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TITLE: Risk of Hepatocellular Cancer After Virological Cure with Direct Acting Antiviral Agents in Individuals with Hepatitis C

PRINCIPAL INVESTIGATOR: Fasiha Kanwal, MD, MSHS

CONTRACTING ORGANIZATION: Baylor College of Medicine, Houston, TX

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14. ABSTRACT Purpose: The overarching goal of this project is to reduce HCC-related morbidity and mortality in persons with chronic hepatitis C (CHC) who have been virologically cured by direct acting antivirals (DAAs). Aims: 1) Examine determinants of HCC in virologically cured patients and develop a risk prediction model for HCC; 2) Conduct a virtual clinical trial using a mathematical model of the natural history of HCC to evaluate benefits vs harms of HCC surveillance; 3) Develop an online HCC Simulator. Design: Using cause-specific Cox proportional hazard models for competing risks, we identified risk factors in a retrospective cohort study of >100,000 patients with DAA-induced SVR. For dynamic risk prediction of HCC, we used the landmark Cox model. We used a mathematical model to simulate a virtual trial comparing long-term effectiveness of no surveillance vs routine surveillance. Finally, we developed an interactive decision support tool. Progress: The project has been completed. Findings: We identified a range of predictors for HCC in virologically cured patients with CHC. Risk factors for HCC were different in patients with and without cirrhosis and some also evolved during follow-up. These factors can help with risk stratification and HCC surveillance decisions in patients with cured HCV. These findings were reported in a manuscript published in the Am J Gastroenterology. The AUCs for the models in patients with and without cirrhosis were 0.72 (95% CI, 0.70-0.74) and 0.68 (95% CI, 0.66-0.70), respectively. We developed a mathematical model of the natural history of HCC in DAA-cured CHC patients. We found that the burden of HCC will shift from viremic to virologically cured CHC patients, and to older populations in the next decade. These findings are reported in a manuscript published in the JAMA Network Open. In a separate analysis, we found that biannual surveillance for HCC in virologically-cured hepatitis C patients with cirrhosis is cost-effective until the age of 65 (manuscript published in the Journal of Hepatology). Our results also showed that routine surveillance is warranted above the HCC incidence threshold of 0.7 per 100-PY, which is lower than the previous 1.5% incidence value used to guide HCC surveillance decisions (manuscript published in Clinical Gastroenterology and Hepatology). Updating clinical guidelines could improve the early diagnosis of HCC. We also developed an online Liver Cancer Simulator to improve patient decision-making and engagement in HCC surveillance. Feedback from providers indicated that the Simulator was acceptable and feasible and that it has a high likelihood of being implemented in their clinical settings. The manuscript reporting the development and usability testing of the online Liver Cancer Simulator is in progress.					
15. SUBJECT TERMS: Hepatocellular carcinoma; Chronic hepatitis C (CHC); Direct-acting antivirals (DAAs); Sustained viral response (SVR); Risk stratification; Protective factors; Risk factors; Risk prediction models; Benefits and harms; Decision support tool; Simulator tool; Cancer surveillance					
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1.INTRODUCTION: Hepatocellular carcinoma (HCC) is the fastest growing cause of cancer deaths in Americans. HCC incidence has increased 3-fold between 1975–2009 and the trend is still upwards. Despite moderate advances in treatment, most HCC patients present with advanced stage and have low survival (5-year <15%). Chronic hepatitis C (CHC) infection is the leading cause of HCC. The direct-acting antiviral (DAA) treatments offer cure from chronic infection. However, the subsequent risk of HCC persists in patients with CHC after virological cure. In fact, virologically-cured CHC is one of the most important emerging risk factors for HCC. While patients with advanced HCC have a median survival of less than 1 year, patients with early HCC who receive potentially curative therapy achieve 5-year survival rates near 70%. Early diagnosis, therefore, is critical to improved survival. However, the long-term harms and benefits of routine HCC surveillance in virologically cured CHC patients have not been evaluated. Furthermore, instead of using a one-size-fits-all approach, surveillance recommendations based on individualized risk factors could be more efficient — such an approach could detect HCC in early stages in high-risk patients and spare many non-HCC patients who do not need surveillance. The goals of this study are to: (1) identify the most salient protective and risk factors, and combine these factors in predictive models that differentiate high from low risk patients; (2) provide data on long-term benefits and harms of HCC surveillance tailored to individualized risk factors; and (3) develop a first publicly available decision support tool, HCC Simulator, for individualized surveillance recommendations.

2.KEYWORDS:

Hepatocellular carcinoma

Chronic hepatitis C

Direct-acting antivirals

Sustained viral response

Risk stratification

Protective factors

Risk factors

Risk prediction models

Benefits and harms

Decision support tool

Simulator tool

Cancer surveillance

3.ACCOMPLISHMENTS:

◦**What were the major goals of the project?**

The Statement of Work includes the following major goals:

Specific Aim 1 (Kanwal Lead): To examine determinants of HCC in virologically cured patients and develop a risk prediction model for HCC in these patients

Major Task 1: Examine determinants of HCC in patients virologically cured with direct acting antiviral (DAA) agents

Subtask 1: Data acquisition from VA Corporate Data Warehouse, data cleaning, variable creation, and cohort identification (Target date 2/28/2020) – 100% complete.

Subtask 2: EMR chart abstractions to confirm HCC (Target date 2/28/2020) – 100% complete.

Subtask 3: Data analysis of HCC predictors (Target date 4/30/2020) – 100% complete.

Major Task 2: Develop & optimize HCC risk prediction model

Subtask 1: Model fitting/Variable selection (Target date 06/30/20) – 100% complete.

Subtask 2: Risk stratification (Target date 07/31/20) – 100% complete.

Subtask 3: Subgroup sensitivity analysis (Target date 08/31/20) – 100% complete.

Specific Aim 2 (Chhatwal Lead, Kanwal Team Participating): To evaluate the benefits vs harms of HCC surveillance in virologically cured patients

Major Task 3: Develop a mathematical model simulating the natural history of HCC that incorporates risk estimates and key factors identified in Aim 1

Subtask 1: Model description – Develop a simulation model (individual-level state-transition model) of the natural history of HCC in virologically cured hepatitis C patients (Target date 08/31/20) – 100% complete.

Subtask 2: Add modules to the simulation model: surveillance and diagnosis, treatment options based on the BCLC stage at diagnosis (Target date 11/30/2020) – 100% complete.

Subtask 3: Liver transplantation - Extend simLT module to simulate the life course of HCC patients on the UNOS waiting list and after the transplant; we will also incorporate HCC recurrence (Target date 11/30/2020) – 100% complete.

Subtask 4: Costs and quality of life – Using published studies, estimate costs associated with the mathematical model's (simHCC's) states (Target date 12/31/2020) – 100% complete.

Major Task 4: Use simHCC to compare long-term effectiveness of no surveillance versus routine surveillance

Subtask 1: Generate a set of outcomes for surveillance vs no surveillance strategies for each risk group (Target date 01/31/21) – 100% complete.

Subtask 2: Conduct probabilistic sensitivity analysis (Target date 02/28/21) – 100% complete.

Subtask 3: Conduct value of information analysis (Target date 04/30/21) – 100% complete.

Specific Aim 3 (Chhatwal Lead, Kanwal Team Participating): To develop HCC Simulator, an online interactive tool for physicians and patients that provides the short- and long-term value of HCC surveillance in different risk groups

Major Task 5: Create a large dataset of hypothetical virologically cured patients

Subtask 1: Using simHCC model, simulate the life course of 1 million patients having different profiles (Target date 05/31/21) – 100% complete.

Subtask 2: Generate a set of graphical outcomes for each patient profile with and without HCC surveillance (Target date 06/30/21) – 100% complete.

Major Task 6: Create an online tool, HCC Simulator

Subtask 1: Create an online platform using RShiny (Target date 09/30/21) – 100% complete.

Subtask 2: Create a homepage for HCC Simulator (Target date 10/31/21) – 100% complete.

Subtask 3: Make the HCC Simulator available on the internet (Target date 11/30/21) – 100% complete.

Major Task 7: Conduct a feasibility study to assess the usability of the HCC Simulator in a clinical setting

Subtask 1 (Chhatwal & Kanwal Teams Combined): Develop focus group and patient interview guides (Target date 12/31/21) – 100% complete.

Subtask 2: Provider and patient recruitment for focus groups and individual patient interviews (Kanwal Team); Conduct focus groups and individual patient interviews (Chhatwal Team Lead; Kanwal Team Supporting) (target date 03/31/22) – 100% complete.

Subtask 3 (Kanwal Team): Transcription services (Target date 04/30/22) – 100% complete.

Subtask 4: Coding and analysis of transcripts (Target date 05/31/22) – 100% complete.

Major Task 8: Incorporate results from focus group and individual patient feedback into the HCC Simulator

Subtask 1: Re-design relevant components of the HCC Simulator based on the feedback (Target date 07/31/22) – 100% complete.

Subtask 2: Launch the HCC Simulator (Target date 08/31/22) – 100% complete.

Major Task 9: Manuscripts and dissemination of results

Subtask 1: Organize a Webinar on use of the HCC Simulator – Seminar scheduled for 03/6/24 – 100% complete.

Subtask 2: Report project results through manuscripts in peer-reviewed journals (Target date 08/31/23) – 100% complete.

1) Predictors of HCC in CHC patients with virologically induced cure

Kramer JR, Cao Y, Li L, Smith D, Chhatwal J, El-Serag HB, Kanwal F. Longitudinal Associations of Risk Factors and Hepatocellular Carcinoma in Patients With Cured Hepatitis C Virus Infection. *Am J Gastroenterol*. 2022 Nov 1;117(11):1834-1844. doi: 10.14309/ajg.0000000000001968. Epub 2022 Aug 23. PMID: 36327437; PMCID: PMC9641546.

2) Risk prediction model to identify patients at high risk for HCC after DAA induced virological cure

Included in above article (doi: 10.14309/ajg.0000000000001968).

3) Cost-effectiveness of personalized HCC surveillance in virologically cured CHC patients

Mueller PP, Chen Q, Ayer T, Nemutlu GS, Hajjar A, Bethea ED, Peters MLB, Lee BP, Janjua NZ, Kanwal F, Chhatwal J. Duration and cost-effectiveness of hepatocellular carcinoma surveillance in hepatitis C patients after viral eradication. *J Hepatol*. 2022 Jul;77(1):55-62. doi: 10.1016/j.jhep.2022.01.027. Epub 2022 Feb 12. PMID: 35157959; PMCID: PMC9618359.

4) When to stop HCC surveillance after virological cure with CHC

Included in above article (doi:10.1016/j.jhep.2022.01.027), as well as the following article:

Chhatwal J, Hajjar A, Mueller PP, Nemutlu G, Kulkarni N, Linton B, Peters M, Kanwal F. Hepatocellular Carcinoma Incidence Threshold for Surveillance in Virologically Cured Hepatitis C Individuals. *Clin Gastroenterol Hepatol*. 2023 Jun 9:S1542-3565(23)00446-9. doi: 10.1016/j.cgh.2023.05.024.

5) A brief report on HCC Simulator – In progress. Both Team A and Team B are working collaboratively and have a draft of the manuscript ready for submission to Hepatology Communications.

◦ **What was accomplished under these goals?** The following was accomplished under these goals:

Specific Aim 1: To examine determinants of HCC in virologically cured patients and develop a risk prediction model for HCC in these patients.

Study Cohort. We included patients ≥18 years who achieved SVR with DAA in any of the 130 VA hospitals. We defined DAA treatment as ≥1 filled prescription of DAA (appendix 1) between 1/1/2014 and 12/31/2018. We used 3 months after the date of DAA completion as the index date for start of follow up to consider time needed to determine SVR. We classified patients as SVR if all HCV RNA tests were negative after the end of

DAA treatment, with ≥ 1 HCV RNA test recorded at least 12 weeks after completion. If no test was available after 12-weeks we used a negative test from 4-12 weeks as SVR (6.9% of cohort). We excluded patients who failed to achieve SVR, who had HCC or liver transplant before or within 3 months of DAA treatment, had prior evidence of cancers with a high likelihood of liver metastases (esophageal, stomach, pancreatic, lung, kidney, breast cancer, and melanoma), and patients did not have evidence of ≥ 1 visit in the VA following end of treatment.

The study **outcome** was new cases of HCC after the date of completing DAA. HCC was defined based on 2 or more instances of ICD-9 (155.0) or ICD-10 codes (C22.0, C22.8, C22.9, D01.5) in CDW or any instance of HCC recorded in the CCR. We also reviewed electronic medical records of cases that had ICD codes but not included in CCR. We followed patients to the development of HCC, liver transplant, death, or last VA visit before December 31, 2021, whichever was earlier.

Predictor variables. These include age, sex, race/ethnicity, marital status, place of residence (rural vs. urban), HCV genotype, previous HCV treatment status, diabetes, hypertension, dyslipidemia, body mass index (BMI), active alcohol use disorder, smoking, and other medical and mental health comorbidity. We also derived laboratory variables including values of bilirubin, AST, ALT, international normalized ratio, platelet tests, hemoglobin, creatinine, and sodium values. We also used FIB-4 to identify patients with cirrhosis/fibrosis at baseline (FIB-4 >3.25) and used serial changes in FIB-4 to examine the decline or increase in fibrosis. All variables were longitudinal and time updating over time.

Statistical analysis. We used cause-specific Cox proportional hazard models for competing risks¹² constructed at three landmark times^{13, 14} (baseline, and 12- and 24-months after index) to examine the associations between risk factors measured at these landmark times and subsequent HCC risk, stratified by cirrhosis status at baseline.

We constructed six separate models (at three separate landmark times for patients with and without cirrhosis). The outcome was the time from the landmark to HCC. At each landmark, the data only included the at-risk patients at that time (e.g., those who are alive without HCC).

The predictor variables included time-independent and time-dependent defined at each landmark time. For continuous measures, we assessed both categorical and continuous values to determine the best performing measure. The predictors also incorporated longitudinal information of a patient up to the landmark time, including change in FIB-4 [defined as remained stable at low risk (≤ 3.25), increased from low (≤ 3.25) to high risk (>3.25), declined from high (>3.25) to low risk (≤ 3.25), or remained stable at high risk (>3.25)] as well as changes in serum albumin, sodium, bilirubin, INR, creatinine, and hemoglobin between baseline and each landmark time. Log-transformation was used for variables with a skewed distribution. For model interpretability, we only considered two-way interactions that are frequently observed in the cohort or suggested by literature.

There was a small amount of missing data. We used multiple imputation generated from the fully conditional specification method of SAS PROC MI to create five imputed datasets and then combined the results using multiple imputation. Each imputed dataset went through a model building process with stepwise selection (entry p-value ≤ 0.10 ; retaining p-value ≤ 0.05). The final model included all predictors selected from at least one dataset. For each landmark time, we forced baseline variable/s in the model if the final model/s included the corresponding change variable. Model fit with imputed datasets was checked using usual model checking procedures and no assumptions were violated.

We conducted 3 sensitivity analyses. We refined our cirrhosis definition by including only patients with a diagnosis of cirrhosis or its complications and excluding those with a FIB-4 <1.45 ; we tested the robustness of our HCC definition by including patients with only 1 ICD code for HCC; and we examined the effect of BMI after excluding HCCs diagnosed in the first 12-months. **Specific objectives:** Our specific objectives were to acquire data from VA Corporate Data Warehouse and complete data cleaning, variable creation, and cohort identification; abstract EMR to confirm HCC; analyze data to identify predictors of HCC risk; develop and optimize HCC prediction models and perform subgroup analyses. We have completed these objectives.

Significant results: In total, 113,563 patients received DAA treatment between January 1, 2014, and December 31, 2018. We excluded 9112 without known SVR status, 1919 with prior HCC and 5034 with prior other cancers, 912 who received liver transplant, and 4019 who did not achieve SVR. Hence, our study cohort included 92,567 patients with SVR without prevalent HCC. The mean age of the overall cohort at baseline was 61.5 years (SD=7.55 year), 96.4% were men, 51.0% were white, and 38.7% were African American. A total of 26.5% had cirrhosis diagnosed at baseline and an additional 5.5% had a FIB-4 value greater than 3.25, 36.7%

had diabetes, 83.1% had hypertension, 51.2% dyslipidemia, and 14.1% had an active alcohol use disorder. At baseline, 43.5% of patients with cirrhosis had diabetes; it increased to 46.4% at 24-month landmark time. Similarly, the proportion of patients with hypertension increased from 86.6% to 89.7% and dyslipidemia increased from 52.1% to 55.6% between baseline and 24-month landmark time. We found similar trends in patients without cirrhosis.

When examining changes in FIB-4 values from baseline to 24-months in patients with FIB-4 available at both time periods, 18.6% of patients with cirrhosis remained stable at high risk. In addition, 16.4% of patients had a high-risk FIB-4 at baseline that declined over time. FIB-4 values for few patients (3.5%) were low-risk at baseline but increased to high-risk. Approximately 61% with cirrhosis had low-risk FIB-4 values both at baseline and 24-months. In patients without cirrhosis where everyone had low FIB-4 at baseline, 97.8% remained stable at low-risk and 2.2% increased from low to high risk at 24-months.

There were 3,247 incident cases of HCC diagnosed during mean 2.51 (SD=1.66) years of follow-up (maximum 7.11 years); 74.0% (n=2,404) were diagnosed in patients with cirrhosis at baseline. In 29,398 patients with cirrhosis, cumulative incidence of HCC was 2.0%, 3.8%, and 5.4% at 1, 2 and 3 years, respectively. In contrast, HCC risk was considerably lower in 63,169 patients without cirrhosis in whom 843 were diagnosed with HCC (0.2%, 0.5%, and 0.8%, respectively) (p-value <0.0001).

In the baseline model, in patients with cirrhosis, the risk of HCC was higher in men (adjusted hazard ratio (HR) =1.89, 95% confidence interval (CI)=1.37-2.59) and lower in African American patients (HR=0.78, 95%CI=0.71-0.86). Patients with genotype 3 had a higher risk of HCC (HR=1.47, 95%CI=1.27-1.71) than those with other genotypes. Patients with a longer duration since cirrhosis diagnosis had higher risk (≥ 5 years vs. <1 year, HR=1.71, 95%CI=1.46-2.00). Serum bilirubin, albumin, presence of varices, and higher FIB-4 were associated with HCC risk. Specifically, HCC risk was 2.5-fold higher (95%CI, 2.11-2.94) in cirrhosis patients who also had FIB-4 >3.25 than those with FIB-4 values <1.45. Patients who were current smokers had an increased risk for HCC than non-smokers (HR=1.32, 95%CI=1.16-1.51). None of the pre-specified interaction terms were significant in the adjusted model at baseline.

Most of the associations observed at baseline persisted in direction and magnitude at 12- and 24-month landmark times, with few notable exceptions. Presence of ascites was associated with an increased risk for HCC at both 12- and 24-months. Changes in serum albumin, bilirubin, and FIB-4 between baseline and landmark times were strongly associated with subsequent risk of HCC. For example, one unit increase in serum bilirubin between baseline and 24-month landmark time was associated with a 22% increase in HCC risk. Compared with patients with persistently low FIB-4 at baseline and 24-months, the risk of HCC was almost 2-fold higher in patients who had persistently high FIB-4 at the time of virological cure and at 24-months (HR=1.70, 95%CI, 1.45-2.00) and 81% higher in patients who were at low risk (FIB-4 $\leq$ 3.25) but increased to high risk (FIB-4>3.25) at 24-months (HR = 1.81, 95% CI = 1.37-2.38). Results were similar in the sensitivity analyses excluding cirrhosis patients with FIB-4<1.45 and including patients with 1 ICD code for HCC.

In patients without cirrhosis, patients with hypertension and diabetes had a 1.5-fold higher risk of HCC than their counterparts. After controlling for diabetes and hypertension, there was no difference in the risk of HCC between patients with BMI higher than 30 compared with BMI 25-30. Risk of HCC was higher in patients with BMI <25, with the highest risk in patients with BMI <18.5 compared with BMI 25-<30, (HR=1.93, 95%CI=1.20-3.12). The risk of HCC for BMI <18.5 was slightly attenuated after excluding patients with HCC in 12-months after index date. Baseline serum albumin and FIB-4 were associated with HCC risk. Patients with baseline FIB-4 between 1.45 and 3.25 had 2.3-fold higher risk of HCC than those with low FIB-4 <1.45 (HR=2.27, 95%CI=1.96-2.63). Prior failure of HCV treatment, HCV genotype 3, and current smoking were also associated with HCC risk in patients without cirrhosis.

Only metabolic traits (diabetes, hypertension) and change in FIB-4 remained associated with HCC risk at all landmark times. At 24-month landmark time, patients with hypertension and diabetes had 1.7 to 1.5-fold higher risk of HCC than their counterparts. Patients who had an increase from FIB-4 of low risk at baseline to high risk at 24-month landmark time had 3-fold increase in HCC risk (HR=3.12, 95%CI, 2.12-4.60).

Following the 24-month landmark time, the 3-year cumulative incidence of HCC varied from 3.4% (95%CI, 3.1%-3.7%) in patients who had persistently low FIB-4 value to 9.2% (95%CI, 8.3%-10.2%) in patients with persistently high FIB-4. Risk of HCC was low in all subgroups without cirrhosis, with few notable exceptions. In patients who increased from low to high risk, the 2- and 3-year cumulative incidence of HCC was 2.4% (95%CI, 1.6%-3.6%) and 3.0% (95%CI, 2.1%-4.4%), respectively. Cumulative 1, 2- and 3-year risk of HCC in 419 patients without cirrhosis who had hypertension, diabetes and who experienced an increase from low to high risk between baseline and 24-month landmark was 3.1%, 5.7%, and 7.2%, respectively.

The AUCs for the models in patients with and without cirrhosis were 0.72 (95% CI, 0.70-0.74) and .0.68 (95% CI, 0.66-0.70), respectively.

Specific Aim 2: To evaluate the benefits vs harms of HCC surveillance in virologically cured patients. For Specific Aim 2, **the major activities** undertaken by the Chhatwal Team, with participation from the Kanwal Team, in Year 2 included developing a mathematical model simulating the natural history of HCC to evaluate the benefits and harms of routine HCC screening in virologically cured patients.

Specifically, we developed a Markov-based state-transition simulation model, simHCC (simulation of HCC) that simulated the natural history of hepatitis C and HCC in patients with advanced fibrosis (METAVIR score F3) or compensated cirrhosis (METAVIR score F4) who achieved SVR after a treatment with direct-acting antivirals. For each patient, we simulated the clinical course of cured hepatitis C, including development and progression of HCC. We assumed that cured advanced fibrosis patients do not progress to compensated cirrhosis after cure. Patients with compensated cirrhosis, on the other hand, may progress to decompensated cirrhosis. Based on the underlying liver disease stage, patients could develop HCC defined by the given incidence rate. In each month, patients could develop HCC at a “very early” stage that could later progress to “early” and “intermediate/advanced” stages. We defined HCC stage based on Barcelona Clinic Liver Cancer (BCLC) staging system and tumor size: “very early HCC” included patients with a tumor less than 2 cm in diameter, “early HCC” for those with a single tumor less than 5 cm or up to three tumors all less than 3 cm, and “intermediate/advanced HCC” for the remaining stages. We considered two causes of mortality: background and liver-related. We also considered that patients with decompensated cirrhosis or with intermediate/advanced HCC were at risk of liver-related mortality. We used published data on the natural history of hepatitis C, competing risk post virological cure, HCC tumor progression, real-world HCC surveillance adherence, contemporary HCC treatment options and associated costs, and utilities of different health states.

We tested biannual HCC surveillance using ultrasound and AFP testing until age 75. The model simulated 50 million patients with mean age of 50 under surveillance and no surveillance to determine the life expectancy benefit of surveillance. The model was developed using C++ programming language with a one-month cycle length. We presented the results of each of the simulated surveillance strategies in terms of life-years (LYs), quality-adjusted life-years (QALYs), total costs, and incremental cost-effectiveness ratio (ICER). Following the recommendations of the Panel on Cost-Effectiveness in Health and Medicine, we discounted both future costs and future QALYs at 3% in the base case analysis. Using this extended model, we conducted three studies.

Study 1

We evaluated the cost effectiveness of HCC surveillance in hepatitis C cured patients. Primary outcomes included life expectancy, quality-adjusted life years (QALYs), total costs, and incremental cost-effectiveness ratio (ICER) of each of the simulated surveillance strategies.

Preliminary results: In virologically-cured patients with cirrhosis, the ICER of biannual surveillance remained below \$100,000/QALY (range: \$85,000-\$98,100) when surveillance was stopped at age 65, rising above \$100,000 if surveillance continued beyond 65. For every 1000 patients, surveillance detected 260 HCCs in ‘very early’/early stage, and 120 in intermediate/advanced stage. In contrast, no surveillance detected 92 HCCs in ‘very early’/early stage, and 274 in intermediate/advanced stage. Compared to no surveillance, HCC surveillance provided QALY gains of 47 per 1000 patients. In virologically-cured patients with advanced fibrosis, the ICER of biannual surveillance remained above \$100,000 irrespective of the stopping age.

Conclusion: Biannual surveillance for HCC in virologically-cured hepatitis C patients with cirrhosis is cost-effective until the age of 65.

Study 2

The AASLD guidance recommends biannual surveillance for hepatocellular carcinoma (HCC) in hepatitis C virus (HCV) infected individuals with cirrhosis if HCC incidence is above 1.5 per 100 person-years (PY). However, the incidence threshold for surveillance in cirrhosis individuals who achieved virological cure with direct-acting antivirals is unknown. Using our microsimulation model, we estimated the HCC incidence above which routine HCC surveillance is cost-effective in this growing population of individuals with virologically cured HCV.

In virologically cured hepatitis C individuals with cirrhosis and advanced fibrosis, HCC surveillance is cost-effective if HCC incidence exceeds 0.7 per 100-PY using \$100,000 per quality-adjusted life-year (QALY)

willingness-to-pay. At this HCC incidence, routine HCC surveillance would result in 2,650 and 5,700 additional life-years per 100,000 cirrhosis and advanced fibrosis persons, respectively, compared to no surveillance. At \$150,000 willingness-to-pay, surveillance is cost-effective if HCC incidence exceeds 0.4 per 100-PY. Sensitivity analysis showed that the threshold mostly remained below 1.5 per 100-PY.

Conclusion. Our study suggests that for patients with virologically cured hepatitis C, routine surveillance is warranted above the HCC incidence threshold of 0.7 per 100-PY, which is lower than the previous 1.5% incidence value used to guide HCC surveillance decisions. Updating clinical guidelines could improve the early diagnosis of HCC. Use of this revised threshold could increase HCC surveillance for hepatitis C patients, providing an opportunity for earlier diagnosis and treatment.

Study 3

We also conducted probabilistic sensitivity analysis and value of information analysis to evaluate the impact of uncertainty of HCC surveillance recommendations. Preliminary results are being analyzed and will be finalized in soon for submission to a journal. We found that HCC disease progression and HCC incidence post virological cure were the two most important parameters. Future studies could reduce uncertainty in HCC progression and HCC incidence in DAA-cured hepatitis C patients.

Specific Aim 3: To develop HCC Simulator, an online interactive tool for physicians and patients that provides the short- and long-term value of HCC surveillance in different risk groups.

For Specific Aim 3, the **major activities** undertaken by the Chhatwal Team, with participation from the Kanwal Team, in Year 3 included the following.

Using the mathematical model, we simulated the life course of hypothetical patients with different risk profiles and stored them in a database. The dataset included cause of death (liver-related, or non-liver-related), development of HCC overtime, and likelihood of detection of HCC with or without surveillance.

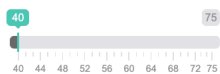
We used the above database to create an online, interactive framework, which allows users to enter specific patient profiles and generate model-predicted long-term outcomes in graphical format. We used RShiny, an R package to develop an interactive online interface of the HCC Simulator. Figure shows the screenshots of Liver Cancer Simulator.

We conducted user-centered design assessments of the Liver Cancer Simulator with providers to assess the feasibility and usability of the Simulator in clinical settings. As part of a user-centered design process, we elicited participants' perceptions on the design and understandability of the Simulator as a decision support tool using focus groups. The themes arising from the focus groups informed the design of a live prototype of the Liver Cancer Simulator. Themes from interviews broadly included how to design the Liver Cancer Simulator to best integrate into the provider workflow and improve the communication of complex information to patients. Discussions frequently considered the topics of patient psychology, motivations, and incentivization; appropriate communication of benefits and risks; and the utility for clinical practice. The final design of the Liver Cancer Simulator was informed by suggestions across each of these domains, emphasizing changes that encourage patient engagement and decision-making in their hepatocellular carcinoma surveillance.

The following are screen shots of the final version of the HCC Simulator.

Choose Risk Factors

Current Age: ?



Sex: ?

- ☒ Male
☐ Female

Race

- ☒ Black
☐ Hispanic
☐ Other

Fibrosis Stage

- ☐ Advanced Fibrosis
☒ Cirrhosis

Additional Risk Factors: ?

- ☐ Diabetes Diagnosis
☐ Hypertension Diagnosis
☐ Alcohol Use

Run Simulator

Tool Introduction and Description

Simulator Purpose:

The Liver Cancer Simulator is an interactive tool that allows patients and physicians to simulate the potential health outcomes for a specific patient with their unique demographic profile. This tool can be used to evaluate the risk of developing liver cancer and to identify the benefits of regular screening for a particular individual.

Tool Overview:

To use the simulator, please input the patient's personal risk factors in the panel to the right. Once your selections have been made, please click the 'run simulator' button to generate the results.

Key Terms:

- **Surveillance** - This refers to a patient undergoing screening with a medical professional. The aim of surveillance is to detect any cancer at the earliest stage possible.
- **Risk Factors** - Any personal characteristic that may impact the occurrence or progression of liver cancer is considered a risk factor in this simulator.
- **Liver Cancer** - Liver cancer is a type of cancer that starts in the liver. Hepatocellular carcinoma (HCC) is the most common type of liver cancer.
- **Liver Cirrhosis** - Cirrhosis is a permanent and end-stage liver disease that occurs due to the accumulation of scar tissue in the liver. Causes of liver cirrhosis include chronic alcohol abuse and hepatitis among others.

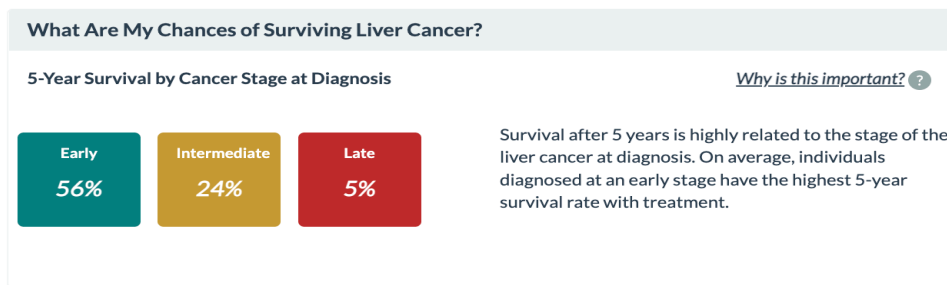
Intro : My Chance of Getting Liver Cancer?

Why is this important? ?

Your 10-Year Chance of Developing Liver Cancer:

👉 18 out of 100 People Like You





◦ **What opportunities for training and professional development has the project provided?**

Two student analysts got an opportunity to gain knowledge of the natural history of HCC in hepatitis C cured patients. This knowledge was transferred in the development of Liver Cancer Simulator, which is intended to be used by patients to understand the risk factors of HCC and importance of early detection of HCC to improve patients survival.

◦ **How were the results disseminated to communities of interest?**

The results were disseminated via meeting presentations and manuscripts. In addition, we are scheduled to present our online Liver Cancer Simulator during a national webinar hosted by the Veterans Affairs Central Office for Gastroenterology and Hepatology. The webinar is attended by liver providers from across the nation and will occur on March 6th 2024, from 2pm-3pm eastern with 35-40 minutes time for presentation and the balance of time for questions. We will also disseminate the online Simulator *via* social media.

◦ **What do you plan to do during the next reporting period to accomplish the goals?**

Nothing to Report.

4.IMPACT:

◦ **What was the impact on the development of the principal discipline(s) of the project?**

Our study provides evidence from a well-characterized cohort of virologically cured patients with HCV but free of cirrhosis that monitoring changes in FIB-4 might have clinical utility, especially in patients with co-existing diabetes and hypertension. In patients with cirrhosis, evolution of FIB-4 and other select markers of liver disease severity could refine risk stratification. We believe risk assessment based on repeat measurements at 2 years is practical and can improve shared decision-making between patients and their physicians by providing a quantifiable personalized HCC risk assessment, including how it changes over time. These findings may guide clinical practice guidelines about management of patients with virologically cured HCV.

Our study also found that biannual surveillance for HCC in virologically-cured hepatitis C patients with cirrhosis is cost-effective until the age of 65. If confirmed in future studies, this finding could have a major impact of screening guidelines for HCC. Our results also showed that routine surveillance is warranted above the HCC incidence threshold of 0.7 per 100-PY, which is lower than the previous 1.5% incidence value used to guide HCC surveillance decisions. Updating clinical guidelines could improve the early diagnosis of HCC. Our online Liver Cancer Simulator can improve patient decision-making and engagement in HCC surveillance.

◦**What was the impact on other disciplines?**

Nothing to report.

◦**What was the impact on technology transfer?**

Nothing to report.

◦**What was the impact on society beyond science and technology?**

Nothing to report.

5.CHANGES/PROBLEMS:

◦**Changes in approach and reasons for change**

Nothing to Report.

◦**Actual or anticipated problems or delays and actions or plans to resolve them**

Despite the following delays, all tasks have now been completed.

During Year 1, the Kanwal team experienced delays due to the COVID-19 emergency. Despite extraordinary efforts by the VA to expand network capabilities to accommodate the sudden and dramatic increase in the number of employees working remotely from home, all team members regularly experienced connection problems and slow response time on all platforms (VINCI, VA secure servers, Outlook Email, Skype, etc.). Mondays, after IT weekend system and program updates, were especially difficult. This caused a delay in the completion of Major Task 2. However, the team tried to compensate for the delay by increasing the data analyst effort to full-time for Year 2.

During Year 2, the Chhatwal team experienced delays due to COVID-19 and a family emergency during which Dr. Chhatwal's availability was limited for about 6 weeks. The team experienced delays in development of a liver transplant module in the simulation model of HCC surveillance (Task 3.3). To move forward, the team used prior liver transplant work, without incorporating recurrence of HCC post liver transplant and treatment. The team was able to finish task 3.3 in Year 3. The Kanwal team also experienced delays during Year 2 due to the COVID-19 emergency "work from home" ongoing IT issues. They hired an additional research coordinator dedicated to Major Task 7 and facilitating the HCC simulator feasibility assessment process in collaboration with the Chhatwal team.

During Year 3, both teams experienced delays related to the IRB approval process at both sites involving changes required for MGH team qualitative expert to conduct interviews with provider and patient participants at the Houston site. A SMART IRB agreement had to be established and protocols at both locations needed to be amended. First, MGH IRB reviewed and then approved their protocol changes on June 30, 2022. Then, the Houston IRB began its review and approved the Houston amended protocol on February 2, 2023. After

Houston IRB approval was received, the Houston team submitted the amended protocol for OHRO review and approval. OHRO issued an approval on MAY 16, 2023 and then reconsidered the approval. OHRO performed a second review and issued a second approval on July 7, 2023. The IRB approval process delays and the OHRO review delays caused a delay in the team's ability to begin Major Task 7 (to conduct a feasibility study to assess the usability of the HCC Simulator) and Major Task 8 (to incorporate results from focus group and individual patient feedback into the HCC Simulator). Recruiting for usability focus groups and interviews had to be delayed until after OHRO approval date (July 7, 2023).

◦ **Changes that had a significant impact on expenditures**

Chhatwal Team – Nothing to report.

Kanwal Team – There were no significant changes to the scope of work. However, due to the delays described above, the Kanwal team received approval to carryforward unspent funds at the end of Year 1 and Year 2.

◦ **Significant changes in use or care of human subjects, vertebrate animals, biohazards, and/or select agents**

Nothing to Report.

6.PRODUCTS:

◦ **Publications, conference papers, and presentations**

■ **Journal publications.**

Chhatwal J, Hajjar A, Mueller PP, Nemutlu G, Kulkarni N, Peters MLB, Kanwal F. Hepatocellular Carcinoma Incidence Threshold for Surveillance in Virologically Cured Hepatitis C Individuals [published online ahead of print, 2023 Jun 9]. Clin Gastroenterol Hepatol. 2023;S1542-3565(23)00446-9. doi:10.1016/j.cgh.2023.05.024 Acknowledgement of Federal support reported.

Mueller PP, Chen Q, Ayer T, Nemutlu GS, Hajjar A, Bethea ED, Peters MLB, Lee BP, Janjua NZ, Kanwal F, Chhatwal J. Duration and cost-effectiveness of hepatocellular carcinoma surveillance in hepatitis C patients after viral eradication. J Hepatol. 2022 Jul;77(1):55-62. doi: 10.1016/j.jhep.2022.01.027. Epub 2022 Feb 12. PubMed PMID: 35157959; PubMed Central PMCID: PMC9618359. Acknowledgement of Federal support reported.

Kramer JR, Cao Y, Li L, Smith D, Chhatwal J, El-Serag HB, Kanwal F. Longitudinal Associations of Risk Factors and Hepatocellular Carcinoma in Patients With Cured Hepatitis C Virus Infection. Am J Gastroenterol. 2022 Nov 1;117(11):1834-1844. doi: 10.14309/ajg.0000000000001968. Epub 2022 Aug 23. PubMed PMID: 36327437; PubMed Central PMCID: PMC9641546. Acknowledgement of Federal support reported.

Chen Q, Ayer T, Adey MG, Wang X, Kanwal F, Chhatwal J. Assessment of Incidence of and Surveillance Burden for Hepatocellular Carcinoma Among Patients With Hepatitis C in the Era of Direct-Acting Antiviral Agents. JAMA Netw Open. 2020 Nov 2;3(11):e2021173. doi: 10.1001/jamanetworkopen.2020.21173. PubMed PMID: 33206188; PubMed Central PMCID: PMC7675109. Acknowledgement of Federal support reported.

■ **Books or other non-periodical, one-time publications.**

Nothing to report.

■ **Other publications, conference papers, and presentations.**

Kramer JR, Cao Y, Li L, Smith D, Chhatwal J, El-Serag HB, Kanwal F. Longitudinal associations between risk factors and subsequent risk of hepatocellular cancer in patients with hepatitis C virus infection and virological cure. 2021 AASLD The Liver Meeting, November 12-15th. Anaheim, CA.

Chhatwal J, Hajjar A, Mueller PP, Nemutlu G, Peters MLB, Kanwal F. Hepatocellular Carcinoma Incidence Threshold for Routine Surveillance is Much Lower in Hepatitis C Cirrhosis Individuals Who Achieve Virological Cure. 2021 AASLD The Liver Meeting, November 12-15th. Anaheim, CA. Also accepted for inclusion in the Best of The Liver Meeting's summary slide deck in the Health Services and Public Health Research category.

Nemutlu G, Mueller PP, Qiushi Chen, Turgay Ayer, Naveed Janjua, Kanwal F, Chhatwal J. Liver Cancer Surveillance in the Era of New Hepatitis C Antiviral Treatments: A Value of Information Analysis. 2021 INFORMS Annual Meeting, October 27-27th 2021. Anaheim, CA.

◦**Website(s) or other Internet site(s)**

<https://livercancersimulator.org/>

The Liver Cancer Simulator is an interactive tool that allows patients and physicians to simulate the potential health outcomes for a specific patient with their unique demographic profile. This tool can be used to evaluate the risk of developing liver cancer and to identify the benefits of regular screening for a particular individual.

◦**Technologies or techniques**

Nothing to report.

◦**Inventions, patent applications, and/or licenses**

Nothing to report.

◦**Other Products**

Nothing to report.

7. PARTICIPANTS & OTHER COLLABORATING ORGANIZATIONS

◦**What individuals have worked on the project?**

Name: Fasiha Kanwal, MD, MSHS

Project Role: Principal Investigator

Researcher Identifier (e.g. ORCID ID): <https://orcid.org/0000-0001-6715-3966>

Nearest person month worked: 2.4

Contribution to Project: As the Principal Investigator, Dr. Kanwal oversees all aspects of the project and has primary responsibility for supervising Aim 1 activities: 1) Data acquisition, data cleaning, variable creation, cohort identification, 2) EMR chart abstractions to confirm HCC, 3) data analysis of HCC predictors, 4) develop and optimize HCC risk prediction model.

Funding Support:

Name: Jennifer R. Kramer, PhD

Project Role: co-Investigator

Researcher Identifier (e.g. ORCID ID): <https://orcid.org/0000-0003-2953-4949>

Nearest person month worked: 2

Contribution to Project: Dr. Kramer is leading the Data Analysis Team based at the VA (Aim 1 to examine determinants of HCC in virologically cured patients and develop a risk prediction model for HCC in these patients). She works closely with the PI, the biostatistician, and the data analyst on data acquisition, and operationalizing study variables. She supervises chart abstractors, oversees data analysis, and interprets results.

Funding Support:

Name: Roxanne Desiderio, BS

Project Role: Research Assistant

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 6

Contribution to Project: Ms. Desiderio conducted electronic medical record (EMR) chart reviews and assisted with administrative tasks, such as meeting scheduling, reporting, and maintaining regulatory documentation.

Funding Support:

Name: Yumei Cao, MS

Project Role: Data Analyst

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 6

Contribution to Project: Ms. Cao is the data analyst for Aim 1 of the project, responsible for the build and upkeep of the study databases, quality control measures, and conducting statistical analyses with the guidance of Drs. Kramer, Richardson, and Kanwal. She performed the programming required to identify the cohort, define the study variables, and construct analytic datasets. Ms. Cao provided weekly summary reports on the state of data analysis at the weekly project meeting headed by Dr. Kanwal (PI).

Funding Support:

Name: Donna Smith, MEd

Project Role: Project Coordinator

Researcher Identifier (e.g. ORCID ID): <https://orcid.org/0000-0003-1906-666X>

Nearest person month worked: 3

Contribution to Project: Ms. Smith is responsible for all administrative and regulatory tasks of the project, including IRB protocol approvals, renewals, and amendments; organizing project team meetings; maintaining study binders; and managing the budget. She coordinates data acquisition requests and data use agreement renewal updates. She will work closely with the core research investigators to coordinate writing and editing of progress reports and will assist with the development and publication of dissemination products.

Funding Support:

Name: Chris Williams, BS

Project Role: IT Manager

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1

Contribution to Project: Mr. Williams is responsible for performing computer server maintenance and upgrades. He provides support and training for study personnel on project-related software programs. He ensures that data privacy standards are maintained and processes Data Use Agreements and PKI for study personnel. These functions are critical part of our data-management security plan to ensure compliance and the safety of all encrypted veteran data.

Funding Support:

Name: Jagpreet Chhatwal, PhD

Project Role: Principal investigator

Researcher Identifier (e.g. ORCID ID): <https://orcid.org/0000-0001-8741-4430>

Nearest person month worked: 2

Contribution to Project: As the Principal Investigator, Dr. Chhatwal has primary responsibility for supervising Aim 2 activities: development of the mathematical model to simulate the natural history of HCC in hepatitis C cured patients, literature review, validation and analysis of the proposed model.

Funding Support:

Name: Ali Hjaar, PhD

Project Role: Postdoc

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 6

Contribution to Project: Dr. Hjaar is a postdoctoral fellow who developed the natural history model of hepatitis C and HCC using a programming language. He also assisted with estimation model inputs and analysis of outcomes.

Funding Support:

Name: Neeti Kulkarni,

Project Role: Analyst

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 6

Contribution to Project: Ms. Kulkarni is a research analyst responsible for conducting literature review of model parameters to evaluate the cost effectiveness of HCC screening in hepatitis C cured persons.

Funding Support:

Name: Alec Aaron,

Project Role: Programmer Analyst

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 3

Contribution to Project: Mr. Aaron is a programmer analyst responsible for developing an online tool to inform HCC screening for patients and providers. He developed the interface of the Liver Cancer Simulator and downloadable reports.

Funding Support:

Name: Mary Ann Ladd, BS

Project Role: Data Manager

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 1

Contribution to Project: Ms. Ladd is the Systems Manager of the MGH Institute for Technology Assessment. She was responsible for overseeing the integration and day-to-day management of computer systems at the Institute for Technology Assessment, and for facilitating electronic communications among collaborators. She worked with the other team members to facilitate data extraction and storage, and ensure that all study data are secure, adequately stored and backed up.

Funding Support:

Name: Asmae Toumi, BS

Project Role: Data Analyst

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 3

Contribution to Project: Ms. Toumi is a data analyst who worked with Dr. Chhatwal to conduct literature review and assist development of the mathematical model of the natural history of HCC.

Funding Support:

Name: Peter Mueller, PhD

Project Role: Research Scientist

Researcher Identifier (e.g. ORCID ID):

Nearest person month worked: 3

Contribution to Project: Dr. Mueller is a research scientist who assisted with the development of the natural history model of hepatitis C and HCC using a programming language, setup of the computer server for computational runs for the model. He also assisted with the analysis of outcomes.

Funding Support:

◦**Has there been a change in the active other support of the PD/PI(s) or senior/key personnel since the last reporting period?**

Nothing to report.

◦**What other organizations were involved as partners?**

MD Anderson Cancer Center (Houston, TX) provided the following types of support:

- In-kind support (partner makes software, computers, equipment, etc., available to project staff)
- Facilities (project staff use the partner's facilities for project activities)

University of Texas Health Science Center (Houston, TX) provided the following types of support:

- In-kind support (partner makes software, computers, equipment, etc., available to project staff)
- Facilities (project staff use the partner's facilities for project activities)

8.SPECIAL REPORTING REQUIREMENTS

◦COLLABORATIVE AWARDS:

The Initiating PI and the Collaborating/Partnering PI are submitting separate reports.

◦QUAD CHARTS:

Nothing to report.

9.APPENDICES:

Appendix I – Journal Publications

Appendix II – Abstracts Presented

ADDITIONAL NOTES:

Nothing to report.

MARKING OF PROPRIETARY INFORMATION:

Nothing to report.

Appendix I

Journal Publications

Chhatwal J, Hajjar A, Mueller PP, Nemutlu G, Kulkarni N, Peters MLB, Kanwal F. Hepatocellular Carcinoma Incidence Threshold for Surveillance in Virologically Cured Hepatitis C Individuals [published online ahead of print, 2023 Jun 9]. *Clin Gastroenterol Hepatol*. 2023;S1542-3565(23)00446-9. doi:10.1016/j.cgh.2023.05.024

Acknowledgement of Federal support reported.

Mueller PP, Chen Q, Ayer T, Nemutlu GS, Hajjar A, Bethea ED, Peters MLB, Lee BP, Janjua NZ, Kanwal F, Chhatwal J. Duration and cost-effectiveness of hepatocellular carcinoma surveillance in hepatitis C patients after viral eradication. *J Hepatol*. 2022 Jul;77(1):55-62. doi: 10.1016/j.jhep.2022.01.027. Epub 2022 Feb 12. PubMed PMID: 35157959; PubMed Central PMCID: PMC9618359. Acknowledgement of Federal support reported.

Kramer JR, Cao Y, Li L, Smith D, Chhatwal J, El-Serag HB, Kanwal F. Longitudinal Associations of Risk Factors and Hepatocellular Carcinoma in Patients With Cured Hepatitis C Virus Infection. *Am J Gastroenterol*. 2022 Nov 1;117(11):1834-1844. doi: 10.14309/ajg.0000000000001968. Epub 2022 Aug 23. PubMed PMID: 36327437; PubMed Central PMCID: PMC9641546. Acknowledgement of Federal support reported.

Chen Q, Ayer T, Adey MG, Wang X, Kanwal F, Chhatwal J. Assessment of Incidence of and Surveillance Burden for Hepatocellular Carcinoma Among Patients With Hepatitis C in the Era of Direct-Acting Antiviral Agents. *JAMA Netw Open*. 2020 Nov 2;3(11):e2021173. doi: 10.1001/jamanetworkopen.2020.21173. PubMed PMID: 33206188; PubMed Central PMCID: PMC7675109. Acknowledgement of Federal support reported.

Hepatocellular Carcinoma Incidence Threshold for Surveillance in Virologically Cured Hepatitis C Individuals

Jagpreet Chhatwal,^{1,2,3} Ali Hajjar,^{1,4} Peter P. Mueller,¹ Gizem Nemutlu,^{1,5} Neeti Kulkarni,¹ Mary Linton B. Peters,^{1,6} and Fasiha Kanwal^{7,8}

¹Institute for Technology Assessment, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts;

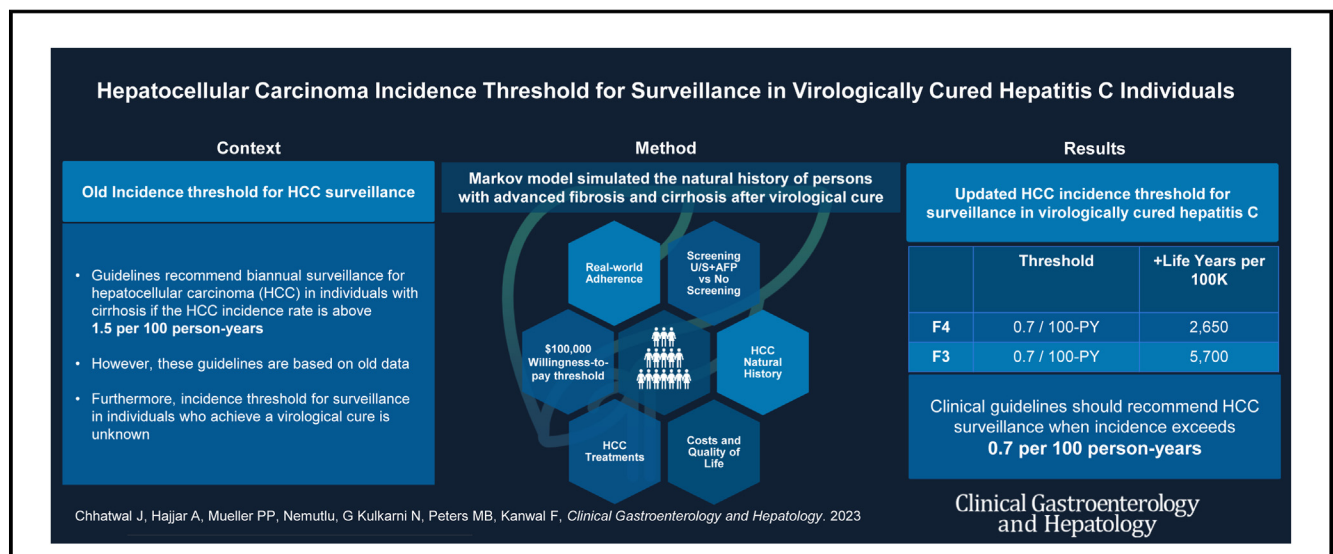
²Dana Farber/Harvard Cancer Center, Boston, Massachusetts; ³Liver Center and Gastrointestinal Division, Massachusetts

General Hospital, Boston, Massachusetts; ⁴Prince Mohammed Bin Salman College of Business & Entrepreneurship, King

Abdullah Economic City, Saudi Arabia; ⁵Brandeis International Business School, Brandeis University, Boston, Massachusetts;

⁶Division of Medical Oncology, Beth Israel Deaconess Medical Center, Boston, Massachusetts; ⁷Department of Medicine,

Baylor College of Medicine, Houston, Texas; and ⁸Houston Veterans Affairs Health Services Research and Development Center of Excellence, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas



BACKGROUND & AIMS:

Guidelines recommend biannual surveillance for hepatocellular carcinoma (HCC) in hepatitis C individuals with cirrhosis if the HCC incidence rate is above 1.5 per 100 person-years (PY). However, the incidence threshold for surveillance in individuals who achieve a virologic cure is unknown. We estimated the HCC incidence rate above which routine HCC surveillance is cost-effective in this growing population of virologically cured hepatitis C individuals with cirrhosis or advanced fibrosis.

METHODS:

We developed a Markov-based microsimulation model of the natural history of HCC in individuals with hepatitis C who achieved virologic cure with oral direct-acting antivirals. We used published data on the natural history of hepatitis C, competing risk post virologic cure, HCC tumor progression, real-world HCC surveillance adherence, contemporary HCC treatment options and associated costs, and utilities of different health states. We estimated the HCC incidence above which biannual HCC surveillance using ultrasound and alpha-fetoprotein would be cost-effective.

RESULTS:

In virologically cured hepatitis C individuals with cirrhosis or advanced fibrosis, HCC surveillance is cost-effective if HCC incidence exceeds 0.7 per 100 PY using \$100,000 per quality-

Abbreviations used in this paper: AFP, alpha-fetoprotein; CT, computed tomography; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; PY, person-years; QALY, quality-adjusted life years; SVR, sustained virologic response.

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1542-3565/\$36.00

<https://doi.org/10.1016/j.cgh.2023.05.024>

adjusted life year willingness-to-pay. At this HCC incidence, routine HCC surveillance would result in 2650 and 5700 additional life years per 100,000 cirrhosis and advanced fibrosis persons, respectively, compared with no surveillance. At \$150,000 willingness-to-pay, surveillance is cost-effective if HCC incidence exceeds 0.4 per 100 PY. Sensitivity analysis showed that the threshold mostly remained below 1.5 per 100 PY.

CONCLUSIONS:

The contemporary HCC incidence threshold is much lower than the previous 1.5% incidence value used to guide HCC surveillance decisions. Updating clinical guidelines could improve the early diagnosis of HCC.

Keywords: Liver Cancer; Screening; Cost-effectiveness Analysis; Prevention.

Direct-acting antivirals have changed the landscape of hepatitis C virus infection and associated sequelae, including hepatocellular carcinoma (HCC). Although successful treatment resulting in a sustained virologic response (SVR) represents a “cure” from the standpoint of persistent infection, the subsequent risk of HCC persists after treatment with oral direct-acting antivirals and remains an important contributor to liver-related morbidity and mortality in today’s era.^{1–3}

With the wide use of direct-acting antivirals, the number of virologically cured hepatitis C persons is expected to increase to 1.6 million in 2025 in the United States.⁴ As such, many hepatitis C patients in clinical practice will be those who have been virologically cured with direct-acting antivirals, instead of viremic, and yet have advanced liver disease, either advanced fibrosis or cirrhosis.^{4,5} For this growing population, routine HCC surveillance can improve early HCC detection and improve survival outcomes.⁶

Clinical practice guidelines recommend ultrasound-based (with or without alpha-fetoprotein [AFP]) surveillance for HCC in patients with cirrhosis if HCC incidence is above 1.5 per 100 person-years (PY).^{7,8} This threshold was established from studies that evaluated the cost-effectiveness of HCC surveillance in individuals with an active viral infection and cannot be extrapolated to persons with cured hepatitis C. Because patients with cured hepatitis C have a lower risk of developing HCC, they can fall below this threshold and therefore might not be candidates for surveillance per this guideline. Virologically cured hepatitis C patients have a higher life expectancy than patients with active hepatitis C, and this could affect effectiveness (and cost-effectiveness) of HCC surveillance.⁹ Furthermore, previous studies could not account for recent advancements in HCC treatment, which would improve the value of HCC surveillance.

The role of HCC surveillance is also uncertain in virologically cured hepatitis C persons with advanced fibrosis, resulting in disparate recommendations from professional societies. The American Association for the Study of Liver Diseases does not recommend HCC surveillance in patients with advanced fibrosis,⁷ whereas the guidelines by the European Association for the Study of the Liver and Asia Pacific Association for the Study of the Liver recommend biannual surveillance in patients with advanced fibrosis.^{8,10} There is a need to examine

the value of routine HCC surveillance in virologically cured hepatitis C persons with advanced fibrosis.¹¹

Our objective was to provide contemporary data on HCC incidence thresholds above which routine HCC surveillance is cost-effective in the growing population of individuals with virologically cured hepatitis C.

Methods

Study Design

We developed a Markov-based state-transition simulation model, *simHCC* (simulation of HCC) that simulated the natural history of hepatitis C and HCC in patients with advanced fibrosis (METAVIR score F3) or compensated cirrhosis (METAVIR score F4) who achieved SVR after treatment with direct-acting antivirals (Figure 1). We tested biannual HCC surveillance using ultrasound and AFP testing until age 75. The model simulated 50 million patients with mean age of 50 under surveillance and no surveillance to determine the life expectancy benefit of surveillance. We determined the HCC incidence above which surveillance would be cost-effective at both willingness-to-pay thresholds. The model was developed using C++ programming language with a 1-month cycle length.

We estimated model inputs from published studies to simulate the natural history of hepatitis C,¹² the risk of HCC in patients who achieved SVR with direct-acting antivirals,^{12–17} HCC tumor progression,¹⁸ the performance characteristics of diagnostic and screening tests,^{19,20} HCC surveillance adherence,¹⁸ and HCC treatments.^{18,21–34} We presented the results of each of the simulated surveillance strategies in terms of life years, quality-adjusted life years (QALYs), total costs, and incremental cost-effectiveness ratio (ICER). Following the recommendations of the Panel on Cost-Effectiveness in Health and Medicine, we discounted both future costs and future QALYs at 3% in the base case analysis.³⁵ We performed our analysis from the healthcare payer perspective.

Natural History of HCC

For each patient, we simulated the clinical course of cured hepatitis C, including development and

progression of HCC (Figure 1). We assumed that advanced fibrosis patients do not progress to compensated cirrhosis after cure.³⁶ On the other hand, patients with compensated cirrhosis may progress to decompensated cirrhosis (Supplementary Table 1). On the basis of the underlying liver disease stage, patients could develop HCC defined by the given incidence rate. In each month, patients could develop HCC at a very early stage that could later progress to early and intermediate/advanced stages. We defined HCC stage on the basis of Barcelona Clinic Liver Cancer staging system and tumor size; very early HCC included patients with a tumor less than 2 cm in diameter, early HCC for those with a single tumor less than 5 cm or up to 3 tumors all less than 3 cm, and intermediate/advanced HCC for the remaining stages.³⁷

We considered 2 causes of mortality, background and liver-related. We estimated the age- and sex-based background mortality from the United States life tables.³⁸ We also considered that patients with decompensated cirrhosis or with intermediate/advanced HCC were at risk of liver-related mortality.^{39–41}

Simulated HCC Surveillance Strategies

We considered 2 surveillance strategies: no surveillance and biannual surveillance for HCC with ultrasound and AFP every 6 months until age 75. We accounted for imperfect adherence to HCC surveillance in real world by

What You Need to Know

Background

Guidelines recommend biannual surveillance for hepatocellular carcinoma (HCC) if the HCC incidence rate is above 1.5 per 100 person-years. However, these guidelines are based on old data, and incidence threshold for surveillance in individuals who achieve a virologic cure is unknown.

Findings

The contemporary HCC incidence threshold is 0.7 per 100 person-years, which is lower than the previous incidence value of 1.5 used to guide HCC surveillance decisions.

Implications for care

Updating the clinical guidelines to recommend HCC surveillance when the risk of HCC increases 0.7 per 100 person-years could improve the early diagnosis of HCC.

using data from a recent retrospective study by Choi et al⁴² and the approach described in Mueller et al,¹⁸ which defines 3 screening groups. There were 22.8% of people who met the definition of consistent screening (having 1 or more abdominal ultrasounds per calendar year), 52.0% of people who met the definition of inconsistent screening (having 1 or more abdominal

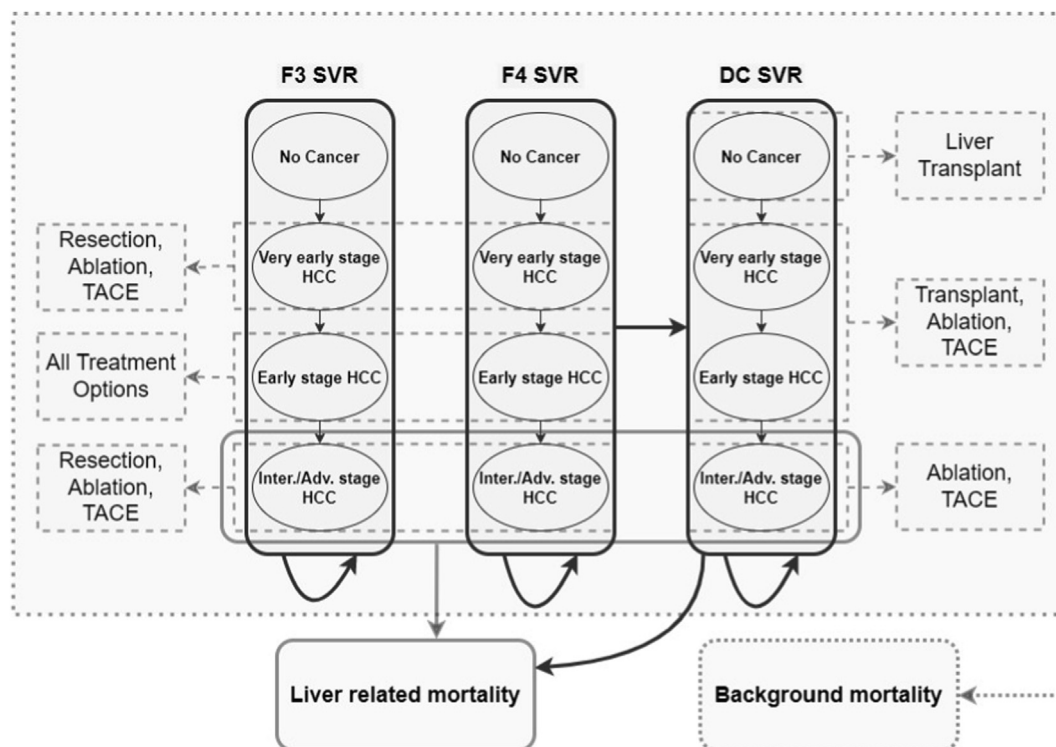


Figure 1. State-transition Markov model represents the natural history of hepatocellular carcinoma (HCC) in hepatitis C patients who achieved a sustained virologic response (SVR) with direct-acting antivirals. This diagram depicts the conceptual model that was used in this study. TACE, transarterial chemoembolization.

ultrasounds during the study period but less than annually), and the remaining 25.2% of people did not attend a single screening appointment in the study's 3-year time horizon.

If the surveillance test was negative (ie, a patient without HCC or a missed HCC), the patient followed their natural history until the next ultrasound (Figure 2). However, if the surveillance test was positive (ie, a patient with HCC or a false-positive result for a patient without HCC), the patient received a noninvasive imaging diagnostic test of magnetic resonance imaging (MRI) or computed tomography (CT) scan. The noninvasive diagnostic test could result in a negative, positive, or indeterminate result. A negative result could be a patient without HCC or a missed HCC; a positive result diagnosed HCC; and an indeterminate result was suspicious but non-diagnostic²⁹ (Appendix). A patient with negative imaging followed their natural history until the next ultrasound test. Patients diagnosed with HCC were no longer following in the simulation model. Patients with indeterminate imaging would undergo further imaging with a different modality (eg, CT if the first noninvasive diagnostic test was MRI), followed by a liver biopsy if the second test was still indeterminate. We assumed that only 1 biopsy was required for confirmation of diagnosis. We estimated the sensitivity and specificity of the screening and diagnostic tests on the basis of recently published studies^{19,20} (Supplementary Table 2).

HCC could also be detected incidentally.⁴³ If an HCC was detected incidentally, we assumed that an ultrasound scan with AFP and a noninvasive imaging diagnostic test were performed to confirm the HCC.⁴³

We assumed that patients with decompensated cirrhosis get biannual HCC screening if they are awaiting liver transplantation. Patients with HCC awaiting liver transplantation were screened every 3 months to confirm the status of tumor.

HCC Treatment

We considered the effect of treatment on overall survival, while accounting for HCC stage and liver fibrosis state (advanced fibrosis, compensated cirrhosis, decompensated cirrhosis).^{21–29} We considered 4 HCC treatment options: ablation, resection, liver transplantation, and a group of palliative treatments including transarterial chemoembolization, selective internal radiotherapy, external beam radiotherapy, and systemic chemotherapy). Selection of treatment depended on HCC stage as well as the liver disease severity (Supplementary Table 3).

We assumed that liver transplant was available only for patients younger than 75 with either decompensated cirrhosis and/or early stage HCC (ie, within Milan criteria), and decompensated patients were not eligible for resection. Treatment distributions by both HCC stage and fibrosis stage were determined from published

observational studies.^{18,40,44} Unlike resection, ablation, and palliative treatment, which were delivered soon after the diagnosis, patients selected for liver transplantation were added to the transplant waitlist for organ availability. Using the Organ Procurement Transplant Network data, we modeled the likelihood of transplantation on the basis of median wait times, which varied depending on the stage of the HCC and fibrosis state. Patients were removed from the waitlist if their HCC progressed to the intermediate/advanced stage; these patients were eligible to receive palliative treatment instead.

Utilities and Cost

We used the published studies to estimate quality-of-life utilities associated with age, liver health states, biopsy procedure and complications, and HCC treatments (Supplementary Table 4).^{32–34,45–48} We considered the costs associated with ultrasound and AFP, diagnostic tests (MRI and CT), biopsy, biopsy complications, management of underlying liver disease (advanced fibrosis, cirrhosis, and decompensated cirrhosis), and the cost of HCC treatment (Supplementary Table 5).^{30,31,40,49,50} We estimated these costs from recent publications that included data from the Centers for Medicare and Medicaid Services. We converted all costs to 2020 United States dollars using the consumer price index.

Model Outcomes

We simulated surveillance and no surveillance strategies using different HCC incidence rates (range, 0.3–2.5 per 100 PY) and estimated the total QALY, costs, and ICER of surveillance vs no surveillance for each incidence rate. The ICER estimates the cost needed to gain 1 additional QALY. Using willingness-to-pay thresholds between \$50,000 and \$150,000 per QALY, we determined the HCC incidence above which routine HCC surveillance would be deemed cost-effective. Some prior studies used the willingness-to-pay threshold of \$50,000 per QALY to determine when HCC surveillance is cost-effective; however, the updated recommendation is to use \$100,000 or \$150,000 per QALY willingness-to-pay threshold.^{51,52} Therefore, our analysis uses \$100,000 or \$150,000 per QALY willingness-to-pay threshold to determine when HCC surveillance is cost-effective.

Sensitivity Analysis

To account for uncertainty in model parameters, we performed one-way and probabilistic sensitivity analyses. We simulated 50 million patients for the one-way sensitivity analyses to assess the impact of the upper and lower bounds of the most 10 sensitive model parameters reported by Mueller et al¹⁸ on the robustness of

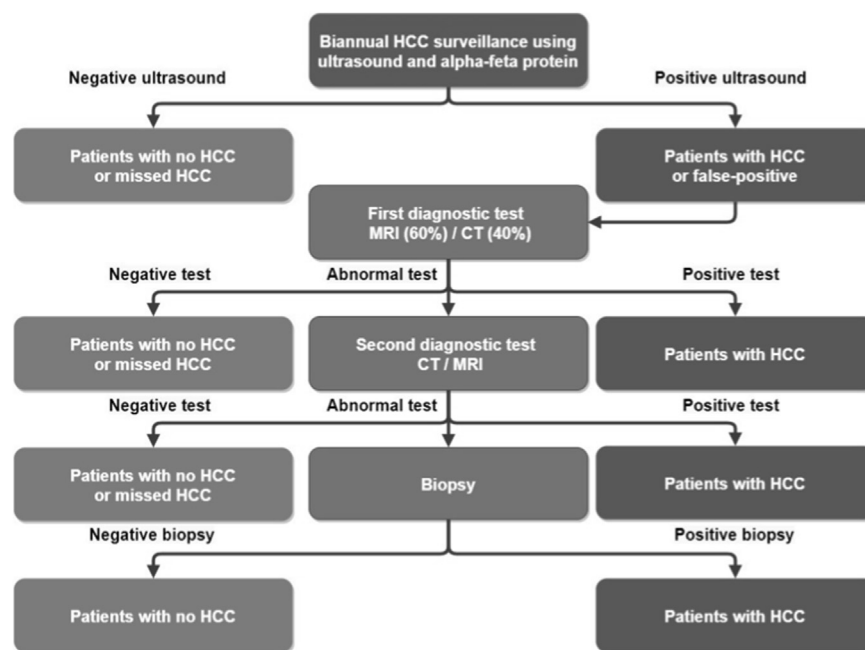


Figure 2. Simulated pathway for diagnosis of hepatocellular carcinoma in patients undergoing routine surveillance. CT, computed tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging.

the HCC incidence threshold above which HCC surveillance is cost-effective.

We conducted probabilistic sensitivity analyses simulating 1000 samples (outer loop) and 50 million patients (inner loop) to estimate the HCC incidence thresholds above which HCC surveillance is cost-effective. We varied the model parameters on the basis of their distributions. The results of the probabilistic sensitivity analyses were presented as box plots, displaying the minimum, first quartile, median, third quartile, and HCC incidence thresholds at \$100,000 and \$150,000 per QALY willingness-to-pay.

Results

Hepatitis C Cured Individuals With Cirrhosis

Figure 3A shows the HCC incidence above which routine HCC surveillance was cost-effective in a 50-year-old virologically cured hepatitis C individual with cirrhosis at different willingness-to-pay thresholds from \$100,000–\$150,000. The ICER of biannual surveillance vs. no surveillance was at or below \$100,000 per QALY when HCC incidence was 0.7 per 100 PY. Therefore, routine biannual HCC surveillance until age 75 was determined to be cost-effective for cirrhotic populations with HCC incidence greater than 0.7 per 100 PY. At this HCC incidence, routine HCC surveillance would result in an additional 5300 life years and 2700 QALY per 100,000 persons undergoing surveillance.

Using the \$50,000 per QALY willingness-to-pay threshold as in the current guidelines for HCC, surveillance was cost-effective in cured individuals with cirrhosis above an HCC incidence of 1.8 per 100 PY. However, using a relaxed \$150,000 per QALY

willingness-to-pay threshold, HCC surveillance was cost-effective above 0.4 per 100-PY HCC incidence.

Hepatitis C Cured Individuals With Advanced Fibrosis

Figure 3B shows the HCC incidence above which HCC surveillance was cost-effective in a 50-year-old virologically cured hepatitis C individual with advanced fibrosis at different willingness-to-pay thresholds. The ICER of biannual surveillance vs no surveillance was at or below \$100,000 per QALY when HCC incidence was 0.7 per 100 PY. Therefore, routine biannual HCC surveillance was determined to be cost-effective for advanced fibrosis populations with HCC incidence greater than 0.7 per 100 PY. At this HCC incidence, routine HCC surveillance would result in an additional 5700 life years and 2900 QALY per 100,000 persons undergoing surveillance.

Using the \$50,000 per QALY willingness-to-pay threshold as in the current guidelines for HCC, surveillance was cost-effective in cured individuals with advanced fibrosis above an HCC incidence of 2.5 per 100 PY. However, using a relaxed \$150,000-per-QALY willingness-to-pay threshold, HCC surveillance was cost-effective above 0.4 per 100-PY HCC incidence.

Sensitivity Analysis

We conducted one-way sensitivity analysis by evaluating the effect of uncertainty in the model parameters on HCC incidence threshold. Figure 4 shows the top 10 most sensitive model input parameters. HCC incidence threshold for routine surveillance in cirrhosis patients was most sensitive to progression of HCC tumor from early to intermediate/advanced stage, followed by treatment

survival after ablation. Of note, HCC incidence threshold exceeded 1.5 100-PY, currently recommended threshold, for only these 2 model parameters. Similarly, in persons with advanced fibrosis, HCC incidence threshold for routine surveillance was most sensitive to progression of HCC tumor from early to intermediate/advanced stage, followed by treatment survival after palliative care.

We conducted probabilistic sensitivity analysis by considering uncertainty in all model parameters simultaneously. Figure 5 shows the box plot of HCC incidence threshold above which routine surveillance was cost-effective using 1000 parameter samples. For individuals with cirrhosis and using the \$100,000 per QALY willingness-to-pay, the 25th and 75th percentiles

for HCC incidence threshold were 0.3 and 1.0 per 100 PY. Using \$150,000 per QALY willingness-to-pay, the 25th and 75th percentiles were 0.3 and 0.8 per 100 PY. For individuals with advanced fibrosis, there was more uncertainty in the HCC incidence threshold. At \$100,000 per QALY willingness-to-pay, the 25th and 75th percentiles for HCC incidence threshold were 0.4 and 1.7 per 100 PY. Using \$150,000 per QALY willingness-to-pay, the 25th and 75th percentiles were 0.3 and 1.6 per 100 PY.

Discussion

As the number of virologically cured hepatitis C individuals increase, there is an urgent unmet need to

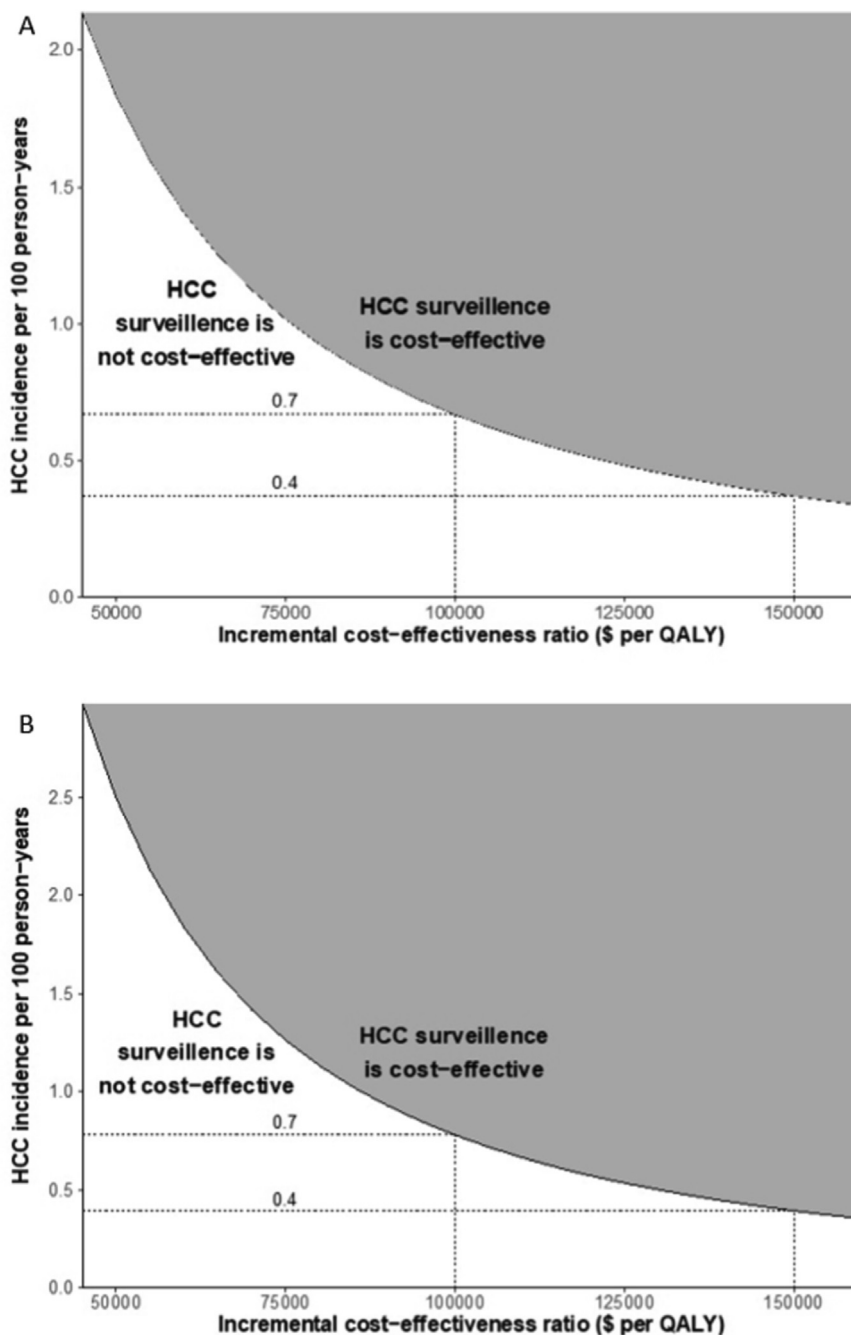


Figure 3. (A) Cost-effectiveness of HCC surveillance for virologically cured hepatitis C patients with compensated cirrhosis at different HCC incidence rates. (B) Cost-effectiveness of HCC surveillance for virologically cured hepatitis C patients with advanced fibrosis at different HCC incidence rates. HCC, hepatocellular carcinoma.

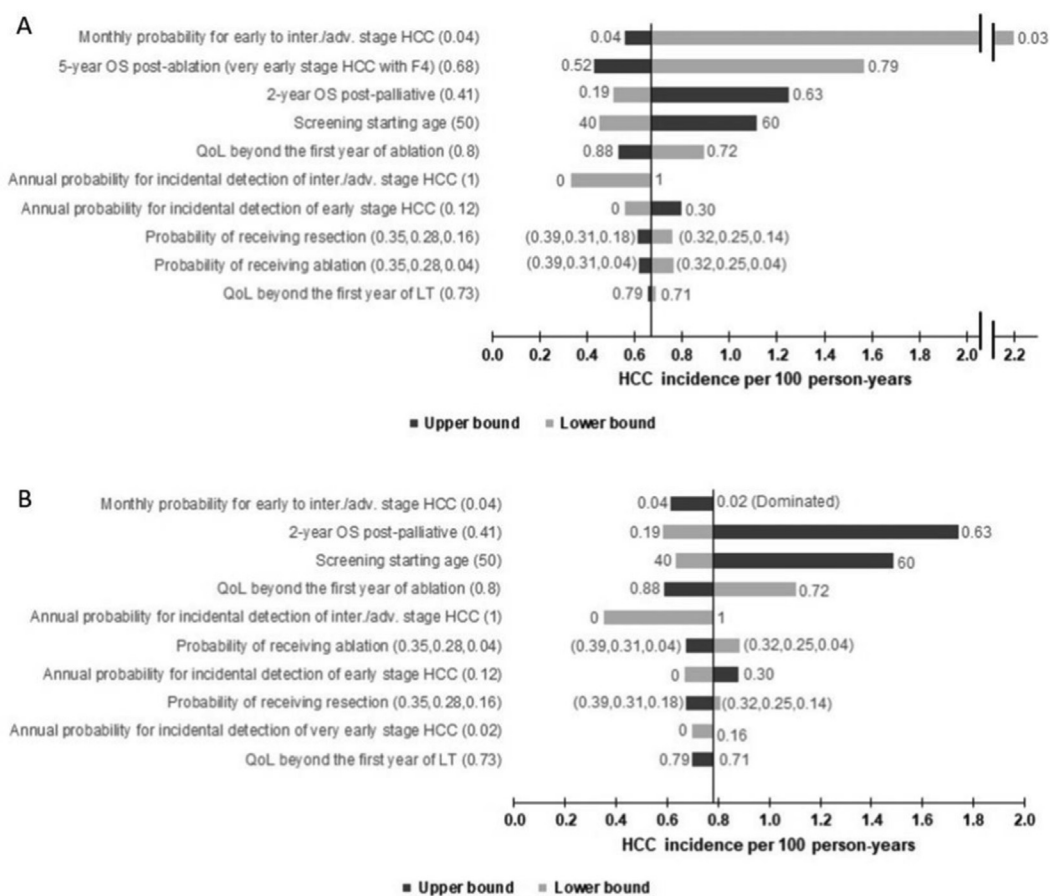


Figure 4. (A) One-way sensitivity analyses that assess the impact of the 10 most sensitive model parameters on the HCC incidence threshold for patients with compensated cirrhosis at a willingness-to-pay ratio of \$100,000/QALY. *Values in parentheses* next to the labels represent the base-case value for each parameter. Note. The 3 values in parentheses for the probability of receiving resection or ablation represent the probability that the assigned treatment will be received by a patient with very early, early, or intermediate/advanced stage HCC, respectively. HCC, hepatocellular carcinoma; LT, liver transplantation; OS, overall survival; QoL, quality of life. (B) One-way sensitivity analyses that assess the impact of the 10 most sensitive model parameters on the HCC incidence threshold for patients with advanced fibrosis at a willingness-to-pay ratio of \$100,000/QALY. *Values in parentheses* next to the labels represent the base-case value for each parameter. Note. The 3 values in parentheses for the probability of receiving resection or ablation represent the probability that the assigned treatment will be received by a patient with very early, early, or intermediate/advanced stage HCC, respectively. HCC, hepatocellular carcinoma; LT, liver transplantation; OS, overall survival; QoL, quality of life.

determine when and which individuals would benefit from routine HCC surveillance. Clinical guidelines recommend routine HCC surveillance with ultrasound (with or without AFP) in cirrhosis patients if HCC incidence exceeds 1.5 per 100 PY. However, this recommendation is based on obsolete data.

Using a clinically validated simulation model, we found that HCC incidence threshold for routine surveillance was substantially lower than 1.5 per 100 PY for almost all virologically cured individuals with cirrhosis or advanced fibrosis. In addition, using updated cost-effectiveness guidelines, we found that HCC surveillance was cost-effective above an HCC incidence rate of 0.7 per 100 PY for patients with either cirrhosis or advanced fibrosis. If a higher willingness-to-pay threshold of \$150,000 per QALY is considered,^{51,52} the incidence threshold for routine HCC surveillance could be as low as 0.4 per 100 PY. Using this contemporary

threshold, a large proportion of patients could benefit from undergoing biannual HCC surveillance.

Our study provides new data that could inform when hepatitis C cured individuals should undergo routine HCC surveillance. The 1.5 per 100 PY incidence threshold is informed by studies that are not recent, used old willingness-to-pay value of \$50,000 per QALY, used retrospective data, and/or did not include different approaches to the management of HCC (eg, liver transplantation and treatment advances).⁵³ The lower HCC incidence threshold of 0.7 per 100 PY for HCC surveillance found in our analysis is primarily driven by the use of the updated willingness-to-pay of \$100,000 to evaluate the cost-effectiveness. A recent cost-effectiveness analysis study showed that HCC incidence threshold for surveillance in virologically cured cirrhosis patients could be 0.55 per 100 PY by using a higher willingness-to-pay for cost-effectiveness.⁵⁴ Although this study's

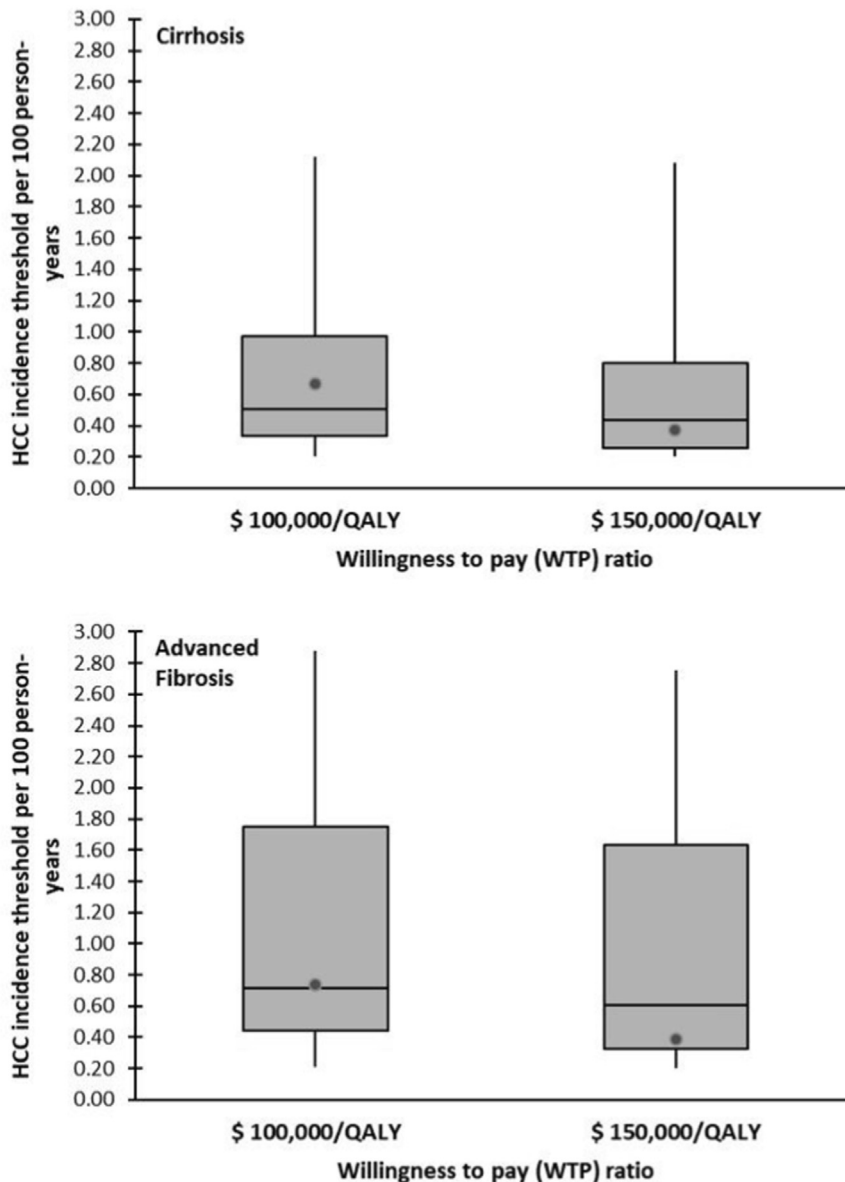


Figure 5. Probabilistic sensitivity analyses for the HCC incidence threshold at which biannual surveillance for HCC is cost-effective in patients with compensated cirrhosis and advanced fibrosis at different willingness-to-pay ratios. HCC, hepatocellular carcinoma.

conclusions align with our findings, our study extends these data by updating the estimates of development, diagnosis, and treatment of HCC and by using the higher willingness-to-pay threshold recommended in recent guidelines. In addition, our study extends this analysis to patients with advanced fibrosis in addition to those with cirrhosis, a group not explicitly described in previous efforts.

Our results suggest that more hepatitis C cured individuals could benefit from routine HCC surveillance. A recent systematic review estimated the HCC incidence in virologically cured advanced fibrosis patients to be 0.63 per 100 PY.⁵⁵ Although HCC surveillance is not cost-effective using 0.7 HCC incidence threshold (at \$100,000 willingness-to-pay), surveillance could be cost-effective using 0.4 incidence threshold (at \$150,000 willingness-to-pay). There is considerable uncertainty regarding HCC incidence in patients with advanced fibrosis, and some subgroups of patients may have HCC

incidence rate above 0.7 per 100 PY. Under current guidelines, these patients would not undergo HCC surveillance, resulting in missed cancers. Future research is needed to identify subgroups of non-cirrhosis patients who have HCC incidence rate higher than 0.7 per 100 PY.

Our study's findings should be interpreted in the context of its limitations. Our results are only applicable to patients undergoing ultrasound and serum AFP-based surveillance. Several new initiatives are evaluating the feasibility of HCC surveillance using other blood-based biomarkers. When such biomarkers become available in clinical practice, the threshold for HCC surveillance could be different than that determined by our study because of differences in test parameters and cost. Second, our study's outcomes depend on studies that assume histologic staging based on liver biopsy; the contemporary use of noninvasive tests as surrogates for fibrosis stage may not provide the same confidence of diagnosis, especially for detecting advanced fibrosis, perhaps leading to less

certainty in the estimate of incidence of HCC in a given population.⁵⁶ We believe future research is needed to estimate the risk of HCC in virologically cured individuals with advanced fibrosis to determine the value of routine HCC surveillance. Third, in our simulated cohort of virologically cured individuals, we did not account for HCC risk or disease progression associated with other underlying liver diseases (eg, alcohol-associated liver disease and nonalcoholic fatty liver disease). Therefore, our results apply to those with advanced fibrosis who continue to have normal liver tests after cure. Finally, the treatment and prognosis of HCC are rapidly evolving, such that the life expectancy of patients with diagnosed HCC may be longer than represented in historical data. This would be likely to impact surveillance and non-surveillance groups equivalently and therefore would have less impact on the value of surveillance.

In summary, our study suggests that for patients with virologically cured hepatitis C, routine surveillance is warranted above the HCC incidence threshold of 0.7 per 100 PY. Use of this revised threshold could increase HCC surveillance for hepatitis C patients, providing an opportunity for earlier diagnosis and treatment.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at <http://doi.org/10.1016/j.cgh.2023.05.024>.

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Correspondence

Address correspondence to: Jagpreet Chhatwal, PhD, MGH Institute for Technology Assessment, 101 Merrimac Street, Suite 1010, Boston, Massachusetts 02114. e-mail: jagchhatwal@mgh.harvard.edu.

CRedit Authorship Contributions

Jagpreet Chhatwal, PhD (Conceptualization: Lead; Funding acquisition: Equal; Methodology: Equal; Supervision: Lead; Writing – original draft: Lead)
 Ali Hajjar (Conceptualization: Equal; Formal analysis: Lead; Methodology: Lead; Writing – review & editing: Lead)
 Peter P. Mueller (Formal analysis: Supporting; Methodology: Supporting; Writing – review & editing: Supporting)
 Gizem Nemutlu (Formal analysis: Supporting; Methodology: Supporting; Writing – review & editing: Supporting)
 Neeti Kulkarni (Formal analysis: Supporting; Visualization: Supporting; Writing – review & editing: Supporting)
 Mary Linton B. Peters (Formal analysis: Supporting; Writing – review & editing: Supporting)
 Fasiha Kanwal (Conceptualization: Equal; Formal analysis: Equal; Funding acquisition: Equal; Supervision: Equal; Writing – review & editing: Lead)

Conflicts of interest

These authors disclose the following: Dr Chhatwal received consulting fee from Bayer and served as a partner to Value Analytics Labs outside the submitted work.

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Appendix

Calibration of a Noninvasive Diagnostic Test's Abnormal Result Probability

The sensitivity and specificity of the ultrasound, MRI, and CT tests performed as part of the diagnostic processes (Figure 2) are estimated from recently published studies.^{21,35} In this section, we present the calibration process used to estimate the probability that an MRI or CT test will result in abnormal imaging, in which a follow-up diagnostic test or biopsy is performed.

We assumed that patients without HCC would not receive treatment. Hence, the probability that a diagnostic test result is positive for patients without HCC is 0 (Supplementary Table 6). For patients with HCC, the probability that a diagnostic test result is positive, in which case the patient will receive treatment, equals to the sensitivity of the diagnostic test. A tumor can be missed with a probability equal to 1–sensitivity of the diagnostic test. We assumed that the sum of the probability of an abnormal test result (p_1) and the probability of a negative test result (p_2) equals to 1–sensitivity of the diagnostic test (ie, $p_1 + p_2 = 1 - \text{sensitivity}$) (Supplementary Table 6).

We used the study by Konerman et al²² for the calibration process. In doing so, we matched the patient's adherence in the model to that reported by Konerman et al. For each diagnostic test (ie, MRI and CT), we estimate the probability of an abnormal test result by running the model multiple times with different p_1 until the number of performed biopsies matches the number of biopsies reported by Konerman et al. Because the study by Konerman et al reported only the number of biopsies performed in patients with cirrhosis, we assumed that the probability of an abnormal test result for F3 patients is similar to that of F4 patients because of limited data.

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Supplementary Table 1. Transition Probabilities Used in simHCC Simulation Model

Model parameter	Base case	Range	Distribution	Parameter 1	Parameter 2	Reference
Transition probabilities						
F4 to DC ^a	0.0075	0.005–0.0107	beta	26.84	3510.17	1
DC to very early HCC	0.078	±10%	beta	358.57	4227.62	2
HCC (very early stage to early stage) ^b	0.06288	0.04083–0.06825	beta	78.79	1174.2	3–5
HCC (early stage to intermediate/advanced stage) ^b	0.03224	0.02081–0.03504	beta	79.45	2384.87	3–5
Intermediate/advanced stage HCC to death from liver disease ^a	0.75	±10%	beta	99.25	33.08	6, 7
DC to death from liver disease ^a	0.265	±10%	beta	293.74	814.70	8
Biopsy complication (no HCC) ^b	0.013	±10%	beta	384.64	29128.22	9
Biopsy complication (HCC) ^b	0.019	±10%	beta	382.23	19,684.64	9
HCC to transplantation (waiting time in days)						
DC (very early or early stage HCC)	52.5	±10%	gamma	400	0.13125	10
Early stage HCC	237.4	±10%	gamma	400	0.59350	10
Overall survival (used in state transitions to death from liver disease)						
Liver transplantation (1-year OS)	0.89	0.884–0.910	beta	2061.38	254.78	11
Liver transplantation (5-year OS)	0.75	0.738–0.790	beta	831.35	277.12	11
Palliative treatment: arterial/chemoembolization (2-year OS)	0.41	0.190–0.630	beta	7.79	11.21	12
Other HCC treatments (5-year OS)						
Very early stage HCC resection	0.663	0.635–0.691	beta	755.13	383.83	13, 14
Early stage HCC resection	0.529	0.501–0.557	beta	671.95	598.27	13, 14
Intermediate/advanced stage HCC resection	0.358	0.319–0.375	beta	419.44	752.19	13, 14
Very early stage HCC ablation (F4)	0.68	0.520–0.790	beta	31.80	14.96	15
Early stage HCC ablation (F4)	0.601	0.538–0.610	beta	444.21	294.91	16, 17
Intermediate/advanced stage HCC ablation (F4)	0.22	0.138–0.300	beta	22.80	80.82	18, 19
Very early stage HCC ablation (DC)	0.31	±10%	beta	275.69	613.63	16
Early stage HCC ablation (DC)	0.31	±10%	beta	275.69	613.63	16
Intermediate/advanced stage HCC ablation (DC)	0.11	±10%	beta	355.89	2879.47	16–19

DC, decompensated cirrhosis; F4, compensated cirrhosis; HCC, hepatocellular carcinoma; LT, liver transplantation; OS, overall survival; QoL, quality of life.

^aAnnual.^bMonthly.

Supplementary Table 2. Performance Characteristics of Screening and Diagnostic Tests Used in simHCC Simulation Model

Model parameter	Base case	Range	Distribution	Parameter 1	Parameter 2	Reference
US sensitivity						
Very early stage HCC (with AFP)	0.63	0.48–0.75	beta	29.86	18.32	20
Early HCC	0.97	0.91–0.99	beta	84.09	3.53	20
US specificity	0.84	0.77–0.89	beta	121.39	24.10	20
MRI sensitivity						
Very early stage HCC	0.76	0.67–0.84	beta	75.16	24.42	21
Early stage HCC	0.88	0.80–0.93	beta	86.12	12.61	21
MRI specificity	0.93	0.84–0.97	beta	60.54	5.48	21
Abnormal MRI	0.147	±10%	beta	326.14	1897.05	Calibrated based on 22
CT sensitivity						
Very early stage HCC	0.68	(0.55–0.79)	beta	38.73	18.76	21
Early stage HCC	0.79	(0.70–0.86)	beta	78.88	21.70	21
Intermediate/advanced stage HCC	1.0	0.9–1.0	beta	–1.00	0.00	21
CT specificity	0.94	(0.87–0.98)	beta	81.93	6.17	21
Abnormal CT	0.142	±10%	beta	328.04	1986.90	Calibrated based on 22

AFP, alpha-fetoprotein; CT, computed tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; US, ultrasound scan.

Supplementary Table 3. Distributions of Hepatocellular Carcinoma Treatment for Patients at Various Stages of Fibrosis¹⁰

Disease state	Resection	Transplant	Ablation	Palliative care
Patients with advanced fibrosis				
Very early stage HCC ⁷	0.35	0.00	0.35	0.30
Early stage HCC ⁷	0.28	0.14	0.28	0.30
Intermediate/advanced stage HCC ³⁶	0.16	0.00	0.04	0.80
Patients with compensated cirrhosis				
Very early stage HCC ⁷	0.35	0.00	0.35	0.30
Early stage HCC ⁷	0.28	0.14	0.28	0.30
Intermediate/advanced stage HCC ³⁶	0.16	0.00	0.04	0.80
Patients with decompensated cirrhosis				
Very early stage HCC	0.00	0.12	0.18	0.70
Early stage HCC	0.00	0.12	0.18	0.70
Intermediate/advanced stage HCC ³⁶	0.00	0.00	0.20	0.80

HCC, hepatocellular carcinoma.

Supplementary Table 4. Model Input Parameters for Health Utilities

Model parameter	Utility base case	Range	Distribution	Parameter 1	Parameter 2	Reference
F3	0.93	0.84–1.00	beta	36.91	2.78	28
F4	0.9	0.81–1.00	beta	35.00	3.89	28
DC	0.8	0.57–1.00	beta	10.28	2.57	28
Biopsy	0.993	±10%	beta	37.32	1.26	29
Biopsy complication	0.98	±10%	beta	41.53	1.83	30, 31
First year, post-transplant	0.69	0.64–0.71	beta	481.24	216.21	32
Subsequent years, post-transplant	0.73	0.71–0.79	beta	358.98	132.77	32
Post-treatment multiplier						
First year, post-resection	0.868	±10%	gamma	400.00	0.002170	33, 34
Subsequent years, post-resection	1.048	±10%	gamma	400.00	0.002620	33, 34
First year, post-ablation	0.884	±10%	gamma	400.00	0.002210	33, 34
Subsequent years, post-ablation	0.795	±10%	gamma	400.00	0.001988	33, 34
First year, post-palliative treatment	0.82	±10%	gamma	400.00	0.002050	33, 34
Subsequent years, post-palliative treatment	0.686	±10%	gamma	400.00	0.001715	33, 34

DC, decompensated cirrhosis; F3, advanced fibrosis; F4, compensated cirrhosis.

Supplementary Table 5. Model Inputs for Cost Parameters

Model parameter	Base case	Range	Distribution	Parameter 1	Parameter 2	Reference
US	166	±25%	gamma	59.7	2.7	23
AFP	47	±25%	gamma	59.4	0.9	7
Abdominal MRI	613	±25%	gamma	59.6	10.1	23
CT	292	±25%	gamma	13.5	20.8	24
Biopsy	871	±25%	gamma	59.4	14.4	23
Biopsy complication	7476	±25%	gamma	59.4	123.9	25
Incidental/symptomatic HCC detection (annual)						
Very early stage HCC	0.016	0.0–0.162	beta	0.14	8.46	26
Early stage HCC	0.121	0.0–0.303	beta	2.12	15.41	26
Intermediate/advanced stage HCC	1.0	0.0–1.0	beta	1.50 ^a	1.50 ^a	26
Health state costs (annual, \$)						
F4	1416	±25%	gamma	59.4	23.5	23
DC	17,420	±25%	gamma	44.6	371.8	23
Treatment-related costs (\$)						
Liver transplant (first year)	205,412	±25%	gamma	64.00	3209.57	23
Liver transplant (subsequent years)	16,944	±25%	gamma	64.00	264.74	23
Cost of hepatic resection	49,369	±25%	gamma	64.00	771.38	23
Cost of local ablation	4236	±25%	gamma	64.00	66.19	23
Cost of palliative treatment (arterial embolization/chemoembolization)	27,014	±25%	gamma	64.00	422.09	27

AFP, alpha-fetoprotein; CT, computed tomography; DC, decompensated cirrhosis; F4, compensated cirrhosis; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; US, ultrasound scan.

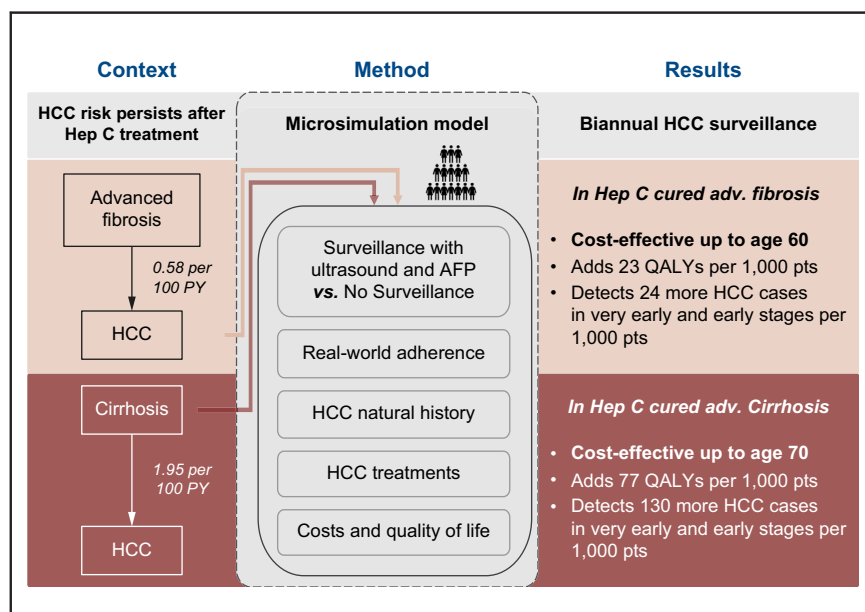
^aDistribution parameters were calculated using the midpoint of the range as the mean, which does not match the base case in the two parameters noted above.

Supplementary Table 6. Probabilities of the Different Diagnostic Test Results

Diagnostic test result	Patients with HCC	Patients without HCC
Positive	Sensitivity	0
Abnormal	p_1	1-Specificity
Negative	p_2	Specificity

Duration and cost-effectiveness of hepatocellular carcinoma surveillance in hepatitis C patients after viral eradication

Graphical abstract



Authors

Peter P. Mueller, Qiushi Chen, Turgay Ayer, ..., Naveed Z. Janjua, Fasiha Kanwal, Jagpreet Chhatwal

Correspondence

jagchhatwal@mgh.harvard.edu (J. Chhatwal).

Lay summary

Individuals who are cured of hepatitis C using oral antiviral drugs remain at risk of developing liver cancer. The value of lifelong screening for liver cancer in these individuals is not known. By simulating the life course of hepatitis C cured individuals, we found that ultrasound-based biannual screening for liver cancer is cost-effective up to age 70 in those with cirrhosis and up to age 60 in those with stable advanced fibrosis.

Highlights

- The value of lifelong surveillance for HCC in individuals after SVR is not known.
- Ultrasound-based bi-annual surveillance for HCC appears to be cost-effective up to age 75 in those with cirrhosis.
- This surveillance strategy was cost effective up to age 60 in those with stable advanced fibrosis.
- Compared with no surveillance, surveillance detected 86 additional HCCs in 'very early'/early stage per 1,000 patients with cirrhosis.



Duration and cost-effectiveness of hepatocellular carcinoma surveillance in hepatitis C patients after viral eradication

Peter P. Mueller^{1,†}, Qiushi Chen^{1,2,†}, Turgay Ayer³, Gizem S. Nemutlu¹, Ali Hajjar¹, Emily D. Bethea^{1,4}, Mary Linton B. Peters^{1,5}, Brian P. Lee⁶, Naveed Z. Janjua^{7,8}, Fasiha Kanwal^{9,10,‡}, Jagpreet Chhatwal^{1,4,*,‡}

¹Institute for Technology Assessment, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA; ²Harold and Inge Marcus Department of Industrial and Manufacturing Engineering, Pennsylvania State University, University Park, PA, USA; ³H. Milton Stewart School of Industrial and Systems Engineering, Georgia Institute of Technology, Atlanta, GA, USA; ⁴Liver Center and Gastrointestinal Division, Massachusetts General Hospital, Boston, MA, USA; ⁵Division of Medical Oncology, Beth Israel Deaconess Medical Center, Boston, MA, USA; ⁶Division of Gastrointestinal and Liver Diseases, University of Southern California, Los Angeles, CA, USA; ⁷British Columbia Centre for Disease Control, Vancouver, BC, Canada; ⁸School of Population and Public Health, University of British Columbia, Vancouver, BC, Canada; ⁹Department of Medicine, Baylor College of Medicine, Houston, TX, USA; ¹⁰Houston Veterans Affairs Health Services Research and Development Center of Excellence, Michael E. DeBakey Veterans Affairs Medical Center, Houston, TX, USA

Background & Aims: Successful treatment of chronic hepatitis C with oral direct-acting antivirals (DAAs) leads to virological cure, however, the subsequent risk of hepatocellular carcinoma (HCC) persists. Our objective was to evaluate the cost-effectiveness of biannual surveillance for HCC in patients cured of hepatitis C and the optimal age to stop surveillance.

Methods: We developed a microsimulation model of the natural history of HCC in individuals with hepatitis C and advanced fibrosis or cirrhosis who achieved virological cure with oral DAAs. We used published data on HCC incidence, tumor progression, real-world HCC surveillance adherence, and costs and utilities of different health states. We compared biannual HCC surveillance using ultrasound and alpha-fetoprotein for varying durations of surveillance (from 5 years to lifetime) vs. no surveillance.

Results: In virologically cured patients with cirrhosis, the incremental cost-effectiveness ratio (ICER) of biannual surveillance remained below \$150,000 per additional quality-adjusted life year (QALY) (range: \$79,500–\$94,800) when surveillance was stopped at age 70, irrespective of the starting age (40–65). Compared with no surveillance, surveillance detected 130 additional HCCs in ‘very early’/early stage and yielded 51 additional QALYs per 1,000 patients with cirrhosis. In virologically cured patients with advanced fibrosis, the ICER of biannual surveillance remained below \$150,000/QALY (range: \$124,600–\$129,800) when surveillance was stopped at age 60, irrespective of the starting age (40–50). Compared with no surveillance, surveillance detected 24 additional HCCs in ‘very early’/early stage and yielded 12 additional QALYs per 1,000 patients with advanced fibrosis.

Conclusion: Biannual surveillance for HCC in patients cured of hepatitis C is cost-effective until the age of 70 for patients with cirrhosis, and until the age of 60 for patients with stable advanced fibrosis.

Lay summary: Individuals who are cured of hepatitis C using oral antiviral drugs remain at risk of developing liver cancer. The value of lifelong screening for liver cancer in these individuals is not known. By simulating the life course of hepatitis C cured individuals, we found that ultrasound-based biannual screening for liver cancer is cost-effective up to age 70 in those with cirrhosis and up to age 60 in those with stable advanced fibrosis. © 2022 European Association for the Study of the Liver. Published by Elsevier B.V. All rights reserved.

Introduction

Chronic hepatitis C is the leading cause of hepatocellular carcinoma (HCC) in the United States. However, with the availability of new direct-acting antivirals (DAAs), 90–100% of patients with hepatitis C, even those who could not be treated with previously available interferon-based therapies, can now achieve a virological cure (defined as a sustained virological response or SVR).¹ Although successful treatment resulting in SVR represents a “cure” from the standpoint of persistent infection, the subsequent risk of HCC persists after treatment with DAAs and remains an important contributor to liver-related morbidity and mortality in the post-DAA era.^{2–4}

With the wide use of DAAs, the number of patients with virologically cured hepatitis C has rapidly increased from 0.5 million in 2012 to 1.5 million in 2020 in the United States.⁵ Similar trends are expected in other countries that have successfully treated a large number of patients with DAAs. Furthermore, the proportion of patients with advanced liver disease among this cohort has increased.⁶ As such, most patients with hepatitis C in clinical practice will be those who have been virologically cured with DAAs and yet have advanced liver disease, either fibrosis or cirrhosis.⁵ For instance, the number of individuals who could potentially benefit from HCC surveillance, i.e., those with advanced liver disease is projected to increase

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* Corresponding author. Address: MGH Institute for Technology Assessment, 101 Merrimac Street, Ste 1010, Boston, MA 02114, USA; Tel.: (617) 724-4445, fax: (617) 726-9414.

E-mail address: jagchhatwal@mgh.harvard.edu (J. Chhatwal).

† Co-first authors.

‡ Co-senior authors.

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from 106,000 in 2012 to 649,000 in 2030.⁶ For this growing population, routine HCC surveillance is critical to improve early cancer detection and improve survival outcomes.⁷

The optimal policy for routine HCC surveillance for patients with virologically cured hepatitis C remains unclear.^{8,9} Despite limited evidence on the cost-effectiveness of HCC surveillance for this patient group, the American Association for the Study of Liver Diseases (AASLD) recommends biannual ultrasound-based (with or without alpha-fetoprotein) surveillance for HCC in patients with cirrhosis who achieve virological cure with DAAs,¹ but does not recommend surveillance in patients with advanced fibrosis. In contrast, the European Association for the Study of the Liver (EASL) guidelines recommend biannual surveillance in patients with cirrhosis as well as bridging fibrosis.¹⁰ Furthermore, none of the guidelines specify any age at which to discontinue surveillance. Virologically cured hepatitis C patients have a higher life expectancy than patients with active hepatitis C,¹¹ and the value of lifetime HCC surveillance in this cohort is not known.

Our study's objective was to perform a comparative cost-effectiveness analysis to determine in which patients, and up to what age, the benefits of HCC surveillance outweigh the costs.

Materials and methods

Overview

We developed a microsimulation model (an individual-level state-transition model) that simulates the natural history of hepatitis C and HCC in patients who achieved SVR after hepatitis C treatment with DAAs. The model was used to evaluate the cost-effectiveness of biannual HCC surveillance by varying the starting age for surveillance from 40 to 70 (base age 50) and stopping age from 50 to lifetime. We incorporated data from recent studies on the risk of HCC in patients who achieved SVR with DAAs,^{2,12–17} real-world adherence to HCC surveillance,¹⁸ the accuracy of screening and diagnostic testing modalities,^{19–22} as well as HCC treatments including liver transplantation for selected patients.^{20,23–35} The model used a monthly time-step. Primary outcomes included life expectancy, quality-adjusted life years (QALYs), total costs, and

incremental cost-effectiveness ratio (ICER) of each of the simulated surveillance strategies.

Baseline population and natural history model

For the baseline population, we created a virtual cohort of 50-year-old patients (mean age of HCV treatment), all of whom had hepatitis C that had been cured by DAA treatment. We developed different patient profiles that varied age (range 40–70), sex, and the extent of liver disease (advanced fibrosis METAVIR score F3 or compensated cirrhosis METAVIR score F4). For each patient, we simulated their remaining lifespan *with* and *without* HCC surveillance. We tracked life expectancy, development of HCC, and stage of HCC at diagnosis for each virtual patient in this simulation model.

For each virtual patient, we simulated the clinical course of cured hepatitis C, including HCC development as well as the progression of liver disease (Fig. 1). In each month, patients could develop HCC at a “very early” stage that could later progress to “early” and “intermediate/advanced” stages. We defined HCC stage based on Barcelona Clinic Liver Cancer staging system and tumor size: “very early HCC” included patients with a tumor less than 2 cm in diameter, “early HCC” for those with a single tumor less than 5 cm or up to 3 tumors all less than 3 cm, and “intermediate/advanced HCC” for the remaining stages. We assumed that patients with F3 advanced fibrosis could not develop cirrhosis once in SVR.³⁶ In each month, patients with F4 cirrhosis could progress to decompensated cirrhosis. The rate of HCC development varied by the extent of liver disease, such that patients without HCC could develop more severe liver disease, thus increasing their risk of HCC (Table S1).

HCC incidence

We used recently published studies to estimate the incidence of HCC among hepatitis C patients who achieved SVR. For patients with compensated cirrhosis (F4 fibrosis stage), we used a weighted average of 6 studies that resulted in an incidence rate of 1.95 per 100 person-years (Supplement Section S1).^{2,12–16} For patients with advanced fibrosis (F3 stage), the HCC incidence

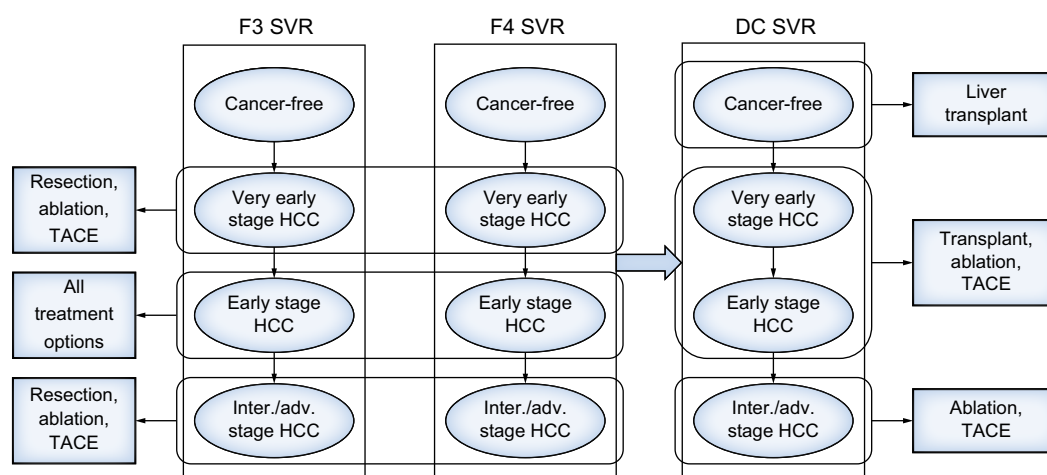


Fig. 1. Model schematic for the natural history of HCC in patients with hepatitis C who achieved an SVR on direct-acting antivirals. Patients could develop HCC and subsequently progress through different stages of HCC. Patients with cirrhosis could also progress to decompensated cirrhosis. DC, decompensated cirrhosis; F3, advanced fibrosis; F4, cirrhosis; HCC, hepatocellular carcinoma; SVR, sustained virologic response; TACE, transarterial chemoembolization.

rate was estimated from 2 studies that resulted in a weighted average of 0.58 per 100 person-years.^{16,17} In a sensitivity analysis, we allowed HCC risk to be higher and lower than the base case values.

HCC surveillance

For each virtual patient, we simulated 'no surveillance' vs. biannual HCC surveillance using both ultrasound and alpha-fetoprotein,^{19,22} as recommended by clinical guidelines. We simulated different HCC surveillance strategies by varying the duration of surveillance from 10 years to lifetime (in 5-year increments). For example, we simulated the following surveillance strategies for a 50-year-old patient: biannual HCC surveillance from age 50 to age 60, 65, 70, etc. If surveillance tests were normal, no further intervention was needed and the patient followed their natural history until the next surveillance test; if the surveillance tests were abnormal, the patient received a contrast-enhanced abdominal MRI to potentially confirm the diagnosis of HCC.^{19–21} After confirmation of HCC, patients began treatment for HCC. HCC could also be detected incidentally regardless of surveillance. We assumed that only a single MRI was required for diagnostic confirmation.^{37,38} We also accounted for imperfect adherence to biannual HCC surveillance as observed in practice (see [Supplementary Section S2](#)).³⁹

HCC treatment

We considered 4 HCC treatment options: ablation, resection, liver transplantation, transarterial chemoembolization, and other palliative treatments (including selective internal radiotherapy, external beam radiotherapy, and systemic chemotherapy). Selection of treatment depended on HCC stage as well as the liver disease severity at diagnosis ([Table S2](#)). Following the guidelines, we assumed that liver transplantation was available only for patients under the age of 75 with either decompensated cirrhosis or "early stage" HCC (i.e., within Milan criteria); and decompensated patients were not eligible for resection. Treatment distributions by both HCC stage and fibrosis stage were determined from published observational studies^{19,40} and expert opinion (see [Supplementary Section S3](#)).

Unlike resection, ablation, and transarterial chemoembolization, which were delivered soon after the diagnosis, patients selected for liver transplantation were assumed to be on the transplant waitlist for organ availability. During each month, patients could receive a liver transplant; the probability of transplant was based on the median wait times that were provided from Organ Procurement Transplant Network data, which were dependent on the HCC tumor stage and liver stage ([Table S1](#)). However, in each month, HCC could progress such that patients were no longer eligible for transplant. In addition, if patients reached the age of 75, they would no longer be eligible for liver transplant (see [Supplementary Section S4](#)).

Costs and quality-of-life

The cost of surveillance tests, HCC treatments, liver transplantation, and general liver disease management were extracted from published sources ([Table S1](#)). All costs were converted to 2020 US dollars using the Consumer Price Index. We also assigned quality-of-life utility weights to each health state and treatment. These utility weights were adjusted by age, liver

disease stage, and for the year of treatment (initial year vs. later years)^{23,32,41,42} ([Table S1](#)).

Model outcomes

For each simulated surveillance strategy and for each patient profile, we estimated the number of HCC cases detected by tumor stage, total QALYs, and costs. All future QALYs and costs were discounted at 3% per year. We then calculated the ICERs for each surveillance strategy. For each surveillance strategy and patient profile, we could determine if surveillance was cost-effective if the ICER remained below the willingness-to-pay threshold of \$150,000 per QALY.⁴³ To reduce first-order uncertainty, we simulated outcomes in 200 million virtual patients.

Subgroup and sensitivity analysis

We evaluated the cost-effectiveness of surveillance in several subgroups described by age, sex, diabetes status, and alcohol use.²

As a part of our sensitivity analyses, we varied the incidence of HCC following SVR across a range informed by several observational studies.^{2,12–17} We further evaluated the impact of uncertainty in each model input on outcomes by conducting *univariate* probabilistic sensitivity analysis on each model input. This was performed by randomly sampling values from each parameter's recommended statistical distribution one at a time ([Table S1](#)). We also conducted a *multivariate* probabilistic sensitivity analysis on *all* model parameters simultaneously by sampling 4,000 sets of parameter values from the recommended statistical distributions and evaluating each parameter set with a population size of 1.5 million. The *multivariate* probabilistic sensitivity analysis results were presented as cost-effectiveness acceptability curves.

Results

Base case cost-effectiveness results for HCC surveillance

[Table 1](#) shows the costs, QALYs, and ICERs of each HCC surveillance strategy. For 50-year-old patients with cirrhosis, the ICER of biannual HCC surveillance was \$93,587 per QALY when the stopping age of surveillance was 70 and \$223,364 per QALY when the stopping age increased to 75 ([Fig. 2A](#), [Table 1](#)), suggesting that HCC surveillance is cost-effective until the age 70 using a willingness-to-pay threshold of \$150,000. Compared with no surveillance, the cost-effective surveillance strategy – surveillance up to age 70 – provided QALY gains of 51 per 1,000 patients at an additional cost of \$2,694,400. Surveillance was cost-effective until the age of 70 regardless of starting age (from 40–65), with the ICERs remaining below the \$150,000-per-QALY threshold ([Fig. 2A](#)). Of note, for 65-year-old patients, the ICER of routine surveillance up to age 75 was \$147,563—below the \$150,000 threshold.

For 50-year-old patients with advanced fibrosis, the ICER of biannual HCC surveillance was \$98,800 per QALY when the stopping age of surveillance was 65 and \$129,781 per QALY when the stopping age increased to 70 ([Fig. 2B](#)), suggesting that HCC surveillance is cost-effective until age 65 using a willingness-to-pay threshold of \$150,000. However, the ICER of surveillance was cost-effective only up to age 60 when the starting age was 40, 45, and 50 ([Fig. 2A](#)). Compared with no surveillance, the cost-effective surveillance strategy –

Table 1. Base case cost-effectiveness results of biannual HCC surveillance in 50-year-old patients with virologically cured hepatitis C.

Surveillance stopping age	Compensated cirrhosis			Advanced fibrosis		
	QALYs	Costs (\$)	ICERs (\$/QALY)	QALYs	Costs (\$)	ICERs (\$/QALY)
No surveillance	11.718	38,534	—	14.384	3,568	—
60	11.755	40,243	46,000	14.396	5,081	129,781
65	11.765	40,819	60,625	14.399	5,649	160,348
70	11.769	41,228	93,587	14.401	6,096	275,280
75	11.770	41,526	223,364	14.401	6,444	772,400

HCC, hepatocellular carcinoma; ICERs, incremental cost-effectiveness ratios; QALYs, quality-adjusted life years.

surveillance up to age 60 – provided QALY gains of 12 per 1,000 patients at an additional cost of \$1,512,900.

For 50-year-old patients with cirrhosis in the “no surveillance” arm, for every 1,000 patients, 381 HCC cases were detected either as incidental findings or through symptoms – 9 were detected in very early stage, 93 in early stage, and 279 in intermediate/advanced stages (Fig. 3). In contrast, the cost-effective surveillance strategy (surveillance every 6 months until the age of 70) detected a total of 389 HCC cases – 82 were detected in very early stage, 150 in early stage, and 157 in intermediate/advanced stages. Therefore, this surveillance strategy detected 130 additional HCCs in ‘very early’/early stage. The surveillance strategy also identified 8 additional patients with HCC who would have died from competing mortality under no surveillance. Similar trends were observed in patients with advanced fibrosis. In 50-year-old patients with advanced fibrosis, 3 cases were detected in a very early stage, 37 in early stage, and 111 in intermediate/advanced stage in the “no surveillance” arm. In contrast, the cost-effective surveillance strategy (surveillance every 6 months until the age of 60) detected 17 cases in very early stage, 47 in early stage, and 88 in intermediate/advanced stage. Therefore, this surveillance strategy detected 24 additional HCCs in ‘very early’/early stage.

Effect of remaining life expectancy on surveillance

We found that biannual HCC surveillance would not be cost-effective in cirrhosis patients if their remaining life expectancy was under 16 years and not cost-effective in advanced fibrosis patients if their life expectancy was under 28 years. This finding did not change with the age of individuals.

Subgroup analysis

In 50-year-old patients with cirrhosis, biannual HCC surveillance was cost-effective until the age of 70 irrespective of alcohol use, male sex, diabetes status, and BMI (Table 2).

In patients with advanced fibrosis, biannual HCC surveillance was found to be cost-effective for an additional 10 years (until the age of 70) for men over the age of 55.

Sensitivity analysis

We evaluated a total of 59 parameters in the univariate probability sensitivity analysis. Tables S3 and S4 show the top 10 parameters, respectively, to which the model was most sensitive in virologically cured patients with compensated cirrhosis and advanced fibrosis, respectively. For individuals with compensated cirrhosis, the cost-effective surveillance strategy was most sensitive to the likelihood of incidental detection of HCC, the

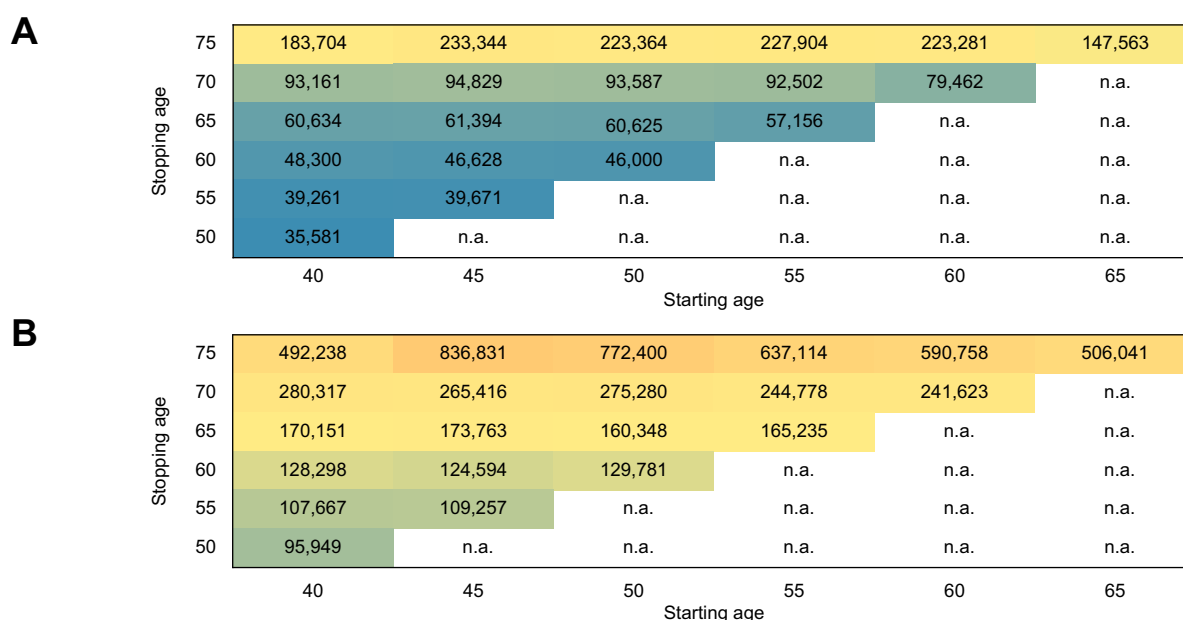


Fig. 2. Incremental cost-effectiveness ratios of biannual HCC surveillance. (A) In patients with cirrhosis and (B) in patients with advanced fibrosis who achieved virological cure with direct-acting antivirals. In patients with cirrhosis, HCC surveillance is cost-effective up to approximately age 70 using a willingness-to-pay threshold of \$150,000 per quality-adjusted life year. In patients with advanced fibrosis, HCC surveillance is cost-effective up to age 60. HCC, hepatocellular carcinoma.

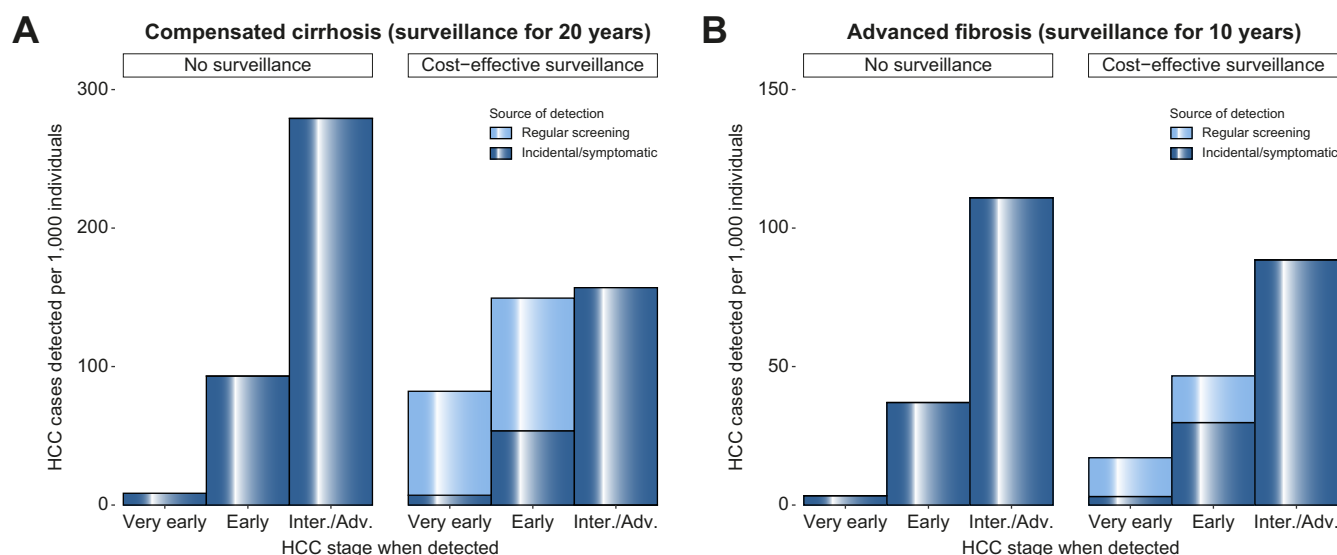


Fig. 3. Number of HCC cases according to surveillance approach. Number of HCC cases detected by tumor size in 50-year-old virologically cured patients under no surveillance vs. biannual surveillance until the age of 70 for patients with cirrhosis and until the age of 60 for patients with advanced fibrosis. CHC, chronic hepatitis C; HCC, hepatocellular carcinoma; SVR, sustained virologic response.

progression rate from early-stage HCC to intermediate/advanced stage HCC, and overall survival following palliative care. For advanced fibrosis individuals, the cost-effective surveillance strategy was most sensitive to the likelihood of incidental detection of HCC, MRI sensitivity for very early-stage HCC, and overall survival following liver transplant.

The results of the multivariate probabilistic sensitivity analysis are presented in the cost-effectiveness acceptability curve (Fig. 4),

which shows the likelihood of the cost-effectiveness of biannual HCC surveillance for different stopping ages when accounting for uncertainty in all model parameters. In patients with cirrhosis, surveillance for 25 years (*i.e.*, until the age 75) – in contrast to age 70 in the base case – was the most cost-effective option at the willingness-to-pay threshold of \$150,000. In patients with advanced fibrosis, surveillance for 20 years (*i.e.*, until age 70) – in contrast to age 60 in the base case – was the most cost-effective strategy at the willingness-to-pay threshold of \$150,000 per QALY. This suggests that the exact duration of HCC surveillance be longer than that reported in the base case results.

Table 2. Cost-effectiveness of HCC surveillance in selected subgroups of 50-year-old patients with virologically cured hepatitis C.

	HCC incidence per 100 person-years	Compensated cirrhosis	
		Cost-effective until age	ICER for 20 years of surveillance
Base case	1.95	70	93,600
Diabetes			
Yes	2.07	70	87,800
No	1.85	70	92,800
Alcohol use*			
Yes	2.15	70	86,500
No	1.66	70	98,900
Sex			
Male	2.01	70	89,500
Body mass index			
≥ 30 kg/m ²	2.48	70	79,100
< 30 kg/m ²	1.81	70	94,100
Male; age > 55; alcohol use: Yes	2.36	70	83,100
Male; age > 55; diabetes: Yes	2.09	70	89,700
		Advanced fibrosis	
		Cost-effective until age	ICER for 10 years of surveillance
Base case	0.58	60	129,800
Male age ≥ 55	1.36	70	89,300

HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio.

*Alcohol use was defined based on the AUDIT-C score ≥ 4 for men and ≥ 3 for women.

Discussion

Patients with hepatitis C that has been cured with oral DAAs remain at risk of developing HCC. With the wide use of DAAs, the number of patients virologically cured will rapidly increase in the near future.⁵ In this study, we evaluated the value of routine surveillance for HCC using a decision-analytic model that simulated the natural history of HCC in hepatitis C cured individuals. We found that biannual HCC surveillance is cost-effective in patients with compensated cirrhosis until the age of 70 and in patients with advanced fibrosis until the age of 60. These findings are important because virologically cured patients have a higher life expectancy than patients with active hepatitis C, and lifelong surveillance may not be warranted in this growing cohort.

Our study's conclusion supports AASLD and EASL's current HCC surveillance recommendations for HCC surveillance in patients with compensated cirrhosis who achieve virological cure with DAAs. For patients with stable advanced fibrosis – for whom the AASLD and EASL surveillance recommendations differ – our results align with the EASL's recommendation of the need for HCC surveillance. Of note, our study also identified an age cut-off at which to stop surveillance in both cohorts, which is not mentioned in either guideline.

An earlier study found that HCC surveillance is cost-effective in hepatitis C individuals who were successfully treated if they have cirrhosis.⁹ However, this study assumed patients would

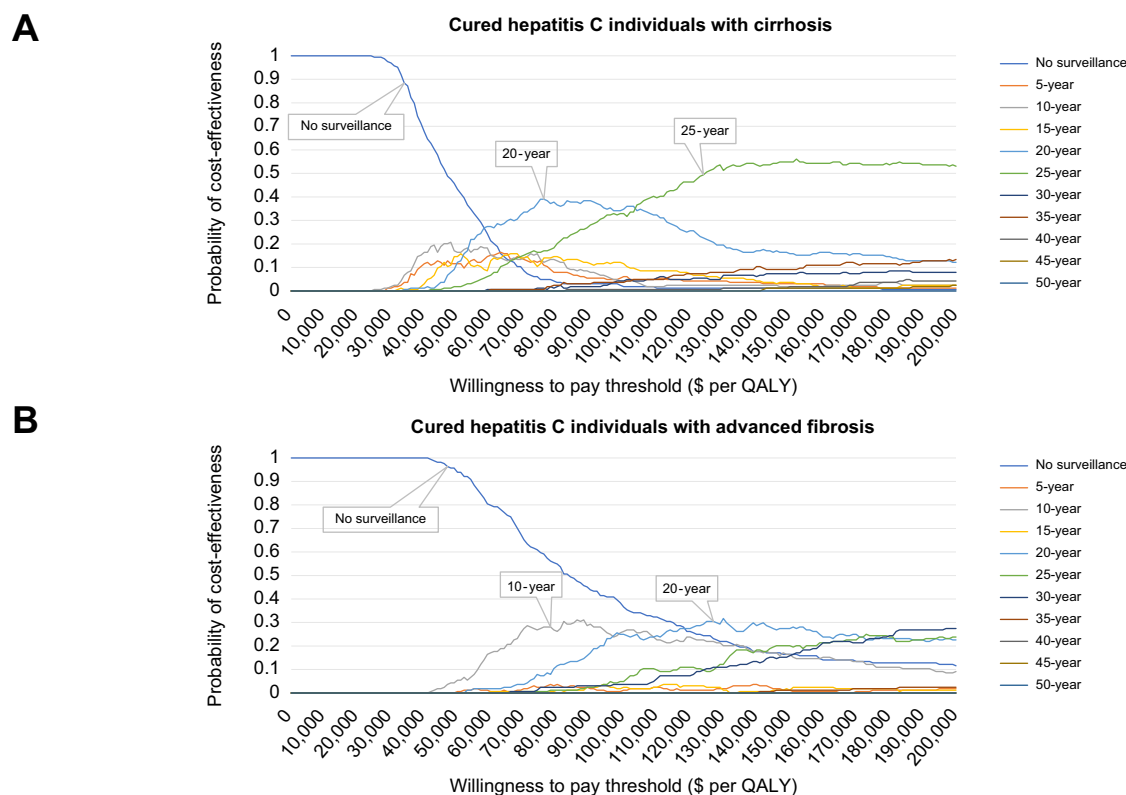


Fig. 4. Cost-effectiveness acceptability curves. Cost-effectiveness acceptability curves showing the probability of cost-effectiveness for each surveillance strategy by different durations of hepatocellular carcinoma surveillance as defined by the stopping age in patients with (A) compensated cirrhosis and (B) advanced fibrosis. QALY, quality-adjusted life year.

undergo HCC surveillance for the duration of their lifetime. In contrast, we opted to test various ages to start and stop surveillance, as we know hepatitis C patients after achieving cure can live longer than those who do not achieve a SVR or those with other etiologies of liver disease. Our study's primary finding — that biannual surveillance is cost-effective until the age of 70 in individuals with compensated cirrhosis or until the age of 60 in individuals with advanced fibrosis — is important for the medical community as they work to define the optimal surveillance policy for HCC.

Surveillance may not be warranted in patients with HCC who are not eligible for curative treatments given factors such as age, comorbidity, liver disease severity, and access to transplant, among others. Therefore, we examined the benefits as well as the harms associated with surveillance in key subgroups, including those with advanced comorbidity. We found that HCC surveillance would not be deemed cost-effective if the remaining life expectancy is less than 16 years in patients with cirrhosis and less than 28 years in patients with advanced fibrosis. While our study found that HCC surveillance is cost-effective in virologically cured patients with advanced fibrosis until the age of 60, there could be subgroups of patients who have an elevated risk of HCC and could benefit from longer durations of surveillance. Therefore, future research is needed to identify risk factors and biomarkers in virologically cured patients with advanced fibrosis who could benefit from routine HCC surveillance.

Early diagnosis of HCC is critical to improved survival — patients with advanced HCC have a median survival of less than 1

year, while patients with early HCC can achieve 5-year survival rates near 70% with resection or transplantation.⁴⁴ Our analysis found that surveillance could produce a substantial stage shift, in which most HCC would be diagnosed at an early stage. Compared with 'no surveillance' arm, surveillance per 1,000 cirrhosis patients detected 130 additional HCCs in 'very early'/early stage and yielded 51 additional QALYs. Similarly, surveillance per 1,000 patients with advanced fibrosis detected 24 additional HCCs in 'very early'/early stage and yielded 12 additional QALYs.

Unlike other major cancers such as breast, prostate, and colorectal, surveillance for HCC remains underutilized in practice.⁴⁵ Several recent observational studies have shown the benefits of routine HCC surveillance.^{7,46} Ideally, a large randomized controlled trial could compare the long-term outcomes of surveillance with a no surveillance control arm;⁴⁷ however, this would be lengthy, and the use of a control arm would strain medical ethics.^{47,48} In this type of situation, decision-analytic models can simulate a virtual trial to generate comparative effectiveness data and inform screening policy. Simulation models are frequently used by policymakers to inform guidelines for cancer screening.^{49–52} Together with other recent reports,^{8,9} we believe our study provides helpful data to policymakers and professional societies in their evaluation of recommendations for HCC surveillance among high-risk patients.

This study has limitations. While our results remain robust for patients with compensated cirrhosis, limited data on HCC incidence in patients with advanced fibrosis warrant further

research before making strong conclusions on the duration of surveillance in these individuals. Second, we assumed that patients with fibrosis successfully treated with DAAs were no longer at risk of progression to cirrhosis, despite the clinical reality that these patients may show progression in cases of alcohol consumption or weight change. Future research is warranted to estimate HCC risk and cost-effectiveness of HCC surveillance in those subgroups. We believe future research should also evaluate the cost-effectiveness of HCC surveillance tailored to dynamic risk factors that change over time. Third, we only modeled primary HCC treatment, whereas most patients with HCC receive a sequence of treatments (such as a combination of ablation and transplantation). However, our estimates of life expectancy after HCC diagnosis and primary treatment included this treatment variability. We opted to simulate surveillance in 5-year increments rather than shorter time frames because such age intervals are easier to implement in practice. Lastly, aside from liver transplantation being restricted to patients under 75, no other age or comorbidity restrictions were assumed for other treatments.

In conclusion, we found that biannual surveillance for HCC in virologically cured patients with cirrhosis is cost-effective until age 70 and in virologically cured patients with stable advanced fibrosis until the age of 60. Future studies should identify subgroups of patients without cirrhosis who remain at risk of developing HCC and could benefit from a longer duration of HCC surveillance.

Abbreviations

AASLD, American Association for the Study of Liver Diseases; DAAs, direct-acting antivirals; EASL, European Association for the Study of the Liver; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year; SVR, sustained virological response.

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Conflict of interest

Dr. Peters received honoraria from Bayer, Exelixis and Agios, travel support from Halozyme, AstraZeneca and Exelixis, research support from Bayer, institutional research support from Taiho, AstraZeneca, BeiGene, Berg, Merck, all outside the submitted work. Dr. Ayer received consulting fee from Merck and served as principal scientist to Value Analytics Labs outside the submitted work. Dr. Chhatwal received consulting fee from Gilead, Merck, and Novo Nordisk, and served as principal scientist to Value Analytics Labs outside the submitted work.

Please refer to the accompanying ICMJE disclosure forms for further details.

Authors' contributions

Study concept and design: Mueller, Chen, Kanwal, Chhatwal. *Acquisition of data:* Mueller, Chen, Nemutlu, Hajjar, Peters, Lee, Janjua, Kanwal, Chhatwal. *Analysis and interpretation of data:* Mueller, Chen, Ayer, Nemutlu, Hajjar, Bethea, Peters, Lee, Janjua, Kanwal, Chhatwal. *Drafting of the manuscript:* Mueller, Chen, Kanwal, Chhatwal. *Critical revision of the manuscript for important intellectual content:* Mueller, Chen, Ayer, Nemutlu, Bethea, Peters, Lee, Janjua, Kanwal, Chhatwal. *Statistical analysis:* Mueller, Chen, Nemutlu, Hajjar, Lee. *Obtained funding:* Kanwal, Chhatwal. *Study supervision:* Chhatwal.

Data availability statement

All data generated from the simulation model are made available in the manuscript.

Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jhep.2022.01.027>.

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Author names in bold designate shared co-first authorship

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Longitudinal Associations of Risk Factors and Hepatocellular Carcinoma in Patients With Cured Hepatitis C Virus Infection

Jennifer R. Kramer, PhD, MPH^{1,3}, Yumei Cao, MS^{1,3}, Liang Li, PhD⁴, Donna Smith, MS¹, Jagpreet Chhatwal, PhD⁵, Hashem B. El-Serag, MD, MPH^{1,2} and Fasiha Kanwal, MD, MSHS^{1,2}

INTRODUCTION: There are limited data on the effect and evolution of risk factors for hepatocellular carcinoma (HCC) in patients with virologically cured hepatitis C virus (HCV) infection.

METHODS: We conducted a retrospective cohort study of patients with HCV who achieved sustained virological response with direct-acting antivirals from 130 Veterans Administration hospitals during 2014–2018, followed through 2021. Cox proportional hazards models were constructed at 3 landmark times (baseline and 12 and 24 months after sustained virological response) to examine associations between demographic, clinical, and behavioral factors and HCC risk, stratified by cirrhosis status.

RESULTS: Among 92,567 patients (32% cirrhosis), 3,247 cases of HCC were diagnosed during a mean follow-up of 2.5 years. In patients with cirrhosis, male sex (hazard ratios [HR]: 1.89, 1.93, and 1.99), cirrhosis duration ≥ 5 years (HR: 1.71, 1.79, and 1.34), varices (HR: 1.73, 1.60, and 1.56), baseline albumin (HR: 0.48, 0.47, and 0.49), and change in albumin (HR: 0.82 and 0.90) predicted HCC risk at each landmark time. HCV genotype 3, previous treatment, bilirubin, smoking, and race influenced HCC risk at baseline, but their effects attenuated over time. In patients without cirrhosis, diabetes (HR: 1.54, 1.42, and 1.47) and hypertension (HR: 1.59, 1.65, and 1.74) were associated with HCC risk at all landmark times. Changes in fibrosis-4 scores over time were associated with HCC risk both in patients with and without cirrhosis.

DISCUSSION: Risk factors for HCC were different in patients with and without cirrhosis and some also evolved during follow-up. These factors can help with risk stratification and HCC surveillance decisions in patients with cured HCV.

SUPPLEMENTARY MATERIAL accompanies this paper at <https://links.lww.com/AJG/C658>, <http://links.lww.com/AJG/C701>, <http://links.lww.com/AJG/C702>

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INTRODUCTION

In patients with chronic infection with hepatitis C virus (HCV), successful treatment with direct-acting antivirals (DAA) reduces HCC risk. However, data from our group and others show that a subsequent risk of HCC persists in many patients after sustained virological response (SVR) (1). Over the next 2 decades, most HCV-related HCC cases are projected to occur in individuals with SVR (2). Yet, decisions on how best to surveil this growing population are based on limited data.

Cirrhosis is the most important risk factor for HCC (3). However, even among patients with cirrhosis, the risk of HCC is not uniform. Some of this may come from the variation in the extent to which the underlying histological lesion (fibrosis)

regresses or progresses over time. Several demographic (e.g., age), clinical (e.g., diabetes or obesity), and behavioral factors (e.g., alcohol use or smoking) may also influence HCC risk. There are limited data on the evolution of these risk factors and their effects on HCC risk at different time points after SVR. These factors may also vary in patients with and without cirrhosis. This information is important to clinicians because identifying patients without cirrhosis but who still may be at risk for HCC can alter surveillance decisions, with more aggressive surveillance considered in those more likely to have a high risk.

Few studies have evaluated HCC risk longitudinally. We examined which risk factors (demographics, comorbidities, and liver/HCV-related) were associated with HCC at the time of SVR and 12

¹Center for Innovations in Quality, Effectiveness and Safety (IQESt), Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA; ²Section of Gastroenterology and Hepatology, Department of Medicine, Baylor College of Medicine, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas, USA; ³Section of Health Services Research, Department of Medicine, Baylor College of Medicine, Houston, Texas, USA; ⁴Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, Texas, USA; ⁵Harvard Medical School, Massachusetts General Hospital Institute for Technology Assessment, Boston, Massachusetts, USA. **Correspondence:** Jennifer R. Kramer, PhD, MPH. E-mail: jkr@bcm.edu

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and 24 months after SVR. We also examined associations of changes in these factors from baseline to different time points in subgroups defined based on presence or absence of baseline cirrhosis.

METHODS

Data sources

We used national data in the US Department of Veterans Affairs (VA) Corporate Data Warehouse (CDW) and Central Cancer Registry (CCR). CDW includes all laboratory test results, pharmacy, and diagnosis (*International Classification of Diseases [ICD]-9* and *ICD-10*) codes for all encounters in the VA. CDW also contains information from the annual Alcohol Use Disorders Identification Test-Concise screen (4) and date of death. CCR is a centralized repository for VA patients with cancer and includes information on date of diagnosis, primary site, and histology.

Study cohort

We included patients ≥ 18 years who achieved SVR with DAA in any of the 130 VA hospitals. We defined DAA treatment as ≥ 1 filled prescription of DAA (see Appendix 1, Supplemental Digital Content 2, <http://links.lww.com/AJG/C701>) between January 1, 2014, and December 31, 2018. We used 3 months after the date of DAA completion as the index date for the start of follow-up to consider time needed to determine SVR. We classified patients as SVR if all HCV RNA tests were negative after the end of DAA treatment, with ≥ 1 HCV RNA test recorded at least 12 weeks after completion. If no test was available after 12 weeks, we used a negative test from 4 to 12 weeks as SVR (6.9% of cohort). We excluded patients who failed to achieve SVR, who had HCC or liver transplant before or within 3 months of DAA treatment, had previous evidence of cancers with a high likelihood of liver metastases (esophageal, stomach, pancreatic, lung, kidney, breast cancer, and melanoma), and who did not have evidence of ≥ 1 visit in the VA after end of treatment.

Outcome

The outcome was HCC defined based on any instance of HCC recorded in the CCR. We also included patients with ≥ 2 ICD-9 or ICD-10 codes or HCC in the CDW (3,5–7). The ICD-based definition had a positive predictive value of 84%–94% in our and others' (8) work. In addition, previously, we reviewed electronic medical records of a random sample of 50 HCC cases that had ≥ 2 ICD codes but not in the CCR; all had evidence of HCC in the electronic medical record (1). We followed patients to the development of HCC, liver transplant, death, or last VA visit before December 31, 2021, whichever was earlier.

Predictor variables

The demographic variables included age, sex, race/ethnicity, marital status, and rural status defined at the index date. Other time-invariant factors including HCV genotype and previous HCV treatment status were defined based on filled prescriptions for interferon, ribavirin, or receipt of any DAA before baseline.

Time-varying factors included cirrhosis diagnosis, duration since cirrhosis diagnosis, fibrosis-4 (FIB-4) score (and individual components of FIB-4), serum albumin, sodium, bilirubin, international normalized ratio, hemoglobin, hepatitis B virus surface antigen, diabetes, body mass index (BMI), hypertension, dyslipidemia, active alcohol use disorder, smoking status, and medical and mental health comorbidity. We defined cirrhosis based on ICD codes for cirrhosis or its complications recorded any time before

baseline or the presence of FIB-4 > 3.25 (as defined below) (9). We used the date of first instance of cirrhosis code(s) as cirrhosis diagnosis date and once present they were presumed to have cirrhosis for the remaining follow-up time. We also used FIB-4 to identify patients with cirrhosis/fibrosis at baseline (FIB-4 > 3.25) and used serial changes in FIB-4 to examine the decline or increase in fibrosis. We used the values of aspartate aminotransferase, alanine aminotransferase (ALT), and platelet tests performed within 24 months and nearest to the index date to derive the baseline value. We found that 90% of patients had their FIB-4 measured within 4 months before their index date. We also calculated FIB-4 at 12-month intervals longitudinally using ALT as the anchor test and selecting the aspartate aminotransferase and platelet tests performed within 6 months of the anchor ALT. We analyzed FIB-4 as a categorical variable defined based on published cutoffs (> 3.25 and < 1.45). A previous study demonstrated that in patients with HCV, FIB-4 of less than 1.45 has a negative predictive value of 94.7% to exclude advanced fibrosis (F3–F4) and a value over 3.25 has a positive predictive value of 82.1% for advanced fibrosis (10). See Appendix 2 (see Supplemental Digital Content 2, <http://links.lww.com/AJG/C702>) for the specification for other predictors.

Statistical analyses

We used cause-specific Cox proportional hazards models for competing risks (11) constructed at 3 landmark times (12,13) (baseline and 12 and 24 months after index) to examine the associations between risk factors measured at these landmark times and subsequent HCC risk, stratified by cirrhosis status at baseline.

We constructed 6 separate models (at 3 separate landmark times for patients with and without cirrhosis). The outcome was the time from the landmark to HCC. At each landmark, the data only included the at-risk patients at that time (e.g., those who are alive without HCC).

The predictor variables included time-independent and time-dependent defined at each landmark time. For continuous measures, we assessed both categorical and continuous values to determine the best performing measure. The predictors also incorporated longitudinal information of a patient up to the landmark time, including change in FIB-4 (defined as remained stable at low risk [≤ 3.25], increased from low [≤ 3.25] to high risk [> 3.25], declined from high [> 3.25] to low risk [≤ 3.25], or remained stable at high risk [> 3.25]) and changes in serum albumin, sodium, bilirubin, international normalized ratio, creatinine, and hemoglobin between baseline and each landmark time. Log transformation was used for variables with a skewed distribution. For model interpretability, we only considered 2-way interactions that are frequently observed in the cohort or suggested by the literature.

There was a small amount of missing data. We used multiple imputation generated from the fully conditional specification method of SAS PROC MI to create 5 imputed data sets and then combined the results using multiple imputation. Each imputed data set went through a model building process with stepwise selection (entry $P \leq 0.10$; retaining $P \leq 0.05$). The final model included all predictors selected from at least 1 data set. For each landmark time, we forced baseline variable(s) in the model if the final model(s) included the corresponding change variable. Model fit with imputed data sets was checked using usual model checking procedures, and no assumptions were violated.

We conducted 3 sensitivity analyses. We refined our cirrhosis definition by including only patients with a diagnosis of cirrhosis or its complications and excluding those with a FIB-4 < 1.45 , we

Table 1. Demographic and clinical characteristics of patients with virologically cured HCV and cirrhosis

	Baseline (N = 29,398)	12-mo landmark (N = 26,648)	24-mo landmark (N = 21,600)
Demographics			
Age in yr, mean (SD)	62.78 (5.95)	63.67 (5.91)	64.48 (5.8)
Sex, n (%)			
Male	28,567 (97.17)	25,884 (97.13)	20,952 (97.0)
Female	831 (2.83)	764 (2.87)	648 (3.0)
Race/ethnicity			
White not Hispanic	15,107 (51.39)	13,618 (51.1)	11,084 (51.31)
African American	10,803 (36.75)	9,873 (37.05)	7,966 (36.88)
White Hispanic	1,383 (4.7)	1,264 (4.74)	1,040 (4.81)
Other	727 (2.47)	660 (2.48)	534 (2.47)
Missing	1,378 (4.69)	1,233 (4.63)	976 (4.52)
Clinical characteristics			
HCV genotype			
1a	16,198 (55.1)	14,738 (55.31)	11,948 (55.31)
1a/1b	1,043 (3.55)	950 (3.56)	773 (3.58)
1b	6,393 (21.75)	5,800 (21.77)	4,815 (22.29)
1-unknown subtype	841 (2.86)	781 (2.93)	678 (3.14)
2	2,356 (8.01)	2,116 (7.94)	1,634 (7.56)
3	1806 (6.14)	1,577 (5.92)	1,191 (5.51)
4, 5, or 6	255 (0.87)	235 (0.88)	191 (0.88)
Missing	506 (1.72)	451 (1.69)	370 (1.71)
Previous HCV treatment			
No	18,241 (62.05)	16,447 (61.72)	13,060 (60.46)
Yes	11,157 (37.95)	10,201 (38.28)	8,540 (39.54)
FIB-4			
<1.45	5,859 (19.93)	6,160 (23.12)	5,430 (25.14)
1.45–3.25	12,756 (43.39)	13,300 (49.91)	10,569 (48.93)
>3.25	10,667 (36.28)	6,571 (24.66)	4,568 (21.15)
Missing	116 (0.39)	617 (2.31)	1,033 (4.78)
Cirrhosis duration, mo	76.92 (57.64)	88.45 (57.17)	100.25 (56.17)
Cirrhosis duration, categorical			
<1 yr	4,874 (16.58)	—	—
1 to <2 yr	2,424 (8.25)	4,380 (16.44)	—
2 to <5 yr	5,873 (19.98)	5,800 (21.77)	6,669 (30.88)
≥5 yr	16,227 (55.2)	16,468 (61.8)	14,931 (69.13)
Varices			
No	25,800 (87.76)	24,644 (92.48)	19,522 (90.38)
Yes	3,598 (12.24)	2004 (7.52)	2078 (9.62)
Ascites			
No	27,187 (92.48)	25,735 (96.57)	20,747 (96.05)
Yes	2,211 (7.52)	913 (3.43)	853 (3.95)
Diabetes			
No	16,618 (56.53)	14,667 (55.04)	11,575 (53.59)
Yes	12,780 (43.47)	11,981 (44.96)	10,025 (46.41)

Table 1. (continued)

	Baseline (N = 29,398)	12-mo landmark (N = 26,648)	24-mo landmark (N = 21,600)
Hypertension			
No	3,943 (13.41)	3,102 (11.64)	2,226 (10.31)
Yes	25,455 (86.59)	23,546 (88.36)	19,374 (89.69)
BMI			
<18.5	365 (1.24)	346 (1.3)	283 (1.31)
18.5 to <25	7,683 (26.13)	6,513 (24.44)	4,967 (23)
25 to <30	11,144 (37.91)	9,639 (36.17)	7,528 (34.85)
≥30	10,103 (34.37)	9,501 (35.65)	7,742 (35.84)
Missing	103 (0.35)	649 (2.44)	1,080 (5.0)
Dyslipidemia			
No	14,089 (47.93)	12,808 (48.06)	9,598 (44.44)
Yes	15,309 (52.07)	13,840 (51.94)	12,002 (55.56)
Chronic kidney disease			
No	25,357 (86.25)	22,725 (85.28)	18,410 (85.23)
Yes	4,041 (13.75)	3,923 (14.72)	3,190 (14.77)
COPD			
No	19,541 (66.47)	17,477 (65.58)	14,085 (65.21)
Yes	9,857 (33.53)	9,171 (34.42)	7,515 (34.79)
Heart failure			
No	26,134 (88.9)	23,569 (88.45)	19,127 (88.55)
Yes	3,264 (11.1)	3,079 (11.55)	2,473 (11.45)
Behavioral factors			
Active alcohol use disorder			
No	22,050 (75.01)	19,339 (72.57)	15,511 (71.81)
Yes	3,984 (13.55)	2,675 (10.04)	2,264 (10.48)
Missing	3,364 (11.44)	4,634 (17.39)	3,825 (17.71)
Smoking			
Current	13,484 (45.87)	11,269 (42.29)	8,601 (39.82)
Former	6,721 (22.86)	6,012 (22.56)	5,174 (23.95)
Nonsmoker	3,614 (12.29)	3,253 (12.21)	2,898 (13.42)
Unknown/Missing	5,579 (18.98)	6,114 (22.94)	4,927 (22.81)
Laboratory data (Mean, SD)			
Albumin (g/dL)	3.78 (0.47)	3.8 (0.46)	3.78 (0.45)
Bilirubin (mg/dL)	0.93 (0.65)	0.92 (0.62)	0.92 (0.61)
Sodium (mmol/L)	138.4 (3.03)	138.4 (3.01)	138.4 (2.94)
Creatinine (mg/dL)	1.16 (1.1)	1.21 (1.18)	1.2 (1.11)
Hemoglobin (g/dL)	13.4 (1.85)	13.4 (1.83)	13.4 (1.8)
INR ^a	1.13 (0.26)	1.26 (0.79)	1.25 (0.73)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; FIB-4, fibrosis-4 index; HCV, hepatitis C virus; INR, international normalized ratio. Table also shows evolution of these characteristics over time.

^aThere were 10.5% missing INR at baseline, 38.4% missing at the 12-mo landmark time, and 54.1% missing at the 24-mo landmark time.

tested the robustness of our HCC definition by including patients with only 1 ICD code for HCC, and we examined the effect of BMI after excluding HCCs diagnosed in the first 12 months.

RESULTS

In total, 113,563 patients received DAA treatment between January 1, 2014, and December 31, 2018. We excluded 9,112 without

Table 2. Demographic and clinical characteristics of patients with virologically cured HCV without cirrhosis

	Baseline (N = 63,169)	12 mo (N = 58,639)	24 mo (N = 46,889)
Demographics			
Age in yr, mean (SD)	60.83 (8.12)	61.84 (7.98)	62.8 (7.66)
Sex, n (%)			
Male	60,670 (96.04)	56,314 (96.04)	45,051 (96.08)
Female	2,499 (3.96)	2,325 (3.96)	1,838 (3.92)
Race/ethnicity			
White not Hispanic	32,061 (50.75)	29,712 (50.67)	23,727 (50.6)
African American	25,038 (39.64)	23,298 (39.73)	18,738 (39.96)
White Hispanic	1,886 (2.99)	1,769 (3.02)	1,412 (3.01)
Other	1,381 (2.19)	1,275 (2.17)	990 (2.11)
Missing	2,803 (4.44)	2,585 (4.41)	2,022 (4.31)
Clinical characteristics			
HCV genotype			
1a	34,808 (55.1)	32,310 (55.1)	25,791 (55.0)
1a/1b	1,978 (3.13)	1,827 (3.12)	1,464 (3.12)
1b	13,465 (21.32)	12,612 (21.51)	10,372 (22.12)
1-unknown subtype	1,380 (2.18)	1,283 (2.19)	1,059 (2.26)
2	6,404 (10.14)	5,913 (10.08)	4,606 (9.82)
3	3,432 (5.43)	3,119 (5.32)	2,318 (4.94)
4, 5, or 6	624 (0.99)	580 (0.99)	466 (0.99)
Missing	1,078 (1.71)	995 (1.7)	813 (1.73)
Previous HCV treatment			
No	45,222 (71.59)	41,850 (71.37)	33,101 (70.59)
Yes	17,947 (28.41)	16,789 (28.63)	13,788 (29.41)
FIB-4			
<1.45	32,934 (52.14)	30,560 (52.12)	23,972 (51.12)
1.45–3.25	29,699 (47.02)	24,251 (41.36)	18,338 (39.11)
>3.25	—	1,174 (2.00)	959 (2.05)
Missing	536 (0.85)	2,654 (4.52)	3,620 (7.72)
Diabetes			
No	42,024 (66.53)	37,839 (64.53)	29,370 (62.64)
Yes	21,145 (33.47)	20,800 (35.47)	17,519 (37.36)
Hypertension			
No	11,711 (18.54)	9,547 (16.28)	6,820 (14.54)
Yes	51,458 (81.46)	49,092 (83.72)	40,069 (85.46)
BMI			
<18.5	868 (1.37)	854 (1.46)	676 (1.44)
18.5 to <25	18,501 (29.29)	16,219 (27.66)	12,298 (26.23)
25 to <30	24,539 (38.85)	21,395 (36.49)	16,548 (35.29)
≥30	18,855 (29.85)	17,523 (29.88)	13,776 (29.38)
Missing	406 (0.64)	2,648 (4.52)	3,591 (7.66)
Dyslipidemia			
No	31,059 (49.17)	27,693 (47.23)	20,710 (44.17)
Yes	32,110 (50.83)	30,946 (52.77)	26,179 (55.83)

Table 2. (continued)

	Baseline (N = 63,169)	12 mo (N = 58,639)	24 mo (N = 46,889)
Chronic kidney disease			
No	57,317 (90.74)	52,624 (89.74)	41,710 (88.95)
Yes	5,852 (9.26)	6,015 (10.26)	5,179 (11.05)
COPD			
No	44,974 (71.2)	40,824 (69.62)	32,158 (68.58)
Yes	18,195 (28.8)	17,815 (30.38)	14,731 (31.42)
Heart failure			
No	59,119 (93.59)	54,536 (93.0)	43,478 (92.73)
Yes	4,050 (6.41)	4,103 (7)	3,411 (7.27)
Behavioral factors			
Active alcohol use disorder			
No	46,806 (74.1)	40,947 (69.83)	32,179 (68.63)
Yes	9,098 (14.4)	6,326 (10.79)	5,448 (11.62)
Missing	7,265 (11.5)	11,366 (19.38)	9,262 (19.75)
Smoking			
Current	31,978 (50.62)	26,435 (45.08)	20,095 (42.86)
Former	12,766 (20.21)	11,860 (20.23)	10,409 (22.2)
Nonsmoker	7,132 (11.29)	6,598 (11.25)	5,732 (12.22)
Unknown/Missing	11,293 (17.88)	13,746 (23.44)	10,653 (22.72)
Laboratory data (mean, SD)			
Albumin (g/dL)	3.98 (0.37)	3.98 (0.37)	3.98 (0.36)
Bilirubin (mg/dL)	0.67 (0.37)	0.68 (0.37)	0.67 (0.38)
Sodium (mmol/L)	138.83 (2.84)	138.43 (2.83)	138.86 (2.8)
Creatinine (mg/dL)	1.1 (0.83)	1.14 (0.92)	1.16 (0.92)
Hemoglobin (g/dL)	14.17 (1.69)	14.16 (1.68)	14.11 (1.69)
INR ^a	1.06 (0.25)	1.17 (0.64)	1.21 (0.67)

BMI, body mass index; COPD, chronic obstructive pulmonary disease; FIB-4, fibrosis-4 index; HCV, hepatitis C virus; INR, international normalized ratio. Table also shows evolution of these characteristics over time.

^aThere were 21.9% missing INR at baseline, 64.0% missing at the 12-mo landmark time, and 76.3% missing at the 24-mo landmark time.

known SVR status, 1,919 with previous HCC and 5,034 with previous other cancers, 912 who received liver transplant and 4,019 who did not achieve SVR. Hence, our study cohort included 92,567 patients with SVR without prevalent HCC.

The mean age of the overall cohort at baseline was 61.5 years (SD = 7.55 years), 96.4% were men, 51.0% were White, and 38.7% were African American (see Supplemental Table 1, Supplemental Digital Content 1, <https://links.lww.com/AJG/C658>). A total of 26.5% had cirrhosis diagnosed at baseline and an additional 5.5% had a FIB-4 value greater than 3.25, 36.7% had diabetes, 83.1% had hypertension, 51.2% had dyslipidemia, and 14.1% had an active alcohol use disorder.

Table 1 displays the characteristics of patients with cirrhosis and their evolution over time. At baseline, 43.5% of patients with cirrhosis had diabetes; it increased to 46.4% at the 24-month landmark time. Similarly, the proportion of patients with hypertension increased from 86.6% to 89.7% and dyslipidemia increased from 52.1% to 55.6% between baseline and 24-month landmark time. We found similar trends in patients without cirrhosis (Table 2).

When examining changes in FIB-4 values from baseline to 24 months in patients with FIB-4 available at both periods, 18.6% of patients with cirrhosis remained stable at high risk. In addition, 16.4% of patients had a high-risk FIB-4 at baseline that declined over time. FIB-4 values for few patients (3.5%) were low risk at baseline but increased to high risk. Approximately 61% with cirrhosis had low-risk FIB-4 values both at baseline and 24 months. In patients without cirrhosis where everyone had low FIB-4 at baseline, 97.8% remained stable at low risk and 2.2% increased from low to high risk at 24 months.

Risk of HCC after DAA treatment

There were 3,247 incident cases of HCC diagnosed during mean 2.51 (SD = 1.66) years of follow-up (maximum 7.11 years); 74.0% (n = 2,404) were diagnosed in patients with cirrhosis at baseline. In 29,398 patients with cirrhosis, a cumulative incidence of HCC was 2.0%, 3.8%, and 5.4% at 1, 2, and 3 years, respectively. By contrast, HCC risk was considerably lower in 63,169 patients without cirrhosis in whom 843 were diagnosed

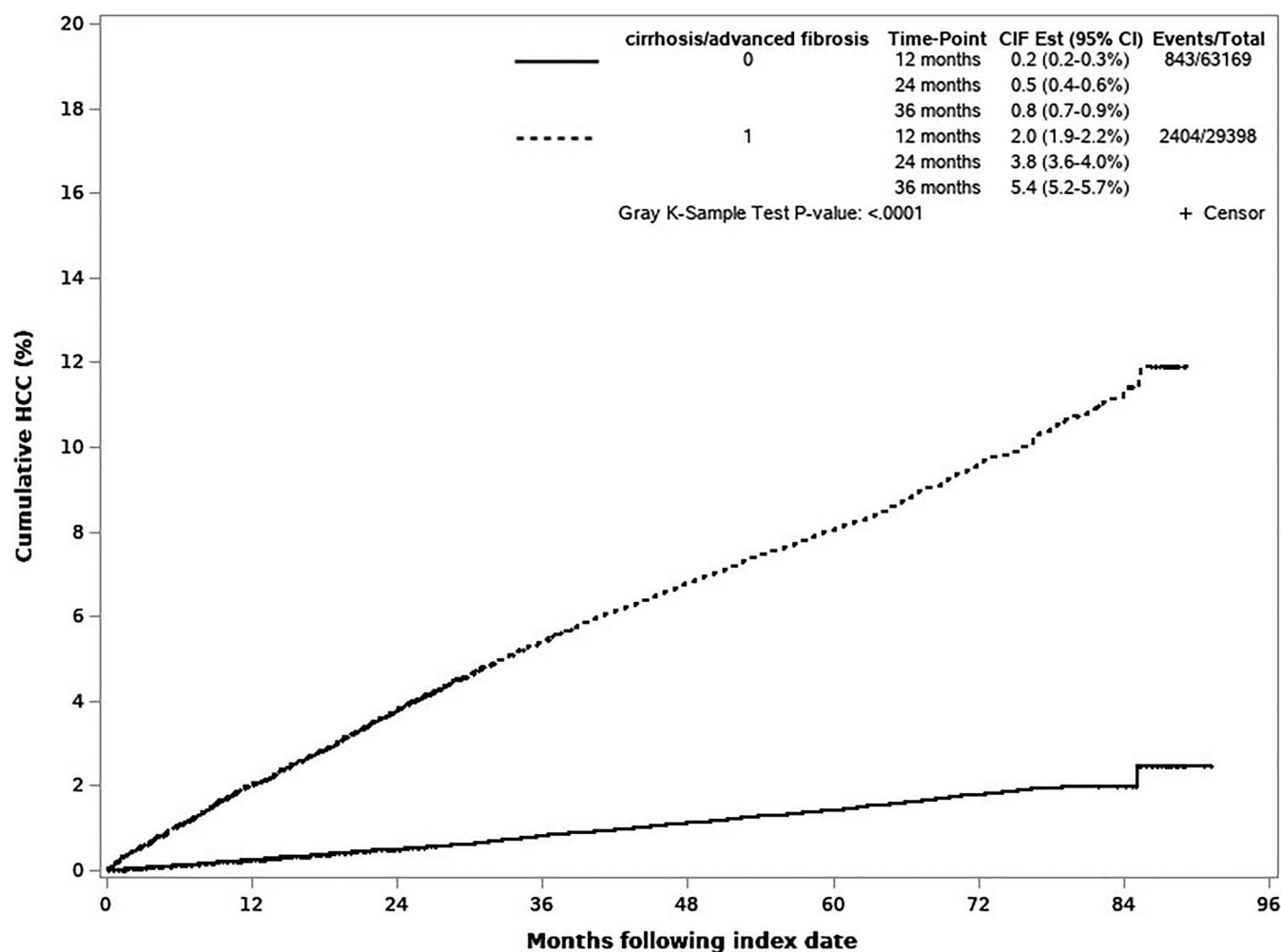


Figure 1. Cumulative incidence of hepatocellular carcinoma in patients with virally cured HCV by baseline cirrhosis status. CI, confidence interval; CIF, cumulative incidence function; HCC, hepatocellular carcinoma; HCV, hepatitis C virus.

with HCC (0.2%, 0.5%, and 0.8%, respectively) ($P < 0.0001$) (Figure 1).

Factors associated with HCC in patients with cirrhosis at baseline

In the baseline model (Table 3), in patients with cirrhosis, the risk of HCC was higher in men (adjusted hazard ratio [HR] = 1.89, 95% confidence interval [CI] = 1.37–2.59) and lower in African American patients (HR = 0.78, 95% CI = 0.71–0.86). Patients with genotype 3 had a higher risk of HCC (HR = 1.47, 95% CI = 1.27–1.71) than those with other genotypes. Patients with a longer duration since cirrhosis diagnosis had a higher risk (≥ 5 vs < 1 year, HR = 1.71, 95% CI = 1.46–2.00). Serum bilirubin, albumin, presence of varices, and higher FIB-4 were associated with HCC risk. Specifically, HCC risk was 2.5-fold higher (95% CI, 2.11–2.94) in patients with cirrhosis who also had FIB-4 > 3.25 than those with FIB-4 values < 1.45 . Patients who were current smokers had an increased risk for HCC than non-smokers (HR = 1.32, 95% CI = 1.16–1.51). None of the pre-specified interaction terms were significant in the adjusted model at baseline.

Longitudinal changes in factors and their associations with HCC in patients with cirrhosis

Most of the associations observed at baseline persisted in direction and magnitude at 12-month and 24-month landmark times, with few notable exceptions. Presence of ascites was associated with an increased risk for HCC at both 12 and 24 months. Changes in serum albumin, bilirubin, and FIB-4 between baseline and landmark times were strongly associated with a subsequent risk of HCC. For example, 1 unit increase in serum bilirubin between baseline and 24-month landmark time was associated with a 22% increase in HCC risk. Compared with patients with persistently low FIB-4 at baseline and 24 months, the risk of HCC was almost 2-fold higher in patients who had persistently high FIB-4 at the time of virological cure and at 24 months (HR = 1.70, 95% CI, 1.45–2.00) and 81% higher in patients who were at low risk (FIB-4 ≤ 3.25) but increased to high risk (FIB-4 > 3.25) at 24 months (HR = 1.81, 95% CI = 1.37–2.38). Results were similar in the sensitivity analyses excluding patients with cirrhosis with FIB-4 < 1.45 and including patients with 1 ICD code for HCC (see Supplemental Tables 4 and 5, Supplemental Digital Content 1, <https://links.lww.com/AJG/C658>).

Table 3. Factors associated with the development of HCC in patients with virologically cured HCV and cirrhosis

Variable	Baseline (N = 29,398)		12 mo (N = 26,648)		24 mo (N = 21,600)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Demographics						
Sex (ref: female)						
Male	1.89 (1.37–2.59)	<0.0001	1.93 (2.79–1.33)	0.0005	1.99 (3.13–1.26)	0.0031
Race/ethnicity (ref: White not Hispanic)						
African American	0.78 (0.71–0.86)	<0.0001	0.83 (0.75–0.93)	0.0017	0.85 (0.74–0.98)	0.0206
White Hispanic	0.89 (0.75–1.07)	0.21	0.89 (0.73–1.10)	0.2781	0.91 (0.71–1.18)	0.4813
Other	1.17 (0.93–1.47)	0.18	1.12 (0.86–1.47)	0.4097	1.33 (0.96–1.84)	0.0865
Clinical characteristics						
HCV genotype (ref: 1a)						
1a/1b	0.93 (0.74–1.16)	0.51	0.89 (0.68–1.16)	0.3915	0.96 (0.70–1.32)	0.7978
1b	1.09 (0.98–1.21)	0.10	1.06 (0.94–1.19)	0.3473	0.97 (0.83–1.12)	0.643
2	0.84 (0.71–0.99)	0.04	0.82 (0.67–1.00)	0.0515	0.78 (0.61–1.00)	0.0466
3	1.47 (1.27–1.71)	<0.0001	1.41 (1.18–1.68)	0.0002	1.35 (1.08–1.69)	0.0087
4, 5, or 6	1.01 (0.63–1.61)	0.97	1.66 (0.97–2.82)	0.2066	1.31 (0.74–2.34)	0.3591
Previous HCV treatment	1.08 (1.00–1.17)	0.06	1.07 (0.97–1.18)	0.1567	1.11 (0.99–1.25)	0.0847
FIB-4 baseline (ref: <1.45)						
1.45–3.25	2.01 (1.71–2.37)	<0.0001	N/A	—	N/A	—
>3.25	2.49 (2.11–2.94)	<0.0001	N/A	—	N/A	—
Change in FIB-4 ^{a,b} (ref: high–high)						
Ref: Low–low						
High–high	N/A	—	1.75 (1.54–1.99)	<.0001	1.70 (1.45–2.00)	<0.0001
High–low	N/A	—	1.17 (1.00–1.36)	0.0456	1.40 (1.19–1.65)	<0.0001
Low–high	N/A	—	1.86 (1.50–2.30)	<.0001	1.81 (1.37–2.38)	<0.0001
Years since cirrhosis diagnosis ^c						
1 to <2 yr	1.41 (1.14–1.74)	0.001	Ref	—	N/A ^d	—
2 to <5 yr	1.47 (1.24–1.74)	<0.0001	1.58 (1.30–1.93)	<0.0001	Ref	—
≥5 yr	1.71 (1.46–2.00)	<0.0001	1.79 (1.49–2.15)	<0.0001	1.34 (1.16–1.55)	<0.0001
Varices	1.73 (1.57–1.91)	<0.0001	1.60 (1.40–1.82)	<0.0001	1.56 (1.34–1.82)	<0.0001
Ascites	NS		1.27 (1.05–1.53)	0.0135	1.33 (1.07–1.66)	0.0106
Baseline albumin, g/dL	0.48 (0.44–0.52)	<0.0001	0.47 (0.41–0.52)	<0.0001	0.49 (0.42–0.57)	<0.0001
Change in albumin ^b , g/dL	N/A	—	0.82 (0.70–0.97)	0.02	0.90 (0.75–1.08)	0.2627
Baseline bilirubin, (log) mg/dL	1.24 (1.15–1.34)	<0.0001	1.30 (1.17–1.45)	<0.0001	1.30 (1.13–1.48)	0.0002
Change in bilirubin ^b , (log) mg/dL	N/A	—	1.20 (1.06–1.36)	0.0033	1.22 (1.06–1.41)	0.0055
Baseline INR ≥2 (ref: <2)	0.83 (0.58–1.18)	0.30	N/A		N/A	—
Baseline sodium, mEq/L	NS	—	0.99 (0.97–1.01)	0.3078	NS	—
Change in sodium ^b , mEq/L	N/A	—	1.01 (0.99–1.03)	0.2883	NS	—
Baseline hemoglobin, g/dL	NS	—	1.03 (1.00–1.07)	0.0745	1.05 (1.00–1.09)	0.0387
Change in hemoglobin ^b , g/dL	N/A	—	1.03 (0.99–1.07)	0.1337	1.04 (1.00–1.09)	0.0715
Behavioral characteristics						
Smoking (ref: nonsmoker)						
Current	1.32 (1.16–1.51)	<0.0001	1.22 (1.05–1.41)	0.0084	1.24 (1.04–1.48)	0.019
Former	1.12 (0.97–1.29)	0.12	1.07 (0.91–1.25)	0.4138	1.08 (0.90–1.31)	0.3891

CI, confidence interval; FIB-4, fibrosis-4 index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; INR, international normalized ratio; N/A, not considered for a model building strategy at given landmark time; NS, not selected through a model building strategy at given landmark time; Ref, reference group.

^aBased on the first date of elevated FIB-4; low–low indicates FIB-4 was <3.25 at both times, high–high indicates FIB-4 was >3.25 at both times, high–low indicates FIB-4 was >3.25 at baseline and <3.25 at the landmark times, and low–high indicates FIB-4 was <3.25 at baseline and increased to >3.25 at the landmark times.

^bChange variables calculated from baseline to 12 mo for the model at the 12-mo landmark time and from baseline to 24 mo for the model at the 24-mo landmark time.

^cReference group for years since cirrhosis diagnosis: Baseline ref: <1 yr; 12 mo ref: 1–<2 yr; 24 mo ref: 2–<5 yr.

^dThis category is not available at the 24-mo landmark time.

Table 4. Factors associated with the development of HCC in patients with virologically cured HCV without cirrhosis at baseline

Variable	Baseline (N = 63,169)		12 mo (N = 58,639)		24 mo (N = 46,889)	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
Clinical characteristics						
HCV genotype (ref: 1a)			NS		NS	
1a/1b	1.13 (0.78–1.63)	0.52	—	—	—	—
1b	1.13 (0.96–1.33)	0.14	—	—	—	—
2	0.81 (0.62–1.06)	0.13	—	—	—	—
3	1.45 (1.09–1.94)	0.01	—	—	—	—
4, 5, or 6	1.14 (0.59–2.21)	0.69	—	—	—	—
Previous HCV treatment	1.32 (1.14–1.52)	0.0001	1.21 (1.03–1.42)	0.02	NS	—
Baseline FIB-4 (ref: <1.45)						
1.45–3.25	2.27 (1.96–2.63)	<0.0001	N/A	—	N/A	—
Change in FIB-4 (ref: low–low) ^a						
Low–high	N/A	—	2.58 (1.82–3.66)	<0.0001	3.12 (2.12–4.60)	<0.0001
Baseline albumin, g/dL	0.64 (0.53–0.76)	<0.0001	0.63 (0.51–0.78)	<0.0001	0.76 (0.58–1.00)	0.05
Change in albumin ^b , g/dL			0.92 (0.70–1.22)	0.57	1.12 (0.82–1.52)	0.47
BMI (ref: 25–<30)						
<18.5	1.93 (1.20–3.12)	0.007	NS	—	NS	—
18.5–<25	1.19 (1.01–1.41)	0.04	NS	—	NS	—
≥30	0.97 (0.82–1.15)	0.75	NS	—	NS	—
Hypertension	1.59 (1.27–1.99)	<0.0001	1.65 (1.26–2.14)	0.0002	1.74 (1.24–2.45)	0.001
Diabetes	1.54 (1.34–1.78)	<0.0001	1.42 (1.22–1.66)	<0.0001	1.47 (1.22–1.76)	<0.0001
Behavioral characteristics						
Smoking (ref: nonsmoker)						
Current	1.46 (1.16–1.84)	0.002	1.22 (0.93–1.61)	0.14	1.24 (0.87–1.76)	0.22
Former	1.24 (0.94–1.63)	0.12	1.20 (0.88–1.63)	0.23	1.18 (0.82–1.69)	0.37

BMI, body mass index; CI, confidence interval; FIB-4, fibrosis-4 index; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; HR, hazard ratio; N/A: not applicable because not considered for a model building strategy at given landmark time; NS, not selected by a model building strategy at given landmark time; Ref, reference group.

^aBased on first date of elevated FIB-4; low–low indicates FIB-4 was <3.25 at both landmark times and low–high indicates FIB-4 was <3.25 at baseline and increased to >3.25 at the landmark times. For the 12-mo period, the change was baseline to 12 mo, and for the 24-mo period, the change was baseline to 24 mo.

^bChange variables calculated from baseline to 12 mo for the model at the 12-mo landmark time and from baseline to 24 mo for the model at the 24-mo landmark time.

Factors associated with HCC in patients without cirrhosis at baseline

In patients without cirrhosis, patients with hypertension and diabetes had a 1.5-fold higher risk of HCC than their counterparts (Table 4). After controlling for diabetes and hypertension, there was no difference in the risk of HCC between patients with BMI higher than 30 compared with BMI 25–30. The risk of HCC was higher in patients with BMI < 25, with the highest risk in patients with BMI < 18.5 compared with BMI 25 to <30 (HR = 1.93, 95% CI = 1.20–3.12). The risk of HCC for BMI < 18.5 was slightly attenuated after excluding patients with HCC in 12 months after the index date (see Supplemental Table 6, Supplemental Digital Content 1, <https://links.lww.com/AJG/C658>).

Baseline serum albumin and FIB-4 were associated with HCC risk. Patients with baseline FIB-4 between 1.45 and 3.25 had a 2.3-fold higher risk of HCC than those with low FIB-4 < 1.45 (HR = 2.27, 95% CI = 1.96–2.63). Previous failure of HCV treatment, HCV genotype 3, and current smoking were also associated with HCC risk in patients without cirrhosis.

Longitudinal changes in factors and their associations with HCC in patients without cirrhosis

Only metabolic traits (diabetes or hypertension) and change in FIB-4 remained associated with HCC risk at all landmark times. At the 24-month landmark time, patients with hypertension and diabetes had a 1.7-fold to 1.5-fold higher risk of HCC than their counterparts. Patients who had an increase of FIB-4 from a low risk at baseline to a high risk at the 24-month landmark time had a 3-fold increase in HCC risk (HR = 3.12, 95% CI, 2.12–4.60).

Cumulative HCC risks in groups based on changes in FIB-4

Figure 2 displays the cumulative incidence rates of HCC in patients with cirrhosis stratified by changes in FIB-4 values between baseline and 24-month landmark. After the 24-month landmark time, the 3-year cumulative incidence of HCC varied from 3.4% (95% CI, 3.1–3.7) in patients who had a persistently low FIB-4 value to 9.2% (95% CI, 8.3–10.2) in patients with a persistently high FIB-4 value. The risk of HCC was low in all subgroups.

Change of FIB-4 from baseline to 24M

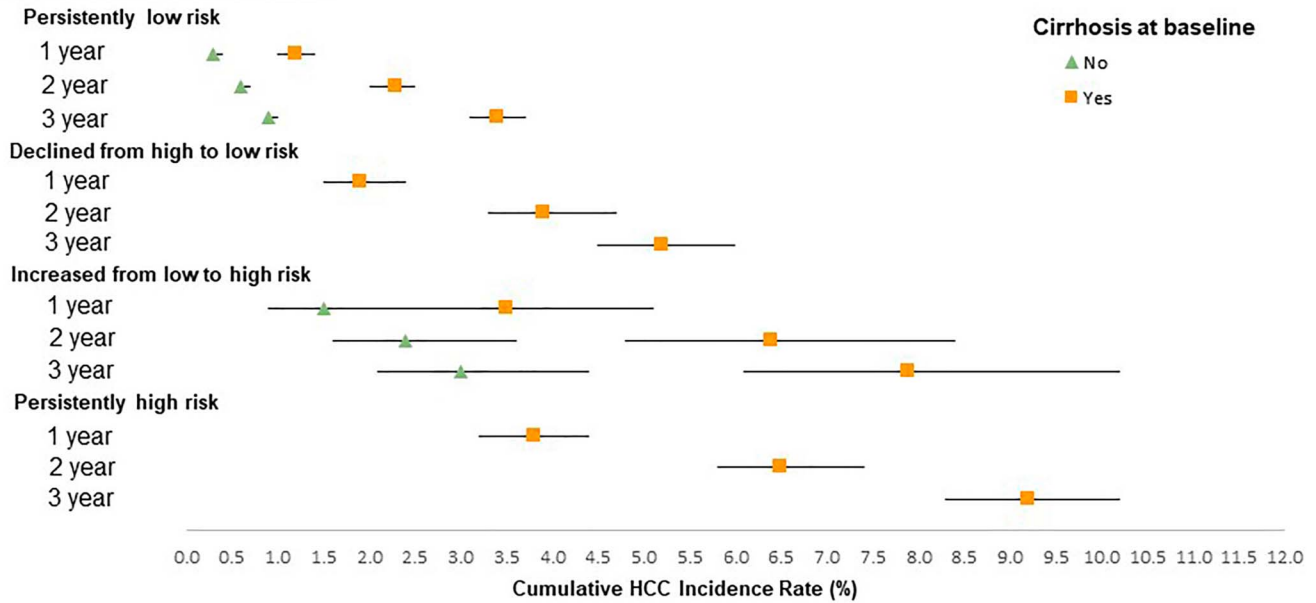


Figure 2. Cumulative incidence rates of hepatocellular carcinoma by various patterns of change of FIB-4 from baseline to 24 months stratified by cirrhosis status. FIB-4, fibrosis-4; HCC, hepatocellular carcinoma.

without cirrhosis, with few notable exceptions. In patients who increased from low to high risk, the 2- and 3-year cumulative incidence of HCC was 2.4% (95% CI, 1.6–3.6) and 3.0% (95% CI, 2.1–4.4), respectively. Cumulative 1-, 2-, and 3-year risks of HCC in 419 patients without cirrhosis who had hypertension, diabetes, and who experienced an increase from low to high risk between baseline and 24-month landmark were 3.1%, 5.7%, and 7.2%, respectively.

DISCUSSION

Our study has 3 key findings.

First, HCC risk factors differed in patients with and without cirrhosis. In patients with cirrhosis, several markers of liver disease severity (cirrhosis duration, albumin, bilirubin, varices, and hemoglobin) were associated with an increased risk of HCC. By contrast, metabolic traits predicted HCC risk in patients without cirrhosis, underscoring the importance of metabolic traits as modifiable targets for risk reduction after virological cure.

Second, changes in several risk factors over time, especially markers of liver fibrosis, could inform risk prediction in patients with virologically cured HCV. A change in FIB-4 scores was associated with incident HCC in patients with and without cirrhosis. These findings were similar to that of Ioannou et al. (14). In our cohort, patients without cirrhosis experienced an increase in FIB-4 over 2 years; two-thirds of these also had diabetes and hypertension suggesting metabolic traits could have played a role in fibrosis progression. A subsequent risk of HCC in this subgroup approached the HCC incidence in patients with cirrhosis. These data are important because in patients with chronic liver diseases, evaluation of the risk of disease progression currently relies only on the most recent risk factor assessment. Our results show that repeat data at a 2-year interval might allow more accurate HCC risk stratification.

Third, our data confirm previous reports that showed that the risk of HCC remains elevated in some groups of patients after SVR (3,14–16). The trends reported here provide support to the

current recommendations about continuing HCC surveillance in virologically cured patients with cirrhosis.

In our cohort, smoking was associated with a higher risk of HCC in patients with cirrhosis. Several constituents of tobacco smoke can promote hepatocarcinogenesis (17–20). We also noted an association between low BMI and high risk of HCC. In a recent study, sarcopenia was associated with an increased risk of developing HCC (21). The exact mechanistic links cannot be explored in this retrospective study but could be related to sarcopenia-associated chronic inflammation, physical inactivity, insulin resistance, and/or vitamin D or zinc deficiency.

Our study has limitations. It was limited to veterans with HCV; however, this cohort represents the largest known HCV-infected cohort in the world with almost complete capture of outcomes. We might have misclassified patients with cirrhosis or HCC. However, we used previously validated algorithms. Fewer than 19.6% of patients with cirrhosis diagnosis at baseline had FIB-4 < 1.45 and excluding these patients in a sensitivity analysis did not affect the results. FIB-4 was missing in 0.7%–6.8% of patients at different landmark times; there were some differences in these patients, but they were small and clinically inconsequential, rendering selection bias less likely (see Supplementary Table 3, Supplemental Digital Content 1, <https://links.lww.com/AJG/C658>). We might have missed HCCs in early stages or HCC diagnosed outside of the VA healthcare system. However, this is unlikely to bias our results because our outcome of interest was any incident HCC (and not early HCC *per se*) and most early HCC progress to advanced stages within a relatively short course of time. Expanding HCC definition to include those with just 1 ICD code did not change study findings.

In conclusion, our study provides evidence from a well-characterized cohort of virologically cured patients with HCV but free of cirrhosis that monitoring changes in FIB-4 might have clinical utility, especially in patients with coexisting diabetes and

hypertension. In patients with cirrhosis, evolution of FIB-4 and other select markers of liver disease severity could refine risk stratification. We believe risk assessment based on repeat measurements at 2 years is practical and can improve shared decision-making between patients and their physicians by providing a quantifiable personalized HCC risk assessment, including how it changes over time.

CONFLICTS OF INTEREST

Guarantor of the article: Fasiha Kanwal, MD, MSHS.

Specific author contributions: J.R.K.: study concept and design, acquisition of data, interpretation of data, drafting and critical revision of the manuscript for important intellectual content, and study supervision. Y.C.: acquisition of data, analysis of data, interpretation of data, and critical revision of the manuscript for important intellectual content. L.L.: analysis of data, interpretation of data, and critical revision of the manuscript for important intellectual content. D.S.: acquisition of data, interpretation of data, and critical revision of the manuscript for important intellectual content. J.C. and H.E.-S.: study concept and design, interpretation of data, and critical revision of the manuscript for important intellectual content. F.K.: study concept and design, acquisition of data, interpretation of data, drafting and critical revision of the manuscript for important intellectual content, and study supervision.

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Study Highlights

WHAT IS KNOWN

- ✓ Hepatitis C virus (HCV) infection is the leading risk factor for hepatocellular carcinoma (HCC).
- ✓ Risk for HCC remains in patients with cured chronic HCV infection.

WHAT IS NEW HERE

- ✓ Risk factors for HCC differed in patients with and without cirrhosis.
- ✓ Longitudinal changes of risk factors over time, especially markers of liver fibrosis, were important predictors of HCC risk.
- ✓ These factors can help with risk stratification and HCC surveillance decisions in patients with cured HCV.

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Assessment of Incidence of and Surveillance Burden for Hepatocellular Carcinoma Among Patients With Hepatitis C in the Era of Direct-Acting Antiviral Agents

Qiushi Chen, PhD; Turgay Ayer, PhD; Madeline G. Adey, MPH; Xiaojie Wang, MS; Fasiha Kanwal, MD, MSHS; Jagpreet Chhatwal, PhD

Abstract

IMPORTANCE In the US, hepatocellular carcinoma (HCC), primarily associated with hepatitis C virus (HCV) infection, is the fastest rising cause of cancer-related death. Wider use of highly effective direct-acting antiviral agents (DAAs) substantially reduces the burden of chronic HCV infection, but the subsequent impacts with HCV-associated HCC remain unknown.

OBJECTIVE To assess projected changes in the incidence rate of and surveillance burden for HCC in the era of DAA treatment for HCV.

DESIGN, SETTING, AND PARTICIPANTS This decision analytical model study was performed from January 2019 to February 2020, using an individual-level state-transition simulation model to simulate disease progression, screening, and different waves of antiviral treatments for HCV in the US from 2012 to 2040.

INTERVENTIONS Current clinical management for chronic HCV infection.

MAIN OUTCOMES AND MEASURES Model outcomes were projected temporal trends and age distribution of incident HCC cases and candidates for HCC surveillance among patients with viremia and patients with virologically cured HCV.

RESULTS The simulation model projected that the annual incidence of HCC among patients with viremia and patients with virologically cured HCV will continue increasing to 24 000 (95% uncertainty interval [UI], 18 000-31 000) cases until 2021. In patients with virologically cured HCV, incident HCC cases are projected to increase from 1000 (95% UI, 500-2100) in 2012 to the peak of 7000 (95% UI, 5000-9600) in 2031 with a subsequent decrease to 6000 (95% UI, 4300-8300) by 2040. The proportion of incident HCC cases that occur in individuals with virologically cured HCV is estimated to increase from 5.3% in 2012 to 45.8% in 2040. The number of candidates for HCC surveillance in the population with virologically cured HCV is projected to increase from 106 000 (95% UI, 70 000-178 000) in 2012 to the peak of 649 000 (95% UI, 512 000-824 000) in 2030 and decrease to 539 000 (95% UI, 421 000-687 000) by 2040, while the proportion of all candidates for surveillance who are virologically cured is estimated to increase from 8.5% to 64.6% during the same period. The average age of HCC incidence and surveillance candidates is estimated to increase from 55 in 2012 to 72 and 71, respectively, by 2040.

CONCLUSIONS AND RELEVANCE The results of this study suggest that the burden of HCC will shift from patients with viremia to patients with virologically cured HCV, and to older populations. Appropriate management may be warranted for early detection of HCC in patients who may no longer be receiving specialty care for liver conditions.

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Key Points

Question What are the projected changes in incidence of and surveillance burden for hepatocellular carcinoma (HCC) among populations with hepatitis C virus (HCV) in the era of direct-acting antiviral agents (DAAs)?

Findings In this decision-analytical model, the incidence of HCC associated with HCV and candidates for HCC surveillance were projected to increase before starting to decrease in the era of DAAs. The burden of HCC associated with HCV was projected to shift from patients with viremia to individuals with virologically cured HCV and to older individuals.

Meaning Results of this study suggest that routine HCC surveillance is needed for early detection of HCC in individuals with virologically cured hepatitis C who may no longer be receiving specialty care of liver diseases.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

Introduction

Hepatocellular carcinoma (HCC) is the fastest rising cause of cancer-related mortality in the US.^{1,2} The incidence of HCC has increased over the last 2 decades owing to the hepatitis C virus (HCV) epidemic.³ Most HCC cases are diagnosed in advanced stages, with a median survival less than 1 year.⁴ Regular surveillance for HCC may help improve early cancer detection rates when curative treatment can be applied and is recommended in patients with HCV-associated cirrhosis.⁵⁻⁷

The availability of direct-acting antiviral agents (DAAs) for HCV treatment has substantially altered the landscape of HCV. Though new DAA regimens can result in a virological cure (ie, sustained virological response [SVR]) in more than 90% of patients with HCV,⁸ many patients remain at risk of developing HCC after virological cure.^{9,10} Current clinical guidelines recommend that patients with virologically cured HCV with cirrhosis (or advanced fibrosis) to undergo routine HCC surveillance every 6 months.^{11,12}

Though the incidence rate of HCC in patients with virologically cured HCV is lower than that in patients with viremia, the absolute number of patients with virologically cured HCV requiring routine HCC surveillance is estimated to increase in the next decade.¹³ Patients with virologically cured HCV may experience improvement in liver function and hence live longer and could undergo surveillance for several years. In contrast, most patients with virologically cured HCV, despite being at risk for HCC, may not undergo routine HCC surveillance because of the perceived lower risk. Previous studies have reported that HCC surveillance rates are much lower in patients receiving primary care vs patients receiving specialty care.^{14,15} Thus, identifying HCC cases through surveillance in this cohort could be more challenging than that in other individuals at risk.

Estimating the burden of HCC surveillance in the cohorts of patients with virologically cured HCV may help guide primary and specialty care providers. The objective of this study was to evaluate the burden of HCC surveillance in the era of new HCV antiviral treatments by projecting the number and the characteristics of new HCC incident cases and candidates for routine HCC surveillance.

Methods

We used a previously developed mathematical model, Hepatitis C Disease Burden Simulation model (HEP-SIM),^{8,16} to simulate the population with HCV who would be considered candidates for HCC surveillance in the era of DAAs in the US. The HEP-SIM is an individual-level state-transition model that simulates the changing landscape of HCV by replicating disease progression, screening for HCV, different waves of antiviral treatments for HCV, and insurance coverage from 2001 to 2040. The model was previously validated with results of the National Health and Nutrition Examination Survey (NHANES) 2003-2010,¹⁷ reports from the Centers for Disease Control and Prevention,¹⁸ and natural history results from a long-term follow-up study of patients with advanced fibrosis.¹⁹ In this study, we projected temporal trends in HCC incidence and the changing characteristics of the number of patients with HCV (patients with viremia and patients with virologically cured HCV) who will be candidates for routine HCC surveillance in the era of DAAs. All data used in this analysis were publicly available and this study thus did not require approval from an institutional review board. This study followed the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) reporting guideline for decision analytical model studies. We describe the major model components; further model details can be found elsewhere.¹⁶

Population Characteristics and Natural History

The population in the HEP-SIM model represented patients with HCV in the US. The population included the NHANES population and the non-NHANES population, including incarcerated (in prisons), homeless, active-duty military, and nursing home populations. Patient HCV genotypes, liver disease states, awareness rate, and age distribution were estimated from published studies and other sources (eTable 1 and eTable 2 in the [Supplement](#)). New incidence of HCV infections was based on

the Centers for Disease Control and Prevention–reported estimates for the years 2006 to 2015 (eTable 3 in the [Supplement](#)), and we assumed that the annual incidence would change at the average rate observed during 2006 to 2015 until 2026 and then become constant.

We simulated the natural history of HCV, which was defined by different stages of liver disease, with chronic HCV infection defined using METAVIR fibrosis scores (F0, no fibrosis; F1, portal fibrosis without septa; F3, numerous septa without fibrosis; and F4, cirrhosis), decompensated cirrhosis, HCC, liver transplant, and liver-related death. Rates of fibrosis progression and decompensation were estimated from published metaregression analysis and observational studies²⁰⁻²² (eTable 4 in the [Supplement](#)). Patients with decompensated cirrhosis or with HCC had higher mortality rates²³ and were eligible to for liver transplant.²⁴⁻²⁶

Screening and Treatment for Patients With HCV in the DAA Era

To accurately represent the HCV disease burden that would subsequently affect the burden of HCC, we simulated the clinical management of HCV, ie, screening and treatment, from 2001 to 2040. In each year, patients with HCV could be diagnosed through usual care, which included risk-based screening (eTable 5 in the [Supplement](#)). Since 2013, we implemented one-time birth-cohort screening for individuals born between 1945 and 1965 among the NHANES, nursing home, and homeless populations in addition to the diagnosis through usual care. From 2020 to projections to 2040, we included one-time universal screening of all adults between aged 18 to 79 years, following the updated screening recommendation by the US Preventive Services Task Force.²⁷ For universal screening, we assumed the screening rate of 9% per year, which is the rate observed in the one-time birth-cohort screening policy.^{28,29}

For HCV treatment, we modeled multiple waves of antiviral treatments available in the US during different periods.¹⁶ The market share of different types of treatment regimens for each HCV genotype was estimated using commercial claims from research organizations (QuintilesIMS and Ipsos) (eTable 6 in the [Supplement](#)). Treatment efficacy measured as SVR rate was dependent on the regimen type, individual HCV genotype, presence of cirrhosis, and failure of previous treatment if any, which were estimated based on data from multiple clinical trials and real-world studies (eTable 7 in the [Supplement](#)). For all populations except individuals who were incarcerated or homeless, the number of patients receiving treatment in each year was estimated based on published data and drug sales until 2016 (eTable 8 in the [Supplement](#)). In the individuals who were incarcerated and homeless, treatment uptake was 1% per year from 2010 to 2016 and 5% per year starting in 2017.³⁰ Our model did not consider treatment for patients with decompensated cirrhosis. With limited treatment capacity, priorities were given to patients with bridging fibrosis (F3) or compensated cirrhosis. Patients whose previous treatment failed may be eligible for retreatment, depending on his previous regimen, new available regimen, and presence of cirrhosis (eTable 7 in the [Supplement](#)).¹⁶

HCC Incidence

Patients with HCV having bridging fibrosis (F3), compensated, and decompensated cirrhosis were at risks of developing HCC.^{9,10,22} The HCC risk in patients with virologically cured HCV was lower than in patients with viremia (eTable 4 in the [Supplement](#)).⁹ Patients with compensated cirrhosis could progress to decompensated cirrhosis even after achieving virological cure of HCV and they remained at risk of developing HCC.³¹ We assumed a lower risk of HCC in patients with decompensated cirrhosis with virologically cured HCV than in those with viremia based on a prospective cohort study.³²

Subpopulations

We considered different subpopulations in the HEP-SIM model (eTable 9 in the [Supplement](#)) based primarily on their health insurance status. We assumed that for the NHANES and nursing home populations, all patients aged 65 years and older were covered by Medicare, and patients aged less than 65 years were covered by private (49.8%), Medicaid (9.2%), or other public insurance (14.3%),

or were uninsured (26.7%) based on NHANES data.^{13,28,33} For the population of individuals who were homeless, the insurance distribution was estimated from a 2012 study (3.2% privately insured, 31.5% Medicaid, 65.3% uninsured).³⁴ We incorporated insurance expansion during the period from 2014 to 2017 owing to the implementation of the Affordable Care Act (eTable 10 in the [Supplement](#)). We also include patients who were incarcerated as a separate population because this population represents a substantial group of viremic infections that were not accounted for in NHANES data.³⁵

Model Outcomes

Our primary model outcome was the number of patients who developed HCC and the number of patients who were candidates for routine HCC surveillance from 2012 to 2040. Candidates for HCC surveillance were defined as patients with F3 fibrosis stage, or compensated cirrhosis, with or without virological cure. In addition, we assumed that 15% (range, 5%-25%) of patients with compensated cirrhosis (eligible for liver transplant) were candidates for HCC surveillance.^{36,37} We further stratified the number of candidates for HCC surveillance by viremia status (ie, with viremia or virologically cured HCV), cirrhosis, and subpopulation category. We also projected the age distribution of HCC incident cases and surveillance candidates for each year. To account for model uncertainty in parameters, we conducted probabilistic sensitivity analysis by sampling model inputs from the recommended statistical distributions³⁸ (eTable 11 in the [Supplement](#)). We evaluated model outputs for sampled parameters by 2000 iterations and presented the 95% uncertainty intervals (UIs) for model outcomes. The simulation model was developed in C++ programming language and all statistical analysis was performed in R version 3.6.0 (R Project for Statistical Computing).

Results

HCC Incidence

This decision analytical model study was conducted from January 2019 to February 2020. In 2012, the annual incidence of HCC among patients with HCV (with viremia and virologically cured HCV) was 18 000 (95% UI, 11 000-32 000). The annual incidence of HCV-associated HCC is projected to increase to 24 000 (95% UI, 18 000-31 000) cases in 2021 and decrease to 13 000 (95% UI, 11 000-16 000) cases by 2040 (**Figure 1**). In 2012, 1000 (95% UI, 500-2100) new HCC cases (5.3% of all new cases) developed in patients with virologically cured HCV; this number is projected to peak at 7000 (95% UI, 5000-9600) new cases (35.0% of all new cases) in 2031 and then decrease to 6000 (95% UI, 4300-8300) new cases (45.8% of all new cases) by 2040. Most of the HCC cases would develop in patients with cirrhosis. The number of new HCC cases among patients with cirrhosis who achieved virological cure increased substantially from 700 (95% UI, 300-1700) in 2012 to 4500 (95% UI, 3000-6700) in 2040 (eFigure 1 in the [Supplement](#)).

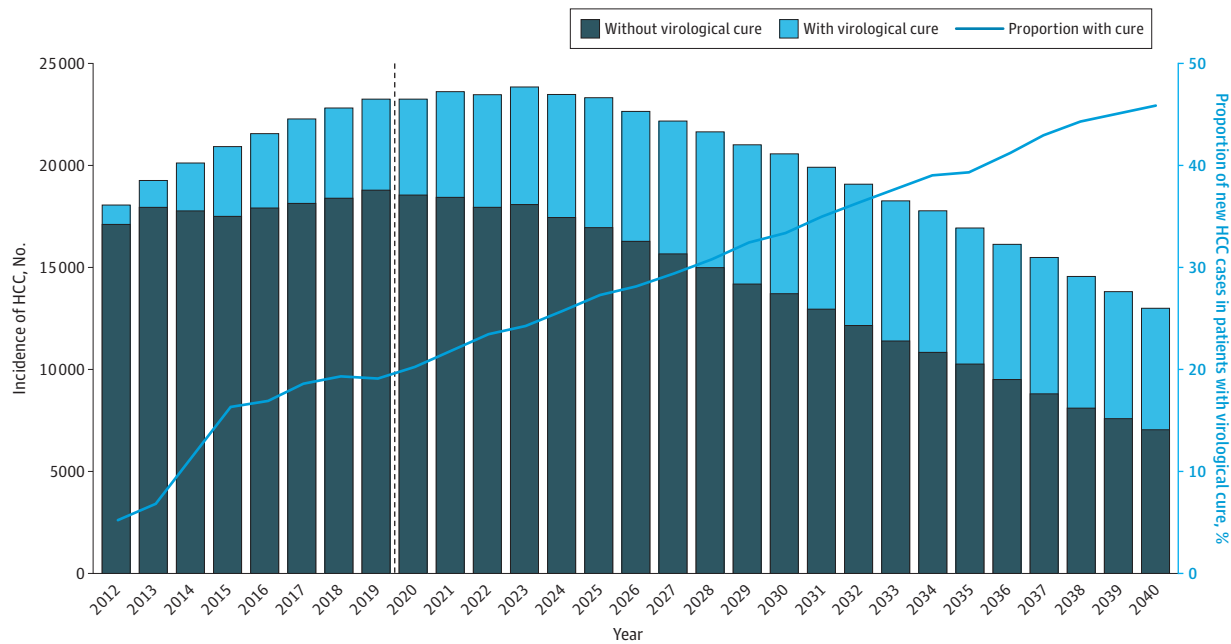
We estimated that between 2012 and 2040, the cumulative incidence of HCV-associated HCC would be 583 000 cases (95% UI, 458 000 cases to 738 000 cases), and 27.1% (95% UI, 20.3%-34.7%) of these cases would develop among patients with virologically cured HCV. The 95% UIs for the annual HCC incidence by virologically cured status in each year are presented in eFigure 2 in the [Supplement](#).

HCC Surveillance Candidates

Our model projected that in 2012, a total of 1.24 million (95% UI, 0.96 million-1.71 million) patients with HCV (with viremia and virologically cured HCV) were at risk of developing HCC and would be candidates for routine HCC surveillance in the US. The number of candidates eligible for HCC surveillance is estimated to increase to 1.49 million (95% UI, 1.23 million to 1.85 million) in 2020 and then gradually decrease to 0.83 million (95% UI, 0.66 million to 1.04 million) by the end of 2040 (**Figure 2**). In 2012, 106 000 (95% UI, 70 000-178 000) surveillance candidates were those who had achieved virological cure; this number is projected to peak at 649 000 (95% UI, 512 000-824 000) in 2030 and then decrease to 539 000 (95% UI, 421 000-687 000) individuals

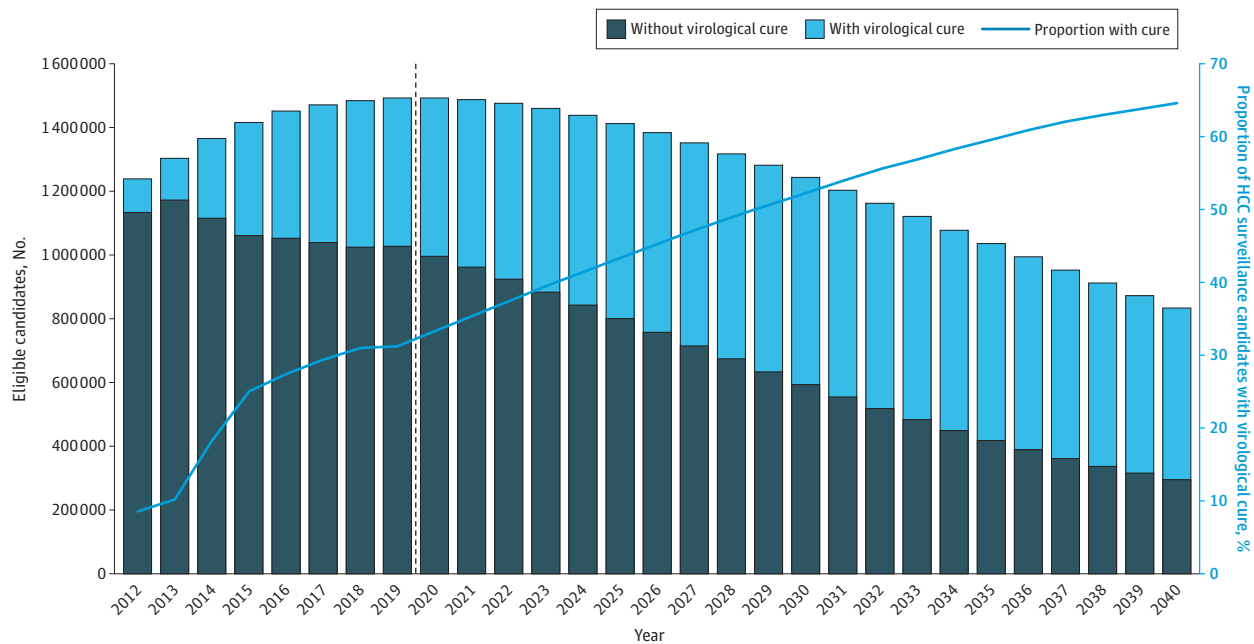
by 2040. However, the proportion of all HCC surveillance candidates who are virologically cured is estimated to increase from 8.5% in 2012 to 64.6% in 2040. We also projected that the proportion of surveillance candidates with cirrhosis (compensated and decompensated) is estimated to increase from 42.8% in 2012 to 49.6% in 2040, and that the proportion of patients with cirrhosis among

Figure 1. Projection of Annual Hepatocellular Carcinoma (HCC) Incidence by Cure Status From 2012 to 2040



The dashed line represents the starting year of the universal hepatitis C virus screening in US adults.

Figure 2. Projection of Number of Candidates for Hepatocellular Carcinoma (HCC) Surveillance by Cure Status From 2012 to 2040



The dashed line represents the starting year of the universal hepatitis C virus screening in US adults.

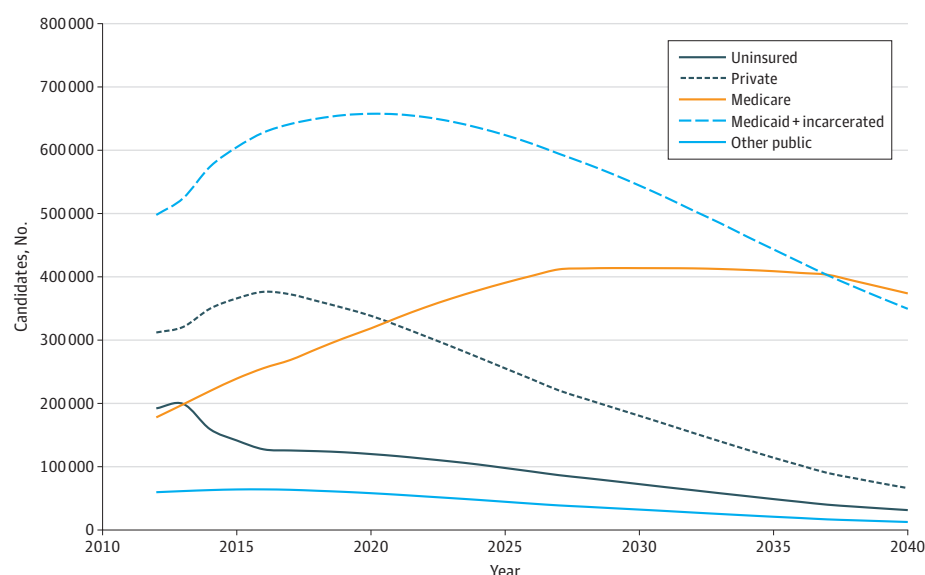
patients with virologically cured HCV is estimated to increase from 34.5% to 43.5% in the same time period (eFigure 3 in the [Supplement](#)).

We further analyzed HCC surveillance candidates by subpopulation (**Figure 3**). In 2012, 312 000 (95% UI, 225 000-443 000) patients (25.2%) who were candidates for HCC surveillance were covered by private insurance, 178 000 (95% UI, 111 000-274 000) patients (14.4%) by Medicare, 498 000 (95% UI, 390 000-679 000) patients (40.2%) and by state-administered programs (including Medicaid and the population incarcerated in state prisons), 60 000 (95% UI, 44 000-85 000) patients (4.8%) by other public insurance, and 192 000 (95% UI, 144 000-265 000) patients (15.5%) were uninsured. The number of HCC surveillance candidates increased in the privately insured pool to 376 000 (95% UI, 277 000-509 000) patients (25.9%) by 2016 and decreased in the uninsured pool to 127 000 (95% UI, 96 000-168 000) patients (8.8%) because of the implementation of the Affordable Care Act in 2014. The number of HCC surveillance candidates covered by Medicare increased further because of the aging population of patients with HCV (with viremia and virologically cured HCV) and is expected to surpass the number of candidates who are privately insured from 2021 to 2040 (Figure 3). Among all payers, the state-administered programs (Medicaid and state prisons) is estimated to have the highest burden of HCC surveillance: the number of HCC surveillance candidates incarcerated in state prisons or covered by Medicaid is projected to peak at 658 000 (95% UI, 557 000-786 000) in 2020 and decrease to 349 000 (95% UI, 280 000-427 000) by the end of 2040.

Aging of HCC Population

The average age of HCC incidence is projected to increase from 55 in 2012 and to 72 in 2040 (eFigure 4 in the [Supplement](#)). The proportion of incident HCC cases older than age of 65 years is projected to increase from 16.4% in 2012 to 76.5% in 2040 (**Figure 4**). Similarly, the average age of surveillance candidates is projected to increase from 55 years in 2012 to 71 years in 2040. The proportion of surveillance candidates aged 65 years and older is projected to increase from 16.1% in 2012 to 73.8% in 2040.

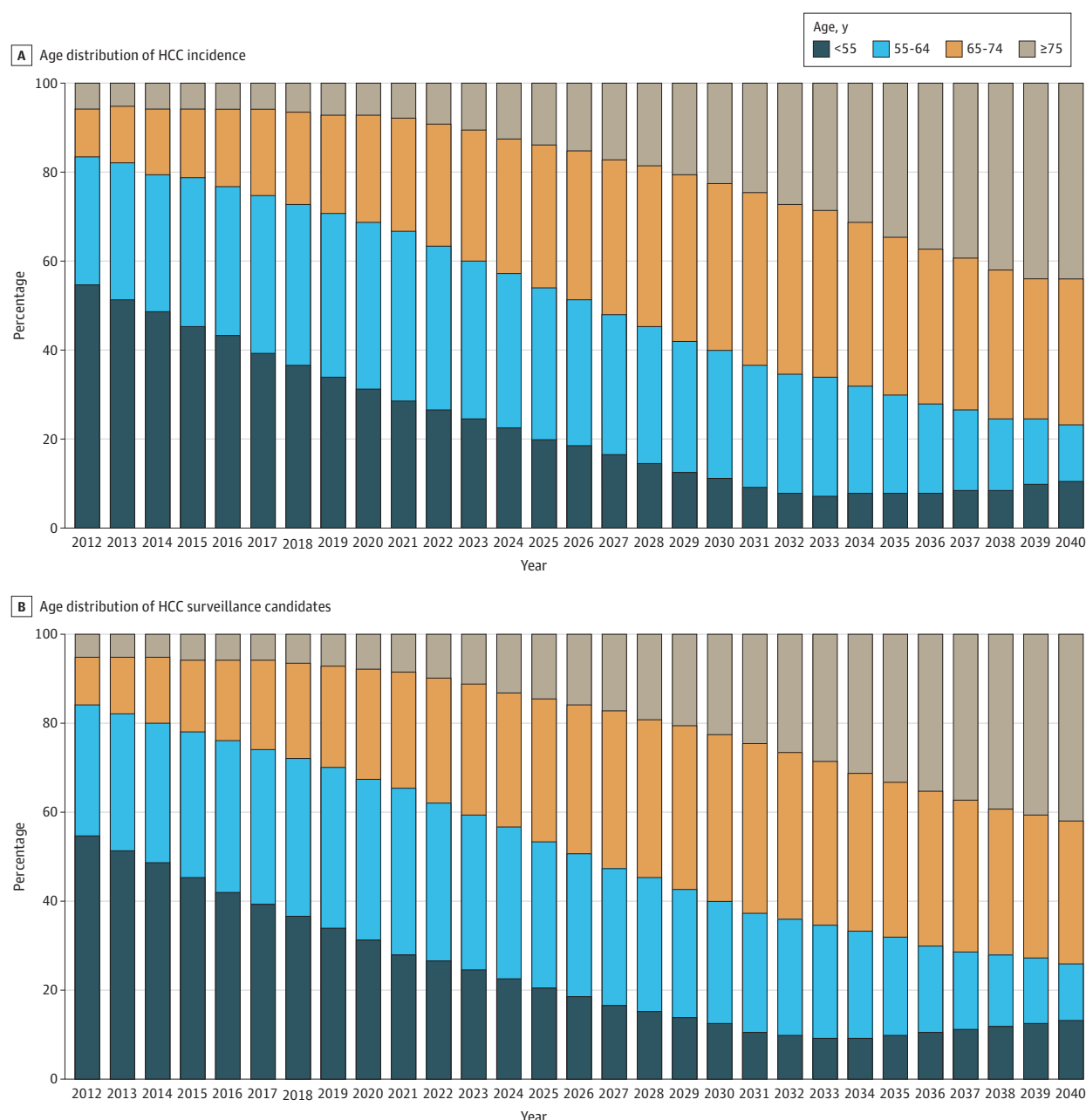
Figure 3. Number of Candidates for Hepatocellular Carcinoma Surveillance by Insurance Subgroup From 2012 to 2040



Discussion

The incidence of HCC has increased over the last 2 decades primarily because of the chronic HCV.³ With the availability and wider use of new DAAs for HCV treatment, the burden of HCC and routine HCC surveillance attributable to HCV could change in the era of DAAs. In this modeling study, we found that the incidence of HCC is estimated to continue to increase until 2021. Between 2012 and 2040, 583 000 patients with HCV (with viremia and virologically cured HCV) were estimated to develop HCC, and 27% of those cases would be among patients with virologically cured HCV. The number of candidates eligible for HCC surveillance is estimated to increase from 1.24 million in 2012 to 1.49 million in 2020, while the burden of surveillance is expected to shift from patients with viremia to individuals who achieved virological cure. In 2012, 9% of all candidates for HCV

Figure 4. Age Distribution of HCC Incidence and HCC Surveillance Candidates From 2012 to 2040



surveillance were virologically cured, which is projected to increase to 65% by 2040. The average age of HCC incidence and surveillance candidates is also projected to shift from 55 years in 2012 to more than 70 years in 2040.

Our study provides insights on the trends in HCC in the DAA era. Some studies³⁹⁻⁴¹ conducted statistical analysis based on cancer registry data predominately in the pre-DAA era. The forecasted incidence was based on historical trends without factoring in the changes in the management of HCV.^{39,42} Thus those findings may not be applicable to the DAA era. While other studies that used DAA-era data reported that the burden of HCC will decrease in the era of DAAs,^{8,13,43} those studies excluded patients with HCV who were incarcerated, homeless, and residing in nursing homes, and were active-duty military personnel. Our study accounted for such populations with less access to screening and treatment for HCV than the general population, and we found that the overall HCC incidence in the population with HCV will continue to increase until 2021 despite the recent availability of highly effective DAAs.

Our study also provides information on the shifting burden of surveillance for HCC and the need to emphasize the clinical treatment for patients with virologically cured HCV. Despite virological cure, patients with advanced fibrosis or cirrhosis will remain at risk of developing HCC. Therefore, as the number of patients with virologically cured HCV increases, the new cases of HCC from this cohort will increase. In addition, the burden of surveillance for HCC will shift from patients with viremia to patients with virologically cured HCV. These changes may have substantial practical implications for the continuum of care. Most of the patients with virologically cured HCV will transition from receiving care from liver specialists to receiving care from primary care physicians. However, most people do not receive regular surveillance in primary care settings⁴⁴ and the knowledge of HCC surveillance in primary care settings remains low.⁴⁵ Therefore, it is vital to emphasize that biannual HCC surveillance is warranted for these patients in primary care settings.

The optimal clinical management of patients with virologically cured HCV remains unclear. While the HCC management guidelines by the European Association for the Study of the Liver recommends routine HCC surveillance in patients with virologically cured HCV having advanced fibrosis and cirrhosis,⁷ the guideline by the American Association for the Study of Liver Diseases recommends routine HCC surveillance only in individuals with cirrhosis without specifying the status of virological cure.⁶

The optimal surveillance strategy in patients with virologically cured HCV will rely on more evidence and studies in the following 3 aspects. First, long-term data are needed for a better understanding of the risk of HCC after DAA-induced virological cure in patients with HCV. It is unclear how much of the current knowledge of the HCC risk among patients with virologically cured HCV from an interferon-based regimen could be used to inform surveillance policies in the era of DAAs. Some studies suggest that patients with HCV cured by DAA regimens could have higher HCC risks than those with HCV cured by interferon-based regimens,^{9,10,46} but the increase was not found to be significant after adjusting for confounders,⁴⁷ and the difference was not found to be conclusive.⁴⁸ In addition, compared with the available data in the interferon-based treatment era, the observations in DAA era are subject to shorter follow-up time and present an older at-risk population.

Second, health economic data are needed to identify cost-effective HCC surveillance policies for patients with virologically cured HCV. The primary reason for not recommending routine surveillance in patients with virologically cured HCV with advanced fibrosis may be that biannual surveillance using ultrasonography and α_1 -fetoprotein testing for the lifetime was not found to be cost-effective in this cohort.^{49,50} Instead of a general surveillance, further research is warranted to identify risk-based surveillance in these patients that could provide a good use of limited resources.⁵⁰ In addition, the optimal age for stopping surveillance is unknown. It is plausible that patients with virologically cured HCV may not need HCC surveillance throughout their remaining lifetime.

Third, tailoring surveillance policies to individual-level factors may be a useful approach, especially as emerging molecular biomarkers show their value in the prediction of HCC risks in addition to current clinical risk factors.⁵¹ Comprehensive risk prediction models can be developed by

integrating multilevel risk factors to further refine the risk predictions.⁵² A tailored surveillance strategy could differentiate the patients at high risk who can benefit more from surveillance compared with the others, and thus further improve the cost-effectiveness and efficiency of medical resource use.^{53,54}

Like any modeling study, our model projection results are subject to inherent uncertainty that arises from the uncertainties in model parameter estimates and model assumptions. Some model parameters and assumptions cannot capture all possible disease variability and diverse real-world clinical practice. Therefore, instead of presenting the prediction of outcomes, our model projection results provide insights on the overall trends of the HCC incidence and surveillance burden, which has also been shown to be robust in the presence of model uncertainty from our sensitivity analysis.

Limitations

This study has limitations. First, we did not explicitly model HCC diagnosis process, which depends on incidence, underlying surveillance strategies, and testing accuracy. We considered HCC as an aggregate health state and used aggregate-level parameters for the population to characterize the overall burden of HCC. Further details would be necessary for analyzing the outcomes of particular HCC surveillance and treatment strategies. Second, our analysis was limited to HCV-associated HCC and did not account for other emerging risk factors such as metabolic disorder (eg, diabetes, nonalcoholic fatty liver disease), hepatitis B, and alcohol consumption. Management of HCC in these other populations at increased risk is becoming increasingly important but would require modeling of different disease factors, which is beyond the scope of this study. In addition, our model did not account for fibrosis regression following successful DAA treatment. Based on recent studies that suggested stable HCC risks following SVR in patients including those with improved noninvasive markers for fibrosis,^{55,56} we assumed that patients would still be candidates for HCC surveillance even if they had fibrosis regression. However, it is possible that the risk of HCC could decrease with fibrosis regression as time from SVR accrues; therefore, our study may have overestimated the burden of HCC surveillance.

Conclusions

This decision analytical model study suggests that the new cases of HCC associated with HCV will continue to increase even in the era of DAAs. We also found that the risk of HCC as well as the burden of HCC surveillance is projected to shift from patients with active HCV to those who had achieved virological cure. Routine HCC surveillance in patients with virologically cured HCV who remain at risk of HCC may help reduce the burden of HCC in the era of new antiviral agents.

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Corresponding Author: Jagpreet Chhatwal, PhD, Massachusetts General Hospital Institute for Technology Assessment, 101 Merrimac St, 10th Floor, Boston, MA 02114 (jagchhatwal@mgh.harvard.edu).

Author Affiliations: Institute for Technology Assessment, Massachusetts General Hospital, Harvard Medical School, Boston (Chen, Adeo, Chhatwal); Harold and Inge Marcus Department of Industrial and Manufacturing Engineering, Pennsylvania State University, University Park (Chen); H. Milton Stewart School of Industrial and Systems Engineering, Georgia Institute of Technology, Atlanta (Ayer, Wang); Department of Medicine, Baylor College of Medicine, Houston, Texas (Kanwal); Houston Veterans Affairs Health Services Research and Development Center of Excellence, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas (Kanwal).

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Acquisition, analysis, or interpretation of data: All authors.

Drafting of the manuscript: Chen, Ayer, Adey, Kanwal, Chhatwal.

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Statistical analysis: Chen.

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SUPPLEMENT.

eTable 1. Population Characteristics of Hepatitis C Patients in the United States

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eTable 3. Annual Hepatitis C Incidence for Years 2001 to 2040

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eFigure 1. Annual HCC Incidence by Cirrhosis Status and SVR Status

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eFigure 3. Number of Candidates for HCC Surveillance by Fibrosis Stage, 2012-2040

eFigure 4. The Average Age of HCC Incidence During 2012-2040 in DAA Era

eReferences

Appendix II

Abstracts Presented

Kramer JR, Cao Y, Li L, Smith D, Chhatwal J, El-Serag HB, Kanwal F. Longitudinal associations between risk factors and subsequent risk of hepatocellular cancer in patients with hepatitis C virus infection and virological cure. 2021 AASLD The Liver Meeting, November 12-15th. Anaheim, CA.

Chhatwal J, Hajjar A, Mueller PP, Nemutlu G, Peters MLB, Kanwal F. Hepatocellular Carcinoma Incidence Threshold for Routine Surveillance is Much Lower in Hepatitis C Cirrhosis Individuals Who Achieve Virological Cure. 2021 AASLD The Liver Meeting, November 12-15th. Anaheim, CA. Also accepted for inclusion in the Best of The Liver Meeting's summary slide deck in the Health Services and Public Health Research category.

Nemutlu G, Mueller PP, Qiushi Chen, Turgay Ayer, Naveed Janjua, Kanwal F, Chhatwal J. Liver Cancer Surveillance in the Era of New Hepatitis C Antiviral Treatments: A Value of Information Analysis. 2021 INFORMS Annual Meeting, October 27-27th 2021. Anaheim, CA.

Kramer JR, Cao Y, Li L, Smith D, Chhatwal J, El-Serag HB, Kanwal F. Longitudinal associations between risk factors and subsequent risk of hepatocellular cancer in patients with hepatitis C virus infection and virological cure. 2021 AASLD The Liver Meeting, November 12-15th. Anaheim, CA.

Background: The risk of hepatocellular carcinoma (HCC) persists in patients with HCV after virological cure. We sought to determine if risk factors for HCC change as time from treatment elapses.

Methods: We utilized the Veterans Affairs data to examine a cohort of patients with HCV who achieved sustained viral response (SVR) from DAAs from 1/1/2014 to 12/31/2018, and followed until HCC diagnosis, death, or 12/31/2019. We utilized cause-specific Cox proportional hazard models constructed at 3 landmark times (baseline, 12 and 24 months after SVR) to examine the associations between demographic (age, race, sex, marital status), clinical (cirrhosis complications, duration of cirrhosis, FIB-4, albumin, sodium, bilirubin, creatinine, sodium, hemoglobin, obesity, hypertension and dyslipidemia), and behavioral factors (alcohol abuse, smoking) measured at these landmark times and the subsequent HCC risk, stratified by cirrhosis status.

Results: We identified 98,612 patients with virologic cure [38.5% Black, mean age 61 yrs]. Almost 32% had cirrhosis at time of SVR. Incident HCC developed in 2,298 patients. Among patients without cirrhosis, the annual incidence rates of HCC was 0.21% and 0.27% in year 1 and 2, respectively. The corresponding estimates were 1.6% and 1.9% in patients with cirrhosis. The association between risk factors and subsequent HCC changed over the landmark time and varied substantially with cirrhosis status. In patients **without cirrhosis**, metabolic traits (diabetes and hypertension) and increase in FIB-4 were strongly associated with HCC risk at all landmark times. In patients **with cirrhosis**, demographic factors (risk lower in females and blacks), viral factors (risk higher in HCV genotype 3), and cirrhosis related factors (risk higher with longer cirrhosis duration, presence of varices, higher bilirubin, and lower albumin) predicted HCC risk at 12 months. Change in serum albumin and FIB-4 scores between baseline and 12-month landmark times also predicted HCC risk. Race, HCV genotype, and bilirubin were no longer predictive of HCC risk at 24-month landmark time, whereas change in hemoglobin from baseline became associated with risk of HCC.

Conclusions: In a cohort of patients with virologically cured HCV infection, risk factors for HCC were different in patients with and without cirrhosis. In patients with cirrhosis, they were mostly disease severity related, whereas metabolic traits were important in patients without cirrhosis. These data could inform HCC surveillance decisions in patients with cured HCV.

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Table: Select risk factors from adjusted models for HCC at 12-months post SVR in patients with HCV infection stratified by cirrhosis status

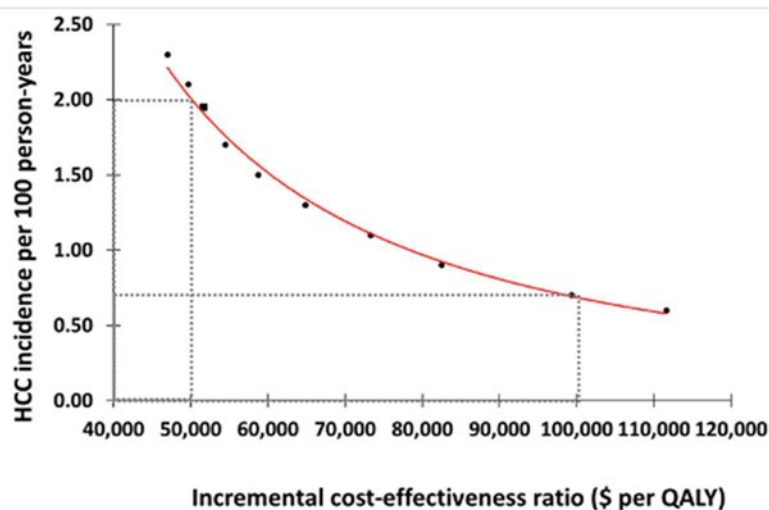
Risk Factor	Patients without cirrhosis HR (95% CI)	Patients with cirrhosis HR (95% CI)
Change in FIB-4 (ref: stays low)		
Low at baseline (≤ 3.25) to high (> 3.25) at 12 mo.	2.36 (1.46-3.79)	1.45 (1.12-1.86)
High at baseline and stays high at 12 mo.	N/A	1.73 (1.50-2.00)
Diabetes	1.42 (1.16-1.75)	N/A
Hypertension	2.13 (1.47-3.07)	N/A
Cirrhosis duration > 60 months	N/A	1.71 (1.39-2.11)
Varices	N/A	1.58 (1.38-1.80)
Bilirubin	N/A	1.25 (1.11-1.41)
Change in albumin	N/A	0.79 (0.67-0.95)

Chhatwal J, Hajjar A, Mueller PP, Nemutlu G, Peters MLB, Kanwal F. Hepatocellular Carcinoma Incidence Threshold for Routine Surveillance is Much Lower in Hepatitis C Cirrhosis Individuals Who Achieve Virological Cure. 2021 AASLD The Liver Meeting, November 12-15th. Anaheim, CA. Also accepted for inclusion in the Best of The Liver Meeting's summary slide deck in the Health Services and Public Health Research category.

Background: The AASLD guidance recommends biannual surveillance for hepatocellular carcinoma (HCC) in hepatitis C virus (HCV) infected individuals with cirrhosis if HCC incidence is above 1.5 per 100 person-years (PY). However, the incidence threshold for surveillance in cirrhosis individuals who achieved virological cure with direct-acting antivirals is unknown. Our objective was to estimate the HCC incidence above which routine HCC surveillance is cost-effective in this growing population of individuals with virologically cured HCV.

Methods: We developed a microsimulation model of the natural history of HCC in individuals with HCV and cirrhosis who achieved virological cure with oral direct-acting antivirals (DAAs). We used published data on the natural history of HCV, competing risk post HCV cure, HCC tumor progression, real-world HCC surveillance adherence, contemporary HCC treatment options and associated costs, and utilities of different health states. We estimated the HCC incidence above which biannual HCC surveillance using ultrasound and alpha-fetoprotein would be deemed cost-effective using willingness-to-pay (WTP) thresholds of \$100,000 per quality-adjusted life year (QALY), as recommended by the 2nd US Panel on Cost-effectiveness.

Results: In 50-year-old virologically cured individuals with HCV cirrhosis, the incremental cost-effectiveness ratio (ICER) of biannual surveillance (up to age 75) vs. no surveillance was \$100,000-per-QALY at HCC incidence of 0.7 per 100-PY (Figure). At this HCC incidence, routine HCC surveillance vs no surveillance would result in additional 2,650 life years gained and 1400 QALYs per 100,000 persons undergoing surveillance. Using the WTP threshold of \$50,000-per-QALY (old willingness-to-pay), HCC surveillance could be cost effective at an annual HCC incidence of 2.0 per 100 PY.



Conclusion: Our study provides an important update on HCC incidence threshold above which routine HCC surveillance is cost-effective in individuals with HCV cirrhosis who achieved cure with DAAs. At the accepted WTP thresholds, HCC surveillance could be cost-effective if the annual incidence rate of HCC exceeds 0.7%, which is much lower than the previous 1.5% incidence used to guide HCC surveillance decisions.

Nemutlu G, Mueller PP, Qiushi Chen, Turgay Ayer, Naveed Janjua, Kanwal F, Chhatwal J. Liver Cancer Surveillance in the Era of New Hepatitis C Antiviral Treatments: A Value of Information Analysis. 2021 INFORMS Annual Meeting, October 27-27th 2021. Anaheim, CA.

The treatment landscape for chronic hepatitis C has changed with the use of direct-acting antivirals; 95-100% of individuals with hepatitis C can now be cured. However, the risk of liver cancer is not eliminated for individuals with advanced liver disease. The value of routine cancer surveillance in this population is widely debated; long-term data on liver cancer incidence is lacking. Our objective was to evaluate the value for future research on liver cancer surveillance in hepatitis C cured individuals using a validated microsimulation model. We estimated the cost-effectiveness of routine surveillance and performed a value of information analysis informed by the population-level expected value of perfect information to determine the value of future research. Our analysis showed that routine surveillance was cost-effective only in individuals with cirrhosis.