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Cost-Effectiveness of Risk Score–Stratified Hepatocellular Carcinoma Screening in Patients with Cirrhosis

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OBJECTIVES: Hepatocellular carcinoma (HCC) surveillance with biannual ultrasound is currently recommended for all patients with cirrhosis. However, clinical implementation of this "one-size-fits-all" approach is challenging as evidenced by its low application rate. We aimed to evaluate the cost-effectiveness of risk-stratified HCC surveillance strategies in patients with cirrhosis.

METHODS: A Markov decision-analytic modeling was performed to simulate a cohort of 50-year-old subjects with compensated cirrhosis. Risk-stratified HCC surveillance strategies was implemented, in which patients were stratified into high-, intermediate-, or low-risk groups by HCC risk biomarker–based scores and assigned to surveillance modalities tailored to HCC risk (2 non-risk-stratified and 14 risk-stratified strategies) and compared with non-stratified biannual ultrasound.

RESULTS: Quality-adjusted life expectancy gains for biannual ultrasound in all patients and risk-stratified strategies compared with no surveillance were 1.3 and 0.9–2.1 years, respectively. Compared with the current standard of biannual ultrasound in all cirrhosis patients, risk-stratified strategies applying magnetic resonance imaging (MRI) and/or ultrasound only in high- and intermediate-risk patients, without screening in low-risk patients, were cost-effective. Abbreviated MRI (AMRI) for high- and intermediate-risk patients had the lowest incremental cost-effectiveness ratio (ICER) of $2,100 per quality-adjusted life year gained. AMRI in intermediate- and high-risk patients had ICERs $<$ $3,000 across a wide range of HCC incidences.

CONCLUSIONS: Risk-stratified HCC surveillance strategies targeting high- and intermediate-risk patients with cirrhosis are cost-effective and outperform the currently recommended non-stratified biannual ultrasound in all patients with cirrhosis.

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INTRODUCTION

Hepatocellular carcinoma (HCC) is the leading cause of death in patients with cirrhosis, largely related to failed early detection. Liver disease societies worldwide recommend HCC screening in cirrhosis using biannual abdominal ultrasound,[1–4] which has been associated with early tumor detection, increased curative treatment receipt, and improved overall survival.[5,6] Although biannual ultrasound for all cirrhotic patients is cost-effective compared with no screening, ultrasound can miss one-third of early-stage HCC due to its suboptimal sensitivity.[7–9] Other imaging modalities with higher sensitivity for early tumor detection, such as dynamic contrast-enhanced magnetic resonance imging (MRI), have not been recommended as alternatives given its higher cost.[1]

HCC screening is recommended when annual HCC incidence exceeds 1.5%, assuming uniform HCC incidence among patients' subgroups with specific liver disease etiology and severity.[1] However, studies have suggested that HCC risk is not uniform across all patients within a clinical risk group, and therefore the current one-size-fits-all approach likely results in overestimated or underestimated HCC risk for each individual.[10] Furthermore, this approach has proved to be difficult to implement in actual clinical practice as evidenced by the low utilization rate $<$20% in the United States due to the sizable cirrhotic population.[11,12] Accurate HCC risk stratification and optimized allocation of medical resources could enable rational and practically feasible implementation of HCC screening.

Prior studies have demonstrated several clinical HCC risk factors in cirrhotics, including older age, male sex, viral etiology of liver disease, Child–Pugh B/C cirrhosis, diabetes, and obesity, although risk prediction based on these variables

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yielded insufficient accuracy.[10,13] Tissue-, blood-, or buccal swab–based molecular HCC risk biomarkers applicable to a wide range of liver disease etiologies, some of which are now clinically available as Laboratory Developed Test, combined with clinical variables have shown capability to predict 5- to 10-fold HCC risk differences using tissue or serum specimens.[14] We aimed to evaluate the cost-effectiveness of risk-stratified HCC screening in cirrhosis based on molecular clinical HCC risk scores.

METHODS

Model and patient population. A previously reported Markov model simulating HCC screening, diagnosis, and therapy based on a health system perspective was refined and updated (TreeAge Pro, Williamstown, MA)[9] following the recommendations.[15] The baseline population was a cohort of 50-year-old subjects with compensated cirrhosis ($n = 10{,}000$) followed up with a 6-month cycle for 30 years (Figure 1). The setting of the study was based in the United States. Transition probabilities were derived from the published literature (Table 1, Supplementary Methods). Reporting followed the CHEERS guidelines (Supplementary Reporting Checklist).[16]

Screening-detected and undetected HCC were distinguished. Depending on the performance of screening modalities, HCC could be detected at an early stage or remain undetected until an advanced stage. HCC detected at an early stage in compensated cirrhosis were eligible for tumor resection, liver transplantation, or local ablative therapies; whereas patients with decompensated cirrhosis and early-stage HCC were eligible for liver transplantation or local ablative therapies. Patients with advanced tumors received palliative treatments, including chemoembolization, systemic therapy, or best supportive care, as recommended by guidelines.[1] Our model assumptions include (1) positive screening tests (i.e., lesions ≥ 1 cm in diameter) were evaluated with diagnostic contrast-enhanced MRI; (2) patients with characteristic findings of HCC on the diagnostic MRI did not undergo further diagnostic evaluation prior to treatment; (3) patients with a positive screening test but negative diagnostic MRI underwent biopsy to evaluate the suspicious nodule; (4) patients with false positive screening tests and subsequent negative biopsy had a follow-up MRI examination and, if the MRI was negative, were returned to prior screening strategy; and (5) HCC risk was stable over time during the observation period.

HCC screening strategies. Based on our preceding cost-effectiveness analysis of HCC screening by different combinations of ultrasound, CT, MRI, and AFP, the most cost-effective strategy, biannual ultrasound with 100% utilization rate (US2×-100%), was chosen as the reference strategy in the current study.[9] The reference strategy was compared with two non-risk-stratified screening strategies: (1) biannual dynamic contrast-enhanced triple-phase MRI (full MRI) with 100% utilization rate (MRI2×-100%); (2) biannual abbreviated contrast-enhanced MRI (AMRI)[17,18] with 100% utilization rate (AMRI2×-100%), and 14 risk-stratified strategies with various combinations of screening modalities assigned for each risk subgroup (Table 2). In each of the risk-stratified strategies, patients were first stratified into high-, intermediate-, and low-risk groups by applying either of the two integrated molecular and clinical HCC risk scores discussed in the next section.[19–22] Subsequently, each risk group was subjected to different screening protocols according to the HCC risk level. The 16 experimental strategies were also compared with another alternative reference strategy, biannual ultrasound with 15% utilization rate (US2×-15%), representing the current real-world usage of HCC screening in the United States.[5]

Baseline estimates of clinical parameters. Table 1 summarizes model parameters, base case values, and plausible

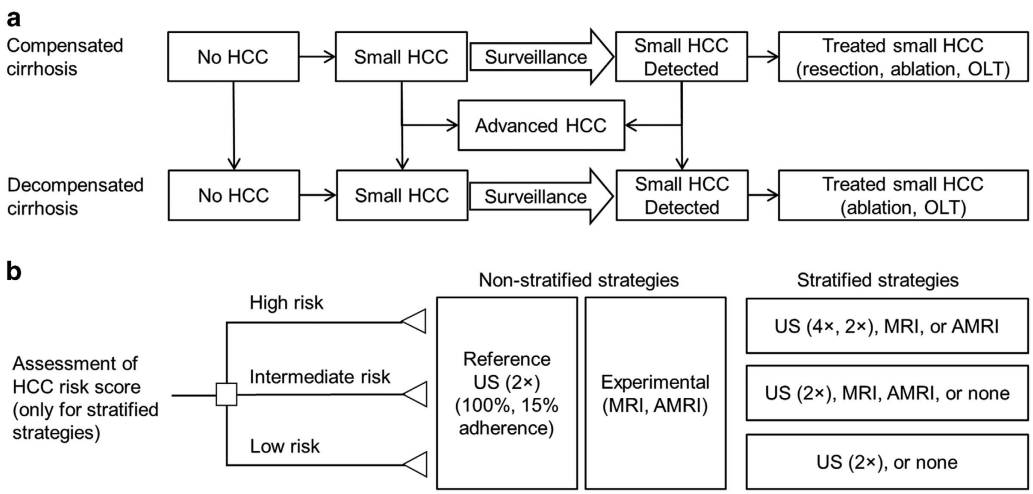

Figure 1 Markov model and hepatocellular carcinoma (HCC) screening strategies. (**a**) Schematic of Markov states, starting from compensated cirrhosis without HCC and progressing throughout the model or die. (**b**) Risk stratification by a HCC risk score classifies subjects into high-, intermediate-, or low-risk groups. In non-stratified strategies, all subjects undergo biannual ultrasound (US; reference), abbreviated magnetic resonance imaging (AMRI), or MRI (experimental strategies), whereas, in risk-stratified strategies, each risk subgroup undergoes different modalities. OLT, orthotopic liver transplantation.

Table 1 Model variables (see Supplementary Table S6 for references)

Variable	Baseline (range tested)
Disease progression	
Age (years)	50 (40–60)
Cycle time	6 months
Compensated cirrhosis prognosis	
Adjusted annual excess mortality of compensated cirrhosis	4% (1.8–8%)
10-year survival of compensated cirrhosis	64% (43–80%)
Annual probability of transition from compensated to decompensated cirrhosis	5% (3–8%)
Decompensated cirrhosis prognosis	
Annual mortality of decompensated cirrhosis	28% (18–30%)
2-year survival of decompensated cirrhosis	52% (49–67%)
HCC prognosis	
Annual mortality of advanced HCC	75% (30–95%)
HCC natural history	
Annual HCC probability	2.9% (0.5–7.0%)
Annual probability of progression from small to advanced HCC	40% (20–70%)
Probability of therapy	
Probability of HCC in compensated cirrhosis to be treated with surgical resection	40% (20–60%)
Probability of liver transplantation for early HCC in compensated cirrhosis	20% (0–50%)
Probability of local ablation for HCC in decompensated cirrhosis	40% (20–100%)
Probability of treatment of early HCC after identification in compensated cirrhosis	69% (50–100%)
Probability of treatment of early HCC after identification in decompensated cirrhosis	30% (0–50%)
Probability of liver transplantation for early HCC in treatment-eligible decompensated cirrhosis	40% (0–80%)
Probability of local ablation for early HCC in treatment-eligible decompensated cirrhosis	60% (20–100%)
Prognosis after therapy	
5-year survival after hepatic resection for HCC	44% (38–51%)
Perioperative mortality of hepatic resection	3.9% (3.7–4.5%)
5-year survival after liver transplantation for HCC	70% (65–80%)
Perioperative mortality of liver transplantation	4.3% (2.3–6.3%)
5-year survival after local ablation for HCC in compensated cirrhosis	46% (32–77%)
5-year survival after local ablation for HCC in decompensated cirrhosis	31% (27–40%)
Perioperative mortality of local ablation	0.3% (0–1.8%)
HCC risk score	
186-gene-based risk score, proportion of each risk group	High: 36% (0–50%) Intermediate: 37% Low: 27% (10–50%)
186-gene-based risk score, annual HCC incidence in each risk group	High: 4.9% (0.8–12%) Intermediate: 3.3% (0.6–8.0%) Low: 0.8% (0.1–1.9%)
EGF genotype-based risk score, proportion of each risk group	High: 14% (0–40%) Intermediate: 29% Low: 57% (0–60%)
EGF genotype-based risk score, annual HCC incidence in each risk group	High: 5% (2.5–10%) Intermediate: 1.8% (0.9–3.6%) Low: 0.4% (0.2–0.8%)
Screening and diagnosis test characteristics	
Probability of being screened for HCC	100% (15–100%)
Reported probability of being screened for HCC	15% (5–60%)
Probability of incidental early HCC in the non-screened group	30% (0–50%)
Ultrasound sensitivity for early-stage HCC screening	63% (35–78%)
Ultrasound specificity for early-stage HCC screening	91% (70–95%)
Screening full MRI sensitivity for early-stage HCC screening	96% (80–100%)
Screening full MRI specificity for early-stage HCC screening	94% (85–98%)
Abbreviated MRI sensitivity for early-stage HCC screening	83% (70–95%)
Abbreviated MRI specificity for early-stage HCC screening	93% (86–96%)
Diagnostic MRI sensitivity for early-stage HCC	88% (78–92%)
Diagnostic MRI specificity for early-stage HCC	94% (85–98%)
HCC biopsy sensitivity	62% (50–100%)
HCC biopsy specificity	100% (80–100%)
Costs ($)	Medicare, National Impatient Sample
Annual cost of compensated cirrhosis	1,220 (610–2,440)
Annual cost of decompensated cirrhosis	15,000 (7,500–30,000)
Annual cost after liver transplantation	14,600 (7,300–29,200)
Annual cost of advanced HCC	41,320 (20,660–82,640)
Cost of hepatic resection	42,540 (21,270–85,080)
Cost of liver transplantation	177,000 (88,500–354,000)
Cost of local ablation	3,650 (1,825–7,300)
Cost of imaging-guided HCC biopsy	750 (375–1,500)
Cost of ultrasound	143 (71–285)
Cost of screening full MRI	528 (264–1,056)
Cost of screening abbreviated MRI	313 (156–626)

Table 1 *(Continued)*

Variable	Baseline (range tested)
Cost of diagnostic MRI	528 (264–528)
Cost of risk score	796 (500–4,000)
Rate of discounting costs	3%
Quality-of-life weights	
Utility of compensated cirrhosis	0.8 (0.6–1.0)
Utility of decompensated cirrhosis	0.65 (0.5–0.8)
Utility after HCC diagnosis	0.3 (0.1–0.4)
Utility after liver transplantation	0.73 (0.5–0.8)

AMRI, abbreviated MRI; EGF, epidermal growth factor; HCC, hepatocellular carcinoma; MRI, magnetic resonance imaging.

ranges based on our previously published model,[9] updated literature review,[5] and expert input for sensitivity analyses.

Natural history of cirrhosis. The adjusted annual excess mortality of compensated cirrhosis was estimated as 4%, and 5% of compensated cirrhosis progress to decompensated cirrhosis each year.[23] Range of annual HCC incidences tested was 0.5–7.0%, covering HCC incidence in global populations with a variety of HCC etiologies.[24–31] Annual progression from small to advanced HCC was 40%, and annual mortality of advanced HCC was 75%.[32,33]

HCC risk-stratification strategies. A pan-etiology (hepatitis B, hepatitis C, hepatitis C after viral cure, alcohol, and non-alcoholic fatty liver disease) 186-gene signature-based HCC risk score, comprised of the liver gene signature, bilirubin, and platelet count, was used as the example of biomarker-based risk stratification.[21,34,35] As an additional example, another HCC risk score based on epidermal growth factor single-nucleotide polymorphism, which can be measured using a buccal swab, was also tested.[19] The score, awaiting external validation, comprises the epidermal growth factor single-nucleotide polymorphism, age, sex, smoking status, alkaline phosphatase level, and platelet count.

HCC screening, treatment, and prognosis. Sensitivity and specificity of screening ultrasound, screening full MRI, AMRI, diagnostic MRI, and biopsy were estimated based on published literature (Table 1,Supplementary Methods). Based on a meta-analysis of HCC treatment utilization, we estimated the probabilities of any treatment in compensated and decompensated cirrhosis patients.[36,37] The proportions of treatment-eligible patients and prognosis after treatment were defined based on population and cohort studies.[9,37–51]

Costs and utility. Screening test costs were calculated based on 2015 Medicare Current Procedural Terminology reimbursement global costs. The AMRI cost was conservatively estimated by halving the technical cost of full MRI[18] (Supplementary Table S1). Cost of the HCC risk biomarker test was calculated as median of multi-gene gapfill Current Procedural Terminology codes in Clinical Laboratory Fee Schedule (Supplementary Table S2). Other direct medical costs were derived from Medicare Current Procedural Terminology reimbursement, Nationwide Inpatient Sample, and published literature and adjusted for inflation to 2014 costs (Table 1). The cost incurred by incidental detection of non-liver-related diseases was outside the scope of this study and therefore not included. Literature-based estimates were used for the quality-of-life weights.

Study outcomes. Model outcomes included lifetime costs, quality-adjusted life expectancy (QALE), and incremental cost-effectiveness ratios (ICERs), defined as incremental cost in US dollars per quality-adjusted life year gained. An ICER < $50,000 was regarded as cost-effective. One- and two-way sensitivity analyses were performed on all model variables.

Patient involvement. Patients were not involved in this study.

RESULTS

Model validity. Overall 1- and 2-year survival in our model (96% and 90%, respectively) were similar to those reported in a systematic review of Child–Pugh A cirrhosis (95% and 90%, respectively).[23] Similarly, 3-year survival rates for screening-detected and non-screening HCC patients in our model (51% and 30%, respectively) recapitulated rates in a recent systematic review (51% and 28%, respectively).[5] Finally, the proportion of screening-detected and non-screening HCC patients undergoing curative therapy in our model (57% and 21%, respectively) was comparable to probabilities in the systematic review (52% and 24%, respectively).[5] These results collectively support the validity of our model.

Life expectancy. The mean QALE for 50-year-old patients with compensated cirrhosis was 6.4 years in the absence of screening. Although the current recommendation in practice guidelines (US2×-100%) resulted in 1.3 months of QALE gain, the real-world ultrasound utilization (US2×-15%) as well as substituting ultrasound with MRI (MRI-15%) or AMRI (AMRI-15%) did not extend QALE (Table 2). Non-stratified use of MRI (MRI-100%) and AMRI (AMRI-100%) yielded QALE gains of 2.0 and 1.8 months, respectively. Risk-stratified strategies yielded QALE gains ranging from 0.9 to 2.1 months compared with no screening (Table 2). Among patients who developed HCC, the mean survival after HCC development was 2.7 years in the absence of

Table 2 Cost-effectiveness of non-stratified and risk-stratified HCC screening strategies

Strategy	QALE	Cost	ICER (vs. US2 × -100%)	ICER (vs. US2 × -15%)
No screening	6.40	$42,961		
Reference strategies				
Regular US screening (100% adherence; US2 × -100%)	6.51	$51,761	Reference	
Regular US screening (15% adherence; US2 × -15%)	6.39	$44,078		Reference
Non-stratified experimental strategies				
MRI for all (MRI-100%)	6.57	$56,871	85,167	71,072
AMRI for all (AMRI-100%)	6.55	$53,883	53,050	61,281
Risk-stratified strategies (for high–intermediate–low risk groups)				
US4 × -US2 × -US2 ×	6.50	$54,601	Dominated	95,664
MRI-US2 × -US2 ×	6.54	$54,442	89,367	69,093
AMRI-US2 × -US2 ×	6.53	$53,437	83,800	66,850
US2 × -US2 × -none	6.52	$50,417	Dominant	48,762
US4 × -US4 × -none	6.51	$54,391	Dominated	85,942
MRI-MRI-none	6.58	$53,966	31,500	52,042
AMRI-AMRI-none	6.56	$51,866	2,100	45,812
US4 × -US2 × -none	6.52	$52,300	53,900	63,246
MRI-US2 × -none	6.55	$52,140	9,475	50,388
AMRI-US2 × -none	6.54	$51,136	Dominant	47,053
US2 × -none-none	6.48	$47,086	Less effective	33,422
US4 × -none-none	6.47	$48,969	Less effective	61,137
MRI-none-none	6.51	$48,809	Dominant	39,425
AMRI-none-none	6.50	$47,804	Less effective	33,873

AMRI, abbreviated magnetic resonance imaging; HCC, hepatocellular carcinoma; ICER, incremental cost-effectiveness ratio; QALE, quality-adjusted life expectancy; US, ultrasound. Dominant, improved QALE with lower cost; dominated, worse QALE with higher cost; less effective, reduced efficacy with lower cost; 2/4 ×, screening two/four times a year; MRI and AMRI are biannual. Risk-stratified strategies are named as screening modality in high-risk subjects–intermediate-risk subjects–low-risk subjects. For example, MRI-none-none corresponds to screening by MRI in high-risk subjects and no screening in intermediate- and low-risk subjects.

screening. The gain in QALE compared with no screening were 2.0 years for US2 × -100%, whereas the gain in the risk-stratified strategies was up to 2.2 years, indicating that survival
of HCC patients is not sacrificed by the risk-stratified strategies.

Costs-effectiveness of risk-stratified HCC screening. In the absence of screening, the mean discounted lifetime cost for a 50-year-old patient with compensated cirrhosis was $42,961, which was increased by $8,322, $13,460, and $10,420 using US2 × -100%, MRI-100%, and AMRI-100% (indicating all patients are screened by biannual ultrasound, MRI, or AMRI), respectively, whereas risk-stratified strategies increased costs by $3,920–$10,900 compared with no screening (Table 2). Compared with the current HCC screening utilization (US2 × -15%), increasing ultrasound utilization to 100% (US2 × -100%), use of MRI (MRI-100%), and use of AMRI (AMRI-100%) resulted in ICERs of $64,072, $68,012, and $58,401 per quality-adjusted life year gained, respectively, which were all above the cost-effectiveness threshold of $50,000.

We next evaluated the stratified strategies. Each stratified HCC screening strategy is described by combining the screening modalities assigned to the HCC high-, intermediate-, and low-risk groups, respectively, separated by a hyphen. For example, an HCC screening strategy applying ultrasound (4 × per year) for high-risk group, ultrasound (2 × per year) for intermediate-risk group, and no screening for low-risk group is presented as "US4 × -US2 × -none". We identified three risk-stratified screening strategies that were cost effective compared with US2 × -100%: MRI-MRI-none, AMRI-AMRI-none, and MRI-US2 × -none, among which AMRI-AMRI-none had the smallest ICER of $2,100, and three strategies dominating the reference: US2 × -US2 × -none, AMRI-US2 × -none, and MRI-none-none (Table 2). When compared with US2 × -15%, six risk-stratified strategies, US2 × -US2 × -none, AMRI-AMRI-none, AMRI-US2 × -none, US2x-none-none, MRI-none-none, and AMRI-none-none, were cost-effective with ICERs ranging from $33,422 to $48,762 per quality-adjusted life year gained. One common feature of the cost-effective risk-stratified strategies was omitted screening for low-risk patients, with minimal to no impact on QALE, which was also confirmed in subgroup analysis for each risk group (Supplementary Table S3). Screening only for high-risk patients was also cost-effective without substantially reducing QALE (Table 2) and may be an alternative screening strategy for resource-limited area that are only able to deliver HCC screening to a small fraction of the at-risk population. Risk-stratified strategies using another HCC risk score based on the epidermal growth factor single-nucleotide polymorphism[19] was similarly cost-effective (Supplementary Table S4).

Factors affecting cost-effectiveness of risk-stratified HCC screening (sensitivity analyses). One-way sensitivity analyses on each model variable were performed to identify

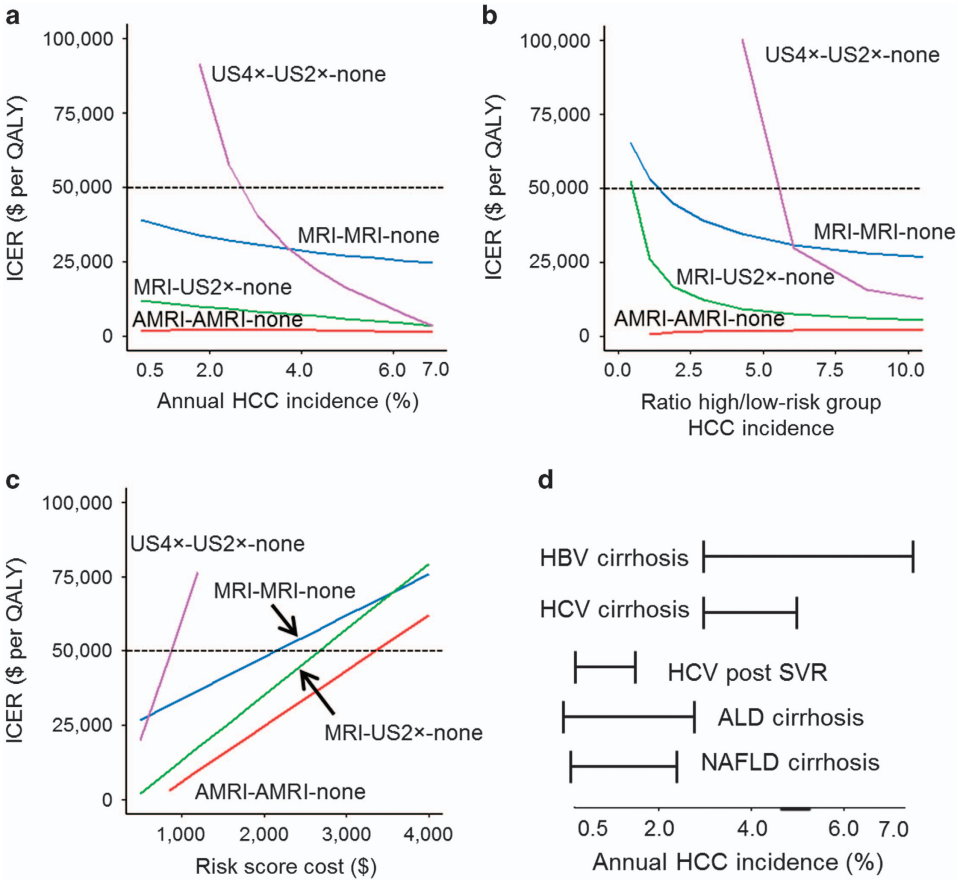

Figure 2 One-way sensitivity analysis of key model parameters and their effect on incremental cost-effectiveness ratio (ICER) compared with non-stratified ultrasound (US)-based screening in 100% of individuals for cost-effective risk-stratified strategies. Only the four non-dominant, risk-stratified strategies with an ICER <$50,000 per quality-adjusted life year (QALY) in the baseline model are shown for (**a**) global annual hepatocellular carcinoma (HCC) incidence, HCC risk score performance, (**b**) defined as ratio of annual HCC incidence in the high- over low-risk group, and (**c**) HCC risk biomarker cost. (**d**) Annual HCC incidence according to HCC etiology projected onto the range of annual HCC incidence tested in sensitivity analysis (Supplementary Table S5). 2/4×, screening two/four times a year; ALD, alcoholic liver disease; AMRI, abbreviated MRI; HBV, hepatitic B virus; HCV, hepatitis C virus; NAFLD, nonalcoholic fatty liver disease; SVR, sustained virological response. Risk-stratified strategies are named as screening modality in high-risk subjects–intermediate-risk subjects–low-risk subjects. For example, MRI-none-none corresponds to screening by MRI in high-risk subjects and no screening in intermediate- and low-risk subjects.

notable drivers of cost-effectiveness. We first assessed a range of annual HCC incidence rates to model a range of different cirrhosis etiologies[24–29] on cost-effectiveness of the four non-dominant, cost-effective (i.e., ICER<$50,000) risk-stratified screening strategies within the range of annual HCC incidence rate between 0.5% and 7%. As expected, all strategies were more cost-effective at higher annual HCC incidence (Figure 2a). MRI-MRI-none had the highest QALE and was cost-effective with an ICER consistently <$50,000. More frequent ultrasound among high-risk patients (US4×-US2×-none) was the only strategy that sharply became non-cost-effective when annual HCC incidence dropped <3%. In contrast, the ICER for AMRI-AMRI-none was consistently low, highlighting its robust performance across a wide range of annual HCC incidences.

We next evaluated HCC risk biomarker test performance (defined as fold difference in annual HCC incidence rates between the high- and low-risk groups with a range of 1.3–10), which showed that AMRI-AMRI-none remained cost-effective when compared with US2×-100% even at the lowest-risk score performance with consistently low ICER, although MRI-MRI-none required approximately greater than twofold difference in HCC incidence between the high- and low-risk groups to be cost-effective (Figure 2b). The costs of the HCC risk biomarker test also affected cost-effectiveness (Figure 2c). MRI-MRI-none had an ICER<$50,000 up to a risk biomarker cost of $2,200, while AMRI-AMRI-none was cost-effective up to a cost of $3,400.

Subsequently, one-way sensitivity analyses were performed for the remaining model variables in a comparison between the reference strategy (US2×-100%) and the non-dominant risk-stratified strategy with the smallest ICER, AMRI-AMRI-none. Ultrasound specificity, AMRI specificity and cost, and HCC risk biomarker cost were identified as the top influential variables (Supplementary Figure S1). AMRI-AMRI-none was not cost-effective when specificity of ultrasound >93%, specificity of AMRI was <89%, or cost of AMRI >$532.

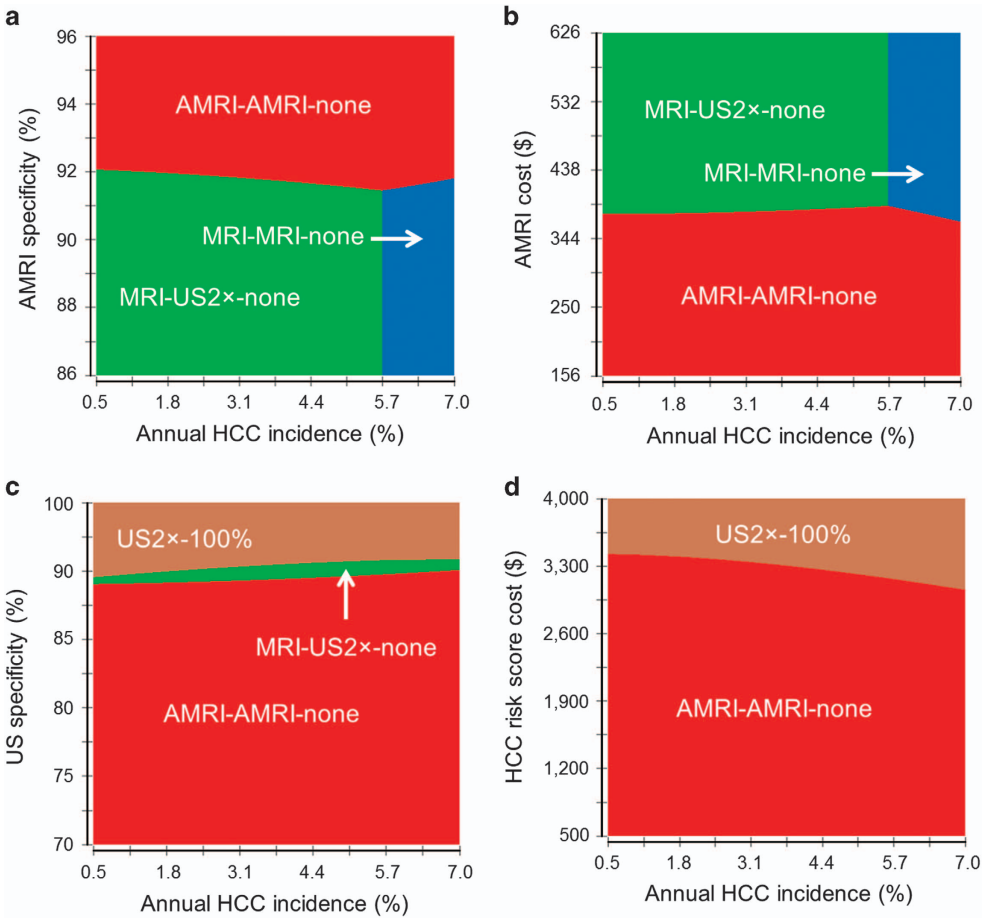

Figure 3 Two-way sensitivity analysis of annual hepatocellular carcinoma (HCC) incidence vs. variables affecting cost-effectiveness of risk-stratified HCC screening. Overall HCC incidence is varied along with model parameters, (**a**) abbreviated MRI (AMRI) specificity, (**b**) AMRI cost, (**c**) ultrasound (US) specificity, and (**d**) HCC risk biomarker cost, with the greatest effect on incremental cost-effectiveness ratio of non-dominant, cost-effective risk-stratified strategies.

Two-way sensitivity analysis of these variables against annual HCC incidence showed that AMRI-AMRI-none was the best strategy when AMRI specificity was >91%, replaced by MRI-US2×-none when AMRI specificity dropped and annual HCC incidence was <5.7% or by MRI-MRI-none when >5.7% (Figure 3a). AMRI-AMRI-none was the most cost-effective strategy across a range of HCC incidences when its cost was <$360 (Figure 3b) and US specificity was <88% (Figure 3c). AMRI-AMRI-none remained the most cost-effective strategy irrespective of annual HCC incidence when the risk biomarker cost was <$2,900 (Figure 3d). The proportion of subjects in the low-risk group did not affect the superiority of AMRI-AMRI-none (Supplementary Figure S2). When varying AMRI cost and specificity, AMRI-AMRI-none remained superior when specificity was >90% or 96% when cost was <$156 or $532, respectively (Supplementary Figure S3).

DISCUSSION

Cirrhosis is a prevalent condition with significant indirect costs approximating $10.2 billion in the United States in 2004.[52] In addition, the human and economic burden of cirrhosis is expected to increase due to an aging population of hepatitis C virus–infected subjects who can develop HCC even a decade after viral cure and increases in prevalence of fatty liver disease.[53] However, as evidenced by low-quality indicators, interventions are urgently needed to improve quality of care in this vulnerable and underserved population.[54] Our study demonstrates for the first time the feasibility and cost-effectiveness of tailored HCC screening, in which cost for low-yield testing among low-risk patients is spared without significant drop in effectiveness. Imaging modalities, such as AMRI, with higher sensitivity while being affordable may, when applied to high-risk patients, improve early tumor detection in a cost-effective manner. Risk-based personalized screening has been increasingly adopted in multiple cancer types, e.g., MRI for *BRCA*-mutated breast cancer, with an intention to allocate costly but more sensitive modalities to those with the greatest need.[55] With the recent development of more accurate HCC risk stratification tools, our study provides a blueprint of how HCC screening can be personalized and advanced into the era of precision medicine.

Of note, incorporation of MRI could become cost-effective if targeted to high- and intermediate-risk patients, with recent

reductions in its costs. Compared with ultrasound, which may be affected by operator's skill/experience as well as the presence of morbid obesity,[8] MRI can yield more robust performance that will be critical considering the rapidly increasing and already highly prevalent obese patients with non-alcoholic fatty liver diseases. The emergence of simplified MRI protocols, such as AMRI, is expected to further lower the bar for introducing MRI-based screening by reducing examination costs and time.

Another issue limiting HCC screening effectiveness is low utilization rates due to providers overlooking at-risk patients and patient barriers to performing screening.[56] Risk-stratified strategies may improve utilization rates as efforts and resources to maximize adherence can be concentrated on the highest-risk patients instead of being diffused among all cirrhotic patients, particularly in centers with limited radiological or subspecialty capacity.

Recent development of robust molecular assays has allowed clinical deployment of already reimbursable multigene biomarker tests.[55] In addition, recent emergence of direct-to-consumer molecular diagnostics may drastically lower the current biomarker costs, which may further improve cost-effectiveness of the risk-stratified HCC screening. Our sensitivity analysis, evaluating a range of these dynamically changing variables, provides quantitative reference for further clinical development of HCC risk biomarker tests and AMRI protocols.

CONFLICT OF INTEREST

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Specific author contributions: N.G., A.S., and Y.H, conceived, designed the study, acquired data, interpreted and analyzed the data, and obtained funding. N.G. and Y.H. performed the statistical analysis. All authors contributed to the conception, critically revised the manuscript for important intellectual content, approved the final version to be published, and L.K., K.A., B.F., C.B., B.T., and R.C. provided administrative, technical, or material support for this study. Y.H. supervised the overall study. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

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Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Current practice guidelines recommend hepatocellular carcinoma (HCC) screening uniformly in all cirrhotic subjects by biannual ultrasound with or without alpha-fetoprotein.
- ✓ The utilization of HCC screening in the general cirrhotic population is $<20\%$.
- ✓ Molecular risk stratification of cirrhotic subjects is clinically feasible and already validated in a wide range of liver disease etiologies.

WHAT IS NEW HERE

- ✓ Our cost-effectiveness analysis shows that HCC screening strategies targeting high- and intermediate-risk patients with cirrhosis are cost-effective.
- ✓ Three risk-stratified strategies, all omitting screening in the lowest-risk subjects, were cost-effective compared with biannual screening without sacrificing net survival benefit.

TRANSLATIONAL IMPACT

- ✓ These findings provide evidence supporting risk-stratified, personalized HCC screening in cirrhotic subjects with currently available modalities and technologies.

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