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# Is non-contrast enhanced magnetic resonance imaging cost-effective for screening of hepatocellular carcinoma?

Genevieve Jingwen Tan[1], MBBS, FRCR, Chau Hung Lee[2], MBBS, FRCR, Yan Sun[3], MSc, PhD, Cher Heng Tan[2,4], MBBS, FRCR

[1]Department of Radiology, Khoo Teck Puat Hospital, [2]Department of Radiology, Tan Tock Seng Hospital, [3]Health Services and Outcomes Research Unit, National Healthcare Group, [4]Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore

**Correspondence:** Dr Genevieve Jingwen Tan, Associate Consultant, Department of Radiology, Khoo Teck Puat Hospital, 90 Yishun Central, Singapore 768828. tan.genevieve.j@ktph.com.sg

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**ABSTRACT**

**Introduction:** Ultrasound (US) is current standard of care for imaging surveillance in patients at risk for hepatocellular carcinoma (HCC). Magnetic resonance imaging (MRI) has been explored as an alternative, given the higher sensitivity of MRI, although this comes at a higher cost. We performed a cost-effective analysis comparing US and a dual-sequence non-contrast MRI (NCEMRI) for HCC surveillance, in the local setting.

**Methods:** Cost-effectiveness analysis of no surveillance, US surveillance and NCEMRI surveillance was performed using Markov modelling and microsimulation. At-risk patient cohort was simulated and followed-up for 40 years to estimate their disease status, direct medical costs, and effectiveness. Quality-adjusted life years (QALYs) and incremental cost effectiveness ratio were calculated.

**Results:** 482,000 patients with an average age of 40 years were simulated and followed up for 40 years. The average total costs and QALYs for the three scenarios – no surveillance, US surveillance and NCEMRI surveillance were S$1,193/7.460 QALYs; S$8,099/11.195 QALYs; S$9,720/11.366 QALYs, respectively.

**Conclusion:** Despite NCEMRI having a superior diagnostic accuracy, it is a less cost-effective strategy than US for HCC surveillance in the general at-risk population. Future local cost-effectiveness analyses should include stratifying surveillance methods with a variety of imaging techniques (US, NCEMRI, CEMRI) based on patients' risk profiles.

*Keywords: cost-effectiveness analysis, hepatocellular carcinoma, magnetic resonance imaging, ultrasound surveillance*

## INTRODUCTION

Hepatocellular carcinoma (HCC) is the 6th most common cancer worldwide and 5th most common cancer among males in Singapore.[1,2] This can in part be attributed to the high prevalence of chronic hepatitis B and C in the Asia-Pacific region, where chronic viral hepatitis induced liver disease is a major risk factor for HCC.[2]

Surveillance for HCC is therefore standard of care for this group of patients and imaging plays a central role. Conventionally, surveillance for HCC is performed with ultrasound (US). Various international guidelines including the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver (EASL) and the Asian Pacific Association for the Study of the Liver (APASL) recommend 6 monthly US with or without alpha-fetoprotein (AFP), as imaging surveillance of HCC has been shown to reduce mortality.[3]

US liver is generally cheap, does not involve ionizing radiation and is therefore suitable for mass population surveillance. However, it is highly dependent on operator technique and patient factors. Lesions near the diaphragm are also easily missed due to tissue depth and respiratory motion. Studies have shown that US has rather low sensitivity for detection of HCC, ranging from 30 to 67%.[4-8] Despite this, US remains the main imaging surveillance modality. Potential alternatives to US with higher accuracy for detection of HCC include contrast-enhanced CT (CECT)[4,7] and contrast-enhanced MRI (CEMRI).[9,10] However risks associated with repeated radiation exposure with CECT as well as the lower accessibility and higher cost of CEMRI make these less attractive imaging modalities for surveillance. Furthermore, current standard CEMRI liver protocols involve multiple sequences which can be relatively time-consuming to scan and subsequently report. Hence, recent studies have proposed cheaper abbreviated MRI protocols in HCC surveillance.[11-15]

Non-contrast enhanced MRI (NCEMRI) has been shown to perform reasonably well for HCC diagnosis,[11,12] with at least one study demonstrating no significant difference in sensitivity and specificity between CEMRI and NCEMRI for detecting hepatic malignancies and distinguishing them from benign entities.[15] The absence of intravenous contrast in NCEMRI reduces cost while at the same time allays concerns over gadolinium toxicity. A large prospective trial that provides a head-to-head comparison between NCEMRI and US is underway in South Korea (MIRACLE-HCC).[16] In terms of sensitivity, even NCEMRI has been shown to be superior to US for HCC detection, ranging from 76 to 95%.[11,12,15,17] It would also be significantly cheaper than CEMRI. Yet, to our knowledge, there does not exist any dedicated study on cost-effectiveness concerning the routine use of NCEMRI for HCC surveillance.

We therefore performed a cost-effective analysis comparing US (which is standard of care) and NCEMRI for surveillance of HCC in at-risk patients.


**METHODS**

This is a cost-effectiveness analysis using Markov modelling and microsimulation. A disease transition model with 7 states has been developed to mimic stepwise disease progression, from at-risk to cancer stage 0, A, B, C, D and to death, based on the Barcelona Clinical Liver Cancer (BCLC) staging system for staging of HCC.[18] The 5 cancer stages are: stage 0, stages A-D (Fig 1). There is a precancerous stage and progression from precancerous stage to early stage HCC (stage 0/A) has been reported to be about 6-8% annually.[19,20]

At-risk patient cohort was simulated and they were followed up for 40 years to estimate their disease status as well as their direct medical costs and effectiveness following 3 surveillance approaches: no surveillance, US surveillance, and dual-sequence NCEMRI surveillance using T2-weighted and diffusion-weighted imaging (Fig 2). 482,000 patients with

average age of 40 years were simulated. The cost analysis was conducted from patient perspective. Although majority of local patients were eligible for government subsidy, the total bill size without government subsidy was used for cost calculation, to reflect overall burden to the healthcare system. Discounting is a technique commonly used in cost-effectiveness analysis to 'make fair' comparisons of programmes whose costs and outcomes occur at different times given the time value of money, and most guidelines recommend equal discounting costs and effects at 3%.[21] Hence, for this study, both cost and effectiveness were discounted at an annual rate of 3%. Direct medical costs for surveillance, treatment, and follow-up care management were collected for evaluation. The incremental cost effectiveness ratio (ICER) was calculated and applied to identify the most cost-effective surveillance approach for HCC among at-risk patients in the Singapore context. The Markov transition cycle, which is defined as equal increments of time during which the patient may make a transition from one disease state to another,[22] is taken to be 6 months. Cost-effective analysis threshold was taken as per capita gross domestic product (GDP) as recommended by the World Health Organization, as this allows a patient to avoid disability-adjusted life-years (DALY) at a low cost.[23]

The following assumptions were made:

1. At-risk patients are first-tier scanned either by dual-sequence NCEMRI or US and outcome of the surveillance test is either positive or negative; only positive patients will then be scanned using full CEMRI study for final diagnosis of HCC.

2. Disease either progresses in a stepwise fashion from one stage to the next or remains at same stage.

3. Cancer stages 0, A & B can be cured or reversed to a previous stage.

4. Cancer stages C & D cannot be cured or reversed to a previous stage.

5. Once diagnosed with HCC, patients follow same treatment protocol; average treatment effects and costs apply to all patients at same stage.

6. False positive patients will be correctly diagnosed at next MRI scan.

7. No treatment for false negative patients; they are likely to be picked up in the follow-up scan in 6 months.

8. Death is all-cause death.

9. All stages can lead to death with different mortality rate.

10. If no surveillance is done, patients are most likely to be diagnosed at stages B, C or D.

Cost data were collected from local healthcare providers and Singapore's Ministry of Health (MOH), while other model parameters like disease transition probabilities, quality of life values, mortality rates, as well as treatment effects etc. at various disease states were derived via literature search.

Sensitivity and specificity for US and NCEMRI for surveillance of patients at risk for HCC was pooled from the literature. A literature search was performed using the PubMed database. Pooled point sensitivity and specificity for US was estimated to be 55.6% and 97.3% respectively.[4-8] This is comparable to a recent meta-analysis which reported US sensitivity and specificity of about 59% and 93% for detection of HCC in both surveillance and non-surveillance settings.[24]

Pooled point sensitivity and specificity for NCEMRI was estimated to be 90% and 91.5% respectively, based on proof-of-concept studies.[11,12,15] This is similar to a recent meta-analysis that reported pooled sensitivity and specificity of 86% and 94% respectively.[25]

There were 2346 cases locally from 2011-2015,[26] giving an average of 469 cases annually in Singapore.

The major risk factors for HCC are chronic hepatitis B infection, non-alcoholic steatohepatitis (NASH) and cirrhosis.

Estimated prevalence of chronic hepatitis B locally is about 180,000 and estimated prevalence of cirrhosis locally is about 45,000, of which the top causes are chronic hepatitis B

63.3%, alcohol-related cirrhosis 11.2%, cryptogenic cirrhosis 9% and chronic hepatitis C 6.9%.[27] Based on this data, the prevalence of non-hepatitis-B-related cirrhosis is estimated at 12,200. NASH lies on a spectrum of non-alcoholic fatty liver disease (NAFLD) and is increasingly being recognised as an important aetiology of HCC and liver cirrhosis, with local prevalence of NAFLD around 29%.[28] Recent evidence suggests that majority of cases of cryptogenic cirrhosis are likely secondary to NASH.[29] For this analysis, NASH-related cirrhosis is therefore categorised as a subtype of cryptogenic cirrhosis. Similar to chronic hepatitis B, it is also known that HCC can develop in NASH without evidence of cirrhosis.[30] The prevalence of NASH and NASH-related cirrhosis is estimated based on the following probabilities: 20% of patients with NAFLD progress to NASH, of which another 20% progress to cirrhosis.[31,32] The prevalence of NASH without cirrhosis is therefore estimated at about 290,000.

The estimated total at-risk population comprising of chronic hepatitis B, NASH without cirrhosis and non-hepatitis B-related cirrhosis, is therefore around 482,000 locally.

A pooled estimate of 83.4% of surveillance ultrasounds were normal,[5-9] while about 4.5% were BCLC stage 0/A cancers, 5.9% were stage B, 3.3% were stage C and 2.3% were stage D.[33] No corresponding data was available for NCEMRI surveillance.

A local study showed 0.8% of patients with chronic hepatitis B, with or without cirrhosis, develop HCC annually.[34] Based on available literature, about 1.6% of patients with alcoholic cirrhosis, 4% of patients with chronic hepatitis C cirrhosis and 2.6% of patients with NASH (with or without cirrhosis) develop HCC annually.[35,36] This gives an estimated pooled transition probability per annum of about 1.1%.

Annual mortality for liver cirrhosis is estimated at 2.7%.[37] Patients with chronic hepatitis B infection without cirrhosis are generally asymptomatic and annual mortality is

assumed to be baseline for the general population at estimated 0.5% per year.[38] This gives an estimated pooled base mortality for at-risk patients of about 1.3% annually.

Based on local surveillance programs, at-risk patients routinely undergo six-monthly consultations and laboratory tests, as well as six-monthly imaging surveillance using hepatobiliary US.

Based on a tumour doubling time of 117-195 days,[39] 40% of hepatocellular carcinomas progress from early/very early stage (stage 0/A) to advanced stage (C/D) without treatment.

The annual percentage increase in mortality is estimated to be 2%.[40]

Based on BCLC stage, annual mortality without treatment was estimated as follows: 36% for stage 0/A, 63% for stage B, 87% for stage C and 93% for stage D.[41]

Treatment for each stage is based on BCLC recommendations. For stage 0/A, treatment options include liver resection and local percutaneous ablation therapy for curative treatment. For stage B, treatment options include transhepatic arterial chemoembolisation (TACE). For stage C, treatment options include chemotherapy (sorafenib) or transhepatic arterial radiotherapy with Y-90. For stage D, there is no specific treatment and best supportive care is usually provided. For patients with known HCC, routine follow-up includes 6-monthly full CEMRI study, clinical consultations, and laboratory tests.

Impact of treatment on mortality depends on the type of treatment as well as cancer stage. Local percutaneous ablation therapy for stage 0/A HCC has been shown to reduce mortality from 36% to 17%, while surgical resection for stage 0/A reduces mortality from 36% to 23% within first year of treatment.[42,43] While TACE improves long-term survival in advanced HCC, it appears to have little effect on annual mortality within the first year of treatment on the mortality of stage B HCC, reducing annual mortality from 63% to 61%.[44] Chemotherapy with sorafenib for stage C HCC shows improvement in mortality within the first

year from 87% to 68%.[45] Symptomatic treatment for stage D HCC does not confer improvement in mortality.

Based on available literature, for purposes of computational analysis, it can be assumed that treatment for early stage disease (stages 0/A) allows a reduction in annual mortality by up to 50% within the first year of treatment while treatment of intermediate and late stage disease (stage B, C, D) will not result in significant reduction in mortality.

Routine surveillance of patients at-risk is assumed to be performed 6-monthly. Direct medical cost for routine surveillance of patients at-risk is summarised in Table 1. Costs are obtained from our local institution, Tan Tock Seng Hospital (TTSH), or estimated from the MOH Guidelines on Fees.

Direct medical cost of treatment is summarised in Table 2. Costs were either obtained from our local institution (TTSH) or from the MOH Guidelines on Fees. Direct non-medical costs such as transportation, as well as indirect costs such as caregiver expenditure and absenteeism, are estimated. For purposes of cost calculation, curative treatment (surgery or percutaneous local ablation therapy) is assumed to be a one-off treatment per year, an average of one course of treatment per year is assumed for TACE and Y-90 radiotherapy, and chemotherapy cost is based on monthly cost.

Patients on treatment are assumed to be followed-up 6-monthly. Direct medical cost for follow-up of patients who have undergone treatment is summarised in Table 3. Duration of follow-up is assumed to be lifelong.

**RESULTS**

A simulated cohort of 482,000 at-risk patients with an average age of 40 years old was studied. After 40 years, all at-risk patients will die if without any surveillance; around 9% of at-risk patients will still be alive if surveillance by US or 10% if surveillance by NCEMRI. The

average total costs and quality-adjusted life years (QALYs) for the three scenarios of no surveillance, surveillance with US or NCEMRI are: S$4,675 / 7.483 QALYs, S$23,803 / 11.242 QALYs, S$177,876 / 11.426 QALYs (Fig 3).

The cost, effectiveness and ICER of the three surveillance approaches are depicted in Table 4. Overall, the incremental QALYs of US and NCEMRI surveillance over no surveillance are S$5,088 and S$43,924 per QALY gained, respectively. The incremental QALY of NCEMRI surveillance over US surveillance is S$837,353 per QALY gained, which is much higher than Singapore's GDP per capita (~S$80,000 in 2019).

**DISCUSSION**

Diagnostic superiority of MRI, even without the use of gadolinium-chelate contrast agents, over US is well-established. However, cost is always cited as a reason against population-based surveillance of at-risk patients in HCC using MRI. Our study confirms that NCEMRI is indeed a less cost-effective surveillance strategy compared to US, with an overall ICER of over S$800,000 per QALY gained, much higher than national GDP. One explanation could be the relatively low transition probability of 1.1% used in our study. This would result in a higher number of at-risk patients undergoing surveillance in order to detect an early stage HCC, reducing cost-effectiveness of NCEMRI. This is because the simulation in our study included all patients at-risk of HCC, including chronic hepatitis B without cirrhosis. This low transition probability could be also attributed to improving control over the natural disease progression of chronic hepatitis B, given that chronic hepatitis B remains the major contributing risk factor for HCC in this region. Other studies on cost-effective analysis simulated cohorts with liver cirrhosis, and in regions where other risk factors such as chronic hepatitis C or alcoholic cirrhosis may play more significant contributing risk for HCC, higher transition probabilities were applied, ranging from 1.5 to 5 %.[9,46,47] The higher transition

probabilities applied in these studies will tend to lead to increased cost-effectiveness as more cases of early HCC are picked up when the disease is still curable.

Although majority of patients locally are eligible for government subsidy for medical treatment, in the context of population health screening and surveillance, the overall cost to the government, healthcare system and taxpayers has to be considered. Therefore based on our analysis, NCEMRI, whilst superior to US for detection of HCC, should currently not be recommended as an alternative to US for HCC surveillance in the general at-risk population.

Kim et al performed a similar analysis comparing CEMRI vs US for HCC surveillance and found CEMRI to be a cost-effective alternative.[9] Our study showed a lower overall gain in QALY of 0.18 using NCEMRI instead of US, compared to 0.22 incremental QALY using CEMRI compared to US shown by Kim et al. Furthermore, Kim's study showed that CEMRI incurred US$5,562 incremental cost and an estimated ICER of US$25,202 per QALY gained when compared to US, considerably lower than the S$ 154,073 incremental cost and an estimated ICER of S$837,353 per QALY gained incurred using NCEMRI demonstrated by our study. The differences in cost-effectiveness are also very likely related to differences in cost of surveillance and HCC treatment in different geographic regions. Additionally, that study analysed patients with cirrhosis which can be considered a higher-risk subgroup. The reported transition probability of 3% could also have accounted for superior cost-effectiveness, compared to our cohort which includes patients with chronic hepatitis B and NASH without cirrhosis.

Other cost-effective analyses compared a variety of imaging surveillance strategies (US vs MRI vs CT), and surveillance intervals (annual vs semi-annual). Andersson et al, comparing 6 imaging surveillance strategies modelled within the USA, found an ICER exceeding US$100,000 for MRI surveillance and deemed MRI least cost-effective compared to US or even CT.[46] This could be because in that study, full multisequence CEMRI was performed,

which increases the cost of the scan compared to CT or US. The findings are similar to our study which showed that NCEMRI is not a cost-effective surveillance modality, even without intravenous contrast. That study analysed a subgroup of patients with compensated cirrhosis, similar to Kim et al,[9] but with a higher transition probability of 5%. A more recent study by Lima et al also simulated a cohort of patients with cirrhosis within Canada. In contrast, despite a transition probability of 1.5% close to that used in our study (1.1%), that study found an ICER of about CAD 40,000 for abbreviated MRI surveillance and concluded that abbreviated MRI protocol could be cost-effective in high-risk cirrhotic patients, where compliance to surveillance is not 100%.[47]

Varying findings from our study and previous analyses from available literature suggests that there is no "one-size-fits-all" imaging surveillance strategy and cost-effectiveness is dependent on factors such as demographics, varying epidemiology of HCC in different geographic regions, national healthcare policies and willingness to pay.

Although our study does not demonstrate cost-effectiveness of NCEMRI as a surveillance tool in all patients at risk for HCC, our findings are in line with the current recommendation that US remains the modality of choice for HCC surveillance. It is possible that by further risk-stratifying patients within our local at-risk population, NCEMRI could potentially be cost-effective for a subgroup of patients at "super-high" risk with higher incidence of HCC, such as those with advanced cirrhosis.

There are several limitations in our study. Due to lack of supporting published evidence, but in order to generate a model for evaluation, we made the assumption that false positive patients and false negative patients would be correctly diagnosed at subsequent visits. Furthermore, given the limited data available, we attributed deaths to all-cause deaths rather than cancer-specific deaths. We believe however that this may be meaningful since the lifespans of HCC patients are often prolonged by locoregional therapies and surgeries within

Asia. Also, for purposes of analysis, we assumed all patients with a positive surveillance test would undergo CEMRI to confirm diagnosis of HCC in our study. In practice, such patients may undergo CECT or even contrast-enhanced US instead, which will affect cost-effectiveness.

For this study, we did not take into account the availability of MRI scanners as a resource because MRI costs typically factor in the depreciation of MRI scanners. Furthermore, the "cost" of surveillance (such as costs of scans, clinic visits, and treatment costs) utilised in our studies reflected the price paid out by patients and/or government, and may not take into account the actual expense incurred, such as scan time and manpower costs. We believe that this better reflects the true cost-effectiveness of the procedure. The calculation of costs incurred by patients at-risk and at different cancer stages was based only on local institutional or MOH guidelines, and we recognise that this may vary between institutions. However published costs from individual institutions were not readily accessible.

Liver transplant is an established treatment option for BCLC stage A HCC. However, liver transplant was not included in our analysis as this an uncommon treatment option locally due to organ shortage.[48] This omission could potentially have influenced the cost-effectiveness of NCEMRI due to the relatively high cost of liver transplant.

Some studies evaluated cost-effectiveness of multiphasic CT for HCC surveillance.[46,47] We also omitted a comparison against CECT, which in our opinion is not acceptable for HCC surveillance imaging due to radiation exposure and the need for potentially nephrotoxic iodinated contrast.

Lastly, model parameters such as disease transition probabilities, quality of life values, mortality rates as well as treatment effects at various disease states were derived from a mixed of local and international data, resulting in a very heterogeneous data set. This could not be avoided due to lack of local data or evidence for certain parameters.

In conclusion, despite NCEMRI having a superior diagnostic accuracy, it is a less cost-effective strategy than US for HCC surveillance in the general at-risk population, from an overall healthcare perspective. Future local cost-effectiveness analyses should include stratifying surveillance methods with a variety of imaging techniques (US, NCEMRI, CEMRI) based on patients' risk profiles. This would enhance our understanding of the cost-effectiveness and impact on overall outcome of patients using various imaging tools for HCC surveillance.

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**Table 1: Estimated direct medical cost of surveillance for patients at risk for HCC (ᵃ estimated for dual-sequence NCEMRI using T2-weighted and diffusion-weighted imaging).**

| Component | Cost (S$) |
|---|---|
| Imaging surveillance: ultrasound | 140 |
| Imaging surveillance: non-contrast MRI | 600[a] |
| Laboratory tests | 50 |
| Clinic consultation | 110 |

**Table 2: Estimated cost of HCC treatment at each cancer stage, based on a combination of BCLC and local treatment guidelines.**

| BCLC Stage | Treatment | Cost (S$) |
|---|---|---|
| 0/A | Liver resection | 14000 |
| | Percutaneous local ablation | 4000 |
| B | TACE | 4300 |
| C | Chemotherapy | 9000 per month |
| | Y-90 radiotherapy | 10000 |
| D | Supportive care | No specific cost |

**Table 3: Estimated direct medical cost for follow-up of patients with HCC who have undergone treatment.**

| Component | Cost (S$) |
|---|---|
| Full MRI study with contrast | 1200 |
| Laboratory tests | 50 |
| Clinic consultation | 110 |

**Table 4: Comparison of costs, effectiveness and ICER of the three surveillance approaches.**

| Approach | Total cost mean (SE) | Total QALYs Mean (SE) | Incremental cost (S$) | Incremental QALYs | ICER |
|---|---|---|---|---|---|
| No surveillance | 4675 (263) | 7.483 (0.044) | | | |
| US surveillance | 23803 (367) | 11.242 (0.074) | 19128 (299) | 3.759 (0.052) | 5088 |
| MRI surveillance | 177876 (1111) | 11.426 (0.074) | 173201 (1135) | 3.943 (0.051) | 43924 |
| MRI vs. US | | | 154,073 | 0.184 | 837,353 |
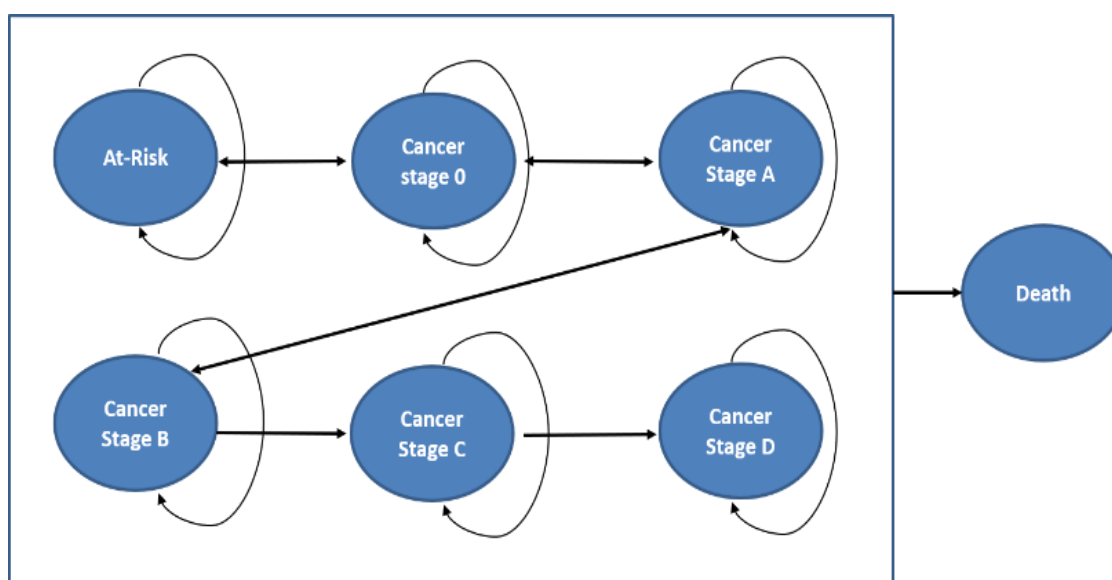


**Fig 1:** Disease progression of HCC through 7 stages.
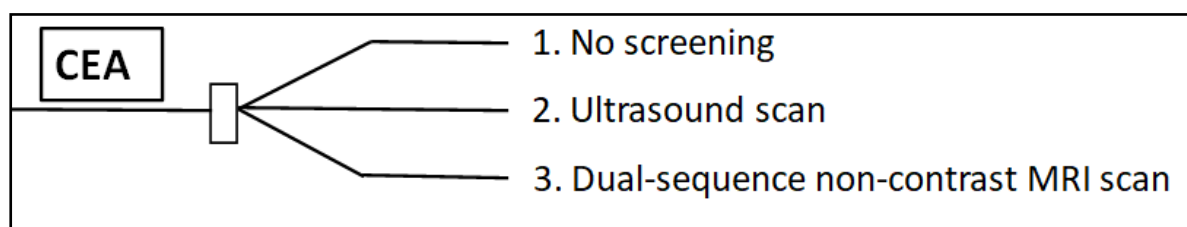


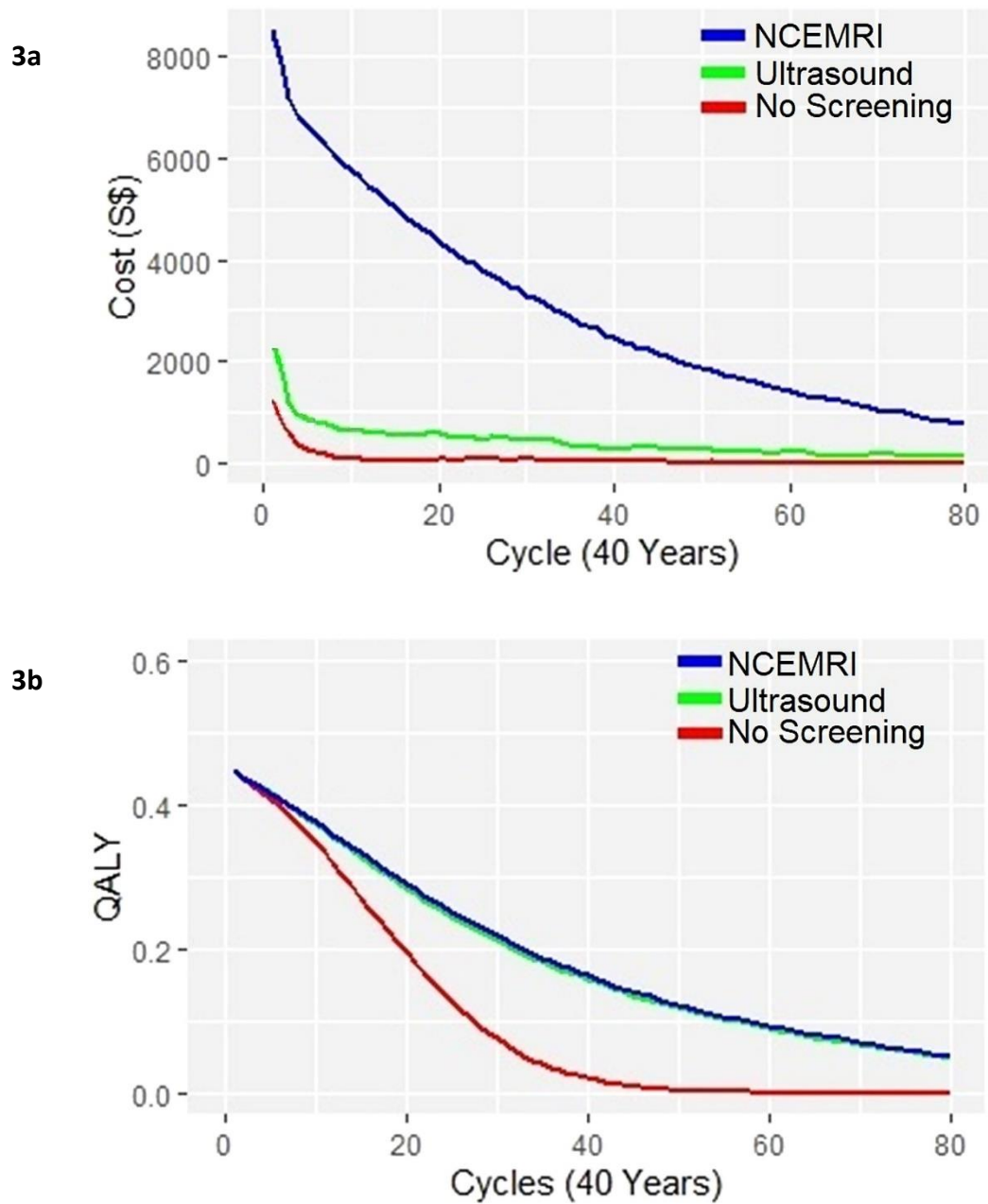**Fig 2:** Cost-effective analysis (CEA) of three surveillance approaches in our study.

**Fig 3.** Cost (a) and QALY (b) of the simulated cohort over 40 years.