Short Communications

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Quantifying the Contribution of Viral Hepatitis Control Policies and Improvement of Hepatitis C Treatment in Japan during 2000-2030 based on Simulation Modelling

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Abstract

Introduction: Chronic hepatitis B virus (HBV) and hepatitis C virus (HCV) infections are major causes of hepatocellular carcinoma (HCC) in Japan. The Japanese government has implemented various countermeasures since the early 2000s, including expanded screening and effective antiviral treatments. Evaluating the long-term impact of these policies is essential for guiding future strategies. **Methods:** We developed a Markov model-based simulation to estimate the annual transition of HBV/HCV carriers, disease progression, and HCC-related outcomes in Japan from 2000 to 2030. Five policy scenarios were set, reflecting the implementation stages of national countermeasures. A sensitivity analysis was also conducted by varying post-2020 hospital visit rates, the proportion of DAA treatment in chronic hepatitis/cirrhosis, and HCC mortality rates. **Results:** The simulation predicted a reduction in HCV carriers from 480,000 in Scenario 1 (no intervention) to 270,000 in Scenario 5 (reflecting 2020 policies). The number of chronic hepatitis and cirrhosis patients also declined significantly, mainly due to the introduction of direct-acting antivirals (DAAs). All scenarios showed a downward trend in new HCC cases and mortality; the decline was most pronounced in Scenario 5. Under Scenario 5, age-adjusted HCC mortality in 2030 was reduced by 53% compared to 2015 level. Sensitivity analysis revealed that variations in hospital visit rates, treatment proportions, and HCC mortality could lead to HCC deaths in 2030 ranging from 5,797 to 7,065. **Discussion:** Our findings suggest that sustained hepatitis countermeasures and the introduction of DAAs have significantly contributed to the decline in HCV-related disease burden in Japan. Simulation modeling provides a useful framework for evaluating past policies and projecting future outcomes.

Keywords: viral hepatitis- Markov model- hepatocellular carcinoma- prediction

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Introduction

Liver cancer, particularly hepatocellular carcinoma (HCC), remains a significant health challenge globally, especially in regions with high prevalence of hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. In Japan, concerted efforts including screening and antiviral treatment have been promoted as part of the Basic Plan to Promote Cancer Control Programs [1, 2]. However, quantifying the impact of these interventions remains a challenge due to long disease progression timelines. Several modeling studies have been conducted globally to estimate the burden of viral hepatitis and the impact of health policies. For example, Razavi et al. [3] developed a global HCV burden model to support WHO elimination goals. Similarly, Polaris Observatory HCV Collaborators [4] provided country-level forecasts of HCV prevalence and mortality. In Japan, Tanaka et al. [5] performed an estimation of HBV/HCV carriers using national datasets, though their model was more descriptive rather than predictive. Other studies have used Markov or microsimulation approaches to model disease progression and treatment impact (e.g., Kabiri et al. [6] for HCV in the US). These studies demonstrate the utility of simulation for informing public health decisions. Our study builds on this foundation, applying a Japan-specific multi-state Markov model to compare historical and counterfactual policy scenarios.

Materials and Methods

Model Structure of Liver Disease Transition

We constructed a state-transition model based on a multi-state Markov framework to simulate the natural history of chronic HBV and HCV infections in Japan, considering various health policy interventions (Figure

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1-a). The model was based on a state-transition approach, with individuals categorized into three groups: uninfected, undiagnosed, and patients receiving care. Disease progression was modeled through four distinct states: Asymptomatic Carriers (AC), Chronic Hepatitis (CH), Liver Cirrhosis (LC), and Hepatocellular Carcinoma (HCC). The model accounted for the fact that, in some cases, patients might develop HCC without progressing through the LC stage, or they might revert to an asymptomatic carrier state.

The transitions between states were modeled with annual probabilities, which allowed for dynamic tracking of disease progression. For HBV, the model did not include a virologic cure since no such treatment exists as of now, whereas for HCV, the availability of Direct-Acting Antivirals (DAA) was included, with a sustained virologic response (SVR) leading to potential clearance of the virus [7].

The simulation was performed annually over a 30-year period, including calculation of 1) newly hospital visits, 2) the number of survivors in each health state, and 3) disease progression based on a Markov model.

Parameters

The key parameters included diagnostic rates, treatment initiation rates, treatment efficacy (SVR), probabilities of progression to LC and HCC, and mortality rates, and were sourced from national surveys, cohort studies, and registry data (Figure 1-b). The number of chronic infections in Japan was based on estimates from Tanaka et al. [5], and the number of undiagnosed carriers was determined using data on seroprevalence among blood donors. Transition probabilities for disease progression were informed by studies of general populations and blood donors screened for HBV and HCV [8, 9]. Mortality rates for liver disease, including HCC-related deaths, were derived from Japan's Cancer statistics [10] and Vital statistics, adjusted using Kamo's method [11] to account for age and population shifts.

Policy Scenarios

Five policy scenarios were modeled to predict the trends in HBV and HCV infections between 2000 and 2030. These scenarios reflected different levels of intervention in terms of diagnosis, treatment initiation, treatment efficiency, and liver-related deaths, based on the implementation of Japan's hepatitis control programs over time.

* Scenario 1 (2000-fix): This scenario assumed no change in diagnostic and treatment rates from 2000 levels through 2030.

* Scenario 2 (2006-fix): This scenario incorporated improvements in diagnostic and treatment rates observed between 2000 and 2006, following initial health policy interventions.

* Scenario 3 (2011-fix): It assumed continued improvements through 2011, including the introduction of the First-term of the Basic Plan to Promote Cancer Control Programs.

* Scenario 4 (2016-fix): This scenario extended the improvements to 2016, reflecting the impact of more recent policies, such as the Second-term of the Basic Plan.

* Scenario 5 (2020-fix): The most recent scenario, which assumed that diagnostic and treatment rates continued to improve through 2020, incorporating the full impact of the Third-term of the Basic Plan.

We also conducted sensitivity analysis to test the robustness of the results under different assumptions for medical institution visit rates, DAA treatment rates, and liver cancer mortality rates.

Results

Estimated Number of Hepatitis Virus Carriers by Each Scenario

The simulation output included time series of the number of individuals in each disease state, new HCC cases, and deaths. (Figure 2-a)-f)). In all scenarios, a decreasing trend over time was observed in the number of carriers, new liver cancer cases, and liver cancer deaths; however, the decline was particularly pronounced in Scenario 5. The emergence of direct-acting antivirals (DAAs) for HCV treatment significantly contributed to the reduction in the number of carriers with chronic hepatitis (Figure 2-c)) and liver cirrhosis (Figure 2-d)). In 2030, the total number of HCV carriers was projected to decrease from 0.480 million in Scenario 1 to 0.28 million in Scenarios 4 and 5, reflecting the effects of enhanced hepatitis control measures and treatment availability. HBV carriers showed less variation across scenarios, remaining relatively constant.

Similarly, the trends in HCV chronic hepatitis and cirrhosis mirrored those of the total number of carriers. The incidence of HCC and HCC-related mortality also followed a declining trend, most notably in Scenarios 4 and 5. By 2030, the incidence of HCC and HCC-related mortality were projected to decrease by 59% and 53%, respectively, in Scenario 5 compared to 2015 levels.

Age-Standardized Mortality Due to Liver Cancer Caused by Hepatitis Virus Infection

The age-adjusted mortality rate for hepatitis virus-related liver cancer in individuals under 75 years old in 2016 was 4.3 per 100,000 in Scenario 2, compared to 3.4 per 100,000 in Scenario 5, reflecting a 20.9% reduction due to improvements in screening and treatment (Figure 2-h)). A similar trend was observed for all ages, where Scenario 5 showed a 20% reduction in liver cancer mortality compared to Scenario 2 (Figure 2-g).

Sensitivity analysis showed that changes in medical institution visit rates, DAA treatment rates, and liver cancer mortality rates in 2030 would lead to variability in liver cancer deaths ranging from 5,798 to 7,065, and new liver cancer cases would range from 6,650 to 6,802 depending on these parameters.

Discussion

This study highlights the impact of Japan's hepatitis control policies and treatment advancements on the future burden of HBV and HCV-related liver diseases. The simulation results indicate that the introduction of

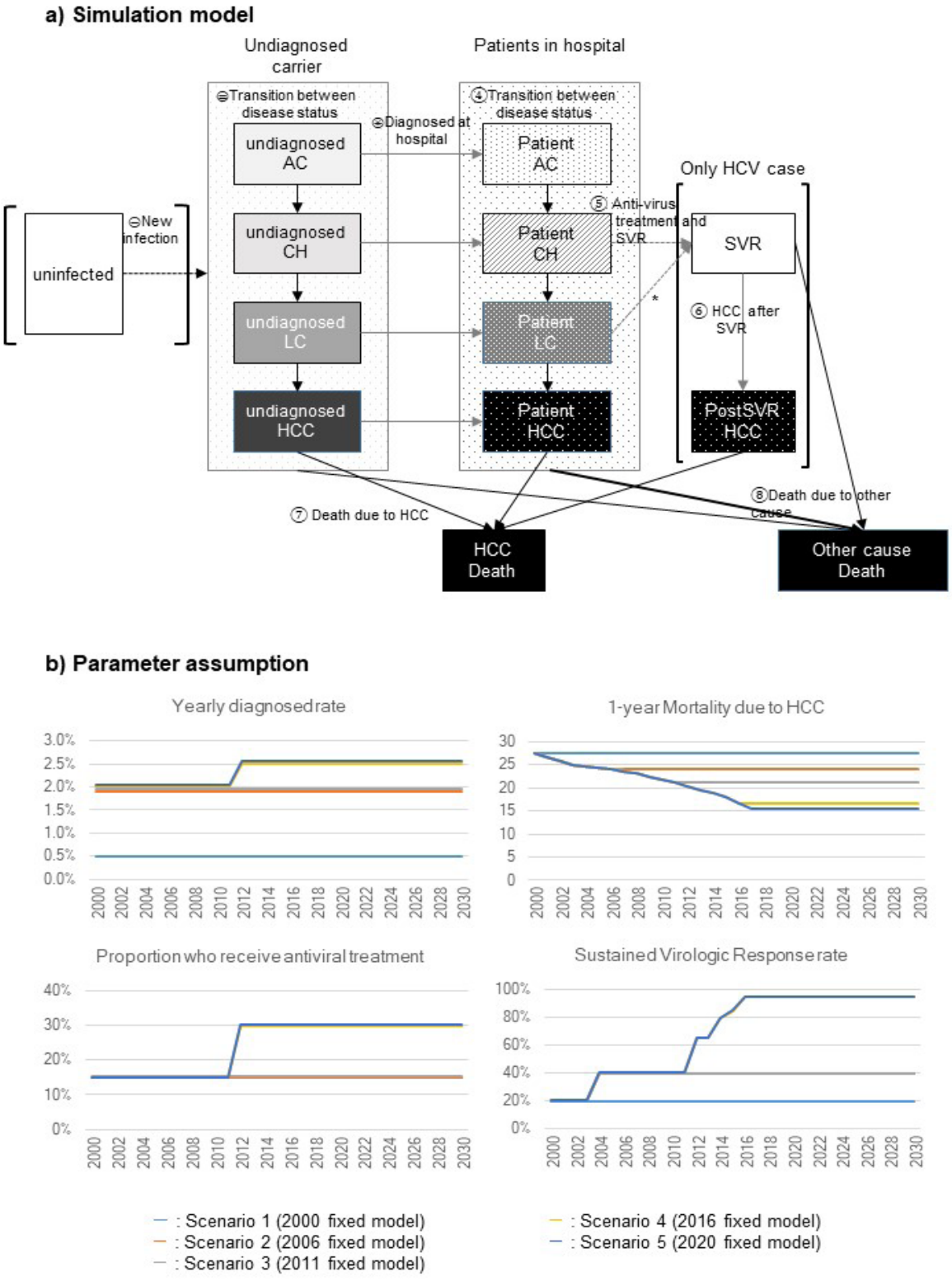

Figure 1. Simulation Setting. a) Model structure: This figure shows the structure of the models for HBV and HCV. The model construction was based on the natural history of liver disease [Asymptomatic carriers (AC), Chronic Hepatitis (CH), Liver Cirrhosis (LC), and Hepatocellular Carcinoma (HCC)] and by subgroups of undiagnosed and patients. For HCV, we considered the potential of sustained virologic response (SVR) after treatment. Death is the absorbing state and is classified into HCC-related deaths and deaths from other causes. b) Parameter assumption: Parameter settings for each scenario are shown. During 2000 to 2030, value of parameters changed by progress of countermeasure and improvement of treatment. Each scenario assumed that such parameters become fixed value after one time point.*: since 2015.

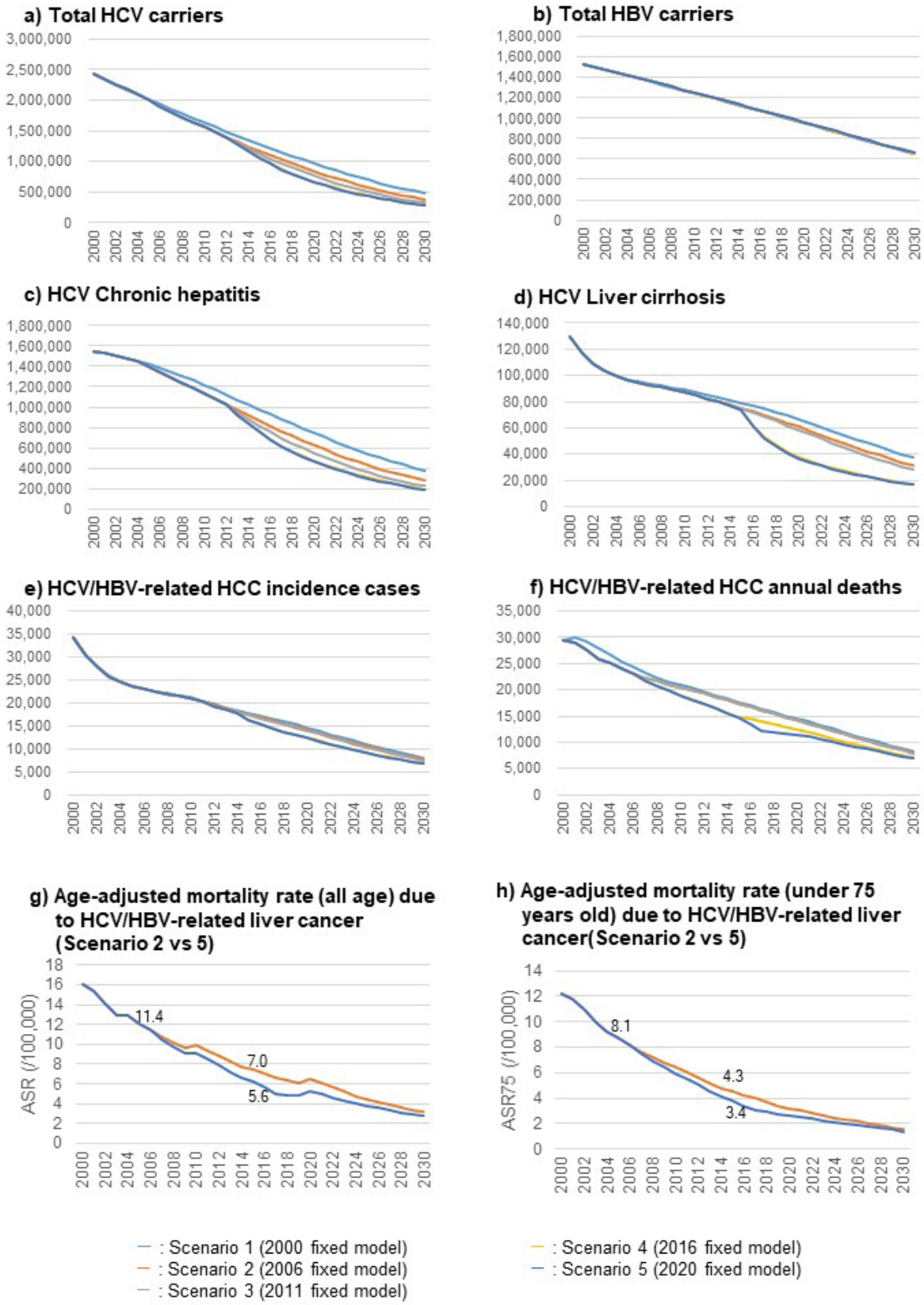

Figure 2. Trend in HCV/HBV Related Epidemiological Indexes (a-f) and Age-Adjusted Mortality due to HCV/HBV-Related Liver Cancer (g, h) by Scenario. Prediction of the dynamics of the epidemiological indexed under each scenario.(a) Total HCV carriers, (b) Total HBV carriers, (c) HCV chronic hepatitis, (d) HCV liver cirrhosis, (e) HCV/HBV-related HCC incidence cases, (f) HCV/HBV related HCC annual deaths. Prediction of the dynamics of the age-adjusted mortality due to HCV/HBV-related liver cancer under each scenario.(g)all age, (h) under 75 years old.

improved screening and antiviral treatments, particularly the use of DAAs for HCV, has the potential to significantly reduce the number of HCV carriers and the incidence of liver cancer by 2030. The reduction in liver cancer mortality observed in the simulation aligns with trends seen in real-world data following the introduction of hepatitis treatment programs [12].

Our results also emphasize the importance of addressing gaps in the cascade of care, particularly in terms of increasing the proportion of undiagnosed carriers who seek treatment. While screening rates have improved, the linkage to care remains a challenge. Strategies to increase the medical institution visit rates and strengthen the coordination between primary care providers and hepatologists are crucial in further reducing the burden of hepatitis-related liver cancer.

One limitation of this study is that we did not model improvements in HBV treatment, as a virologic cure for HBV is not yet available. However, future advancements in HBV treatment could lead to significant changes in the number of HBV carriers and associated liver cancer deaths. Additionally, our model assumed a fixed ratio for the number of hepatitis patients, which may not fully reflect changes in the healthcare system over time. Further refinements in data collection and model assumptions could improve the accuracy of the predictions.

This mathematical modeling study provides valuable insights into the potential impact of Japan's hepatitis control policies on the future trends of HBV and HCV infections and liver cancer mortality. The results underscore the importance of continued efforts in screening, treatment, and improving the cascade of care to further reduce the burden of hepatitis-related liver diseases.

Author Contribution Statement

JT, TA, KK conceived and designed the study and the data analysis concept. JT, TA, SI acquired the data. TA, SI analyzed the data. JT, TA, KK interpreted the data. TA, KK drafted the manuscript. All authors read and approved the final version of the manuscript.

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Abbreviations

HCC, Hepatocellular Carcinoma; HBV, hepatitis B virus; HCC, hepatitis C virus; HBIG, hepatitis B Immunoglobulin; DAA, Direct acting antivirals; IFN, Interferon; WHO, World health organization; AC, asymptomatic carriers; CH, chronic hepatitis; LC, liver cirrhosis; HCC, hepatocellular carcinoma; SVR, Sustained Virologic Response

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Scientific Body Approval / Student Thesis

This study is not part of an approved student thesis and was not specifically approved by any scientific body.

Ethical approval and consent to participate

We only used the open data and published data available as in the public domain; ethics approval was not required for them.

Availability of Data

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Competing interests

The authors declare no conflicts of interest that pertain to this work.

Study Registration

This study was not registered in any clinical trial registry or systematic review database, as it is a modeling study not subject to such registration requirements.

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