Estimating the cost-effectiveness of screening for hepatitis C virus infection in Japan

Kota Nagai, MSc[a,b]; Kazuki Ide, PhD[a,c]; Yohei Kawasaki, PhD[d]; Sachiko Tanaka-Mizuno, PhD[e]; Kahori Seto, DDS, PhD[a]; Shinji Iwane, MD, PhD[f]; Yuichiro Eguchi, MD, PhD[f]; Koji Kawakami, MD, PhD[a,c]*

[a] Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Yoshida-konoecho, Sakyo-ku, Kyoto 606-8501, Japan; [b] Eisai Co., Ltd., 4-6-10 Koishikawa, Bunkyo-ku, Tokyo 112-8088, Japan; [c] Center for the Promotion of Interdisciplinary Education and Research, Kyoto University, Kyoto 606-8501, Japan; [d] Biostatistics Section, Clinical Research Center, Chiba University Hospital, 1-8-1 Inohana, Chuo-ku, Chiba-shi, Chiba 260-8677, Japan; [e] Department of Medical Statistics, Shiga University of Medical Science, Seta Tsukinowa-cho, Otsu, Shiga 520-2192, Japan; [f] Liver Center, Saga University Hospital, Nabeshima, Saga 849-8501, Japan

***Correspondence:**

Koji Kawakami, MD, PhD

Department of Pharmacoepidemiology

Graduate School of Medicine and Public Health, Kyoto University

Yoshida- Konoe-cho, Sakyo-ku, Kyoto 606-8501, Japan

Tel: +81-75-753-9469, Fax: +81-75-753-4469

Email: kawakami.koji.4e@kyoto-u.ac.jp

Running title: Cost-effectiveness of screening for HCV in Japan

Funding: This study received no funding support.

Conflict of interest: K.N. is an employee of Eisai Co., Ltd. K.K. has received consulting fees from Shin Nippon Biomedical Laboratories, Ltd.; research funds from Olympus Corporation, Sumitomo Dainippon Pharma Co., Ltd., Bayer Yakuhin Ltd., Stella Pharma Corporation, Novartis Pharma K.K., CMIC Co., Ltd., Amgen Astellas BioPharma K.K., Suntory Beverage & Food Ltd., Medical Platform Co., Ltd.; and owns stocks in School Health Record Center Co., Ltd., Real World Data Co., Ltd. No other disclosures were reported.

Abstract

Aim: The management of hepatitis C virus (HCV) has changed with the advent of interferon (IFN) free treatment and the declining prevalence of HCV infection, which may impact the cost-effectiveness of the screening. We aimed to compare the cost-effectiveness and clinical outcomes of three screening strategies in Japanese general population: no screening, screening plus IFN-based therapy, and screening plus IFN-free therapy.

Methods: We developed a decision analytic Markov model for screening intervention and natural history of HCV. Model parameters were derived from published literature. A lifetime horizon and the healthcare payer perspective were taken. Sub-analyses included high screening scenario with improved rates of screening and attending referral in addition to heterogeneity analysis by age subgroup.

Results: In the base case, incremental cost-effectiveness ratio (ICER) in the Japanese general population aged 40–89 years was JPY 1,124,482 and JPY 1,085,183 per quality-adjusted life year (QALY) gained for screening plus IFN-free therapy compared to no screening and screening plus IFN-based therapy, respectively. Screening plus IFN-free therapy remained cost-effective below JPY 5,000,000/QALY gained in sensitivity analyses. ICERs were lower in the younger population. Nearly 0.2% of HCV-related deaths were avoided by 1.5% of the general population screened followed by IFN-free therapy relative to no screening; the impact was greater with improved rates of screening and attending referral.

Conclusions: Screening and subsequent IFN-free therapy for HCV appears to be cost-effective. Early diagnosis and treatment would produce favorable ICER. Improved

rates of screening and attending referral would result in further reduction of disease progression.

Keywords: cost-effectiveness, direct-acting antiviral, hepatitis C virus, Japan, screening

Introduction

An estimated 71 million people have chronic hepatitis C virus (HCV) infection worldwide, and nearly 400,000 patients die annually from HCV-related liver diseases such as liver cirrhosis and hepatocellular carcinoma (HCC).[1] In Japan, approximately 2 million individuals were estimated to be infected with HCV in the year 2000,[2] and approximately 30,000 patients annually die of liver cancer.[3] Infection with HCV is the leading cause of cirrhosis and liver cancer in Japan.[4,5] National health care costs for hepatitis virus and malignant neoplasm on liver and intrahepatic bile duct in Japan were approximately 170 and 150 billion yen in 2014, respectively.[6] Infection with HCV has a significant public impact; therefore, early diagnosis and treatment are important.

In Japan, the nationwide screening for hepatitis was initiated in 2002.[7,8] The Basic Guidelines for Promotion of Control Measures for Hepatitis was issued in 2011, and it recommends Japanese citizens receive at least one screening for hepatitis.[7] At least 13 million people received hepatitis testing with the recommended systems between fiscal year 2002 and 2011.[8] Previous research reported that the Japanese national screening followed by the treatment of conventional pegylated interferon (IFN) plus ribavirin (RBV) therapy was cost-effective compared with no screening.[9]

Recently, the landscape in this therapeutic area has seen a change. First, treatment of HCV has dramatically advanced by the development of highly effective and well-tolerated direct-acting antivirals (DAAs), especially IFN-free DAAs. While DAAs are expected to achieve high rates of sustained viral response (SVR), the cost of these drugs has created controversy in the world.[10] Higher efficacy and tolerability are likely to increase treatment opportunities, resulting in an escalation of overall treatment costs, while higher cure rates will contribute to reducing downstream costs related to

progressive liver disease. Second, the prevalence of HCV infection is declining globally.[11,12] Low prevalence of HCV will have a negative impact on the cost-effectiveness of the screening.[13]

The recent screening for HCV could be considered costly due to the expensive treatment costs and the lower prevalence of HCV. Furthermore, it has been reported that one of issues of the screening was that a certain proportion of individuals who tested positive had not attended referral to physicians after the testing.[8,14,15] Linkage to care after screening could also affect the cost-effectiveness of screening for HCV. However, the cost-effectiveness of screening for HCV in consideration of these factors has not been assessed in Japan. To assess the cost-effectiveness of one-time screening followed by IFN-free therapy in the Japanese general population, we compared the efficacy and cost of screening plus IFN-free therapy with those of no screening and screening plus IFN-based therapy, by using a decision analytic Markov state-transition model that accounts for IFN-free DAA treatment, age-dependent prevalence of HCV, and linkage to care.

Methods

Model structure

We created a Markov state transition model for the natural history of HCV, with an incorporated decision tree for the screening intervention using TreeAge Pro 2015 decision modeling software (TreeAge Software Inc, Williamstown, MA, USA) to compare the cost-effectiveness and clinical outcomes of the three screening strategies in the Japanese general population from the perspective of healthcare payers. The

model included the general Japanese population aged 40–89 years. People were stratified into five age groups based on the age-dependent prevalence of HCV: aged 40–49, 50–59, 60–69, 70–79, and 80–89 years. The starting age within each age cohort was set at 45, 55, 65, 75, and 85 years.

The decision model for the screening was based in part on the model of Coffin et al., and it reflected the screening procedure proposed by the Ministry of Health, Labour and Welfare (MHLW) in Japan (Figure 1A).[16,17] The model assumed multi-steps from receiving screening to treatment, which included initial testing for HCV antibodies (HCV-Ab) to identify HCV infection, subsequent HCV-RNA testing for people who showed low or moderate titers in HCV-Ab testing, attending referral for care including thorough examination for people with suspected infection due to HCV-Ab high titers or HCV-RNA positive results at the screening, and access to treatment. Six health state consequences from the decision tree were included in the Markov model: undiagnosed patients with chronic hepatitis C (CHC) or compensated cirrhosis (CC), diagnosed but untreated patients with CHC or CC, and diagnosed and treated patients with CHC or CC. Uninfected individuals did not enter the Markov model. The total proportion of patients treated was based on the screening rate, the proportion of false negative in HCV-Ab testing, the proportion of attending referral and care, and the proportion of those receiving treatment of CHC or CC by treatment strategy.

The Markov model was based primarily on the model of Igarashi et al. (Figure 1B).[18] Only patients who were in the category to avail the opportunity for treatment in the decision tree model received anti-viral therapy by genotype within the first model cycle. All patients were assumed to be treatment naïve. Patients with CHC or CC who achieved SVR moved to the SVR health state. These patients were assumed to be still

exposed to the lower risk of HCC incidence. Patients who failed to achieve SVR had the same risks for disease progression as undiagnosed or untreated patients and progressed to advanced disease states such as decompensated cirrhosis (DCC), HCC, and liver transplant (LT). We did not consider re-treatment of CHC and CC. Undiagnosed patients were assumed to remain unidentified up to the development of DCC or HCC and not to incur the costs of CHC and CC health states. Untreated patients were also assumed not to initiate the treatment of liver disease until the development of DCC or HCC. However, the costs for CHC and CC health states were incurred in untreated patients. Background age- and gender-specific general population mortality were also incorporated into each health state of the model. A lifetime horizon and annual cycles with a half-cycle correction of utility values and health state costs were modeled.

Strategies for screening and treatment

Three strategies, no screening, screening plus IFN-based therapy, and screening plus IFN-free therapy, were evaluated. Treatment options by each strategy were based on the HCV treatment guidelines in Japan (Table 1).[19] We selected simeprevir (SMV) and sofosbuvir (SOF) as DAAs for IFN-based therapy and IFN-free therapy, respectively, in the base-case analysis. Combination therapy of pegylated interferon and ribavirin (PegIFN + RBV) was used for treatment of CC in the arm of screening plus IFN-based therapy because this was standard therapy for CC prior to the advent of IFN-free DAAs.

Model inputs

Screening and population characteristics

The composition of the study population by age group corresponded to that of the population estimates in Japanese statistics in 2014.[20] Age-dependent prevalence of HCV infection was estimated from the MHLW report on Health Promotion Services in 2014.[21] In our base-case model, we assumed that 1.5% of the population would receive screening for HCV based on the number of individuals who received screening under Health Promotion Services in 2014 and the proportion of individuals who recognize that they have received screening previously.[15,21] We also set that 68.9% of persons with suspected infection would attend the referral after receiving the screening and 85.0% of the patients would visit the hospital for care continuously.[15] The proportion of those receiving IFN-based therapy and IFN-free therapy was assumed as 57.6% and 90.0% based on the MHLW grants research and expert opinion, respectively.[22] A false negative rate of 1.1% and false positive rates or past infection by age group in the initial HCV-Ab test were incorporated into the decision model (Table 2).[21,23] All individuals who showed high titers in HCV-Ab test were assumed to be infected. The proportion of patients with high titers of anti-HCV-Ab was estimated based on the Japanese statistics [21]. We assumed that the HCV RNA test led to a conclusive diagnosis of HCV infection.

It is reported that the major HCV genotypes are genotype 1 and 2 in Japan, and hence, we did not consider the other genotypes due to their rare prevalence.[24] Distribution of HCV genotype and proportion of patients with CC by age group at

screening were estimated from Japanese literatures (Table 2).[24,25] Distribution of male and female patients was assumed to be equal.

Treatment

Treatment options and the efficacy by screening strategy are shown in Table 1. The SVR rates for each treatment regimen using DAA were obtained from Japanese phase 3 trials.[26–31] The efficacy data for PegIFN + RBV were derived from previous Japanese research.[18,32] We selected pegylated interferon alpha-2b for PegIFN + RBV because this was preponderantly used compared with pegylated interferon alpha-2a. Treatment-related adverse events, discontinuation rate, and prevalence of resistance-associated variants were not considered.

Transition probabilities

Annual transition rates for the analyses were set based on the literature (Table 2).[9,18, 33–37] Annual mortality rates by age and sex were taken from the Japanese abridged life table (2014).[38]

Cost and health utilities

Only the direct medical costs were considered from the perspective of healthcare payers. Cost data and their sources are described in Table 2. Laboratory costs and provider fees for screening and subsequent thorough examination were based on the 2016 edition of the medical fee index for the Japanese healthcare system.[39] Costs for initial evaluation in attending referral for the definitive diagnosis of HCV infection and investigations for treatment initiation including HCC risk assessment were estimated

based on expert opinions. Drug costs were derived from the 2016 edition of the National Health Insurance drug list.[40] The daily drug costs of sofosbuvir/ledipasvir (SOF 400 mg/LDV 90 mg daily), SOF (400 mg daily), SMV (100 mg daily), IFN (pegylated IFN 2b, 1.5 μg × weight of patient per week), RBV (800 mg daily), daclatasvir (DCV 60 mg daily), asunaprevir (ASV 200 mg daily), and ombitasvir/paritaprevir/ritonavir (OBV 25 mg/PTV 150 mg/r 100 mg daily) were JPY 54,796.90, JPY 42,239.60, JPY 13,122.80, JPY 4,372.43, JPY 2,320.40, JPY 7,902.90, JPY 5,694.80, and JPY 46,115.00, respectively. Treatment costs were calculated by multiplying the daily drug costs by the treatment duration based on the package inserts (Table 2). Annual health state costs were collected from Japanese sources.[18,34,36] Patients with CHC and CC who achieved SVR continued to incur annual costs for follow-up and management of CHC or CC.

Health state utility values were derived from Japanese literature (Table 2).[18,36,41] The utility increment by achieving SVR was referred from the research by Igarashi et al.[18] We did not consider treatment-related utility increments or decrements due to data scarcity. We assumed that the health-related utilities were the same between undiagnosed and diagnosed patients.

Analysis

Clinical outcomes were quality adjusted life years (QALYs) gained and lifetime risk of DCC, HCC, LT, and HCV-related death avoided. Economic outcomes were lifetime direct medical costs and incremental cost-effectiveness ratio (ICER). In this study, willingness-to-pay (WTP) was set to JPY 5,000,000 per QALY based on the report of Shiroiwa et al.[42] Future costs and QALYs were discounted at 2% annually according to

Japanese guidelines.[43] In addition to the base-case analysis, we also performed a heterogeneity analysis by stratified age population.

Deterministic one-way sensitivity analysis (DSA) was conducted to examine the influence of uncertain model inputs on the model outcome. We varied all parameter assumptions except background mortality rate and costs for HCV-Ab and HCV-RNA testing. The ranges for SVR of DAAs and proportion of patients with CC at screening were set based on 95% confidential intervals (CIs) calculated using an exact binomial distribution. Starting age was varied within each of the age groups of 40–49, 50–59, 60–69, 70–79, and 80–89 years. Time horizon was varied between 20 and 70 years. Discount rate ranged between 0 and 4%.[43] The ranges for the other parameters were set based on the literature or by varying each parameter by 10 to 50% more or less than the base-case value (Table 2).[18,32] We showed the ten most influential parameters on tornado diagrams. Probabilistic sensitivity analysis (PSA) was also performed for (i) screening plus IFN-free therapy vs. no screening and (ii) screening plus IFN-free therapy vs. screening plus IFN-based therapy, with a WTP range of JPY 0–10,000,000, using a second-order Monte Carlo simulation for 10,000 iterations. We set the PSA parameters based on the Briggs method and the Japanese literature.[18,44,45] All probabilistic parameters and utilities except for utility increment were assumed to follow beta distributions. Costs and utility increment were assumed to follow gamma distributions.

We also generated three scenarios to estimate the impact of different assumptions on the cost-effectiveness of screening approach. First, we substituted DCV + ASV and OBV/PTV/r therapy recommended by Japanese guidelines for base case SOF/LDV therapy for HCV genotype 1 infection. Second, we set the high-screening

scenario, which improved rate of screening from 1.5% to 10.0% and each proportion of attending referral for initial visit and subsequent care up to 90.0% to examine the effect of promotion of screening and consolidated linkage to care on the cost-effectiveness of screening. Third, we estimated the impact of declining prevalence of HCV in the future on the cost-effectiveness of screening plus IFN-free therapy relative to no screening by adjusting the prevalence of HCV by age group.

Results

Cost-effectiveness

In our base-case model, approximately 53% and 34% of screened patients received antiviral therapy in the arm of screening plus IFN-free therapy and screening plus IFN-based therapy, respectively. The strategy of screening plus IFN-free therapy was not only costlier but also more effective than both strategies of no screening and screening plus IFN-based therapy (Table 3). Screening plus IFN-free therapy was cost-effective compared with no screening and screening plus IFN-based therapy under a WTP of JPY 5,000,000 per QALY gained in the base-case model, with ICERs of JPY 1,124,482/QALY and JPY 1,085,183/QALY, respectively. In the age subgroup analysis, ICERs were lower in the younger population (Table 3). Except for population aged 85 years, screening plus IFN-free therapy was cost-effective under the setting WTP. Strategy of screening plus IFN-free therapy improved health outcomes compared with other strategies. Base-case screening plus IFN-free therapy avoided approximately 0.06% and 0.03% of DCC events, 0.3% and 0.1% of HCC, 0.004% and 0.002% of liver transplantation, and 0.2% and 0.1% of liver-related deaths compared with no screening

and screening plus IFN-based therapy, respectively.

DSA indicated that the variables such as discount rate, transition probability from CHC to HCC, and time horizon had a larger effect on the cost-effectiveness estimates in comparison with the no screening arm and screening plus IFN-free therapy arm (Figure 2A). Higher ICERs (i.e., lower cost-effectiveness) were observed when the upper bound of the discount rate and lower bound of transition probability from CHC to HCC were applied. The maximum ICER, which exceeded JPY 2,000,000 per QALY, was observed when the time horizon was shortened to 20 years. Discount rate, time horizon, and regimen cost of SOF/LDV for 12 weeks had a larger impact on the cost-effectiveness estimates between screening plus IFN-based therapy and screening plus IFN-free therapy (Figure 2B). Nevertheless, screening followed by IFN-free DAA therapy was consistently cost-effective relative to the other strategies within the parameter ranges at a WTP threshold of JPY 5,000,000 per QALY gained. PSA indicated that screening plus IFN-free therapy in the overall population was more cost-effective than no screening and screening plus IFN-based therapy when WTP was more than JPY 1,239,000 and JPY 1,260,000 per QALY, respectively (Figure 3). The probability that the strategy of screening followed by IFN-free therapy was cost-effective compared with other strategies was more than 95% in all age subpopulations except in the population aged 85, when WTP was JPY 5,000,000 per QALY.

Scenario analysis

Three scenario analyses were performed to examine the cost-effectiveness of the screening strategies under different assumptions.

First, when DCV + ASV therapy and OBV/PTV/r therapy were substituted for SOF based therapy, the strategy of screening plus IFN-free therapy was still more cost-effective than the other strategies (Table 3).

Second, when we generated the high screening scenario to permit 10% of the population to be screened and permit 81% of screened patients to be linked to care, the scenario with improved rate of screening and linkage to care became costlier but also more effective than the base case screening plus IFN-free therapy. However, the ICERs relative to no screening and screening plus IFN-based therapy modestly decreased in the setting of the high screening scenario (Table 3). High screening scenario averted approximately 0.51% and 0.46% of DCC, 2.5% and 2.3% of HCC, 0.004% and 0.003% of liver transplantation, and 2.3% and 2.0% of liver-related deaths compared with the no screening strategy and base-case screening plus IFN-free therapy strategy, respectively.

Third, one-way sensitivity analysis of prevalence of HCV by age subgroup indicated that a lower prevalence of HCV aggravated the cost-effectiveness of screening plus IFN-free therapy to that of the no screening (Figure 4). The ICERs remained below a WTP so long as the prevalence of HCV was at least 0.01%, 0.01%, 0.02%, and 0.04% in people aged 45, 55, 65, and 75 years, respectively.

Discussion

In this study, we examined whether screening followed by IFN-free therapy was cost-effective compared with no screening and screening followed by IFN-based therapy in the Japanese general population aged 40–89 years by using a decision analytic Markov

model. The model considered IFN-free DAA therapy, declining age-dependent prevalence of HCV by age group, and linkage to care after screening. The ICERs for screening plus IFN-free therapy in the overall population were JPY 1,124,482 and JPY 1,085,183 per QALY gained in comparison with no screening and screening plus IFN-based therapy. The ICERs for screening plus IFN-free therapy were definitively lower than a WTP of JPY 5,000,000 per QALY, which is often used as a threshold for cost-effectiveness in Japan. These model results were robust in sensitivity analyses. Previous research reported that screening plus conventional IFN-based therapy was more cost-effective than no screening.[9,16,46] It is important to note that the previous publications need to be carefully interpreted due to the declining prevalence of HCV and the advent of more effective and expensive DAAs.[13] Regardless of the low prevalence of HCV and the expensive treatment costs of DAA, screening followed by IFN-free therapy for HCV was cost-effective in our model.

The results of age subgroup analyses indicated that screening in the younger population tended to be more cost-effective than that in the older population, which supports the importance of early diagnosis and treatment of HCV. One of the reasons for the lower ICERs observed in the younger population is the longer life expectancy of younger people, which contributes to reducing downstream costs related to progressive liver disease relative to the investment in interventions for screening and treatment in the short term. This is also supported by the results of the sensitivity analysis, which showed that time horizon was one of the largest influencing factors on the cost-effectiveness. Our results were consistent with previous studies.[9,46,47]

In Japan, the MHLW revised the Basic Guidelines for Promotion of Control Measures for hepatitis in 2016 and recommended further promotion of hepatitis virus

testing and consolidated linkage to care after screening as approaches to achieve a reduction in the number of patients with HCV progressing to cirrhosis and liver cancer.[8] In this study, base-case screening and IFN-free therapy in the general population avoided approximately 0.1% of DCC and 0.3% of HCC compared with that of the no screening arm. When we set the high screening scenario with improved rates of screening and attending referral, further reduction of lifetime risk of progressive liver diseases was observed without any negative impact on the cost-effectiveness of screening. This suggests that our analysis supported the promotion of screening recommended by MHLW from the perspective of not only clinical- but also cost-effectiveness.

Prevalence of HCV also affected the results of the model. In our model, cost-effectiveness of screening for HCV was inversely correlated with its prevalence. The cost-effectiveness was more susceptible to the declining prevalence in the older population, which suggested that early diagnosis and treatment were supported from the cost-effectiveness perspective. In Japan, prevalence of HCV infection is steadily declining.[11,48] In addition, there are regional differences in the prevalence of HCV and the screening rate in Japan.[21,48] This suggests that a more efficient screening approach by region might be necessary to overcome the aggravated cost-effectiveness of the screening in the future era of lower prevalence and incidence of HCV, although the current prevalence is within the acceptable range on a cost-effectiveness basis. In our model, improvement of attending referral for care modestly decreased ICER between screening plus IFN-free therapy and no screening. This suggests that consolidated linkage, which is recommended in the Japanese guideline, is one of the approaches to

improve screening efficiency although the contribution was not large in our base-case model setting.

Shiroiwa et al. reported that WTP threshold per QALY should vary from JPY 2,000,000 to JPY 8,000,000 depending on the severity of health states, while the mean and median WTP were around JPY 5,000,000.[42] Even if a threshold of JPY 2,000,000 per QALY is applied, the strategy of screening plus IFN-free therapy in the overall population was cost-effective relative to the other strategies in the base-case analysis and had more than an 83% probability of being cost-effective in PSA (Table 3, Figure 3). At a threshold of JPY 8,000,000 per QALY, the base-case screening plus IFN-free therapy was cost-effective in all populations, and the probability of being cost-effective relative to no screening was 78%, even in the population aged 85 years. In this study, it is noted that the ICER of base-case screening plus IFN-free therapy relative to no screening in the population aged 85 years was more than JPY 5,000,000 per QALY, while those in the other populations were less than JPY 2,000,000 per QALY. The ICER was reduced to JPY 3,196,711 per QALY, when the age of the cohort was lowered from 85 to 80 in DSA (data not shown). A recent study reported that age is not sufficient to assess the cost-effectiveness of DAA therapy in the elderly population and that geriatric (frailty) status in addition to the fibrosis stage are important determinants.[49] ICERs were lower in non-frail patients with advanced fibrosis. Although we could not consider these factors in the model due to data scarcity, this finding suggests that specific members of the elderly population would be eligible for screening plus IFN-free therapy from the viewpoint of health economics. This certainly warrants further investigation to identify such an eligible elderly population.

Our model was based in part on the validated models from previous studies, and it was also validated in the comparison of incidence of CC and survival rate in other studies.[36,50,51] When we ran the model using the parameter values in the base case, the predicted incidence of CC and survival rate of our model was well-matched with those of other studies (data not shown).[36,50,51]

This study has several limitations. First, our model included many variables related to screening, characteristics of population, natural history of CHC, treatment efficacy, costs, and utilities, many of which were only estimates. Therefore, we performed sensitivity analyses and attempted to address this limitation. Second, the screening rate and prevalence of HCV were estimated from the report on Health Promotion Service in Japan[21] and the screening results from the service for examination of specific infectious diseases and the workplace were not reflected due to lack of available data. However, the prevalence of HCV in the service for examination of specific infectious diseases was reported to be almost the same or slightly higher than that under the Health Promotion Service.[52] Also, Sugiyama et al. reported that the workplace population tended to show a higher prevalence of HCV compared with blood donors who could be considered the general population.[53] Therefore, the limitation on prevalence would not have a large impact on the model results, which were also supported by our sensitivity analysis. In this study, the screening rate by age group population was not considered. The setting of the screening rate in this study could produce conservative economic results because the screening rate of population aged 80 years and older is likely to be relatively low compared with those of other age group populations.[21] Third, adverse events, discontinuation rate, compliance, and disutility of IFN-based therapy and IFN-free therapy were not considered in our model.

It should be noted that these could overestimate the cost-effectiveness of screening plus IFN-based therapy or IFN-free therapy relative to no screening. Fourth, the SVR rate of each DAA therapy used in the model was based on the efficacy data of clinical trials, not real-world effectiveness. However, recent research has reported that real-world effectiveness and safety of DAA therapies were consistent with the results of those pivotal trials.[54] Fifth, variable transition probabilities by age cohort were not considered. These may overestimate and underestimate the risk of disease progression in the younger and older population, respectively. Also, we did not incorporate transmission risk reduction and annual screening into the model, which could affect the cost-effectiveness and clinical outcomes of the screening strategy. Finally, development of HCC after SVR with IFN-free DAA therapies remains uncertain in comparison with that of IFN-based therapies, which were reported to reduce incidence of HCC.[55] However, a recent study has reported that IFN-free therapies could result in a reduced incidence of HCC.[56]

In conclusion, our analysis suggested that the screening approach for HCV followed by IFN-free therapy would be cost-effective compared with the approaches of no screening and screening followed by IFN-based therapy in the Japanese healthcare environment. Early diagnosis and treatment based on the age at screening and improved rates of screening and attending referral for care would likely result in improvement of clinical outcomes with a favorable ICER at the current level of prevalence. While our results supported the government initiatives to identify more infected individuals and ensure their treatment by further promotion of screening and consolidated linkage to care, given the circumstances of declining prevalence and incidence of HCV, a more efficient screening approach might be required in the future.

Acknowledgements

The authors would like to thank Hiroshi Isoda, MD, Satoshi Oeda, MD, PhD, and Kaori Inoue, MD of Liver Center, Saga University Hospital; and Keisuke Matsubayashi, MD, MSc of Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University for their valuable comments. We thank Editage (www.editage.jp) for English language editing. This study received no funding support.

References

1. World Health Organization. Hepatitis C fact sheet 2017. Available at: http://www.who.int/mediacentre/factsheets/fs164/en/. Accessed August 21, 2017.
2. Higuchi M, Tanaka E, Kiyosawa K. Epidemiology and clinical aspects on hepatitis C. Jpn J Infect Dis 2002; 55: 69-77.
3. Cancer Registry and Statistics. Cancer Information Service, National Cancer Center, Japan. (In Japanese) Available at: http://ganjoho.jp/reg_stat/statistics/dl/index.html. Accessed August 21, 2017.
4. Michitaka K, Nishiguchi S, Aoyagi Y, et al. Etiology of liver cirrhosis in Japan: a nationwide survey. J Gastroenterol 2010; 45: 86-94.
5. Kudo M, Izumi N, Ichida T, et al. Report of the 19th follow-up survey of primary liver cancer in Japan. Hepatol Res 2016; 46: 372-90.
6. Portal Site of Official Statistics of Japan (e-Stat). Medical care expenditure in fiscal year 2014. (In Japanese) Available at: https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00450032&tstat=000001020931&cycle=8&tclass1=000001088216&tclass2=000001088217&stat_infid=000031457719&second=1&second2=1. Accessed August 21, 2017.
7. Ministry of Health, Labour and Welfare. Basic guidelines for promotion of control measures for hepatitis. Available at: http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/hourei-17e.pdf. Accessed August 21, 2017.
8. Oza N, Isoda H, Ono T, Kanto T. Current activities and future directions of comprehensive hepatitis control measures in Japan: The supportive role of the

Hepatitis Information Center in building a solid foundation. Hepatol Res 2017; 47: 487-496.

9. Nakamura J, Terajima K, Aoyagi Y, Akazawa K. Cost-effectiveness of the national screening program for hepatitis C virus in the general population and the high-risk groups. Tohoku J Exp Med 2008; 215: 33-42.
10. Iyengar S, Tay-Teo K, Vogler S, et al. Prices, Costs, and Affordability of New Medicines for Hepatitis C in 30 Countries: An Economic Analysis. PLoS Med 2016; 13: e1002032.
11. Polaris Observatory HCV Collaborators. Global prevalence and genotype distribution of hepatitis C virus infection in 2015: a modelling study. Lancet Gastroenterol Hepatol 2017; 2: 161-176.
12. Chung H, Ueda T, Kudo M. Changing trends in hepatitis C infection over the past 50 years in Japan. Intervirology 2010; 53: 39-43.
13. Geue C, Wu O, Xin Y, et al. Cost-Effectiveness of HBV and HCV Screening Strategies--A Systematic Review of Existing Modelling Techniques. PLoS One 2015; 10: e0145022.
14. Holmberg SD, Spradling PR, Moorman AC, Denniston MM. Hepatitis C in the United States. N Engl J Med 2013; 368: 1859-61.
15. Kaishima T, Fujii T, Matsuoka T, et al. Study of the issues of receiving hepatitis screening and the rate of consulting hospitals -The rate of recognized receiving hepatitis screening and that of the unrecognized-. Kanzo 2016; 57: 634-48.
16. Coffin PO, Scott JD, Golden MR, Sullivan SD. Cost-effectiveness and population outcomes of general population screening for hepatitis C. Clin Infect Dis 2012; 54: 1259-71.

17. Ministry of Health, Labour and Welfare. Partial revision of viral hepatitis testing based on Health Promotion Service. (In Japanese) Available at: http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/hourei-140331-4.pdf. Accessed August 21, 2017.
18. Igarashi A, Tang W, Guerra I, Marié L, Cure S, Lopresti M. Cost-utility analysis of ledipasvir/sofosbuvir for the treatment of genotype 1 chronic hepatitis C in Japan. Curr Med Res Opin 2017; 33: 11-21.
19. Asahina Y, Izumi N, Hiromitsu K, et al. JSH Guidelines for the Management of Hepatitis C Virus Infection: A 2016 update for genotype 1 and 2. Hepatol Res 2016; 46: 129-65.
20. Statistics Bureau, Ministry of Internal Affairs and Communications, Population Estimates 2014. Available at: https://www.e-stat.go.jp/en/stat-search/files?page=1&layout=datalist&toukei=00200524&tstat=000000090001&cycle=7&year=20140&month=0&tclass1=000001011679. Accessed August 21, 2017.
21. Portal Site of Official Statistics of Japan (e-Stat). Statistics of hepatitis screening in fiscal year 2014. (In Japanese) Available at: https://www.e-stat.go.jp/stat-search/files?page=1&layout=datalist&toukei=00450025&tstat=000001030884&cycle=8&tclass1=000001082097&tclass2=000001082102&stat_infid=000031394422&second=1&second2=1. Accessed August 21, 2017.
22. Kaishima T, Tanaka J, Sakamune K, et al. Survey on the trend of awareness after receiving hepatitis screening (fiscal year 2013 version). Ministry of Health, Labour and Welfare grants system. (In Japanese) Available at: http://mhlw-grants.niph.go.jp/niph/search/NIDD00.do?resrchNum=201519001B. Accessed 21 August 2017

23. Colin C, Lanoir D, Touzet S, et al. Sensitivity and specificity of third-generation hepatitis C virus antibody detection assays: an analysis of the literature. J Viral Hepat 2001; 8: 87-95.
24. Matsuo J, Mizui M, Okita H, et al. Follow up of the 987 blood donors found with hepatitis C virus infection over 9-18 years. Hepatol Res 2012; 42: 637-47.
25. Mizui M, Tanaka J, Katayama K, et al. Liver disease in hepatitis C virus carriers identified at blood donation and their outcomes with or without interferon treatment: study on 1019 carriers followed for 5-10 years. Hepatol Res 2007; 37: 994-1001.
26. Hayashi N, Izumi N, Kumada H, et al. Simeprevir with peginterferon/ribavirin for treatment-naive hepatitis C genotype 1 patients in Japan: CONCERTO-1, a phase III trial. J Hepatol 2014; 61: 219-27.
27. Kumada H, Hayashi N, Izumi N, et al. Simeprevir (TMC435) once daily with peginterferon-α-2b and ribavirin in patients with genotype 1 hepatitis C virus infection: The CONCERTO-4 study. Hepatol Res 2015; 45: 501-13.
28. Mizokami M, Yokosuka O, Takehara T, et al. Ledipasvir and sofosbuvir fixed-dose combination with and without ribavirin for 12 weeks in treatment-naive and previously treated Japanese patients with genotype 1 hepatitis C: an open-label, randomised, phase 3 trial. The Lancet Infectious Diseases 2015; 15: 645-653.
29. Kumada H, Chayama K, Rodrigues L, Jr., et al. Randomized phase 3 trial of ombitasvir/paritaprevir/ritonavir for hepatitis C virus genotype 1b-infected Japanese patients with or without cirrhosis. Hepatology 2015; 62: 1037-46.
30. Kumada H, Suzuki Y, Ikeda K, et al. Daclatasvir plus asunaprevir for chronic HCV genotype 1b infection. Hepatology 2014; 59: 2083-91.

31. Omata M, Nishiguchi S, Ueno Y, et al. Sofosbuvir plus ribavirin in Japanese patients with chronic genotype 2 HCV infection: an open-label, phase 3 trial. J Viral Hepat 2014; 21: 762-8.
32. Igarashi A, Tang W, Cure S, et al. Cost-utility analysis of sofosbuvir for the treatment of genotype 2 chronic hepatitis C in Japan. Curr Med Res Opin 2017; 33: 1-10.
33. Suka M. Development of the fundamental model for HCV. Ministry of Health, Labour and Welfare grants system. (In Japanese) Available at: http://mhlw-grants.niph.go.jp/niph/search/NIDD00.do?resrchNum=201333004B. Accessed 16 September 2015
34. Ishida H, Yotsuyanagi H. Study of the cost-effectiveness of the standard treatment for chronic hepatitis C. Ministry of Health, Labour and Welfare grants system. (In Japanese) Available at: http://mhlw-grants.niph.go.jp/niph/search/NIDD00.do?resrchNum=201333004B. Accessed 16 September 2015
35. Kuwabara H, Westerhout K, Treur M, Cerri K, Mahlich J, Yatsuhashi H. Cost-effectiveness analysis of simeprevir in combination with peginterferon and ribavirin for treatment-naive chronic hepatitis C genotype 1 patients in Japan. J Med Econ 2015; 18: 502-11.
36. Virabhak S, Yasui K, Yamazaki K, et al. Cost-effectiveness of direct-acting antiviral regimen ombitasvir/paritaprevir/ritonavir in treatment-naive and treatment-experienced patients infected with chronic hepatitis C virus genotype 1b in Japan. J Med Econ 2016; 19: 1144-1156.

37. McEwan P, Ward T, Webster S, et al. Estimating the cost-effectiveness of daclatasvir plus asunaprevir in difficult to treat Japanese patients chronically infected with hepatitis C genotype 1b. Hepatol Res 2016; 46: 423-33.
38. Ministry of Health, Labour and Welfare. Abridged life tables for Japan 2014. Available at: https://www.mhlw.go.jp/english/database/db-hw/lifetb14/index.html. Accessed August 21, 2017
39. Ministry of health, labour and welfare. Various information of medical fee. 2016. (In Japanese) Available at: http://www.iryohoken.go.jp/shinryohoshu/kaitei/doKaitei28. Accessed August 21, 2017.
40. Yakugyo kenkyukai. National Health Insurance Drug Dictionary, 2016th ed. Japan: JIHO, 2016.
41. Sugimori H, Ikeda S, Hirao T, et al. Study of utility for hepatitis. Ministry of Health, Labour and Welfare grants system. (In Japanese) Available at: https://mhlw-grants.niph.go.jp/niph/search/NIDD00.do?resrchNum=201333004B. Accessed August 21, 2017
42. Shiroiwa T, Igarashi A, Fukuda T, Ikeda S. WTP for a QALY and health states: More money for severer health states? Cost Eff Resour Alloc 2013; 11: 22.
43. Shiroiwa T, Fukuda T, Ikeda S, Takura T, Moriwaki K. Development of an Official Guideline for the Economic Evaluation of Drugs/Medical Devices in Japan. Value Health 2017; 20: 372-378.
44. Briggs A, Sculpher M, Claxton K. Decision modelling for health economic evaluation. New York: Oxford University Press, 2006.

45. Briggs AH, Ades AE, Price MJ. Probabilistic sensitivity analysis for decision trees with multiple branches: use of the Dirichlet distribution in a Bayesian framework. Med Decis Making 2003; 23: 341-50

46. Ruggeri M, Coretti S, Gasbarrini A, Cicchetti A. Economic assessment of an anti-HCV screening program in Italy. Value Health 2013; 16: 965-72.

47. Kim DY, Han KH, Jun B, et al. Estimating the Cost-Effectiveness of One-Time Screening and Treatment for Hepatitis C in Korea. PLoS One 2017; 12: e0167770.

48. Tanaka J, Koyama T, Mizui M, et al. Total numbers of undiagnosed carriers of hepatitis C and B viruses in Japan estimated by age- and area-specific prevalence on the national scale. Intervirology 2011; 54: 185-95.

49. Ciaccio A, Cortesi PA, Bellelli G, et al. Direct-acting antivirals combination for elderly patients with chronic hepatitis C: A cost-effectiveness analysis. Liver Int 2017; 37: 982-94.

50. Yamasaki K, Tomohiro M, Nagao Y, et al. Effects and outcomes of interferon treatment in Japanese hepatitis C patients. BMC Gastroenterol 2012; 12: 139.

51. Kasahara A, Tanaka H, Okanoue T, et al. Interferon treatment improves survival in chronic hepatitis C patients showing biochemical as well as virological responses by preventing liver-related death. J Viral Hepat 2004; 11: 148-56.

52. Ministry of Health, Labour and Welfare. Result of hepatitis screening based on Service for Specific Infectious Diseases Testing in fiscal year 2014. (In Japanese) Available at: http://www.mhlw.go.jp/bunya/kenkou/kekkaku-kansenshou09/pdf/kensa-14.pdf. Accessed August 21, 2017.

53. Sugiyama A, Fujii T, Nagashima S, et al. Pilot study for hepatitis virus screening among employees as an effective approach to encourage employees who screened positive to receive medical care in Japan. Hepatol Res 2018; 48: E291-E302.
54. Younossi ZM, Park H, Gordon SC, et al. Real-world outcomes of ledipasvir/sofosbuvir in treatment-naive patients with hepatitis C. Am J Manag Care 2016; 22: SP205-11.
55. Morgan RL, Baack B, Smith BD, Yartel A, Pitasi M, Falck-Ytter Y. 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.
56. Ogata F, Kobayashi M, Akuta N, et al. Outcome of all-oral direct-acting antiviral regimens on the rate of development of hepatocellular carcinoma in patients with hepatitis C virus genotype 1-related chronic liver disease. Oncology 2017; 93: 92-98.

Table 1. Strategies of screening followed by treatment and the SVR by treatment option

Strategy	Indication	Treatment regimen (Length of treatment)	SVR rate	Range	Distribution	Source
No screening	All	No treatment	0	0	N/A	Assumption
Screening and treatment with IFN-based therapy	G1 CHC	SMV + PegIFN + RBV (24 weeks)	0.891	0.829–0.936	Beta	Hayashi *et al.*[26], Kumada *et al.*[27]
	G1 CC	PegIFN + RBV (48 weeks)	0.191	0.094–0.314	Beta	Igarashi *et al.*[18]
	G2 CHC	PegIFN + RBV (24 weeks)	0.789	0.720–0.851	Beta	Igarashi *et al.*[32]
	G2 CC	PegIFN + RBV (48 weeks)	0.833	0.636–0.962	Beta	Igarashi *et al.*[32]
Screening and treatment with IFN-free therapy	G1 CHC	SOF/LDV (12 weeks)	1.000	0.949–1.000	Beta	Mizokami *et al.*[28]
		OBV/PTV/r (12 weeks)†	0.942	N/A	N/A	Kumada *et al.*[29]
		DCV + ASV (24 weeks)†	0.871	N/A	N/A	Kumada *et al.*[30]
	G1 CC	SOF/LDV (12 weeks)	1.000	0.949–1.000	Beta	Assumed equal to CHC (Mizokami *et al.*[28])
		OBV/PTV/r (12 weeks)†	0.905	N/A	N/A	Kumada *et al.*[29]
		DCV + ASV (24 weeks)†	0.871	N/A	N/A	Assumed equal to CHC (Kumada *et al.*[30])
	G2 CHC	SOF + RBV (12 weeks)	0.976	0.915–0.997	Beta	Omata *et al.*[31]
	G2 CC	SOF + RBV (12 weeks)	0.976	0.915–0.997	Beta	Assumed equal to CHC (Omata *et al.*[31])

†Anti-viral therapies with OBV/PTV/r and DCV + ASV were selected for scenario analysis. The sensitivity analyses were not conducted.

CC, compensated cirrhosis; CHC, chronic hepatitis C; G1, genotype 1; G2, genotype 2; IFN, interferon; LDV, ledipasvir; N/A, not applicable; PegIFN, pegylated interferon alfa-2b, RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response.

Table 2. Model input parameters

Variable	Base case	Range	Distribution	Source
Study population				
Population prevalence				
Age 40–49	0.0022	0.0018–0.0026	Beta	Estimation based on Japanese government statistics[21]
Age 50–59	0.0035	0.0028–0.0042	Beta	Estimation based on Japanese government statistics[21]
Age 60–69	0.0036	0.0029–0.0043	Beta	Estimation based on Japanese government statistics[21]
Age 70–79	0.0060	0.0048–0.0072	Beta	Estimation based on Japanese government statistics[21]
Age ≥80	0.0136	0.0109–0.0163	Beta	Estimation based on Japanese government statistics[21]
Baseline patient characteristics				
Proportion of male	0.50	0.40–0.60	Beta	Assumption
Proportion of genotype 1	0.65	0.59–0.72	Beta	Matsuo *et al.*[24]
Proportion of CC				
Age 40–49	0.003	0.000–0.018	Beta	Mizui *et al.*[25]
Age 50–59	0.006	0.001–0.023	Beta	Mizui *et al.*[25]
Age ≥60	0.019	0.002–0.067	Beta	Mizui *et al.*[25]
Time horizon (years)	70	20–70	N/A	
Discount rates	0.02	0–0.04	N/A	Shiroiwa *et al.*[43]
Screening				
Proportion receiving screening	0.015	0.012–0.018	Beta	Assumption from Japanese government statistics[21] and Kaishima *et al.*[15]
Proportion of attending referral	0.689	0.551–0.827	Beta	Kaishima *et al.*[15]
Proportion of continuously attending care	0.850	0.680–1.000	Beta	Kaishima *et al.*[15]
Proportion receiving IFN-free DAA therapy	0.900	0.810–0.990	Beta	Assumption
Proportion receiving IFN-based therapy	0.576	0.461–0.691	Beta	Assumption from Kaishima *et al.*[22]
Proportion of patients with high titer in HCV Ab test	0.805	0.725–0.886	Beta	Assumption from Japanese government statistics[21]
Proportion of false negative in HCV Ab test	0.011	0–0.060	Beta	Colin *et al.*[23]
Proportion of false positive in HCV Ab test or past infection				
Age 40–49	0.0026	0.0021–0.0031	Beta	Estimation based on Japanese government statistics[21]
Age 50–59	0.0040	0.0032–0.0048	Beta	Estimation based on Japanese government statistics[21]
Age 60–69	0.0047	0.0037–0.0056	Beta	Estimation based on Japanese government statistics[21]
Age 70–79	0.0077	0.0062–0.0093	Beta	Estimation based on Japanese government statistics[21]

Age ≥80	0.0128	0.0102–0.0153	Beta	Estimation based on Japanese government statistics[21]
Transition probability				
CHC to CC	0.0190	0.0095–0.0285	Beta	Virabhak *et al.* [36]
CHC to HCC	0.0290	0.0145–0.0435	Beta	Suka *et al.* [33]
CC to DCC	0.0560	0.0280–0.0840	Beta	Suka *et al.* [33]
CC to HCC	0.0560	0.0280–0.0840	Beta	Suka *et al.* [33]
DCC to HCC	0.0560	0.0280–0.0840	Beta	Suka *et al.* [33]
DCC to LT	0.0035	0.0018–0.0053	Beta	Ishida *et al.* [34]
DCC to death	0.1510	0.0755–0.2265	Beta	Suka *et al.* [33]
HCC to LT	0.0030	0.0015–0.0045	Beta	Kuwabara *et al.* [35]
HCC to death	0.1940	0.1455–0.2425	Beta	Nakamura *et al.* [9], Igarashi *et al.* [18]
LT to death	0.2090	0.1045–0.3135	Beta	Ishida *et al* [34]
Post-LT to death	0.0180	0.0090–0.0270	Beta	Ishida *et al.* [34]
CHC SVR to HCC	0.0020	0.0010–0.0030	Beta	Virabhak *et al.* [36]
CC SVR to HCC	0.0180	0.0090–0.0270	Beta	McEwan *et al.* [37], Virabhak *et al.* [36]
Laboratory costs and provider fees (JPY)				
HCV-Ab test	1,140	N/A	N/A	NHI medical fees[39]
HCV-RNA test	4,500	N/A	N/A	NHI medical fees[39]
Detailed examination at initial visit	20,750	16,600–24,900	N/A	Assumption
Investigations for treatment initiation	14,180	11,344–17,016	N/A	Assumption
Health states costs (JPY)				
CHC	171,101	128,326–213,876	Gamma	Igarashi *et al.* [18]
CC	478,613	358,960–598,266	Gamma	Igarashi *et al.* [18]
DCC	706,585	529,939–883,231	Gamma	Igarashi *et al.* [18]
HCC	1,517,641	1,138,231–1,897,051	Gamma	Igarashi *et al.* [18]
LT	14,995,200	7,497,600–22,492,800	Gamma	Ishida *et al.* [34]
Post LT	2,019,000	1,009,500–3,028,500	Gamma	Ishida *et al.* [34]
SVR from CHC	57,186	28,593–85,779	Gamma	Virabhak *et al.* [36]
SVR from CC	124,439	62,220–186,659	Gamma	Virabhak *et al.* [36]
Drug costs (JPY)				
SOF/LDV regimen (12 week)	4,602,940	3,452,205–5,753,675	N/A	NHI Drug List[40]
SOF + RBV regimen (12 week)	3,743,040	2,807,280–4,678,800	N/A	NHI Drug List[40]
SMV + PegIFN + RBV regimen (24 week)	2,226,710	1,670,033–2,783,388	N/A	NHI Drug List[40]

PegIFN + RBV regimen (24 week)	1,124,395	843,296–1,405,494	N/A	NHI Drug List[40]
DCV + ASV regimen (24 week)	2,284,414	N/A	N/A	NHI Drug List[40]
OBV/PTV/r regimen (12 week)	3,873,660	N/A	N/A	NHI Drug List[40]
Utility				
CHC	0.854	0.684–0.940	Beta	Virabhak *et al.* [36]
CC	0.737	0.590–0.884	Beta	Sugimori *et al.* [41]
DCC	0.671	0.537–0.805	Beta	Sugimori *et al.* [41]
HCC	0.566	0.453–0.679	Beta	Igarashi *et al.* [18]
LT	0.651	0.521–0.781	Beta	Sugimori *et al.* [41]
Post-LT	0.651	0.521–0.781	Beta	Sugimori *et al.* [41]
SVR (utility increment)	0.040	0.032–0.048	Gamma	Igarashi *et al.* [18]

Ab, antibody; ASV, asunaprevir; CC, compensated cirrhosis; CHC, chronic hepatitis C; DAA, direct-acting antiviral agents; DCV, daclatasvir; DCC, decompensated cirrhosis; G1, genotype 1; G2, genotype 2; HCC, hepatocellular carcinoma; HCV, hepatitis c virus; IFN, interferon; LDV, ledipasvir; LT, liver transplantation; N/A, not applicable; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir; PegIFN, pegylated interferon alfa-2b; RBV, ribavirin; SMV, simeprevir; SOF/LDV, sofosbuvir/ledipasvir; SVR, sustained virologic response.

Table 3. Cost-effectiveness results

Strategy	Absolute		Incremental (vs. no screening)			
	Cost (JPY)/patient	QALY/patient	Cost (JPY)/patient	QALY/patient	ICER (vs. no screening)	ICER (vs. screening and IFN-based therapy)
Base case (Overall population)						
No screening	2,191,127	9.153				
Screening and IFN-based therapy	2,208,445	9.168	17,318	0.015	1,156,832	
Screening and IFN-free therapy	2,221,817	9.180	30,690	0.027	1,124,482	1,085,183
Scenario						
DCV + ASV therapy for genotype 1	2,212,094	9.178	20,966	0.025	839,169	364,329
OBV/PTV/r therapy for genotype 1	2,219,046	9.179	27,919	0.026	1,063,714	940,099
High screening scenario	2,464,578	9.404	273,451	0.252	1,086,625	1,082,185
Age subgroup						
People aged 45 years						
No screening	4,048,845	14.150				
Screening and IFN-based therapy	4,070,815	14.189	21,970	0.039	560,090	
Screening and IFN-free therapy	4,076,951	14.221	28,106	0.071	394,959	192,136
People aged 55 years						
No screening	3,501,068	12.884				
Screening and IFN-based therapy	3,519,944	12.912	18,877	0.028	676,219	
Screening and IFN-free therapy	3,527,842	12.935	26,775	0.051	527,762	346,138
People aged 65 years						
No screening	2,751,975	10.935				
Screening and IFN-based therapy	2,770,798	10.952	18,823	0.017	1,092,738	
Screening and IFN-free therapy	2,781,463	10.966	29,488	0.032	934,255	743,853
People aged 75 years						
No screening	1,780,373	8.256				
Screening and IFN-based therapy	1,797,075	8.264	16,702	0.009	1,939,158	
Screening and IFN-free therapy	1,811,858	8.271	31,485	0.016	1,992,774	2,057,032
People aged 85 years						
No screening	837,250	5.079				
Screening and IFN-based therapy	851,646	5.082	14,396	0.003	4,498,536	
Screening and IFN-free therapy	870,942	5.085	33,692	0.006	5,736,299	7,218,095

ASV, asunaprevir; DCV, daclatasvir; ICER, incremental cost-effectiveness ratio; IFN, interferon; JPY, Japanese yen; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir; QALY, quality adjusted life year; SOF, sofosbuvir.

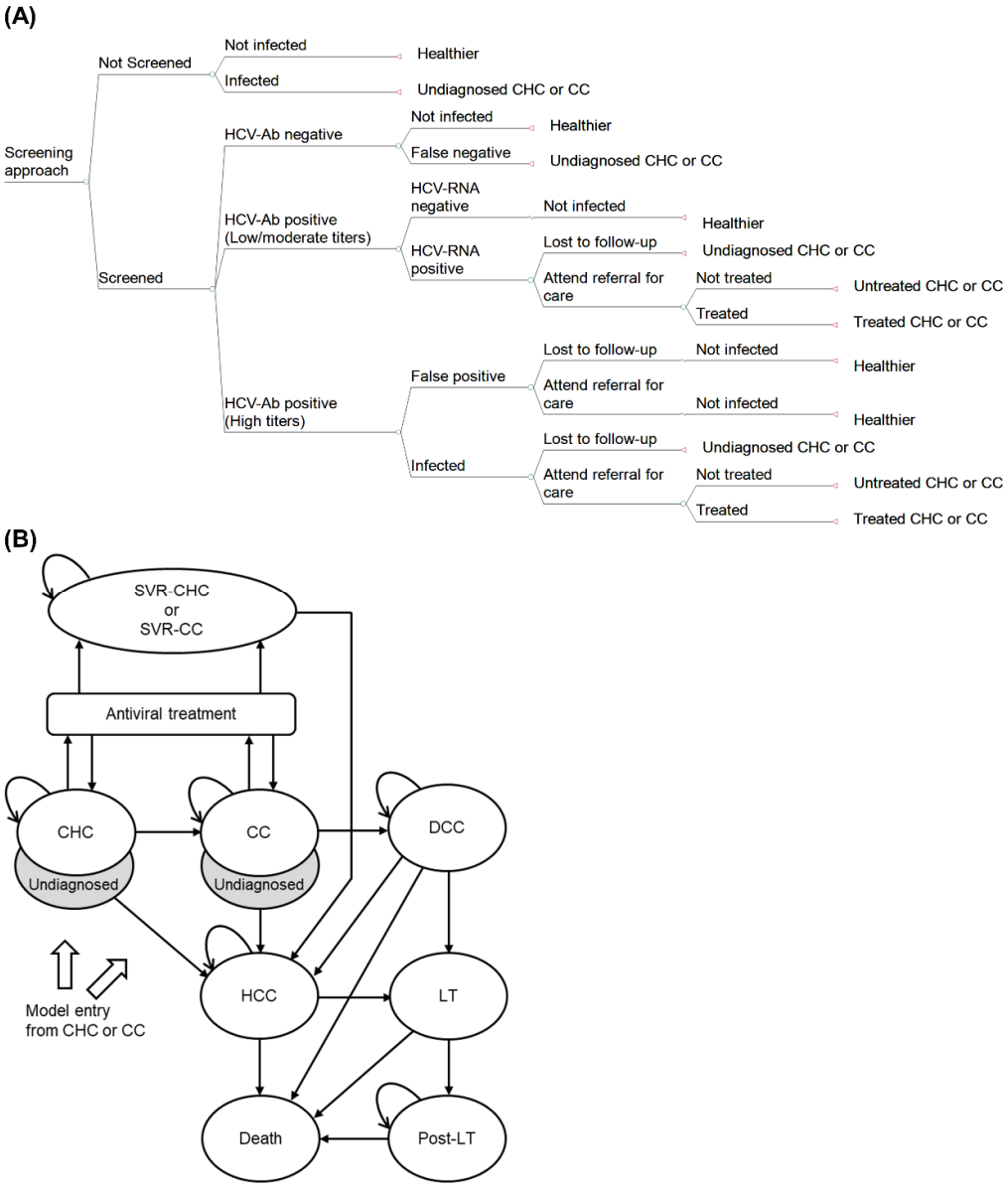

Figure 1. Decision tree and Markov model for HCV screening. Outcomes of (A) decision tree are stratified to states of CHC or CC in (B) Markov model. Ab, antibody; CC, compensated cirrhosis; CHC, chronic hepatitis C; DCC, decompensated cirrhosis; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; LT, liver transplantation; SVR, sustained virological response.

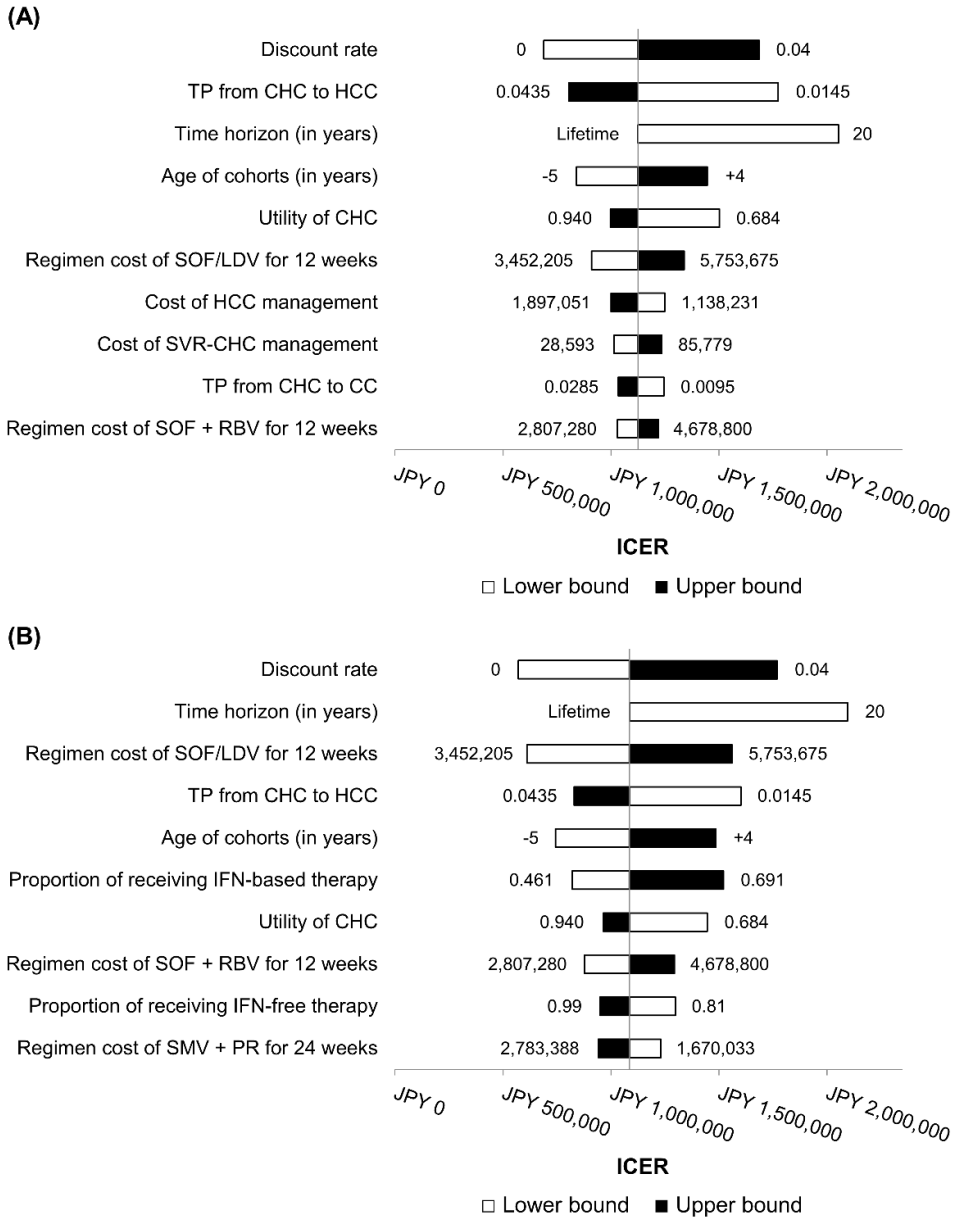

Figure 2. Tornado diagram of one-way sensitivity analysis in (A) screening followed by IFN-free therapy vs. no screening; and (B) screening followed by IFN-free therapy vs. screening followed by IFN-based therapy. CHC, chronic hepatitis C; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; IFN, interferon; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virological response; TP, transition probability.

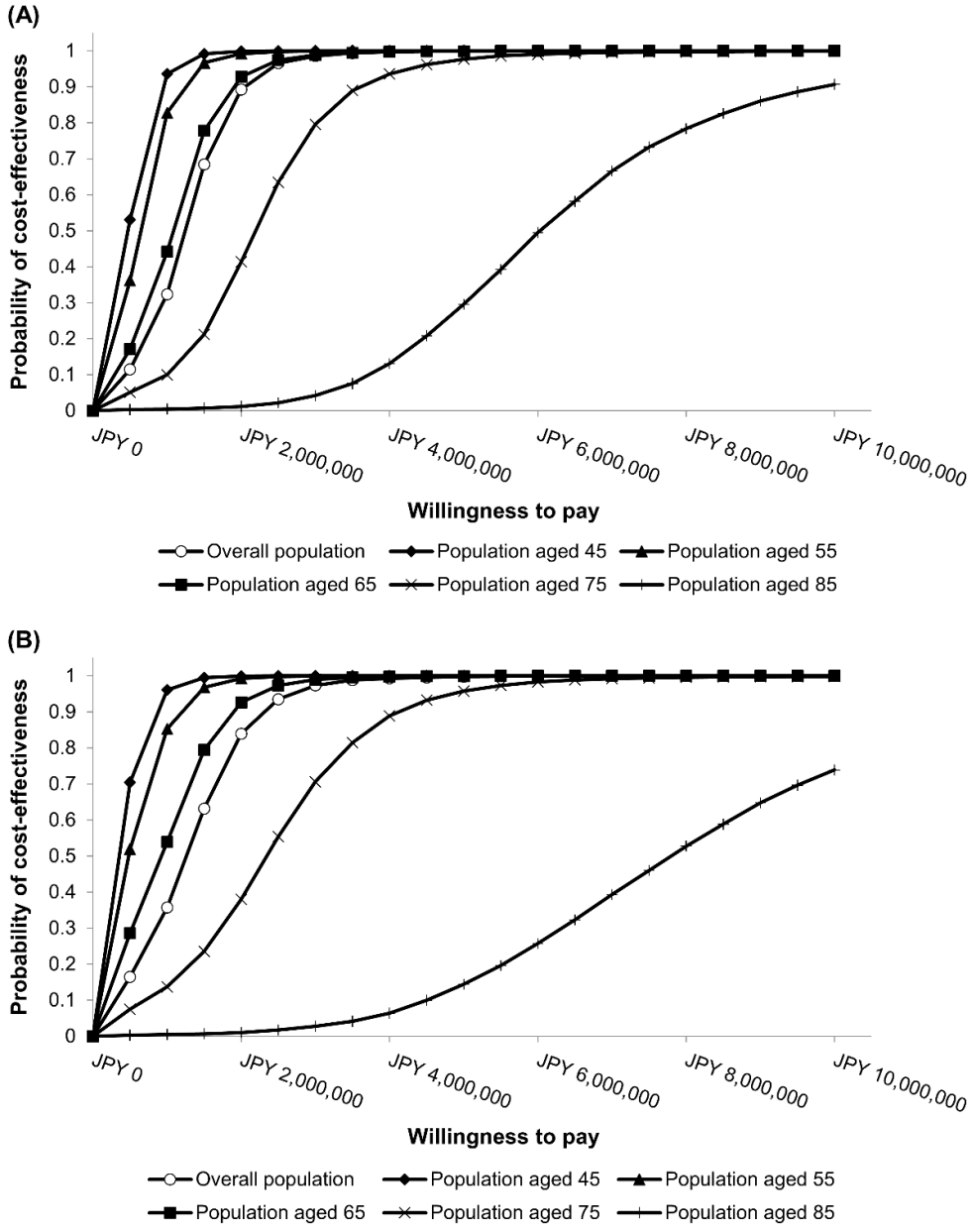

Figure 3. Cost-effectiveness acceptability curves in (A) screening plus IFN-free therapy vs. no screening; and (B) screening plus IFN-free therapy vs. screening plus IFN-based therapy. IFN, interferon.

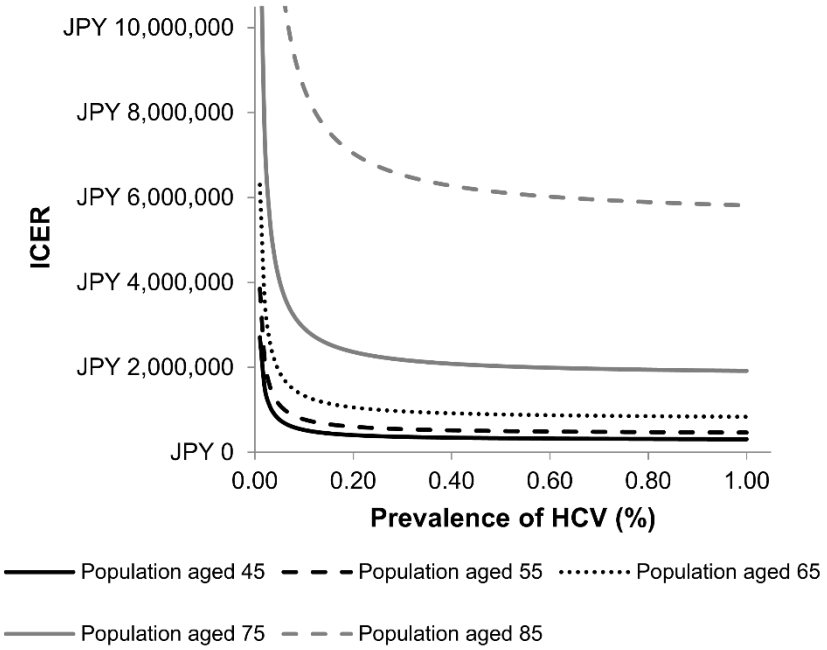

Figure 4. Impact of prevalence of HCV on incremental cost-effectiveness ratio in screening plus IFN-free therapy vs. no screening. HCV, hepatitis C virus; ICER, incremental cost-effectiveness ratio.