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Cost-Effectiveness of Hepatocellular Carcinoma Surveillance: An Assessment of Benefits and Harms

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INTRODUCTION: **The value of hepatocellular carcinoma (HCC) surveillance is defined by the balance of benefits, i.e., early tumor detection, and potential harms, related to false positive and indeterminate results. Although physical harms can be observed in 15%–20% of patients with cirrhosis undergoing HCC surveillance, previous cost-effectiveness analyses have not incorporated costs of harms. We aimed to evaluate the cost-effectiveness of HCC surveillance including both benefits and harms.**

DESIGN: **We constructed a Markov model to compare surveillance strategies of ultrasound (US) alone, US and alpha fetoprotein (AFP), and no surveillance in 1 million simulated patients with compensated cirrhosis. Harms included imaging and biopsy in patients undergoing surveillance for HCC. Model inputs were based on literature review, and costs were derived from the Medicare fee schedule, with all costs inflated to 2018 dollars. The primary outcome was the incremental cost-effectiveness ratio per incremental quality-adjusted life-year.**

RESULTS: **In the base case analysis, US with AFP was the dominant strategy over both US alone and no surveillance. In a probabilistic sensitivity analysis, US with AFP was the most cost-effective strategy in 80.1% of simulations at a willingness-to-pay threshold of $100,000 per quality-adjusted life-year. In our threshold analyses, an HCC incidence >0.4% per year and surveillance adherence >19.5% biannually were necessary for US with AFP to be cost-effective compared with no surveillance.**

DISCUSSION: **Accounting for both surveillance-related benefits and harms, US and AFP is more cost-effective for HCC surveillance than US alone or no surveillance in patients with compensated cirrhosis.**

INTRODUCTION

Despite improvements in treatment over time, hepatocellular carcinoma (HCC) continues to be a highly morbid tumor with an incidence-to-mortality ratio that approaches one (1). It is the fastest increasing cause of cancer-related death over the past decade in the United States and the third leading cause of cancer-related death worldwide (1–3). However, prognosis for HCC highly depends on tumor stage at diagnosis. Although patients detected at late stages are only eligible for palliative therapies and have a median survival less than 1 year, patients detected at an early stage can undergo curative therapy and achieve 5-year survival exceeding 70% (4,5).

More than 90% of HCC in the United States and Europe occur in the setting of cirrhosis, and HCC is the leading cause of death in patients with compensated cirrhosis (6). Given an identifiable at-risk population and selective availability of curative treatments for HCC detected at an early stage, several professional societies including the American Association for the Study of Liver

Diseases and National Comprehensive Cancer Network recommend routine HCC surveillance using an abdominal ultrasound (US) with or without a serum blood test, alpha fetoprotein (AFP), in patients with cirrhosis (7,8).

There is increasing recognition that the value of cancer screening programs must consider both benefits and potential harms of screening. Although this is best accomplished through a randomized controlled trial, a previous attempt of a randomized controlled trial was prematurely closed because of inadequate enrollment (9). Therefore, we are forced to depend on level II and modeling data to evaluate the value of HCC surveillance. Several cohort studies have evaluated the benefits of HCC surveillance and demonstrated an association with early detection and improved survival, even after adjusting for lead time and length time bias (10–12). Although screening harms have been well described for many cancer screening programs, there have been only 2 studies to date describing potential harms of HCC surveillance in patients with cirrhosis (13,14). Both studies reported diagnostic

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evaluation owing to false positive or indeterminate screening examinations in approximately 20% of patients, with some patients undergoing repeated computed tomography (CT)/MRI examinations or invasive evaluation, such as liver biopsy (13,14). Previous decision and cost-effectiveness analyses preceded these data on screening harms, thereby failing to comprehensively account for the consequences of false positive or indeterminate surveillance results. In this study, we present a cost-effectiveness analysis evaluating HCC surveillance using US with or without AFP, incorporating recent data on benefits and harms, in a cohort of patients with compensated cirrhosis.

METHODS
Model overview
We developed a probabilistic decision analytical microsimulation state-transition Markov model (15) using dedicated software (TreeAge version 19.1.1, Williamstown, MA). The analysis was performed according to the published guidelines of economic analyses (16,17). We simulated a cohort of 1,000,000 patients with diagnosed compensated cirrhosis at cohort entry, who were followed up at a referral center over their lifetime horizon. We modeled only compensated cirrhosis because of previous analyses showing limited effectiveness of surveillance in patients who are decompensated (i.e., Child Pugh class B and C) (18).

Surveillance strategies
Three surveillance strategies were modeled: no surveillance, semiannual US, and semiannual US with AFP. Patients in the no surveillance arm would experience the natural history of cirrhosis. Irrespective of surveillance strategy, for patients who developed HCC, there is a chance of incidental tumor detection, depending on tumor stage and the degree of hepatic decompensation, across all 3 arms. Otherwise, the sensitivity and specificity of each modality used across arms governed the likelihood of early detection and surveillance consequences. False negative results followed the progressive natural history of HCC until detected incidentally, symptomatically, or by follow-up imaging. False positive results underwent evaluation by a variable number of CT/MRI scans or liver biopsy that were conditional on the trigger (AFP vs US) and history of previous false positive results. True positive nodules were also evaluated by variable number of CT/MRI, with or without liver biopsy, for confirmation.

Modeling parameters
Surveillance test characteristics and clinical outcomes depended on the patient's disease severity and the duration in a given health state. All health states and the potential interstate transitions are depicted in Supplementary Figure 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B550, and the workup of patients with US-detected liver nodules is depicted in Supplemental Figure 2, Supplementary Digital Content 1, http://links.lww.com/AJG/B551. The time-dependent risk of decompensation was modeled using a cumulative risk function competing with the risk of death (19). Once patients developed HCC staged at diagnosis, with subsequent survival, utilities and costs were assigned to each particular stage. For patients with undiagnosed HCC, their utilities were commensurate with their stage of cirrhosis. Death due to HCC and/or decompensation (when present) was modeled in a similar fashion accounting for the competing risk of liver transplantation for persons selected for the liver transplant waitlist. Table 1 details the model parameters and their sources. Transition probabilities are modeled as β, triangular, or tabular distributions. We assumed that time spent evaluating a false positive surveillance result was associated with a 5% absolute reduction in health-state utility while patients were in the false positive state. Costs were modeled as triangular distributions. All costs (inflated to 2018 US dollars), life-years, and utilities were discounted at a rate of 3% per annum.

Model procedures
The goal of this analysis was to model 2 outcomes simultaneously based on the generation of discounted costs (2018 US dollars) and discounted quality-adjusted life-years (QALYs) that accrue over time. Because there is uncertainty intrinsic to all input parameters (i.e., confidence intervals or ranges of values), our primary analysis was a microsimulation that accounted for 1,000,000 unique combinations within the input parameter distributions. Then, we conducted a probabilistic sensitivity analysis that is a second-order evaluation of uncertainty where each of the 1,000,000 simulated patients could experience 10,000 random samples within each parameter's distribution. The end result of this analysis is the probability of cost-effectiveness (cost per QALY) for a given strategy in the overall set of simulations. We calculated the incremental cost-effectiveness ratios for the competing strategies and interpreted the results about the contemporary willingness-to-pay (WTP) threshold. The WTP threshold is the amount per person that society is willing to pay to adopt a new clinical strategy for an additional QALY over the current acceptable strategy. It is generally considered to be 2–3 times the individual share of gross domestic product (42). We not only discuss most results in WTP of $100,000 but also assess the probability of cost-effectiveness for each strategy across a range of WTP up to $200,000 in "cost-acceptability curves." We performed 2 threshold analyses, varying incidence of HCC and consistent adherence to HCC surveillance, to determine the parameters at which there was a transition in the preferred strategy seen in the base case.

RESULTS
Base case
In our base case analysis, we modeled a 2% annual HCC incidence rate for a cohort of 1,000,000 patients with compensated cirrhosis, resulting in a 23% lifetime risk of HCC. The proportion of HCC diagnosed at an early stage, as defined by Milan criteria, was 74%, 83%, and 91% for no surveillance, US alone, and US with AFP arms, respectively. The average lifetime discounted costs and QALYs are described in Table 1. The number of CT/MRI required for each diagnosis of HCC was 1.4, 8.0, and 9.7 for the no surveillance, US alone, and US with AFP arms, respectively. The survival of each arm was 10.93 years, 10.92 years, and 10.84 years for US with AFP, US alone, and the no surveillance arms, respectively. US with AFP was the dominant strategy given that it yielded more QALYs (6.02) at the lowest cost.

Sensitivity analyses
When the strategies were evaluated over a range of potential screening-related harms (i.e., minimum or maximum number of CT/MRIs to arrive at an HCC diagnosis), the benefits of US with AFP surveillance were attenuated but without altering the overall rankings (Table 2).

For all values within the modeled parameters, US with AFP remained a dominant strategy compared with US alone and no

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Table 1. Model input parameters

Input variable	Value	Range	References
HCC incidence			
Incidence in compensated cirrhosis (yearly)	2%	1%–3%	(20–23)
Incidence in decompensated cirrhosis (yearly)	4%	2%–6%	(20–23)
Screening effectiveness and diagnostics			
Sensitivity of US alone for > early-stage HCC	84%	76%–92%	(24)
Sensitivity of US alone for early-stage HCC	45%	30%–62%	(24)
Specificity of US alone	91%	86%–94%	(24)
Sensitivity of US with AFP for > early-stage HCC	97%	91%–99%	(24)
Sensitivity of US with AFP for early HCC	63%	48%–75%	(24)
Specificity of US with AFP	84%	77%–89%	(24)
Ultrasound leads to CT/MRI because of false positive	12%	8%–16%	(13,14)
AFP leads to CT/MRI because of a false positive	8%	5%–11%	(13,14)
Number of CT/MRI completed before diagnosis of HCC	1.5	1–3	(13,14)
Number of CT/MRI completed without diagnosis of HCC for false positive AFP	1.2	1.0–1.5	(14)
Number of CT/MRI completed without diagnosis of HCC for false positive US	2.5	2–4	(13,14)
Proportion of patients biopsied	0.3%	0.1%–0.5%	(13,14)
Biopsy bleeding or biliary injury	0.6%	0.3%–0.9%	(14)
Death from biopsy	0.08%	0.04%–.10%	(14)
Biopsy false negative	30%	22%–36%	(14)
Disease progression			
Decompensated cirrhosis to palliative care (annually)	4%	2%–10%	(25)
Advanced HCC to palliative care (annually)	70%	60%–80%	(26)
Early-stage HCC to intermediate-stage HCC (no treatment; annual)	5%	3%–9%	(27)
Intermediate-stage HCC to advanced-stage HCC (no treatment; annual)	15%	12%–18%	(28)
Transplant			
Liver transplant for HCC (probability at 6 mo)	14.1%	10%–18%	(29)
Liver transplant for HCC (probability at 12 mo)	60%	20%–80%	(29)
Liver transplant for HCC (probability at 24 mo)	90.6%	75%–100%	(29)
Liver transplant wait time	4.2 mo	1.6–7.7 mo	(30)
Costs (2018 US dollars)			
Abdominal US	$142.35	133.31–194.52	(31)
AFP	$18.64	$16.32-$20.71	(32)

Table 1. (*continued*)

Input variable	Value	Range	References
MRI abdomen with and without contrast	$498.78	$441.32–$648.29	(31)
CT abdomen with and without contrast	$273.54	$236.67–$346.40	(31)
Liver biopsy	$1,034.87	$846.05–$1,223.70	(31)
Liver biopsy complications	$5,449	$1,385–$35,273	(33)
Liver transplant (first year)	$354,672	$283,543–$364,672	(31,34)
Liver transplant (after first year)	$49,906	$44,814–$54,447	(31,34)
HCC early-stage costs (annual)	$64,798	$35,512–$131,951	(35)
HCC intermediate-stage costs (annual)	$93,522	$42,091–$168,287	(35)
HCC advanced-stage costs (annual)	$84,405	$36,480–$115,797	(35)
Compensated cirrhosis costs (annual)	$26,024	$5,157–$312,287	(36)
Decompensated cirrhosis costs (annual)	$68,604	$13,810–$823,248	(36)
Palliative care costs (daily)	$193	$151–$744	(37)
Utilities			
HCC early stage	0.72	0.62–0.82	(38)
HCC intermediate stage	0.69	0.62–0.78	(38,39)
HCC advanced stage	0.65	0.52–0.78	(38,39)
Compensated cirrhosis	0.78	0.71–0.89	(38,39)
Decompensated cirrhosis	0.60	0.46–0.71	(38,39)
Decompensated cirrhosis and HCC	0.57	0.46–0.68	(38,39)
Postliver transplant (year 1)	0.69	0.55–0.78	(40)
Postliver transplant (subsequent yr)	0.79	0.62–0.91	(40)
Palliative care	0.40	0.37–0.42	(41)

AFP, alpha fetoprotein; CT, computed tomography; HCC, hepatocellular carcinoma; US, ultrasound.

surveillance. This included all ranges of modeled harms and benefits associated with surveillance (i.e., across all sensitivity analyses). We conducted several 1-way sensitivity analyses to establish the salient model parameters in the comparison between US alone and no surveillance strategies. In Figure 1, we used a tornado diagram to illustrate how the cost-effectiveness of US alone screening relative to no surveillance varies in accordance with the incidence of HCC and the screening test characteristics within the modeled variable parameters. This analysis demonstrates that higher rates of HCC and higher sensitivity/specificity for US alone improve the cost-effectiveness of US alone surveillance. However, across the range of all modeled parameters, the incremental cost-per-QALY of US alone is within the traditional WTP threshold of $100,000 per QALY. In Supplemental Table 1, Supplementary Digital Content 1, http://links.lww.com/AJG/B552, we demonstrate the results of the 1-way sensitivity analysis for all the input parameters. The cost-effectiveness of US vs no surveillance is sensitive to incidence of HCC in compensated cirrhosis, specificity of US, cost of compensated cirrhosis care, and probability of liver transplantation. In a probabilistic sensitivity analysis (Figure 2), as the WTP per incremental QALY rises, the proportion of modeled samples where US with AFP is most cost-effective rises whereas no surveillance falls. No surveillance is the preferred strategy in 15.3% of samples whereas US with AFP is preferred in 73.2% at a WTP threshold of $50,000, compared with 10.1% and 80.3% of cases,

respectively, at a WTP threshold of $100,000. Finally, we varied incidental detection of early HCC within the no surveillance arm from 0% to 25% for every cycle. At 0%-incidental probability, the proportion of early HCC detected for the population is 32% (occurring entirely during the decompensated health state), rising to 58% early detection at 10% and 74% at 25% incidental detection.

Threshold analysis

In 2 threshold analyses, we established the HCC incidence and surveillance adherence thresholds for our model. First, in Figure 3a, we demonstrate a threshold-analysis for HCC incidence. The cost per QALY is shown across a range of HCC incidence from 0% to 5% per year. As the incidence of HCC rises above 0, the cost per QALY of screening declines. The HCC incidence threshold at which US with AFP falls below $100,000/QALY compared with no surveillance is 0.4%/year, with US with AFP yielding the lowest cost per QALY for all HCC incidences >0.7%/year.

Second, in Figure 3b, we show the cost per QALY across a range of consistent adherence rates for HCC surveillance (18%–100%). As adherence to screening allocation rises, this cost per QALY falls. For all adherence rates >19.5%, US with AFP yields the lowest cost per QALY. US with AFP has an incremental cost-effectiveness ratio below $100,000/QALY at all adherence rates and becomes dominant compared with no surveillance

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Table 2. Cost-effectiveness of hepatocellular carcinoma surveillance strategies with base case inputs

	Average overall cost (USD)	Incremental cost (USD)	Average overall QALYs	Incremental QALYs	Cost per incremental QALY
US with AFP	1,254,173.20	0.00	6.02	0.00	—
US alone	1,257,879.04	3,705.84	6.00	−0.02	Dominated
No surveillance	1,266,358.65	12,185.45	5.98	−0.04	Dominated
Maximum cross-sectional imaging before diagnosis					
US with AFP	1,256,329.35	0.00	6.02	0.00	—
US alone	1,260,328.23	3,998.88	5.99	−0.03	Dominated
No surveillance	1,268,173.63	11,844.29	5.99	−0.03	Dominated
Minimum cross-sectional imaging before diagnosis					
US with AFP	1,251,775.31	0.00	6.03	0.00	—
US alone	1,254,641.51	2,866.21	6.02	−0.01	Dominated
No surveillance	1,265,725.43	13,950.12	5.98	−0.05	Dominated

AFP, alpha fetoprotein; QALY, quality-adjusted life-year; US, ultrasound.

(i.e., has more QALYs at lower cost) when consistent adherence exceeds 59%.

DISCUSSION

HCC surveillance is associated with improved early detection of HCC and overall improved survival (11,24). However, emerging data on potential surveillance-related harms including false positive results that can lead to unnecessary testing and psychological distress have called into question the value of HCC surveillance (13). Our study, modeling cost-effectiveness of surveillance integrating potential screening harms, advances knowledge about HCC surveillance cost-effectiveness. First, we found that US with AFP was the cost-effective strategy compared with both no surveillance and US alone strategies. Specifically, US with AFP maximizes early detection of HCC with the lowest costs and highest QALYs. Sensitivity analyses demonstrate that US with AFP becomes a superior strategy when the incidence of HCC is >0.4% and is robust to sensitivity analyses across the range of published screening test characteristics.

What these data mean for screening research

First, early detection of HCC for a population at risk of HCC is beneficial. Although the mechanisms underlying the benefits of surveillance are not explicitly clear from this study, our findings demonstrate that surveillance increases the rate of early detection and that the cost-effectiveness of screening is robust to the harms of
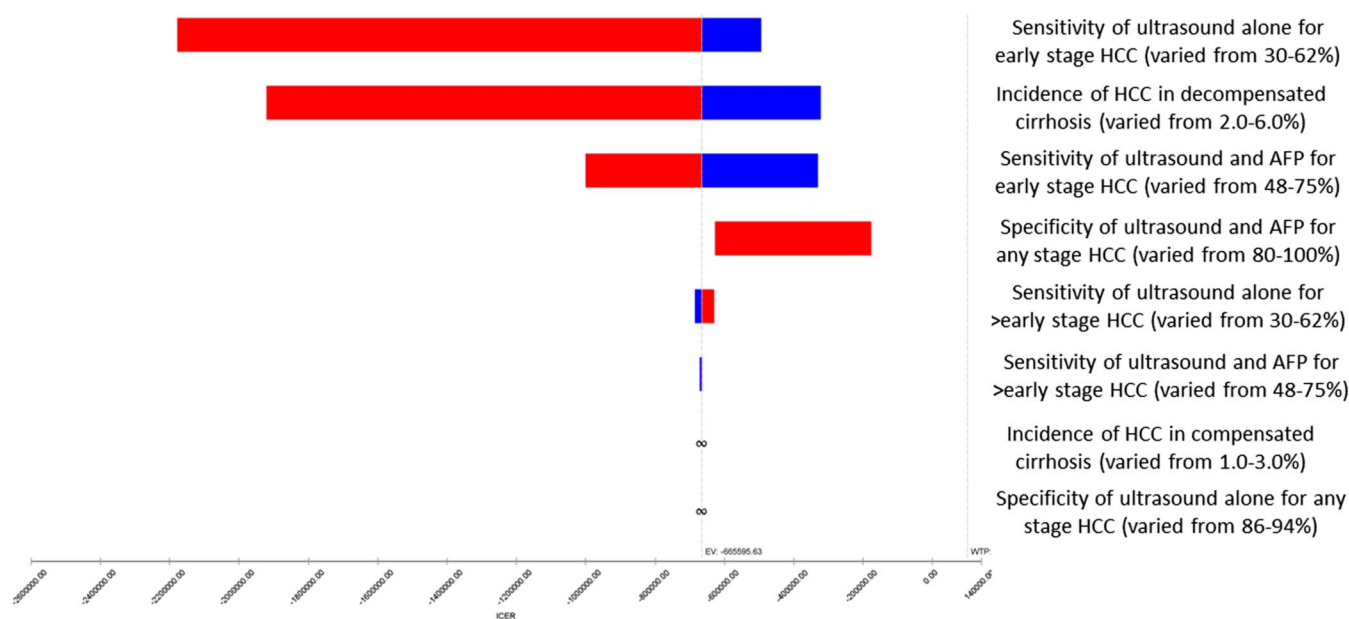
Figure 1. Tornado plot showing 1-way sensitivity analyses for ultrasound vs no surveillance. AFP, alpha fetoprotein; HCC, hepatocellular carcinoma.
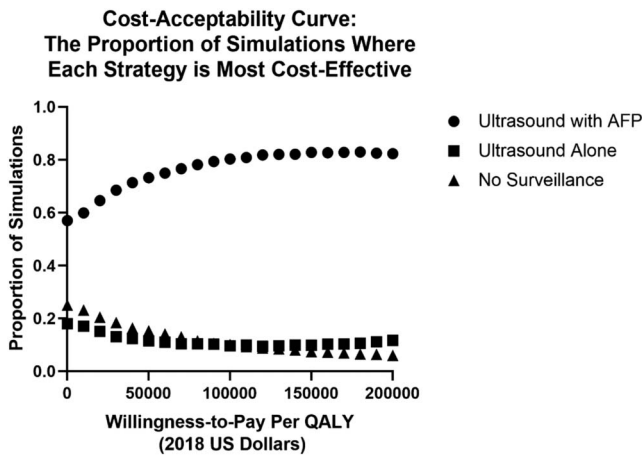
Figure 2. Cost-effectiveness acceptability curves for no surveillance, ultrasound surveillance, and surveillance with ultrasound with AFP. AFP, alpha fetoprotein; QALY, quality-adjusted life-year.

screening (false positives and additional testing). However, these benefits are less clear for persons with a low (≤0.4%) risk of HCC, such as those with F3 fibrosis in the setting of HCV or non-alcoholic steatohepatitis where the annual incidence of HCC is 0.3%–0.5% (20,43,44). Surveillance in this population of patients without cirrhosis remains controversial, and our study indicates that there might be a subgroup of patients with advanced fibrosis but without cirrhosis, where HCC surveillance is cost-effective. Second, although the specificity of US with AFP is lower than US alone, data have suggested that differential use of follow-up diagnostic testing might mitigate the physical harms and resultant costs related to false positive AFP results (11,24). Furthermore, US with AFP has improved sensitivity for early-stage HCC detection relative to US alone, driving its cost-effectiveness. US with AFP was associated with the most CT/MRI tests for each diagnosis of HCC; however, this did not negatively affect its relative cost-effectiveness. Third, we demonstrated that adherence to surveillance has a significant impact on the cost-effectiveness of any surveillance strategy. Although this is important given previous studies highlighting underuse of HCC surveillance in clinical practice (45–47), the threshold of adherence for HCC surveillance using US with AFP to remain cost-

effective is relatively low at 19.5%, highlighting the dominance of this surveillance strategy. We found that US with AFP surveillance is dominant over no surveillance once consistent surveillance adherence exceeds 59%, setting an aspirational threshold to maximize surveillance value.

Several published modeling studies have evaluated the cost-effectiveness of US surveillance (48,49); however, no previous study has included real world harms data. Many of the existing cost-effectiveness studies have shown that surveillance with US alone was the most cost-effective strategy when compared with other competing strategies, including US with AFP and multiphasic cross-sectional modalities (48,50,51). Our results are discordant with the literature, given inclusion of more recent data detailing the sensitivity of US with AFP and the integration of surveillance harms instead of simply relying on specificity measurements. Published cohort studies have shown that many patients with false positive AFP results are simply monitored instead of undergoing diagnostic testing, whereas those with US are more likely to follow-up testing (14).

Ideally, to minimize harms of surveillance, while maximizing benefits, the highest intensity surveillance should be directed to those patients at highest risk. A precision approach to surveillance has been modeled to be the most cost-effective; however, we currently lack well-validated stratification tools for HCC risk (52). Certain populations, such as those with elevated body mass index and those with decompensated cirrhosis, have lower quality imaging using US and might benefit from surveillance using multiphasic cross-sectional imaging; however, this strategy deserves further study (53). Although development of risk stratification methods and evaluation of novel surveillance techniques are underway, further efforts must be undertaken to increase the consistent receipt of surveillance in patients with cirrhosis and certain populations with chronic hepatitis B. Interventions to better identify undiagnosed cirrhosis are needed because up to 25% of patients with HCC are unaware they have cirrhosis before their HCC diagnosis (54,55).

Our study has notable strengths and weaknesses. Markov modeling has known limitations based on assumption and the quality of the input data. Several of the input sources were from single sources; however, the robustness of the findings across the model ranges, suggesting that additional inputs would not
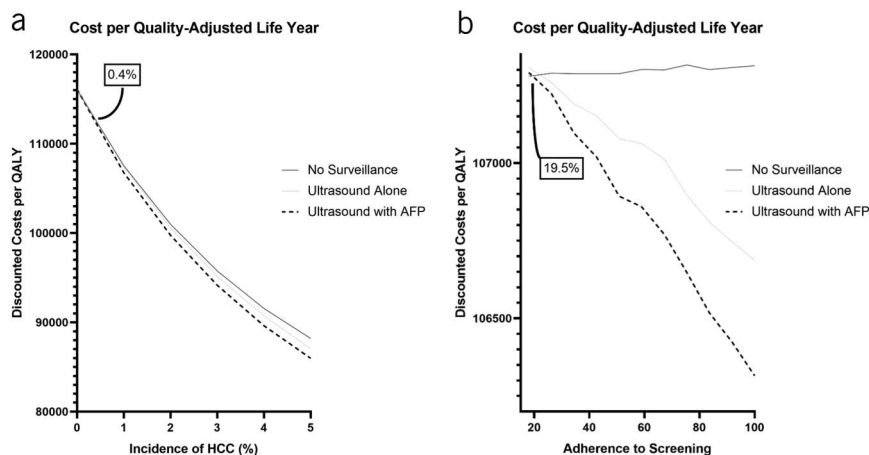
Figure 3. (**a**) Threshold analysis of the cost per QALY with varying HCC incidence. (**b**) Threshold analysis of the cost per QALY with varying adherence to HCC surveillance strategies. AFP, alpha fetoprotein; HCC, hepatocellular carcinoma; QALY, quality-adjusted life-year.

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dramatically affect our results. Surveillance harms have psychological consequences for patients and might decrease QALYs; however, we currently lack data on the patient-reported impact of surveillance harms, so we made estimates on decrements in QALYs with surveillance-related harms while patients were in a false positive state. Despite increased harms associated with US with AFP, it remained the most cost-effective strategy. Finally, our cost-effectiveness analysis was restricted to currently available strategies, given limited phase III data evaluating benefits and harms for novel biomarker panels that are currently undergoing evaluation (56).

In conclusion, we have shown that HCC surveillance using US with AFP is the most cost-effectiveness strategy, compared with US alone and no surveillance, across a wide range of parameters. Surveillance using US with AFP is cost-effective at an adherence threshold of 19.5% and becomes dominant over no surveillance once adherence >59%, highlighting the need for interventions to improve recognition of cirrhosis and increase surveillance use among at-risk patients. Although awaiting newer imaging and serum-based surveillance modalities, our data highlight the need for interventions to promote surveillance using US with AFP among at-risk patients.

CONFLICTS OF INTEREST

Study Highlights

WHAT IS KNOWN

✓ HCC surveillance is associated with early detection and improved survival.
✓ The optimal surveillance strategy, when accounting for harms, is unknown.

WHAT IS NEW HERE

✓ When accounting for real world harms, surveillance with US with AFP is the dominant surveillance strategy.
✓ HCC surveillance with US with AFP is cost-effective with incidence greater than 0.4% and biannual adherence greater than 19.5%.

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