Original Article

# Cost-effectiveness analysis of glecaprevir/pibrentasvir regimen for treating Chinese patients with chronic hepatitis C genotype 1 and genotype 2 infection

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**Background:** Hepatitis C virus (HCV) infection is an important health threat in China to which direct acting antivirals (DAAs) are very effective. In 2019, another novel DAA glecaprevir/pibrentasvir (GLE/PIB) was officially approved. Knowledge of its cost-effectiveness would be informative for clinical decision-making but has not been evaluated. This study aims to evaluate the cost-effectiveness of GLE/PIB to inform policy-making on drug reimbursement and HCV eradication.

**Methods:** Markov models were developed from the payers' perspective and simulated the lifetime experience of adult patients chronically infected with HCV genotype 1 or genotype 2. Two regimens, GLE/PIB and pegylated interferon (pegIFN) plus ribavirin (RBV), were compared in cost and quality adjusted life years (QALY) with both outcomes being discounted to 2020 values. The incremental cost-effectiveness ratio (ICER) was computed to reflect the incremental benefit of GLE/PIB versus pegIFN + RBV. The robustness of the model outcomes was examined using deterministic and probabilistic sensitivity analysis (PSA) to identify influential parameters and to assess the probability of GLE/PIB being cost-effective. The GDP per capita in China in 2019 ($10,275) was used as the threshold for cost-effectiveness.

**Results:** For the entire target population, GLE/PIB was the dominant regimen attaining a cost-saving of $255 and 1.17 more QALYs relative to pegIFN + RBV. The finding was more pronounced for HCV genotype 1 infection by saving $1,656 and creating 1.37 more QALYs. At the $10,275 threshold, the probability of GLE/PIB being cost-effective was 99.32% overall and 99.85% for HCV genotype 1 infection. The age of starting DAA treatment, price of pegIFN + RBV, cost of cirrhosis treatment and duration of the GLE/PIB regimen were the five most influential factors. For the patients with HCV genotype 2 infection, the ICER of GLE/PIB was $12,914/QALY with 95% confidence interval of $4,047/QALY to $37,640/QALY. The GLE/PIB regimen statistically cannot be ruled out as a cost-effective option for HCV genotype 2 infection.

**Conclusions:** GLE/PIB is a cost-effective strategy to treat chronic HCV genotype 1 and HCV genotype 2 infection in China. This regimen should be initiated at a younger age to maximize its value. To achieve

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national eradication, it may be timely to consider replacing pegIFN + RBV with DAAs, such as GLE/PIB, as the first-line treatment.

**Keywords:** Glecaprevir/pibrentasvir (GLE/PIB); direct acting antiviral (DAA); cost-effectiveness; Markov model; hepatitis C virus (HCV); health economics

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## Introduction

Hepatitis C virus (HCV) is a major global epidemic and of significant public health and economic importance in China. Like most developed countries, China is now entering the era of all-oral regimens for HCV treatment which is based on direct acting antiviral agents (DAAs). This is considered a necessary step towards achieving the WHO target of HCV elimination by 2030 (1). Although China is a latecomer to the DAA campaign, most DAAs have been marketed in China since sofosbuvir/velpatasvir was first approved in 2018 (2). Thereafter, approval of DAAs have accelerated. To date, nine drugs have been listed for government procurement according to the China Healthcare Security Administration (CHSA) (3), thus allowing for expanded accessibility to DAAs in Chinese patients.

China has a huge HCV burden of 10 million infections, most of which are chronic cases (4). Chronic HCV infection (CHC) is debilitating and can lead to liver fibrosis, cirrhosis and other severe and expensive end-stage liver diseases such as decompensated cirrhosis (DCC) and hepatocellular carcinoma (HCC), both of which may require liver transplantation (LT). It was estimated that HCC patients in China have contributed to more than 93,000 liver-related deaths (LDs) in 2005. Patients with HCV also experienced declines in quality of life (QoL) compared to the general population. From an economic perspective, annual medical expenses of HCV amounted to RMB 7.5 billion, and total annual work productivity loss from CHC was greater than RMB 18.11 billion in China (5).

DAAs are highly effective in curing CHC and are poised to play an important role in HCV elimination in China. Most pan-genetic DAAs have achieved a sustained virologic response (SVR) rate of above 95%, much higher than the traditional standard-of-care (SOC) comprising interferon (IFN) and ribavirin (RBV) (6). SVR rate refers to the proportion of patients who have HCV clearance from the blood after a full course of treatment and is an important index for drug efficacy. Besides the high SVR rates, DAA regimens also have a short treatment duration and a good safety profile. They can be administered orally compared to the injectable SOC regimen, thus contributing to higher drug compliance. Several studies have shown that DAA-based oral regimens were cost-effective or even cost-saving relative to IFN-based regimens (7-10).

In 2019, the glecaprevir/pibrentasvir (GLE/PIB) tablet was approved in China. GLE/PIB belongs to the pan-genetic DAA class and has been marketed in the form of a fixed dose combination of glecaprevir, a NS3/4 inhibitor, and pibrentasvir, a NS5A inhibitor. The average current price for a GLE/PIB tablet (100 mg/40 mg) is RMB 410 (3). A clinical trial recruiting Chinese patients showed that GLE/PIB achieved an SVR of 99.44% and 97.84% in HCV genotype 1 and HCV genotype 2 infections respectively, while the serious adverse event (SAE) rate was only 1.66%. In comparison, the corresponding SVRs when using the first line agents pegylated IFN (pegIFN) + RBV were 57.88% and 81.32% respectively. Studies in Japan and Brazil have indicated that GLE/PIB could be an economical option for HCV treatment given its excellent clinical efficacy (7,11).

Despite the clinical and potential economic advantages of DAA, more specifically GLE/PIB, it could still be a long time before DAAs replace the SOC. Most DAAs are currently not covered by national health insurance, while expenses for pegIFN + RBV are reimbursed at 70% to 90%. The prices of DAAs were generally considered high against the average Chinese income level although these prices were agreed through negotiations between the government and the pharmaceutical industry. The agreed prices were published on official websites as reference price (3). Therefore, the use of DAAs is still limited in spite of clinical guidelines starting to recommend the pan-genetic regimens as the preferable treatment strategy for all types of HCV infection.

 

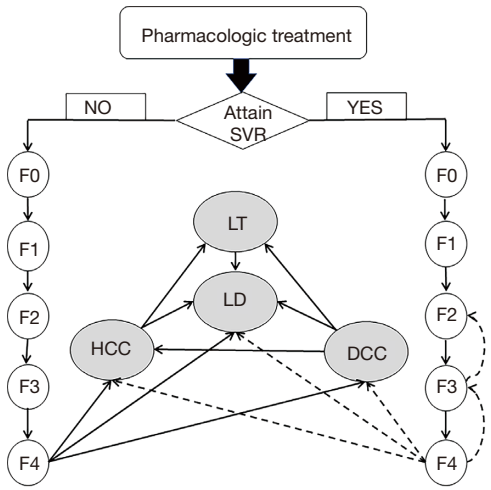


**Figure 1** Natural history of chronic HCV progression. Dashed line represents the slow transition or regression due to sustained virologic response. DCC, decompensated cirrhosis; F0, METAVIR fibrosis score 0; F1, METAVIR fibrosis score 1; F2, METAVIR fibrosis score 2; F3, METAVIR fibrosis score 3; F4, METAVIR fibrosis score 4; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LD, liver-related death; LT, liver transplantation; SVR, sustained virologic response.

Therefore, this study was conducted to evaluate the cost-effectiveness of GLE/PIB in the treatment of CHC in China. Furthermore, we aim to identify key factors to inform policy making, clinical practice, price negotiation and drug imbursement.

We present the following article in accordance with the CHEERS reporting checklist (available at https://dx.doi.org/10.21037/apm-21-863).

## Methods

This was a model-based cost-effectiveness analysis from a healthcare payer's perspective. The clinical pathway of a cohort of CHC patients was simulated using a Markov cohort model: a state-transition model quantitatively simulating the experience of the target population through a series of health states. As patients progress through health states, the cost of disease management and quality adjusted life years (QALYs) cumulate until the modelling terminates at the time of 99% of cohort deaths. Thus, we adopted a lifetime horizon setting. Markov cycle was set as one year.

### *Target population*

The target population was treatment-naïve Chinese CHC patients aged 18 years and older who have not developed liver fibrosis. Pediatric patients were excluded as this group requires substantial modification of the treatment regimen. The model focused on the two most popular HCV genotypes in China mainland, namely genotype 1 and genotype 2 (12).

### *Model conceptualization and construction*

The model was conceptualized based-on the natural history of CHC with the major assumptions as below (*Figure 1*).

(I) Fibrosis progressed in a linear path from no fibrosis to cirrhosis. The jumping among fibrosis states was not considered (13).
(II) HCC occurred only after the development of cirrhosis. The risk of HCC was assumed negligible for patients in pre-cirrhosis stages.
(III) Patients achieving SVR underwent fibrosis progression, although slower than those without an SVR (14).
(IV) SVR represented the overall clinical efficacy therefore treatment failure due to virological breakthrough, relapse or drug discontinuation was not explicitly modelled.
(V) Patients' long-term health outcomes were associated with their SVR status and independent of the regimens used in the past.
(VI) The effect of reinfection or retreatment on the long-term cost-effectiveness was considered minor and thus not modelled explicitly (15).

A series of Markov states were defined corresponding to health states characterizing CHC progression and clinical outcomes. These states were METAVIR fibrosis scores F0 (CHC patients without fibrosis), F1 (portal fibrosis without septa), F2 (portal fibrosis with few septa), F3 (numerous septa without cirrhosis) and F4 (cirrhosis), DCC, HCC, LT, LD and all-cause death. Modelling started at the initiation of pharmacologic treatment as per the prevailing clinical protocol. As the disease progressed, a patient with CHC would develop liver fibrosis and later cirrhosis. This was followed by severe complications or end stage liver diseases such as DCC, HCC and LT. LD was modelled to reflect the excessive deaths due to liver failure. Throughout the

 

lifetime horizon, the target population was subject to all-cause mortality which was estimated using Chinese lifetables (16). Half-cycle correction was implemented to improve the precision of the model results. The model was populated with the most accurate and recent data accessible. To improve the relevance of model outputs to decision-making stakeholders in China, great efforts were made to retrieve data on Chinese patients. If multiple resources were available for one parameter, meta-analytic methods were applied to synthesize the data. The model was built using Treeage Pro Suite 2019 (TreeAge Pro 2020, R1. TreeAge Software, Williamstown, MA, USA).

### *Candidate strategy and the reference case*

The candidate strategy was GLE/PIB (100 mg/400 mg) for 8–16 weeks, as per the Clinical Guideline for Treatment and Prevention of HCV Infection jointly issued by the Chinese Society of Hepatology and the Chinese Society of Infectious Diseases (17). The reference case was the traditional SOC in China consisting of pegIFN + RBV for 48 weeks (18,19).

### *SVR and its comprehensive effect*

The primary efficacy parameter for each regimen was the SVR rate at 24 weeks (SVR-24) after the end of treatment (*Table 1*). For the GLE/PIB regimen, the SVR-24 was obtained from a recent clinical trial on Chinese patients (20). For the pegIFN + RBV regimen, the SVR-24 was obtained from real-world studies (18,19,21). SAE rates were independently modelled as they consumed medical resources and decreased patient utility. Failing to model SAE explicitly could underestimate the value of the GLE/PIB regimen as it is associated with a lower SAE. The SAE rates of both regimens were used from the same studies to maintain consistency among different inputted parameters of the same model.

Given that the higher SVR is the main advantage distinguishing all-oral DAA regimens from IFN-based regimens, our model fully captured the multiple effects associated with the SVR, which were not only restricted to clinical aspects, but also to cost (*Table 1*). The clinical effect of SVR was represented with fibrosis regression (F4 to F3, F3 to F2), and reduced risk of HCC, DCC and LD for patients with cirrhosis (23-25). In addition, the cost of managing each stage of fibrosis was reduced compared to those without the SVR (22). However, once patients developed DCC, HCC or LT, we assumed that the past SVR would not affect subsequent disease progression.

### *Transition probabilities*

Data on fibrosis progression of Chinese patients is lacking, so we used the estimates from the most recent meta-analysis summarizing fibrosis progression of CHC (27). The transitions after cirrhosis were estimated using data synthesized from multiple studies. The probability of LT for patients with DCC or HCC was extracted from a report of the China Liver Transplantation Registry (28) (*Table 2*).

### *Cost*

From the perspective of payers, only direct medical costs were collected measuring the opportunity cost for HCV management (*Table 2*). Direct medical costs encompass drug costs, monitoring costs, hospitalization, LT and other costs due to the consumption of healthcare services. Drug costs were calculated using the reference prices of GLE/PIB, pegIFN and RBV published on an official website (3). These prices represent the acquisition cost of the drugs borne by public hospitals. We used the average of province-specific prices to represent the national level. Costs for health states were retrieved from studies on Chinese patient samples. Costs reported in different years were adjusted by the annual consumer price index (CPI) to the constant US dollar ($) in 2020.

### *Utility*

Utility was represented by QoL scores in the EQ-5D (*Table 2*). Utility data were extracted from the literature and further adjusted with the QoL estimates from a meta-analysis including data on the Chinese population (29,30,35).

### *Statistical analysis*

The overall cost-effectiveness of GLE/PIB was evaluated at base-case analysis where all parameters assumed the best estimates. The total cost and QALYs for GLE/PIB and pegIFN + RBV were computed separately and compared to generate the incremental cost-effectiveness ratio (ICER) which was the difference in cost divided by the difference in QALYs between the two regimens. The ICER represents the amount that a jurisdiction needs to pay for one additional QALY created by GLE/PIB. Subgroup analysis by HCV genotype was conducted with the view

 

**Table 1** Clinical efficacy of the GLE/PIB and pegIFN + RBV and SVR effect on cost and health outcomes

| Clinical parameter | Expected value | Lower limit | Higher limit | Distribution | Distribution parameter | | Source |
|---|---|---|---|---|---|---|---|
| Clinical efficacy of GLE/PIB (%) | | | | | | | |
| SVR for HCV genotype 1 infection | 99.44 | 96.92 | 100 | Beta | 178 | 1 | (20) |
| SVR for HCV genotype 2 infection | 97.84 | 93.82 | 100 | Beta | 136 | 3 | |
| SAE | 1.66 | 0.34 | 2.97 | Beta | 6 | 356 | |
| Clinical efficacy of pegIFN + RBV (%) | | | | | | | |
| SVR for genotype 1 | 57.88 | 49.48 | 67.29 | Beta | 169 | 123 | (18,19,21) |
| SVR for genotype 2 | 81.32 | 68.75 | 95.53 | Beta | 148 | 34 | |
| SAE | 8.70 | 2.42 | 20.79 | Beta | 4 | 42 | |
| Comprehensive effect of SVR | | | | | | | |
| Cost reduction (RR) | 0.709 | 0.592 | 0.855 | Log normal | −0.344 | 0.094 | (22) |
| Fibrosis regression (%) | 13.66 | 8.39 | 20.17 | Beta | 137 | 863 | (14) |
| Reduction of progression from cirrhosis to end stage liver disease (HR) | | | | | | | |
| Cirrhosis to DCC | 0.16 | 0.04 | 0.59 | Log normal | −1.833 | 0.687 | (23-26) |
| Cirrhosis to HCC | 0.24 | 0.18 | 0.31 | Log normal | | | |
| Cirrhosis to death | 0.23 | 0.1 | 0.52 | Log normal | −1.470 | 0.421 | |

DCC, decompensated cirrhosis; GLE, glecaprevir; HCC, Hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; ICER, Incremental Cost-Effectiveness Ratio; pegIFN, pegylated interferon; PIB, pibrentasvir; QALY, quality adjusted life year; RBV, ribavirin; RR, relative risk; SAE, serious adverse event; SVR, sustained virologic response.

**Table 2** Inputted model parameters

| Model parameter | Expected value | Lower limit | Higher limit | Distribution | Distribution parameter | | Source |
|---|---|---|---|---|---|---|---|
| Direct medical cost of HCV treatment ($) | | | | | | | |
| F0-3 | 1,971 | 593 | 7,565 | Gamma | 3,344 | 1,162 | (29,30) |
| Cirrhosis | 4,760 | 884 | 26,766 | Gamma | 6,182 | 4,314 | |
| HCC | 28,936 | 4,618 | 97,943 | Gamma | 28,936 | 15,554 | (8,10,31) |
| LT during 1st year | 147,854 | 36,765 | 76,923 | Gamma | 147,854 | 64,591 | (29,31,32) |
| LT 2nd year onwards | 24,374 | 7,352 | 9,457 | Gamma | 24,374 | 10,560 | (22,29) |
| DCC | 14,477 | 2,589 | 50,441 | Gamma | 14,477 | 7,975 | (8,10,29) |
| Transition probability (%) | | | | | | | |
| F0 to F1 | 10.70 | 9.70 | 11.80 | Beta | 1070 | 8930 | (27) |
| F1 to F2 | 8.20 | 7.40 | 9.10 | Beta | 82 | 918 | |
| F2 to F3 | 11.70 | 10.70 | 12.90 | Beta | 117 | 883 | |
| F3 to cirrhosis | 11.60 | 10.40 | 13.10 | Beta | 116 | 884 | |
| Cirrhosis to DCC | 4.28 | 3.80 | 5.30 | Beta | 43 | 957 | (8,10,33) |
| Cirrhosis to HCC | 1.90 | 1.70 | 2.10 | Beta | 19 | 981 | |

**Table 2** (*continued*)

**Table 2** (*continued*)

| Model parameter | Expected value | Lower limit | Higher limit | Distribution | Distribution parameter | | Source |
|---|---|---|---|---|---|---|---|
| Cirrhosis to death | 2.73 | 1.38 | 4.08 | Beta | 27 | 973 | |
| DCC to LT | 3.76 | 0.03 | 10.40 | Beta | 3.76 | 96.24 | (34) |
| DCC to death during 1st year diagnosis | 14.7 | 5.20 | 26.00 | Beta | 14.7 | 85.3 | |
| DCC to HCC | 3.75 | 2.10 | 6.80 | Beta | 37.5 | 962.5 | |
| HCC to LT | 2.12 | 0.05 | 4.00 | Beta | 21.2 | 978.8 | (29) |
| HCC to death | 44.80 | 34.90 | 57.60 | Beta | 49.6 | 110.4 | |
| Death rate of year 1 post-LT | 23.51 | 20.90 | 26.25 | Beta | 235.1 | 764.9 | (28) |
| Death rate of year 2 post-LT | 8.22 | 6.58 | 10.08 | Beta | 82.2 | 917.8 | |
| Death rate of year 3 post-LT | 8.22 | 6.58 | 10.08 | Beta | 82.2 | 917.8 | |
| Death rate of year 4 post-LT | 5.11 | 3.82 | 6.65 | Beta | 51.1 | 948.9 | |
| All-cause death | Age-gender specific mortality of China life table of 2019 | | | | | | (16) |
| Proportion of genotypes in China (%) | | | | | | | |
| HCV genotype 1 | 62.78 | 59.54 | 66.02 | Beta | 628 | 372 | (12) |
| HCV genotype 2 | 17.39 | 15.67 | 19.11 | Beta | 174 | 826 | |
| Utility | | | | | | | |
| F0/F1 without SVR | 0.878 | 0.751 | 0.985 | Normal | 0.878 | 0.039 | (29,30,35) |
| F2/F3 without SVR | 0.863 | 0.701 | 0.985 | Normal | 0.863 | 0.0473 | |
| Cirrhosis | 0.792 | 0.67 | 0.907 | Normal | 0.792 | 0.0395 | |
| DCC | 0.576 | 0.41 | 0.66 | Normal | 0.576 | 0.0417 | |
| HCC | 0.685 | 0.532 | 0.821 | Normal | 0.685 | 0.0482 | |
| LT during 1st year | 0.663 | 0.563 | 0.8 | Normal | 0.663 | 0.0395 | |
| LT from 2nd year onwards | 0.773 | 0.636 | 0.85 | Normal | 0.773 | 0.0357 | |
| F0/F1 with SVR | 0.928 | 0.806 | 1 | Normal | 0.928 | 0.0323 | |
| F2 with SVR | 0.911 | 0.791 | 1 | Normal | 0.911 | 0.0348 | |
| F3 with SVR | 0.893 | 0.766 | 1 | Normal | 0.893 | 0.039 | |
| Cirrhosis with SVR | 0.85 | 0.722 | 0.955 | Normal | 0.85 | 0.0388 | |
| Other parameters | | | | | | | |
| Discount rate (%) | 3 | 0 | 5 | | | | (36) |
| WTP ($/QALY) | 10,275 | | | – | | | (37) |

DCC, decompensated cirrhosis; F0, METAVIR fibrosis score 0; F1, METAVIR fibrosis score 1; F2, METAVIR fibrosis score 2; F3, METAVIR fibrosis score 3; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; QALY, quality adjusted life year; SVR, sustained virologic response; WTP, willingness-to-pay.

**Table 3** Overall and genotype-specific cost effectiveness of GLE/PIB

| Population | Regimen | Cost ($) | Incremental cost ($) | Utility (QALY) | Incremental utility (QALY) | ICER ($/QALY) |
|---|---|---|---|---|---|---|
| Overall | PegIFN/RBV | 51,887 | | 23.34 | | |
| | GLE/PIB | 51,632 | −255 | 24.51 | 1.17 | Dominant |
| HCV genotype 1 | PegIFN/RBV | 53,025 | | 23.17 | | |
| | GLE/PIB | 51,369 | −1,656 | 24.54 | 1.37 | Dominant |
| HCV genotype 2 | PegIFN/RBV | 44,670 | 0 | 23.94 | 0 | 0 |
| | GLE/PIB | 51,696 | 7,026 | 24.49 | 0.55 | 12,914 |

GLE, glecaprevir; HCV, hepatitis C virus; ICER, Incremental Cost-Effectiveness Ratio; pegIFN, pegylated interferon; PIB, pibrentasvir; RBV, ribavirin; QALY, quality adjusted life year.

that patients with a different genotype have demonstrated different responsiveness to DAA and thus downstream CHC prognosis. Models were built for HCV genotype 1 and genotype 2 infected patients separately and genotype-specific ICERs were estimated.

Following the WHO rule, the per capita GDP of China in 2019 RMB 70,581 ($10,275 when applying the average exchange rate of 6.91 for the year) was used conservatively as the willingness-to-pay (WTP) threshold in our study. The regimen with an ICER less than $10,275 for one QALY gained was considered cost-effective. Cost and QALYs were both discounted on an annual rate of 3% to the constant value in 2020 (38).

Both deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were carried out to primarily examine the robustness of model decisions. One-way DSA also assessed the influence of parameters within their plausible ranges. PSA evaluated the random uncertainty of models by running 10,000 Monte Carlo simulations on all relevant parameter distributions. PSA results were presented as cost-effectiveness acceptability curves (CEAC).

## Results

### *Base-case analysis*

For the target population, changing from the pegIFN + RBV regimen to the GLE/PIB regimen would create 1.17 more QALYs with an average saving of $255 (*Table 3*). Thus, the pegIFN + RBV regimen was economically dominated by the GLE/PIB regimen in the Chinese healthcare context. The cost-effectiveness of the GLE/PIB regimen appeared to be genotype specific. For HCV genotype 1 infection, the GLE/PIB regimen would save $1,656 yet create 1.37 more QALYs on one patient, thus exhibiting economic dominance over the pegIFN + RBV regimen. This economic superiority was not present for HCV genotype 2 infection which was associated with an ICER of $12,914/QALY, which was higher than our WTP standard of $10,275.

### *Deterministic sensitivity analysis*

The cost-effectiveness of the GLE/PIB regimen appeared to be robust to plausible variations of all parameters (*Figure 2*). Although the ICER varied greatly with some parameters, it remained below the threshold of $10,275/QALY. The ten most impactful parameters identified in the DSA were, in the descending order, price of pegIFN, age starting treatment, cost of treating cirrhosis, duration of the GLE/PIB regimen, price of RBV, cost reduction due to SVR, cost of DCC treatment, cost of fibrosis treatment, price of the GLE/PIB tablets and cost of treating HCC (*Figure 2*).

All the 10 parameters were cost-related. Their results were in the direction as expected theoretically. For instance, as the price of the pegIFN + RBV regimen decreased, the ICER associated with the GLE/PIB regimen increased, suggesting that the GLE/PIB regimen was a relatively expensive option. Likewise, reducing the price and treatment duration of the GLE/PIB regimen would lead to this strategy being more cost-effective or cost-saving. If the GLE/PIB regimen was administered at a younger age, the DAA regimen would gain more favor than if administered at an older age.

### *Probabilistic sensitivity analysis*

PSA results confirmed the findings of the base-case analysis that the GLE/PIB regimen was cost-saving for the entire

 

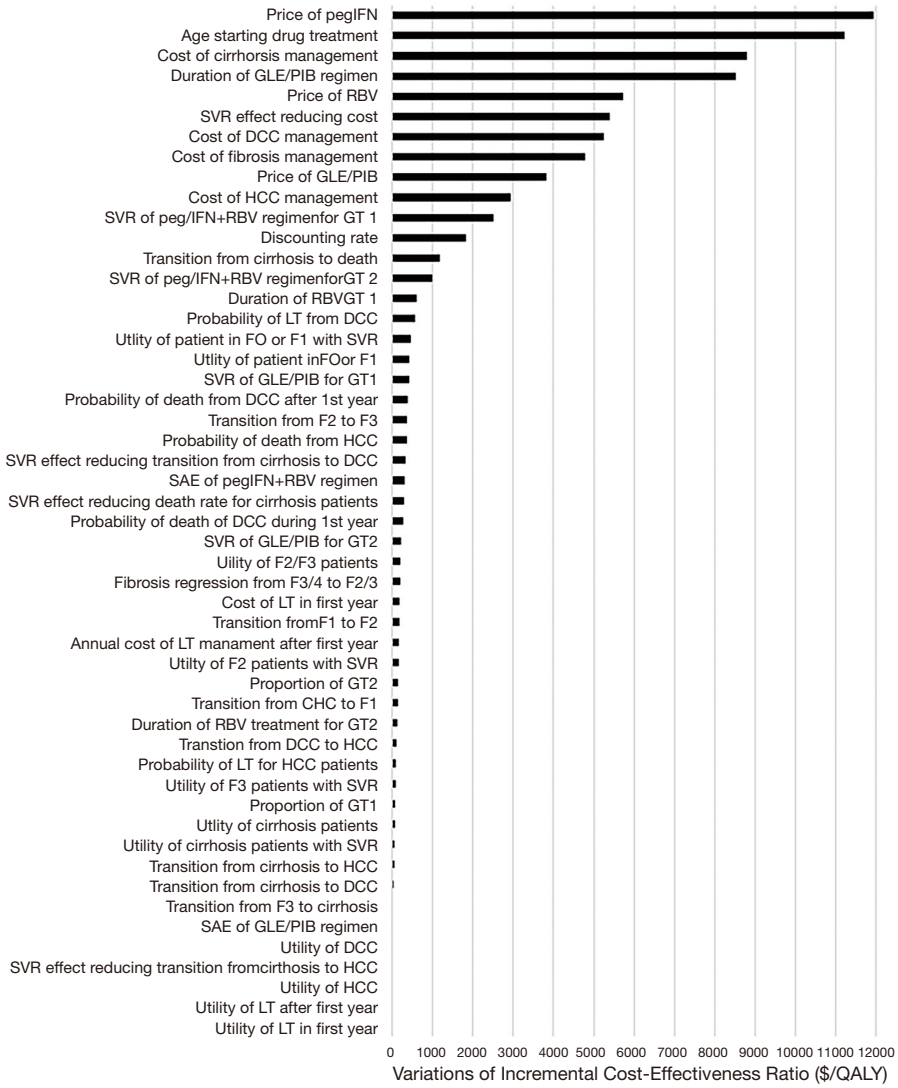


**Figure 2** Deterministic sensitivity analysis evaluating effects of model parameters on model outputs. DCC, decompensated cirrhosis; F0, METAVIR fibrosis score 0; F1, METAVIR fibrosis score 1; F2, METAVIR fibrosis score 2; F3, METAVIR fibrosis score 3; F4, METAVIR fibrosis score 4; GLE, glecaprevir; GT, genotype; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LD, liver-related death; LT, liver transplantation; pegIFN, pegylated interferon; PIB, pibrentasvir; RBV, ribavirin; SAE, serious adverse event; SVR, sustained virologic response.

target population compared with the pegIFN + RBV regimen. As shown in the CEAC, the probability of being cost-effective for the GLE/PIB regimen was 50.99%, which was higher than 50%, at the null WTP (*Figure 3*). At the threshold of $10,275/QALY, the probability reached 99.32%. Additionally, the cost-effectiveness of GLE/PIB was robust across the full chosen range of WTP.

For the HCV genotype 1 infected patients, the GLE/PIB regimen was cost-saving 66.28% of the time and cost-effective 33.57% of the time (*Table 4*). While for HCV genotype 2 infected patients, the GLE/PIB regimen was the preferred regimen only when the WTP threshold was above $13,380. At the threshold of $10,275/QALY, the likelihood that the GLE/PIB regimen was the cost-effective option was 30.92% (*Figure 3*). Although the GLE/PIB regimen lost advantage to the pegIFN + RBV regimen in treating HCV

 

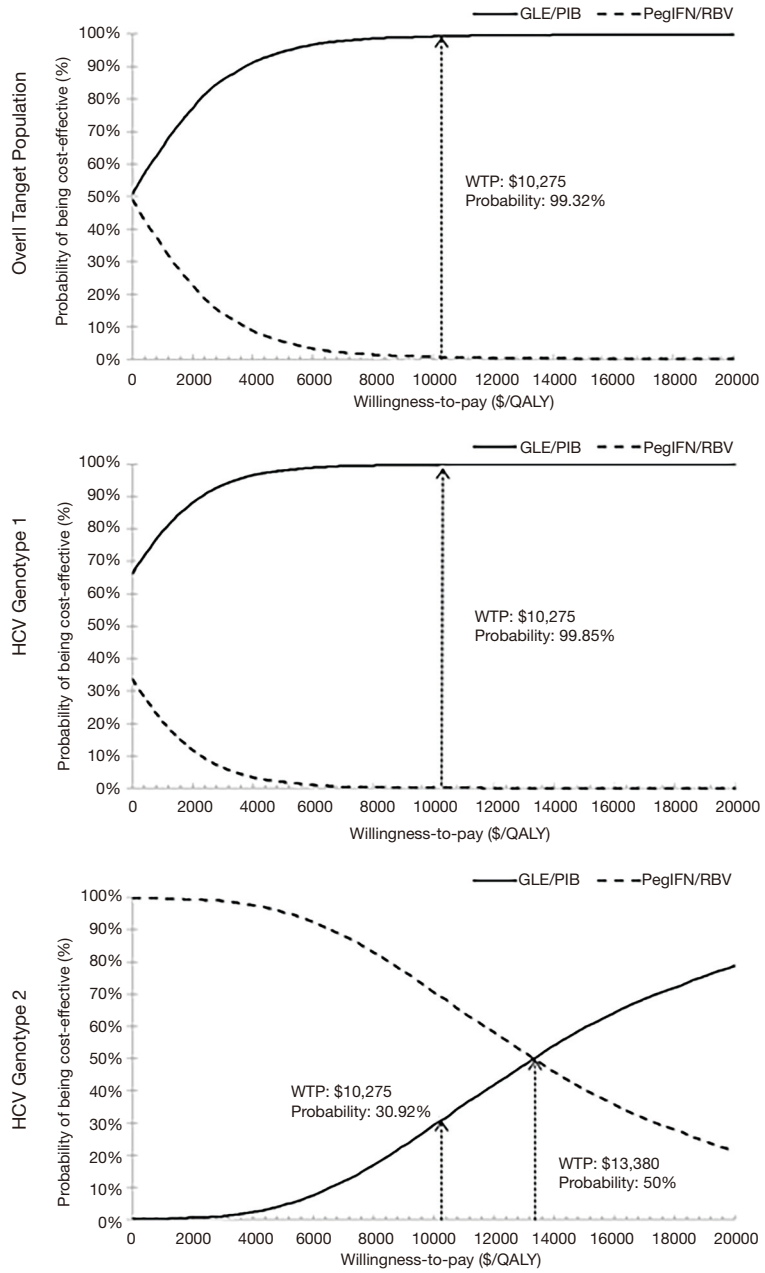


**Figure 3** Overall and genotype-specific cost-effectiveness acceptability curve showing the probability of cost-effectiveness. GLE, glecaprevir; HCV, hepatitis C virus; pegIFN, pegylated interferon; PIB, pibrentasvir; QALY, quality adjusted life year; RBV, ribavirin; WTP, willingness-to-pay.

genotype 2 infections, the 95% CI of its ICER covered the Chinese WTP of $10,275 (*Table 4*). Therefore, statistically, it cannot be ruled out that the GLE/PIB regimen was a potential cost-effective strategy for HCV genotype 2 infected patients.

## Discussion

From the perspective of payers, our study found that the GLE/PIB regimen is generally cost-saving in treating Chinese CHC patients with HCV genotype 1 or genotype 2 infections in the context of the Chinese healthcare

 

**Table 4** Probability of cost-effectiveness of GLE/PIB for the entire target population and genotype subpopulations

| Population | ICER($/QALY) | 95% CI for ICER ($/QALY) | Dominant (%) | Cost-effective (%) | Cost-ineffective (%) |
|---|---|---|---|---|---|
| Overall | Dominant | – | 50.99 | 48.33 | 0.68 |
| HCV genotype 1 | Dominant | – | 66.28 | 33.57 | 0.15 |
| HCV genotype 2 | 12,914 | 4,047–37,640 | 0.19 | 30.73 | 69.08 |

CI, confidence interval; GLE, glecaprevir; HCV, hepatitis C virus; ICER, Incremental Cost-Effectiveness Ratio; PIB, pibrentasvir; QALY, quality adjusted life year.

system. For an average adult patient naïve to pharmacologic treatment, the GLE/PIB regimen was associated with a life-time cost reduction of $255 and a gain of 1.17 QALYs compared to the pegIFN + RBV regimen. The cost-saving effect is more pronounced for CHC patients with HCV genotype 1 infection, while for HCV genotype 2 infection, the ICER associated with the GLE/PIB regimen was $12,914/QALY, which exceeded the GDP per capita threshold.

The cost-effectiveness of the GLE/PIB regimen appeared to be genotype-specific (*Table 3*) although the GLE/PIB regimen is a pan-genetic DAA. We speculate that the inter-genotype ICER difference has been driven by the genotype-specific SVR of the pegIFN + RBV regimen, as other parameters were almost the same between the two genotype models. The SVR of the pegIFN + RBV regimen for HCV genotype 1 infection was 57.88%, lower than the 81.32% for HCV genotype 2 infection. Given the similar SVR of the GLE/PIB regimen for HCV genotype 1 infection (99.44%) and genotype 2 infection (97.84%), the SVR increment was 41.57% (99.44% *vs.* 57.88%) for HCV genotype 1 infection whereas it was only 16.52% (97.84% *vs.* 81.32%) for HCV genotype 2 infection. Since SVR is a strong factor for cost-reduction as well as fibrosis progression (14,22,26), HCV genotype 2 infected patients would not benefit as much as HCV genotype 1 infected patients from the GLE/PIB regimen, thus making the all-oral regimen less attractive.

Despite the ICER of the GLE/PIB regimen being above the threshold for HCV genotype 2 infected patients, its 95%CI covered the WTP threshold. This means that the GLE/PIB regimen, statistically, cannot be ruled out as a cost-effective strategy for chronic infection with HCV genotype 2 (*Table 4*). In addition, the WHO recommended a threefold GDP per capita as the upper limit for the cost-effectiveness threshold ($30,825/QALY) and is larger than the ICER of $12,914/QALY associated with HCV genotype 2. The GLE/PIB regimen would be considered as cost-effective by a broad standard. Our study chose to be conservative because of the uneven economic development across China. For less developed areas with lower GDP, a cost-effectiveness decision based-on a threefold GDP per capita would not be applicable or feasible. The WHO has stated that national HCV elimination relies heavily on the universal coverage. In line with this principle, our findings based-on a stringent WTP threshold would better inform universal coverage of DAA in China.

The GLE/PIB regimen is the new generation of pan-genetic DAAs. International studies have shown that the GLE/PIB regimen is a valuable option for HCV treatment. Ferreira *et al.* found that the GLE/PIB regimen is cost-effective for treating Brazilian patients with HCV genotype 1 infection in the early fibrosis stages. It is superior to the sofosbuvir + velpatasvir regimen and the sofosbuvir + daclatasvir regimen (11). A Japanese study reached a similar conclusion that the GLE/PIB regimen is the best strategy among the four DAA regimens (7). In the US, the GLE/PIB regimen is considered a better value-for-money DAA than its predecessors (39). Similar to the above studies, our findings suggest that the GLE/PIB regimen is cost-effective in Chinese patients.

The well-established clinical efficacy of DAAs has stimulated great interest in their economic value in China (10,29,30,40). Taking the pegIFN + RBV regimen as the common base-case comparator and HCV genotype 1b infection as the target population, the sofosbuvir-ledipasvir regimen was shown to be economically advantageous (30). A 12-week course of sofosbuvir combined with ledipasvir or daclatasvir was also found to be cost-saving or cost-effective (21). The Daclatasvir + asunaprevir regimen has been reported as cost-effective. A comprehensive evaluation of several DAA strategies showed DAAs to be cost-effective or cost-saving in the Chinese healthcare context, despite being generally expensive (40). However, none of the previous studies evaluated the GLE/PIB regimen relative to the common baseline pegIFN + RBV regimen. Our results

 

corroborate the previous findings and further suggest that the newly approved GLE/PIB regimen is another preferred DAA for CHC management. It appears that the pegIFN + RBV regimen should be considered suboptimal to DAAs and it may be the time to replace the pegIFN-based regimen with DAA-based regimens as the first-line CHC treatment.

It has not yet been established when to initiate DAA treatment. Physicians start with the pegIFN + RBV regimen as first line treatment and then progress to the more expensive DAAs once the first line treatment fails or becomes intolerable. Our findings suggest that starting the GLE/PIB regimen as first line treatment at a younger age is cost-effective in the long term. Upfront spending on DAAs would be well balanced by cost-saving for expensive future complications. The GLE/PIB regimen continued to be cost-saving until the age of 53 years after which its ICER increased sharply in a linear fashion. Delaying the GLE/PIB treatment has proven to be an ineffective strategy from an economic point of view. Our findings promote the proactive use of DAAs, specifically the GLE/PIB regimen, to create more value for the patient and society alike. This finding was supported by other studies in Chinese and Scottish populations (10,41).

An advantage of our study is that we used more Chinese-specific data than other studies to better inform decision making specifically in a Chinese setting (10,29,30,42). The up-to-date SVR data of the GLE/PIB regimen and the pegIFN + RBV regimen were obtained from recent studies based on Chinese patients. The drug cost of the GLE/PIB regimen was the price actually charged to payers as per the National Health Commission of the People's Republic of China (3), rather than a hypothetical price or reference to a foreign price. The probabilities of receiving a LT and LT-related death are specific to local policies and the availability of live donors and quality of basic care. Therefore, we used data from the China Liver Transplantation Registry thereby ensuring that our findings were more relevant to the Chinese healthcare system (28).

The biggest difference in methodology distinguishing our study from others is that we assumed post-SVR fibrosis progression irrespective of the severity of baseline fibrosis. Previous studies normally did not assume post-SVR fibrosis progression unless patients had already developed cirrhosis (8,30,42). This may not be scientifically sound as post-SVR fibrosis progression was only observed in some studies (14). Excluding post-SVR progression would risk overestimating the value of DAAs. Another methodological distinction is that our study modelled the target population from the age of 18 which is approximately 25 years younger than other modelled cohorts (29,30,40). This is in line with the WHO target for countrywide HCV eradication.

### *Limitations*

As we used a Markov cohort model, our study could not adequately accommodate the demographic or clinical heterogeneity of the target population. The cost and QALY values may lack precision. Due to the lack of large-scale prospective studies on Chinese CHC, our models were unable to be validated against external data sources raising doubts about model validity. The dynamic nature of disease progression is not fully reflected, although age-dependent and time-dependent techniques were applied to parameters like LT-related death and all-cause mortality. Microsimulation is required to deal with heterogeneity and disease dynamics and such a study is ongoing in our team. The SVR of the GLE/PIB regimen was extracted from clinical trials. This may have over-estimated the effectiveness of the GLE/PIB regimen because in the real-world SVR may be lower (43). Our study did not clearly model treatment discontinuation, retreatment, reinfection or virus break-through where the GLE/PIB regimen is also superior to the pegIFN + RBV regimen. The advantage of the GLE/PIB regimen would thus be masked in some way. Lastly, the societal perspective is considered as the gold standard for HCV modeling. Our study did not take a societal perspective due to data availability. Thus, the economic value of the GLE/PIB regimen could be very conservative.

## Conclusions

GLE/PIB is a cost-effective treatment strategy for Chinese patients with chronic HCV genotype 1 and HCV genotype 2 infections. It is cost-saving for the most prevalent HCV genotype in China. The GLE/PIB regimen should be initiated at a younger age to maximize its value. To achieve the WHO target of HCV eradication, it is the time to replace the pegIFN + RBV regimen with DAAs as the first-line treatment for chronic HCV infection.

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## References

1. World Health Organization. Global Health Sector Strategy on Viral Hepatitis, 2016-2021 World Health Organization; 2016.
2. National Health Commission of the People's Republic of China. National essential drug list (2018). National Health Commission of the People's Republic of China, 2018.
3. Yaozhi. Price of Listed Drugs 2020. Available online: https://www.yaozh.com/
4. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017;2:161-76.
5. Ye X, Xu X, Xie Q, et al. Impact of Sofosbuvir-Based Regimens for Chronic Hepatitis C Infection: A Work Productivity Model from Mainland China. Value in Health 2018;21:S6.
6. Xie Q, Xuan JW, Tang H, et al. Hepatitis C virus cure with direct acting antivirals: Clinical, economic, societal and patient value for China. World J Hepatol 2019;11:421-41.
7. Kawaguchi I, Chayama K, Gonzalez YS, et al. A Cost-Effectiveness Analysis of Glecaprevir/Pibrentasvir Versus Existing Direct-Acting Antivirals to Treat Chronic Hepatitis C in Japan. Adv Ther 2020;37:457-76.
8. Lu Y, Jin X, Duan CA, et al. Cost-effectiveness of daclatasvir plus asunaprevir for chronic hepatitis C genotype 1b treatment-naïve patients in China. PLoS One 2018;13:e0195117.
9. Chen P, Ma A, Liu Q. Cost-Effectiveness of Elbasvir/Grazoprevir Versus Daclatasvir Plus Asunaprevir in Patients with Chronic Hepatitis C Virus Genotype 1b Infection in China. Clin Drug Investig 2018;38:1031-9.
10. Chen H, Chen L. Estimating cost-effectiveness associated with all-oral regimen for chronic hepatitis C in China. PLoS One 2017;12:e0175189.
11. Ferreira VL, Leonart LP, Pedroso MLA, et al. Cost-utility analysis of interferon-free treatments for patients with early-stage genotype 1 hepatitis C virus in Brazil. Rev Soc Bras Med Trop 2020;53:e20190594.
12. Zhang Y, Chen LM, He M. Hepatitis C Virus in mainland China with an emphasis on genotype and subtype distribution. Virol J 2017;14:41.
13. Lingala S, Ghany MG. Natural History of Hepatitis C. Gastroenterol Clin North Am 2015;44:717-34.
14. Balmaceda JB, Aepfelbacher J, Belliveau O, et al. Long-term changes in hepatic fibrosis following hepatitis C viral clearance in patients with and without HIV. Antivir Ther 2019;24:451-7.
15. Simmons B, Saleem J, Hill A, et al. Risk of Late Relapse or Reinfection With Hepatitis C Virus After Achieving a Sustained Virological Response: A Systematic Review and Meta-analysis. Clin Infect Dis 2016;62:683-94.
16. WHO. Global Health Observatory data repository: Life tables by country China. World Health Organization World Health Organization 2019. Accessed 2020-04-25. Available online: https://apps.who.int/gho/

 

data/?theme=main&vid=60340
17. Chinese Society of Hepatology and Chinese Society of Infectious Diseases CMA. Guidelines for the Prevention and Treatment of Hepatitis C (2019 Version). Journal of Clinical Hepatology 2019;35:2670-86.
18. Rao HY, Li H, Chen H, et al. Real-world treatment patterns and clinical outcomes of HCV treatment-naive patients in China: an interim analysis from the CCgenos study. J Gastroenterol Hepatol 2017;32:244-52.
19. Li Y, Wang J, Wang J, et al. SVR Rates of HCV-infected population under PEG-IFN-α/R treatment in Northwest China. Virol J 2017;14:62.
20. Wei L, Wang G, Alami NN, et al. Glecaprevir-pibrentasvir to treat chronic hepatitis C virus infection in Asia: two multicentre, phase 3 studies- a randomised, double-blind study (VOYAGE-1) and an open-label, single-arm study (VOYAGE-2). Lancet Gastroenterol Hepatol 2020;5:839-49.
21. Ji D, Chen GF, Wang C, et al. Twelve-week ribavirin-free direct-acting antivirals for treatment-experienced Chinese with HCV genotype 1b infection including cirrhotic patients. Hepatol Int 2016;10:789-98.
22. Wu B, Li T, Chen H, et al. Cost-effectiveness of nucleoside analog therapy for hepatitis B in China: a Markov analysis. Value Health 2010;13:592-600.
23. Morgan RL, Baack B, Smith BD, et al. Eradication of hepatitis C virus infection and the development of hepatocellular carcinoma: a meta-analysis of observational studies. Ann Intern Med 2013;158:329-37.
24. Backus LI, Belperio PS, Shahoumian TA, et al. Impact of Sustained Virologic Response with Direct-Acting Antiviral Treatment on Mortality in Patients with Advanced Liver Disease. Hepatology 2019;69:487-97.
25. El-Raziky M, Khairy M, Fouad A, et al. Effect of Direct-Acting Agents on Fibrosis Regression in Chronic Hepatitis C Virus Patients' Treatment Compared with Interferon-Containing Regimens. J Interferon Cytokine Res 2018;38:129-36.
26. Singal AG, Volk ML, Jensen D, et al. A sustained viral response is associated with reduced liver-related morbidity and mortality in patients with hepatitis C virus. Clin Gastroenterol Hepatol 2010;8:280-8.e1.
27. Erman A, Krahn MD, Hansen T, et al. Estimation of fibrosis progression rates for chronic hepatitis C: a systematic review and meta-analysis update. BMJ Open 2019;9:e027491.
28. Wang H, Jiang W, Zhou Z, et al. Liver transplantation in mainland China: the overview of CLTR 2011 annual scientific report. Hepatobiliary Surg Nutr 2013;2:188-97.
29. Liu Y, Wang Z, Tobe RG, et al. Cost Effectiveness of Daclatasvir Plus Asunaprevir Therapy for Chinese Patients with Chronic Hepatitis C Virus Genotype 1b. Clin Drug Investig 2018;38:427-37.
30. Chen GF, Wei L, Chen J, et al. Will Sofosbuvir/Ledipasvir (Harvoni) Be Cost-Effective and Affordable for Chinese Patients Infected with Hepatitis C Virus? An Economic Analysis Using Real-World Data. PLoS One 2016;11:e0155934.
31. Chen H, Chen J, Lu Z, et al. Establish Pharmacoeconomics Model for Treatment of Chronic Hepatitis C with Markov Model. Chinese Journal of Health Statistics 2016;33:5.
32. Hu M, Chen W. Assessment of total economic burden of chronic hepatitis B (CHB)-related diseases in Beijing and Guangzhou, China. Value Health 2009;12 Suppl 3:S89-92.
33. Lee MH, Huang CF, Lai HC, et al. Clinical Efficacy and Post-Treatment Seromarkers Associated with the Risk of Hepatocellular Carcinoma among Chronic Hepatitis C Patients. Sci Rep 2017;7:3718.
34. Najafzadeh M, Andersson K, Shrank WH, et al. Cost-effectiveness of novel regimens for the treatment of hepatitis C virus. Ann Intern Med 2015;162:407-19.
35. Buchanan-Hughes AM, Buti M, Hanman K, et al. Health state utility values measured using the EuroQol 5-dimensions questionnaire in adults with chronic hepatitis C: a systematic literature review and meta-analysis. Qual Life Res 2019;28:297-319.
36. Sanders GD, Neumann PJ, Basu A, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA 2016;316:1093-103.
37. China National Bureau of Statistics. Report of Gross Demostic Product. China National Bureau of Statistics, Beijing, China. 2020. Accessed 2020-08-05. Available online: https://data.stats.gov.cn/easyquery.htm?cn=C01
38. Weinstein MC, Siegel JE, Gold MR, et al. Recommendations of the Panel on Cost-effectiveness in Health and Medicine. JAMA 1996;276:1253-8.
39. Tatar M, Keeshin SW, Mailliard M, et al. Cost-effectiveness of Universal and Targeted Hepatitis C Virus Screening in the United States. JAMA Netw Open 2020;3:e2015756.
40. Wu B, Wang Z, Xie Q. Cost-effectiveness of novel regimens for Chinese patients with chronic hepatitis C. Curr Med Res Opin 2019;35:847-57.
41. Pinsky B, Mitchell D, Sanchez Y, et al. Early versus

 

delayed hepatitis C treatment provides increased health benefits at lower costs: A pan-genotypic cost effectiveness analysis set in Scotland. J Hepatol 2018;68:S32.
42. Chen PY, Liu Q, Li HC, et al. The Cost-Effectiveness Analysis of Elbasvir/Grazoprevir Versus Peginterferon Alpha-2A in Combination with Ribavirin in Patients with Chronic Hepatitis C Genotype 1b Infection in China. Value in Health 2018;21:S65.
43. Ikeda H, Watanabe T, Atsukawa M, et al. Evaluation of 8-week glecaprevir/pibrentasvir treatment in direct-acting antiviral-naïve noncirrhotic HCV genotype 1 and 2infected patients in a real-world setting in Japan. J Viral Hepat 2019;26:1266-75.

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