liu CH, Su TH, Liu CJ, Chen PJ, Chen DS, Kao JH. Sofosbuvir/velpatasvir/voxilaprevir plus ribavirin for chronic hepatitis C patients with direct acting antiviral failures: implications for viral elimination in Taiwan. J Formos Med Assoc. 2020;119:1871–1875
31. Wong YJ, Kumar R, Kumar R, Tan J, Liu CH, Hui VK, et al. Treatment outcomes of sofosbuvir/velpatasvir/voxilaprevir among NS5A inhibitor-experienced patients with hepatitis C: real-world data from a multicenter Asian registry. J Gastroenterol Hepatol. 2022;37:1642–1644
32. Liu CH, Liang CC, Liu CJ, Lin CL, Su TH, Yang HC, et al. Comparison of Abbott RealTime HCV Genotype II with Versant Line Probe Assay 2.0 for hepatitis C virus genotyping. J Clin Microbiol. 2015;53:1754–1757
33. Prati D, Taioli E, Zanella A, Della Torre E, Butelli S, Del Vecchio E, et al. Updated definitions of healthy ranges for serum alanine aminotransferase levels. Ann Intern Med. 2002;137:1–10
34. Liu CH, Lin JW, Liu CJ, Su TH, Wu JH, Tseng TC, et al. Long-term evolution of estimated glomerular filtration rate in patients with antiviral treatment for hepatitis C virus infection. Clin Gastroenterol Hepatol 2022. https://doi.org/10.1016/j.cgh.2022.01.050. Epub ahead of print. PMID: 35131346.
35. Sterling RK, Lissen E, Clumeck N, Sola R, Correa MC, Montaner J, et al; APRICOT Clinical Investigators. Development of a simple noninvasive index to predict significant fibrosis in patients with HIV/HCV coinfection. Hepatology 2006;43:1317–25.
36. Sarrazin C, Cooper CL, Manns MP, Reddy KR, Kowdley KV, Roberts SK, et al. No impact of resistance-associated substitutions

on the efficacy of sofosbuvir, velpatasvir, and voxilaprevir for 12 weeks in HCV DAA-experienced patients. J Hepatol. 2018;69:1221–1230
37. Liu CH, Yu ML, Peng CY, Hsieh TY, Huang YH, Su WW, et al. Comorbidities, concomitant medications and potential drug-drug interactions with interferon-free direct-acting antiviral agents in hepatitis C patients in Taiwan. Aliment Pharmacol Ther. 2018;48:1290–1300
38. Liu CH, Liu CJ, Su TH, Fang YJ, Yang HC, Chen PJ, et al. Hepatitis B virus reactivation in patients receiving interferon-free direct-acting antiviral agents for chronic hepatitis C virus infection. Open Forum Infect Dis. 2017;4:ofx028.
39. Xie J, Xu B, Wei L, Huang C, Liu W. Effectiveness and Safety of Sofosbuvir/velpatasvir/voxilaprevir as a hepatitis C virus infection salvage therapy in the real world: a systematic review and meta-analysis. Infect Dis Ther. 2022;11:1661–1682
40. Wilson E, Covert E, Hoffmann J, Comstock E, Emmanuel B, Tang L, et al. A pilot study of safety and efficacy of HCV retreatment with sofosbuvir/velpatasvir/voxilaprevir in patients with or without HIV (RESOLVE STUDY). J Hepatol. 2019;71:498–504
41. Pearlman B, Perrys M, Hinds A. Sofosbuvir/velpatasvir/voxilaprevir for previous treatment failures with glecaprevir/pibrentasvir in chronic hepatitis C infection. Am J Gastroenterol. 2019;114:1550–1552
42. Ruane P, Strasser SI, Gane EJ, Hyland RH, Shao J, Dvory-Sobol H, et al. Sofosbuvir/velpatasvir/voxilaprevir for patients with HCV who previously received a sofosbuvir/velpatasvir-containing regimen: results from a retreatment study. J Viral Hepat. 2019;26:770–773
43. Kalliokoski A, Niemi M. Impact of OATP transporters on pharmacokinetics. Br J Pharmacol. 2009;158:693–705
44. Ing Lorenzini K, Girardin F. Direct-acting antiviral interactions with opioids, alcohol or illicit drugs of abuse in HCV-infected patients. Liver Int. 2020;40:32–44
45. Liu CH, Lee MH, Lin JW, Liu CJ, Su TH, Tseng TC, et al. Evolution of eGFR in chronic HCV patients receiving sofosbuvir-based or sofosbuvir-free direct-acting antivirals. J Hepatol. 2020;72:839–846
46. Kanda T, Lau GKK, Wei L, Moriyama M, Yu ML, Chuang WL, et al. APASL clinical practice recommendation: how to treat HCV-infected patients with renal impairment? Hepatol Int. 2019;13:103–109
47. Patel S, Martin MT, Flamm SL. Sofosbuvir/velpatasvir/voxilaprevir for hepatitis C virus retreatment in decompensated cirrhosis. Liver Int. 2021;41:3024–3027

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