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Economic evaluation of hepatocellular carcinoma surveillance in chronic hepatitis B patients with virological remission

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Abstract

Background Subsequent risk of hepatocellular carcinoma (HCC) persists in chronic hepatitis B (CHB) patients with virological remission. We aimed to assess the cost-effectiveness of HCC surveillance in those patients and determine appropriate age to commence or discontinue surveillance.

Methods We developed an individual-based state transition model, simulating the advancement of HCC in CHB patients with virological remission. We used this model to compare the incremental cost-effectiveness ratio (ICER) and long-term health outcomes of biannual or annual HCC surveillance for varying durations with no surveillance.

Results For compensated cirrhosis patients with CHB, biannual surveillance was not cost-effective for all age groups, while annual surveillance was cost-effective for patients aged 55 to 70 (ICER USD 28,076 / quality-adjusted life years [QALY] gained), which detected 176 additional early HCC cases in a 100,000-person cohort compared to no surveillance. In CHB patients with advanced fibrosis, annual surveillance for patients aged 40 to 75 was the most cost-effective strategy (ICER USD 4,984/QALY gained), which detected 289 additional early HCC per 100,000 patients.

Conclusions Annual surveillance for patients with compensated cirrhosis or advanced fibrosis was a more cost-effective option that demonstrated substantial economic benefits, being slightly less effective than biannual surveillance at a significantly lower cost, providing insights for professionals in evaluating HCC surveillance among high-risk patients in China.

Lay summary

The most cost-effective age group for surveillance of hepatocellular carcinoma (HCC) varied depending on the stage of the disease. Regular annual surveillance for patients with compensated cirrhosis or advanced fibrosis was more cost-effective option, showing great economic and clinical benefits with slightly less effective than biannual surveillance but significantly lower cost.

Keywords Liver cancer, Screening, Microsimulation modeling, Cost-effectiveness

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Background

China bears the largest burden of liver cancer worldwide, with 410,000 cases and 391,200 deaths in 2020, accounting for almost half of the new cases and deaths attributed to liver cancer across the globe [1]. The primary cause of hepatocellular carcinoma (HCC) in China is predominantly chronic hepatitis B (CHB), with over 80% of individuals diagnosed with HCC testing positive for hepatitis B virus (HBV) [2]. China has established a relatively comprehensive surveillance system for HBV epidemiology, known as the National Notifiable Disease Reporting System (NNDRS) [3]. In 1992, HBV vaccination was incorporated into the routine immunization schedule for infants, and since 2005, the cost of HBV vaccination has been covered by public health insurance [4]. These national efforts have significantly reduced the prevalence of HBsAg seroprevalence from 9.6% during 1984 to 3.0% in 2021 [5]. However, current medical surveillance systems are unable to capture asymptomatic infections and also do not pay attention to those patients with virological remission.

The approved nucleos(t)ide analogues (NAs) used in the treatment of CHB have demonstrated strong antiviral effectiveness, leading to a notable decrease in the risk of HBV-related diseases and HCC [6]. Despite their ability to suppress HBV replication in the long term, many studies have indicated that the risk of HCC still exists in CHB patients remaining in virological remission after treatment with NAs [7, 8]. Pieces of evidence have shown that HCC can occur in CHB patients even after hepatitis B surface antigen (HBsAg) loss, and the annual incidence of HCC was 3.68% in a cohort study [7, 9]. HCC has a dismal prognosis with an extremely low 5-year survival rate of 18% unless diagnosed at stages with no symptoms [10]. If detected early, improved chances of survival through curative treatments, including radiofrequency ablation (RFA), surgical removal, and liver transplantation, are available [10, 11].

Regular surveillance can identify early-stage HCC that is still amenable to curative treatment, thereby improving long-term survival outcomes [12]. Currently, most studies are focused on expanding screening and treatment for HBV-positive patients [13, 14]. Given the residual HCC risk after successful NA treatment, CHB patients with virological remission were recommended to continue regular HCC surveillance [15, 16]. However, there is a paucity of studies exploring the necessity of HCC surveillance in these patients, as well as the cost-effectiveness of regular surveillance, particularly in the Chinese context where the burden of HBV is particularly heavy. This study assesses the cost-effectiveness of implementing biannual or annual HCC surveillance among CHB patients with virological remission after NA treatment and provides information on when to start HCC surveillance.

Methods

Baseline population

The baseline population consisted of a cohort of 100,000 CHB patients aged 40 to 70 years (with a greater risk of developing HCC) [17]. These patients have achieved virological remission following NA treatment, which is defined as the loss of HBsAg accompanied by undetectable levels of HBV DNA in the serum [18], and without any previous known diagnosis of HCC.

Model overview

We have developed an individual-based state transition model, referred to as a microsimulation model. The model mainly includes a natural history component and a surveillance component, which is designed to simulate the progression of HCC in HBV patients achieving virological remission after NA treatment. We utilized this model to assess the cost-effectiveness of implementing biannual or annual surveillance for HCC at different initiation ages, spanning from 40 to 65, as well as considering different cessation ages, ranging from 50 to 75 (average life expectancy 77 years of the Chinese population in 2021) [19]. The model employed a monthly timeframe and evaluated the effectiveness of various surveillance strategies by measuring quality-adjusted life years (QALYs), incremental cost-effectiveness ratios (ICERs) and costs. The model was constructed using TreeAge Pro 2022 suite software (Williamstown, MA, USA), and the analyses were executed with R Studio (version 4.2.2) using the R packages tidyverse (version 1.3.2) and ggplot2 (version 3.4.0). The results of this study were presented in line with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) [20].

Nature history

We conducted simulations of the clinical course of HBV, including the progression of liver diseases and HCC (Fig. 1). Details of the model's parameters are provided in Supplementary Table 1. Briefly, the parameters were derived primarily from published literature or previous modeling studies. The disease progression parameters were mainly obtained from long-term cohort study results. To reduce parameter variability, we used a weighted average approach to estimate average rates. For instance, for patients with compensated cirrhosis (F4 stage), we calculated the hepatocellular carcinoma incidence rate by averaging the findings of three studies [8, 21, 22], yielding a weighted average of 2.37 cases per 100 person-years. For non-cirrhotic patients with advanced fibrosis (F3 stage), we used a weighted average from four studies [21, 23–25], resulting in an incidence rate of 0.46 per 100 person-years. Treatment effectiveness and patient survival parameters were prioritized based on results from randomized controlled trials. Parameters

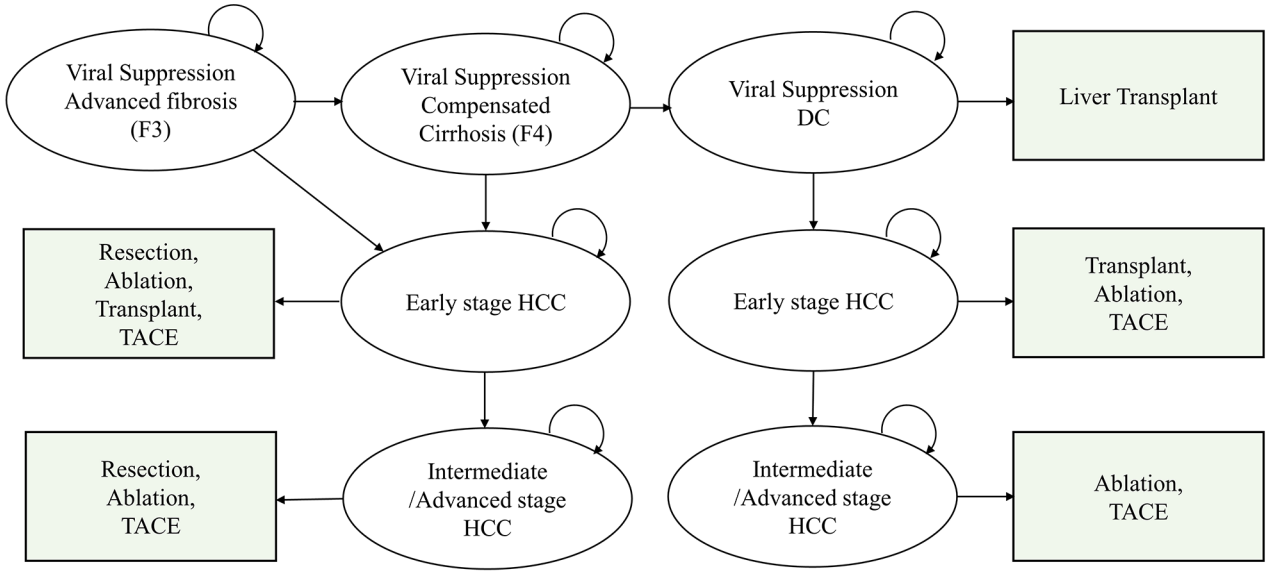

Fig. 1 Model schematic for the natural history of HCC in CHB patients with virological remission. Patients could develop HCC and subsequently progress through different stages of HCC. Natural death also can occur in all states. DC, decompensated cirrhosis; HCC, hepatocellular carcinoma; TACE, transarterial chemoembolization and other palliative treatments

for screening and diagnostic accuracy were selected from two systematic reviews and meta-analyses. Finally, cost parameters were determined within the context of China.

Patients face the risk of developing HCC at an "early" stage, which may subsequently progress to "intermediate/advanced" stages, with the definition of HCC stage based on the Milan Criteria [26] and China's liver cancer staging system and tumor size [17]. Patients with a diameter under 5 cm or a maximum of 3 tumors, each measuring under 3 cm, were categorized as having "early HCC". On the other hand, the remaining stages were classified as "intermediate/advanced HCC". The annual progression rate from "early stage" to "intermediate/advanced stage" is estimated to be 0.4581 based on the tumor doubling times (Supplementary Sect. 1). In the univariate sensitivity analysis, we varied the HCC risk and progression rate by setting values above and below the base case values.

HCC surveillance

We conducted simulations for every virtual patient to compare the outcomes of "no surveillance" versus biannual/annual HCC surveillance, monitoring the progression of HCC and the stage at which it was detected for each patient. The surveillance involved the use of both ultrasound and AFP, which is in accordance with clinical guidelines [17]. By altering the duration of surveillance in increments of 5 years from 10 years to lifetime, we simulated various HCC surveillance strategies. For example, we conducted simulations for a 40-year-old patient with biannual or annual HCC surveillance from age 40 to 50, 55, 60, and so on. If the surveillance tests showed normal results, the patient proceeded with their regular course until the next examination. Nevertheless, if the results were abnormal, the patient had to undergo contrast-enhanced abdominal magnetic resonance imaging (MRI) to possibly verify the diagnosis of HCC. Our assumption was that a solitary MRI would be sufficient to confirm the diagnosis [27]. For patients in the no surveillance group, HCC could also be identified incidentally.

After confirmation of HCC, the patient was started on treatment for HCC. We evaluated 4 treatments for HCC, including resection, ablation, liver transplantation and transarterial chemoembolization, as well as other palliative treatments, such as systemic chemotherapy, external radiotherapy and selective internal radiotherapy. The choice of treatment is based on the stage of HCC and the severity of liver disease at the time of diagnosis (Supplementary Table 2). According to the guidelines, liver transplantation was considered suitable exclusively for patients aged 75 years or younger who presented either with decompensated cirrhosis or HCC at early stages, meeting the Milan criteria. It is noted that patients with decompensated cirrhosis were deemed ineligible for resection (Supplementary Sect. 2) [17]. Details of treatment allocation based on HCC stage and fibrosis stage are detailed in Supplementary Sect. 3.

Costs and utility

Published sources were used to obtain the expenses associated with HCC surveillance and treatment, liver transplantation, and management of liver diseases in general [28]. The costs were converted to US dollars using the

exchange rates applicable in 2021. We assigned utility weights to both health states and treatments, taking into account their impact on quality of life. These weights were adjusted based on the patient's age and the stage of their liver disease [23]. We applied a 3% yearly discount rate to all future costs and QALYs [14] (Supplementary Table 1).

Model outcomes

We evaluated the cases of HCC identified by tumor stage, total QALYs, and expenses for every simulated monitoring approach and patient profile. We evaluated the cost-effectiveness of diverse surveillance strategies at various initial screening ages using two approaches. First, we estimated the incremental cost-effectiveness ratio (ICER) for each surveillance approach compared to no surveillance. The ICER represents the additional costs per QALY gained. Second, we determined the ICER for each surveillance strategy compared to the next strategy at the same age to commence surveillance. There is a lack of information on the willingness to pay (WTP) of the Chinese population, and we have used the definition of cost-effectiveness developed by the World Health Organization [29]. According to this definition, we consider an ICER of less than one times the gross domestic product (GDP) per capita in China to be highly cost-effective. We classified ICERs between one and three times GDP per capita as cost-effective, and ICERs above three times GDP per capita were not cost-effective. As of 2020, the GDP per capita in China was US $10,756 [30].

Sensitivity analysis

To better understand the effect of uncertainty in each input of the models, we utilized a univariate sensitivity analysis on each input variable, as shown in Supplementary Table 1. Additionally, our study employed a comprehensive multivariate probabilistic sensitivity analysis where 1,000 sets of parameter values were sampled from their respective distributions. Each parameter set was evaluated using a population size of 10,000. The outcomes of this analysis were then represented using cost-effectiveness acceptability curves.

Results

Table 1 presents the costs, QALYs and ICERs of biannual HCC surveillance strategies. Compared with no surveillance, for patients with compensated cirrhosis, biannual surveillance was not cost-effective at the WTP threshold (USD 32,268/QALY gained). The study revealed that conducting biannual surveillance for advanced fibrosis in individuals aged 40 had the most favorable incremental cost-effectiveness ratio (ICER) when discontinuing surveillance at the age of 65. This approach was associated with an ICER of USD 4,760/QALY gained. Conversely, the highest ICER was identified when surveillance was discontinued at 50 years of age, leading to a cost of USD 18,900 per QALY gained. Surveillance up to age 75 (USD 12,970/QALY gained) provided most QALY gains of 0.67 at an additional cost of USD 6,446 and was the most cost-effective strategy, with an ICER below the WTP threshold. Surveillance starting from compensated cirrhosis was less effective and more costly than surveillance starting from advanced fibrosis.

The costs, QALYs and ICERs of annual HCC surveillance strategies are shown in Table 2. Regarding patients with compensated cirrhosis, annual surveillance was found to be more cost-effective than biannual surveillance. At the willingness-to-pay (WTP) threshold, targeting surveillance toward patients aged 40–50 yielded an ICER of USD 25,511/QALY gained. Similarly, targeting patients aged 55–70 resulted in an ICER of USD 28,076/QALY gained, while targeting those aged 55–65 led to an ICER of USD 32,072/QALY gained. Therefore, annual surveillance in these age groups proved to be a more economically viable option. In the case of 40-year-old patients with advanced fibrosis, the ICER of annual surveillance was found to be the lowest when the surveillance was discontinued at the age of 60, with an ICER of USD 2,759 per QALY gained, and was highest when the stopping age was 55 (USD 34,363/QALY gained), which was not cost-effective with the ICERs exceeding the WTP threshold (USD 32,268/QALY gained). The effectiveness of biannual surveillance is marginally superior to that of annual surveillance, but costs are also higher.

We plotted the cost-effectiveness frontiers of HCC surveillance at different surveillance intervals for CHB patients with compensated cirrhosis or advanced fibrosis (Fig. 2). For patients with compensated cirrhosis, compared with no surveillance, biannual surveillance was not cost-effective at any age group, as it exceeded the WTP threshold (Fig. 2A), while annual surveillance for some age groups was cost-effective, and surveillance targeting patients aged 55–70 (USD 28,076/QALY gained) was the most cost-effective (Fig. 2B). For patients with advanced fibrosis, compared with no surveillance, biannual (Fig. 2C) and annual (Fig. 2D) surveillance for any age group were nondominated. Surveillance targeting those aged 40–75 was the most cost-effective strategy, either biannual (USD 12,970/QALY gained) or annual (USD 4,984/QALY gained) surveillance intervals.

For 40-year-old patients with compensated cirrhosis, after 35 years in the "no surveillance" arm, there were 5,331 HCC cases per 100,000 patients, of which 358 were detected either incidentally or through symptoms. Among these, 58 cases were discovered at an early stage, while 300 cases were detected at intermediate or advanced stages. In contrast, after 15 years of annual surveillance (from 55 to 70), there were 3,178 HCC cases,

Table 1 Cost-effectiveness results of biannual HCC surveillance in CHB patients with virological remission

Surveillance age group		compensated cirrhosis				advanced fibrosis (non-cirrhotic)			
		Costs per patient ($)	QALYs gained per patient	ICERs vs. no surveillance (US$/QALY)	ICER vs. next screening strategy (US$/QALY)	Costs per patient ($)	QALYs gained per patient	ICERs vs. no surveillance (US$/QALY)	ICER vs. next screening strategy (US$/QALY)
No surveillance		86,161	11.533	/	/	6,011	14.820	/	/
Surveillance (Biannual)									
Start age	**Stop age**								
40	50	92,711	11.597	102,472	102,472	7,467	14.897	18,900	18,900
	55	99,077	11.740	62,512	44,613	8,121	15.009	11,171	5,846
	60	106,303	11.845	64,625	68,779	9,492	15.123	11,501	12,049
	65	115,324	12.027	59,120	49,673	10,546	15.344	8,654	4,760
	70	119,492	12.143	54,652	35,749	11,527	15.419	9,215	13,161
	75	123,954	12.212	55,690	64,894	12,457	15.490	9,616	12,970
45	55	96,490	11.739	50,146	50,146	7,800	14.964	12,461	12,461
	60	103,062	11.832	56,536	70,694	9,113	15.051	13,418	14,987
	65	112,072	12.017	53,571	48,773	10,161	15.275	9,128	4,691
	70	116,071	12.133	49,855	34,397	11,149	15.351	9,689	13,063
	75	120,523	12.202	51,358	64,403	12,074	15.422	10,070	12,882
50	60	102,844	11.863	50,661	50,661	9,636	15.089	13,473	13,473
	65	112,030	12.016	53,636	60,039	10,683	15.274	10,296	5,667
	70	115,576	12.135	48,876	29,668	11,726	15.371	10,378	10,764
	75	119,840	12.201	50,442	64,758	12,447	15.429	10,578	12,484
55	65	101,671	11.846	49,632	49,632	9,236	15.167	9,313	9,313
	70	106,223	11.925	51,236	57,573	10,309	15.231	10,462	16,628
	75	110,585	11.996	52,782	61,289	10,888	15.304	10,081	7,937
60	70	100,985	11.785	58,964	58,964	8,725	15.116	9,173	9,173
	75	104,049	11.841	58,149	54,505	9,361	15.167	9,674	12,607
65	75	94,813	11.708	49,429	49,429	8,076	14.970	13,751	13,751

CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

of which 408 were detected as regular surveillance or incidental findings. Among them, 234 were detected at an early stage, and 174 were detected at intermediate/advanced stages (Fig. 3A). As a result, this approach successfully identified an additional 176 cases of HCC at an early stage, leading to a decrease of 126 cases in the number of HCC cases detected at intermediate or advanced stages.

Comparable patterns were noticed among patients with advanced fibrosis (Fig. 3B). Among 40-year-old non-cirrhotic patients with no HCC surveillance, 52 HCC cases were incidentally diagnosed at an early stage and 257 at an intermediate/advanced stage. On the other hand, the biannual surveillance conducted over a span of 35 years (from 40 to 75) identified 329 cases at an early stage and 52 cases at the intermediate/advanced stages. In comparison, the annual surveillance conducted over the same 35-year period detected 341 cases at an early stage and 53 cases at the intermediate/advanced stage. Therefore, the 35-year biannual surveillance detected 277 additional HCC cases in the early stage and avoided 205 cases of intermediate/advanced HCC. The 35-year annual surveillance detected 12 additional HCC cases in the early stage and 1 additional HCC case in intermediate/advanced HCC compared with biannual surveillance, which may be caused by the longer surveillance interval. The number of HCC cases with different surveillance strategies on the cost-effectiveness frontier is shown in Supplementary Fig. 1.

Sensitivity analysis

In the univariate probability sensitivity analysis, we assessed a total of 50 parameters. The ten most important parameters of the three cost-effective strategies affecting HCC surveillance in patients with compensated cirrhosis or advanced fibrosis are shown in the tornado diagram (Supplementary Fig. 2). For patients with compensated cirrhosis, the cost-effective strategy (annual surveillance from 55 to 70) was most sensitive to the probability from compensated cirrhosis to hepatocellular carcinoma. For patients with advanced fibrosis, the cost-effective strategies (biannual or annual surveillance from 40 to 75) were most sensitive to the probability from hepatitis B with advanced fibrosis to hepatocellular carcinoma.

Table 2 Cost-effectiveness results of annual HCC surveillance in CHB patients with virological remission

Surveillance age group		compensated cirrhosis				advanced fibrosis (non-cirrhotic)			
		Costs per patient ($)	QALYs gained per patient	ICERs vs. no surveillance (US$/QALY)	ICER vs. next screening strategy (US$/QALY)	Costs per patient ($)	QALYs gained per patient	ICERs vs. no surveillance (US$/QALY)	ICER vs. next screening strategy (US$/QALY)
No surveillance		86,161	11.533	/	/	6,011	14.820	/	/
Surveillance (Annual)									
Start age	**Stop age**								
40	50	88,090	11.609	25,511	25,511	6,490	14.906	5,582	5,582
	55	91,784	11.687	36,475	47,028	9,053	14.981	18,960	34,363
	60	96,631	11.855	32,545	28,928	9,359	15.091	12,347	2,759
	65	102,875	12.018	34,488	38,325	10,495	15.309	9,167	5,213
	70	105,911	12.119	33,742	30,151	11,350	15.405	9,136	8,979
	75	108,207	12.180	34,072	37,196	11,675	15.470	8,720	4,984
45	55	92,279	11.658	49,181	49,181	9,140	14.940	26,099	26,099
	60	96,977	11.795	41,369	34,279	9,515	15.022	17,330	4,554
	65	102,968	11.963	39,144	35,680	10,535	15.236	10,886	4,780
	70	105,797	12.064	36,990	27,875	11,417	15.337	10,460	8,713
	75	107,985	12.127	36,744	34,674	11,736	15.403	9,822	4,825
50	60	96,004	11.817	34,726	34,726	9,527	15.030	16,768	16,768
	65	101,448	11.973	34,804	34,947	10,926	15.236	11,824	6,792
	70	104,657	12.078	33,952	30,407	11,988	15.343	11,443	9,959
	75	106,890	12.140	34,192	36,311	12,346	15.405	10,839	5,762
55	65	95,256	11.817	32,072	32,072	8,288	15.099	8,156	8,156
	70	98,293	11.925	30,969	28,076	9,347	15.197	8,864	10,901
	75	100,639	11.965	33,529	58,543	9,903	15.271	8,635	7,474
60	70	96,077	11.754	45,022	45,022	8,787	15.044	12,424	12,424
	75	98,005	11.847	37,809	20,731	9,132	15.100	11,171	6,166
65	75	91,698	11.701	33,100	33,100	8,057	14.951	15,612	15,612

CHB, chronic hepatitis B; HCC, hepatocellular carcinoma; QALY, quality-adjusted life years; ICER, incremental cost-effectiveness ratio

The results of the multivariate probabilistic sensitivity analysis are presented in Fig. 4, which shows the cost-effectiveness acceptability curve. It depicts the probability of age-specific HCC surveillance being cost-effective, taking into account the uncertainty in all model parameters. At a threshold of USD 32,268 (3 times GDP), the annual surveillance for compensated cirrhosis patients aged 55–70 years had a 25% probability of being cost-effective. At one-time GDP per capita, biannual surveillance for advanced fibrosis patients aged 40–75 years was the leading cost-effective strategy (33%). For annual surveillance among patients with advanced fibrosis, targeting patients aged 55–65 years and patients aged 40–75 years was the most cost-effective strategy at one-time GDP per capita (33%).

Discussion

Currently, there is a research gap in the HCC surveillance among CHB patients with virological remission. This is an economic evaluation study to assess the regular surveillance for HCC of Chinese patients, which may provide important information on the necessity of HCC surveillance, the appropriate age to initiate or stop surveillance, as well as the surveillance intervals. Our analysis revealed several key findings. First, we determined that the cost-effective age group for HCC surveillance varied depending on the stage of the disease. Our analysis determined that individuals aged between 55 and 70 years with compensated cirrhosis are the appropriate demographic for surveillance. Conversely, for advanced fibrosis, the most cost-effective strategy involved annual surveillance for individuals aged 40 to 75. Second, surveillance starting from compensated cirrhosis was less effective and more costly than surveillance starting from advanced fibrosis, and in addition, regardless of the stage at which surveillance began, biannual surveillance was more costly but also more effective than annual surveillance. Finally, our study demonstrated that routine surveillance had the potential to facilitate a significant stage shift in HCC diagnosis. Specifically, a greater proportion of HCC cases could be detected at an early stage, while the number of intermediate/advanced stage cases was substantially reduced.

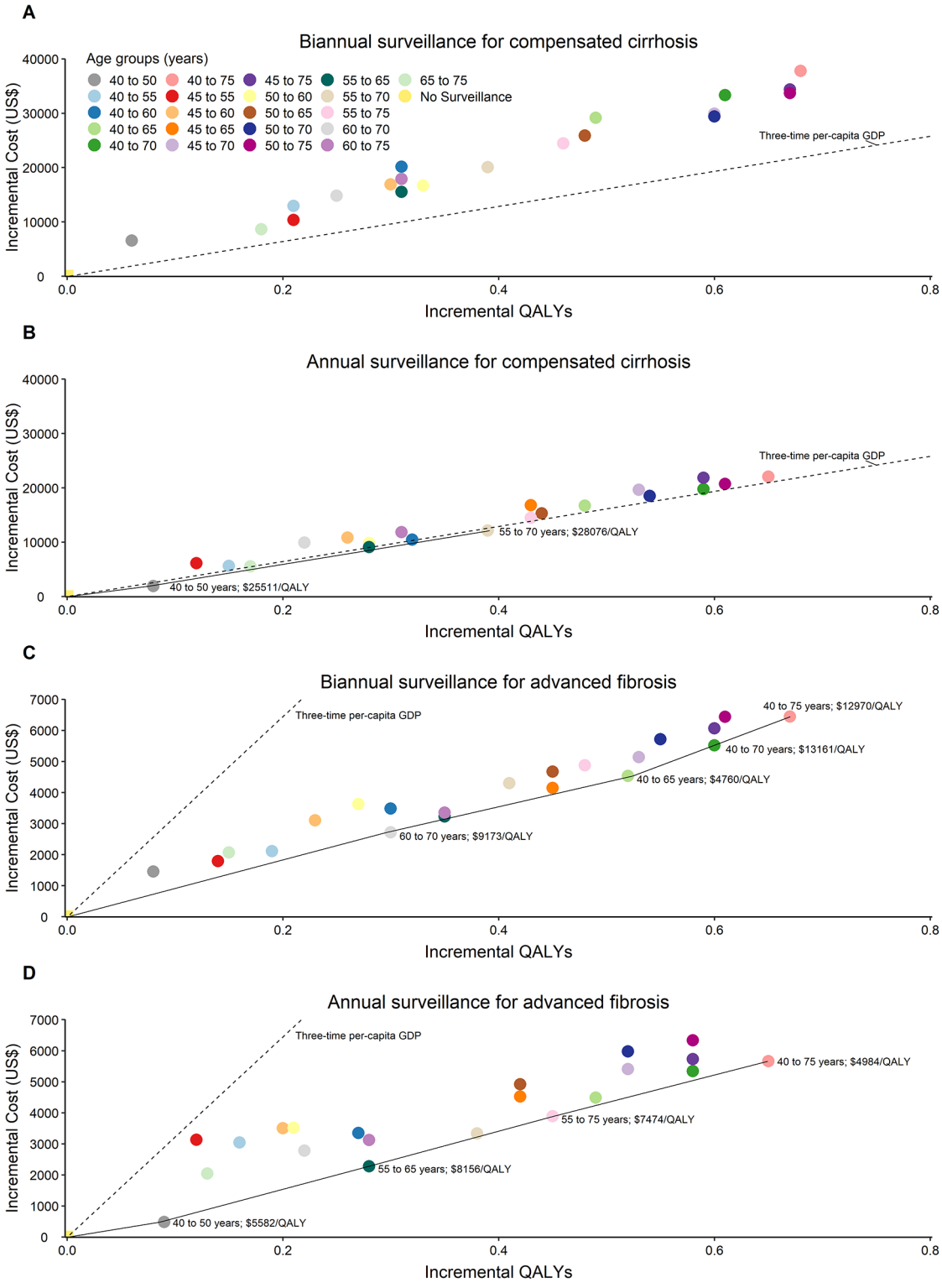

Fig. 2 Cost-effectiveness for all HCC surveillance strategies. Solid line = cost-effectiveness frontier. Strategies on the cost-effectiveness frontier dominate strategies above the frontier. GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-years

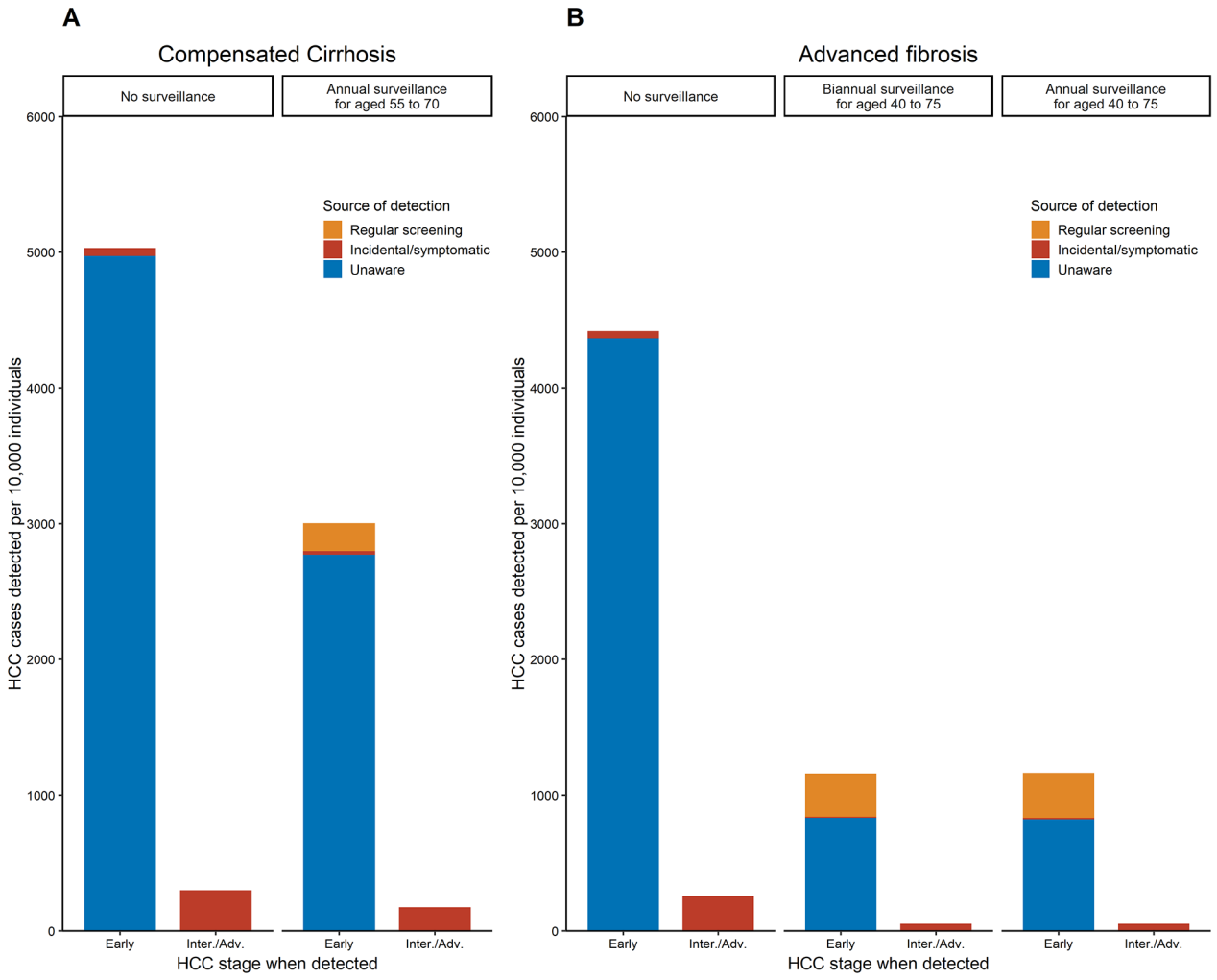

Fig. 3 Number of HCC cases according to surveillance strategy. (**A**) Number of HCC cases detected by tumor size in patients with compensated cirrhosis who achieved virological remission under no surveillance vs. annual surveillance for aged 55 to 70; (**B**) Number of HCC cases detected by tumor size in patients with advanced fibrosis who achieved virological remission under no surveillance vs. biannual surveillance for aged 40 to 75 vs. annual surveillance for aged 40 to 75. HCC, hepatocellular carcinoma; Inter./adv., intermediate/advanced

Our findings support the current recommendations of the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of Liver (EASL) for the surveillance of HCC among compensated cirrhosis patients who achieved virological remission [16, 31]. Furthermore, our study may provide important insights into cost-effective surveillance and the appropriate age threshold to discontinue surveillance for compensated cirrhosis in China. Specifically, our modeling study may support annual surveillance for patients with compensated cirrhosis aged 55 to 70. It is interesting to note that the Asian Pacific Association for the Study of the Liver (APASL) guidelines suggest monitoring for liver cancer in specific high-risk groups, such as those with advanced fibrosis, even if they do not have cirrhosis [32], whereas the AASLD guidelines do not recommend liver cancer surveillance for patients without cirrhosis [31]. Our results revealed that surveillance for hepatitis B patients aged 40 to 75 who achieved virological remission with advanced fibrosis was also cost-effective, whether biannual or annual surveillance. For patients at different stages of chronic hepatitis, different age groups are recommended for regular HCC surveillance. This will provide evidence for healthcare professionals to carry out regular follow-up of such patients in clinical practice.

Annual surveillance was the most cost-effective choice regardless of fibrosis stage, mainly due to the comparatively low HCC incidence in patients with viral remission. Similar findings have been illustrated in an early study in which annual surveillance for HCV-infected patients who have obtained sustained virologic response (SVR) was the cost-effective strategy under different surveillance intervals [33]. In addition, it would be more cost-effective to start surveillance at an earlier stage of the disease, with

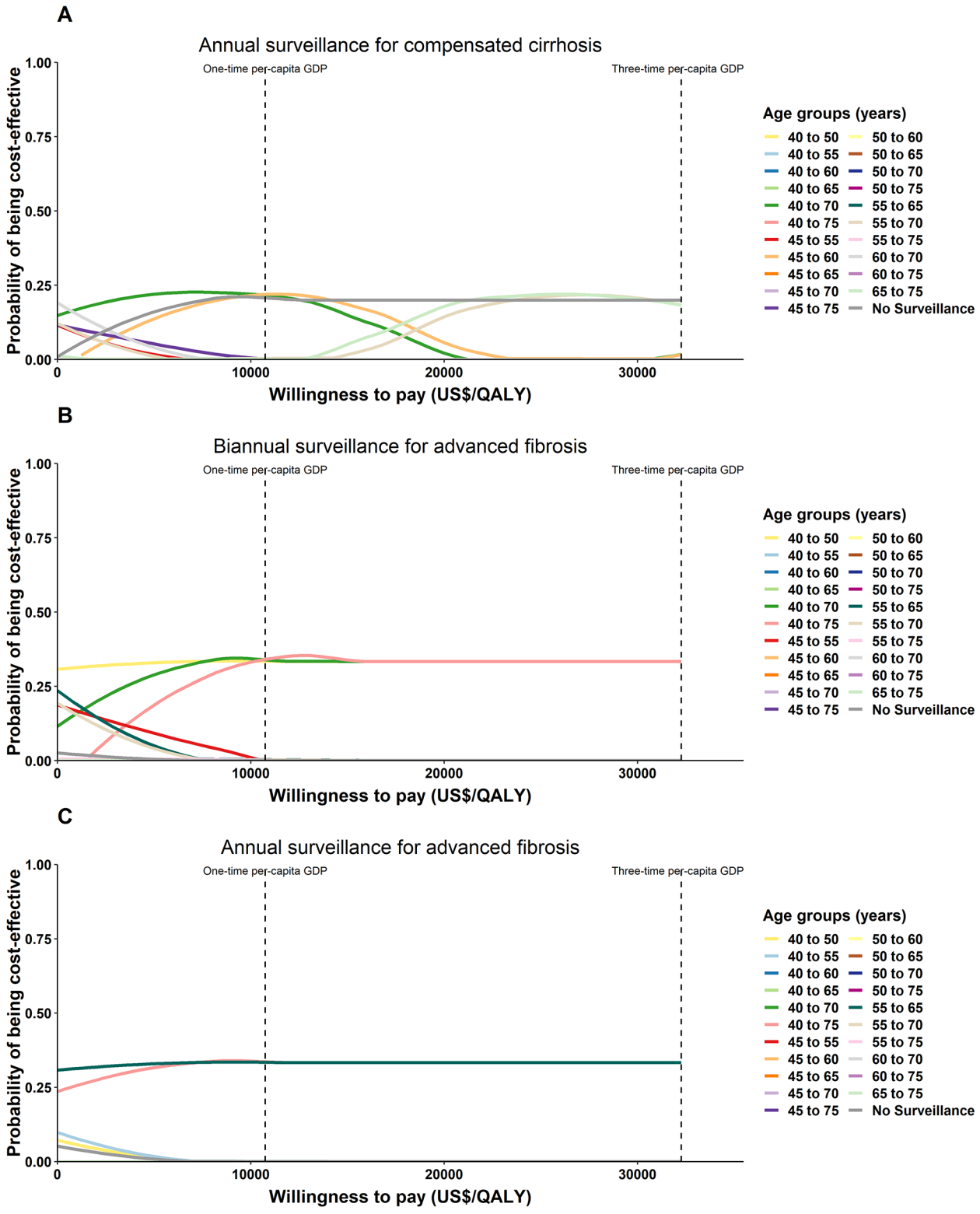

Fig. 4 Cost-effectiveness acceptability curves for different HCC surveillance strategies. GDP, gross domestic product; QALY, quality-adjusted life-years

HCC surveillance for patients with advanced fibrosis being relatively less expensive than in compensated cirrhosis patients but with better outcomes, partly due to a higher HCC incidence as well as a higher competing risk of liver-associated deaths in the advanced stages [34].

Ensuring regular HCC surveillance plays a crucial role in enhancing survival rates, as it facilitates early detection of HCC and improves accessibility to curative first-line treatment. Patients with HCC diagnosed at advanced stages have a median survival of approximately one year and are treated with systemic therapies. However, curative options for early-stage HCC may result in a 5-year survival rate surpassing 70% [10]. According to our model, surveillance may produce a significant shift in the stage of HCC diagnosis, resulting in the early detection of most cases. The stage at the time of diagnosis is the paramount factor influencing the overall survival of patients with HCC. Individuals harboring small, localized tumors possess the opportunity to undergo curative treatments, including resection, ablation, or liver transplantation, which can yield significantly better long-term survival outcomes [35]. Therefore, the objective of implementing a surveillance program for HCC is to detect tumors during the early stages in individuals at high risk. This enables them to undergo curative treatments, leading to enhanced long-term survival rates and ultimately reducing liver cancer mortality. Additionally, the public health insurance provided by the state can also assist in the HCC surveillance. By 2015, the population coverage of public health insurance in China had exceeded 95%, and at least 70% of insurance-listed healthcare expenditures are publicly funded [36]. This included a portion of the tests and medical care for HBV and HCC, as well as a portion of the first-line antiviral agents for HBV [37, 38].

The benefits of routine HCC surveillance have been shown in several observational studies [12]. However, there is a scarcity of randomized controlled trials to evaluate the long-term benefits of HCC surveillance among CHB patients, which would be a costly and lengthy process [10, 39]. Incorporating a control group would present ethical challenges in the clinical trials, as nearly 99% of patients are unwilling to accept the possibility of being randomly assigned to the group that does not receive surveillance [40]. In this case, a decision analysis model can simulate a virtual trial showing the long-term health outcomes among a specific population to generate data on the relative effectiveness of different approaches and is frequently used to assist policymakers in developing strategies [41]. This study could provide valuable information for professionals to assess the surveillance of HCC among high-risk people in China.

This study has limitations. First, the cost and willingness-to-pay thresholds associated with the model are specific to China. A degree of caution is required when extrapolating the results to distinct settings. Second, we assumed a high adherence rate for surveillance in that 90% of patients completed the follow-up processes for each surveillance test. Third, we decided to model surveillance at 5-year intervals instead of shorter intervals because this age grouping is more practical to apply in real-world scenarios. Fourth, in our study, there were no restrictions on other treatments except for liver transplantation, which was restricted to patients under 75 years old. Fifth, this study was focused on age factors, while there are other risk factors, such as comorbidities, body mass index and sex, and future research is warranted in subgroups with other risk factors.

Conclusions

In summary, our research indicated that conducting HCC surveillance every six months in compensated cirrhosis patients who have achieved viral remission of HBV was not economically viable in China, whereas annual surveillance in those with compensated cirrhosis was cost-effective, especially for patients aged 55 to 70 years. Additionally, for advanced fibrosis patients, annual surveillance of HCC was the most cost-effective for patients aged 40 to 75 years. Regular HCC surveillance detected earlier HCC cases and reduced the intermediate or advanced cases, demonstrating substantial economic and clinical benefits and improving survival. This study may provide some insights for professional societies to evaluate HCC surveillance among high-risk patients in China.

Abbreviations

HCC	hepatocellular carcinoma
CHB	chronic hepatitis B
HBV	Hepatitis B virus
NA	nucleos(t)ide analogues
ICER	incremental cost-effectiveness ratio
QALY	quality-adjusted life years
HBsAg	Hepatitis B surface antigen
RFA	radiofrequency ablation
EASL	the European Association for the Study of Liver
AASLD	the American Association for the Study of Liver Diseases
AFP	alpha-fetoprotein
MRI	magnetic resonance imaging
WTP	willingness to pay
GDP	gross domestic product
APASL	Asian Pacific Association for the Study of the Liver
SVR	sustained virologic response

Supplementary Information

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Supplementary Material 1

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Data availability
All data and materials relevant to the study are included in the article or uploaded as supplementary information.

Declarations

Ethics approval and consent to participate
This article does not contain any studies with human participants or animals performed by any of the authors.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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References

1. Rumgay H, Arnold M, Ferlay J, Lesi O, Cabasag CJ, Vignat J, et al. Global burden of primary liver cancer in 2020 and predictions to 2040. J Hepatol. 2022;77(6):1598–606.
2. Islami F, Chen W, Yu XQ, Lortet-Tieulent J, Zheng R, Flanders WD, et al. Cancer deaths and cases attributable to lifestyle factors and infections in China, 2013. Ann Oncol. 2017;28(10):2567–74.
3. Cui F, Drobeniuc J, Hadler SC, Hutin YJ, Ma F, Wiersma S, et al. Review of hepatitis B surveillance in China: improving information to frame future directions in prevention and control. Vaccine. 2013;31(Suppl 9):79–84.
4. Song P, Feng X, Zhang K, Song T, Ma K, Kokudo N, et al. Screening for and surveillance of high-risk patients with HBV-related chronic liver disease: promoting the early detection of hepatocellular carcinoma in China. Biosci Trends. 2013;7(1):1–6.
5. Liu Z, Lin C, Mao X, Guo C, Suo C, Zhu D, et al. Changing prevalence of chronic hepatitis B virus infection in China between 1973 and 2021: a systematic literature review and meta-analysis of 3740 studies and 231 million people. Gut. 2023;72(12):2354–63.
6. Hou JL, Zhao W, Lee C, Hann HW, Peng CY, Tanwandee T, et al. Outcomes of long-term treatment of chronic HBV infection with entecavir or other agents from a Randomized Trial in 24 countries. Clin Gastroenterol Hepatol. 2020;18(2):457–67.
7. Papatheodoridis GV, Manolakopoulos S, Touloumi G, Vourli G, Raptopoulou-Gigi M, Vafiadis-Zoumbouli I, et al. Virological suppression does not prevent the development of hepatocellular carcinoma in HBeAg-negative chronic hepatitis B patients with cirrhosis receiving oral antiviral(s) starting with lamivudine monotherapy: results of the nationwide HEPNET. Greece Cohort Study Gut. 2011;60(8):1109–16.
8. Papatheodoridis GV, Chan HL, Hansen BE, Janssen HL, Lampertico P. Risk of hepatocellular carcinoma in chronic hepatitis B: assessment and modification with current antiviral therapy. J Hepatol. 2015;62(4):956–67.
9. Simonetti J, Bulkow L, McMahon BJ, Homan C, Snowball M, Negus S, et al. Clearance of hepatitis B surface antigen and risk of hepatocellular carcinoma in a cohort chronically infected with hepatitis B virus. Hepatology. 2010;51(5):1531–7.
10. Villanueva A, Hepatocellular Carcinoma. N Engl J Med. 2019;380(15):1450–62.
11. Bruix J, Sherman M. American Association for the Study of Liver D, management of hepatocellular carcinoma: an update. Hepatology. 2011;53(3):1020–2.
12. Singal AG, Pillai A, Tiro J. Early detection, curative treatment, and survival rates for hepatocellular carcinoma surveillance in patients with cirrhosis: a meta-analysis. PLoS Med. 2014;11(4):e1001624.
13. Zhang S, Wang C, Liu B, Lu QB, Shang J, Zhou Y, et al. Cost-effectiveness of expanded antiviral treatment for chronic hepatitis B virus infection in China: an economic evaluation. Lancet Reg Health West Pac. 2023;35:100738.
14. Su S, Wong WC, Zou Z, Cheng DD, Ong JJ, Chan P, et al. Cost-effectiveness of universal screening for chronic hepatitis B virus infection in China: an economic evaluation. Lancet Glob Health. 2022;10(2):e278–87.
15. Choi WM, Yip TC, Wong GL, Kim WR, Yee LJ, Brooks-Rooney C, et al. Hepatocellular carcinoma risk in patients with chronic hepatitis B receiving tenofovir- vs. entecavir-based regimens: individual patient data meta-analysis. J Hepatol. 2023;78(3):534–42.
16. European Association for the Study of the Liver, EASL Clinical Practice Guidelines. Management of hepatocellular carcinoma. J Hepatol. 2018;69(1):182–236.
17. National Health Commission of the People's Republic of China Medical Administration hospital Authority. Guidelines for diagnosis and treatment of primary liver cancer in China (2022 edition). Chin J Hepatol. 2022;30(4):367–88.
18. Revill PA, Chisari FV, Block JM, Dandri M, Gehring AJ, Guo H, et al. A global scientific strategy to cure hepatitis B. Lancet Gastroenterol Hepatol. 2019;4(7):545–58.
19. Macrotrends. accessed Dec 19, China life expectancy 1950–2022. https://www.macrotrends.net/countries/CHN/china/life-expectancy (2022).
20. Husereau D, Drummond M, Augustovski F, de Bekker-Grob E, Briggs AH, Carswell C, et al. Consolidated Health Economic evaluation reporting standards 2022 (CHEERS 2022) Statement: Updated Reporting Guidance for Health Economic Evaluations. Value Health. 2022;25(1):3–9.
21. Huang CF, Jang TY, Jun DW, Ahn SB, An J, Enomoto M, et al. On-treatment gamma-glutamyl transferase predicts the development of hepatocellular carcinoma in chronic hepatitis B patients. Liver Int. 2022;42(1):59–68.
22. Yip TC, Wong VW, Chan HL, Tse YK, Lui GC, Wong GL. Tenofovir is Associated with Lower Risk of Hepatocellular Carcinoma Than Entecavir in patients with chronic HBV infection in China. Gastroenterology. 2020;158(1):215–25.
23. Toy M, Hutton D, McCulloch K, Romero N, Revill PA, Penicaud MC, et al. The price tag of a potential cure for chronic hepatitis B infection: a cost threshold analysis for USA, China and Australia. Liver Int. 2022;42(1):16–25.
24. Wong GL, Chan HL, Mak CW, Lee SK, Ip ZM, Lam AT, et al. Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients with liver cirrhosis. Hepatology. 2013;58(5):1537–47.
25. Choi WM, Kim GA, Choi J, Han S, Lim YS. Increasing on-treatment hepatocellular carcinoma risk with decreasing baseline viral load in HBeAg-positive chronic hepatitis B. J Clin Invest. 2022;132(10):e154833.
26. Mazzaferro V, Bhoori S, Sposito C, Bongini M, Langer M, Miceli R, et al. Milan criteria in liver transplantation for hepatocellular carcinoma: an evidence-based analysis of 15 years of experience. Liver Transpl. 2011;17(Suppl 2):S44–57.
27. Lima PH, Fan B, Berube J, Cerny M, Olivie D, Giard JM, et al. Cost-Utility Analysis of Imaging for Surveillance and Diagnosis of Hepatocellular Carcinoma. AJR Am J Roentgenol. 2019;213(1):17–25.
28. Zhang S, Ma Q, Liang S, Xiao H, Zhuang G, Zou Y, et al. Annual economic burden of hepatitis B virus-related diseases among hospitalized patients in twelve cities in China. J Viral Hepat. 2016;23(3):202–10.
29. Bertram MY, Lauer JA, Stenberg K, Edejer TTT. Methods for the Economic Evaluation of Health Care Interventions for Priority Setting in the Health System: an Update from WHO CHOICE. Int J Health Policy Manag. 2021;10(11):673–7.
30. Department of Population and Employment Statistics, National Bureau of Statistics of China. China statistical yearbook 2021. Beijing: China Statistics; 2021.

31. Marrero JA, Kulik LM, Sirlin CB, Zhu AX, Finn RS, Abecassis MM, et al. Diagnosis, staging, and management of Hepatocellular Carcinoma: 2018 Practice Guidance by the American Association for the study of Liver diseases. Hepatology. 2018;68(2):723–50.
32. Omata M, Cheng AL, Kokudo N, Kudo M, Lee JM, Jia J, et al. Asia-Pacific clinical practice guidelines on the management of hepatocellular carcinoma: a 2017 update. Hepatol Int. 2017;11(4):317–70.
33. Farhang Zangneh H, Wong WWL, Sander B, Bell CM, Mumtaz K, Kowgier M, et al. Cost Effectiveness of Hepatocellular Carcinoma Surveillance after a sustained Virologic response to therapy in patients with Hepatitis C virus infection and Advanced Fibrosis. Clin Gastroenterol Hepatol. 2019;17(9):1840–9.
34. Singal AG, Lampertico P, Nahon P. Epidemiology and surveillance for hepatocellular carcinoma: new trends. J Hepatol. 2020;72(2):250–61.
35. Forner A, Reig M, Bruix J, Hepatocellular carcinoma. Lancet. 2018;391(10127):1301–14.
36. Cheng H, Liu S, Luo S, Chan P, Chen Z, Le LV, et al. Uptake of hepatitis B antiviral treatment: a panel data analysis of 31 provinces in China (2013–2020). Liver Int. 2022;42(8):1762–9.
37. Marley G, Seto WK, Yan W, Chan P, Tucker JD, Tang W, et al. What facilitates hepatitis B and hepatitis C testing and the role of stigma among primary care patients in China? J Viral Hepat. 2022;29(8):637–45.
38. Shan S, Zhao X, Jia J. Comprehensive approach to controlling chronic hepatitis B in China. Clin Mol Hepatol. 2024;30(2):135–43.
39. Sherman M. Whither hepatocellular carcinoma screening? Hepatology. 2012;56(6):2412–4.
40. Poustchi H, Farrell GC, Strasser SI, Lee AU, McCaughan GW, George J. Feasibility of conducting a randomized control trial for liver cancer screening: is a randomized controlled trial for liver cancer screening feasible or still needed? Hepatology 2011, 54(6): 1998–2004.
41. Kim JJ, Burger EA, Regan C, Sy S. Screening for Cervical Cancer in Primary Care: a decision analysis for the US Preventive Services Task Force. JAMA. 2018;320(7):706–14.

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