Original Article

Cost-effectiveness analyses of anti-hepatitis C virus treatments using quality of life scoring among patients with chronic liver disease in Hiroshima prefecture, Japan

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Aim: We estimated the cost-effectiveness of direct-acting antiviral treatment (DAA) compared to triple therapy (simeprevir, pegylated interferon-α [Peg-IFN], and ribavirin [RBV]) (scenario 1), Peg-IFN + RBV (scenario 2), and non-antiviral therapy (scenario 3).

Methods: Cost-effectiveness was evaluated as incremental cost-effectiveness ratios (ICERs) using direct costs and indirect costs, which included loss of wages during the patient’s lifetime due to early death caused by viral hepatitis infection. Quality of life (QOL) scores were determined by EQ-5D-3L questionnaire survey on 200 HCV patients in Hiroshima.

Results: The QOL scores for chronic hepatitis, liver cirrhosis, and hepatocellular carcinoma were estimated as 0.871, 0.774, and 0.780, respectively. The follow-up period that the ICER of scenario 1 becomes shortest (cost <¥6 million) was 25 years after treatment in men and women who started treatment at the age of 20–60. In contrast, those of scenarios 2 and 3 was 10 years after treatment in patients who started treatment at age <80 years. Based on the sensitivity analysis in scenario 1, the most significant factor affecting the value of ICER is the QOL score after sustained virologic response (SVR), followed by the SVR rate of DAA or follow-up period.

Conclusions: Direct-acting antiviral treatment was estimated to be cost-effective from 10 to 25 years after treatment, depending on the SVR rate of the drugs and the age of onset of treatment. In order to increase the cost-effectiveness of DAA treatment, measures or effort to improve the QOL score of patients after SVR are necessary.

Key words: cost-effectiveness analysis, direct acting antiviral, EQ-5D, hepatitis C virus, incremental cost-effectiveness ratio, loss of productivity, Markov model, QALY

INTRODUCTION

THE WORLD HEALTH Organization has reported that approximately 2 billion people are infected with the hepatitis B virus (HBV) and approximately 270 million people are persistent HBV carriers. Furthermore, approximately 130–150 million people are persistently infected with the hepatitis C virus (HCV), and >1 million deaths each year are thought to be caused by liver diseases that are associated with HBV and HCV infections.1 In Japan, approximately 1.9–2.3 million people have persistent HCV infections,2 and hepatitis-related diseases are widespread. At the 69th World Health Assembly (May 2016), the Global Strategy on Viral Hepatitis 2016–2020 was unanimously adopted, with a goal of eliminating hepatitis B and C by 2030. The main targets are to reduce the annual number of deaths by 65% and to increase the treatment rate to 80% by 2030.3 Gilead Sciences Co. Ltd. supplies inexpensive direct acting antiviral treatment (DAA) to low- and middle-income countries, such as Cuba, Pakistan, the Philippines, and Egypt, which increases local access to chronic hepatitis C treatment.4

Japan has developed interventions to target HBV and HCV carriers, which include prevention and control measures. Furthermore, hepatitis testing has been carried out and promoted since the 1990s. Since the 2000s, each
Japanese prefecture and district have implemented measures that are based on the “Basic Act on Hepatitis Measures”, which aim to increase the rates of examination, diagnosis, and treatment using free-of-charge hepatitis testing, reimbursement for some hepatitis-related medical expenses, and regional hospitals that specialize in treating liver disease. The countermeasure should focus on the effective treatment and follow-up after screening, and Japan has shifted from screening to treatment.\(^5\) In addition, several highly effective, albeit expensive, direct-acting antiviral (DAA) treatments have been developed to eliminate HCV infection by directly affecting the enzymatic activity of the HCV. Many clinical studies reported effectiveness, safety, and impact on patients’ quality of life (QOL) of DAA.\(^6\)–\(^9\) However, concerns have been raised regarding the cost-effectiveness of expensive medical technologies, and their burden on Japan’s health insurance system. Therefore, the present study examined the cost-effectiveness of DAA and triple therapy (simeprevir [SMV], pegylated interferon-α [Peg-IFN], and ribavirin [RBV]).

The target population was defined as HCV carriers in the Hiroshima prefecture, which has had a screening system since 1992 but still has a high mortality rate for hepatocellular carcinoma (HCC).\(^10\) Hiroshima currently serves as a model district for Japan, and has introduced advanced countermeasures that include carrier surveillance and early releases of new hepatitis treatments. Thus, we collected data regarding the epidemiology of HCV infections, as well as the carrier rate, rate of receiving antiviral therapy, and disease states (HCC, liver cirrhosis [LC], and chronic hepatitis [CH]). Furthermore, QOL scores for patients in Hiroshima were estimated according to their disease state. This cost-effectiveness study might help facilitate region-specific hepatitis control measures.

### METHODS

#### Ethical considerations

THIS STUDY’S PROTOCOL was approved by our institutional ethics committee (Epi E-43). The main objectives were explained to all participants and informed consent was obtained after confirming that the participants understood these objectives.

#### Patients and study design

The QOL scores were estimated using data from 212 patients who were treated as outpatients or inpatients at Hiroshima University Hospital (Hiroshima, Japan) between August and September 2015. The required sample size was calculated using the following formula,\(^11\) with absolute accuracy of 0.03 and a QOL standard deviation of 0.1:

\[
N = \frac{4 \times 1.96^2 \, S^2}{W^2}
\]

In that equation, \(S\) denotes the QOL standard deviation, \(W\) denotes the absolute accuracy, and 1.96 is the cut-off for the upper 2.5% of the normal distribution. The required sample size was calculated to be 129 (43 cases each for CH, LC, and HCC), and we ultimately targeted 215 cases based on an assumed response rate of 60%. The patients were categorized according to their liver disease state, and they provided information regarding their age and sex before self-administering the Japanese version of the EQ-5D-3 L questionnaire (mobility, self-care, usual activities, pain, and anxiety).\(^12\) The average health-related QOL scores were calculated according to disease state based on the conversion table.\(^12\)

#### Model structure

The Markov model (Fig. 1) was used to simulate the cumulative disease states (asymptomatic carriers [AC], CH, LC,
HCC, sustained virologic response [SVR], and death) among HCV carriers with or without treatment. This model included the SVR rates for DAA, triple therapy, and Peg-IFN + RBV, the rates of receiving antiviral therapy, the mortality rate for all causes, and annual transition probability matrices.13 Three treatment strategies were assumed in scenario 1 (DAA vs. triple therapy), scenario 2 (DAA vs. Peg-IFN + RBV) and scenario 3 (DAA vs. non-antiviral treatment). The following assumptions were made: (i) the six liver disease states (AC, CH, LC, HCC, SVR, and death) are mutually exclusive and collectively exhaustive; (ii) the rates of visiting a medical institution are 100% for the first time, 65% for the next time for CH, 80% for LC, and 95% for HCC (Table 1); (iii) only CH is eligible for anti-HCV treatment; (iv) the targeted age range for anti-HCV treatment is 20–90 years; (v) the rate of receiving antiviral therapy is 65% for CH (Table 1); (vi) if patients with CH do not respond to antiviral treatment (non-SVR), the transition from CH to AC is zero; (vii) the SVR rate for each age group is constant (0% for non-antiviral treatment in scenario 3, 45% for Peg-IFN + RBV in scenario 2, 88.6% for triple therapy in scenario 1, and 100% for DAA);14 (viii) the model is limited by an age of 100 years; (ix) the annual discount rates for costs and quality-adjusted life years (QALY) are 2%.15

### Model development

#### Model population

The numbers of untreated patients in Hiroshima prefecture were estimated using the following formula (Table 1):

$$UP_{ijd} = P_{ij} \times HCV_{ij} \times 0.7 \times LDS_{ijd}.$$  

In that equation, $i$ denotes sex (1 for men, 2 for women), $j$ denotes age (1 for 20–24 years, 2 for 25–29 years, 17 for $\geq 100$ years), $d$ denotes the disease state at the start of follow-up (1 for AC, 2 for CH, 3 for LC), $UP_{ijd}$ denotes the estimated number of untreated HCV carriers in Hiroshima, $P_{ij}$ denotes the population of Hiroshima, $HCV_{ij}$ denotes the anti-HCV positivity rate in Hiroshima, $LDS_{ijd}$ denotes the proportion of each liver disease state (e.g., $LDS_{111}$ is the proportion of AC among male 20–24-year-old HCV carriers).18

#### Base setting value

In the base setting value, treatment is started at the age of 50 years, the discount rate is 2%, the rate of receiving antiviral therapy is 65%,10 the SVR rate after DAA treatment is

| Age, years | Population of Hiroshima (2010)† | Estimated no. of HCV carriers‡ | Diagnosed in men§ | Diagnosed in women§ |
|------------|--------------------------------|--------------------------------|-------------------|-------------------|
|            | Total                          | Men               | Women             | AC    | CH   | LC   | HCC | AC    | CH   | LC   | HCC |
| 20–24      | 137 098                        | 69 684            | 67 414            | 120   | 54   | 66   | 19   | 35    | 22   | 0    | 0    |
| 25–29      | 153 042                        | 77 217            | 75 825            | 134   | 59   | 75   | 21   | 38    | 50   | 5    | 0    |
| 30–34      | 178 636                        | 89 808            | 88 828            | 263   | 126  | 137  | 45   | 81    | 91   | 46   | 0    |
| 35–39      | 216 328                        | 108 188           | 108 141           | 318   | 152  | 166  | 54   | 98    | 111  | 55   | 0    |
| 40–44      | 184 012                        | 91 510            | 92 502            | 972   | 525  | 447  | 183  | 338   | 260  | 187  | 0    |
| 45–49      | 168 328                        | 83 426            | 84 902            | 888   | 478  | 410  | 167  | 308   | 239  | 171  | 0    |
| 50–54      | 167 126                        | 82 409            | 84 717            | 1501  | 813  | 688  | 329  | 477   | 360  | 325  | 3    |
| 55–59      | 191 535                        | 94 642            | 96 893            | 1719  | 933  | 786  | 378  | 547   | 411  | 371  | 4    |
| 60–64      | 232 762                        | 113 986           | 118 776           | 2931  | 1444 | 1487 | 505  | 867   | 766  | 699  | 22   |
| 65–69      | 189 386                        | 90 135            | 99 251            | 2386  | 1143 | 1243 | 400  | 685   | 640  | 584  | 19   |
| 70–74      | 151 666                        | 69 745            | 81 921            | 3595  | 1685 | 1910 | 590  | 1011  | 983  | 898  | 29   |
| 75–79      | 133 626                        | 56 550            | 77 076            | 3161  | 1365 | 1796 | 478  | 819   | 925  | 844  | 27   |
| 80–84      | 103 132                        | 39 509            | 63 623            | 2437  | 954  | 1483 | 334  | 572   | 764  | 697  | 22   |
| 85–89      | 61 669                         | 19 156            | 42 513            | 1455  | 464  | 991  | 162  | 278   | 510  | 466  | 15   |
| 90–94      | 27 347                         | 67 35            | 20 612            | 643   | 163  | 480  | 57   | 98    | 247  | 226  | 7    |
| 95–99      | 8 439                          | 16 49            | 67 990            | 198   | 40   | 158  | 14   | 24    | 82   | 74   | 2    |
| ≥100       | 13 935                         | 190              | 1205             | 32    | 5    | 27   | 2    | 3     | 14   | 13   | 0    |
| Total      | 22 753                         | 10 403           | 12 350           | 3738  | 6279 | 204  | 182  | 6497  | 5703 | 150  | 0    |

†Vital Statistics in Japan (2010), Ministry of Health, Labour and Welfeare.
‡Tanaka J et al. Intervirology 2004; 47: 32–42.
§Mizui M et al. Hepatol Res 2007; 37: 994–1001.
100%,\(^{19}\) triple therapy is 88.6% and Peg-IFN + RBV is 45%, the QOL score after SVR is 1.000, and the drug costs are set according to the National Drug Tariff (April 2016).

**Mortality rate**

The annual mortality rates were assumed to be 0.225 for HCC\(^{20}\) and 0.061 for LC.\(^{21}\) Mortality rates for all causes of death in Hiroshima prefecture were calculated according to 2010 mortality data (Table 2).\(^{22}\)

**Direct costs**

Direct costs include the cost of treatment and drugs. The total costs\(^{23}\) of HCV antiviral treatment for CH were estimated to be ¥4 603 000 for DAA (12 weeks) and ¥1 837 000 for triple therapy (24 weeks for Peg-IFN + RBV, and 12 weeks for SMV). ¥1 470 000 for Peg-IFN + RBV (48 weeks) based on the National Drug Tariff (April 2016). The total costs of non-antiviral treatment for CH, LC, and HCC were estimated using an insurance and clinical practice survey that was published by the Ministry of Health, Labour, and Welfare in June 2011.\(^{24}\) The numbers of CH, LC, and HCC cases were calculated based on the 2014 Patient Survey in Japan,\(^{25}\) using codes for viral hepatitis (International Classification of Diseases and Related Health Problems, 10th revision [ICD-10] codes: B15–B19), liver cirrhosis except alcoholic cirrhosis (ICD-10: K74.3–K74.6), and malignant neoplasm of the liver and intrahepatic bile duct (ICD-10: C22). Based on these factors, the per-capita medical costs were estimated to be ¥540 000 for CH, ¥527 000 for LC, and ¥2 160 000 for HCC. These medical costs included consultations, treatment, radiographic imaging, pathological testing, surgery, hospital charges, and nutritional support for inpatients (Table 2).

**Indirect costs**

Indirect costs include loss of productivity, which was defined as the “loss of wages during the patient’s lifetime due to early death caused by viral hepatitis infection,” and was estimated using the human capital valuation method:\(^{15}\)

\[
L_D = \sum_{i=D}^{D+LE_D-1} \frac{E_i \times W_i}{(1 + r)^{i-1}}
\]

In that equation, \(D\) denotes age at death, \(L_D\) denotes the loss of wages during the patient’s lifetime due to early death at age \(D\), \(LE_D\) denotes life expectancy at age \(D\), \(i\) denotes the index of age, \(r\) denotes the discount rate (2%)\(^{15}\) and \(E_i\) and \(W_i\) denote the employment rate and annual wages at age \(i\), respectively. The employment rate was based on the 2015 Labour Force Survey\(^{26}\) the annual income was based on the 2015 Basic Survey on Wage Structure.\(^{27}\) Life expectancy was based on the 2010 Life Table.\(^{22}\)
Model outcomes
The total costs and QALYs for DAA, triple therapy (scenario 1), Peg-IFN + RBV (scenario 2), and non-antiviral treatment (scenario 3) were used to calculate the incremental cost-effectiveness ratios (ICERs), based on the guidelines for Economic Evaluation of Health Care Technology in Japan,\(^{15}\) to compare the treatments for 5-year increments ranging from 5 years to 50 years after starting treatment:
\[
\text{ICER} = \frac{\text{Total costs}_{\text{DAA}} - \text{Total costs}_{\text{triple therapy or Peg-IFN + RBV or non-antiviral treatment}}}{\text{QALYs}_{\text{DAA}} - \text{QALYs}_{\text{triple therapy or Peg-IFN + RBV or non-antiviral treatment}}}
\]

In our study, the cut-off ICER value for determining cost-effectiveness was set to ¥5 million or ¥6 million.\(^{28}\)

Sensitivity analysis
In scenario 1, sensitivity analyses were carried out to assess the influence of specific input parameters on the cost-effectiveness results: patient age (±10 years), discounting (±2%), patient sex (male/female), follow-up period (±10 years), HCC treatment cost (±20%), DAA cost (±20% based on the 2015 National Drug Tariff), DAA SVR (100–95%), QOL scores after SVR (1.000–0.871), and the rate of receiving DAA therapy (65–85%).

RESULTS
Quality of life scores
Among the 212 eligible patients, 200 patients (94.3%) responded to the QOL questionnaires (105 men [52.5%] and 95 women [47.5%]). The largest age subgroups were 60–69 years old (65 patients, 32.5%) and 70–79 years old (62 patients, 31.0%). The disease states were CH for 108 patients (54.0%), LC for 24 patients (12.0%), and HCC for 68 patients (34.0%) (Table 3). The results from the EQ-5D-3L questionnaires are summarized in Table 3. The average QOL scores for patients in Hiroshima prefecture were estimated to be 0.871 for CH, 0.774 for LC, and 0.780 for HCC (Table 4).

Table 3 Number of respondents to each dimension of the EQ-5D-3L questionnaire among 200 hepatitis C virus (HCV) patients in Hiroshima prefecture, Japan

| EQ-5D dimension | CH  n = 108 | Comp-LC  n = 20 | Decomp-LC  n = 4 | HCC  n = 68 |
|------------------|------------|-----------------|-----------------|----------|
| Mobility         |            |                 |                 |          |
| No problem       | 93 (86.1)  | 14 (70.0)       | 1 (25.0)        | 42 (61.8) |
| Some problems    | 15 (13.9)  | 5 (25.0)        | 3 (75.0)        | 26 (38.2) |
| Extreme problems | 0 (0.0)    | 1 (5.0)         | 0 (0.0)         | 0 (0.0)  |
| Self-care        |            |                 |                 |          |
| No problem       | 105 (97.2)| 19 (95.0)       | 2 (50.0)        | 57 (83.8) |
| Some problems    | 2 (1.9)    | 1 (5.0)         | 2 (50.0)        | 9 (13.2) |
| Extreme problems | 1 (0.9)    | 0 (0.0)         | 0 (0.0)         | 2 (3.0)  |
| Usual activities |            |                 |                 |          |
| No problem       | 90 (83.3)  | 11 (55.0)       | 1 (25.0)        | 40 (58.8) |
| Some problems    | 17 (15.7)  | 9 (45.0)        | 3 (75.0)        | 24 (35.3) |
| Extreme problems | 1 (1.0)    | 0 (0.0)         | 0 (0.0)         | 4 (5.9)  |
| Pain/discomfort  |            |                 |                 |          |
| No pain/discomfort | 80 (74.1)| 12 (60.0)       | 1 (25.0)        | 38 (55.9) |
| Moderate pain/discomfort | 23 (21.3)| 8 (40.0)       | 2 (50.0)        | 29 (42.6) |
| Extreme pain/discomfort | 5 (4.6) | 0 (0.0)        | 1 (25.0)        | 1 (5.9)  |
| Anxiety/depression |         |                 |                 |          |
| No anxiety/depression | 85 (78.7)| 16 (80.0)      | 3 (75.0)        | 50 (73.5) |
| Moderate anxiety/depression | 20 (18.5)| 4 (20.0)      | 0 (0.0)         | 17 (25.0) |
| Extreme anxiety/depression | 3 (2.8) | 0 (0.0)        | 1 (25.0)        | 1 (1.5)  |

Data are shown as n (%).
CH, chronic hepatitis; Comp-LC, compensated liver cirrhosis; Decomp-LC, decompensated liver cirrhosis; HCC, hepatocellular carcinoma.
In the base setting value, treatment is started at the age of 50 years. In scenario 1 (DAA vs. triple therapy), the ICERs for direct costs (treatment and drug costs) after 25 years of follow-up (i.e., ≥75 years old) were estimated according to disease state (Table 5) and were ¥5 671 000/QALY for men and ¥6 075 000/QALY for women. The ICERs for both direct and indirect costs (loss of productivity) after 25 years follow-up were ¥5 018 000/QALY for men and ¥5 712 000/QALY for women (Table 6). In scenario 2 (DAA vs. Peg-IFN + RBV) and scenario 3 (DAA vs. non-antiviral treatment), the ICERs for direct costs after 10 years of follow-up were ¥2 863 000/QALY for men and ¥3 467 000/QALY for women, and ¥1 715 000/QALY for men and ¥2 203 000/QALY for women, respectively.

### Incremental cost-effectiveness ratios according to sex and age at the start of treatment

In scenario 1, ICERs for direct costs according to sex and age at the start of treatment were estimated (Fig. 2a). In scenario 1, the case of DAA treatment started at age of 50 years old for men (¥5 671 000/QALY) and 60 years old for women (¥5 959 000/QALY); the ICER values reach cost-effectiveness within shortest period at 25 years. In men who started treatment at the age of 20 years, the follow-up period that the ICER < ¥6 million was 35 years after treatment (¥5 124 000/QALY), compared to 30 years after treatment in men who started treatment at 50 years old. In women, the follow-up period was 35 years after treatment (¥3 467 000/QALY), compared to 30 years after treatment in women who started treatment at 50 years old.
treatment at the age of 30 years (¥5 587 000/QALY), 40 years (¥4 799 000/QALY), or 60 years (¥5 651 000/QALY).

In women who started treatment at the age of 20, the follow-up period that the ICER becomes < ¥6 million was 40 years after treatment (¥5 041 000/QALY), compared to 30 years after treatment in those who started treatment at the age of 40 years (¥5 619 000/QALY) or 50 years (¥4 591 000/QALY).

In both men and women who started treatment at the age of ≥ 80 years, the ICER values did not reach cost-effectiveness (< ¥6 million) before 100 years of age; however, the ICER values decreased slightly.

In scenario 2, the follow-up period after treatment that the ICER becomes < ¥6 million was 10 years for men and women who started treatment at the age of under 80 (Fig. 2b). That is, in men who started treatment at the age of 20 years (¥3 357 000/QALY), 30 years (¥3 369 000/QALY), 40 years (¥3 118 000/QALY), 50 years (¥2 863 000/QALY), 60 years (¥2 403 000/QALY), 70 years (¥2 885 000/QALY), or 80 years (¥4 493 000/QALY), the follow-up time to an ICER of < ¥6 million was 10 years after treatment.

In women who started treatment at the age of 20 years (¥3 997 000/QALY), 30 years (¥3 884 000/QALY), 40 years (¥3 802 000/QALY), 50 years (¥3 467 000/QALY), 60 years (¥3 064 000/QALY), 70 years (¥3 314 000/QALY), or 80 years (¥4 305 000/QALY), the follow-up time to an ICER of < ¥6 million was also 10 years after treatment.

In scenario 3, the follow-up period after treatment that the ICER becomes < ¥6 million was also 10 years for men and women who started treatment at age < 80 years. Although in patients who started treatment at the age of 90 years the ICER values did not reach cost-effectiveness (< ¥6 million), the value decreased remarkably (Fig. 2c).

**Sensitivity analyses**

The results of the sensitivity analyses are shown in Figure 3 and Table 7. In the case of changing QOL score after SVR from 1.0 (base setting value; base) to 0.871, the ICERs in men were ¥4 555 000 (base)–11 552 000/QALY and the ICERs in women were ¥4 591 000 (base)–12 130 000/QALY. In the case of changing the SVR rate of DAA treatment from 100% (base) to 95%, the ICERs in men were ¥4 555 000 (base)–9 502 000/QALY and the ICERs in men were ¥4 555 000 (base)–9 502 000/QALY.
In the case of changing the DAA costs from -20% (¥3 682 000) to +20% (¥5 524 000), the ICERs in men were ¥2 435 000–6 675 000/QALY and the ICERs in women were ¥2 468 000–6 713 000/QALY. In the case of changing the follow-up period from 20 years to 40 years, the ICERs in men were ¥7 679 000–3 674 000/QALY and the ICERs in women were ¥8 668 000–3 230 000/QALY. In the case of changing the rate of receiving DAA therapy from 65% (base) to 85%, the ICERs in men were ¥4 555 000 (base)–1 865 000/QALY and the ICERs in women were ¥4 591 000 (base)–1 858 000/QALY.

DISCUSSION

Declining birth rates and prolonged lifespans have been associated with remarkable increases in national healthcare costs, as the introduction of expensive but innovative drugs can create drastic changes in medical care. These treatments must be evaluated for safety, effectiveness, and cost-effectiveness, highlighting the need for new criteria that incorporate direct and indirect costs, as well as the resulting changes in QOL. Other countries have developed specialized cost-effectiveness evaluations for depression and cancer treatments and a Japanese cost-effectiveness subcommittee was established in 2012. One pilot study in Japan was completed in 2016, and a full-scale study is planned for 2018.

There are several recently published reports that are related to our study, that is, cost-effectiveness of DAA. showed the cost-effectiveness of DAA treatment (daclatasvir + asunaprevir) compared to simeprevir + pegylated interferon-α [Peg-IFNα], and ribavirin [RBV]) in scenario 1, 45% for Peg-IFN + RBV in scenario 2, 0% for non-antiviral treatment in scenario 3, and 100% for direct-acting antiviral (DAA) treatment. (a) Scenario 1, DAA vs. triple therapy. (b) Scenario 2, DAA vs. Peg-IFN + RBV. (c) Scenario 3, DAA vs. non-antiviral treatment. [Color figure can be viewed at wileyonlinelibrary.com]
Figure 3 Univariate sensitivity analyses of the base setting value of incremental cost-effectiveness ratios (ICERs) of antihepatitis C virus treatments among patients with chronic liver disease in Hiroshima prefecture, Japan. Bars indicate the change in the ICERs for each parameter. DAA, direct-acting antiviral; HCC, hepatocellular carcinoma; QALY, quality-adjusted life years; QOL, quality of life; SVR, sustained virologic response. [Color figure can be viewed at wileyonlinelibrary.com]

Table 7 Univariate sensitivity analysis of base-case

| Scenario                                      | Incremental cost, ¥1000 | Incremental QALY | ICER, ¥1000/QALY | Incremental cost, ¥1000 | Incremental QALY | ICER, ¥1000/QALY |
|-----------------------------------------------|-------------------------|------------------|------------------|-------------------------|------------------|------------------|
| Direct cost                                   |                         |                  |                  |                         |                  |                  |
| Base case†                                     | 1,917,577               | 421              | 4,555            | 1,661,855               | 362              | 4,591            |
| Age (+10 years)                               | 2,622,153               | 464              | 5,651            | 3,066,868               | 625              | 4,907            |
| Age (−10 years)                               | 1,151,718               | 240              | 4,799            | 949,663                 | 169              | 5,619            |
| Discount rate (0%)                            | 1,795,368               | 582              | 3,085            | 1,618,349               | 514              | 3,149            |
| Discount rate (4%)                            | 1,991,965               | 313              | 6,364            | 1,676,073               | 264              | 6,349            |
| Follow-up period (+10 years)                  | 1,851,505               | 504              | 3,674            | 1,566,649               | 485              | 3,230            |
| Follow-up period (−10 years)                  | 2,057,944               | 268              | 7,679            | 1,785,628               | 206              | 8,668            |
| HCC treatment costs (+20%)                    | 1,886,459               | 421              | 4,481            | 1,644,106               | 362              | 4,542            |
| HCC treatment costs (−20%)                    | 1,948,695               | 421              | 4,629            | 1,679,603               | 362              | 4,640            |
| DAA costs (+20%)                              | 2,809,980               | 421              | 6,675            | 2,430,284               | 362              | 6,713            |
| DAA costs (−20%)                              | 1,025,174               | 421              | 2,435            | 893,425                 | 362              | 2,468            |
| DAA costs (2015 National Drug Tariff)         | 3,580,296               | 421              | 8,504            | 3,093,587               | 362              | 8,546            |
| DAA SVR (95%)                                 | 2,252,024               | 237              | 9,502            | 1,945,160               | 203              | 9,582            |
| QOL scores for SVR (0.871)                    | 1,917,577               | 166              | 11,552           | 1,661,855               | 137              | 12,130           |
| Receipt rate of anti-virus therapy (+20%)     | 2,867,682               | 1538             | 18,65            | 2,495,492               | 1343             | 18,58            |
| Direct + indirect cost                        |                         |                  |                  |                         |                  |                  |
| Base case†                                     | 1,683,073               | 421              | 3,998            | 1,547,984               | 362              | 4,276            |
| HCC death rate (+5%)                          | 1,698,504               | 431              | 3,941            | 1,561,108               | 368              | 4,242            |
| HCC death rate (−5%)                          | 1,659,733               | 407              | 4,078            | 1,529,987               | 355              | 4,310            |

†In the base treatment scenario, age at the start of treatment is 50 years, follow-up period is 30 years, discount rate is 2%, the receipt rate of antiviral therapy is 65%, direct-acting antiviral (DAA) sustained virologic response (SVR) is 100%, quality of life (QOL) scores for SVR is 1.00, and the drug cost is according to the National Drug Tariff (April 2016). HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; Peg-IFNα, pegylated interferon-α; LDV, ledipasvir; QALY, quality-adjusted life years; RBV, ribavirin; SMV, simeprevir; SOF, sofosbuvir.
on disability-adjusted life-years as an index of cost-effectiveness, and it was concluded that the elimination model promoting DAA treatment is the most cost-effective as DAA treatment can reduce the cost per year of disability to the lowest level.\textsuperscript{34}

In this study, we could estimate ICERs as an index of cost-effectiveness classified by sex and age groups applying transition probabilities calculated from a Japanese cohort study. We were also able to report, for the first time, the cost-effectiveness of DAA treatment by age of starting treatment and by follow-up period after SVR. Furthermore, this study pointed out the importance of evaluating the cost-effectiveness of DAA treatment according to different medical subsidies systems, hepatitis virus examination rates, medical institution receiving rates, and HCV carrier rates for each administrative district.

The present study estimated QOL scores among HCV carriers specifically residing in Hiroshima prefecture using the EQ-5D-3L questionnaire. Because every prefecture has its own parameters, such as the QOL scores, estimated number of HCV carriers in 2010, the rates of receiving antiviral treatments, and the mortality rate, the ICER value might also vary in every prefecture. As the reference model for other prefectures, using prefecture-specific parameters, we simulated age- and sex-specific ICER values in Hiroshima prefecture for DAA treatment compared to triple therapy, Peg-IFN + RBV, or non-antiviral treatment.

The EQ-5D tool was developed by the EuroQol Group, which was established in 1987, and has been translated into >170 languages as the international standard for calculating QALYs.\textsuperscript{35} The Japanese version of EQ-5D-3L was released in 1997 and has been certified by the EuroQol Group.\textsuperscript{36} However, the QOL scores using for cost-effectiveness analyses have typically been calculated using the EQ-5D tool, which assigns a score of 0 to death and a score of 1 to healthy status.\textsuperscript{37} We used ICERs to evaluate cost-effectiveness, which reflect the cost to achieve 1 QALY. According to Shiroiwa \textit{et al.},\textsuperscript{28,38} the willingness-to-pay threshold is ¥5–6 million/QALY, which has been considered as a reference of cut-off value for determination of cost-effectiveness in Japan; this value was applied in this study.

The direct costs showed a decreasing trend for ICERs in both sexes and every age group after treatment, although men tended to have lower ICERs than women during the early follow-up period after treatment. In scenario 1, that is, compared to triple therapy, DAA treatment was cost-effective for patients who started treatment at the age of 20–60 years, followed by 25–35 years after treatment. However, DAA treatment was not relatively cost-effective if DAA treatment was started at >70 years, even for survival to age 100 years, which is likely related to the high all-cause mortality rate. In this analysis, we assumed the discount rate was 2%, that is, values of QALY and costs in future were discounted by length of follow-up period. The discount rate (2%) is used to calculate future value discounted to the present. For example, ¥1 million after 10 years will be ¥836 000 for the current value, and QALY 1 after 10 years will be 0.84 of the current value. QALY is associated with the progress of hepatitis. In younger generation, the period until liver pathology progresses to LC/HCC is longer than elderly. The treatment costs are same for each generations. However due to the adaptation of the discount rates, the QALY in the distant future becomes lower as a current value. Therefore in younger generation QALY estimated lower than the elderly generation. For this reason, if the discount rate is 0%, DAA treatment is more cost-effective in scenario 1 after 25 years of treatment for all generations who started treatment at age <70 years.

Furthermore, in scenarios 2 or 3, that is, compared to Peg-IFN + RBV or non-antiviral treatment, DAA treatment was estimated to be cost-effective after 10 years of treatment in all age patients, excluding those who started treatment at the age of 90 years. Even in patients who started treatment at the age of 90 years, the ICER values decreased remarkably after 10 years of treatment, but did not reach ¥6 million. In our study, elderly people in Japan have little or no income, and there is no difference in indirect costs between treated patients with SVR and untreated patients. From our analysis, it means indirect costs may not significantly affect the ICER in some populations where most HCV patients are elderly.

The Ministry of Health, Labour, and Welfare guidelines\textsuperscript{15} indicate that public nursing costs and indirect costs (loss of productivity) should not be included in the preliminary evaluation of cost-effectiveness, although they should be considered in subsequent evaluations. This may be because loss of productivity among HCV carriers is generally related to “loss of incomes/wages due to HCV-related early death” and “loss due to a decline in the job performance” (i.e., absenteeism).\textsuperscript{39} Thus, the present study estimated loss of productivity due to “a loss of income caused by early death due to HCV infection,” but excluded indirect costs due to absenteeism in order to prevent double counting of absenteeism.\textsuperscript{40}

In scenario 1 (DAA vs. triple therapy), based on the sensitivity analysis, QOL scores after SVR had significantly greater effects on the ICER values than the receiving rate of DAA treatment or SVR rate of DAA treatment. It indicates that, in order to increase cost-effectiveness of DAA treatment, measures or effort to improve the QOL score of patients after SVR are important. Therefore, in order to avoid the risk of carcinogenesis after SVR, which is
reported by some clinical research, it is considered that patients after SVR need to visit medical institutions periodically. It is important to explain the follow-up system currently being maintained in each prefecture to patients and obtain their understanding. By encouraging patients to register in this system, regular check-ups will be possible. Providing information on health promotion (e.g., exercise and nutrition) using the system to registrants might assist in maintaining and improving their QOL.

Because of their relatively short life expectancy, DAA treatment did not show cost-effectiveness for patients who started treatment at the age >80 years. However, in Japan, the HCV carrier rate among older people is higher than that among young people; for example, approximately 50% of HCV carriers in Hiroshima were over the age of 80 years (Table 2). Furthermore, the new HCV infection rate in Japan is very low (0.7/100,000 person-years [95% confidence interval, 0.6–0.9]). However, the cause of HCV infection is unclear in up to 60% of new hepatitis C cases, and the incidence of HCV infection in women is highest among the age groups 50–60 years and 20–30 years. Therefore, DAA treatment for HCV carriers aged >60 years might still be effective for preventing new HCV infections.

This study has several limitations. First, the incidence of HCC after SVR was assumed to be zero in this study, but there are some reported cases that have developed HCC. In terms of HCV infection prevention, DAA treatment should be recommended to elderly patients. To improve the cost-effectiveness of DAA treatment, strategies to increase the QOL scores of HCV patients after SVR are important.

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