Cost Effectiveness Analysis of Hepatocellular Carcinoma Surveillance using Abdominal Ultrasound in Hepatitis B Patients

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Abstract

Hepatocellular carcinoma (HCC) is a disease with a high mortality rate. The surveillance of HCC with ultrasound in hepatitis B patients can improve survival. However, there is no national policy data in Thailand that indicates that hepatitis B patients should receive ultrasound surveillance. This study aims to determine the cost-effectiveness of HCC surveillance, which can be analyzed and displayed in a cost-to-health outcome model. This cost-effectiveness analysis used the decision tree model to assess 1) direct medical cost, 2) direct non-medical cost, and 3) indirect cost. The uncertainty of variables was analyzed. Results were presented as incremental cost-effectiveness ratio (ICER). The ICER of less than 160,000 THB/QALY gained is considered cost-effective according to the threshold of willingness to pay in Thailand. The HCC surveillance group and the non-surveillance group had 0.99 and 0.86 life-year gained (LYG) and 0.68 and 0.58 quality-adjusted life-year gained (QALY gained), respectively. The cost per QALY gained in the HCC surveillance group was 32,518 baht, which is cheaper than 54,589 baht in the non-surveillance group. Besides, the surveillance group had an ICER of 104,392 baht per QALY gained compared with the non-surveillance group. The surveillance for HCC in hepatitis B patients with ultrasound is cost-effective when comparing the willingness to pay in Thailand and 160,000 baht for QALY gained. The study results can be potentially used as information to enhance the policy of public health economics in HCC surveillance of hepatitis B patients.

Keywords: *Hepatocellular carcinoma, Hepatitis B infection, Cost-effectiveness analysis, Abdominal ultrasound, Incremental cost-effectiveness ratio*

1. Introduction

Hepatocellular carcinoma (HCC) is common cancer with a high mortality rate and a high incidence of new cases and mortality rate in Asia and worldwide (Sung et al., 2021). The prevalence of HCC in Thailand among males and females was 22.3 cases per 100,000 population (Chonprasertsuk & Vilaichone, 2017), which is mainly caused by viral hepatitis B. The patients with hepatitis B without cirrhosis were reported to develop an HCC of 0.6% per year (Marrero et al., 2018). Since HCC has no symptoms at the early stage and often presents with a symptom at the late and unresectable stage, resulting in delayed diagnosis and poor survival outcomes.

Currently, ultrasound plays an important role in the surveillance of HCC due to its simplicity and inexpensive non-invasive imaging study. Thus, the surveillance can facilitate the screening of new patients with HCC, including the detection of early or surgical stages of lesions towards a timely surgery. A study found that the early stage of HCC diagnosis with prompt treatment can increase the survival rate by more than 60% (Lim et al., 2012). Besides, there is a higher survival rate in the surveillance group than in the non-surveillance group (Zhang, Yang, & Tang, 2004; Singal, Pillai, & Tiro, 2014).

Although the surveillance of HCC with ultrasound can be beneficial, there is no national policy in Thailand for surveillance of hepatitis B patients. Therefore, the cost-effectiveness data is required to support the assessment of cost-effective health economics of HCC surveillance in this group of patients as important information for a public health policy. A study in the United States analyzed the cost-effectiveness of HCC surveillance by using a model of incremental cost-effectiveness ratio (ICER), which yielded a cost of $30,700 for ICER (Andersson, Salomon, Goldie, & Chung, 2008). In Canada, the outcome of the cost-effective analysis was a cost of 35,108 for ICER (Lima et al., 2019). Regarding the willingness to pay of each country, the data has shown that HCC surveillance could enhance an increase in quality-adjusted life years. Thus, it was cost-effective in patients with screening and surveillance compared to those without the screening and surveillance.

In 2010, Chulabhorn Hospital established a surveillance program for 2,283 hepatitis B patients at high risk for HCC every six months of follow-up for early detection and treatment. Diagnostic data were collected, and follow-up was performed with ultrasound, including information on HCC for five years for the analysis of cost-effectiveness in HCC screening and surveillance. Thus, this study aims to analyze the monetary cost and effective results in health outcomes, that is, QALY gained, to determine the cost-effectiveness of screening and surveillance for HCC in hepatitis B patients. The data could potentially be useful information to consider for the policy in public health economics for the surveillance of HCC in Thailand.

2. Objectives

To study the cost-effectiveness of HCC surveillance with abdominal ultrasound in hepatitis B patients by evaluating the incremental cost-effectiveness ratio (ICER)

3. Materials and Methods

Study populations

This study divided the population into two comparison groups: ultrasound surveillance and non-surveillance groups.

The HCC surveillance group comprised 2,283 patients; both males and females aged 20-65 years who attended abdominal ultrasounds and had a history of positive immunosuppression for Hepatitis B Surface Antigen. The exclusion criteria were those with a history of cancer within 5 years, chronic hepatitis B treatment, concomitant of hepatitis B and hepatitis C or human immunodeficiency virus (HIV) infection, and decompensated cirrhosis.

The non-surveillance group consisted of 92 patients with HCC at Chulabhorn Hospital from 2016 to 2018; both males and females aged 20-65 years who had positive immunologic Hepatitis B surface Antigen (HBsAg) (Figure 1).

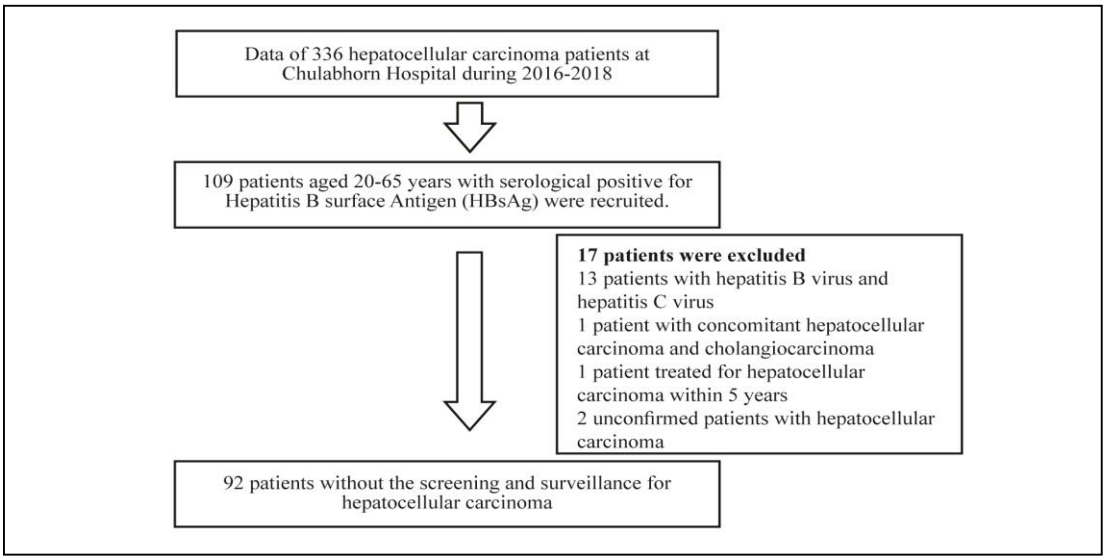

Figure 1 Patients without screening and surveillance group

Model structure

Decision trees were used (Figures 2 and 3) to assess costs and health outcomes by using the American Association for the Study of Liver Disease (AASLD) Guideline (Marrero et al., 2018), with a recommendation for abdominal ultrasound examination every six months. When liver nodule size 1 cm and above are detected, there should be a confirmation by computed tomography (CT) or magnetic resonance imaging (MRI). Also, biopsy-confirmed results are required when HCC is detected early, which can be treated by liver resection, liver transplant, radiofrequency ablation (RFA), or Trans-arterial chemoembolization (TACE). Systemic chemotherapy such as sorafenib or palliative care can be given in late-stage of HCC patients. In the case of equivocal CT, MRI results, and not giving a definite diagnosis, follow-up with CT or MRI is recommended. For other benign nodules, lesions less than 1 cm in size, and non-detectable lesions, an ultrasound follow-up every six months is recommended by the AASLD guideline.

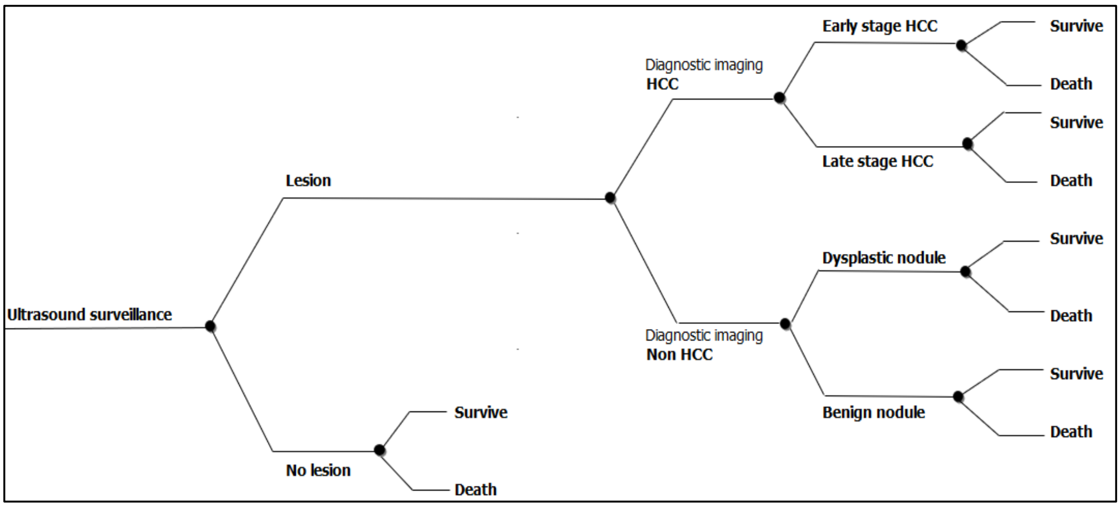

Figure 2 Decision tree of the surveillance group for hepatocellular carcinoma using abdominal ultrasound

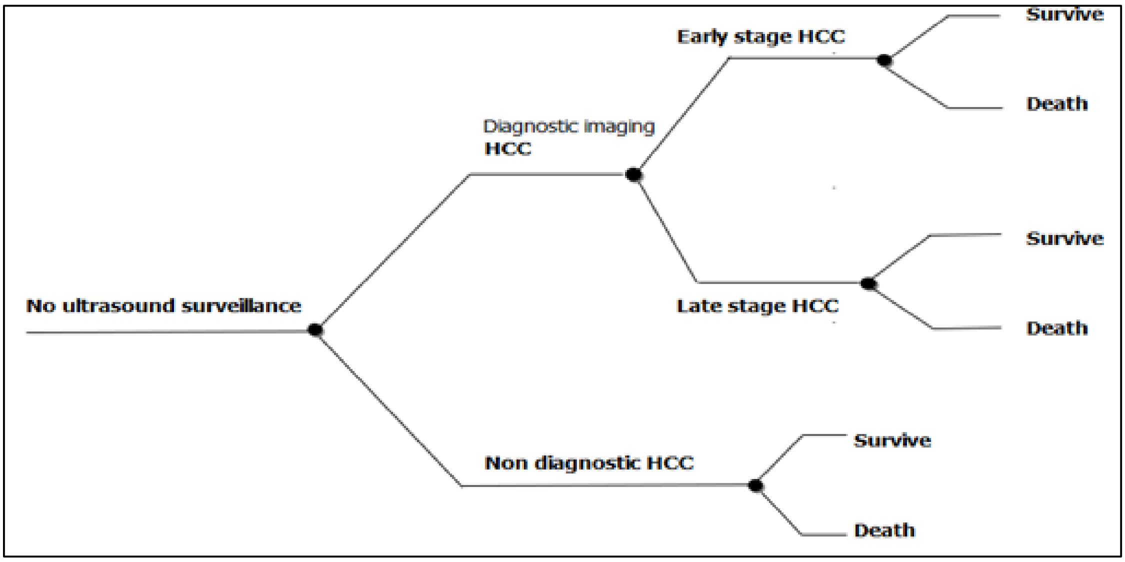

Figure 3 Decision tree of the non-surveillance for hepatocellular carcinoma using abdominal ultrasound

Model assumption

Data analysis from decision trees was based on the following assumptions: 1) Ultrasound HCC screening was performed and interpreted by a radiologist with ultrasound follow-up every 6 months for 5 years, 2) HCC staging was categorized by the Barcelona Clinic Liver Cancer (BCLC) guidelines, including the early-stage (BCLC stage 0, A, B) and the late-stage (BCLC stage C and D), 3) Calculation of survival periods in both groups from date of death by using data from Chulabhorn Hospital database system and basic patient rights database system, 4) Costs of treatment, such as palliative care based on palliative treatment in Chulabhorn Hospital calculated by the diagnosis-related groups (DRGs) and costs of food, travel, and income loss from a patient and a relative, and 5) Group of patients without ultrasound screening and surveillance for HCC and non-hospitalized to be considered as a hepatitis B virus patient with no lesions and a survival rate of 95% according to expert opinions.

Cost Measurement

The cost-effectiveness study was conducted from a societal perspective, including direct medical cost, direct non-medical cost, and indirect cost, (as shown in Table 1), which covered costs for screening, treatment, and follow-up of HCC.

The calculation of diagnostic and follow-up costs was done from the collecting number of examinations to find an average of each examination referenced by the National Health Security Office (NHSO) price. The diagnosis consisted of ultrasound upper abdomen, CT chest without contrast media, CT chest with contrast media, CT upper abdomen, CT whole abdomen, MRI liver, MRI upper abdomen, MRI whole abdomen, and liver biopsy. The hospitalized treatment costs included liver resection, radiofrequency ablation, TACE, chemotherapy, and palliative care based on the diagnosis-related groups (DRGs) system in the HCC code or C22.0, calculated in the TGrp5103 and TGrp6305 DRG calculating software programs and follow-up cost according to physician's opinion, including CT or MRI.

Uncertainty analysis

To analyze costs and health outcomes using a decision tree model, variable data were taken from many different sources, such as costs, utilities, and probabilities of disease (Table 2). Therefore, the uncertainty analysis was important in determining which variable had the greatest impact on health outcomes. The uncertainty analysis of variables in this study could be divided into two methods: one-way analysis and probabilistic sensitivity analysis (PSA).

A one-way analysis is performed by changing one variable and then analyzing the change in incremental cost-effectiveness ratio (ICER). The results were displayed as a Tornado diagram.

Probabilistic sensitivity analysis (PSA) is performed by changing multiple variables simultaneously with Microsoft Office Excel 2010. The same number of possible variables were repeated 1,000 times, and the costs and health outcomes data were analyzed based on their distribution characteristics. This method was called Monte Carlo simulations. Probabilities & utilities and cost were distributed as beta and gamma distribution, respectively.

Health outcomes

Health outcomes were presented as QALY gained by multiplying the life-year gained with the utility in Table 3 as the incremental cost-effectiveness ratio (ICER). Determining cost-effectiveness in HCC surveillance with ultrasound must maintain ICER less than the willingness to pay in Thailand at 160,000 baht per QALY. Therefore, the HCC surveillance in hepatitis B patients was considered cost-effective in health economics in Thailand.

Table 1 Cost parameters.

Costs	Distribution	Mean	Standard Error	Source
Diagnostic procedures				
Ultrasound upper abdomen	Gamma	800.00	800.00	Comptroller General's Department
Ultrasound-guided for biopsy	Gamma	2,300.00	2,300.00	Comptroller General's Department
Liver biopsy	Gamma	500.00	500.00	Comptroller General's Department
Ultrasound for fine-needle aspiration	Gamma	2,000.00	2,000.00	Comptroller General's Department
CT chest noncontrast	Gamma	4,000.00	4,000.00	Comptroller General's Department
CT chest with contrast	Gamma	6,000.00	6,000.00	Comptroller General's Department
CT upper abdomen	Gamma	6,000.00	6,000.00	Comptroller General's Department
CT whole abdomen	Gamma	10,000.00	10,000.00	Comptroller General's Department
MRI liver	Gamma	8,000.00	8,000.00	Comptroller General's Department
MRI upper abdomen	Gamma	8,000.00	8,000.00	Comptroller General's Department
MRI whole abdomen	Gamma	16,000.00	16,000.00	Comptroller General's Department
Treatment procedures				
Hepatectomy of the surveillance group	Gamma	89,986.42	89,986.42	DRG Chulabhorn Hospital
Hepatectomy of the non-surveillance group	Gamma	62,226.91	62,226.91	DRG Chulabhorn Hospital
RFA of the surveillance group	Gamma	79,204.81	79,204.81	DRG Chulabhorn Hospital
RFA of the non-surveillance group	Gamma	80,716.91	80,716.91	DRG Chulabhorn Hospital
TACE of the surveillance group	Gamma	50,832.06	50,832.06	DRG Chulabhorn Hospital
TACE of the non-surveillance group	Gamma	62,676.04	62,676.04	DRG Chulabhorn Hospital
Sorafenib of the non-surveillance group	Gamma	1,593.00	1,593.00	DRG Chulabhorn Hospital
Palliative care of the non-surveillance group	Gamma	32,060.93	32,060.93	DRG Chulabhorn Hospital
Paracentesis of the non-surveillance group	Gamma	31,872.20	31,872.20	DRG Chulabhorn Hospital
Transportation cost of patient and/or caregiver	Gamma	142.55	142.55	(Riewpaiboon, 2011)
Food cost of patient and/or caregiver	Gamma	52.51	52.51	(Riewpaiboon, 2011)
Patient's loss of earned income	Gamma	80.29	80.29	(Riewpaiboon, 2011)
Caregiver's loss of earned income	Gamma	95.51	95.51	(Riewpaiboon, 2011)

4. Results and Discussion

Cost-effectiveness analysis

The cost-effectiveness study of ultrasound HCC screening and surveillance in hepatitis B patients by using examination costs, which included direct medical cost, direct non-medical cost, and indirect cost, together with the decision tree model for outcome analysis as QALY gained in Table 4. The patients in the HCC surveillance group and those in the non-surveillance group had 0.99 and 0.86 life-year gained (LYG), 0.68 and 0.58 QALY gained, respectively. Also, the cost per QALY gained for the HCC surveillance group and the non-surveillance group was 32,518 baht vs. 54,589 baht. The ICER of the HCC surveillance group is about 104,392 baht per QALY gained as compared with the non-surveillance group. The ICER of surveillance is less than the threshold Thailand is willing to pay at the cost of 160,000 baht per QALY gained.

Table 2 Probability parameters of disease.

Probabilities	Distribution	Mean	Standard Error	Source
Surveillance group				
Probability of US with lesion ≥ 1 cm	Beta	0.2383	0.0089	(Ungtrakul et al., 2016)
Probability of diagnostic confirmed HCC	Beta	0.0349	0.0079	(Ungtrakul et al., 2016)
Probability of early-stage HCC	Beta	1.0000	0.0000	(Ungtrakul et al., 2016)
Probability of dysplastic nodule	Beta	0.0343	0.0079	(Ungtrakul et al., 2016)
Probability of survival of early-stage HCC	Beta	0.6316	0.1107	(Ungtrakul et al., 2016)
Probability of survival of dysplastic nodule	Beta	1.0000	0.0000	(Ungtrakul et al., 2016)
Probability of survival of benign nodule	Beta	1.0000	0.0000	(Ungtrakul et al., 2016)
Probability of survival of patient without lesion	Beta	1.0000	0.0000	(Ungtrakul et al., 2016)
Probability of hepatectomy of the surveillance group	Beta	0.3684	0.1107	(Ungtrakul et al., 2016)
Probability of RFA of the surveillance group	Beta	0.5263	0.1145	(Ungtrakul et al., 2016)
Probability of TACE of the surveillance group	Beta	0.1053	0.0704	(Ungtrakul et al., 2016)
Non-surveillance group				
Probability of diagnostic confirmed HCC	Beta	0.1000	0.0300	(Ungtrakul et al., 2016)
Probability of early HCC from imaging positive	Beta	0.5326	0.0520	(Ungtrakul et al., 2016)
Probability of survival of early-stage HCC	Beta	0.0612	0.0342	(Ungtrakul et al., 2016)
Probability of survival of late-stage HCC	Beta	0.0000	0.0000	(Ungtrakul et al., 2016)
Probability of survival of non-diagnostic HCC	Beta	0.9500	0.0000	(Ungtrakul et al., 2016)
Probability of hepatectomy in the non-surveillance group	Beta	0.0612	0.0342	(Ungtrakul et al., 2016)
Probability of RFA in the non-surveillance group	Beta	0.0612	0.0342	(Ungtrakul et al., 2016)
Probability of TACE in the non-surveillance group	Beta	0.8980	0.0432	(Ungtrakul et al., 2016)
Probability of sorafenib in the non-surveillance group	Beta	0.1163	0.0489	(Ungtrakul et al., 2016)
Probability of palliative in the non-surveillance group	Beta	0.6744	0.0715	(Ungtrakul et al., 2016)
Probability of paracentesis in the non-surveillance group	Beta	0.1860	0.0593	(Ungtrakul et al., 2016)

Table 3 Utility parameters.

Utility	Distribution	Mean	Standard Error	Source
Chronic hepatitis B	Beta	0.68	0.0214	(Levy et al., 2008)
Early-stage HCC	Beta	0.53	0.0918	(Wongphan & Bundhamcharoen, 2018)
Late-stage HCC	Beta	0.32	0.0001	(Wongphan & Bundhamcharoen, 2018)

Table 4 Estimated costs and health outcomes between the two groups

	Non- surveillance group	Surveillance group
Costs (baht)	31,832	22,019
LYG (year)	0.86	0.99
QALY gained (year)	0.58	0.68
Costs / QALY gained (baht/year)	54,589	32,518
ICER (baht/QALY gained	-	104,392

**LYG: life-year gained, QALY; Quality-adjusted life year, ICER: Incremental cost-effectiveness ratio*

Table 5 Estimated costs and health outcomes between the two groups when analyzing the sensitivity by changing multiple variables

	Non-surveillance group	Surveillance group
Costs (baht)	32,612	22,274
LYG (year)	0.86	0.99
QALY gained (year)	0.58	0.68
Costs / QALY gained (baht/year)	56,628	32,897
ICER (baht/QALY gained)	-	109,221

**LYG: life-year gained, QALY; Quality-adjusted life year, ICER: Incremental cost-effectiveness ratio*

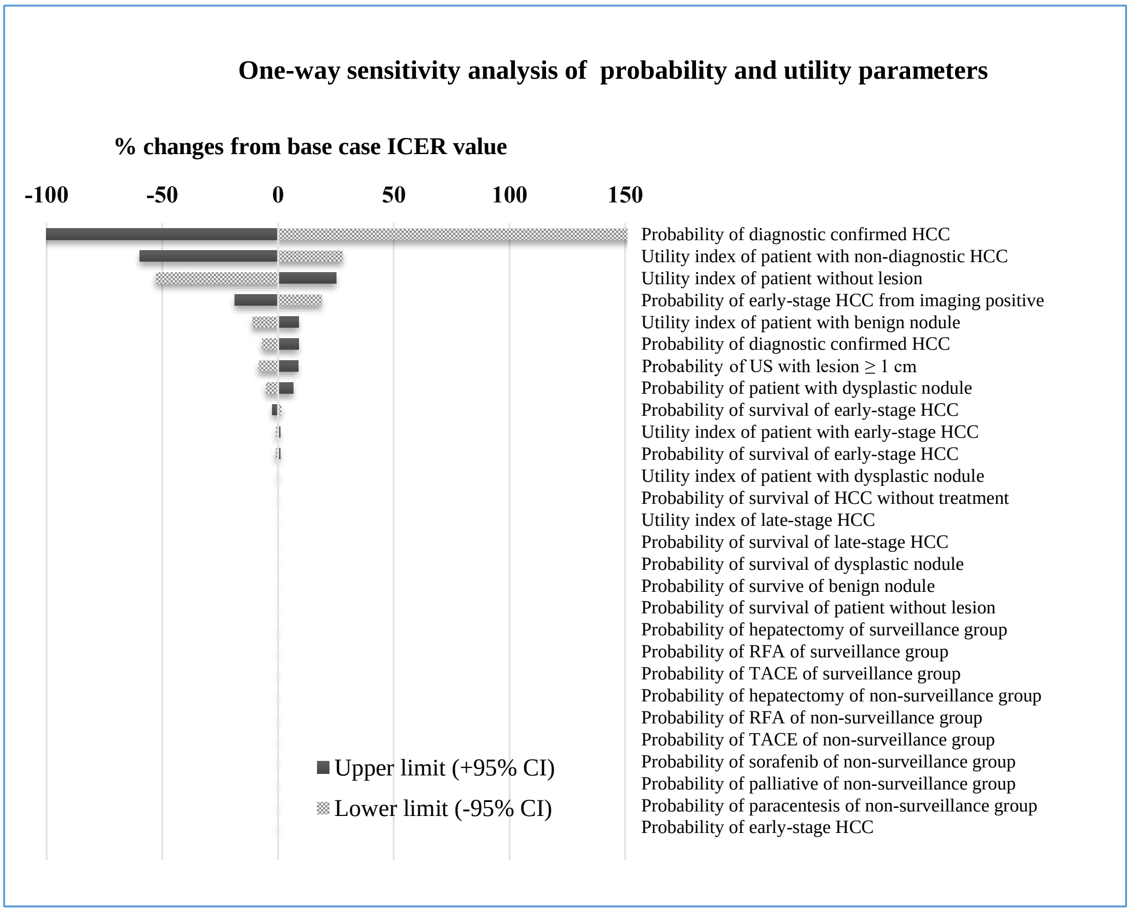

Figure 3 Tornado diagram of probability and utility parameters

Uncertainty analysis

The uncertainty analysis of variables by one-way analysis in Figures 3 and 4 showed that the cost of TACE in the non-surveillance group was the most impact variable affecting the change in an ICER. When increasing the mean cost of TACE (62,676 baht, Table 1) to 231,204 baht, the change in ICER was greater than 150%. If the cost of TACE in the non-surveillance group were lower to 1,586 baht, the ICER would be 100% less.

Meanwhile, another variable affecting the change in ICER was the probability of HCC diagnosis in the non-surveillance group and the cost of ultrasound upper abdomen for diagnosis in the surveillance group, respectively. When all variables were changed simultaneously with possible variables repeated 1,000 times by randomization of probabilistic sensitivity analysis (PSA), it was found that the HCC surveillance group had an ICER of 109,221 baht per QALY gained when compared to the non-surveillance group. Also, compared to the willingness to pay in Thailand, it was found that screening and surveillance were cost-effective in health economics, as shown in Table 5.

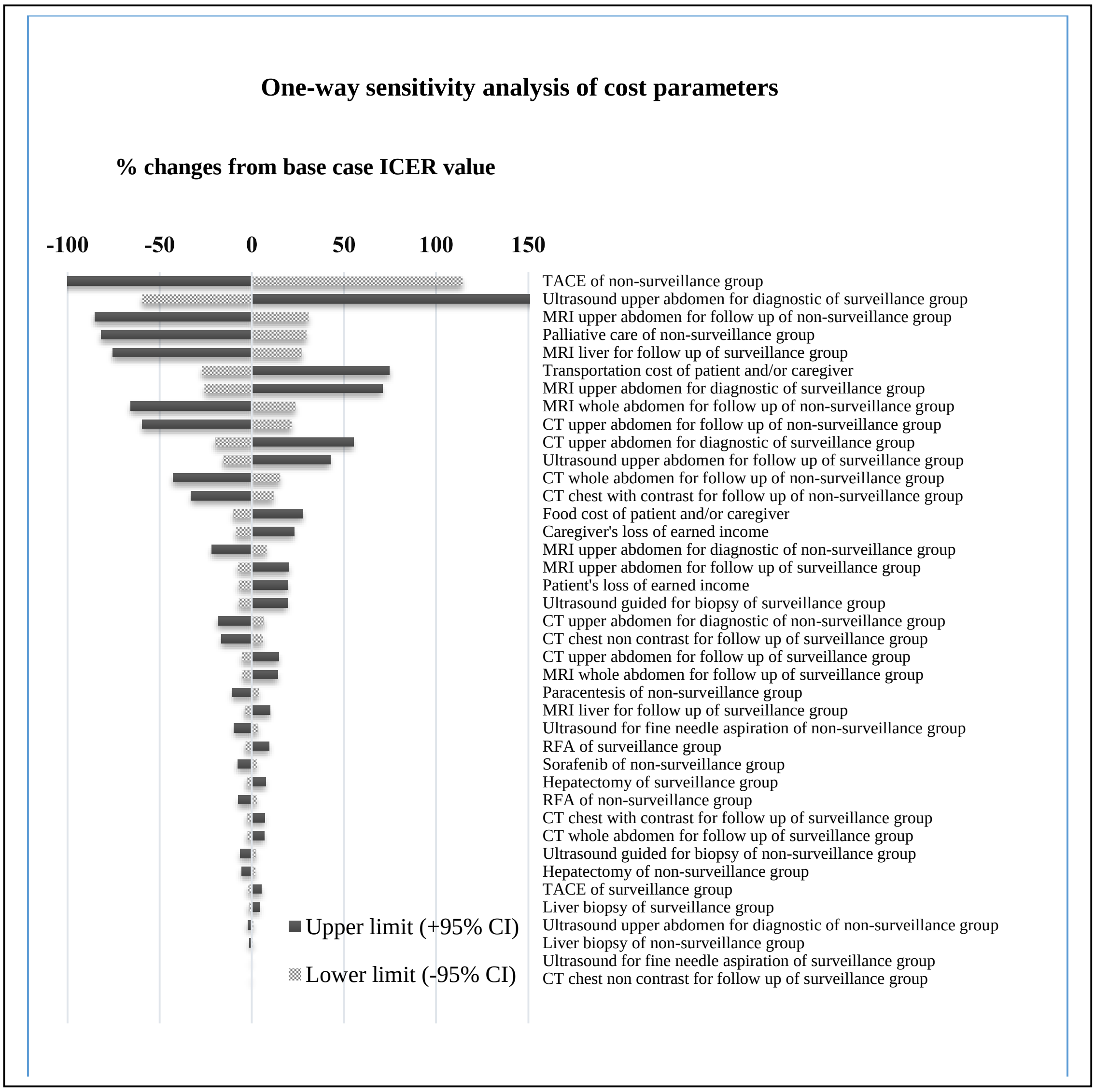

Figure 4 Tornado diagram of cost parameters

5. Conclusion

The cost-effective study of ultrasound surveillance in hepatitis B patients showed that the HCC surveillance cohort had an ICER equal to 104,392 baht per QALY gained, which was cost-effective compared to the willingness to pay in Thailand 160,000 baht per QALY gained. The results were consistent with a study in Thailand to assess the health economics of HCC screening and surveillance in chronic hepatitis B patients by using the Markov model for analyzing costs and health outcomes. The surveillance of HCC using ultrasound every six months alone and the ultrasound screening combined with Alpha-fetoprotein every six months were cost-effective, with ICER of 118,796 and 123,451 baht per QALY gained, respectively (Sangmala, Chaikledkaew, Tanwandee, & Pongchareonsuk, 2014). Our study result was also compatible with other studies from the United States that assess the cost-effectiveness of HCC surveillance in patients with cirrhosis, which recommended the screening and surveillance with ultrasound every 6 months as cost-effective when compared to the willingness to pay, using ICER of $30,700 per QALY gained (Andersson et al., 2008). Likewise, a study in Canada on the cost-effectiveness of hepatocellular screening in patients with cirrhosis yielded that the screening with ultrasound and CT was cost-effective with an ICER of 35,108 Canadian dollars per QALY gained (Lima et al., 2019).

There are some limitations to this study. Firstly, the ultrasound surveillance of HCC in the hepatitis B cohort included males and females starting age of 20 years who were younger than the recommended guideline of the AASLD Guideline, which recommended initiating the screening and surveillance in hepatitis B males aged 40 years and females aged 50 years. However, given the circumstance that including younger patients may add unnecessary cost to the HCC surveillance group but still the outcome of ICER/QALY gained is still within Thailand's willingness to pay threshold. Secondly, the frequent surveillance protocol to follow up ultrasound every six months may cause fewer compliants of the patient to regularly visit for surveillance, resulting in a less total number of ultrasound studies to calculate the cost of surveillance. Thirdly, the calculation of direct medical costs when patients were hospitalized was based on the diagnosis-related groups (DRGs) according to the National Health Security System (NHSO) base rate. Therefore, the information obtained was suitable for the policy on health economics policy in the system of national health security. On the other hand, if the data obtained from actual health care benefit individuals, the cost may change according to treatment eligibility.

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7. References

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