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Cost-Utility of Sofosbuvir/Velpatasvir for Chronic Hepatitis C Genotype 1b Infection in China

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Abstract

Objective This study aimed to estimate the cost-utility of sofosbuvir/velpatasvir (SOF/VEL) compared with other direct-acting antivirals (DAAs) in Chinese HCV patients.

Methods A state-transition Markov model was developed to estimate the disease progression of HCV genotype 1b patients over a lifetime horizon. From the health care system perspective, the model measured the lifetime costs, quality-adjusted life years (QALYs) and incremental cost-utility ratio (ICURs) of SOF/VEL versus sofosbuvir + ribavirin (SR), sofosbuvir + dasabuvir (SD), daclatasvir + asunaprevir (DCV/ASV), ombitasvir/paritaprevir/ritonavir + dasabuvir (3D), and elbasvir/grazoprevir (EBR/GZR). SVR rates, clinical inputs and utilities were derived from published literature. The medical costs consisted of drug costs and health costs for Markov health states. Drug costs were from the market price survey, and health costs for Markov health states were sourced from a Chinese study. Costs and utilities were discounted at an annual rate of 5%. One-way and probabilistic sensitivity analyses were conducted to test the impact of input parameters on the results.

Results SOF/VEL was economically dominant over SR and SD. However, 3D was economically dominant versus SOF/VEL. Compared to DCV/ASV, SOF/VEL was cost-effective with the ICUR of

$1522 per QALY. Compared to EBR/GZR, it was not cost-effective with the ICUR of $369,627 per QALY. One-way sensitivity analysis demonstrated that reducing the cost of SOF/VEL to the lower value of confidence interval, resulted in dominance over EBR/GZR and 3D. Probabilistic sensitivity analysis demonstrated that 3D was cost-effective in 100% of iterations in GT1b patients and SOF/VEL was not cost-effective.

Conclusions Compared with other oral direct-acting antiviral agents, SOF/VEL treatment was not the most cost-effectiveness option for patients with chronic HCV GT1b in China. Lower the price of SOF/VEL will make it cost-effective while simplifying treatment and achieving the goal of HCV elimination.

Strengths and limitations of this study

To our knowledge, this is the first study including all available all-oral DAAs for the treatment of HCV 1b patients and comparing the cost-effectiveness of SOF/VEL with all other DAAs in the Chinese setting.

The findings have direct relevance to policy decision makers considering the health policy to incorporate DAAs into the healthcare system.

Some of the parameters were retrieved from published literature due to the absence of the real-world data in China, which may result in some bias on our results.

Only the HCV genotype 1b was considered in this study, other genotypes were not included, which may restrict the generalibility of findings in this study.

Introduction

Chronic hepatitis C (CHC) is a major public health problem worldwide. It is estimated that there are around 71 million individuals chronically infected with HCV, leading to approximately 399,000 deaths each year.[1, 2] In China, the number of HCV-infected patients was estimated to be approximate 10 million in 2006, and the most prevalent genotype is HCV genotype (GT) 1b.[3, 4] The Chinese Center for Disease Control and Prevention reported that the incidence was showing an increasing trend, with an estimated 200,000 new cases annually from 2014 to 2018. The undiagnosed and untreated chronic HCV-infected patients are likely to develop serious liver-related complications such as decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC), leading to substantial clinical and economic burden.[5, 6]

The endpoint of treating HCV infection is achieving sustained virologic response (SVR), which can significantly reduce the risk of liver disease progression and avoid conversion to end-stage liver diseases.[7] Patients achieving SVR are associated with lower costs and improved quality of life.[8] Therefore, the treatment of HCV and achievement of SVR are of critical significance in reducing the health and economic burdens among CHC patients.

For decades, the standard of care for HCV-infected patients in china has been based on pegylated interferon plus ribavirin (PR) therapy, which is associated with low efficacy, long treatment durations, poor tolerability and much adverse event rates, especially in cirrhotic patients.[9] The introduction of direct-acting antivirals (DAAs), with improved SVR and fewer side effects, has revolutionized HCV treatment. The latest Chinese guideline has suggested that DAA regimens should be applied if patients could afford medical expenses.[9] In recent years, a range of drugs have been approved for HCV treatment by the Chinese State Food and Drug Administration (CFDA). These all-oral regimens for HCV-infected patients, including sofosbuvir plus ribavirin (SR), sofosbuvir plus daclatasvir (SD), daclatasvir plus asunaprevir (DCV/ASV), ombitasvir/paritaprevir/ritonavir plus dasabuvir (3D), elbasvir/grazoprevir (EBR/GZR), and sofosbuvir/velpatasvir (SOF/VEL), have been currently available in China. All these interferon-free regimens resulted in higher efficacy and shorter duration, compared with interferon-based regimens.[10,11] Specially, SOF/VEL was listed in the National Essential Medicines List of China as the only full-oral, direct anti-HCV drug in 2018. Unlike other DAAs, SOF/VEL is a pan-genotypic drug, which is the first fixed-dosage regimen able to achieve high rates of SVR, after only 12 weeks of treatment across all genotypes, all fibrosis scores and typologies of patients.[12]

At the present, it is not clear whether SOF/VEL is cost-effective in Chinese HCV GT1b patients. Therefore, the objective of this study was to estimate the cost-effectiveness of SOF/VEL compared with other available DAA regimens for treatment of hepatitis HCV GT1b patients.

Methods

We used a state-transition Markov model to estimate the economic benefits of SOF/VEL regimen in Chinese patients with HCV GT1b, from the health care system perspective. The model simulated the disease progression of HCV patients who received treatment with SOF/VEL or comparators. The model used an annual cycle length and a lifetime horizon. A discount rate of 5% was used for costs and

utilities in this model.

Patients characteristics

The base-case population in the model represented treatment-naive patients infected with HCV GT1b, the major genotype in China. According to a Chinese study, the mean age of Chinese HCV-infected patients were 44.5 years,[4] so it was assumed that the patients entered the model at the age of 45 years old in this study. The baseline distribution was defined by the METAVIR fibrosis stages: no fibrosis (F0), portal fibrosis with no septa (F1), portal fibrosis with few septa (F2), numerous septa without cirrhosis (F3), and compensated cirrhosis (F4).[13] Based on another Chinese investigation,[14] the fibrosis distribution was as follows: F0 (0.8%), F1 (45.5%), F2 (41.3%), F3 (9.9%), and F4 (2.5%), respectively. Co-infection with HBV or HIV was not included. Due to the small proportion of treatment-experienced patients, only the treatment-naïve patients were considered.

Model structure and assumptions

The structure of the model was based on other models of HCV disease which have been published and validated in health economic analyses.[15-17] The model consisted of 14 health states (Fig.1). Fibrosis stage was defined by the METAVIR fibrosis scoring system and it was assumed that patients enter the model with a given fibrosis score: F0, F1, F2, F3, F4. Patients may develop the more serious liver fibrosis, advanced liver disease (i.e., DC, HCC, LT), or may keep that health state. If patients achieved SVR after the successful treatment, the disease progression was to halt. However, it allowed for the transitions from SVR to DC or HCC for patients with cirrhosis (F4) at a lower rate. Patients at the stage of compensated cirrhosis (F4) were at risk of developing DC or HCC. If a patient developed DC and/or HCC, then the patient may receive a liver transplant. Patients with advance liver disease had higher mortality rates than other patients. All the other patients had the same mortality rate as the general population.

It was assumed that there was no disease progression during treatment. Only cirrhotic patients (F4) could progress to DC and HCC and it still had risk of DC and HCC even if they achieved SVR. Adverse events were not considered due to the minimal rates in these interferon-free regimens.

Model comparators and clinical inputs

DCV+ASV, SOF/VEL, EBR/GZR, 3D and SOF-based regimens (SR: the combination of sofosbuvir and RBV; SD: the combination of sofosbuvir and dasabuvir) are all recommended for chronic GT1b

infection in the Chinese setting. The duration of DCV+ASV and SR are 24 weeks, and for the other three regimens are 12 weeks. The treatment effectiveness was defined as SVR. The SVRs of DCV+ASV, SOF/VEL, EBR/GZR, 3D were derived from international multicenter clinical trials.[18-22] The SVR of SD was derived from a systematic review.[23] The SVR of SR was obtained from a clinical trial in the Chinese setting.[24] The clinical inputs are shown in Table 1.

Transition probabilities

The transition probabilities are shown in Table 1. The rates of fibrosis progression between F0 to F4 were derived from a meta-analysis.[25] The probability from F4 to DC and HCC and from DC to HCC were estimated from published literature.[26,27] Patients achieving SVR were assumed to develop DC or HCC at a lower rate according to a prospective study.[28] The probabilities of liver transplantation of DC or HCC were obtained from published studies, in which the proportion of liver transplantation was derived from a previous study and was adjusted based on the donation rate ratio between Chinese (0.6 per million) and individuals of Western countries (34.4 per million).[29] The mortality rates associated with DC, HCC, liver transplantation in first year and liver transplantation in subsequent years, which were higher than general mortality, were sourced from the published literature.[28,30] Age-specific all-cause mortality rates were obtained from the life tables of the World Health Organization (WHO) member states.

Direct medical costs

The Chinese healthcare perspective was adopted in this study. All costs were inflated to 2019 using the China Consumer Price Index and converted to US dollars using official exchange rates as of 2019 (1 USD=6.90 CNY). The medical costs consisted of drug costs and liver-related health state costs (Table 1). Drug costs were based on local charges without discounts as the DAAs have not been reimbursed in social health insurance system of China. The annual costs of F0-F4, DC, HCC were derived from a survey of HCV-infected patients in China, which included costs of liver-related care (e.g., laboratory tests, procedures, medications, and hospitalizations).[31] The annual costs associated with liver transplant and post-liver transplant were obtained from a study in the context of China.[32] Patients after SVR were assumed to incur no medical costs. Future costs were discounted at 5% per year.

Health utilities

Utility weights for each health state of liver disease were mainly obtained from a published systematic

review.[33] The quality of life (QOL) of patients with SVR was based on a published study.[34] Disutility was not considered during the therapy. The utilities are shown in table 1.

Model analysis

Costs and quality-adjusted life years (QALYs) were discounted at 5% per year. Incremental cost-utility ratios (ICURs) were reported to show cost-utility of SOF/VEL regimen relative to the comparator. We calculated ICURs by dividing the incremental costs by the incremental QALYs for the SOF/VEL regimen compared each of the comparators. In cases in which the SOF/VEL regimen was less costly and more effective than a comparator, it was concluded to be economically dominant. In other cases, ICURs were reported. US28,106/QALY, the three times Chinese gross domestic product (GDP) per capita, was used to be the willingness to pay threshold. In cases the ICUR of SOF/VEL was lower than US28,106/QALY, it was regarded as cost-effective. Otherwise, it was not cost-effective.

Sensitivity analysis

One-way sensitivity analyses were conducted to test the effect of varying input parameters on the ICUR of SOF/VEL treatment regimen compared to the comparator. The efficacy, costs, progression rates, utilities, and discount rates were tested under the ranges defined in the inputs tables (Table 1). The 95% confidence interval (CI) of each parameter was used to be the varying range; in case the 95% CI was not available, the 25% of parameter would be used. In addition, discount rate varied ranging from 3% to 5%. The results were presented by tornado diagrams.

A probabilistic sensitivity analysis (PSA) was conducted in which all the input parameters were varied simultaneously. Inputs were sampled from predefined distributions with 1000 iterations (Table 1). The key parameters of each specific distribution were calculated from the mean and standard error. Beta distribution was applied to transition probabilities and utilities. Gamma distribution was applied to costs. Uniform distribution was applied in which the parameters were not available. Results of the PSA were presented using cost-effectiveness acceptability curves, which reflect the probability that the regimens will be cost effective at various willingness-to-pay thresholds.

Results

Base-case analysis

Results of the base-case are presented in Table 2. Compared with SD and SR, SOF/VEL was dominant with higher effectiveness and lower cost. The ICURs of SOF/VEL versus DCV/ASV was $1522,

which was lower than the threshold of $28,106 per QALY. The ICURs of SOF/VEL versus EBR/GZR was $369,627, which exceeded the threshold. Compared with 3D, SOF/VEL was dominated with higher costs and fewer QALYs. All in all, 3D is the most effective strategy in GT1b HCV patients, followed by the EBR/GZR, SOF/VEL strategies.

The treatment costs among regimens ranged from $9,792 to $19,118 (difference $9,326) and QALYs ranged from 13.2262 to 13.4435 (difference 0.2173). Costs were lowest for 3D and highest for SR; QALYs were highest for 3D and lowest for DCV/ASV. Compared with sofosbuvir-based regimens (SR and SD), the second-generation DAAs (3D, EBR/GZR, SOF/VEL, DCV/ASV) resulted in fewer costs and more QALYs.

Deterministic sensitivity analysis

The 10 input parameters, to which ICURs were most sensitive, were presented in tornado diagrams (Fig. 2). ICURs were most sensitive to SVR rates and drug costs. However, only the cost of drugs can lead to changes of results. Reducing the cost of SOF/VEL to the lower bound of confidence interval, $8701, resulted in dominance over EBR/GZR. SOF/VEL was dominated by 3D in the base-analysis, but reducing the cost of SOF/VEL to the lower value of confidence interval of $7945, resulted in SOF/VEL dominating the comparator of 3D. However, compared to DCV/ASV and SR, SOF/VEL was cost-effective no matter what parameter changes within the given range were.

Probabilistic sensitivity analysis

The result of probability sensitivity analysis was consistent with the base-case results. The cost-effectiveness acceptability curve showed that, 3D was to be cost-effective in 100% of the 1000 PSA iterations run, at a willingness-to-pay threshold up to $28,106 per QALY (Fig.3). The probabilities that SOF/VEL and other DAA regimens would be cost-effective were 0%.

Discussion

This study evaluated the cost-utility of all DAAs used among GT1b HCV patients in China. The base-case results showed that SOF/VEL was economically dominant relative to SR and SD. Compared with DCV/ASV, SOF/VEL was also more cost-effective. However, relative to EBR/GZR, SOF/VEL was not cost-effectiveness in GT1b HCV patients. 3D was dominant over SOF/VEL and all other DAAs regimens.

To our knowledge, this is the first study including all available all-oral DAAs for the treatment of HCV 1b patients and comparing the cost-effectiveness of SOF/VEL with all other DAAs in the Chinese setting. It is more comprehensive and practical than previous study. Previous analyses in China have evaluated the cost-effectiveness of DAA regimen in GT1b HCV patients. Chen H et al. and Chen GF et al. compared DAAs with PR;[34,36] however, results of these two analyses may have potential deviation as the drug costs were from foreign countries because DAAs had not been approved in China when they did their studies. In another analysis, Liu et al. conducted the cost-effectiveness of DCV/ASV with PR, and the result showed that DCV/ASV were cost-effective relative to PR-based treatment or general interferon treatment.[29] Another study indicated that EBR/GZR was more cost-effectiveness than DCV/ASV.[37] In addition, Wu et al. evaluated cost-effectiveness of DAAs including DCV/ASV, 3D, SR, SD, which showed 3D was most-effective in Chinese 1b patients.[32]

There are several cost-effectiveness studies in other countries comparing the SOF/VEL with other all-oral DAA treatments. Corman et al. compared SOF/VEL with EBR/GZR, 3D, LDV/SOF by subtype (GT1a or 1b) and cirrhosis status, the results indicated that SOF/VEL was economically dominant relative to both 3D and LDV/SOF in GT1b treatment-naïve noncirrhotic patients, whereas SOF/VEL was dominated by EBR/GZR.[16] In our study, 3D was dominant compared with SOF/VEL, of which the reason was the cost of 3D was obviously lower than SOF/VEL, contrary to the situation in America. Another study conducted in India evaluated the cost-effectiveness of SOF/VEL versus genotype-dependent treatments, the results showed the pan-genotypic SOF/VEL was cost-effective for HCV treatment compared with genotype-dependent SD or LDV/SOF,[38] which was similar to our analysis.

The sensitivity analysis demonstrated that drug costs could result in significant impacts on the ICURs of SOF/VEL, because the cost of SOF/VEL was 18% higher than the least expensive comparators, 3D and EBR/GZR, and yet the SVR rates difference between these regimens was small. Achieving better cost-effectiveness of SOF/VEL has significant health policy implications in China, where most of the HCV patients are from rural areas, mainly in the low-income group, and prone to be impoverished due to disease. Because medical technologies and equipments in rural areas are relatively constrained, HCV patients have to go to hospitals in big cities for diagnosis and treatment. Specifically, only large hospitals in big cities can perform genotyping test. The cost-effectiveness of SOF/VEL may be

favorable if great inconvenience and extra direct non-medical expenses in the process of visiting a doctor and curing HCV are considered in the economic evaluation from a broader prospective. Thus, in order to achieve the goal of HCV elimination by 2030 within limited health resources in China, the SOF/VEL regimen, a pan-genotypic DAA treatment, has considerable significances. The pan-genotypic treatment provides 'an opportunity to simplify the care pathway by removing the need for genotyping and thus simplifying procurement and supply chains'.[35] It does not need to test the genotype and METAVIR fibrosis scores, and can be used in patients with all genotype and all METAVIR fibrosis stages. Treatment simplification of SOF/VEL is of particular significance in achieving the goal of HCV elimination in China and other developing countries with limited resource. As a result, SOF/VEL was listed in the National Essential Medicines List of China in 2018.

Although the pan-genotypic treatment, SOF/VEL, could simply the process of HCV treatment, the results of this study indicated that it is not the most cost-effective therapy in treating GT1b HCV Chinese patients from health care system. The conclusion is also driven by another cost parameter: the cost of genotyping test of only $115 in China, which is trivial in comparison to DAA drug cost. In the resource-limited setting, a possible ideal policy option is to reduce the price of SOF/VEL by the negotiation between government and drug manufacturers, which will make more underserved HCV patients having access to the treatment.

The analysis has some limitations. Firstly, SVR rates were from several international multicenter clinical trials due to the absence of the effectiveness of real-world clinical setting in China. Although the DAAs have been available since 2017, we still need some time to get the real-world effectiveness data. The future studies will evaluate the real-world effectiveness when data are available. Secondly, the transition probabilities were also obtained from the international literature, in the absence of Chinese sources, which may result in some bias on our results. Thirdly, the costs were estimated from market prices, the results may differ from the final discounted prices after negotiated agreements. Finally, SOF/VEL may be the most cost-effective treatment in other genotypes; however, our research did not include other genotypes. In future studies, we will include other genotypes to evaluate the cost-effective of SOF/VEL comprehensively.

Conclusion

This modeling study demonstrated SOF/VEL to be cost-effective compared with SR, SD and DCV/ASV, but not cost-effective versus EBR/GZR and 3D in HCV GT1b patients. The government should negotiate with pharmaceutical companies to bring down the price of SOF/VEL, which will make it cost-effective while simplifying the treatment of HCV and achieving the goal of HCV elimination by 2030.

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Patient and Public Involvement

Patients or public were not involved.

Author contributions

YHY and XJS designed the study. YHY, GQZ, and XJS collected the data. YHY performed the analyses. YHY drafted the manuscript. XJS and LZS interpreted the results and edited the manuscript. All authors have read and approved the final manuscript.

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Competing interests

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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No additional data are available.

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Table 1 model inputs

Parameter	Base case	Lower limit	Higher limit	Distribution	Parameter1	Parameter2	Reference
SVR rates							
SOF/VEL, NC	0.984	0.960	0.996	Uniform	0.960	0.996	[17]
SOF/VEL, C	0.958	0.789	0.999	Uniform	0.789	0.999	[17]
EBR/GZR, NC	0.980	0.937	1	Uniform	0.937	1	[18]
EBR/GZR, C	1	0.937	1	Uniform	0.937	1	[18]
3D, NC	0.993	0.976	1	Uniform	0.976	1	[19]
3D, C	0.942	0.892	0.991	Uniform	0.892	0.991	[20]
DCV/ASV, NC	0.889	0.85	0.94	Uniform	0.85	0.94	[21]
DCV/ASV, C	0.911	0.85	0.94	Uniform	0.85	0.94	[21]
SD, NC	0.98	0.95	1	Uniform	0.95	1	[22]
SD, C	0.98	0.95	1	Uniform	0.95	1	[22]
SR, NC	0.94	0.87	0.99	Uniform	0.87	0.99	[23]
SR, C	0.94	0.87	0.99	Uniform	0.87	0.99	[23]
Annual transition probabilities							
Fibrosis progression							
F0-F1	0.117	0.104	0.130	Beta	274.98	2075.30	[24]
F1-F2	0.085	0.075	0.096	Beta	210.06	2261.18	[24]
F2-F3	0.120	0.109	0.133	Beta	288.05	2112.38	[24]
F3-F4	0.116	0.104	0.129	Beta	270.61	2062.22	[24]
Cirrhosis progression							
F4-DC	0.039	0.010	0.079	Beta	3.51	86.48	[25]
F4-HCC	0.014	0.010	0.079	Beta	0.18	12.38	[25]
F4-SVR to DC	0.003	0.002	0.004	Beta	96	31821	[26]
F4-SVR to DC	0.006	0.005	0.007	Beta	95	15814	[26]
Liver disease progression							
DC-HCC	0.068	0.054	0.082	Beta	89	1226	[28]
Receiving liver transplant							
DC-LT	0.0003	0.0002	0.0011	Beta	0	0.1	[28]
HCC-LT	0.0005	0.0	0.0024	Beta	4.1	8788.8	[28]
Mortality rates							
DC-Death	0.129	0.1032	0.5124	Beta	147.03	983.97	[27]
HCC-Death	0.427	0.3416	0.5124	Beta	117.1	155.23	[27]
LT-Death	0.116	0.060	0.420	Beta	1.3	9.9	[29]
PLT-Death	0.044	0.060	0.420	Beta	4.7	101.6	[29]
Drug costs							Local charge
SOF/VEL	10087	7565	12608				

EBR/GZR	8548	6411	10685				
3D	8546	6409	10682				
DCV/ASV	8378	6283	10472				
SD	12302	9226	15377				
SR	17096	12822	21370				
Annual health state costs							
F0-F3	992	671	1313	Gamma	6002	0.165	[30]
F4	2823	1001	4646	Gamma	8570	0.329	[30]
DC	6287	3820	8755	Gamma	31403	0.200	[30]
HCC	13272	9544	17000	Gamma	92610	0.143	[30]
LT(first year)	56719	40983	81956	Gamma	308255	0.184	[31]
LT(subsequent years)	9016	8196	10077	Gamma	170113	0.053	[31]
Utilities							
F0-F3	0.790	0.632	0.948	Beta	19.4	5.2	[32]
F4	0.748	0.598	0.898	Beta	23.5	7.9	[32]
DC	0.672	0.538	0.806	Beta	30.8	15.0	[32]
HCC	0.610	0.488	0.732	Beta	36.8	23.6	[32]
LT(first year)	0.560	0.520	0.780	Beta	33.0	17.8	[32]
LT(subsequent years)	0.709	0.567	0.851	Beta	27.2	11.2	[32]
Post-SVR	0.87	0.65	1	Uniform	0.65	1	[33]

SVR, sustained virologic response; NC, non-cirrhotic; C, cirrhotic; SR, sofosbuvir plus ribavirin; SD, sofosbuvir plus daclatasvir; ASV, asunaprevir; DCV, daclatasvir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; VEL, velpatasvir;

F0-F4, METAVIR liver fibrosis scores; CC compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; PLT, post liver transplant

Table 2 Base case results

Treatment regimen	Discounted costs($)	Discounted QALYs	Incremental costs($)	Incremental QALYs	ICUR, SOF/VEL($/QALY)
SR	19,118	13.3342	-7716	0.0921	Dominant
SD	13,727	13.4207	-2325	0.0056	Dominant
DCV/ASV	11,155	13.2262	247	0.2001	1,234/QALY
3D	9,792	13.4435	1510	-0.0172	dominated
EBR/GZR	9,966	13.4228	1436	0.0040	359,000/QALY
SOF/VEL	11,402	13.4263	-	-	-

Note: SOF/VEL is considered the reference treatment.

SR, sofosbuvir plus ribavirin; SD, sofosbuvir plus daclatasvir; ASV, asunaprevir; DCV, daclatasvir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; VEL, velpatasvir; QALY, quality-adjusted life year; ICUR, incremental cost-utility ratio.

Figure legends

Figure 1: model structure. F0-F4: METAVIR liver fibrosis scores; DC, F0-F4, METAVIR liver fibrosis scores; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant(first year); PLT, liver transplant (subsequent years); SVR, sustained virologic response.

Figure 2: Tornado diagrams showed the impact of lower and upper values of each parameter in incremental cost-effectiveness ratio of SOF/VEL over other DAAs.

(a) SOF/VEL vs EBR/GZR. (b) SOF/VEL vs 3D. (c) SOF/VEL vs ASV/DCV. (d) SD vs SOF/VEL. (e) SR vs SOF/VEL. The effect of 10 influential variables is shown. Each bar shows the variation in ICER, blue color, low value; red color, high value). WTP: willingness to pay; ICER: incremental cost-effectiveness ratio; SR, sofosbuvir plus ribavirin; SD, sofosbuvir plus daclatasvir; ASV, asunaprevir; DCV, daclatasvir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; VEL, velpatasvir.

Figure 3 : Acceptability curves comparing the cost-effectiveness of different competing strategies. SR, sofosbuvir plus ribavirin; SD, sofosbuvir plus daclatasvir; ASV, asunaprevir; DCV, daclatasvir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; VEL, velpatasvir.

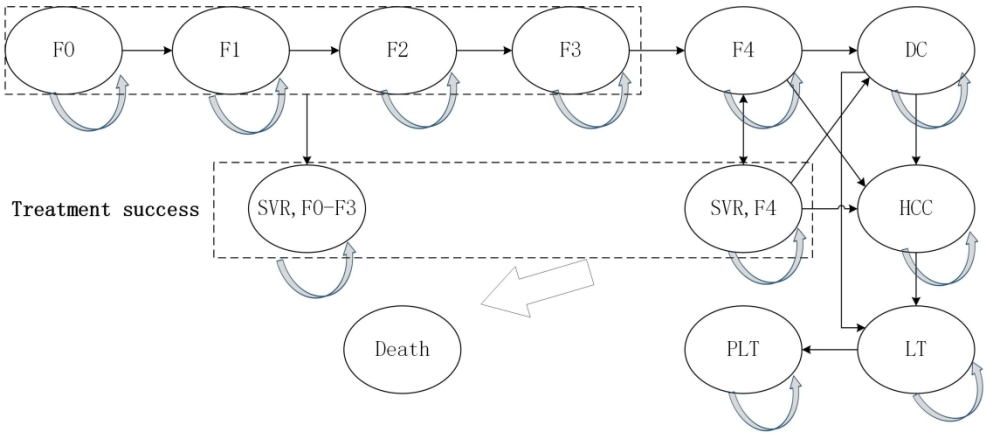

Figure 1: model structure. F0-F4: METAVIR liver fibrosis scores; DC, F0-F4, METAVIR liver fibrosis scores; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant(first year); PLT, liver transplant (subsequent years); SVR, sustained virologic response.

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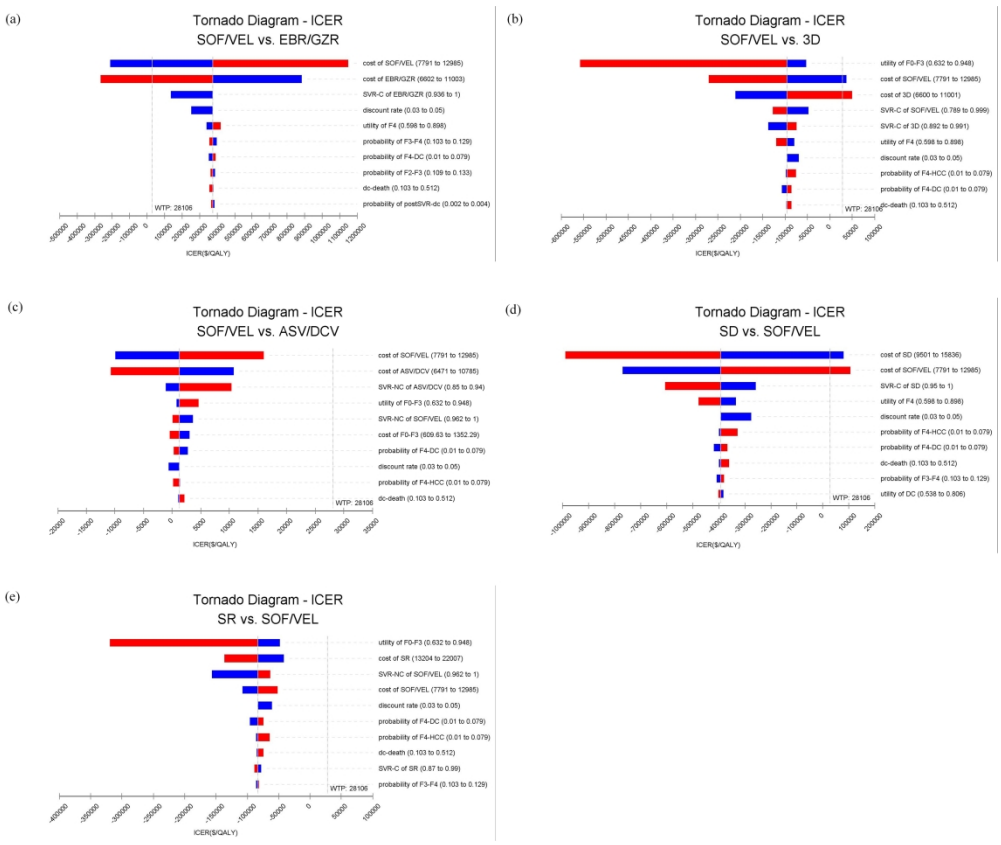

Figure 2: Tornado diagrams showed the impact of lower and upper values of each parameter in incremental cost-effectiveness ratio of SOF/VEL over other DAAs. (a) SOF/VEL vs EBR/GZR. (b) SOF/VEL vs 3D. (c) SOF/VEL vs ASV/DCV. (d) SD vs SOF/VEL. (e) SR vs SOF/VEL. The effect of 10 influential variables is shown. Each bar shows the variation in ICER, blue color, low value; red color, high value). WTP: willingness to pay; ICER: incremental cost-effectiveness ratio; SR, sofosbuvir plus ribavirin; SD, sofosbuvir plus daclatasvir; ASV, asunaprevir; DCV, daclatasvir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; VEL, velpatasvir.

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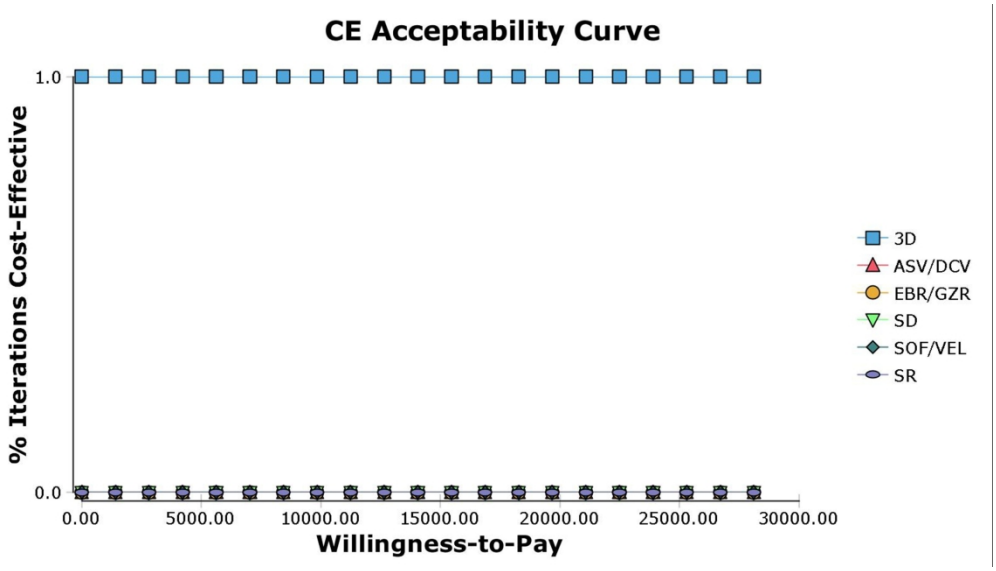

Figure 3 : Acceptability curves comparing the cost-effectiveness of different competing strategies. SR, sofosbuvir plus ribavirin; SD, sofosbuvir plus daclatasvir; ASV, asunaprevir; DCV, daclatasvir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; VEL, velpatasvir.

282x158mm (300 x 300 DPI)

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	P1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	P1
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	P2-3
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	P4
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	P3
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	P3
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	P4
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	P3
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	P3
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	P6
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	P5

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	P5
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	P5
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	P5
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	P4
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	P4
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	P6
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	P6
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	P6-7
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	

		of methodological assumptions (such as discount rate, study perspective).	NA
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	P7
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	P7-9
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	P10
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	P10

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

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Cost-Utility of Sofosbuvir/Velpatasvir versus other direct-acting antivirals for Chronic Hepatitis C Genotype 1b Infection in China

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Cost-Utility of Sofosbuvir/Velpatasvir versus other direct-acting antivirals for Chronic Hepatitis C Genotype 1b Infection in China

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Keywords: cost-utility, Markov model, sofosbuvir/velpatasvir, chronic hepatitis c

Word count: 2852 words

Abstract

Objective This study aimed to estimate the cost-utility of sofosbuvir/velpatasvir (SOF/VEL) compared with other direct-acting antivirals (DAAs) in Chinese Hepatitis C Virus (HCV) patients.

Design A Markov model was developed to estimate the disease progression of HCV patients over a lifetime horizon from the health care system perspective. Efficacy, clinical inputs and utilities were derived from published literature. Drug costs were from the market price survey, and health costs for Markov health states were sourced from a Chinese study. Costs and utilities were discounted at an annual rate of 5%. One-way and probabilistic sensitivity analyses were conducted to test the impact of input parameters on the results.

Interventions SOF/VEL was compared with sofosbuvir + ribavirin (SR), sofosbuvir + dasabuvir (SD), daclatasvir + asunaprevir (DCV/ASV), ombitasvir/paritaprevir/ritonavir + dasabuvir (3D), and elbasvir/grazoprevir (EBR/GZR).

Primary and secondary outcomes Costs, quality-adjusted life years (QALYs) and incremental cost-utility ratios (ICURs).

Results SOF/VEL was economically dominant over SR and SD. However, 3D was economically dominant versus SOF/VEL. Compared to DCV/ASV, SOF/VEL was cost-effective with the ICUR of $1522 per QALY. Compared to EBR/GZR, it was not cost-effective with the ICUR of $369,627 per QALY. One-way sensitivity analysis demonstrated that reducing the cost of SOF/VEL to the lower value of confidence interval, resulted in dominance over EBR/GZR and 3D. Probabilistic sensitivity analysis demonstrated that 3D was cost-effective in 100% of iterations in genotype (GT) 1b patients and SOF/VEL was not cost-effective.

Conclusions Compared with other oral direct-acting antiviral agents, SOF/VEL treatment was not the most cost-effectiveness option for patients with chronic HCV GT1b in China. Lower the price of SOF/VEL will make it cost-effective while simplifying treatment and achieving the goal of HCV elimination.

Strengths and limitations of this study

To our knowledge, this is the first study including all available all-oral DAAs for the treatment of HCV GT1b patients and comparing the cost-effectiveness of SOF/VEL with all other DAAs in the Chinese setting.

Some of the parameters were retrieved from published literature due to the absence of the real-world data in China, which may result in some bias on our results.

Only the HCV GT1b was considered in this study, other genotypes were not included, which may restrict the generalibility of findings in this study.

Introduction

Chronic hepatitis C (CHC) is a major public health problem worldwide. It is estimated that there are around 71 million individuals chronically infected with Hepatitis C Virus (HCV), leading to approximately 399,000 deaths each year.[1, 2] In China, the number of HCV-infected patients was estimated to be approximate 10 million in 2006, and the most prevalent genotype is HCV genotype (GT) 1b (56.8%), followed by GT2 (15.8%) , GT3 (8.7%), and GT6 (5.7%) .[3, 4] The Chinese Center for Disease Control and Prevention reported that the incidence was showing an increasing trend, with an estimated 200,000 new cases annually from 2014 to 2018. The undiagnosed and untreated chronic HCV-infected patients are likely to develop serious liver-related complications such as decompensated cirrhosis (DC) and hepatocellular carcinoma (HCC), leading to substantial clinical and economic

burden.[5, 6]

The endpoint of treating HCV infection is achieving sustained virologic response (SVR), which can significantly reduce the risk of liver disease progression and avoid conversion to end-stage liver diseases.[7] Patients achieving SVR are associated with lower costs and improved quality of life.[8] Therefore, the treatment of HCV and achievement of SVR are of critical significance in reducing the health and economic burdens among CHC patients.

For decades, the standard of care for HCV-infected patients in china has been based on pegylated interferon plus ribavirin (PR) therapy, which is associated with low efficacy, long treatment durations, poor tolerability and much adverse event rates, especially in cirrhotic patients.[9] The introduction of direct-acting antivirals (DAAs), with improved SVR and fewer side effects, has revolutionized HCV treatment. The latest Chinese guideline has suggested that DAA regimens should be applied if patients could afford medical expenses.[9] In recent years, a range of drugs have been approved for HCV treatment by the Chinese State Food and Drug Administration (CFDA). These all-oral regimens for HCV-infected patients, including sofosbuvir plus ribavirin (SR), sofosbuvir plus daclatasvir (SD), daclatasvir plus asunaprevir (DCV/ASV), ombitasvir/paritaprevir/ritonavir plus dasabuvir (3D), elbasvir/grazoprevir (EBR/GZR), and sofosbuvir/velpatasvir (SOF/VEL), have been currently available in China. All these interferon-free regimens resulted in higher efficacy and shorter duration, compared with interferon-based regimens.[10,11] Specially, SOF/VEL was listed in the National Essential Medicines List of China as the only full-oral, direct anti-HCV drug in 2018. Unlike other DAAs, SOF/VEL is a pan-genotypic drug, which is the first fixed-dosage regimen able to achieve high rates of SVR, after only 12 weeks of treatment across all genotypes, all fibrosis scores and typologies of patients.[12]

At the present, it is not clear whether SOF/VEL is cost-effective in Chinese HCV GT1b patients. Therefore, the objective of this study was to estimate the cost-effectiveness of SOF/VEL compared with other available DAA regimens for treatment of hepatitis HCV GT1b patients.

Methods

The Markov model can simulate the progression of HCV patient through the natural history of HCV and treatment. We used a state-transition Markov model to estimate the economic benefits of SOF/VEL regimen in Chinese patients with HCV GT1b, from the health care system perspective. The model

simulated the disease progression of HCV patients who received treatment with SOF/VEL or comparators. The model used an annual cycle length and a lifetime horizon. A discount rate of 5% was used for costs and utilities in this model, which was based on the recommendations in the China guideline for pharmacoeconomic evaluations.

Patients characteristics

The base-case population in the model represented treatment-naive patients infected with HCV GT1b, the major genotype in China. According to a Chinese study, the mean age of Chinese HCV-infected patients were 44.5 years,[4] so it was assumed that the patients entered the model at the age of 45 years old in this study. The baseline distribution was defined by the METAVIR fibrosis stages: no fibrosis (F0), portal fibrosis with no septa (F1), portal fibrosis with few septa (F2), numerous septa without cirrhosis (F3), and compensated cirrhosis (F4).[13] Based on another Chinese investigation,[14] the fibrosis distribution was as follows: F0 (0.8%), F1 (45.5%), F2 (41.3%), F3 (9.9%), and F4 (2.5%), respectively. Co-infection with HBV or HIV was not included. Due to the small proportion of treatment-experienced patients, only the treatment-naïve patients were considered.

Model structure and assumptions

The structure of the model was based on other models of HCV disease which have been published and validated in health economic analyses.[15-17] The model consisted of 14 health states (Fig.1). Fibrosis stage was defined by the METAVIR fibrosis scoring system and it was assumed that patients enter the model with a given fibrosis score: F0, F1, F2, F3, F4. Patients may develop the more serious liver fibrosis, advanced liver disease (i.e., DC, HCC, LT), or may keep that health state. If patients achieved SVR after the successful treatment, the disease progression was to halt. However, it allowed for the transitions from SVR to DC or HCC for patients with cirrhosis (F4) at a lower rate. Patients at the stage of compensated cirrhosis (F4) were at risk of developing DC or HCC. If a patient developed DC and/or HCC, then the patient may receive a liver transplant. Patients with advance liver disease had higher mortality rates than other patients. All the other patients had the same mortality rate as the general population.

It was assumed that there was no disease progression during treatment. Only cirrhotic patients (F4) could progress to DC and HCC and it still had risk of DC and HCC even if they achieved SVR. Adverse events were not considered due to the minimal rates in these interferon-free regimens.

Model comparators and clinical inputs

DCV+ASV, SOF/VEL, EBR/GZR, 3D and SOF-based regimens (SR: the combination of sofosbuvir and RBV; SD: the combination of sofosbuvir and dasabuvir) are all recommended for chronic GT1b infection in the Chinese setting. The duration of DCV+ASV and SR are 24 weeks, and for the other three regimens are 12 weeks. The treatment effectiveness was defined as SVR. The SVRs of DCV+ASV, SOF/VEL, EBR/GZR, 3D were derived from international multicenter clinical trials.[18-22] The SVR of SD was derived from a systematic review.[23] The SVR of SR was obtained from a clinical trial in the Chinese setting.[24] The clinical inputs are shown in Table 1.

Transition probabilities

The transition probabilities are shown in Table 1. The rates of fibrosis progression between F0 to F4 were derived from a meta-analysis.[25] The probability from F4 to DC and HCC and from DC to HCC were estimated from published literature.[26,27] Patients achieving SVR were assumed to develop DC or HCC at a lower rate according to a prospective study.[28] The probabilities of liver transplantation of DC or HCC were obtained from published studies, in which the proportion of liver transplantation was derived from a previous study and was adjusted based on the donation rate ratio between Chinese (0.6 per million) and individuals of Western countries (34.4 per million).[29] The mortality rates associated with DC, HCC, liver transplantation in first year and liver transplantation in subsequent years, which were higher than general mortality, were sourced from the published literature.[28,30] Age-specific all-cause mortality rates were obtained from the life tables of the World Health Organization (WHO) member states.

Direct medical costs

The Chinese healthcare perspective was adopted in this study. All costs were inflated to 2019 using the China Consumer Price Index and converted to US dollars using official exchange rates as of 2019 (1 USD=6.90 CNY). The medical costs consisted of drug costs and liver-related health state costs (Table 1). Drug costs were based on local charges without discounts because the majority of DAAs were not included in the national drug reimbursement list. The annual costs of F0-F4, DC, HCC were derived from a survey of HCV-infected patients in China, which included costs of liver-related care (e.g., laboratory tests, procedures, medications, and hospitalizations).[31] The annual costs associated with liver transplant and post-liver transplant were obtained from a study in the context of China.[32]

Patients after SVR were assumed to incur no medical costs. Future costs were discounted at 5% per year.

Health utilities

Utility weights for each health state of liver disease were mainly obtained from a published systematic review.[33] The quality of life (QOL) of patients with SVR was based on a published study.[34] Disutility was not considered during the therapy. The utilities are shown in table 1.

Model analysis

Costs and quality-adjusted life years (QALYs) were discounted at 5% per year. Incremental cost-utility ratios (ICURs) were reported to show cost-utility of SOF/VEL regimen relative to the comparator. We calculated ICURs by dividing the incremental costs by the incremental QALYs for the SOF/VEL regimen compared each of the comparators. In cases in which the SOF/VEL regimen was less costly and more effective than a comparator, it was concluded to be economically dominant. In other cases, ICURs were reported. US28,106/QALY, the three times Chinese gross domestic product (GDP) per capita, was used to be the willingness to pay threshold. In cases the ICUR of SOF/VEL was lower than US28,106/QALY, it was regarded as cost-effective. Otherwise, it was not cost-effective.

Sensitivity analysis

One-way sensitivity analyses were conducted to test the effect of varying input parameters on the ICUR of SOF/VEL treatment regimen compared to the comparator. The efficacy, costs, progression rates, utilities, and discount rates were tested under the ranges defined in the inputs tables (Table 1). The 95% confidence interval (CI) of each parameter was used to be the varying range; in case the 95% CI was not available, the 25% of parameter would be used. In addition, discount rate varied ranging from 3% to 5%. The results were presented by tornado diagrams.

A probabilistic sensitivity analysis (PSA) was conducted in which all the input parameters were varied simultaneously. Inputs were sampled from predefined distributions with 1000 iterations (Table 1). The key parameters of each specific distribution were calculated from the mean and standard error. Beta distribution was applied to transition probabilities and utilities. Gamma distribution was applied to costs. Uniform distribution was applied in which the parameters were not available. Results of the PSA were presented using cost-effectiveness acceptability curves, which reflect the probability that the regimens will be cost effective at various willingness-to-pay thresholds.

Patient and public involvement

The research study did not involve any direct patient and public involvement.

Results

Base-case analysis

Results of the base-case are presented in Table 2. Compared with SD and SR, SOF/VEL was dominant with higher effectiveness and lower cost. The ICURs of SOF/VEL versus DCV/ASV was $1522, which was lower than the threshold of $28,106 per QALY. The ICURs of SOF/VEL versus EBR/GZR was $369,627, which exceeded the threshold. Compared with 3D, SOF/VEL was dominated with higher costs and fewer QALYs. All in all, 3D is the most effective strategy in GT1b HCV patients, followed by the EBR/GZR, SOF/VEL strategies.

The treatment costs among regimens ranged from $9,792 to $19,118 (difference $9,326) and QALYs ranged from 13.2262 to 13.4435 (difference 0.2173). Costs were lowest for 3D and highest for SR; QALYs were highest for 3D and lowest for DCV/ASV. Compared with sofosbuvir-based regimens (SR and SD), the second-generation DAAs (3D, EBR/GZR, SOF/VEL, DCV/ASV) resulted in fewer costs and more QALYs.

Deterministic sensitivity analysis

The 10 input parameters, to which ICURs were most sensitive, were presented in tornado diagrams (Fig. 2). ICURs were most sensitive to SVR rates and drug costs. However, only the cost of drugs can lead to changes of results. Reducing the cost of SOF/VEL to the lower bound of confidence interval, $8701, resulted in dominance over EBR/GZR. SOF/VEL was dominated by 3D in the base-analysis, but reducing the cost of SOF/VEL to the lower value of confidence interval of $7945, resulted in SOF/VEL dominating the comparator of 3D. However, compared to DCV/ASV and SR, SOF/VEL was cost-effective no matter what parameter changes within the given range were.

Probabilistic sensitivity analysis

The result of probability sensitivity analysis was consistent with the base-case results. The cost-effectiveness acceptability curve showed that, 3D was to be cost-effective in 100% of the 1000 PSA iterations run, at a willingness-to-pay threshold up to $28,106 per QALY (Fig.3). The probabilities that SOF/VEL and other DAA regimens would be cost-effective were 0%.

Discussion

This study evaluated the cost-utility of all DAAs used among GT1b HCV patients in China. The base-case results showed that SOF/VEL was economically dominant relative to SR and SD. Compared with DCV/ASV, SOF/VEL was also more cost-effective. However, relative to EBR/GZR, SOF/VEL was not cost-effectiveness in GT1b HCV patients. 3D was dominant over SOF/VEL and all other DAAs regimens.

To our knowledge, this is the first study including all available all-oral DAAs for the treatment of HCV 1b patients and comparing the cost-effectiveness of SOF/VEL with all other DAAs in the Chinese setting. It is more comprehensive and practical than previous study. Previous analyses in China have evaluated the cost-effectiveness of DAA regimen in GT1b HCV patients. Chen H et al. and Chen GF et al. compared DAAs with PR;[34-35] however, results of these two analyses may have potential deviation as the drug costs were from foreign countries because DAAs had not been approved in China when they did their studies. In another analysis, Liu et al. conducted the cost-effectiveness of DCV/ASV with PR, and the result showed that DCV/ASV were cost-effective relative to PR-based treatment or general interferon treatment.[29] Another study indicated that EBR/GZR was more cost-effectiveness than DCV/ASV.[36] In addition, Wu et al. evaluated cost-effectiveness of DAAs including DCV/ASV, 3D, SR, SD, which showed 3D was most-effective in Chinese 1b patients.[32]

There are several cost-effectiveness studies in other countries comparing the SOF/VEL with other all-oral DAA treatments. Corman et al. compared SOF/VEL with EBR/GZR, 3D, LDV/SOF by subtype (GT1a or 1b) and cirrhosis status, the results indicated that SOF/VEL was economically dominant relative to both 3D and LDV/SOF in GT1b treatment-naïve noncirrhotic patients, whereas SOF/VEL was dominated by EBR/GZR.[16] In our study, 3D was dominant compared with SOF/VEL, of which the reason was the cost of 3D was obviously lower than SOF/VEL, contrary to the situation in America. Another study conducted in India evaluated the cost-effectiveness of SOF/VEL versus genotype-dependent treatments, the results showed the pan-genotypic SOF/VEL was cost-effective for HCV treatment compared with genotype-dependent SD or LDV/SOF,[37] which was similar to our analysis.

The sensitivity analysis demonstrated that drug costs could result in significant impacts on the ICURs of SOF/VEL, because the cost of SOF/VEL was 18% higher than the least expensive comparators, 3D and EBR/GZR, and yet the SVR rates difference between these regimens was small. Achieving better

cost-effectiveness of SOF/VEL has significant health policy implications in China, where most of the HCV patients are from rural areas, mainly in the low-income group, and prone to be impoverished due to disease. Because medical technologies and equipment in rural areas are relatively constrained, HCV patients have to go to hospitals in big cities for diagnosis and treatment. Specifically, only large hospitals in big cities can perform genotyping test. The cost-effectiveness of SOF/VEL may be favorable if great inconvenience and extra direct non-medical expenses in the process of visiting a doctor and curing HCV are considered in the economic evaluation from a broader prospective. Thus, in order to achieve the goal of HCV elimination by 2030 within limited health resources in China, the SOF/VEL regimen, a pan-genotypic DAA treatment, has considerable significances. The pan-genotypic treatment provides 'an opportunity to simplify the care pathway by removing the need for genotyping and thus simplifying procurement and supply chains'.[38] It does not need to test the genotype and METAVIR fibrosis scores, and can be used in patients with all genotype and all METAVIR fibrosis stages. Treatment simplification of SOF/VEL is of particular significance in achieving the goal of HCV elimination in China and other developing countries with limited resource. As a result, SOF/VEL was listed in the National Essential Medicines List of China in 2018.

Although the pan-genotypic treatment, SOF/VEL, could simply the process of HCV treatment, the results of this study indicated that it is not the most cost-effective therapy in treating GT1b HCV Chinese patients from health care system. The conclusion is also driven by another cost parameter: the cost of genotyping test of only $115 in China, which is trivial in comparison to DAA drug cost. If the price of SOF/VEL can be reduced to a reasonable level, more patients will afford this drug, which will make more patients be treated and cured. In addition, it will save much costs for medical insurance payer. In the resource-limited setting, a possible ideal policy option is to reduce the price of SOF/VEL by the negotiation between government and drug manufacturers, which will make more underserved HCV patients having access to the treatment. It will be a triple win situation for medical insurance payer, drug companies and patients.

The analysis has some limitations. Firstly, SVR rates were from several international multicenter clinical trials due to the absence of the effectiveness of real-world clinical setting in China. Although the DAAs have been available since 2017, we still need some time to get the real-world effectiveness data. The future studies will evaluate the real-world effectiveness when data are available. Secondly,

the transition probabilities were also obtained from the international literature, in the absence of Chinese sources, which may result in some bias on our results. Thirdly, the costs were estimated from market prices, and the results may differ from the final discounted prices after negotiated agreements. In addition, SOF/VEL may be the most cost-effective treatment in other genotypes; however, our research did not include other genotypes. In future studies, we will include other genotypes to evaluate the cost-effective of SOF/VEL comprehensively. Finally, the lifetime model was built to simulate the progression of HCV, and the benefits of treatment in preventing transmission was not considered, which may have underestimated the value of HCV treatment.

Conclusion

This modeling study demonstrated SOF/VEL to be cost-effective compared with SR, SD and DCV/ASV, but not cost-effective versus EBR/GZR and 3D in HCV GT1b patients. The government should negotiate with pharmaceutical companies to bring down the price of SOF/VEL, which will make it cost-effective while simplifying the treatment of HCV and achieving the goal of HCV elimination by 2030.

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Patient and Public Involvement

Patients or public were not involved.

Author contributions

YHY and XJS designed the study. YHY, GQZ, and XJS collected the data. YHY performed the analyses. YHY drafted the manuscript. XJS and LZS interpreted the results and edited the manuscript. All authors have read and approved the final manuscript.

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Competing interests

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

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No additional data are available.

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Table 1 model inputs

Parameter	Base case	Lower limit	Higher limit	Distribution	Parameter1	Parameter2	Reference
SVR rates							
SOF/VEL, NC	0.984	0.960	0.996	Uniform	0.960	0.996	[18]
SOF/VEL, C	0.958	0.789	0.999	Uniform	0.789	0.999	[18]
EBR/GZR, NC	0.980	0.937	1	Uniform	0.937	1	[19]
EBR/GZR, C	1	0.937	1	Uniform	0.937	1	[19]
3D, NC	0.993	0.976	1	Uniform	0.976	1	[20]
3D, C	0.942	0.892	0.991	Uniform	0.892	0.991	[21]
DCV/ASV, NC	0.889	0.85	0.94	Uniform	0.85	0.94	[22]
DCV/ASV, C	0.911	0.85	0.94	Uniform	0.85	0.94	[22]
SD, NC	0.98	0.95	1	Uniform	0.95	1	[23]
SD, C	0.98	0.95	1	Uniform	0.95	1	[23]
SR, NC	0.94	0.87	0.99	Uniform	0.87	0.99	[24]
SR, C	0.94	0.87	0.99	Uniform	0.87	0.99	[24]
Annual transition probabilities							
Fibrosis progression							
F0-F1	0.117	0.104	0.130	Beta	274.98	2075.30	[25]
F1-F2	0.085	0.075	0.096	Beta	210.06	2261.18	[25]
F2-F3	0.120	0.109	0.133	Beta	288.05	2112.38	[25]
F3-F4	0.116	0.104	0.129	Beta	270.61	2062.22	[25]
Cirrhosis progression							
F4-DC	0.039	0.010	0.079	Beta	3.51	86.48	[26]
F4-HCC	0.014	0.010	0.079	Beta	0.18	12.38	[26]
F4-SVR to DC	0.003	0.002	0.004	Beta	96	31821	[27]

F4-SVR to DC	0.006	0.005	0.007	Beta	95	15814	[27]
Liver disease progression							
DC-HCC	0.068	0.054	0.082	Beta	89	1226	[28]
Receiving liver transplant							
DC-LT	0.0003	0.0002	0.0011	Beta	0	0.1	[29]
HCC-LT	0.0005	0.0	0.0024	Beta	4.1	8788.8	[29]
Mortality rates							
DC-Death	0.129	0.1032	0.5124	Beta	147.03	983.97	[28]
HCC-Death	0.427	0.3416	0.5124	Beta	117.1	155.23	[28]
LT-Death	0.116	0.060	0.420	Beta	1.3	9.9	[30]
PLT-Death	0.044	0.060	0.420	Beta	4.7	101.6	[30]
Drug costs							Local charge
SOF/VEL	10087	7565	12608				
EBR/GZR	8548	6411	10685				
3D	8546	6409	10682				
DCV/ASV	8378	6283	10472				
SD	12302	9226	15377				
SR	17096	12822	21370				
Annual health state costs							
F0-F3	992	671	1313	Gamma	6002	0.165	[31]
F4	2823	1001	4646	Gamma	8570	0.329	[31]
DC	6287	3820	8755	Gamma	31403	0.200	[31]
HCC	13272	9544	17000	Gamma	92610	0.143	[31]
LT(first year)	56719	40983	81956	Gamma	308255	0.184	[32]
LT(subsequent years)	9016	8196	10077	Gamma	170113	0.053	[32]
Utilities							
F0-F3	0.790	0.632	0.948	Beta	19.4	5.2	[33,35]
F4	0.748	0.598	0.898	Beta	23.5	7.9	[33,35]
DC	0.672	0.538	0.806	Beta	30.8	15.0	[33,35]
HCC	0.610	0.488	0.732	Beta	36.8	23.6	[33,35]
LT(first year)	0.560	0.520	0.780	Beta	33.0	17.8	[33,35]
LT(subsequent years)	0.709	0.567	0.851	Beta	27.2	11.2	[33,35]
Post-SVR	0.87	0.65	1	Uniform	0.65	1	[34]

SVR, sustained virologic response; NC, non-cirrhotic; C, cirrhotic; SR, sofosbuvir plus ribavirin; SD, sofosbuvir plus daclatasvir; ASV, asunaprevir; DCV, daclatasvir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; VEL, velpatasvir;

F0-F4, METAVIR liver fibrosis scores; CC compensated cirrhosis; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant; PLT, post liver transplant

Table 2 Base case results

Treatment regimen	Discounted costs($)	Discounted QALYs	Incremental costs($)	Incremental QALYs	ICUR, SOF/VEL($/QALY)
SR	19,118	13.3342	-7716	0.0921	Dominant
SD	13,727	13.4207	-2325	0.0056	Dominant
DCV/ASV	11,155	13.2262	247	0.2001	1,234/QALY
3D	9,792	13.4435	1510	-0.0172	dominated
EBR/GZR	9,966	13.4228	1436	0.0040	359,000/QALY
SOF/VEL	11,402	13.4263	-	-	-

Note: SOF/VEL is considered the reference treatment.

SR, sofosbuvir plus ribavirin; SD, sofosbuvir plus daclatasvir; ASV, asunaprevir; DCV, daclatasvir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; VEL, velpatasvir; QALY, quality-adjusted life year; ICUR, incremental cost-utility ratio.

Figure legends

Figure 1: model structure. F0-F4: METAVIR liver fibrosis scores; DC, F0-F4, METAVIR liver fibrosis scores; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant(first year); PLT, liver transplant (subsequent years); SVR, sustained virologic response.

Figure 2: Tornado diagrams showed the impact of lower and upper values of each parameter in incremental cost-effectiveness ratio of SOF/VEL over other DAAs.

(a) SOF/VEL vs EBR/GZR. (b) SOF/VEL vs 3D. (c) SOF/VEL vs ASV/DCV. (d) SD vs SOF/VEL. (e) SR vs SOF/VEL. The effect of 10 influential variables is shown. Each bar shows the variation in ICER, blue color, low value; red color, high value). WTP: willingness to pay; ICER: incremental cost-effectiveness ratio; SR, sofosbuvir plus ribavirin; SD, sofosbuvir plus daclatasvir; ASV, asunaprevir; DCV, daclatasvir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; VEL, velpatasvir.

Figure 3 : Acceptability curves comparing the cost-effectiveness of different competing strategies. SR, sofosbuvir plus ribavirin; SD, sofosbuvir plus daclatasvir; ASV, asunaprevir; DCV, daclatasvir; 3D,

ombitasvir/paritaprevir/ritonavir + dasabuvir; EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; VEL, velpatasvir.

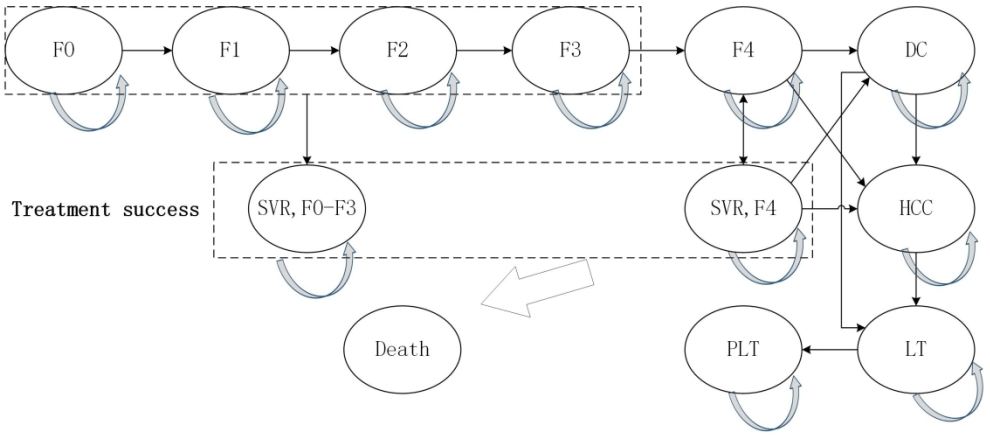

Figure 1: model structure. F0-F4: METAVIR liver fibrosis scores; DC, F0-F4, METAVIR liver fibrosis scores; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplant(first year); PLT, liver transplant (subsequent years); SVR, sustained virologic response.

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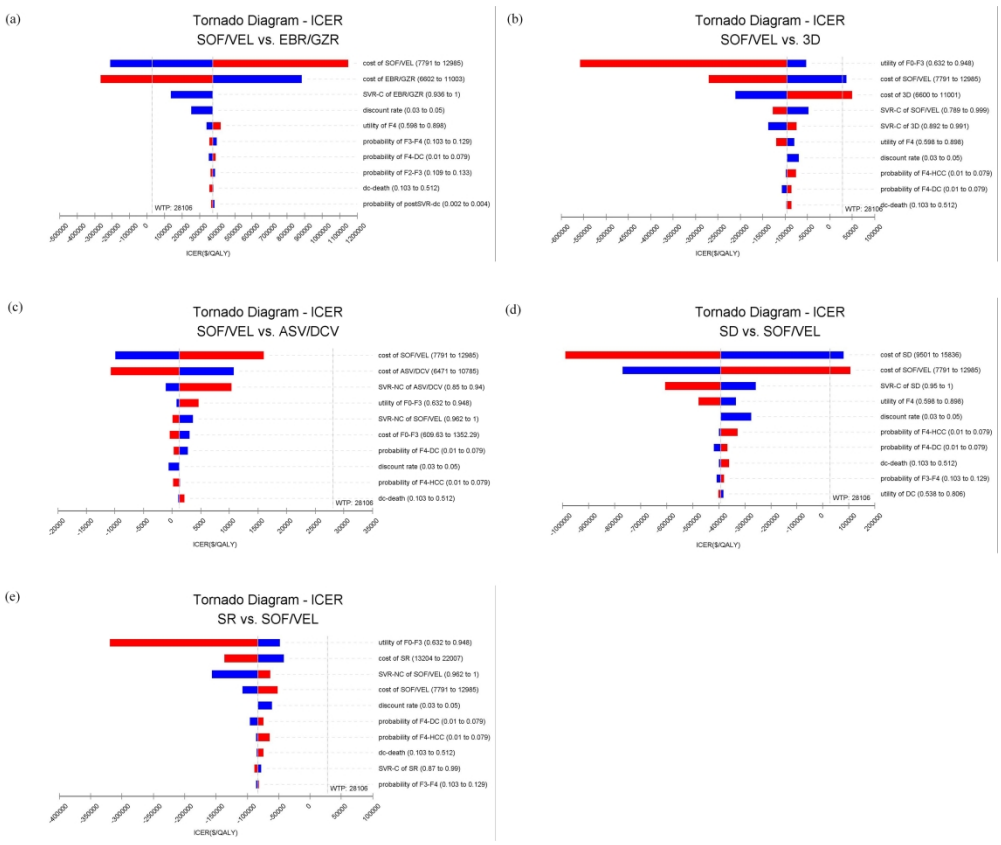

Figure 2: Tornado diagrams showed the impact of lower and upper values of each parameter in incremental cost-effectiveness ratio of SOF/VEL over other DAAs. (a) SOF/VEL vs EBR/GZR. (b) SOF/VEL vs 3D. (c) SOF/VEL vs ASV/DCV. (d) SD vs SOF/VEL. (e) SR vs SOF/VEL. The effect of 10 influential variables is shown. Each bar shows the variation in ICER, blue color, low value; red color, high value). WTP: willingness to pay; ICER: incremental cost-effectiveness ratio; SR, sofosbuvir plus ribavirin; SD, sofosbuvir plus daclatasvir; ASV, asunaprevir; DCV, daclatasvir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; VEL, velpatasvir.

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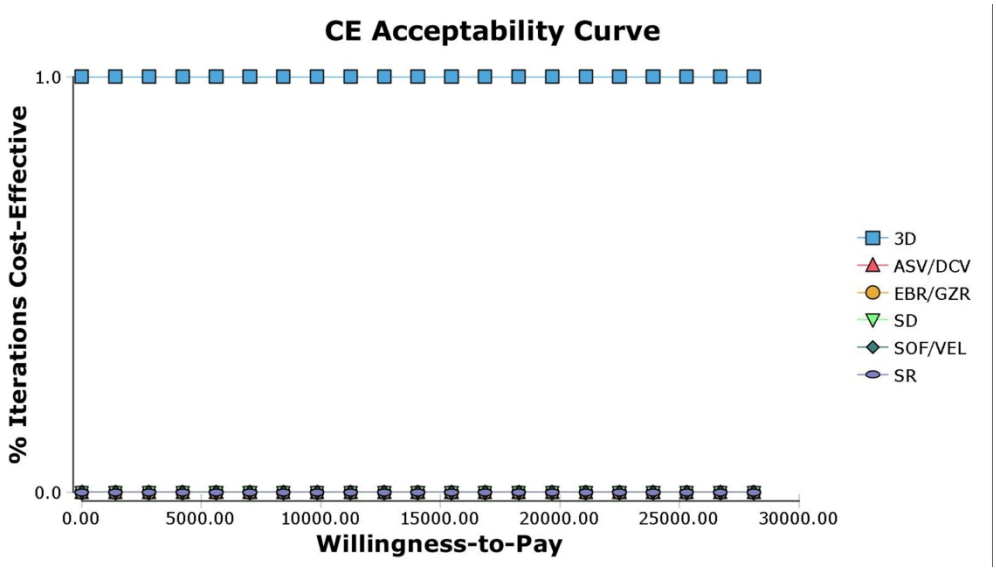

Figure 3 : Acceptability curves comparing the cost-effectiveness of different competing strategies. SR, sofosbuvir plus ribavirin; SD, sofosbuvir plus daclatasvir; ASV, asunaprevir; DCV, daclatasvir; 3D, ombitasvir/paritaprevir/ritonavir + dasabuvir; EBR, elbasvir; GZR, grazoprevir; SOF, sofosbuvir; VEL, velpatasvir.

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CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

The **ISPOR CHEERS Task Force Report**, *Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluations Publication Guidelines Good Reporting Practices Task Force*, provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	P1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	P1
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	P2-3
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	P4
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	P3
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	P3
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	P4
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	P3
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	P3
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	P6
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	P5

	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	P5
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	NA
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	NA
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	P5
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	P5
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	P4
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	P4
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	P6
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	P6
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	P6-7
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact	

		of methodological assumptions (such as discount rate, study perspective).	NA
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	P7
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	NA
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	P7-9
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	P10
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	P10

For consistency, the CHEERS Statement checklist format is based on the format of the CONSORT statement checklist

The **ISPOR CHEERS Task Force Report** provides examples and further discussion of the 24-item CHEERS Checklist and the CHEERS Statement. It may be accessed via the *Value in Health* link or via the ISPOR Health Economic Evaluation Publication Guidelines – CHEERS: Good Reporting Practices webpage: http://www.ispor.org/TaskForces/EconomicPubGuidelines.asp

The citation for the CHEERS Task Force Report is:
Husereau D, Drummond M, Petrou S, et al. Consolidated health economic evaluation reporting standards (CHEERS)—Explanation and elaboration: A report of the ISPOR health economic evaluations publication guidelines good reporting practices task force. Value Health 2013;16:231-50.