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Cost-Effectiveness of a Biomarker-Based Screening Strategy for Hepatocellular Carcinoma in Patients with Cirrhosis

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Keywords
Cirrhosis · Liver cancer · Early detection · Biomarker · Modeling · Surveillance · Ultrasound

Abstract

Introduction: Given suboptimal performance of ultrasound-based surveillance for early hepatocellular carcinoma (HCC) detection in patients with cirrhosis, there is interest in alternative surveillance strategies, including blood-based biomarkers. We aimed to evaluate the cost-effectiveness of biomarker-based surveillance in patients with cirrhosis. ***Methods:*** We constructed a decision-analytic model to compare ultrasound/alpha-fetoprotein (AFP) and biomarker-based surveillance strategies in 1,000,000 simulated patients with compensated cirrhosis. Model inputs for adherence, benefits, and harms of each strategy were based on literature review, and costs were derived from the Medicare fee schedule. Primary outcomes were quality-adjusted life-years (QALY) and incremental cost-effectiveness ratio (ICER) of the surveillance strategies, with cost-effectiveness assessed at a threshold of USD 150,000 per QALY. We performed sensitivity analyses for HCC incidence, test performance characteristics, surveillance adherence, and biomarker costs. ***Results:*** In the base case, both ultrasound/AFP and biomarker-based surveillance were cost-effective versus no surveillance, with ICERs of USD 105,620, and USD 101,295, per QALY, respectively. Biomarker-based surveillance was also cost-effective versus ultrasound/AFP, with an ICER of USD 14,800 per QALY. Biomarker sensitivity exceeding 80%, cost below USD 210, or adherence exceeding 58% were necessary for biomarker-based screening to be cost-effective versus ultrasound/AFP. In two-way sensitivity analyses, biomarker costs were directly related with test sensitivity and adherence, whereas sensitivity and adherence were inversely related. In a probabilistic sensitivity analysis, biomarker-based screening was the most cost-effective strategy in most (65%) simulations. ***Conclusion:*** Biomarker-based screening appears cost-effective for HCC screening, but results are sensitive to test sensitivity, adherence, and costs.

Introduction

Hepatocellular carcinoma (HCC) is the third leading cause of cancer-related death worldwide and is one of the few cancers with a rising mortality [1]. HCC screening is recommended by professional society guidelines, including

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those from the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL) and Asian Pacific Association for the Study of the Liver (APASL), given the marked difference in prognosis between patients with early-stage HCC versus those with more advanced tumor burden [2, 3]. Patients with early-stage HCC are amenable to curative surgical treatments, affording 5-year survival exceeding 60%, whereas palliative therapies for more advanced tumor burden yields median survival of 1–3 years [4]. Accordingly, cohort studies in cirrhosis patient populations have consistently reported an association between screening receipt and improved clinical outcomes including early-stage HCC detection and improved survival [5–7].

The cornerstone of HCC screening remains semiannual abdominal ultrasound (US), with or without alpha-fetoprotein (AFP), given several advantages including being readily available, cheap, and noninvasive. However, this strategy has suboptimal sensitivity to detect HCC at an early stage, with a meta-analysis demonstrating a pooled sensitivity of only 63% when the two tests were used in combination [8]. Patients with nonviral etiologies of liver disease and obese individuals have increased odds of poor US visualization, further impairing sensitivity for early HCC detection in these patient populations [9, 10]. Second, evolving data suggest that false-positive or indeterminate screening results can lead to potential physical, financial, and psychological harms, lowering the overall value of this approach [7, 11–13]. Finally, several patient and provider barriers result in underuse of imaging-based HCC screening, further mitigating effectiveness to reduce HCC-related mortality in clinical practice [14–17].

These limitations of US-based screening have prompted provider and patient interest in alternative imaging- and biomarker-based screening strategies [18, 19]. A biomarker-based approach may be particularly promising as it could offer equal, if not better, test performance but also address screening barriers to increase screening utilization [19]. Although AFP remains the only biomarker to have completed all five phases of biomarker validation, recent multi-center studies have provided phase II and phase III validation for promising biomarker panels, including GALAD and methylated HCC blood tests [20–26]. GALAD is currently available for use and two methylated DNA panels have been granted breakthrough designation from the FDA. Although further data specifically for HCC detection in patients with cirrhosis are still needed, multi-cancer detection platforms offer another emerging biomarker-based option. Available data demonstrate clinical performance estimates for early-stage HCC sensitivity and specificity; however, data are needed to evaluate potential clinical utility of biomarker-based strategies. In the absence of large clinical utility trials, which will take several years to complete, decision-analytic models provide a powerful tool to fill this knowledge gap and evaluate the value of biomarker-based tests. The aim of our study was to characterize cost-effectiveness of biomarker-based screening and identify minimum thresholds to achieve cost-effectiveness compared to US-based screening.

Methods

Overview of Model

We developed a decision-analytic state-transition model (online suppl. Fig. 1; for all online suppl. material, see https://doi.org/10.1159/000539895), in accordance with published recommendations [27]. We simulated a cohort of 1,000,000 patients with compensated cirrhosis from any etiology, age ≥50 years at cohort entry, who were followed over their lifetime horizon. Analyses were conducted using TreeAge version 19.1.1, Williamstown, MA, USA.

Screening Strategies

We modeled three screening strategies using 6-month cycle intervals: no screening, semiannual ultrasound with AFP and semiannual biomarker-based screening. We did not model semiannual ultrasound alone, given prior data showing ultrasound and AFP was the preferred strategy [28]. Patients in the no screening arm experienced the natural history of cirrhosis. In the base case, we assumed 60% adherence for each of the screening arms [29]. Irrespective of screening strategy, for patients who developed HCC, there was a chance of incidental tumor detection, dependent on tumor stage and the degree of hepatic decompensation. Otherwise, sensitivity and specificity of each modality governed the likelihood of early detection and screening consequences. Base case estimates for sensitivity and specificity of the biomarker-based strategy were based on a combination of AFP, AFP-L3, and DCP given this combination (i.e., GALAD) is currently undergoing prospective validation; estimates for other emerging biomarkers were evaluated in sensitivity analyses. False-negative results followed the progressive natural history of HCC until detected incidentally, symptomatically, or by follow-up screening testing. False-positive results underwent evaluation by a variable number of CT/MRI scans or liver biopsy. True positive nodules were also evaluated by variable number of CT/MRI, with or without liver biopsy, for confirmation.

Modeling Parameters

Screening test-characteristics and clinical outcomes were dependent on the patient's disease severity and the duration in each health-state. The time-dependent risk of decompensation was modeled using a cumulative risk function competing with the risk of death. We assumed annual HCC incidence rate of 2% and

Table 1. List of variable inputs for the decision-analytic model

Input variable	Value	Range	References
HCC incidence			
Annual HCC incidence in compensated cirrhosis, %	2	1–3	[30–35]
Annual HCC incidence in decompensated cirrhosis, %	4	2–6	[32–35]
Screening effectiveness and diagnostics			
Sensitivity of US with AFP for HCC beyond an early stage, %	97	91–99	[8]
Sensitivity of US with AFP for early-stage HCC, %	63	48–75	[8]
Specificity of US with AFP, %	84	77–89	[8]
Biomarker sensitivity for HCC beyond an early stage, %	87	74–96	[20, 25, 36–39]
Biomarker sensitivity for early-stage HCC, %	70	74–96	[20, 25, 36–39]
Biomarker specificity, %	84	74–92	[20, 25, 36–39]
Physical harms (diagnostic CT/MRI) due to US false-positive results, %	12	8–16	[11, 40]
Physical harms (diagnostic CT/MRI) due to AFP false-positive results, %	8	5–11	[11, 40]
Number of CT/MRI completed prior to diagnosis of HCC in patients undergoing US screening	1.5	1–3	[11, 40]
Number of CT/MRI without HCC diagnosis for false-positive US	2.5	2–4	[11, 40]
Number of CT/MRI without HCC diagnosis for false-positive AFP or biomarker	1.2	1.0–1.5	[11]
Proportion of patients biopsied, %	0.3	0.1–0.5	[11, 40]
Biopsy bleeding or biliary injury, %	0.6	0.3–0.9	[11]
Death from biopsy, %	0.08	0.04–0.10	[11]
Biopsy false negative, %	30	22–36	[11]
Annual rates of disease progression			
Early-stage HCC to intermediate stage HCC, without treatment, %	90	85–95	[41]
Intermediate stage HCC to advanced stage HCC, without treatment, %	80	70–90	[42]
Advanced HCC to palliative care, %	80	70–90	[43]
Transplant			
Liver transplant for HCC, probability at 6 months, %	14.1	10–18	[44]
Liver transplant for HCC, probability at 12 months, %	60	20–80	[44]
Liver transplant for HCC, probability at 24 months, %	90.6	75–100	[44]
Waitlist for HCC, years	1.1	0.6–2.0	
Waitlist for decompensated cirrhosis, years	0.5	0.5–1.0	
Survival estimates			
Compensated cirrhosis, years	9.8	7.2–13.0	[45]
Decompensated cirrhosis, years	2.5	0.5–5.0	[45–47]
Early-stage HCC, years	6.5	1.0–19.0	[48, 49]
Intermediate-stage HCC, years	3.7	0–8.5	[48, 49]
Late-stage HCC, years	1.5	0–2.5	[48, 50]
Costs (2021 US Dollars), USD			
Abdominal US	158.01	147.97–215.92	[51]
AFP	20.69	18.12–22.99	[52]
Blood-based biomarker	200	116–600	[51]
MRI abdomen with and without contrast[a]	553.65	489.87–719.60	[51]
CT abdomen with and without contrast	303.63	262.70–384.50	[51]
Liver biopsy	1,148.71	939.12–1,358.31	[51]
Liver biopsy complications	6,048.39	1,537.35–39,153.03	[53]
Liver transplant (first year)	393,685.92	314,732.73–404,785.92	[51, 54]
Liver transplant (after first year)	55,395.66	49,743.54–60,436.17	[51, 54]
Early-stage HCC (annual)	50,001	26,777–92,737	[55]
Intermediate-stage HCC (annual)	93,221	42,254–222,397	[55]

Table 1 (continued)

Input variable	Value	Range	References
Advanced-stage HCC (annual)	84,342	38,230–192,070	[55]
Compensated cirrhosis (annual)	3,832	1,233–11,308	[55]
Decompensated cirrhosis (annual)	13,412	4,316–39,578	[55]
Palliative care (daily)	214.23	167.61–825.84	[56]
Utilities			
Early-stage HCC	0.72	0.62–0.82	[57]
Intermediate-stage HCC	0.69	0.62–0.78	[57, 58]
Advanced-stage HCC	0.65	0.52–0.78	[57, 58]
Compensated cirrhosis	0.85	0.68–0.98	[57, 58, 59]
Decompensated cirrhosis	0.78	0.53–0.93	[57–59]
Decompensated cirrhosis and HCC	0.57	0.46–0.68	[57, 58]
Post-liver transplant (year 1)	0.69	0.55–0.78	[60]
Post-liver transplant (subsequent years)	0.86	0.62–0.91	[60]
Palliative care	0.40	0.37–0.42	[61]

AFP, alpha-fetoprotein; CT, computed tomography; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging; US, ultrasound. [a]The same costs were applied for full and abbreviated MRI given the lack of different billing codes.

4% for patients with compensated and decompensated cirrhosis, respectively. Although HCC incidence rates have decreased with a recent shift to increasing nonviral etiologies, recent prospective cohorts still suggest an annual incidence of 2% per year [30, 31]. Once a patient developed HCC, we assigned survival, utilities and costs based on tumor stage at diagnosis. These estimates accounted for recommended first-line treatment, as well as potential second-line treatments based on likelihood of stage migration of downstaging, including liver transplantation. For patients with undiagnosed HCC, their utilities were commensurate with their stage of cirrhosis. Death due to HCC and/or decompensation 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 as well as their sources. Transition probabilities are modelled as beta, triangular, or tabular distributions based on the reported distribution in the literature [62]. We assumed that time spent evaluating a false-positive screening result was associated with a 5% absolute reduction in health-state utility during each cycle that a false positive was being evaluated. Costs were modeled as triangular distributions. All costs (inflated to 2021 US dollars), life-years, and utilities were discounted at a rate of 3% per annum.

Statistical Analysis

Our primary outcomes were the quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) for the competing strategies, interpreted with reference to the contemporary willingness-to-pay (WTP) threshold. The WTP threshold is generally considered to be 2–3 times the individual share of gross domestic product, which was defined as USD 150,000 in this analysis. The ICER was determined based on discounted costs (2021 US dollars) and discounted QALYs that accrue over time. Secondary outcomes included total costs and proportion of early-stage HCC.

We performed one-way sensitivity analyses with inputs for which there was potential uncertainty around the estimate and that could influence ICER estimates: HCC incidence, test performance characteristics, ultrasound/AFP performance characteristics, adherence to screening, and test costs. We also performed an analysis varying the number of MRI exams that patients would undergo after false-positive biomarker results, considering patients with false-positive AFP results typically undergo fewer diagnostic imaging studies than those with false-positive ultrasound results [11]. Although some estimates, e.g., ultrasound and AFP performance characteristics, were based on robust empirical data, we still included in one-way sensitivity analyses given potential variation across sites and patient subgroups [9, 63]. We performed two-way sensitivity analysis, varying biomarker sensitivity, costs, and adherence to inform cut-offs at which there is a transition in the preferred strategy.

As there is uncertainty intrinsic to all input parameters (i.e., confidence intervals or ranges of values), we used a microsimulation that accounted for 1,000,000 unique combinations within the input parameter distributions. We then 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 result of the probabilistic sensitivity analysis is the probability of cost-effectiveness (cost per QALY) for a given strategy in the overall set of simulations.

Results

Base Case

The cohort of 1,000,000 patients with compensated cirrhosis at baseline experienced a 16% lifetime-risk of HCC over a median survival of 10.6–11.1 years

Table 2. Cost-effectiveness of screening strategies, varying physical harms related to false-positive biomarker results

	Proportion early-stage HCC, %	Average overall cost, USD	Incremental cost, USD	Average QALYs	Incremental QALYs	ICER
Base case						
No screening	6	118,401	Reference	7.53	Reference	Reference
US + AFP	50	139,525	21,124	7.73	0.20	105,620
Biomarker	56	139,673	21,272	7.74	0.21	101,295*
Two diagnostic CT/MRI after false-positive result and then back to screening						
US + AFP		139,079	20,678	7.72	0.19	108,832

AFP, alpha-fetoprotein; ICER, incremental cost-effectiveness ratio; MRI, magnetic resonance imaging; US, ultrasound; QALY, quality-adjusted life years. *The ICER for biomarker-based surveillance versus US/AFP is USD 14,800 per QALY.

depending on the strategy. At a screening adherence of 60%, the proportion of HCC diagnosed at an early stage, as defined by Milan criteria, were 6%, 50%, and 56% for no screening, ultrasound with AFP, and biomarker-based screening, respectively.

The average lifetime discounted costs and QALYs are described in Table 2. Compared with no screening, incremental costs of the US/AFP and biomarker strategies were USD 21,124 and USD 21,272, respectively, yielding 0.20 and 0.21 incremental QALYs, respectively. In the base case, US/AFP and biomarker-based screening were cost-effective versus no screening at a WTP threshold of USD 150,000 per QALY, with ICERs of USD 105,620 and USD 101,295 per QALY, respectively.

Compared to ultrasound/AFP, the incremental cost of biomarker-based strategy was USD 148, with 0.01 increased QALYs. Therefore, the ICER for biomarker-based surveillance versus ultrasound/AFP was only USD 14,800 per QALY.

One-Way Sensitivity Analyses

Lower screening costs, increased test performance (sensitivity and specificity), increased screening adherence, and increased HCC incidence rates improved cost-effectiveness of the screening strategies. Thresholds for each of these inputs, at which the biomarker strategy becomes cost-effective, at a WTP threshold of USD 150,000 per QALY, are detailed in Table 3.

Biomarker-based screening remained cost-effective compared to US/AFP among populations in whom HCC incidence exceeded 1.6% per year, sensitivity of the biomarker exceeded 80%, specificity exceeded 55%, and adherence exceeded 53%. Cost-effectiveness was also sensitive to biomarker cost, with cost-effectiveness preserved if costs were below USD 210. Biomarker-based screening remained cost-effective compared to no screening if biomarker sensitivity exceeded 50%, adherence exceeded 37%, annual HCC incidence exceeded 0.7%, and biomarker costs were below USD 908. Cost-effectiveness of the biomarker-based strategy did not appear sensitive to changes in diagnostic algorithms for false-positive results. Thresholds for each of these inputs, at which the biomarker strategy becomes cost-effective, at a WTP threshold of USD 100,000 per QALY, are detailed in online supplementary Table 1.

Two-Way Sensitivity Analyses for Biomarker-Based Screening

We next performed two-way sensitivity analyses varying costs, early-stage HCC sensitivity, and adherence for a biomarker-based strategy (Fig. 1a–c). When varying biomarker costs and sensitivity, we demonstrated the biomarker-based strategy must achieve a minimum sensitivity of 67% for early HCC detection, with an increasing threshold based on biomarker cost (Fig. 1a). For example, the biomarker must achieve sensitivities of 73% and 78% if priced at USD 150 and USD 250, respectively. Similarly, the required biomarker sensitivity to be deemed cost-effective varied by screening adherence (Fig. 1b). A biomarker sensitivity of 77% is required if adherence is 55%; however, sensitivity could be substantially lower at 50% if adherence is increased to 85%. Finally, there was a direct relationship between biomarker adherence and cost (Fig. 1c). The permissible biomarker costs to retain cost-effectiveness increased with biomarker adherence, from USD 150 with adherence of 58% to USD 250 with adherence of 62% and USD 380 if adherence is increased to 65%.

Table 3. Thresholds at which biomarker screening strategies are cost-effective using one-way sensitivity analysis

Input variable	Range tested	Biomarker versus no screening	Biomarker versus US-AFP
Annual HCC incidence, %	0–5	≥0.7	≥1.6
Adherence to biomarker screening, %	0–100	≥37	≥53
Sensitivity of biomarker for early-stage HCC, %	50–100	≥50	≥80
Specificity of biomarker, %	0–100	>0	≥55
Costs of biomarker, USD	1–1,000	≤908	≤210

Analyses performed at a WTP threshold of USD 150,000 per QALY. AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma; US, ultrasound.

Probabilistic Analyses

In a probabilistic sensitivity analysis (Fig. 2), the biomarker was the most cost-effective strategy in most simulations (65%) at a WTP threshold of USD 150,000. The biomarker-based strategy becomes cost-effective in a higher proportion of simulations than no screening at a threshold of approximately USD 120,000.

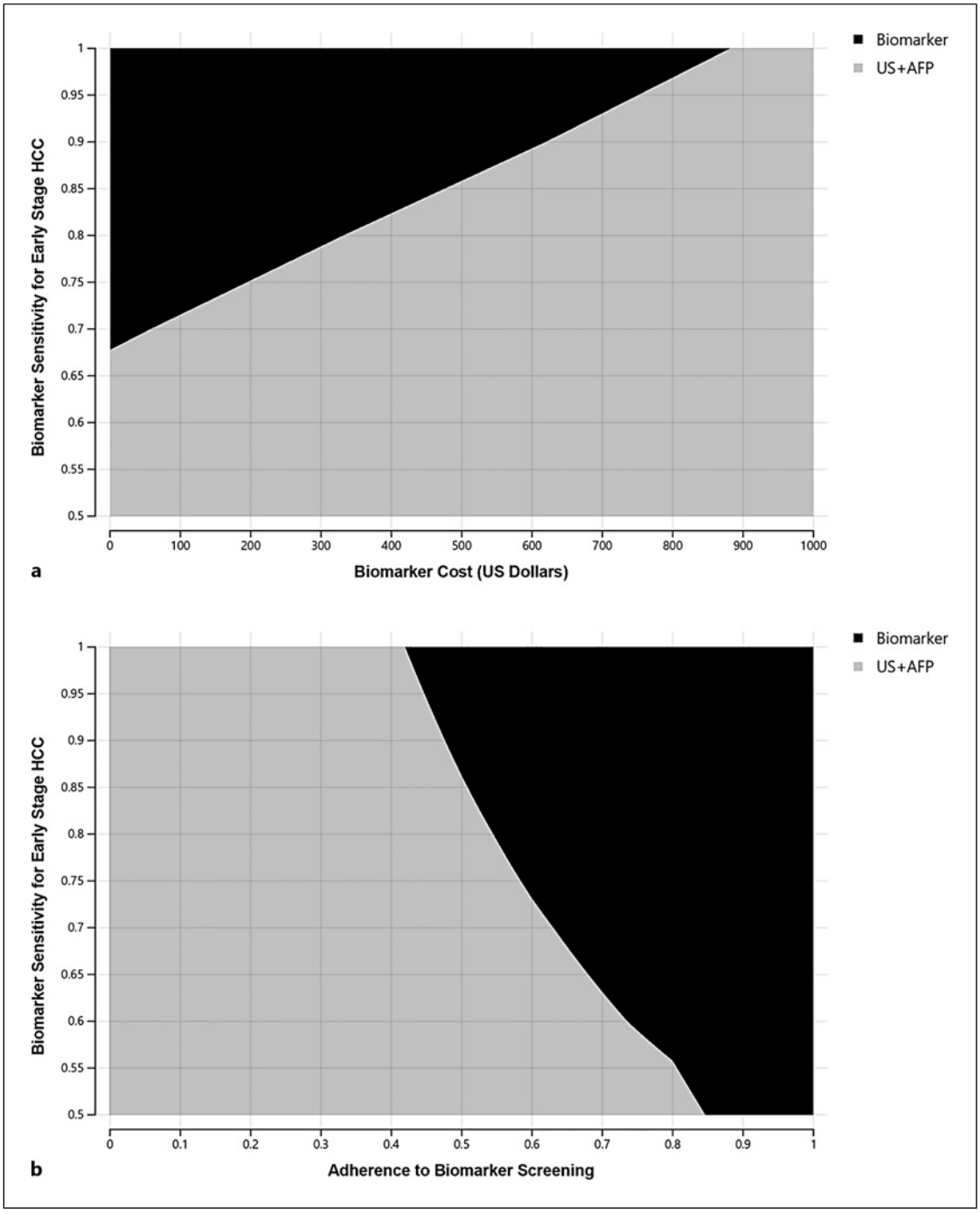
Discussion

Professional society guidelines have recommended abdominal ultrasound with or without AFP for HCC screening in patients with cirrhosis for over 2 decades, although there has been increasing interest in alternative screening modalities considering data showing suboptimal test performance [2, 3]. Our cost-effectiveness analysis advances our understanding of the viability of transitioning to a biomarker-based strategy in the future. We found that ultrasound/AFP and biomarker-based screening were cost-effective in the base case compared to no screening, at a threshold of USD 150,000 per QALY, although biomarker-based screening had the lowest ICER and was preferred in a higher proportion of simulations. Sensitivity analyses demonstrated that cost-effectiveness of alternative screening strategies was sensitive to several inputs including screening adherence, costs, and sensitivity for early-stage HCC.

While our results suggest that ultrasound/AFP and biomarker screening are cost-effective in the base case, this was true at a WTP threshold of USD 150,000 per QALY but not USD 100,000 per QALY. We believe reasons for a higher required WTP threshold for HCC screening cost-effectiveness are increased costs related to cirrhosis management compared to prior models and the improved prognosis of patients with intermediate and advanced stage HCC, mitigating the incremental benefits of early HCC detection. Patients with limited intermediate-stage HCC, within UNOS-downstaging criteria, can undergo liver transplantation if successfully downstaged [64, 65]. Similarly, advances in systemic therapies have increased median overall survival from approximately 11 months–18 months and ~20% achieving survival exceeding 3 years [50].

The WTP threshold for HCC surveillance may differ geographically, with regions disproportionately impacted with high HCC mortality more willing to invest in HCC surveillance programs. For example, Japan has historically had a robust, more costly, HCC surveillance program including ultrasound, biomarkers, and possibly CT/MRI with high adherence rates, which has translated into improved early HCC detection and reduced HCC mortality compared to other regions [66, 67]. Compared to ultrasound, biomarker-based surveillance was slightly more costly and provided slightly higher QALYs, yielding a lower ICER of only ~USD 15,000 per QALY. Beyond relative cost-effectiveness, regions would need to consider other factors when deciding between ultrasound and biomarker-based surveillance strategies including prevalence of risk factors that can impact ultrasound performance (e.g., obesity and nonviral etiologies of liver disease) and access to high-quality ultrasounds [9, 10]. Even within countries, there may be regional variation in ultrasound access (e.g., rural-urban disparities) that may impact choice of preferred surveillance strategy.

We found a biomarker-based strategy was preferred to both no screening and ultrasound/AFP in most probabilistic sensitivity analyses at WTP thresholds of USD 150,000; however, biomarker-based screening may not be optimal for all populations. Ultrasound is known to be operator dependent as well as varied performance based on patient characteristics such as obesity and liver disease etiology, with better performance in nonobese patients and those with viral-related cirrhosis [9, 10]. Similarly, biomarkers may have variable performance by liver disease etiology or underlying liver dysfunction [25, 63].



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These data highlight that precision screening strategies, in which screening tests and intensity are tailored to HCC risk and expected test performance, would be preferable to a "one-size-fits-all" strategy. A prior cost-effectiveness model suggested a tailored strategy would be cost-effective, although this was based on older estimates for risk stratification screening test performance, and costs, so this bears repeat assessment [68].

Our two-way sensitivity analyses also provide important insights into thresholds for future biomarker candidates, highlighting the interactive nature of biomarker sensitivity, adherence, and costs. For example, a

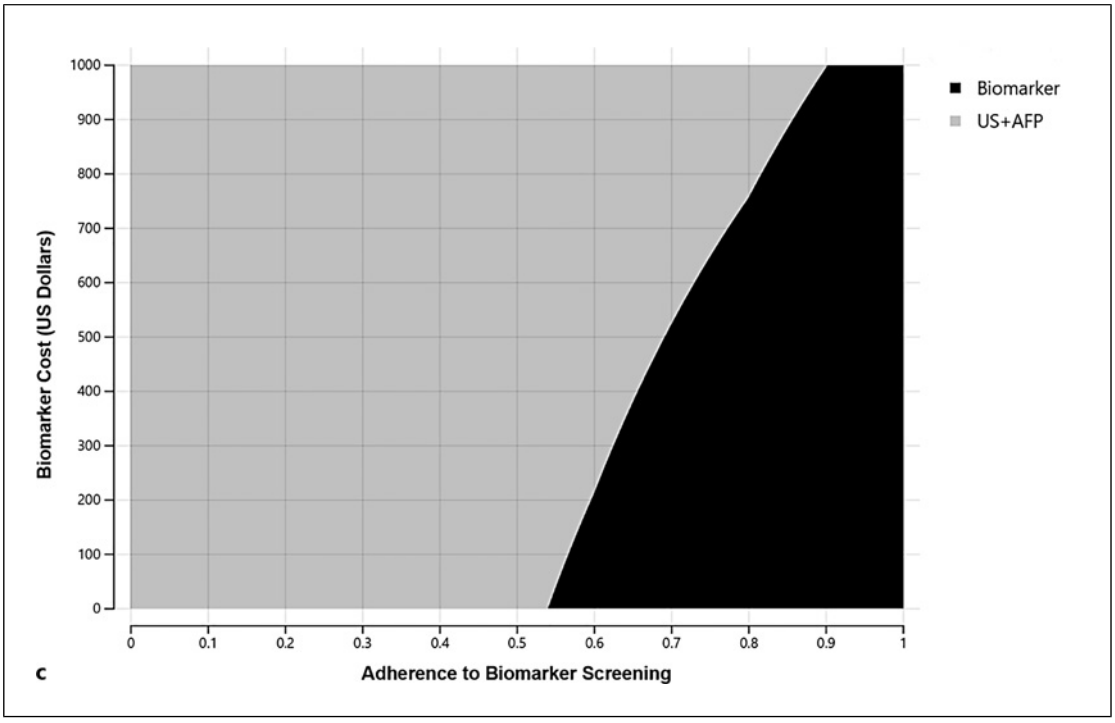

Fig. 1. a Two-way sensitivity analysis varying biomarker costs and sensitivity. **b** Two-way sensitivity analysis varying biomarker adherence and sensitivity. **c** Two-way sensitivity analysis varying biomarker costs and adherence. No screening is not cost-effective in any analyses.

biomarker priced at USD 180, i.e., matching that of ultrasound of AFP, would need to achieve a higher sensitivity of 73% or adherence of 58% to be cost-effective. We also evaluated the interaction between test adherence and required test performance in two-way sensitivity analyses. These data are important given underuse of ultrasound-based screening across geographic locations, contributing to a gap between ultrasound/AFP efficacy in ideal settings and its effectiveness when implemented in clinical practice [29]. Several patient and provider-reported barriers contributing to screening underuse, such as need for a separate radiologic appointment, would be mitigated if not eliminated by a biomarker-based strategy, in which testing would be largely point of care [15–17, 69]. Therefore, a biomarker-based strategy would need a sensitivity >90% for early-stage HCC with adherence at 45% to achieve cost-effectiveness compared to only 67% if adherence increased to 65%. These interactions are critical to consider as one evaluates effectiveness of biomarker-based screening when implemented in clinical practice, compared to simply referencing reported efficacy in trial populations. It should also be noted that there is an inherent trade-off between sensitivity and specificity that must be considered for biomarker optimal biomarker thresholds and performance. Biomarkers should achieve high sensitivity but must consider preserving sufficient specificity to minimize potential screening-related harms.

Our results must be interpreted considering the study's limitations. Markov modeling is inherently based on assumptions and the quality of the input data. Most results were based on meta-analyses or triangulated from several data sources; however, some inputs were from single studies, which may limit generalizability of performance estimates and practice patterns and applicability of cost-effectiveness conclusions. Similarly, many estimates were derived from studies in the USA or Europe, so results may not apply equally to all regions globally. To account for this possibility, we demonstrated robustness of our findings across model ranges in one-way sensitivity analyses. Second, we incorporated data on screening physical harms based on current literature, although there are currently few data on psychological harms that may also impact QALYs after positive results. Third, our cost-effectiveness analysis was based on biomarker performance results from phase II studies and early phase III studies, which may overestimate performance in subsequent larger scale phase III and IV cohort

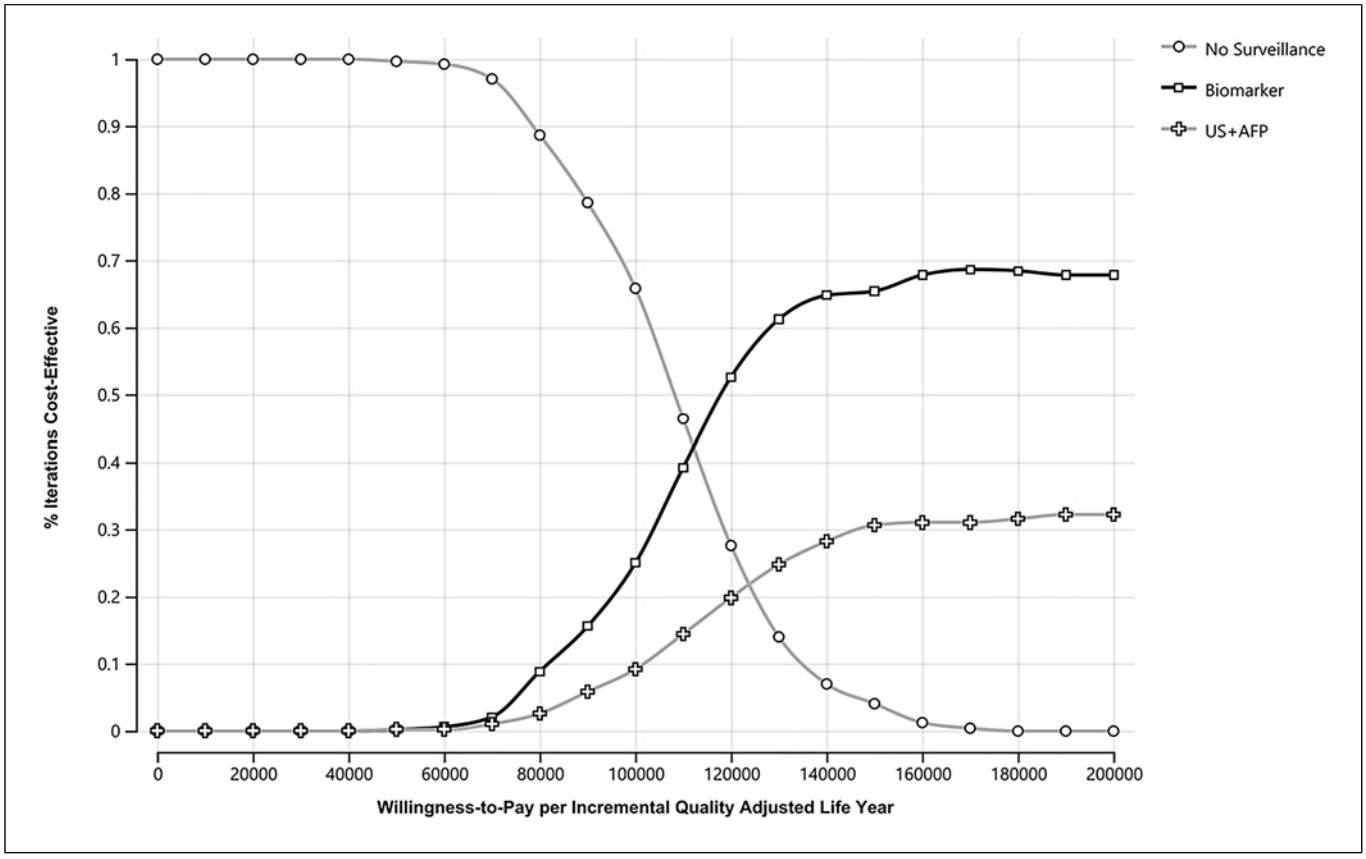

Fig. 2. Cost acceptability curves In a probabilistic sensitivity analysis, the curves demonstrate the proportion of samples in which each of the three modeled strategies are cost-effective at WTP thresholds ranging from USD 0 to 200,000 per incremental QALY. The three strategies are for biomarker screening, US/AFP-based screening, and no screening.

studies. Once again, we attempted to account for this possibility by varying biomarker sensitivity and specificity across wide ranges in one-way and two-way sensitivity analyses. We believe these weaknesses are outweighed by our study's strengths including clinical significance, robust up-to-date model inputs for screening benefits and harms, and innovation evaluating biomarker-based screening strategies.

In conclusion, we have demonstrated that biomarker-based HCC screening is likely cost-effective across a wide range of parameters at a threshold of USD 150,000 per QALY, although it was not cost-effective at a more conservative threshold of USD 100,000 per QALY. Our data highlight that evaluation of clinical utility and cost-effectiveness of screening strategies will depend on more than test performance but also other factors such as adherence and costs. Future modeling studies should aim to validate these results as well as identify subgroups of patients for whom biomarker-based screening is preferred.

Statement of Ethics

Ethical approval and consent were not required as this study was based on publicly available data.

Conflict of Interest Statement

Amit G. Singal has served as a consultant or on advisory boards for Bayer, FujiFilm Medical Sciences, Exact Sciences, Roche, Glycotest, and GRAIL. Neehar Parikh has served as a consultant or on advisory boards for Bayer, Wako Diagnostics, Exact Sciences, Glycotest, and Freenome. Jagpreet Chhatwal has served as a consultant to Bayer and holds equity in Value Analytics Labs. None of the other authors have any relevant conflicts of interest.

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responsibility of the authors and does not necessarily represent the official views of the National Institute of Health. The funding agencies had no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; or preparation of the manuscript.

Author Contributions

Dr. Amit G. Singal had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design (Amit G. Singal, Neehar Parikh, Elliot Tapper); analysis of the data (Elliot Tapper); interpretation of the data (Amit G. Singal, Neehar Parikh, Elliot Tapper); drafting of the manuscript (Amit G. Singal); critical revision of the manuscript for important intellectual content (Amit G. Singal, Jagpreet Chhatwal, Neehar Parikh, Elliot Tapper); obtained funding (Amit G. Singal). All authors approve final version of the manuscript.

Data Availability Statement

All data generated or analyzed during this study are included in this article and its online supplementary material files. Further inquiries can be directed to the corresponding author.

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