Original Article

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

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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 the 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. Subanalyses 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, the incremental cost-effectiveness ratio in the Japanese general population aged 40–89 years was ¥1,124,482 and ¥1,085,183 per quality-adjusted life year gained for screening plus IFN-free therapy compared with no screening and screening plus IFN-based therapy, respectively. Screening plus IFN-free therapy remained cost-effective below ¥5,000,000 per quality-adjusted life year gained in sensitivity analyses. Incremental cost-effectiveness ratios 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 a favorable incremental cost-effectiveness ratio. Improved rates of screening and attending referral would result in further reduction of disease progression.

Key words: 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 healthcare costs for hepatitis virus and malignant neoplasm on the liver and intrahepatic bile duct in Japan were approximately ¥170 billion and ¥150 billion 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. At least 13 million people received hepatitis testing with the recommended systems between fiscal year 2002 and 2011. 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.

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. Although DAAs are expected to achieve high rates of sustained viral response (SVR), the cost of these drugs has created controversy in the world. Higher efficacy and tolerability are likely to increase treatment opportunities, resulting in an escalation of overall treatment costs, whereas higher cure rates will contribute to reducing downstream costs related to progressive liver disease. Second, the prevalence of HCV infection is declining globally. A low prevalence of HCV will have a negative impact on the cost-effectiveness of the screening.

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 the issues of the screening was that a certain proportion of individuals who tested positive had not attended referral for physicians after the testing. 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, Labor and Welfare (MHLW) in Japan (Fig. 1a). The model assumed multisteps 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. (Fig. 1b). Only patients who were in the category to avail the opportunity for treatment in the decision tree model received antiviral therapy by genotype within the first model cycle. All patients were assumed to be treatment naive. Patients with CHC or CC who achieved SVR moved to the SVR health state. These patients were assumed to still be 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. 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 sex-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). We selected simeprevir and sofosbuvir (SOF) as DAAs for IFN-based therapy and IFN-free therapy, respectively, in the base-case analysis. Combination therapy of pegylated IFN 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 before 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. Age-dependent prevalence of HCV infection was estimated from the MHLW report on Health Promotion Services in 2014. 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. 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. 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. 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). All individuals who showed high
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      | NA           | 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] and 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]       |
|                                   | G1 CC      | SOF/LDV (12 weeks)                      | 0.942    | NA      | NA           | Kumada *et al.* [29]         |
|                                   | G1 CC      | DCV + ASV (24 weeks)†                   | 0.871    | NA      | NA           | 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 ombitasvir/paritaprevir/ritonavir (OBV/PTV/r) and daclatasvir (DCV) + asunaprevir (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; NA, not applicable; PegIFN, pegylated interferon alfa-2b; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir; SVR, sustained virologic response.
| Variable                      | Base case | Range           | Distribution | Source                                           |
|-------------------------------|-----------|-----------------|--------------|-------------------------------------------------|
| **Study population**          |           |                 |              |                                                 |
| Population prevalence        | 0.0022    | 0.0018–0.0026   | Beta         | Estimation based on Japanese government statistics |
| Age 40–49 years               | 0.0035    | 0.0028–0.0042   | Beta         | Estimation based on Japanese government statistics |
| Age 50–59 years               | 0.0036    | 0.0029–0.0043   | Beta         | Estimation based on Japanese government statistics |
| Age 60–69 years               | 0.0060    | 0.0048–0.0072   | Beta         | Estimation based on Japanese government statistics |
| Age 70–79 years               | 0.0136    | 0.0109–0.0163   | Beta         | Estimation based on Japanese government statistics |
| Age ≥80 years                 |           |                 |              |                                                 |
| **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.                                    |
| Proportion of CC              |           |                 | Beta         |                                                 |
| Age 40–49 years               | 0.003    | 0.000–0.018     | Beta         | Mizui et al.                                    |
| Age 50–59 years               | 0.006    | 0.001–0.023     | Beta         | Mizui et al.                                    |
| Age ≥60 years                 | 0.019    | 0.002–0.067     | Beta         | Mizui et al.                                    |
| Time horizon (years)          | 70        | 20–70           | NA           |                                                 |
| Discount rates                | 0.02      | 0.0–0.04        | NA           | Shiraiwa et al.                                  |
| **Screening**                 |           |                 |              |                                                 |
| Proportion receiving screening| 0.015     | 0.012–0.018     | Beta         | Assumption from Japanese government statistics and Kaishima et al. |
| Proportion of attending referral| 0.689    | 0.551–0.827     | Beta         | Kaishima et al.                                  |
| Proportion of continuously attending care | 0.850 | 0.680–1.000 | Beta | Kaishima et al.                                  |
| 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 |
| Proportion of false negative in HCV-Ab test | 0.011 | 0.0–0.060 | Beta | Colin et al.23                                   |
| Proportion of false positive in HCV-Ab test or past infection |           |                 | Beta         | Estimation based on Japanese government statistics |
| Age 40–49 years               | 0.0026    | 0.0021–0.0031   | Beta         | Estimation based on Japanese government statistics |
| Age 50–59 years               | 0.0040    | 0.0032–0.0048   | Beta         | Estimation based on Japanese government statistics |
| Age 60–69 years               | 0.0047    | 0.0037–0.0056   | Beta         | Estimation based on Japanese government statistics |
| Age 70–79 years               | 0.0077    | 0.0062–0.0093   | Beta         | Estimation based on Japanese government statistics |
| Age ≥80 years                 | 0.0128    | 0.0102–0.0153   | Beta         | Estimation based on Japanese government statistics |
| **Transition probability**    |           |                 |              |                                                 |
| CHC to CC                     | 0.0190    | 0.0095–0.0285   | Beta         | Virabhak et al.                                 |
| CHC to HCC                    | 0.0290    | 0.0145–0.0435   | Beta         | Suka et al.3                              |
| CC to DCC                     | 0.0560    | 0.0280–0.0840   | Beta         | Suka et al.3                              |
| CC to HCC                     | 0.0560    | 0.0280–0.0840   | Beta         | Suka et al.3                              |
| DCC to HCC                    | 0.0560    | 0.0280–0.0840   | Beta         | Suka et al.3                              |
| DCC to LT                     | 0.0035    | 0.0018–0.0053   | Beta         | Ishida et al.24                               |
| DCC to death                  | 0.1510    | 0.0755–0.2265   | Beta         | Suka et al.3                              |

(Continues)
| Variable                     | Base case | Range         | Distribution | Source                                      |
|------------------------------|-----------|---------------|--------------|---------------------------------------------|
| 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         | Vinabhak 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 (¥) |           |               |              |                                             |
| HCV-Ab test                  | 1140      | NA            | NA           | NHI medical fees 39                        |
| HCV-RNA test                 | 4500      | NA            | NA           | NHI medical fees 39                        |
| Detailed examination at initial visit | 20 750    | 16 600−24 900 | NA           | Assumption                                  |
| Investigations for treatment initiation | 14 180    | 11 344−17 016 | NA           | Assumption                                  |
| Health states costs (¥)      |           |               |              |                                             |
| 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       | Vinabhak et al. 36                         |
| SVR from CC                  | 124 439   | 62 220−186 659 | Gamma       | Vinabhak et al. 36                         |
| Drug costs (¥)               |           |               |              |                                             |
| SOF/LDV regimen (12 week)    | 4 602 940 | 3 452 205−5 753 675 | NA           | NHI Drug List 60                           |
| SOF + RBV regimen (12 week)  | 3 743 040 | 2 807 280−4 678 800 | NA           | NHI Drug List 60                           |
| SMV + PegIFN + RBV regimen (24 week) | 2 226 710 | 1 670 033−2 783 388 | NA           | NHI Drug List 60                           |
| PegIFN + RBV regimen (24 week) | 1 124 395 | 843 296−1 405 494 | NA           | NHI Drug List 60                           |
| DCV + ASV regimen (24 week)  | 2 284 414 | NA            | NA           | NHI Drug List 60                           |
| OBV/PTV/r regimen (12 week)  | 3 873 660 | NA            | NA           | NHI Drug List 60                           |
| Utility                      |           |               |              |                                             |
| CHC                          | 0.854     | 0.684−0.940   | Beta         | Vinabhak et al. 36                         |
| CC                           | 0.737     | 0.590−0.884   | Beta         | Sugimori et al. 31                         |
| DCC                          | 0.671     | 0.553−0.805   | Beta         | Sugimori et al. 31                         |
| HCC                          | 0.566     | 0.453−0.679   | Beta         | Igarashi et al. 18                         |
| LT                           | 0.651     | 0.521−0.781   | Beta         | Sugimori et al. 31                         |
| Post-LT                      | 0.651     | 0.521−0.781   | Beta         | Sugimori et al. 31                         |
| 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; DCC, decompensated cirrhosis; DCV, daclatasvir; G1, genotype 1; G2, genotype 2; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IFN, interferon; LDV, ledipasvir; LT, liver transplantation; NA, 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.
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 the HCV genotype and the proportion of patients with CC by age group at screening were estimated from Japanese literature (Table 2).  ^24,25 The 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 III 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 SOF/ledipasvir (SOF 400 mg/ledipasvir 90 mg daily), SOF (400 mg daily), simeprevir (100 mg daily), IFN (pegylated IFN-2b, 1.5 μg × weight of patient per week), RBV (800 mg daily), daclatasvir (60 mg daily), asunaprevir (200 mg daily), and ombitasvir/paritaprevir/ritonavir (ombitasvir 25 mg/paritaprevir 150 mg/ritonavir 100 mg daily) were ¥54,796.90, ¥42,239.60, ¥13,122.80, ¥43,724.43, ¥23,204.40, ¥7,902.90, ¥5,694.80, and ¥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.

Statistical analysis

Clinical outcomes were quality-adjusted life years (QALYs) gained, and lifetime risk of DCC, HCC, liver transplant, 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 ¥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 was conducted to examine the influence of uncertain model inputs on the model outcome. We varied all parameter assumptions, except for background mortality rate and costs for HCV-Ab and HCV-RNA testing. The ranges for SVR of DAA and proportion of patients with CC at screening were set on 95% confidential intervals (CIs) calculated using an exact binomial distribution. Starting age varied within each of the age groups of 40–49, 50–59, 60–69, 70–79, and 80–89 years. Time horizon varied between 20 and 70 years. The 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 10–50% more or less than the base-case value (Table 2).  ^18,32 We showed the 10 most influential parameters on tornado diagrams. Probabilistic sensitivity analysis (PSA) was also performed for: (i) screening plus IFN-free therapy versus no screening; and (ii) screening plus IFN-free therapy versus screening plus IFN-based therapy, with a WTP range of ¥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 the screening approach. First, we substituted daclatasvir + asunaprevir and ombitasvir/paritaprevir/ritonavir therapy recommended by Japanese guidelines for base-case SOF/ledipasvir therapy for HCV genotype 1 infection. Second, we set the high-screening scenario, which improved the 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 more costly, 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 ¥5 000 000 per QALY gained in the base-case model, with ICERs of ¥1 124 482/QALY and ¥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. The 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.

Deterministic one-way sensitivity analysis showed 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 (Fig. 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 ¥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/ledipasvir for 12 weeks had a larger impact on the cost-effectiveness estimates between screening plus IFN-based therapy and screening plus IFN-free therapy (Fig. 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 ¥5 000 000 per QALY gained. PSA showed 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 ¥1 239 000 and ¥1 260 000 per QALY, respectively (Fig. 3). The probability that the strategy of screening followed by IFN-free therapy was cost-effective compared with other strategies was >95% in all age subpopulations, except in the population aged 85 years, when WTP was ¥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 daclatasvir + asunaprevir therapy and ombitasvir/paritaprevir/ritonavir 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 the improved rate of screening and linkage to care became more costly, 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 showed that a lower prevalence of HCV aggravated the cost-effectiveness of screening plus IFN-free therapy to that of the no screening (Fig. 4). The ICERs remained below a WTP so long as the prevalence of HCV...
| Strategy | Absolute | Incremental (vs. no screening) | ICER (vs. screening and IFN-based therapy) |
|----------|----------|-------------------------------|-------------------------------------------|
|          | Cost (¥)/patient | QALY/patient | Cost (¥)/patient | QALY/patient | (vs. no screening) | (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 | 1,085,183 |
| Screening and IFN-free therapy | 2,221,817 | 9,180 | 30,690 | 0.027 | 1,124,482 | | |
| 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; OBV/PTV/r, ombitasvir/paritaprevir/ritonavir; QALY, quality-adjusted life year; SOF, sofosbuvir.
was at least 0.01%, 0.01%, 0.02%, and 0.04% in people aged 45, 55, 65, and 75 years, respectively.

DISCUSSION

IN THE PRESENT study, we examined whether screening followed by interferon (IFN)-free therapy versus no screening; and (b) screening followed by IFN-free therapy versus screening followed by IFN-based therapy. CHC, chronic hepatitis C; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; LDV, ledipasvir; RBV, ribavirin; SOF, sofosbuvir; SVR, sustained virologic response; TP, transition probability.

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

The ICERs for screening plus IFN-free therapy were definitively lower than a WTP of ¥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. 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. 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 showed 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. The present 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 the present 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 effectiveness, but also cost-effectiveness.

The prevalence of HCV also affected the results of the model. In our model, the cost-effectiveness of screening for HCV was inversely correlated with its prevalence. The cost-effectiveness was more susceptible to the declining

**Figure 3** Cost-effectiveness acceptability curves in (a) screening plus interferon-free therapy versus no screening; and (b) screening plus interferon-free therapy versus screening plus interferon-based therapy. JPY, Japanese yen.

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prevalence in the older population, which suggested that early diagnosis and treatment were supported from the cost-effectiveness perspective. In Japan, the prevalence of HCV infection is steadily declining.\textsuperscript{11,48} In addition, there are regional differences in the prevalence of HCV and the screening rate in Japan.\textsuperscript{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 ¥2 000 000 to ¥8 000 000 depending on the severity of health states, whereas the mean and median WTP were around ¥5 000 000.\textsuperscript{42} Even if a threshold of ¥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 >83% probability of being cost-effective in PSA (Table 3; Fig. 3). At a threshold of ¥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 ¥5 000 000 per QALY, whereas those in the other populations were less than ¥2 000 000 per QALY.

The ICER was reduced to ¥3 196 711 per QALY, when the age of the cohort was lowered from 85 years to 80 years in deterministic one-way sensitivity analysis (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.\textsuperscript{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 the incidence of CC and survival rate in other studies.\textsuperscript{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).\textsuperscript{36,50,51}

The present study had 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,\textsuperscript{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. 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. Therefore, the limitation on prevalence would not have a large impact on the model results, which were also supported by our sensitivity analysis. In the present 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 the population aged ≥80 years is likely to be relatively low compared with those of other age group populations. 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. 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 the incidence of HCC. However, a recent study has reported that IFN-free therapies could result in a reduced incidence of HCC.

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. Although 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.

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