COST-EFFECTIVENESS ANALYSIS OF ULTRASONOGRAPHY SCREENING FOR NON-ALCOHOLIC FATTY LIVER DISEASE IN METABOLIC SYNDROME PATIENTS

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การประเมินต้นทุนประสิทธิผลของการตรวจอัลตราซาวนด์เพื่อคัดกรองภาวะไขมันพอกตับในผู้ป่วยกลุ่มโรคอ้วนลงพุง

นางสาวพจมาน พิศาลประภา

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Thesis Title	COST-EFFECTIVENESS ANALYSIS OF ULTRASONOGRAPHY SCREENING FOR NON-ALCOHOLIC FATTY LIVER DISEASE IN METABOLIC SYNDROME PATIENTS
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พจมาน พิศาลประภา : การประเมินต้นทุนประสิทธิผลของการตรวจอัลตราซาวนด์เพื่อคัดกรองภาวะไขมันพอกตับในผู้ป่วยกลุ่มโรคอ้วนลงพุง (COST-EFFECTIVENESS ANALYSIS OF ULTRASONOGRAPHY SCREENING FOR NON-ALCOHOLIC FATTY LIVER DISEASE IN METABOLIC SYNDROME PATIENTS) อ.ที่ปรึกษาวิทยานิพนธ์หลัก: รศ. ดร. ศิริเพ็ญ ศุภกาญจนกันติ, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม: ศ. ดร.ณธร ชัยญาคุณาพฤกษ์, หน้า.

ภูมิหลัง/วัตถุประสงค์: ภาวะไขมันพอกตับเป็นปัญหาที่เพิ่มขึ้นอย่างรวดเร็วทั่วโลกรวมทั้งภูมิภาคเอเชียแปซิฟิก ภาวะนี้สามารถวินิจฉัยโดยการตรวจอัลตราซาวนด์ซึ่งเป็นวิธีที่ปลอดภัยและราคาถูก นอกจากนี้ ยังมีความไวและความจำเพาะสูง กลุ่มโรคอ้วนลงพุงเป็นภาวะที่พบได้บ่อยและจัดเป็นปัจจัยเสี่ยงที่สำคัญของภาวะไขมันพอกตับ อย่างไรก็ตาม ในปัจจุบันยังไม่มีข้อมูลเกี่ยวกับการประเมินต้นทุนประสิทธิผลของการตรวจอัลตราซาวนด์เพื่อคัดกรองภาวะไขมันพอกตับร่วมกับให้การรักษาด้วยการปรับเปลี่ยนพฤติกรรมในผู้ป่วยกลุ่มที่มีความเสี่ยงสูง การศึกษานี้มีวัตถุประสงค์เพื่อประเมินต้นทุนประสิทธิผลของการตรวจอัลตราซาวนด์เพื่อคัดกรองภาวะไขมันพอกตับในผู้ป่วยกลุ่มโรคอ้วนลงพุงในบริบทของประเทศไทย

วัสดุและวิธีการ: การประเมินต้นทุนประสิทธิผลทำโดยสร้างแบบจำลองต้นแบบ ซึ่งประกอบด้วยแผนภาพต้นไม้และแบบจำลองมาร์คอฟตลอดช่วงอายุขัยของผู้ป่วยโดยใช้มุมมองทางด้านสังคม เพื่อเปรียบเทียบต้นทุนและผลที่ได้รับทางด้านสุขภาพจากการตรวจคัดกรองภาวะไขมันพอกตับด้วยอัลตราซาวนด์ร่วมกับการรักษาโดยให้ลดน้ำหนักในผู้ป่วยกลุ่มโรคอ้วนลงพุงที่มีอายุ 50 ปี กับผู้ป่วยที่ไม่ได้รับการตรวจคัดกรอง ข้อมูลด้านประสิทธิผลและอรรถประโยชน์ในแบบจำลองได้จากการทบทวนวรรณกรรมอย่างเป็นระบบ ส่วนข้อมูลด้านต้นทุนและอัตราตายได้จากฐานข้อมูลของประเทศไทย ต้นทุนทั้งหมดจะใช้หน่วยเป็นบาท และปรับเป็นมูลค่าสำหรับปี ค.ศ. 2014 อัตราคิดลดเท่ากับร้อยละ 3 ต่อปีทั้งต้นทุนและผลลัพท์ ร่วมกับมีการวิเคราะห์ความไวด้วยวิธี one-way และ probabilistic

ผลการศึกษา: การประเมินผลวัดได้จากอัตราส่วนของส่วนต่างต้นทุนต่อประสิทธิผลส่วนเพิ่มที่น้อยกว่าหรือเท่ากับ 160,000 บาทต่อ 1 ปีสุขภาวะที่เพิ่มขึ้นจะถือว่าคุ้มค่า การตรวจคัดกรองด้วยอัลตราซาวนด์ร่วมกับการรักษาโดยการให้ลดน้ำหนักมีต้นทุนประสิทธิผลที่คุ้มค่า โดยมีอัตราส่วนของส่วนต่างต้นทุนต่อประสิทธิผลส่วนเพิ่มเท่ากับ 19,706 บาทต่อ 1 ปีสุขภาวะที่เพิ่มขึ้นเมื่อเปรียบเทียบกับผู้ป่วยที่ไม่ได้ตรวจคัดกรอง โอกาสที่ผู้ป่วยไขมันพอกตับที่มีปริมาณพังผืดในตับน้อยจะกลายเป็นปริมาณมาก โอกาสที่ผู้ป่วยที่มีปริมาณพังผืดในตับมากจะกลายเป็นโรคตับแข็งระยะเริ่มต้น และประสิทธิผลของการลดน้ำหนักในการลดปริมาณพังผืดในตับ เป็นสามปัจจัยหลักที่มีผลต่ออัตราส่วนของส่วนต่างต้นทุนต่อประสิทธิผลส่วนเพิ่ม และถ้ายึดตามค่าความเต็มใจที่จะจ่ายของประเทศไทย โอกาสที่การตรวจคัดกรองด้วยอัลตราซาวนด์จะมีความคุ้มค่าเท่ากับร้อยละ 67

สรุป: การตรวจอัลตราซาวนด์เพื่อคัดกรองภาวะไขมันพอกตับในผู้ป่วยกลุ่มโรคอ้วนลงพุงร่วมกับการให้การรักษาโดยให้ลดน้ำหนักตั้งแต่เริ่มต้น มีต้นทุนประสิทธิผลที่คุ้มค่าสำหรับประเทศไทย โดยมีความไม่แน่นอนต่ำ ผู้กำหนดนโยบายของประเทศอาจนำข้อมูลจากการศึกษานี้มาใช้ในการตัดสินใจในอนาคตได้

สาขาวิชา	เศรษฐศาสตร์สาธารณสุขและการจัดการบริการสุขภาพ	ลายมือชื่อนิสิต ______________
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POCHAMANA PHISALPRAPA: COST-EFFECTIVENESS ANALYSIS OF ULTRASONOGRAPHY SCREENING FOR NON-ALCOHOLIC FATTY LIVER DISEASE IN METABOLIC SYNDROME PATIENTS. ADVISOR: ASSOC. PROF. SIRIPEN SUPAKANKUNTI, Ph.D., CO-ADVISOR: PROF. NATHORN CHAIYAKUNAPRUK, Ph.D., pp.

Background/Aimed: Non-alcoholic fatty liver disease (NAFLD) is an emerging problem worldwide including the Asia-Pacific region. It can be diagnosed by non-invasive and low-cost liver ultrasonography with high sensitivity and specificity. Metabolic syndrome is also a common and well known as a major risk factor for NAFLD. However, there are no current data on the cost-effectiveness analysis of early screening ultrasonography with lifestyle modification as an early intervention in this high risk group. This study aimed to perform the cost-effectiveness analysis of ultrasonography screening for NAFLD in metabolic syndrome patients in the context of Thailand.

Materials and Methods: A cost- effectiveness analysis using a hybrid model consisting of a decision tree and Markov models was conducted over the patients' lifetimes under societal perspective to compare costs and health benefits of ultrasonography screening for NAFLD with intervention by weight reduction in a cohort of metabolic syndrome patients aged 50 years versus no screening. The effectiveness and utility parameters were determined by systematic literature reviews, while costs and mortality parameters were determined using Thailand database analysis. All costs were presented in 2014 Thai Baht, THB. The discount rate of 3% was applied for both costs and outcomes. One-way and probabilistic sensitivity analyses were also performed.

Results: The outcome measurement was the Incremental Cost-Effectiveness Ratio (ICER), with 160,000 THB or less per 1 Quality-Adjusted Life Year (QALY) gained considered as cost-effective. Ultrasonography screening with weight reduction was cost-effective with ICER of 19,706 THB/QALY gained when comparison with no screening. The annual probability of no advanced fibrosis progression to advanced fibrosis, the annual probability of advanced fibrosis progression to compensated cirrhosis, and risk reduction of weight reduction were the most three influential parameters on ICERs. According to willingness-to-pay of Thailand, the probability of ultrasonography screening being cost-effective was 67%.

Conclusions: Ultrasonography screening for NAFLD with weight reduction in metabolic syndrome patients is a cost-effective screening in Thailand with low sensitive. Policy makers may consider our findings as part of information for their decision making.

Field of Study:	Health Economics and Health Care Management	Student's Signature	....
		Advisor's Signature	....
Academic Year:	2014	Co-Advisor's Signature	....

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LIST OF ABBREVIATIONS

ABBREVIATIONS	FULL NAME
AASLD	American Association for the Study of Liver Diseases
AF	Advanced fibrosis
ALT	Alanine aminotransferase
ASMR	Age-specific mortality rate
AST	Aspartate aminotransferase
CPI	Consumer price index
CT	Computed tomography
HCC	Hepatocellular carcinoma
ICER	Incremental Cost-Effectiveness Ratio
IF	Indeterminate fibrosis
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectroscopy
NAF	No advanced fibrosis
NAFLD	Non-alcoholic fatty liver disease
NASH	Non-alcoholic steatohepatitis
PSA	Probabilistic sensitivity analysis
THB	Thai Baht
QALY	Quality-Adjusted Life Year
US	Ultrasonography
USD	United States Dollar

CHAPTER I

INTRODUCTION

1.1 Problems and its significance

Non-alcoholic fatty liver disease (NAFLD) is the condition where fat accumulates in the liver without evidence of excessive alcohol consumption and other causes of chronic liver disease. NAFLD is the most common cause of hepatic steatosis. According to the recent guideline established by the American Association for the Study of Liver Diseases (AASLD) 2012 (Chalasani et al., 2012), the criteria for diagnosis of NAFLD are:

1) Hepatic steatosis or fatty change of the liver proved by either hepatic tissue from liver biopsy or liver imaging
2) No excessive alcohol consumption (ethanol intake less than 210 grams/week for men and less than 140 grams/week for women)
3) No other causes of hepatic steatosis
4) No other influential factors of chronic liver disease

NAFLD is categorized into 2 groups according to histology first being simple steatosis and the second being Non-alcoholic steatohepatitis (NASH). Simple steatosis is diagnosed with the presence of hepatic steatosis without evidence of hepatocytes injury or ballooning of the hepatic cells. Therefore, simple steatosis poses a low risk of hepatic-related complications and death while NASH is more severe condition. NASH defined as the presence of a fatty liver causing hepatic cells inflammation or injury. NASH has a higher risk of liver-related mortality from cirrhosis and hepatic cancer such as hepatocellular carcinoma (HCC).

Amongst the chronic liver diseases, the worldwide prevalence of NAFLD is the highest, hence, it has become an emerging problem in all regions including Asia-Pacific countries. Moreover, the burden caused by the disease will continue to grow in the future and has the potential to become a global disease in the next century. The overall incidence of NAFLD has rapidly increased and was parallel and correlated with the increase of type 2 diabetes and obesity (Vernon, Baranova, & Younossi, 2011). The prevalence of NAFLD is increasingly prevalent in patients with metabolic conditions or insulin resistance-related diseases. A popular major risk factor of NAFLD is metabolic syndrome. In addition, it may be concluded that NAFLD is the liver based evidence of the metabolic syndrome patients.

NAFLD had a strong association with many metabolic and cardiovascular risk factors such as obesity, dyslipidemia, diabetes mellitus, and coronary artery disease (Anstee, Targher, & Day, 2013). A study of ultrasonography in type 2 diabetes patients reported that the prevalence of NAFLD was very high (69%) (Leite, Salles, Araujo, Villela-Nogueira, & Cardoso, 2009). The prevalence of NAFLD patients with dyslipidemia at the clinics was approximately 50 percent (Assy et al., 2000). Most studies concluded that many risk factors of metabolic syndrome were associated with NAFLD especially in obese patients except in the Asian countries, that NAFLD was often reported in non-obesity (Vernon et al., 2011).

The prevalence of NAFLD has been reported using many diagnostic tools (both invasive and non-invasive tests). Currently, liver biopsy is the gold standard for diagnosis and staging of NAFLD but since the procedure is highly invasive, it cannot be applied to population-based studies. A Korean study on 589 potential liver transplant donors showed that the prevalence of NAFLD was 51% (J. Y. Lee et al., 2007). In addition, over 10 to 12 years cohort study in 35,519 Japanese by using ultrasonography reported that occurrence of NAFLD was increased from 13 percent to 30 percent (Kojima, Watanabe, Numata, Ogawa, & Matsuzaki, 2003). Moreover, the prevalence rate of NAFLD diagnosed by ultrasonography was 17% in India (Deepak Amarapurkar et al., 2007). In a recent multicenter study in Spain, patients from 25 primary care centers were randomly selected and tested by ultrasonography. After the patients with chronic liver disease and excessive alcohol intake were excluded, the prevalence of NAFLD was 33 and 20 percent in men and women, respectively (Caballería et al., 2010). A similar study conducted in Brooke Army Medical Center revealed a higher number of ultrasonography diagnosed NAFLD (46%), of which 12% of the patients were confirmed by biopsy, or 30% of ultrasound detected patients (Browning et al., 2004). Moreover, a study in Italy revealed that the prevalence of suspected NAFLD with chronic liver disease was 25% and NAFLD without chronic liver disease was 20% (Bedogni et al., 2005).

Recently, a systematic review of the epidemiology and natural history of NAFLD was implemented. It has been proposed that the estimate of overall prevalence of NAFLD was 6-35 percent (median of 20 percent) in the general population worldwide, based on different investigation tools. On the other hand, the approximated occurrence of NASH is lower than simple steatosis since it ranges from 3-5 percent (Vernon et al., 2011). The prevalence of NAFLD is rapidly increasing worldwide, most probably, as a result of western lifestyle, lack of exercise, and increase prevalence of obesity in the Asia-Pacific countries. The prevalence of NAFLD has increased rapidly in the past two decades (Liu, 2012). The prevalence is higher in the very high risk patients such as type 2 diabetes mellitus (50%), obesity

(30-76%) and morbid obesity (up to 98%) (Vernon et al., 2011) and up to 5% of these patients may develop unpredicted liver cirrhosis (Haentjens et al., 2009). Although, the incidence of NAFLD in patients suffering from metabolic syndrome in western countries is still more common than the Asian countries; however, the incidence of NAFLD in this group of Asians including Thais had rapidly increased to 67 percent even in the non-obese patients (Phisalprapa et al., 2014).

The long run outcomes of the NAFLD patients have been documented in several studies in recent years as the condition may progress to liver cirrhosis, HCC, liver failure, and death. NAFLD increases overall mortality when compared with control population. A meta-analysis on survival of patients with NAFLD has been published (Musso, Gambino, Cassader, & Pagano, 2011). When compared to reference populations, overall mortality of patients with NAFLD and NASH is significantly higher (Adams et al., 2005; Ekstedt et al., 2006; Söderberg et al., 2010). Its major causes of death are the cardiovascular disease (28% of total mortality). In addition, there is an increased risk of death from extra-hepatic cancers (25% of total mortality) and as a result of liver-related death (13% of total mortality), being the third leading cause of death in NAFLD patients and the 11th leading cause of death in the general population (Musso et al., 2011).

Even if NAFLD will represent an important public health burden in the near future, the condition’s natural history, predictors, and factors determining severity are insufficiently understood because of limitations in regards to best diagnostic modalities since most patients are asymptomatic until late and very severe complications occur.

In metabolic syndrome patients who had early detection of NAFLD, there were many effective strategies to treat and prevent the progression of the disease to more advanced stages such as life style modification, tight control of the risk factors, and specific medications (vitamin E and pioglitazone) (Mahady, Wong, Craig, & George, 2012) whereas the patients who had late detection will face with the serious and high cost complications. Thus, early non-invasive detection of NAFLD is clinically important.

For early detection of this condition, there are numerous non-invasive diagnostic procedures for NAFLD and NASH besides that of invasive-liver biopsy. Nevertheless, it is important to emphasize that although elevated liver enzyme or alanine aminotransferase (ALT) is generally related to histological NASH. A majority of patients with normal ALT levels (less than 40 U/L) may also have NAFLD and some of them have already developed advanced cirrhosis. The serum ALT was normal in 80 percent of the NAFLD patients (Browning et al., 2004; Phisalprapa et al., 2014). Therefore, serum ALT alone cannot rule out significant chronic hepatic disease in patients suspected with NAFLD anymore, especially those with type 2 diabetes mellitus or hepatomegaly (DN Amarapurkar & Patel, 2003).

Non-invasive radiological methods used to determine the prevalence of NAFLD are ultrasonography (US), computed tomography (CT), and magnetic resonance imaging (MRI) yields more sensitivity including specificity (Bohte, van Werven, Bipat, & Stoker, 2011). Liver ultrasonography is most popular procedure used to evaluate the presence of fatty liver in the clinical practice and population-based studies because of its simplicity, non-invasiveness, inexpensiveness, plus accessibility. In the present day, ultrasonography can be used as an early and a standard imaging diagnostic tool of NAFLD in many cases (Hernaez et al., 2011). However, several limitations of ultrasonography including its low sensitivity to mild fatty changes of the liver (less than 20-30%), operator dependency, subjective interpretations, and limited ability to quantify the severity of fat infiltration have raised concerns. Within the NAFLD spectrum, fat can both occur separately and coexist with inflammation and/or fibrosis. Therefore, in order to estimate the place within the NAFLD spectrum, fat, inflammation, and fibrosis are to be determined ideally. Qualitative ultrasonography is a valid and reliable method for diagnosing NAFLD, i.e. an abundance of liver fat (Hamaguchi et al., 2007; Joseph, Saverymuttu, Al-Sam, Cook, & Maxwell, 1991; Saverymuttu, Joseph, & Maxwell, 1986). Validity is decreased in (morbidly) obese people (de Moura Almeida et al., 2008; Mottin et al., 2004). Moreover, ultrasonography is currently unable to determine hepatic inflammation, which means that it is unable to distinguish steatosis and steatohepatitis.

Health Technology Assessment (HTA) has been used around the world including Asia Pacific region. Thailand has a long history of using HTA for health policy decision making (Roseman CB, Patrick WK, & Tucker RV, 1991; Sivalal S, 2009). In Thailand, the outcome measurement of the Incremental Cost-Effectiveness Ratio (ICER) of 160,000 Thai Baht (THB) or less per 1 Quality-Adjusted Life Year (QALY) gained considered as cost-effective (Thai Working Group on health Technology Assessment Guidelines in Thailand, 2008).

Today, the occurrence of NAFLD has rapidly increased and the cost of ultrasonography screening is quite cheap in Thailand when compared with other countries. In addition, the cost-effectiveness issues of ultrasonography screening with intervention after early diagnosis especially in the high risk group such as metabolic syndrome patients did not have been reported. This information can be used as supporting evidence for the National health policy decision making.

1.2 Research questions

1.2.1 Primary research question

1. Is ultrasonography screening for NAFLD with weight reduction in metabolic syndrome patients cost-effective?

1.2.2 Secondary research question

1. How many cases prevented from cirrhosis, HCC, and death by ultrasonography screening with weight reduction at each period after screening?
2. What is the additional costs per 1 life-year (LY) saved by ultrasonography screening with weight reduction?
3. What is the additional cost per 1 QALY gained by ultrasonography screening with weight reduction?
4. What are the effects of the parameter uncertainties in the models?

1.3 Research objectives

1.3.1 General objectives

1. To evaluate the cost-effectiveness analysis of ultrasonography screening for NAFLD with weight reduction in the patients with metabolic syndrome

1.3.2 Specific objectives

1. To evaluate the number of cases prevented from cirrhosis, HCC, and death by ultrasonography screening with weight reduction at each period after screening

2. To evaluate the cost-effectiveness analysis of ultrasonography screening with weight reduction in terms of the additional costs per 1 LY saved

3. To evaluate the cost-utility analysis of ultrasonography screening with weight reduction in terms of the additional cost per QALY gained

4. To evaluate effect of the uncertainties of the parameters in the models

1.4 Hypotheses

Ultrasonography screening with weight reduction is cost-effective when compared with metabolic syndrome patients, who do not receive the screening and intervention in terms of

- Cost saving from decrease progression to cirrhosis, HCC, and death
- Increase life years saved
- Increase QALY gained
- Low Incremental Cost-Effectiveness Ratio

1.5 Scope of the study

The study aims to evaluate ultrasonography screening for NAFLD with weight reduction in metabolic syndrome patients in terms of cost-effectiveness analysis and cost-utility analysis. This study used primary data from a descriptive cross-sectional study that reported the prevalence of NAFLD in metabolic syndrome patients at Siriraj Hospital, Mahidol University, the largest tertiary care center in Thailand. It was conducted with metabolic syndrome patients at internal medicine out-patient department between November 2011 and October 2013. A hybrid model consisting of decision tree and Markov models were used to approximate relevant costs and health outcomes of ultrasonography screening for NAFLD with weight reduction in metabolic syndrome patients who screened compared to metabolic syndrome patients who did not receive screening. Early intervention of interest is weight reduction, which was added on the screening test when the NAFLD patients were diagnosed by ultrasonography, because weight reduction is only one intervention that has been reported the efficacy of hepatic fibrosis regression. Due to limitations of ultrasonography in sensitivity and specificity, this model was classified into four sub-categories; true positive, false positive, false negative, and true negative of ultrasonography to improve the accuracy of the model. Our model was developed to mimic the natural history of NAFLD and clinical practice. Since NAFLD could be a life-long condition, the lifetime horizon was chosen in this study. We undertook this study using a social perspective in costing calculation as advised by the Thailand's health technology assessment guideline (Thai Working Group on health Technology Assessment Guidelines in Thailand, 2008). We performed a cost-effectiveness analysis and a cost-utility analysis expressing findings as incremental cost per life year saved and incremental cost per QALY gained.

For the input parameters, prevalence of NAFLD in each state (no advanced fibrosis, indeterminate fibrosis, advanced fibrosis, and cirrhosis), sensitivity, and specificity of ultrasonography, annual transitional probabilities, costs, and utilities were filled in the Markov models. These parameters were obtained from a data set of Siriraj Hospital and systematic literature search from other studies (local and international publications) which were the most applicable with Thai population.

1.6 Possible benefits of the study

There is an absence of knowledge regarding long-term benefits and cost-effectiveness of ultrasonography screening for NAFLD with weight reduction in metabolic syndrome patients. If this study shows that the ultrasonography screening with intervention is cost-effective, it will contribute as new knowledge and can be implemented as a policy. High risk patients will receive the appropriate screening at a lower cost from a national health policy. They will receive an early diagnosis of NAFLD and receive early appropriate treatments to prevent more serious and high costs complications.

CHAPTER II

LITERATURE REVIEW

Several studies has reported the evolution of histological changes of the liver in patients with NAFLD but solely small numbers of patients with relatively short follow- up has been included. Though patients with simple steatosis are slowly progress to histological changes where patients with NASH are rapidly and severely progress to liver cirrhosis (Musso et al., 2011; Vernon et al., 2011). Several studies have been stated long term outcomes of patients with NAFLD. In compare with control group of populations, the overall mortality of patients with NAFLD is much higher. Cardiovascular and liver disorders stand as the common cause of death.

The potential development of cirrhosis and hepatocellular carcinoma can be prevented by early diagnosis and treatments towards NASH. One of the study stated that liver biopsy is well established and standardized test for hepatic steatosis evaluation though it is invasive. However, the study has possible sampling error due to small sample size and inter-observer variability (Charatcharoenwitthaya & Lindor, 2007).

Non-invasive and systematic screening tests for NAFLD have been proposed specifically for the high risk population. Gaps in the area of knowledge of natural history, diagnosis and treatment are still significant for NAFLD at the recent age. In majority of the individuals with NAFLD even among NASH patients, serum alanine aminotransferase can show normal titer as its sensitivity does not sufficient to serve as screening tests (Browning et al., 2004; Phisalprapa et al., 2014).

Comparatively liver ultrasonography is more sensitive in potential but the cost would be more expensive. Ultrasonography diagnosis for NAFLD cannot differentiate among steatosis and steatohepatitis, stated in the past study. Moreover, differentiation among steatosis and other diffuse liver diseases with characteristic of increase echogenicity remains as significant limitation (Taylor, Gorelick, Rosenfield, & Riely, 1981).

Role of non-invasive imaging modalities as an alternative to invasive-liver biopsy in order to detect and quantify fatty liver have been focused in the recent day studies. Plenty of comparisons among the sensitivity and specificity of different imaging techniques were reported. Currently accepted the best non-invasive technique and standardized tool increasingly used for early detection of NAFLD instead of liver biopsy is magnetic resonance spectroscopy (1H-MRS). But no evidence based consensus has been found on this topic at recent.

The accuracy of ultrasound (US), computed tomography (CT), magnetic resonance imaging (MRI) and magnetic resonance spectroscopy for the evaluation of fatty liver has been studied by using systematic review and meta-analysis summarizing in order to compare with liver biopsy as the standardized test (Bohte et al., 2011). Forty-six articles had been included in that study. 73.3-90.5% for US, 46.1-72.0% for CT, 82.0-97.4% for MRI and 72.7-88.5% for 1H-MRS were expressed as means sensitivity ranges for each subgroup. Mean specificity ranges stated 69.6-85.2% for US, 88.1-94.6% for CT, 76.1-95.3% for MRI and 92.0-95.7% for 1H-MRS. In all subgroups, MRI and 1H-MRS stated better overall performance than ultrasonography and computed tomography. The models of choices for accuracy and early evaluation of fatty liver can regard as MRI and 1H-MRS but the high costs would be raised as concerns.

The ultrasonography had a quite high reliable and accurate detection towards moderate to severe fatty liver diseases if compare with gold standard liver biopsy, a recent meta-analysis study stated (Hernaez et al., 2011). In clinical and population-based studies, ultrasound stands as imaging tool of choice for screening NAFLD due to its low costs, safety and easily accessibility. The overall sensitivity and specificity of ultrasound for the detection of moderate to severe fatty liver showed 84.8% (95% CI: 79.5-88.9) and 93.6% (95% CI: 87.2-97.0) respectively in the meta-analysis of diagnostic accuracy finding including forty-nine studies (4,720 participants). The receiving operating characteristics (ROC) curve showed 0.93 (95% CI: 0.91-0.95) meaning that the sensitivity and specificity of ultrasound was similar to the rest of other imaging techniques specifically, computed tomography or magnetic resonance imaging.

Total 171 patients with various causes of hepatitis who undergo liver biopsies were reviewed retrospectively and the result showed that ultrasonography could assess the severity of fatty liver with moderate accuracy (Wang et al., 2014).74.3% in evaluating the presence of fatty liver and 61.4% in evaluating fatty liver severity were found out as the agreement rates between ultrasonography and liver biopsy.

In conclusion, ultrasonography can be regarded as an established screening tool to detect fatty liver disease with acceptable sensitivity and specificity. Nevertheless the possible inaccuracy of the test, inability to differentiate fibrosis from fatty liver, in-reproducibility and the exact quantification of fat accumulation remains as the limitation of ultrasonography technique (Lupşor-Platon et al., 2014).

Screening for NAFLD in adults who visited primary care clinics has been recommended by AASLD in 2012 (Chalasani et al., 2012). However, in the recent day, the high risk individuals visiting diabetes mellitus or obesity clinics are not advised to undergo screening for NAFLD because of the reason of possible uncertainty of diagnostic tests and treatment options along with lack of knowledge related to the long-term advantages and cost-effectiveness issues.

In Thailand, there is a descriptive, retrospective study in unit cost of mobile ultrasonography for screening renal calculi (Kessomboon, Kessomboon, & Premgamone, 2010). The mobile team consists of two trained general practitioners, a nurse, two assistants, and two drivers using two ultrasonography equipments. The findings revealed that there were 28,440 people screened and 2,617 renal calculi cases were detected. Cost per person screened was only 71.3 THB and cost per renal calculi case detected was 775.4 THB while labor cost was 67 percent as the highest component of the total cost. This unit cost of mobile renal ultrasonography is low when compared with the price of liver ultrasonography in Thailand (around 500-1,000 THB). However, the unit cost of liver ultrasonography in Thailand is quite cheap when compared with the United State and European countries. Additionally, the results may be more significantly cost-effective when compared with developed countries.

For the treatment modalities of NAFLD, we need an effective treatment to slow its progression (Sanyal et al., 2011). No approved therapies for NAFLD have been discovered, though several drugs have been evaluated in the clinical trials (Chalasani et al., 2012). There was a recent study in cost-utility analysis of the choice of treatment for the NASH patients conducted where pioglitazone and vitamin E were compared with lifestyle modification alone by using a third party payer perspective by using the deterministic Markov model (Mahady et al., 2012). The Incremental Cost-Effectiveness Ratio with 50,000 Australian dollars or less per QALY considered cost-effective had been shown as the outcome measure. Pioglitazone or vitamin E administration with additional lifestyle modification showed ICER of 2,748 and 8,475 Australian dollars per QALY gained and regarded as cost-effective. Moreover, pioglitazone showed ICER 2,056 Australian dollars per QALY gained and more cost-effective than vitamin E. Either in case of the total drug cost was greater than 16,000 Australian dollars per annum or the annual probability of developing cirrhosis from advanced fibrosis was less than 2%, the pioglitazone was not cost-effective as indicated by sensitivity analyses.

Lifestyle modification focusing on weight reduction remains the cornerstone of NAFLD management (Chalasani et al., 2012; Nascimbeni et al., 2013). Recent studies have reported that a holistic lifestyle modification based on increased physical activity and/or reduction of energy intake during 6-12 months can improve in biochemical (aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyltransferase levels) and metabolic (fasting glucose and insulin sensitivity) parameters, and decreases steatosis and necroinflammation detected in paired histologic finding (Dixon, Bhathal, Hughes, & O'Brien, 2004; Eckard et al., 2013; Lazo et al., 2010; Promrat et al., 2010; Thoma, Day, & Trenell, 2012; Vilar Gomez et al., 2009; Wong et al., 2013). However, the relationships between fibrosis improvement and weight reduction have been inconsistent among many studies (Promrat et al., 2010; Thoma et al., 2012; Vilar Gomez et al., 2009). Recent studies have reported that degree of weight reduction appears to be positively correlated with histologic improvements (Anstee et al., 2013; Harrison, Fecht, Brunt, & Neuschwander-Tetri, 2009; Petersen et al., 2005; Promrat et al., 2010) and most of them concluded that at least 7%-10% of weight reduction is required to improve in NAFLD activity score (NAS) and their components (steatosis, lobular inflammation, and ballooning), Nevertheless, this improvement did not extend to fibrosis. However, these conclusions have been based on a small number of well conducted trials or observational studies that might limit information. In addition, prospective studies reporting changes in overall NASH-related histology after successful weight-reduction programs through lifestyle modification are lacking. To date, only a few studies have evaluated the impact of lifestyle modification on NAFLD. Marked differences in the study designs and small patient figures in those trials have led to inconclusive recommendations for weight reduction as a strategy to treat NAFLD.

According to AASLD guideline 2012, weight loss resulting from either hypocaloric diet alone or along with increased physical activity (Strength 1, Evidence A) generally lessen the hepatic steatosis, reduction of at least 3-5% of body weight appears necessary to improve steatosis, greater weight loss (up to 10%) possibly need to improve necroinflammation (Strength 1, Evidence B) and hepatic steatosis might be decreased with exercise alone in adults with NAFLD but its ability to improve other aspects of liver histology has not been discovered yet (Strength 1, Evidence B) (Chalasani et al., 2012).

Thus, there was a study prospectively evaluated the impact of a program of lifestyle changes through a combined between exercise and diet restriction on histologic improvement of NASH patients followed in the routine clinical practice, and to evaluate the relationship between the degree of weight reduction and improvements in overall NASH-related parameters. This is the most recent study published in 2015 which showed the risk reduction of fibrosis progression from the benefit of weight reduction. It was obtained from the prospective study of 293 NASH patients who proven by liver biopsy. They were encouraged to change the life style as standard recommendation for over 52 weeks to reduce their weight from June 2009 to May 2013, at a tertiary medical care in Havana, Cuba. Liver biopsies were collected when the study began and at week 52 of the diet before histological analysis was conducted. This study showed that of the patients, who underwent lifestyle changes for 52 weeks, 25 percent had achieved a resolution of steatohepatitis and 19 percent had regression of fibrosis. At week 52, 30 percent had lost 5% or more of their body weight. A higher proportion of subjects with 5% weight reduction or more had NASH resolution (58%) than subjects that lost less than 5% of their body weight ($p < .001$). For the patients who lost 10% of their weight or more, 90 percent had resolution of NASH and 45 percent had regression of fibrosis. The results of our study provide empirical support that modest (7%-10%) and greater (>10%) weight reduction are necessary to induce significant improvements in liver histology of overweight and obese patients with NASH. A more intensive weight reduction is needed to achieve this important goal and sustained weight loss is required to reverse these histologic lesions. Moreover, in patients achieving weight losses >5%, the fibrosis scores were improved or remained stable in 94% whereas most of the patients with fibrosis worsening (93%) were associated with little or no weight reduction (<5%).

For the cost-utility analysis, we used the utility of each health state to calculate QALY gained as the health outcome or effectiveness. Utility measures of HRQoL are the values that the patients feel to their overall health status. In clinical studies, utility measurement scored the patients' health state into the level between 0 (equal to death) and 1 (equal to perfect health). These measures allow for comparison of patient outcomes of different diseases. There are 2 different approaches to utility measurement. The first is to classify patients into categories based on their responses to questions about their functional status, as for instance the Quality of Well-Being Questionnaire and the European Quality of Life Measure (EUROQoL). The second is to ask patients to assign a single rating to their overall health by rating scale, standard gamble, time tradeoff, or willingness to pay. Utilities are used as weights to adjust life years for the quality of life in order to calculate QALY.

In present, there are no evidence-based studies related to cost-effectiveness of ultrasonography screening test for NAFLD with intervention after early diagnosed in metabolic syndrome patients even though, this issue is rapidly increasing the burden worldwide including in Thailand. If this study's results can prove that ultrasonography screening with weight reduction is cost-effective, policy makers may consider this information for their decision making of including ultrasonography screening in health-benefit package process. It can become a national health policy allowing the high risk group patients to receive earlier accessible healthcare at low costs. These patients will get the appropriate treatment to prevent more serious complications and improve their quality of life.

CHAPTER III

RESEARCH METHODOLOGY

3.1 Study design

This research is a descriptive study focused on the cost-effectiveness analysis of ultrasonography screening for NAFLD with weight reduction as an early intervention in patients with metabolic syndrome

3.2 Data collection

This study used primary data from a descriptive cross-sectional study that reported the prevalence of Non-alcoholic fatty liver disease in metabolic syndrome patients at Siriraj Hospital, Mahidol University, and largest tertiary care center in Thailand. It was conducted with metabolic syndrome patients at internal medicine out-patient department between November 2011 and October 2013. Five hundred and nine metabolic syndrome patients agreed to take part in this investigation receiving blood tests and upper abdominal ultrasonography. Interview and physical examination were performed for each subject. Using standard questionnaires, patients were interviewed for demographic, medical history and medication.

Diagnostic criteria of metabolic syndrome

Metabolic syndrome, according to “the Harmonizing the Metabolic Syndrome definition” (Alberti et al., 2009), is defined as having three or more of the following five components:

1) Abdominal obesity or elevated waist circumference: a cut-off point for Asian population is a waist circumference of ≥ 90 cm in males and ≥ 80 cm in females

2) Elevated triglyceride: ≥ 150 mg/dL or treated for dyslipidemia

3) Low HDL-cholesterol: < 40 mg/dL in males and < 50 mg/dL in females

4) High blood pressure: ≥ 130/85 mmHg or treated for hypertension

5) High fasting plasma glucose: ≥ 100 mg/dL or having diabetes or under drug treatment of elevated glucose

Inclusion criteria

1) Age more than 18 years

2) Patients who were diagnosed with metabolic syndrome according to the harmonizing criteria at internal medicine out-patient department of Siriraj Hospital

3) Signed consent form

Exclusion criteria

1) Patients who has ethanol consumption of more than 21 drinks (male) and 14 drinks (female) per week

2) Patients who used medications such as corticosteroids, amiodarone, methotrexate, and tamoxifen which can cause fatty change in the liver

3) Patients infected with chronic hepatitis B or chronic hepatitis C

The ultrasonography diagnostic patterns of fatty liver disease were estimated by two gastrointestinal-specialist radiologists on the foundations of the presence of a bright liver (brightness and posterior attenuation) with echoes that are stronger in the hepatic parenchyma than in the renal parenchyma, blurred vessels and lumen narrowing of hepatic veins in the absence of findings that indicates other chronic liver disease. The degree of fatty liver disease analyzed by ultrasonography that reflects the degree of hepatic steatosis. According to the bright liver score, patients were categorized into 4 groups. Patients with bright liver score equaling to 0 were classified as no fatty liver, and the bright liver score equal to 1, 2, and 3 were classified as mild, moderate, and severe degree of fatty liver, respectively.

Generally, presence of steatohepatitis and advanced fibrosis are considered as strong predictors of worse hepatic outcomes in the NAFLD patients than the degree of fat (Chalasani et al., 2012). But liver biopsy procedure is not a practical for all patients and it is difficult to implement in a population-based research (Angulo, 2010). Thus, there have been many cross-sectional studies to identify steatohepatitis and advanced fibrosis by non-invasive strategies (Machado & Cortez-Pinto, 2013).

The NAFLD Fibrosis Score (NAFLD-FS) is the widely investigated non-invasive tools to cross-sectional predict advanced fibrosis in NAFLD (Angulo et al., 2007). The NAFLD Fibrosis Score was constructed by utilizing 6 variables. This scoring system can be implemented to distinguish between advanced fibrosis and no advanced fibrosis patients. For prediction of severity of fibrosis, the regression formula is:

NAFLD fibrosis score = -1.675 + 0.037 x age (years) + 0.094 x body mass index (kg/m^2) + 1.13 x impaired fasting plasma glucose or diabetes mellitus (if yes = 1, no = 0) + 0.99 x AST/ALT ratio - 0.013 x platelet ($x10^9/L$) - 0.66 x albumin (g/dL)

Using the area under the ROC curve, 2 cut-off points identified the advanced fibrosis (> 0.676), indeterminate (-1.455 - 0.676), and no advanced fibrosis (< -1.455).

In this cross-sectional study, a total of five hundred and nine metabolic syndrome patients were tested by abdominal ultrasonography while using bright liver score, degrees of fat were recorded and the severities of fibrosis using the NAFLD Fibrosis Score were calculated.

3.3 Conceptual framework

This conceptual framework provides an overview about the steps of research plan and the information needed to be collected and calculated. For this study, conceptual framework showed five main steps of the economic evaluation (Figure 1).

Step 1: A hybrid model consisting of decision tree and Markov models was established. The primary data, secondary data, data from systematic literature review and meta-analysis were filled in the model.

Step 2: Total costs between the group of patients who received ultrasonography screening with weight reduction versus the controlled group who did not receive the screening and intervention were compared.

Step 3: The effectiveness in terms of number of cases prevented from cirrhosis and HCC progression, and death, life-years saved, and QALYs gained were compared between two groups

Step 4: The Incremental Cost Effectiveness Ratio was analyzed.

Step 5: The uncertainties of the parameters were tested by using one-way sensitivity analyses with Tornado diagrams and probabilistic sensitivity analyses.

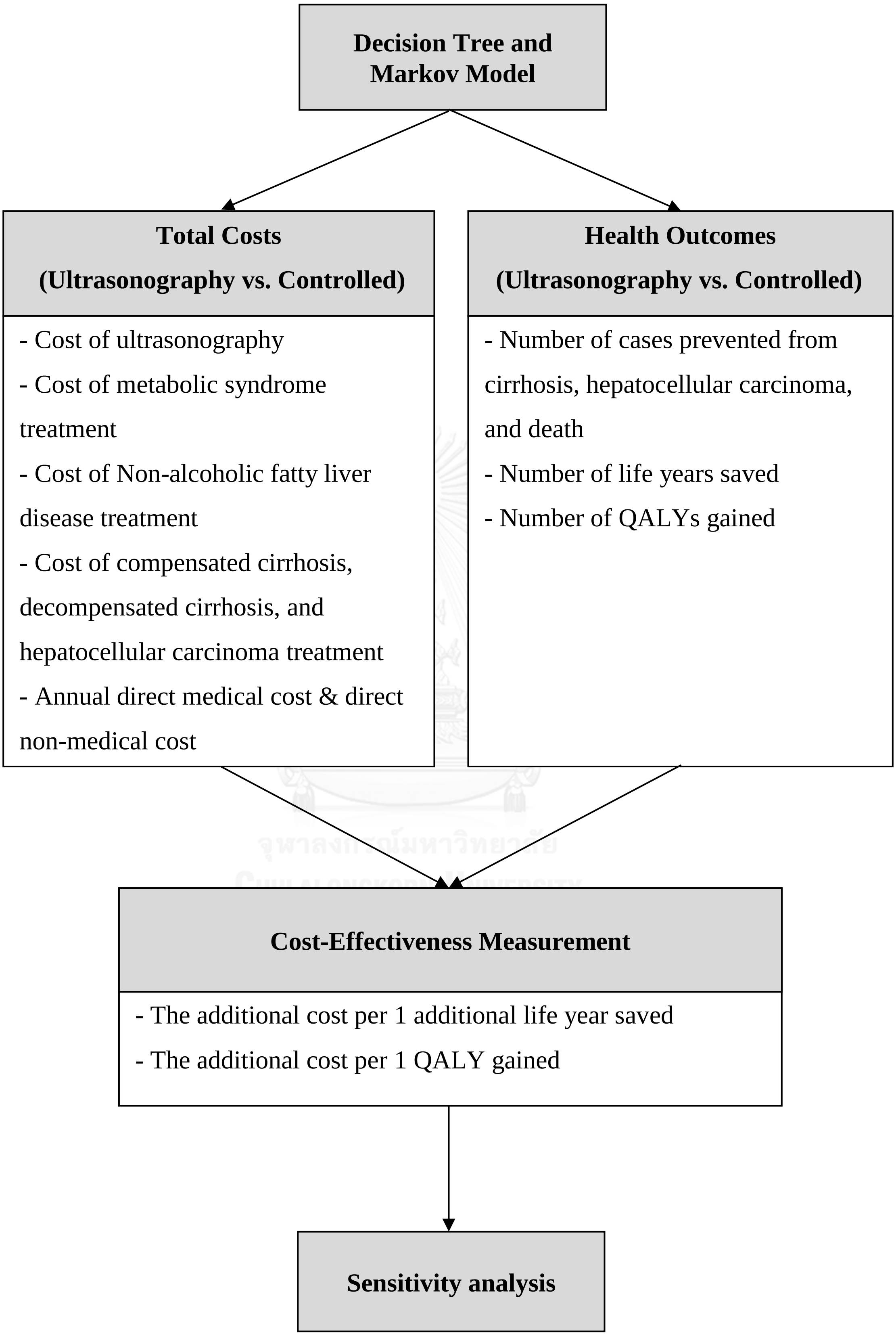


Figure 1. Conceptual framework

Overall description of cost-effectiveness analysis

A hybrid model consisting of decision tree and Markov models was used to approximate the relevant costs and health outcomes of ultrasonography screening for NAFLD with weight reduction in metabolic syndrome patients who screened compared to metabolic syndrome patients who did not receive screening. Early intervention of interest is weight reduction, which was added on the screening test when the NAFLD patients were diagnosed by ultrasonography, because weight reduction is only one intervention that has been reported the efficacy and effectiveness of hepatic fibrosis regression. Due to limitations of ultrasonography in sensitivity and specificity, this model were classified as 4 subgroups; true positive, false positive, false negative, and true negative of ultrasonography to improve the accuracy of the model (Figure 2). Our model was developed to mimic the natural history of NAFLD and medical practice. Since NAFLD could be a life-long condition, the lifetime horizon was chosen in this study. We undertook this study using a societal perspective in costing calculation as suggested by the Thailand's health technology assessment guideline (Thai Working Group on health Technology Assessment Guidelines in Thailand, 2008).

We performed a cost-effectiveness analysis and a cost-utility analysis expressing findings as incremental cost per life year saved and incremental cost per QALY gained.

3.4 The Economic model

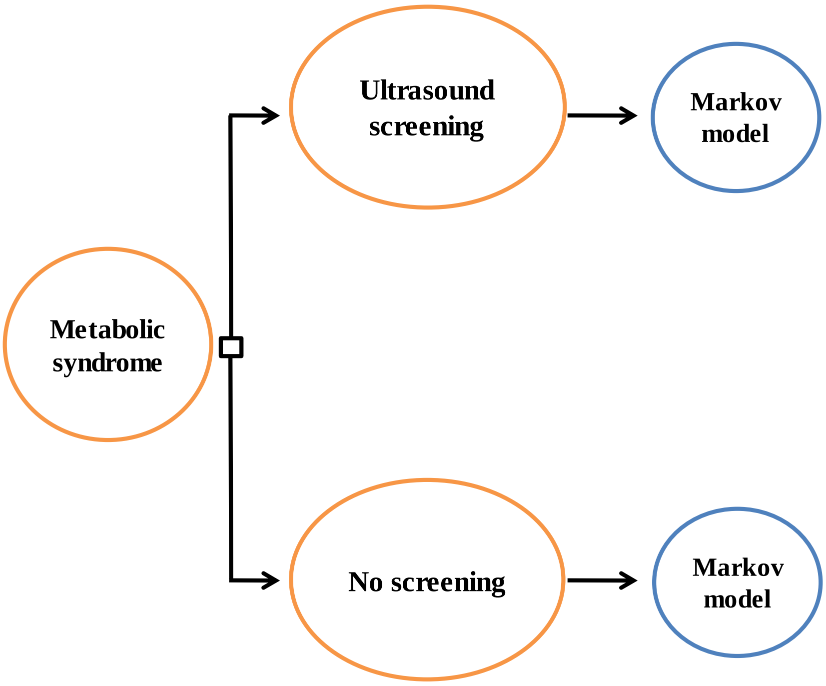
The hybrid model consisting of decision tree and Markov models was shown in Figures 2 and 3. A decision tree model was constructed to divide metabolic syndrome patients into two groups; screening with weight reduction and no screening groups. However, the whole effect of screening with weight reduction such as death and long-term effects of slow disease progression to cirrhosis including HCC cannot be captured with only decision tree model. Thus, estimation of long-term clinical and economic outcomes is vital since they are associated with those who have survived using another model. Therefore, Markov models were developed using a lifetime horizon with a one-year cycle length to capture long-term costs and health outcomes of ultrasonography screening for NAFLD in metabolic syndrome patients group with weight reduction compared to no screening group based on a societal perspective in costing calculation.

The model was established to create the natural history of disease progression in patients with NAFLD. These patients were categorized into 3 levels of fibrosis severity: no advanced fibrosis, indeterminate fibrosis, and advanced fibrosis by using the NAFLD Fibrosis Score. Patients could remain in the same state or move to other states. No advanced fibrosis and indeterminate fibrosis states could progress to advanced fibrosis. Conversely, advanced fibrosis could regress to no advanced fibrosis. Moreover, advanced fibrosis could develop to either compensated or decompensated cirrhosis each year with the different in chance. Compensated cirrhosis could progress to decompensated cirrhosis. And finally, both compensated and decompensated cirrhosis could transform to HCC and death. Those in cirrhotic state could die without developing HCC. Patients in the compensated, decompensated cirrhosis state, and HCC cannot reverse to a primary state and those with HCC could only move to a death state as shown in Figure 3.

Because the primary data set from Siriraj Hospital on the prevalence of NAFLD in Thailand showed a mean age of metabolic syndrome patients at 61 years, we used the starting age of ultrasonography screening at 50 years for prevention benefit. In clinical practice, we should screen for the disease approximately 10 years before the disease occurs. Otherwise, it might be too late to detect and the intervention might be less effective.

However, we also analyzed the ICER of start screening-age at 40 and 60 years for compared with the base case of 50 years. And the start screening-age of 40 and 60 years were evaluated the uncertainty by sensitivity analyses in both one way and probabilistic sensitivity analyses.

A hypothetical cohort of 1,000 individuals of metabolic syndrome patients at age 40, 50, and 60 years were simulated in the model. However, because of the limitations of ultrasonography, patients who received screening and diagnosed with NAFLD or no NAFLD by ultrasonography were divided into 4 categories; true positive, false positive, false negative, and true negative screening. The prevalence of NAFLD by ultrasonography including ratios of no advanced fibrosis : indeterminate fibrosis : advanced fibrosis of each age interval were different as shown in Table 1. These prevalence data and ratios used in the model were not similar depending on the age interval.



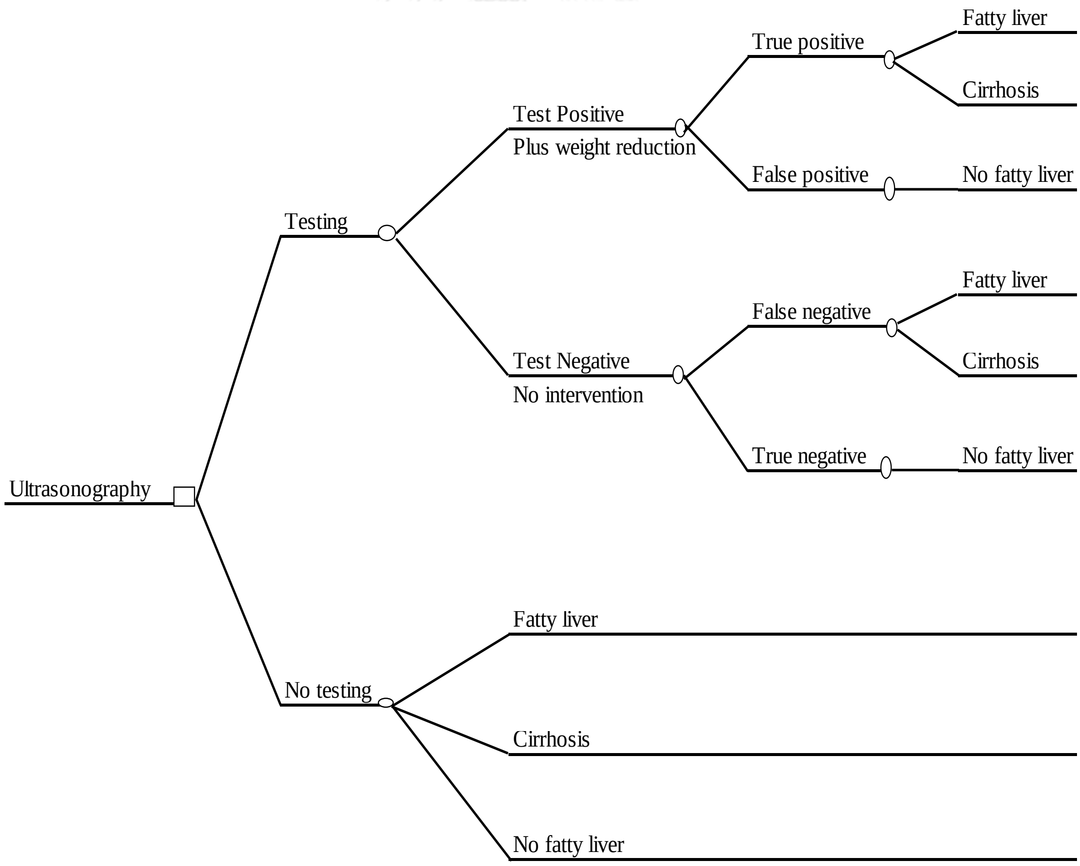
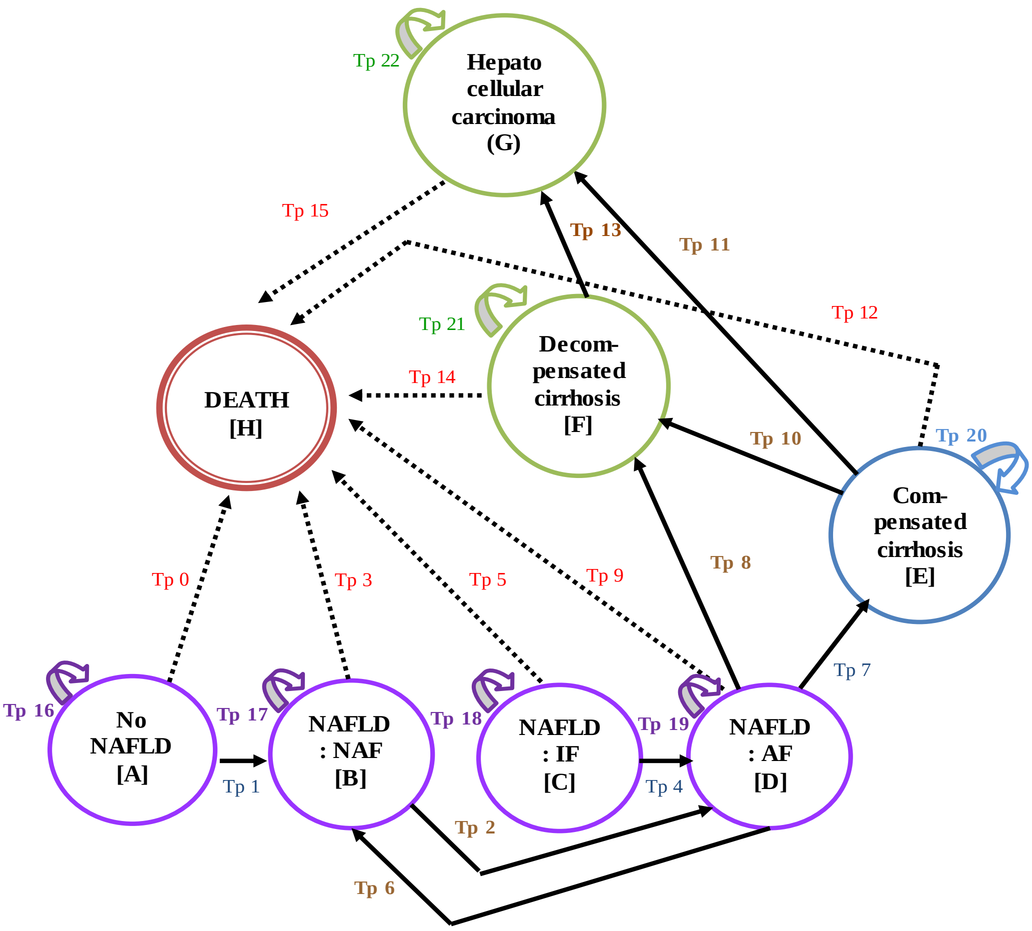


Figure 2. Decision tree model



NAFLD, Non-alcoholic fatty liver disease; NAF, non-advanced fibrosis; IF, indeterminate fibrosis; AF, advanced fibrosis

Figure 3. Markov model

In the screening group, when NAFLD was diagnosed, all of the NAFLD patients received the standard treatment for NAFLD such as life style modification, weight reduction, tight control of the risk factors, and/or standard medications. In this study, we used the data of weight reduction as an early intervention of NAFLD treatment for calculation of transitional probabilities of advanced fibrosis and cirrhosis progression. Because all of NAFLD patients should receive this modality of treatment as the most effectiveness standard of care even if general practitioners or specialists treated them and it was only one intervention which could be used to reverse hepatic fibrosis.

In the controlled group, data of NAFLD prevalence and the ratio of each degree of fibrosis in each age interval group used in the Markov models were the same as the screening group. However, the differences between no screening and screening group was the treatment intervention (weight reduction) when they could receive earlier diagnosis.

Input parameters

Prevalence of NAFLD in each state (no advanced fibrosis, indeterminate fibrosis, advanced fibrosis, and cirrhosis) (Table 1.), sensitivity, and specificity of ultrasonography, annual transitional probabilities, costs, and utilities which filled in the Markov models as the input parameters were demonstrated in Table 2. These input parameters were obtained from a data set of Siriraj Hospital and systematic literature search from other studies (local and international publications).

Table 1. Prevalence of Non-alcoholic fatty liver disease and ratios of several degree of fibrosis in each age interval (Phisalprapa et al., 2014)

Age	Average age	N	Cirrhosis	NAFLD	No NAFLD	NAF	IF	AF
< 30	28	3	0	1.000	0.000	1.000	0.000	0.000
30-39.9	37	16	0	0.813	0.188	0.846	0.154	0.000
40-49.9	46	50	0	0.780	0.220	0.487	0.513	0.000
50-59.9	56	176	0.006	0.744	0.250	0.598	0.371	0.030
60-69.9	65	149	0	0.631	0.369	0.202	0.723	0.074
70-79.9	74	96	0	0.594	0.406	0.175	0.614	0.211
≥ 80	82	19	0.053	0.316	0.632	0.000	0.714	0.286
Total	**61**	**509**	**0.004**	**0.674**	**0.322**	**0.409**	**0.519**	**0.072**

NAFLD, Non-alcoholic fatty liver disease; NAF, non-advanced fibrosis; IF, indeterminate fibrosis; AF, advanced fibrosis

Table 2. Input parameters used in the Markov model

Parameters	Distri-bution	Mean	95% CI	SE	References
Yearly discount rate (%)					
Costs		3	0-6		
Outcomes		3	0-6		
Prevalence on ultrasonography					
NAFLD	Beta	67.4%	63.3-71.5%	0.021	(Phisalprapa et al., 2014)
Cirrhosis	Beta	0.4%	0-0.9%	0.003	(Phisalprapa et al., 2014)
Total	Beta	67.8%	63.7-71.8%	0.021	(Phisalprapa et al., 2014)
NAFLD fibrosis score					
No advanced fibrosis	Beta	37.7%	33.5-41.9%	0.021	(Phisalprapa et al., 2014)
Indeterminate	Beta	54.4%	50.1-58.7%	0.022	(Phisalprapa et al., 2014)
Advanced fibrosis	Beta	7.9%	5.5-10.2%	0.012	(Phisalprapa et al., 2014)
Ultrasonography					
Overall sensitivity	Beta	84.8%	79.5-88.9%	0.027	(Hernaez et al., 2011)
Overall specificity	Beta	93.6%	87.2-97.0%	0.033	(Hernaez et al., 2011)
Annual transitional probability					
Annual incidence of NAFLD	Beta	0.055	0.022-0.088	0.017	(Hamaguchi et al., 2005)
From no advanced to advanced fibrosis	Beta	0.029	0.010-0.047	0.009	(Singh et al., 2014)
From indeterminate to advanced fibrosis	Beta	0.029	0.010-0.047	0.009	(Singh et al., 2014)
From advanced to no advanced fibrosis	Beta	0.065	0-0.130	0.033	(Singh et al., 2014)
From advanced fibrosis to compensated cirrhosis	Beta	0.04	0.02-0.06	0.010	(Bhala et al., 2011; Ekstedt et al., 2006)
From advanced fibrosis to decompensated cirrhosis	Beta	0.028	0.007-0.048	0.010	(Bhala et al., 2011)
From compensated to decompensated cirrhosis	Beta	0.06	0.04-0.16	0.051	(Hui et al., 2003; Sanyal et al., 2006)
From compensated cirrhosis to hepatocellular carcinoma	Beta	0.03	0.007-0.053	0.012	(Ascha et al., 2010; Ratziu et al., 2002; Sanyal et al., 2006)
From decompensated cirrhosis to hepatocellular carcinoma	Beta	0.03	0.007-0.053	0.012	(Ascha et al., 2010; Ratziu et al., 2002; Sanyal et al., 2006; Yatsuji et al., 2009),
From HCC to death	Beta	0.449	0.392-0.507	0.029	(Leerapun et al., 2013)
Thai Age-specific mortality rate	Beta				Life table, WHO 2013
Hazard ratio					
NAFLD	Log normal	1.29	1.00-1.58	0.165	(Ekstedt et al., 2015)
Cirrhosis	Log normal	3.13	2.35-3.91	0.399	(Ekstedt et al., 2015)
Risk reduction					
Weight reduction (fibrosis regression)	Beta	0.191	0.146-0.236	0.023	(Vilar-Gomez et al., 2015)
Annual direct medical cost					
Ultrasonography	Gamma	947	710-1184	121	Siriraj Hospital, 2014
Treatment metabolic syndrome	Gamma	2644	1983-3305	337	(Riewpaiboon, 2011)
Treatment NAFLD	Gamma	925	694-1156	118	(Riewpaiboon, 2011)
Treatment of compensated cirrhosis	Gamma	94147	70610-117684	12009	(Thongsawat et al., 2014)
Treatment of decompensated cirrhosis	Gamma	158037	118528-197546	20158	(Thongsawat et al., 2014)
Treatment of hepatocellular carcinoma	Gamma	171657	128743-214571	21895	(Thongsawat et al., 2014)
Annual direct non-medical cost					
Transportation	Gamma	655	491-819	84	(Riewpaiboon, 2011)
Food	Gamma	214	181-301	27	(Riewpaiboon, 2011)
Utility					
Metabolic syndrome	Beta	0.89	0.884-0.896	0.003	(Y.-J. Lee, Woo, Ahn, Cho, & Kim, 2011)
NAFLD	Beta	0.84	0.70-0.98	0.071	(Tongsiri & Cairns, 2011; Younossi, Boparai, McCormick, Price, & Guyatt, 2001)
Compensated cirrhosis	Beta	0.748	0.666-0.830	0.042	(McLernon, Dillon, & Donnan, 2008)
Decompensated cirrhosis	Beta	0.672	0.590-0.754	0.042	(McLernon et al., 2008)
Hepatocellular carcinoma	Beta	0.38	0.36-0.41	0.015	(Levy et al., 2008)

NAFLD, Non-alcoholic fatty liver disease

Clinical effectiveness and probability data

The primary data of the prevalence of NAFLD in each state and age interval were obtained from a cross-sectional study at Siriraj Hospital (Phisalprapa et al., 2014).

The sensitivity and specificity of ultrasonography were obtained from a recent meta-analysis. This study showed that ultrasonography has high detecting reliability and accuracy of moderate to severe fatty liver when compared to the gold standard of liver biopsy (Hernaez et al., 2011). Forty-nine studies (4,720 participants) were included for the meta-analysis of diagnostic accuracy. The overall sensitivity and specificity of ultrasound for the detection of moderate to severe fatty liver were 84.8% (95% CI: 79.5-88.9) and 93.6% (95% CI: 87.2-97.0), respectively. It proposed that the sensitivity and specificity of ultrasound were similar to that of other imaging techniques (CT and MRI).

The annual incidence of NAFLD was obtained from a prospective observational study in 4,401 apparently healthy Japanese at a medical health checkup program conducted in a general hospital (Hamaguchi et al., 2005). This study aimed to analyze the relationship between NAFLD and metabolic syndrome. At baseline, 812 of 4,401 (18.5%) participants had NAFLD. Of these, 435 of 4,401 cases were diagnosed of metabolic syndrome and 254 of 435 (58.4%) were diagnosed of NAFLD. During the follow-up period of 414 ± 128 days, there were 27 new cases (6.2%) of NAFLD among the participants, who were disease-free at baseline and completed a second examination.

Regression of NAFLD was found in 16% (113 of 704 participants), who suffered from the disease at baseline and completed a second examination. Males and females meeting the criteria for the metabolic syndrome at baseline were more likely to develop NAFLD during follow-up (adjusted odds ratio, 4.00 [95% CI, 2.63-6.08] and 11.20 [95% CI, 4.85-25.87]). NAFLD was less likely to regress in the patients with metabolic syndrome at baseline.

The annual probability of no advanced fibrosis progression to advanced fibrosis, indeterminate fibrosis progression to advanced fibrosis, and advanced fibrosis regression to no advanced fibrosis were obtained from a systematic review and meta-analysis evaluating the fibrosis progression in NAFLD (Singh et al., 2014). This study enrolled the studies of adults with NAFLD that collected paired liver biopsy specimens at least 1 year apart. The author had pinpointed 11 cohort studies including 411 patients with biopsy-proven NAFLD (150 with simple steatosis and 261 with NASH). At baseline, the distribution of fibrosis for stages 0, 1, 2, 3, and 4 was 35.8%, 32.5%, 16.7%, 9.3%, and 5.7%, respectively. Over 2145.5 person-years of follow-up evaluation, the percentage of fibrosis progression, stable fibrosis, and improvement in fibrosis stage were 33.6, 43.1, and 22.3 while the annual fibrosis progression rate in simple steatosis patients with stage 0 fibrosis at baseline was 0.07 stages (95% CI, 0.02-0.11) when compared to 0.14 stages in patients with NASH (95% CI, 0.07-0.21). Hence, these findings correspond to 1 stage of progression over 14.3 years for patients with simple steatosis (95% CI, 9.1-50.0) and 7.1 years for patients with NASH (95% CI, 4.8-14.3).

The annual probability of advanced fibrosis progression to compensated cirrhosis was obtained from two studies. The first study was an International Collaborative Study evaluating the natural history of NAFLD with advanced fibrosis or cirrhosis (Bhala et al., 2011). This prospective research studied 247 NAFLD patients from 4 centers (Australia, United States, United Kingdom and Italy) whose natural history was compared with 264 other patients with chronic hepatitis C infection. Both the cohorts were advanced fibrosis or stage 3 and cirrhosis Child-Pugh A or stage 4 confirmed by liver histology. In the NAFLD cohort, follow-up period was 85.6 ± 54.5 months. The second study was a cohort study in 129 NAFLD patients diagnosed with biopsy-proven (Ekstedt et al., 2006). The average follow-up was 13.7 ± 1.3 years. Progression of liver fibrosis occurred in 41%.

The annual probability of advanced fibrosis progression to decompensated cirrhosis was also obtained from an International Collaborative Study evaluating the natural history of NAFLD with advanced fibrosis or cirrhosis (Bhala et al., 2011). 48 (19.4%) patients developed liver-related complications with some developing more than one complication at follow-up. It was additionally found that 26 (10.5%) cases developed gastroesophageal varices, 19 (7.7%) developed ascites, liver failure, hepatopulmonary syndrome, and/or encephalopathy, and 6 (2.4%) developed HCC (4 of total were initially in stage 4 fibrosis).

The annual probability of compensated to decompensated cirrhosis was obtained from two studies. Both of them had evaluated long-term outcomes of cirrhosis in NASH compared to hepatitis C (Hui et al., 2003; Sanyal et al., 2006). The mean follow-up period of the first study was 84 months. Nine of the twenty three NASH-associated cirrhosis cases developed liver-related morbidity and hepatic decompensation (8 ascites and/or encephalopathy, 1 variceal bleeding). The second study compared 152 patients with cirrhosis as a result of NASH with 150 matched patients with cirrhosis as a result of HCV. Over 10 years, patients with Child Pugh A cirrhosis due to NASH also had a considerably lower risk of decompensation, defined by a 2-point increase in Child-Turcotte-Pugh score (p < .007). Cirrhosis caused by NASH was associated with a lower rate of development of ascites (14/101 vs. 40/97 patients at risk; p < .006).

The annual probability of compensated cirrhosis to HCC was obtained from 3 studies. The first study evaluated incidences and risk factors of HCC in patients with NASH between 2003 and 2007. All patients were monitored by using serial abdominal CT and serum alpha-fetoprotein (AFP) every 6 months to assess for HCC. Kaplan-Meier analysis was conducted to estimate the cumulative incidence of HCC. The median follow-up was 3.2 years when 25/195 (12.8%) of NASH cirrhosis and 64/315 (20.3%) of chronic hepatitis C cirrhosis developed HCC (p = 0.03). Yearly cumulative incidence of HCC was 2.6% in patients with NASH cirrhosis, compared with 4.0% in patients with chronic hepatitis C cirrhosis (p = 0.09) (Ascha et al., 2010). The second study evaluated in survival, liver failure, and HCC in obesity-related cryptogenic cirrhosis between 1988 and 2000. HCC was detected in 8 of 27 (27%) overweight patients with cryptogenic cirrhosis versus 21% of matched HCV cirrhosis in the controlled group (Ratziu et al., 2002). And the third study compared NASH cirrhosis and chronic hepatitis C cirrhosis. This study showed that NASH had lower risk of HCC development significantly (10/149 vs. 25/147 patients; p < .01) (Sanyal et al., 2006).

The annual probability of decompensated cirrhosis to HCC was obtained from 4 studies (Ascha et al., 2010; Ratziu et al., 2002; Sanyal et al., 2006; Yatsuji et al., 2009). These studies compared the outcomes between NASH cirrhosis and cirrhosis caused by HCV. Although the outcome of the NASH group was better than the HCV cirrhotic group, NASH cirrhosis followed a similar course to HCV cirrhosis. The 5-

year HCC rate was 11.3% for NASH and 30.5% for HCV. According to a multivariate analysis, the occurrence of HCC and the Child-Turcotte-Pugh class are significant risk factors for mortality in NASH patients (HCC: hazard ratio [HR] 7.96 (95% CI 2.45-25.88) and Child-Turcotte-Pugh class A: HR 0.17, 95% CI 0.06-0.50).

For the annual probability of death in each state, we calculated the risk of death based on the multiplication of the age-specific mortality rate (ASMR) of Thailand's general population from Thailand life table World Health Organization (WHO) 2013 and hazard ratio (HR) of NAFLD. The probability of death in the fatty liver state (no advanced fibrosis, indeterminate fibrosis, and advanced fibrosis) was calculated by multiplication of ASMR and the hazard ratio of NAFLD patients; 1.29 (95% CI 1.04-1.59, p = 0.020). And the probability of death in the cirrhotic state (compensated and decompensated) was calculated by multiplication of ASMR and hazard ratio of cirrhosis; 3.13 (95% CI 1.08-9.12, p = 0.036) (Ekstedt et al., 2015).

In addition, HCC was the difficult disease with a large number of modalities of treatment and the prognosis of HCC was different among the countries due to limitations of treatment. Thus the probability of death for patients with HCC in this Markov model, a combination of the ASMR of NAFLD patients with Thailand data in prognosis of HCC (Leerapun et al., 2013) was used. This study evaluated the clinical features, prognostic factors, and overall survival for HCC in northern Thailand. The medical records of 287 HCC patients between July 2007 and June 2010 were reviewed; the average age of HCC patients was 53.8 years. Implementing Barcelona-Clinic Liver Cancer staging for HCC, patients at early stage, intermediate stage, advanced stage, and terminal stage were 40 (13.9%), 105 (36.6%), 95 (33.1%), and 43

(15.0%). The mean follow-up time was 20.1 months. The overall survival of HCC at year 1, 2, and 3 were 55.0, 34.0, and 31.3 percent, respectively.

Moreover, after NAFLD patients were earlier diagnosed by ultrasonography, they will receive life style modification and weight reduction counselling as an early standard treatment intervention. The risk reduction of fibrosis progression from the benefit of weight reduction was obtained from the prospective study of 293 NASH patients who proven by liver biopsy. They were encouraged to change the life style as standard recommendation for over 52 weeks to reduce their weight from June 2009 to May 2013, at a tertiary medical care in Havana, Cuba. For this data, we used from the most recent study in Cuba because there was no data in Thailand. And this is the first large prospective study conducted in real-world clinical practice that explores the potential benefit of a 12-month of lifestyle intervention on histologic NASH-related features. Liver biopsies were collected when the study began and at week 52 of the diet before histological analysis was conducted. This study showed that of the patients, who underwent lifestyle changes for 52 weeks, 72 (25%) had achieved a resolution of steatohepatitis and 56 (19%) had regression of fibrosis. At week 52, 88 subjects (30%) had lost 5% or more of their weight. A higher proportion of subjects with 5% weight loss or more had NASH resolution (51/88, 58%) than subjects that lost less than 5% of their weight ($p < .001$). For the patients who lost 10% of their weight or more, 90% had resolution of NASH and 45% had regression of fibrosis.

Cost data

This study was undertaken using the societal perspective in costing calculation because it was already included all stakeholders. Direct medical costs, direct non-medical costs, and indirect cost were included for provider’s perspective whereas only direct medical costs and direct non-medical costs were included for patient's perspective. Because for the health outcome of QALY gained, it was assumed that loss attributable to the inability to work, decrease earning ability, and long term disability due to illness would be captured in the disutility of QALY, therefore indirect costs were not included as to evade double counting.

However, for the health outcome of life year saved, we should calculated the indirect costs due to illness and intangible costs such as the patients' suffering and anxiety after they were diagnosed of NAFLD even it was true positive or false positive. But in this study we do not included because data is not available in Thailand. In addition, for the societal perspective, the government should have the policies of good environment for changing patient behavior, healthy diet campaign, increase health education, and getting incentive for who loss body weight. These costs should be included for calculation but there was no available data of these costs.

The all costs data were obtained from data and published articles in Thailand. All costs were converted and reported in 2014 THB (1 United States Dollar, USD = 32.91 THB) and using the consumer price index (CPI) (Bank of Thailand, 2014). All future costs were discounted at a rate of 3%. These costs were retrieved using reference prices published by standard cost lists for health technology assessment, Health Intervention and Technology Assessment (HITAP), Ministry of Public Health (Riewpaiboon, 2011). All cost parameters are presented in Table 2.

Our analysis included the six categories of cost;

- Cost of ultrasonography
- Cost of metabolic syndrome treatment
- Cost of NAFLD treatment

- Cost of treatment for compensated cirrhosis
- Cost of treatment for decompensated cirrhosis
- Cost of treatment for HCC

For all of metabolic syndrome patients, the total cost included direct medical costs (laboratory tests, medication for controlled co-morbid disease, and cost at out-patients visit 4 times per year) and direct non-medical cost for treatment metabolic syndrome.

For all of NAFLD patients who were early diagnosed by ultrasonography, the total costs included the cost of treatment metabolic syndrome and added on with the cost of ultrasonography and cost of treatment NAFLD (laboratory tests and cost of counselling for weight reduction at out-patient visit).

For the patients who progressed to cirrhotic states (compensated and decompensated) or HCC state, the total costs were also added on the cost of treatment compensated cirrhosis, decompensated cirrhosis, or HCC.

Cost of ultrasonography

The unit cost of ultrasonography was calculated by using data of year 2014 from Siriraj Hospital as shown in Table 3. The ultrasonography unit is a patient care cost center (PCC) responsible for direct patient services whereas supportive cost center (SCC) provide support for patient care via laundry, transport, administration, and others.

The direct cost of ultrasonography cost center was then calculated by summing labor, capital, and materials costs. Labor costs consist of salaries and fringe benefits while for staffs that work in more than one cost center, labor costs was calculated in ratio based on the working time in each cost center. Capital costs included annualized discounted depreciation of building, equipment, vehicles, and the opportunity cost of land and using the straight-line depreciation with step down approach, it was assumed that the services from the capital items were divided equally over the useful life of the capital items. The depreciation cost was calculated by implementing the economic approach. The interest was calculated for the whole period of the useful life, and then discounted to the time of analysis by using an annuity factor. In this study, we used replacement cost instead of original cost. Replacement cost adjusts the original cost with an inflation adjustment factor, which is calculated using the consumer price index (CPI) factor.

The useful life of buildings and structure were considered to be 20 years; the useful life of ultrasonography machine was assumed to be 8 years. A discount rate of 3 percent was used to calculate the cost of depreciable assets and the opportunity cost of land. Materials costs cover radiology materials and utilities. After deriving the direct cost of each cost center, we allocated the direct cost of SCCs to PCCs. After being allocated to PCCs, the direct costs of SCCs are known as the indirect costs of PCCs. These indirect costs included all costs that could not be allocated directly to final cost centers. With this calculation, the unit cost include both direct costs and overhead costs incurred in treating a patient. The common overhead departments are the administration, nursing administration, laundry, kitchen, maintenance, transport, and store. Then the unit cost of ultrasonography were calculated by the formula of

$$\text{Unit cost} = \frac{\text{Total cost}}{\text{Total outcome}} \text{ in one period of time}$$

Table 3. Unit cost calculation of ultrasonography from Siriraj Hospital (year 2014)

Parameters	**Number**
Number of test per year	19,387
Time per test (minutes)	20
Direct cost (PCCs)	
Labor cost	
- Medical instructors	60.9
- Residents/Service staffs	353.2
- Nurses and technicians	133.4
- Supporting team	22.7
Total of labor cost	570.2
Capital cost	247.5
Material cost	43.5
Indirect cost (SCCs)/administrative	86.1
Unit cost (THB/test)	**947.3**

Cost of treatment metabolic syndrome and NAFLD

The direct medical costs and direct non-medical costs (transportation, meals, accommodation and facilities) of treatment metabolic syndrome and NAFLD were obtained from a standard cost list of Thailand HTA (Riewpaiboon, 2011).

Cost of treatment complications

The cost for treatment of compensated cirrhosis, decompensated cirrhosis, and HCC were obtained from a large study in 5 tertiary care hospitals in Thailand (Thongsawat et al., 2014). It evaluated the resource utilization of chronic hepatitis C in Thailand in the aspect of economic burden. Resource utilization data for each patient during a 12-month follow-up period were calculated. The reference prices published by the Thai government were used to estimate the cost for each health state. The total costs of each state were calculated from laboratory and diagnostic tests, procedures, medications excluding antiviral drug, and hospitalization.

Utility data

Metabolic syndrome is a combination of abnormalities including abdominal obesity, high blood pressure (BP), dyslipidemia and impaired glucose metabolism. People with metabolic syndrome have an increased risk of developing diabetes and cardiovascular disease. In addition, several components of metabolic syndrome and metabolic syndrome-related adverse events such as diabetes and cardiovascular disease have been associated with decreased Health-Related Quality of Life (HRQoL). For the health state of metabolic syndrome patients, we obtained from a large cross-sectional study in Korea (Y.-J. Lee et al., 2011). This study evaluated in the HRQoL in 8,941 Korean adults compared between the participants with and without metabolic syndrome in the National Health and Nutrition Examination Survey, 2007-2008. The prevalence of metabolic syndrome was 26.2%. The mean value of the EUROQoL five-dimension (EQ-5D) in participants with metabolic syndrome was 0.89 ± 0.003 compared with 0.93 ± 0.002 in the participants without metabolic syndrome ($p < .0001$).

Because there were no prior HRQoL studies performed in NAFLD patients such as chronic liver disease, compensated cirrhosis, or decompensated cirrhosis, we used the level of utility from systematic review of other causes of chronic liver disease. Furthermore, compensated cirrhosis, decompensated cirrhosis, and HCC represented a common pathway of chronic liver disease, we assumed that, regardless of the initial causes, the level of quality of life associated with these conditions were similar.

For the NAFLD state, we obtained the utility from two studies. The first study applied 0.77 as utility of Thai general population for this group of patients (Tongsiri & Cairns, 2011) because NAFLD patient can live as a healthy person. And the second study was the assessment of utilities and HRQoL in patients with chronic liver disease. The chronic liver disease state without cirrhotic complication had a utility score of 0.84 ± 0.14 (Younossi et al., 2001).

For the compensated and decompensated cirrhosis states, we obtained utility data from a systematic review of health-state utilities in liver disease (McLernon et al., 2008). Thirty studies measured utilities of liver diseases/disease states. Half of these estimated utilities for hepatitis viruses: hepatitis A (n=1), hepatitis B (n=4), and hepatitis C (n=10). The EQ-5D (n=10) is the most popular method followed by visual analogue scale (n=9), time trade off (n=6), and standard gamble (n=4). The pooled mean estimates in the patients with compensated cirrhosis and decompensated cirrhosis using the EQ-5D were 0.748 and 0.672, respectively.

For the health state of HCC, we obtained the utility from a study of chronic hepatitis B patients because there were no data of utility of HCC from NASH cirrhosis (Levy et al., 2008). And the utility of HCC should be the same in any causes because it is the most advanced state of disease. The sample in this study included 534 CHB-infected patients and 600 uninfected respondents. HCC had a strong impact with utility of 0.38 (95% CI 0.36-0.41).

Health outcomes measurement

The health outcomes of the model were measured in terms of number of cases prevented from cirrhosis, HCC, and death by ultrasonography at each period after screening, number of life-years saved, and number of QALYs gained. QALYs combined data on life expectancy (LE) with data reflecting quality of life or utility unit.

3.5 Data analysis

All data were analyzed by using the cost-effectiveness and cost-utility analysis. The total costs and the effectiveness of ultrasonography screening with weight reduction and no screening were compared in terms of ICER.

Cost-effectiveness analysis

Base-case analysis

The first outcomes of interest were clinical outcomes of number of cases prevented from cirrhosis, HCC, and death by ultrasonography screening with weight reduction.

And the other outcomes were lifetime costs, life-years saved, QALYs gained, ICER per LY saved, and ICER per QALY gained.

The cost-effectiveness ultrasonography screening with weight reduction was assessed by calculating its ICER according to the following formula:

$$\frac{\text{Total costs}_{\text{screening}} - \text{Total costs}_{\text{no screening}}}{\text{Outcomes}_{\text{screening}} - \text{Outcomes}_{\text{no screening}}}$$

The results were presented as ICER of ultrasonography screening for NAFLD and early intervention of weight reduction compared with no screening. For base-case analysis, we calculated the expected lifetime costs and outcomes for each group. We used the starting age of ultrasonography screening at 50 years as base case for screening and prevention benefit. All future costs and outcomes were discounted at a rate of 3% per annum as recommended by Thai HTA method guideline (Thai Working Group on health Technology Assessment Guidelines in Thailand, 2008).

Because of the limitation of ultrasonography, there were 4 categories of metabolic syndrome patients in the ultrasonography screening group:

- True positive: In this group, the costs were calculated by summing of costs of ultrasonography, cost of treatment metabolic syndrome and NAFLD, and cost of treatment cirrhotic complications. The effectiveness was number of cases prevented from cirrhotic complication, number of LY saved and QALYs gained after early intervention.

- False positive: In this group, the costs were calculated the same as true positive group but because the patients that received the over diagnosis of NAFLD, did not have NAFLD and no significant fibrosis thus, no effectiveness was gained.

- False negative: In this group, the costs were calculated by summing of costs of ultrasonography and cost of treatment metabolic syndrome but it did not include the cost of treatment NAFLD. Thus, these patients did not receive early intervention because of miss diagnosis and no effectiveness was gained in this group.

- True negative: In this group, the costs were calculated by summing of costs of ultrasonography and cost of treatment metabolic syndrome. The effectiveness was the same as controlled group (no screening).

The overall results were presented as an ICER in THB per 1 life-year saved or 1 QALY gained as shown in Figure 1. If ICER was negative, it indicated cost saving.

In case of ICER being positive, a threshold value interpretation of cost-effectiveness of the findings was founded on an official willingness-to-pay (WTP) of the Thai Health Economic Working Group (HEWG) or 1 GNI per capita per QALY gained. They recommended a ceiling threshold of cost-effective intervention at 160,000 THB per QALY gained.

3.6 Sensitivity analysis

One-way sensitivity analyses were performed to study the effects of altering uncertainty parameters within the 95% CI ranges including all clinical effects, costs, utilities, and discounting rate on the ICER in the model. The results of one-way sensitivity are presented using a tornado diagram. Tornado diagrams were used for comparing the relative importance of variables. It could identify which one-way sensitivity analysis had the greatest impact on model results. For each uncertainty variable considered, the estimates for what the low, base, and high outcomes would be. The sensitive variable was modeled as uncertain value while all other variables were constant at baseline values. In tornado diagrams, the first ten bars represent the items that contributed the most to the variability of the outcome. The decision maker should focus on these parameters. In addition, a probabilistic sensitivity analysis was conducted to simultaneously examine the effects of all parameter uncertainty using a Monte Carlo simulation performed by Microsoft Excel 2003 (Microsoft Corp., Redmond, WA) (Briggs. A, Sculpher. M, & Claxton. K, 2006). The distributions of each probability were assigned following (Limwattananon S, 2008) : (a) probability and utility parameters, whose values ranged between zero and one, were specified to beta distributions, (b) costs, whose characters values above zero, were assigned to gamma distributions, and (c) hazard ratios were given to a log-normal distribution. A

Monte Carlo simulation was run for 1,000 sets of the simulation to give a range of values for total costs, outcomes, and ICERs. Results of the PSA were presented as cost-effectiveness acceptability curve (Figure 11 & 12). The expected net monetary benefit (NMB) was calculated for WTP of 160,000 THB threshold in Thailand in order to show the probability that ultrasonography is cost-effective for monetary values that a decision-maker might be willing to pay.

3.7 Ethical issues

Because this study is a cost-effectiveness analysis using the economic model and it was not directly contacted to the patients, the ethical issues were irrelevant.

CHAPTER IV

RESULTS

4.1 Base case analysis

Because the primary data set from Siriraj Hospital on the prevalence of NAFLD in Thailand shows a mean age of metabolic syndrome patients at 61 years, we used the starting age of ultrasonography screening at 50 years for prevention benefit. In clinical practice, we should screen for the disease approximately 10 years before the disease occurs. Otherwise, it might be too late to detect and the intervention might be less effective.

The clinical-related health outcomes of the number of cases prevented from cirrhosis, HCC, and death by ultrasonography screening with weight reduction for the base case of metabolic syndrome patients aged 50 years were shown in Table 4 and Figure 4. At ten years after ultrasonography screening and weight reduction as an early intervention, the number of cases prevented from cirrhosis, HCC, and death were 1094.0, 53.2, and 129.5 per 100,000 screening, respectively. At twenty years after screening and intervention, the number of cases prevented from cirrhosis, HCC, and death were 1538.7, 101.8, and 874.7 per 100,000 screening, respectively.

Table 4. Number of cases prevented from cirrhosis, HCC, and death of start screening-age at 50 years

Years after screening	Cirrhotic prevention (per 100,000 screening)	HCC prevention (per 100,000 screening)	Death prevention (per 100,000 screening)
0	0	0	0
1	19.9	0	0
2	81.1	0.6	0.2
3	173.3	2.8	1.3
4	287.9	6.7	4.2
5	415.7	12.3	11.5
6	552.1	19.2	23.0
7	692.7	27.0	39.5
8	833.8	35.5	61.4
9	972.8	44.4	89.0
10	**1094.0**	**53.2**	**129.5**
11	1207.3	61.7	176.1
12	1312.0	69.6	228.2
13	1407.4	77.1	285.5
14	1493.3	84.0	347.2
15	1534.8	89.9	429.3
16	1566.6	94.2	513.2
17	1589.3	97.6	598.1
18	1603.6	100.0	682.9
19	1610.2	101.8	767.1
20	**1538.7**	**101.8**	**874.7**
21	1467.8	99.7	973.0
22	1397.8	96.5	1061.6
23	1329.1	92.7	1140.5
24	1261.8	88.6	1209.9
25	1121.8	83.2	1278.1
26	999.3	76.2	1326.0
27	891.8	68.9	1356.0
28	797.0	62.0	1370.7
29	713.2	55.6	1372.6
30	**595.6**	**49.0**	**1347.0**
31	500.1	42.1	1306.5
32	421.9	35.9	1255.2
33	357.6	30.4	1196.7
34	304.2	25.8	1133.8
35	233.1	21.3	1032.3
36	180.8	17.0	931.5
37	141.8	13.5	834.8
38	112.2	10.6	743.9
39	89.5	8.4	660.0
40	**61.1**	**6.3**	**544.6**

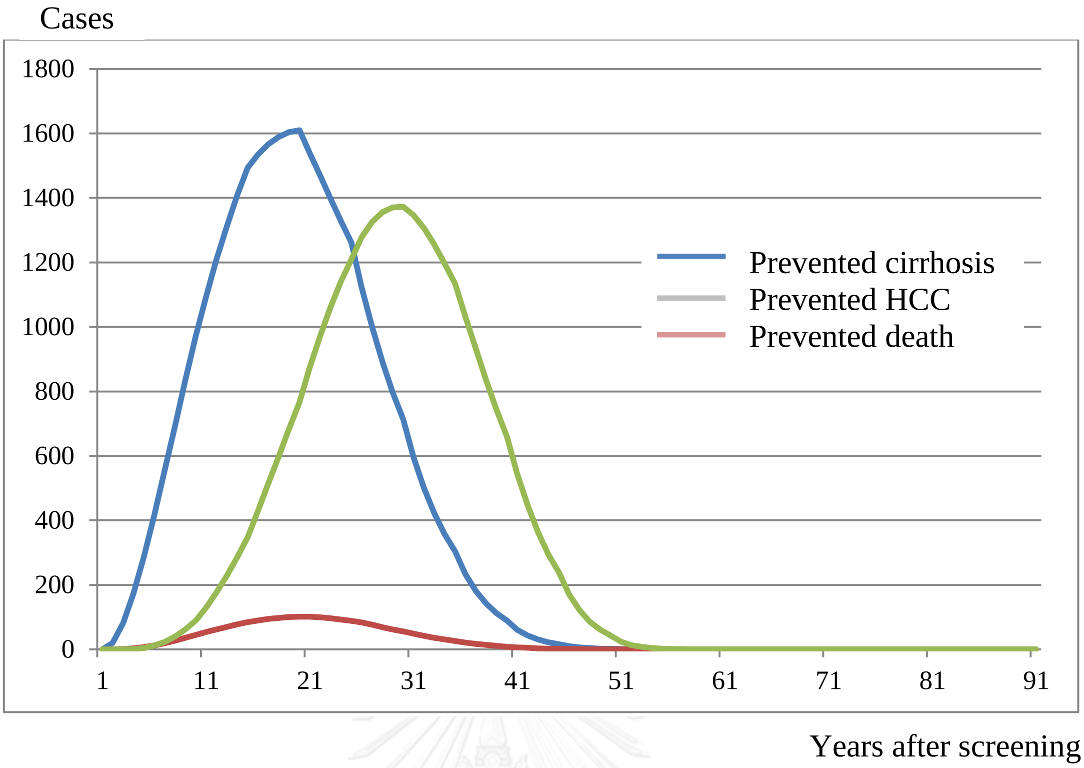


Figure 4. Number of cases prevented from cirrhosis, HCC, and death of start screening-age at 50 years

For patients, who had received first ultrasonography screening with weight reduction at 40 and 60 years, the number of cases prevented from cirrhosis, HCC, and death were shown in Figure 5 & 6. At start screening-age of 40 years, there are better clinical health outcomes than start screening-age at 60 years. Moreover, ten years after ultrasonography screening with weight reduction, the number of cases prevented from cirrhosis, HCC, and death were 1182.3, 55.4, and 93.4 per 100,000 screening whereas the number of cases prevented from cirrhosis, HCC, and death were 803.0, 42.1, and 190.1 per 100,000 screening when compared with first screening age at 60 years.

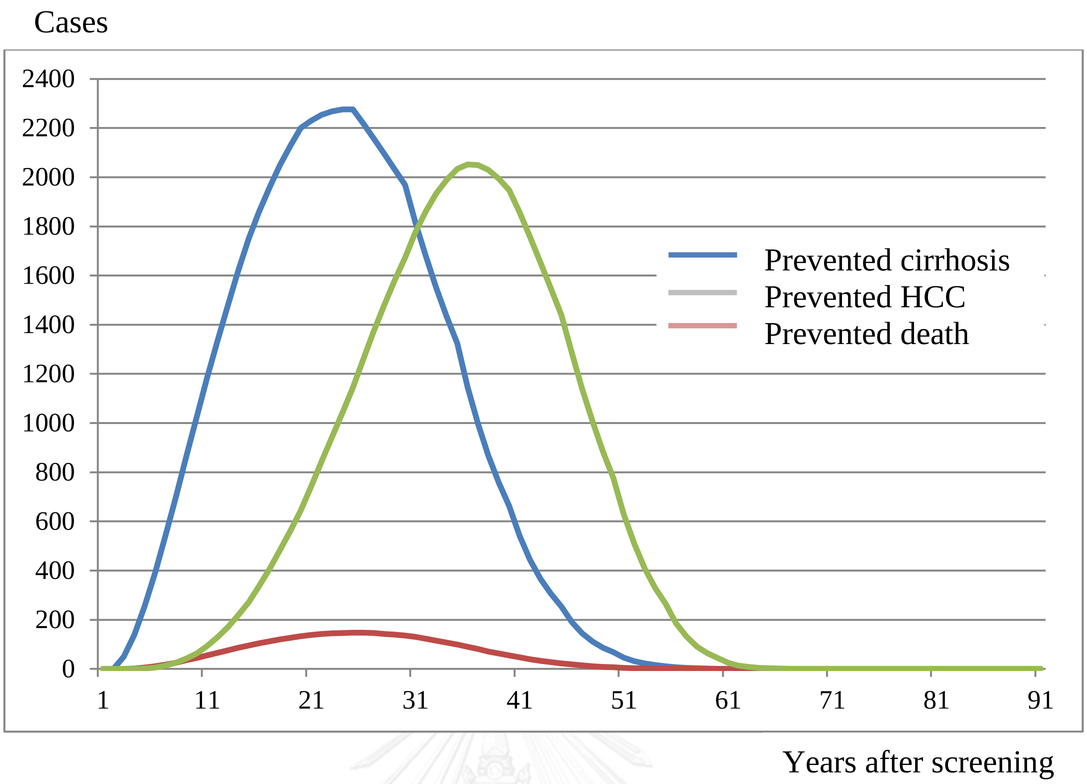


Figure 5. Number of cases prevented from cirrhosis, HCC, and death of start screening-age at 40 years

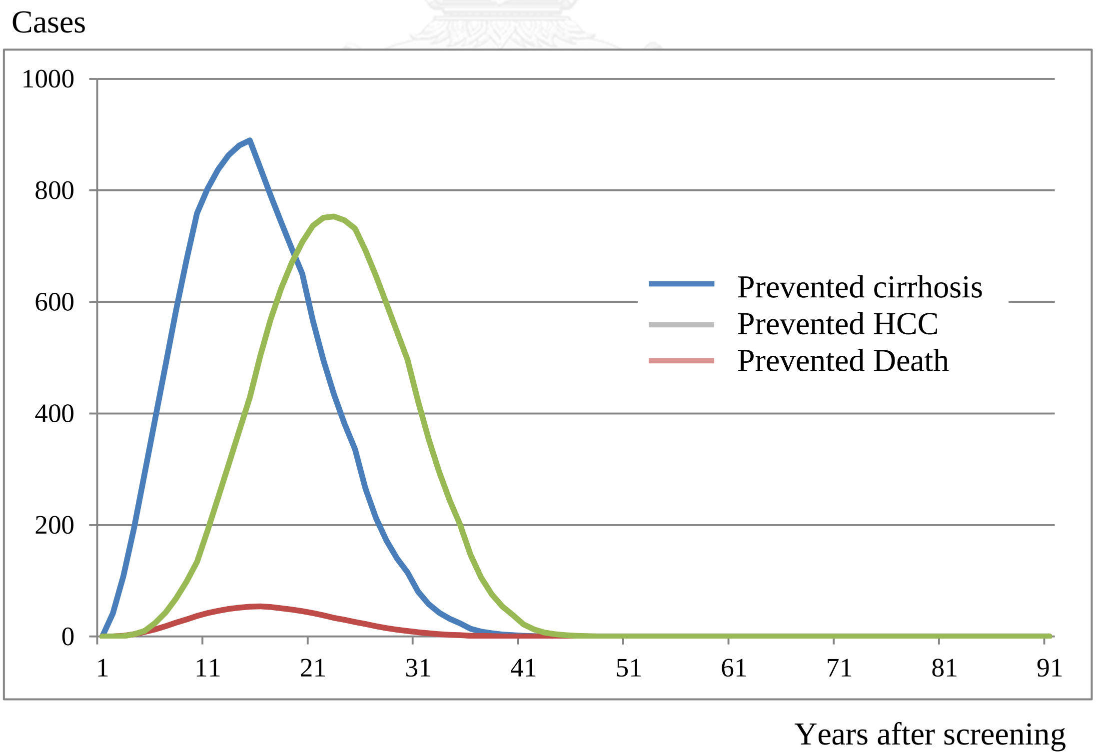


Figure 6. Number of cases prevented from cirrhosis, HCC, and death of start screening-age at 60 years

Our base-case analysis of screening-age at 50 years demonstrated the estimated life time costs for ultrasonography screening for NAFLD plus intervention by weight reduction versus no ultrasonography screening as 197,568 THB and 194,819 THB, respectively, while the estimated life-years were 17.19 and 17.06 years and QALYs were 14.38 and 14.24 QALYs, respectively. The ultrasonography screening plus weight reduction was more costly than no ultrasonography but it delivered greater health benefits. For cost-utility analysis, the outcome measurement was ICER of 160,000 THB or less, which is considered as cost-effective. When compared to no screening, an incremental cost per life-year saved was 21,025 THB per life-year saved and incremental cost per QALY gained was 19,706 THB per QALY gained from screening ultrasonography with weight reduction (Table 5).

Table 5. Results from base case analysis of start screening-age at 50 years

Results	**Discounted**	
	No screening	**Screening**
Life expectancy (years)	17.06	17.19
QALYs (years)	14.2438	14.3833
Total costs (THB)	194,819	197,568
Incremental costs (THB)		2,748.85
Life-years saved (years)		0.13074
QALYs gained (years)		0.13949
ICER/LY saved (THB)		21,025
ICER/QALY (THB)		19,706

QALY, Quality-Adjusted life year; THB, Thai Baht; LY, life-year; ICER, Incremental Cost-Effectiveness Ratio

However, for the health outcome of life year saved, we should calculated the indirect costs due to illness and intangible costs such as the patients' suffering and anxiety after they were diagnosed of NAFLD even it was true positive or false positive. But in this study we do not included because of no available data in Thailand.

When the starting ages of screening were 30, 40, 50, 60, 70, and 80 years, the ICERs were -60,284 THB, -30,913 THB, 19,706 THB, 108,176 THB, 201,421 THB, and 553,528 THB, respectively. The results showed cost-saving in screenings at ages before 47 years and the ICER showed cost-effective in any screening age before 65 years (Figure 7).

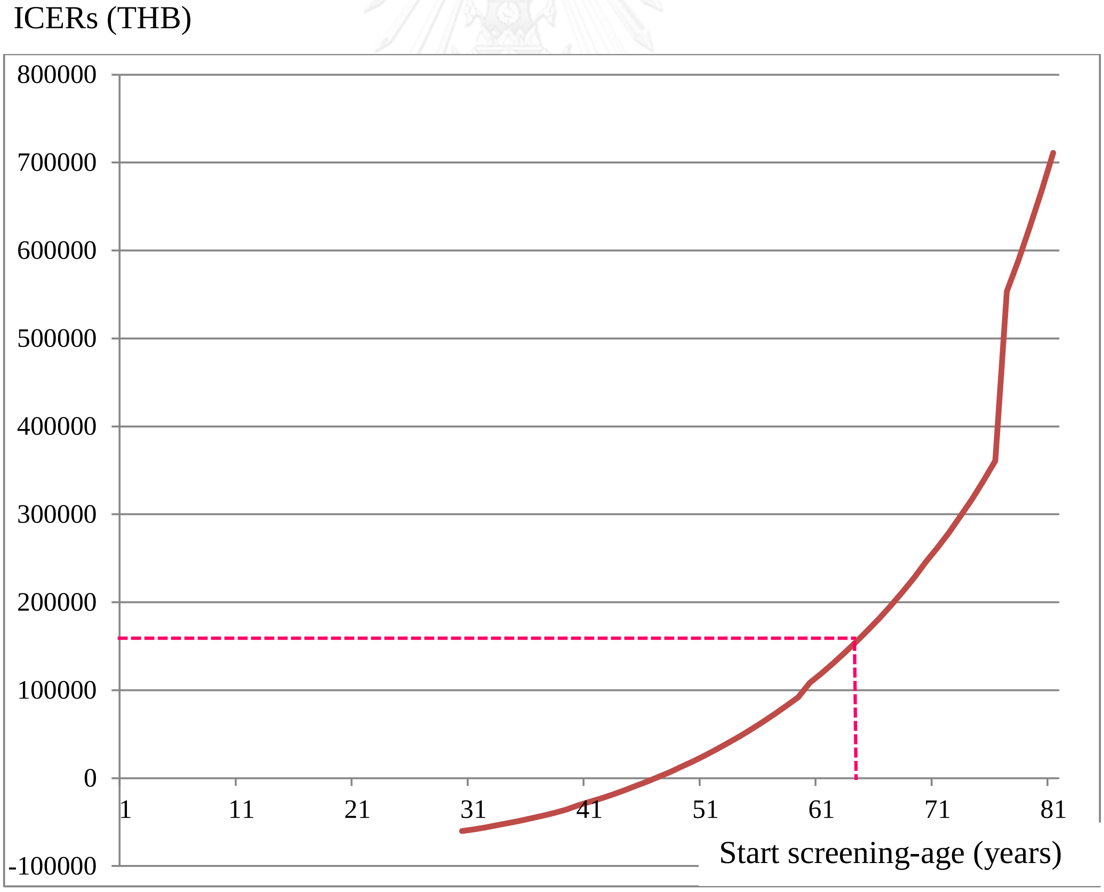


Figure 7. Incremental Cost-Effectiveness Ratios of each start screening-age

4.2 Sensitivity analysis

4.2.1 One-way sensitivity analyses: Tornado diagrams

The series of one-way sensitivity analyses that tested for influential variables in ultrasonography screening with intervention strategy are shown in Figure 8-10 as Tornado diagrams of the different screening ages. The vertical line represents the ICER for the base case estimate. Given the uncertainties inherent in the base case analysis, the robustness of the results was tested in sensitivity analyses.

For the starting screening-age at 40 years, the most influential variables in our model were the annual probability of no advanced fibrosis progression to advanced fibrosis. When varying this probability from 0.029 to 0.011 and 0.047, the ICER was changed to 41,536 THB and -59,274 THB, respectively. Risk reduction of weight reduction was the second influential parameter. When varying this rate from 0.191 to 0.146 and 0.236, the cost-effectiveness value was 17,936 THB and -61,162 THB, respectively. When varying the annual probability of indeterminate fibrosis progression to advanced fibrosis to 0.011 and 0.047, the ICER was changed to 25,458 THB and -52,502 THB. And when varying the annual probability of advanced fibrosis progression to compensated cirrhosis to 0.02 and 0.06, the ICER was changed to 18,462 THB and -54,104 THB, respectively. However, sensitivity analysis indicated that ultrasonography screening with weight reduction remained cost-effective across the ranges tested for these annual probabilities, costs, and utilities even others parameters were changed (Figure 8).

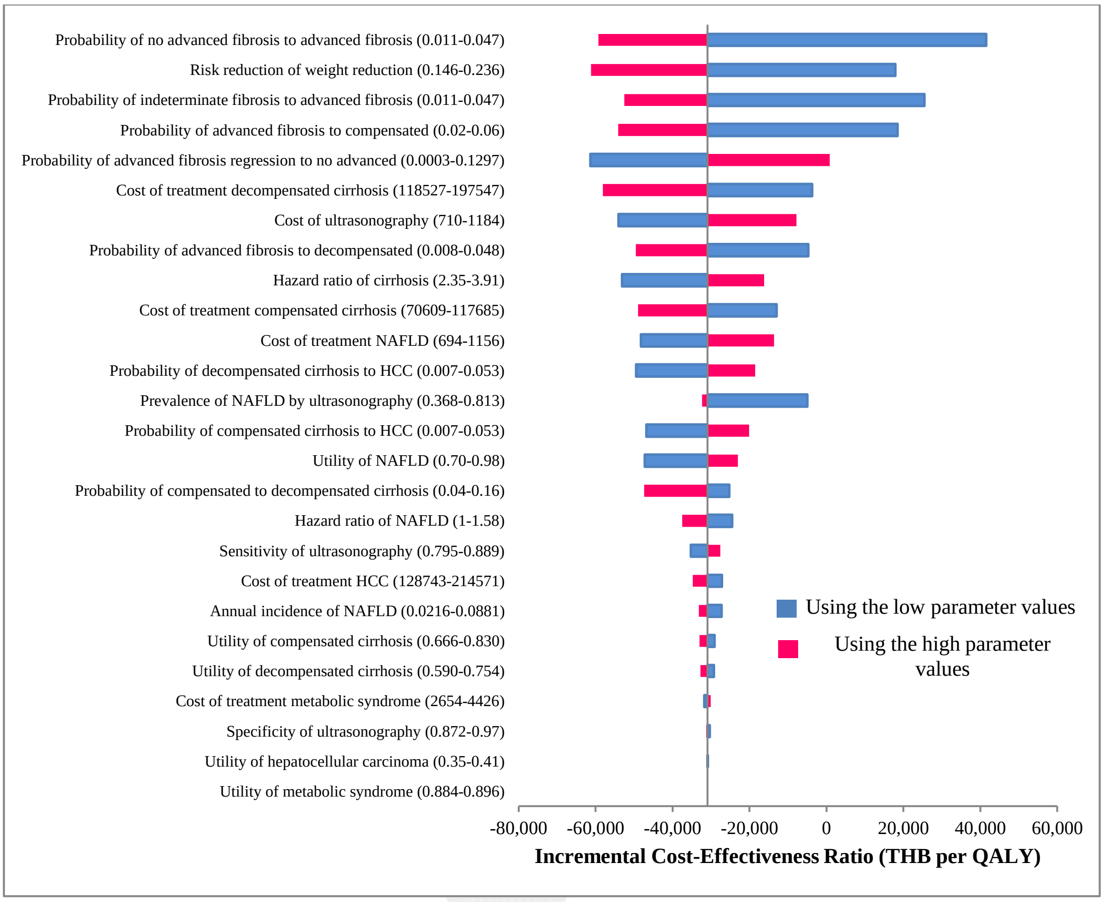


Figure 8. Tornado diagrams of start screening-age at 40 years

For the start screening-age at 50 years, the most influential variables in our model were the annual probability of no advanced fibrosis progression to advanced fibrosis. When varying this probability from 0.029 to 0.011 and 0.047, the ICER was changed to 134,262 THB and -22,375 THB, respectively. The annual probability of advanced fibrosis progression to compensated cirrhosis was the second influential parameter. When varying this rate from 0.04 to 0.02 and 0.06, the ICER was 88,181 THB and -12,144 THB, respectively. When varying the risk reduction of weight reduction from 0.191 to 0.146 and 0.236, the cost-effectiveness value was 80,088 THB and -17,662 THB. Nevertheless, sensitivity analysis indicated that ultrasonography screening with weight reduction remained cost-effective for these probabilities, costs, and utilities even others parameters were changed (Figure 9).

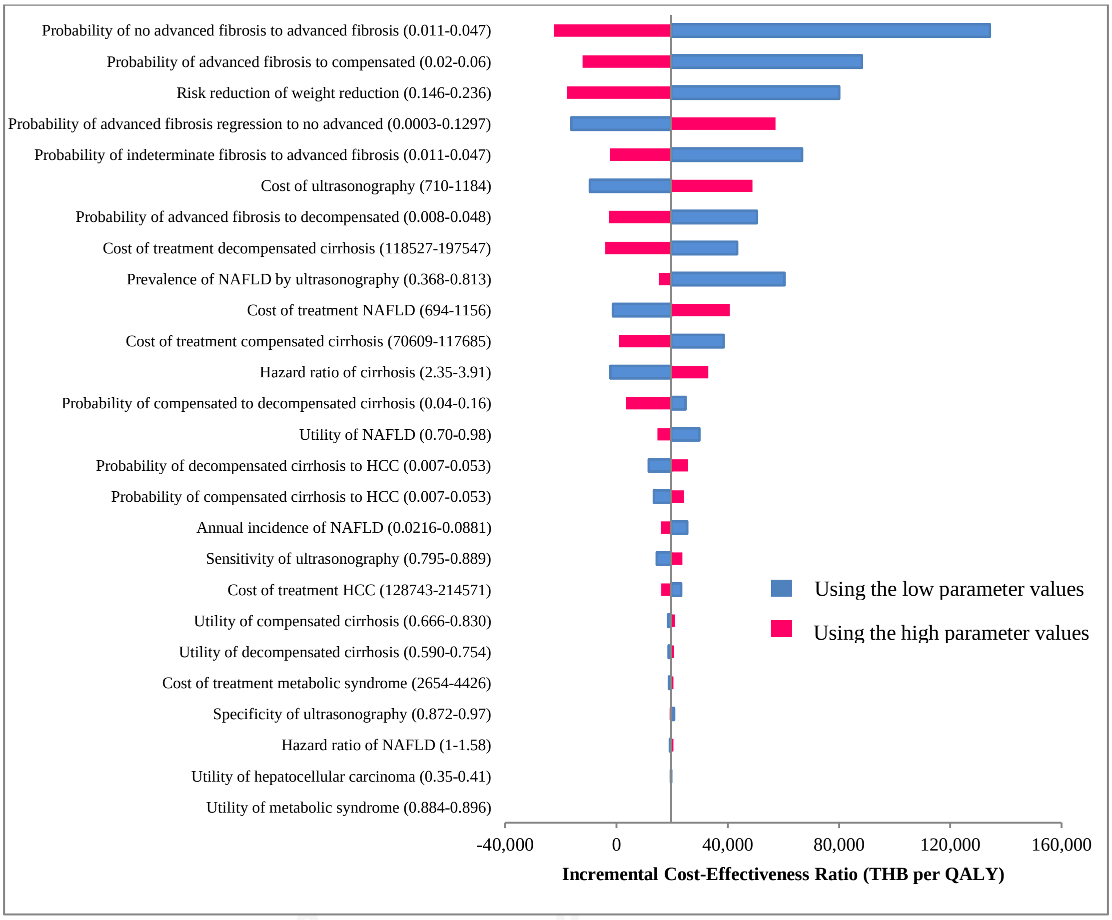


Figure 9. Tornado diagrams of start screening-age at 50 years

For the start screening-age at 60 years, the most influential variables in our model were the annual probability of indeterminate fibrosis progression to advanced fibrosis. When varying this probability to 0.011 and 0.047, the ICER was 251,868 THB and 54,282 THB, respectively. The annual probability of advanced fibrosis progression to compensated cirrhosis was the second influential parameter. When varying this rate to 0.02 and 0.06, the cost-effectiveness value was 214, 338 THB and 60,058 THB. When varying the risk reduction of weight reduction from 0.191 to

0.146 and 0.236, the ICER was changed to 189,538 THB and 57,837 THB. When varying the annual probability of no advanced fibrosis progression to advanced fibrosis to 0.011 and 0.047, the ICER was changed to 168,690 THB and 74,669 THB. According to the cut-off cost-effective ICER of 160,000 THB, these results showed that these four parameters, the prevalence of NAFLD, and the utility of NAFLD were sensitive and ICERs were not cost-effective in some ranges of these variables (Figure 10).

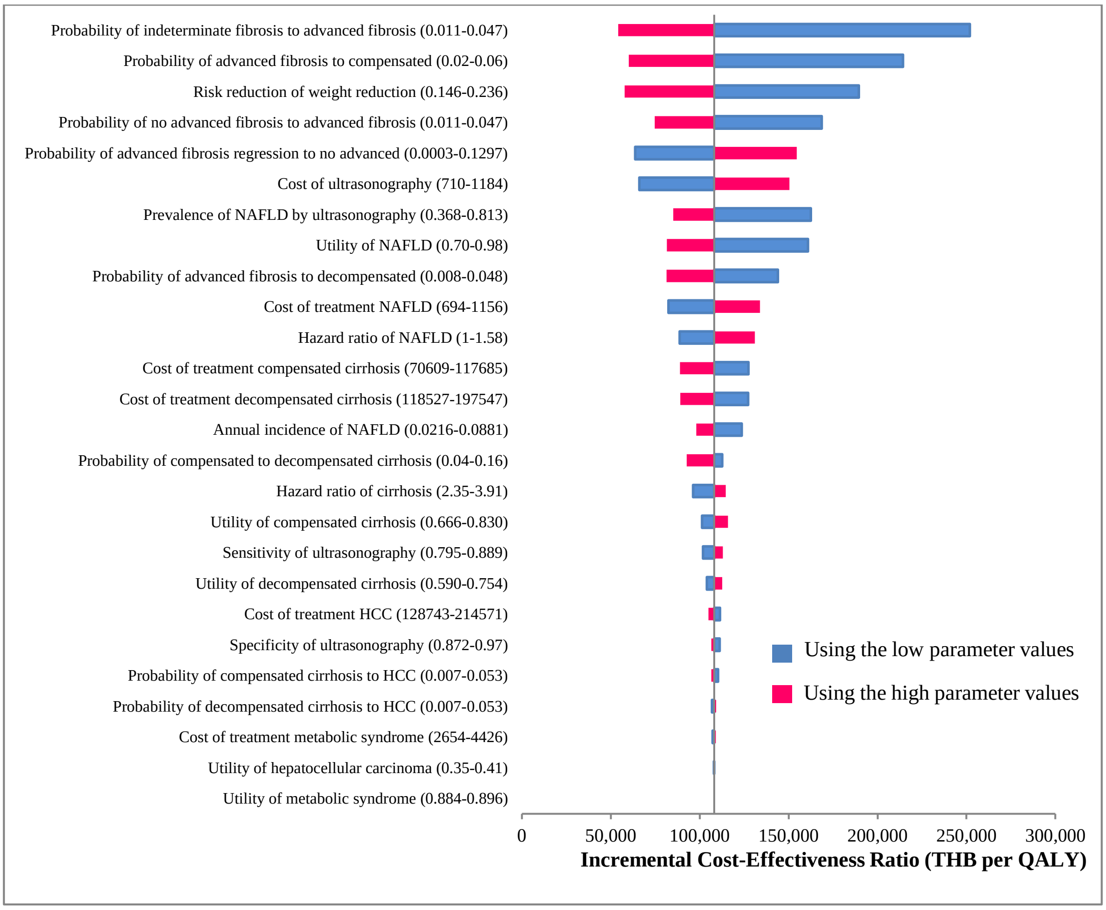


Figure 10. Tornado diagrams of start screening-age at 60 years

4.2.2 Probabilistic sensitivity analysis

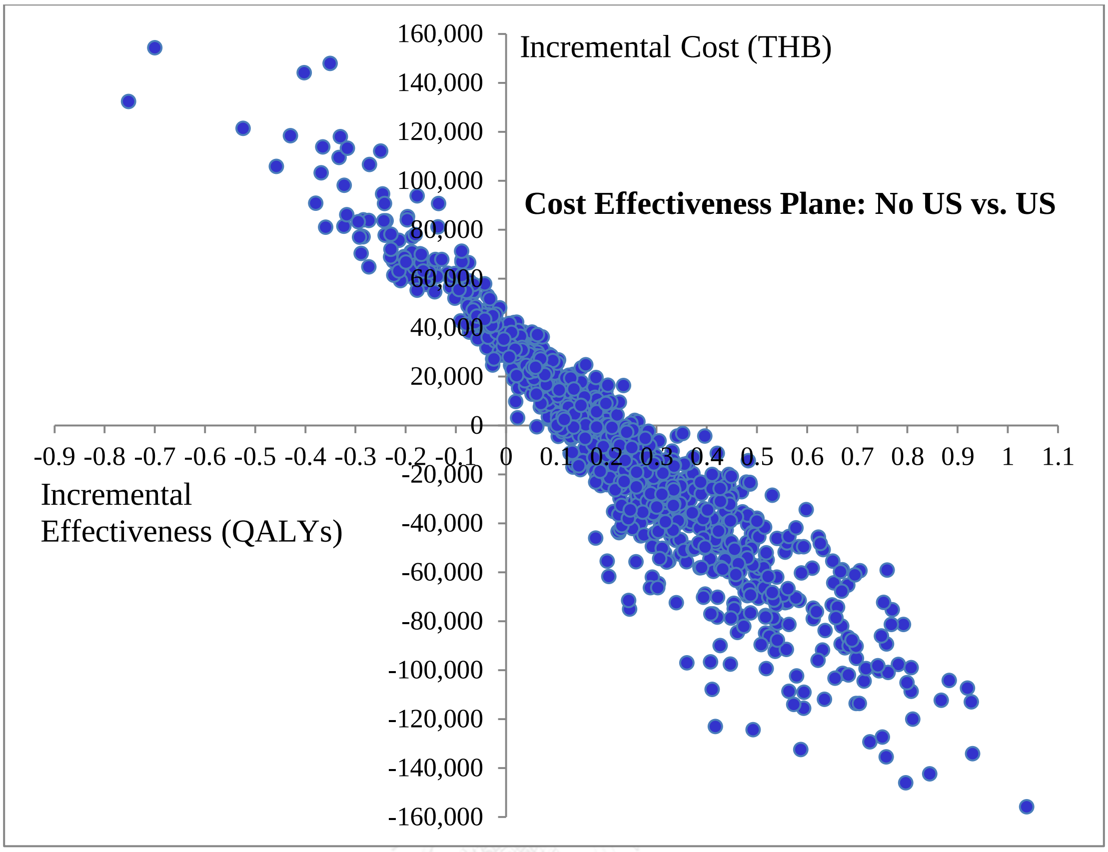
In addition, a probabilistic sensitivity analysis was conducted to simultaneously examine the effects of all parameters' uncertainties using a Monte

Carlo simulation performed by Microsoft Excel 2003. A Monte Carlo simulation was run for 1,000 sets of the simulation to give a range of values for total costs, outcomes, and ICERs.

Results of the PSA were presented as cost-effectiveness acceptability curve of ultrasonography screenings started at different ages (Figure 11-13). The expected net monetary benefit (NMB) was calculated for WTP of 160,000 THB threshold in Thailand in order to show the probability that ultrasonography is cost-effective for monetary values that a decision-maker might be willing to pay.

The result of 1,000 simulations of PSA for screening age of 40 years showed that ultrasonography screening plus weight reduction was estimated to have lower costs and higher effectiveness when compared to standard treatment [Figure 11 (a)]. Cost-effectiveness acceptability curve (CEAC) showed that at threshold value of 160,000 THB, ultrasonography screening plus weight reduction had 70% of being cost-effective when compared to no screening [Figure 11 (b)].

The PSA of screening age at 50 years and 60 years showed that ultrasonography screening plus weight reduction was estimated to have higher costs and higher effectiveness when compared to standard treatment [Figure 12 (a) and 13 (a)]. CEAC showed that at threshold value of 160,000 THB, ultrasonography screening plus weight reduction had 67% and 55% of being cost-effective when compared with no screening [Figure 12 (b) and 13 (b)].



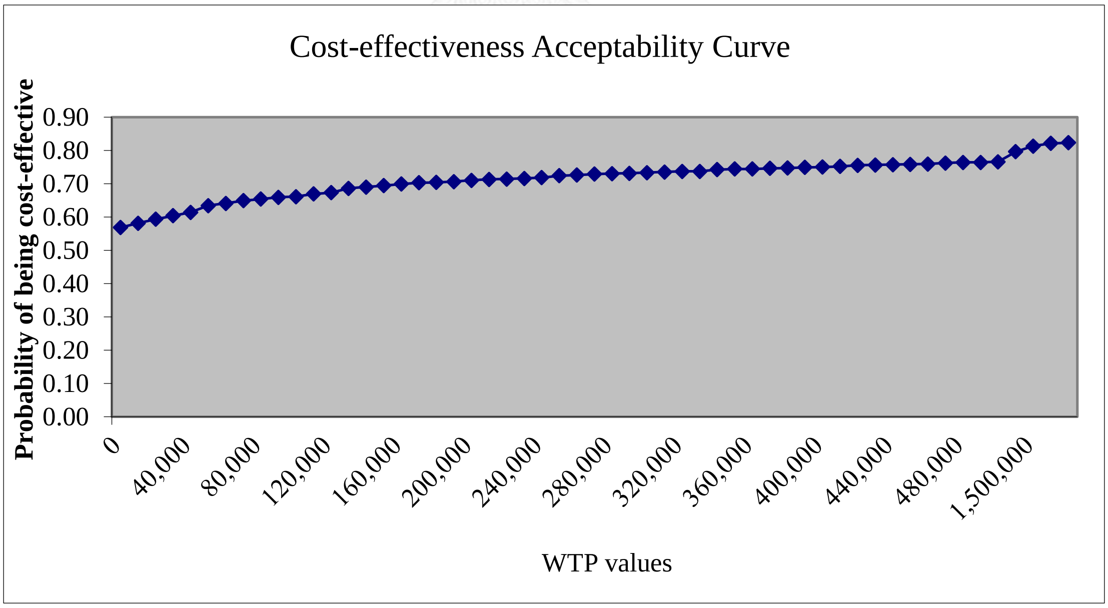
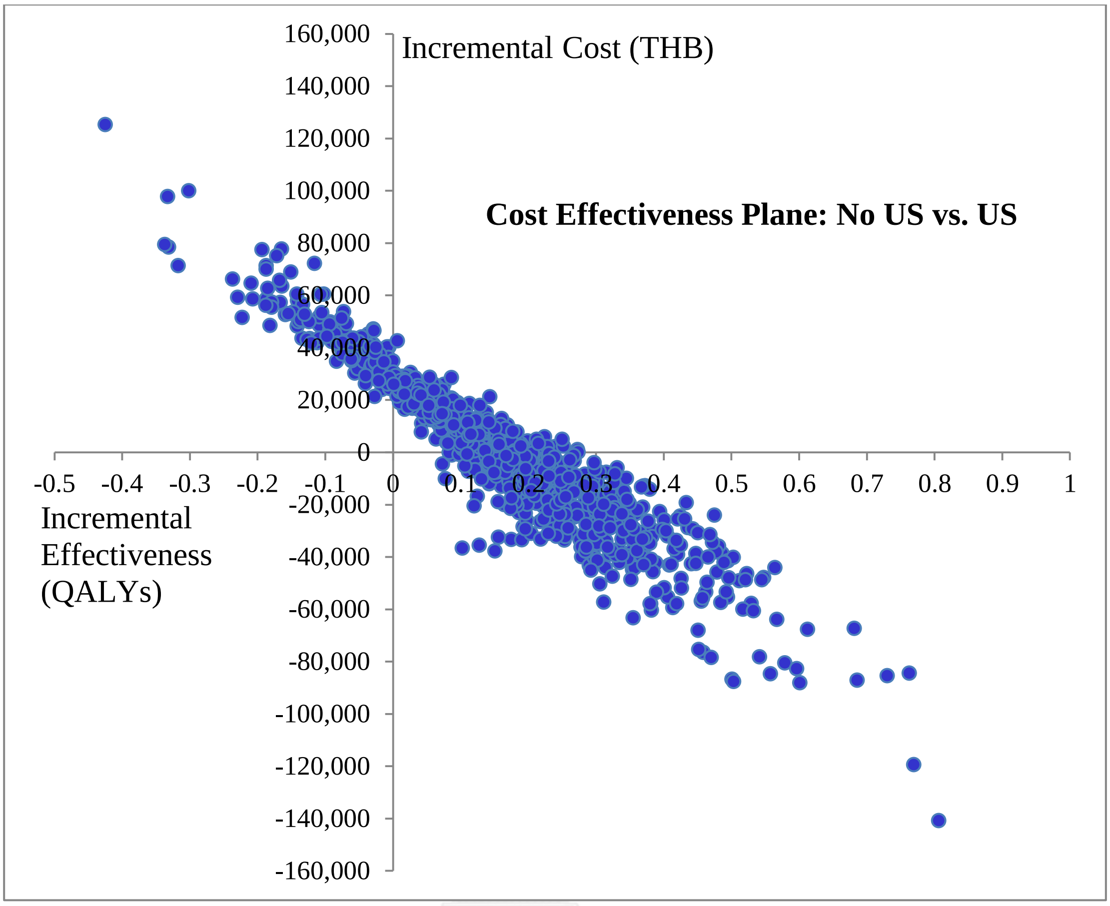


Figure 11. (a) Probabilistic sensitivity analysis, (b) Cost-effectiveness acceptability curve of start screening-age at 40 years



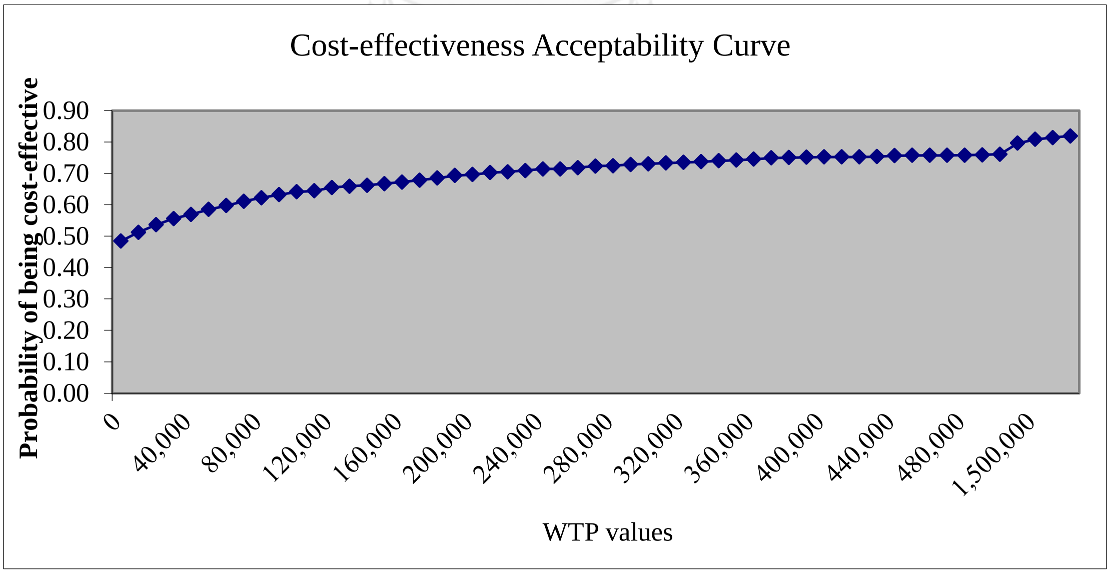
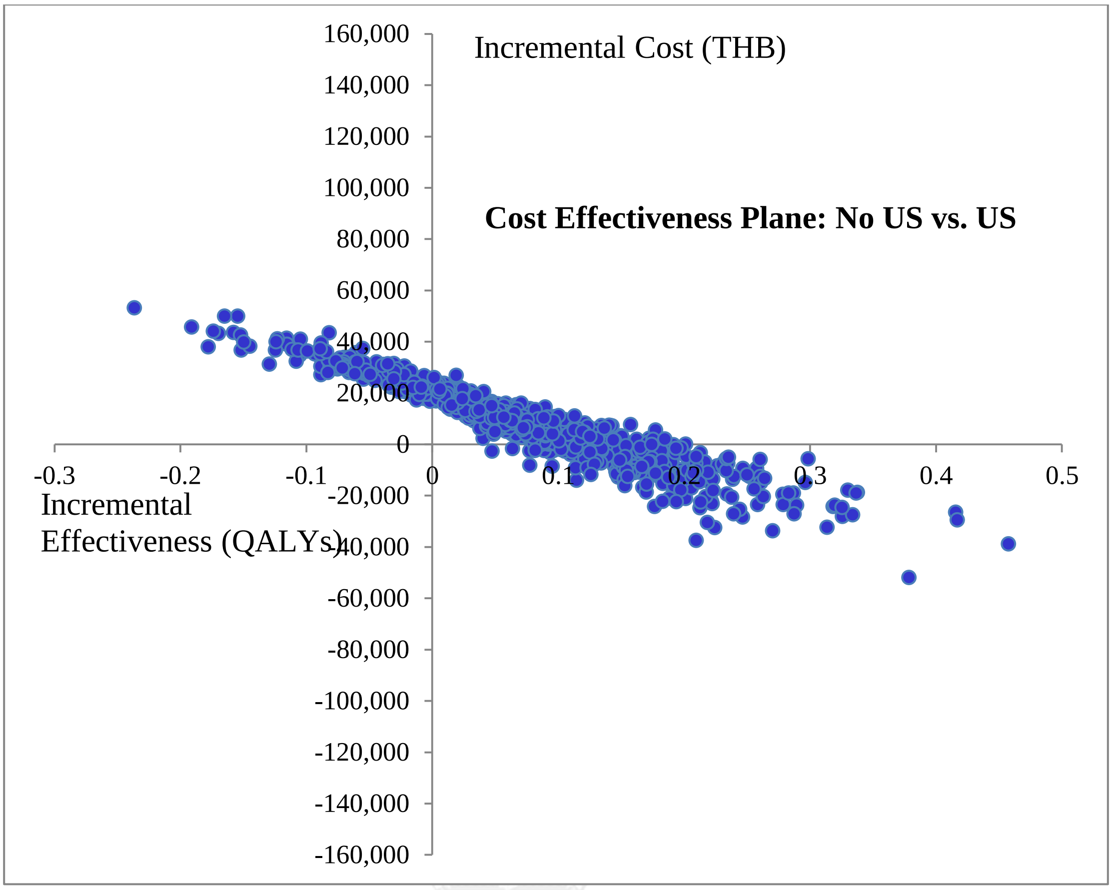


Figure 12. (a) Probabilistic sensitivity analysis, (b) Cost-effectiveness acceptability curve of start screening-age at 50 years



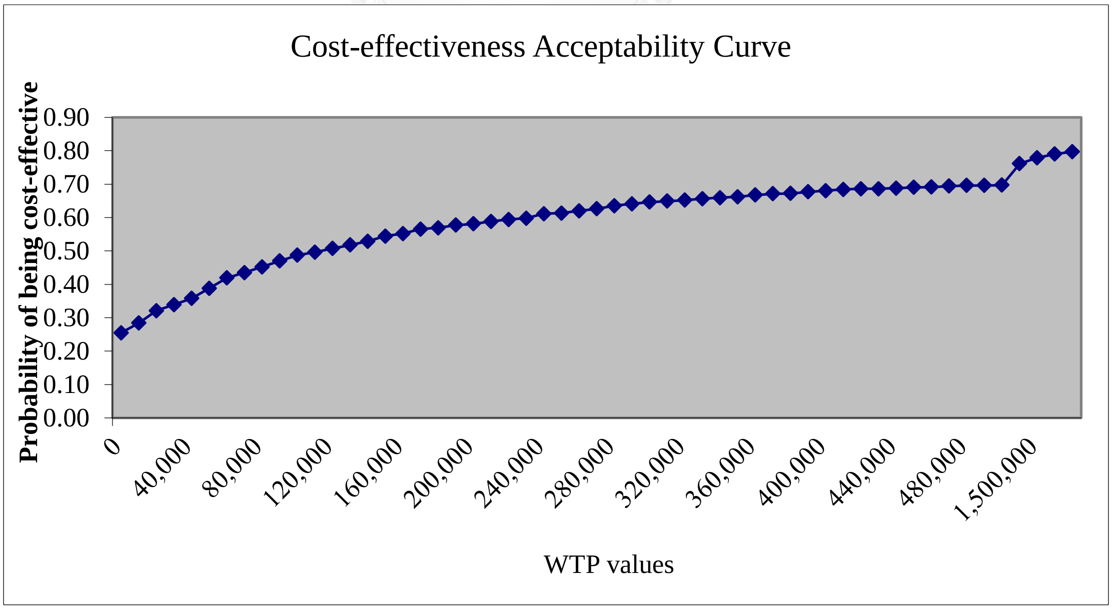


Figure 13. (a) Probabilistic sensitivity analysis, (b) Cost-effectiveness acceptability curve of start screening-age at 60 years

CHAPTER V

DISCUSSION

5.1 Discussion

Our findings demonstrated that ultrasonography screening with early intervention as weight reduction had clinical benefits of prevented cirrhosis, HCC, and death. This impact was greater when the starting ages of screening were at 40 and 50 years than at 60 years.

In addition, the screening with weight reduction is cost-effective for early detection of NAFLD in metabolic syndrome patients especially when the age of screening was less than 65 years when compared with no screening considering the local context on the willingness to pay value. Moreover, when the starting ages of screening were less than 47 years, the results showed cost-saving. For the base case of screening age at 50 years, ultrasonography screening with weight reduction was cost-effective at an ICER of 19,706 THB per QALY gained compared with no screening.

There was a study conducted on effectiveness and efficacy of hepatic screening programs to detect NAFLD in the periodic health check-ups (Nomura, Yano, Shinozaki, & Tagawa, 2004). This study was performed on 411 Japanese workers testing serum ALT, AST, and GGT. The diagnosis of NAFLD was based on ultrasonography findings. The prevalence of NAFLD was 12.3%. The diagnostic performance of ALT was far from excellent. The area under the curves was only 0.69 with the PPV 15-28%. The price of the program was estimated at 4 USD. The liver screening program resulted to be insufficient and BMI monitoring may provide a more suitable and inexpensive alternative. The effectiveness of the program is open to question considering the generally benign prognosis of the disease in the absence of any accompanying morbid conditions and the high price of the program.

In addition, it has been shown that patients with NAFLD (by ultrasonography and serum ALT) have more consultations with specialists and use more medications compared to subjects without NAFLD suggesting that screening and treatment might potentially cut down health care expenditure. The increased medication use in NAFLD was largely attributable to diabetes and lipid lowering medication (Baumeister et al., 2008).

On the other hand, our findings showed that ultrasonography screening with weight reduction was cost-effective in metabolic syndrome patients because the high risk group was more selective of screening and had higher incidence of NAFLD than general population. And even the treatment of NAFLD, after early diagnosis, was an increase in cost but it also prevented the higher costs complications as a result of disease progression.

The key factors of these good results included reduced progression to fibrosis with weight reduction intervention and inexpensive unit cost of ultrasonography. Moreover, small differences in effectiveness may lead to large cost savings at a population level when expensive outcomes such as liver cirrhosis and hepatic cancer are avoided.

Given the uncertainties inherent in the base case analysis, the robustness of the results was tested in sensitivity analyses. The series of one-way sensitivity analyses that tested for influential variables in the ultrasonography screening with intervention strategy were shown as Tornado diagrams of the different screening age.

For the start screening-age at 40 years, the most influential variables were the annual probability of no advanced fibrosis progression to advanced fibrosis, risk reduction of weight reduction, and the annual probability of indeterminate fibrosis progression to advanced fibrosis. For the start screening age of 50 years, the most influential variables were the annual probability of no advanced fibrosis progression to advanced fibrosis, the annual probability of advanced fibrosis progression to compensated cirrhosis, and risk reduction of weight reduction. However, sensitivity analysis indicated that ultrasonography screening with weight reduction remained cost-effective across the ranges tested for these probabilities, costs and utilities including other parameters, which were changed if the starting age of screening were at 40 and 50 years.

For the start screening-age at 60 years, there were six parameters that were sensitive and ICERs were not cost-effective in some range of these variables. These variables were the annual probability of indeterminate fibrosis progression to advanced fibrosis, the annual probability of advanced fibrosis progression to compensated cirrhosis, risk reduction of weight reduction, the annual probability of no advanced fibrosis progression to advanced fibrosis, the prevalence of NAFLD, and the utility of NAFLD, respectively.

If the starting age of screening was at 40 or 50 years, most of our findings had low sensitive and the probability of being cost-effective was quite high (70% and 67%, respectively). However, there were six parameters, which were highly sensitive in the starting age of screening of 60 years and the probability of being cost-effective was lower (55%). The findings can be used as one of the supportive evidence for decision makers.

Although ultrasonography had limitation in sensitivity, specificity, and accuracy especially in the rural area, However, for our sensitivity analyses, the sensitivity and specificity of ultrasonography were not sensitive in one way sensitivity analyses as shown in Tornado diagrams in start screening-age at 40, 50, and 60 years.

For this study, the prevalence of NAFLD in Thai metabolic syndrome patients with a mean age of 61 years from the primary data set of Siriraj Hospital, we used the starting age of ultrasonography screening at 50 years with prevention benefit as the base case. Because, in clinical practice, we should screen for the disease approximately 10 years before the disease occurs. Otherwise, it might be too late to detect and the intervention might be less effective. In addition, the results showed that the screening age of less than 47 years is cost saving. The ICER of ultrasonography screening in the start screening-age at 40 years was negative value (-30,913 THB per QALY gained). However, the program of screening plus intervention could be more effective only in the case of patients with good awareness and compliance while screening should not be too early at the active working period or start screening-age at 30 years or less. The intervention of weight reduction could be more efficient if the patients were concerned for their health state and had the knowledge about NAFLD. If patients, who received an early diagnosis of NAFLD, do not change their life style, the screening would be meaningless. It emphasized that the risk reduction of weight reduction was the important and sensitive parameter in any age of screening.

Patients who are at risk for disease progression and have low awareness in addition to the lack of a screening modality or reliable diagnostic test explains why the progressive development of NAFLD often goes unnoticed in many cases until cirrhosis were established (Ratziu et al., 2012). Until such screening tests are available, general practitioners and specialists, who meet patient population with a high prevalence of NAFLD, should be aware of risk factors for disease progression for early intervention.

To our knowledge, there are no studies related to the cost-effectiveness of ultrasonography screening for NAFLD in metabolic syndrome patients even though the disease is rapidly increasing burden worldwide including in Thailand. Our study is the first study that has determined the cost-effectiveness of ultrasonography screening with weight reduction as an intervention. The international guidelines by AASLD 2012 (Chalasani et al., 2012) argued that there should be screening for NAFLD, at least in the higher-risk patients who visited diabetes mellitus and obesity clinics. The knowledge of the diagnosis, natural history, and treatment of NAFLD were lack in now a day. Since liver biochemistries can be normal in NAFLD and NASH, they may not be good enough for screening tests whereas liver ultrasonography is more sensitive but it is more expensive. It is not advised in the present day due to uncertainty of diagnostic tests and treatment options, along with less of knowledge related to the long-term benefits and cost-effectiveness of the NAFLD screening.

Moreover, despite currently being the most common hepatic condition worldwide and likely increasing in occurrence, screening on NAFLD has not been recommended because the World Health Organization (WHO) has published a screening criteria, originally introduced by Wilson and Jungner (JMGJY, 1968) and expanded later (Andermann, Blancquaert, Beauchamp, & Déry, 2008). Although ultrasonography is a tool used as a screening tool with acceptable sensitivity and specificity in detecting fatty liver, the limitations of the technique include its low accuracy, inability to differentiate fibrosis from fatty liver, in-reproducibility and inability to exactly quantify fat accumulation (Lupşor-Platon et al., 2014).

Although, ultrasonography has some of limitations, however, for the more accurate of the model, we also considered the 4 results' probabilities: true positive, false positive, false negative, and true negative.

In addition, we adjusted the mortality rates of these patients by incorporating Thai age specific mortality rate (ASMR) to reflect Thai population (Health Information Group. Bureau of Health Policy and Strategy). Despite no available data of survival for NASH cirrhosis related HCC patients, we used the combination of the ASMR of NAFLD patients with Thailand data regarding prognosis of HCC from any causes (Leerapun et al., 2013).

Along with the lack of utility value of NAFLD, NASH cirrhosis, and NASH cirrhosis related HCC patients in Thailand, we applied 0.77 as the utility of Thai general population for this group of patients (Tongsiri & Cairns, 2011) because an NAFLD patient can live as a healthy person and we also adjusted the utility of chronic liver disease from other causes by using data from a systematic review of utilities of liver disease. However, the sensitivity analyses indicated that the ICER/QALY gained was not sensitive to changes by the utility data in our model.

For our results, it may not be generalized for screening NAFLD in the general population because the samples were focused only on the high risk group as metabolic syndrome. Although, the results showed that ultrasonography screening was cost-effective, the budget of this program was quite high because of the large number of metabolic syndrome population in Thailand. If we can develop other non-invasive tool as a scoring system to predict for very high risk group in the sub-particular group of metabolic syndrome population, it may decrease burden of government budget and be more effective.

In addition, the prevention program does not like the curative program, because if the screening was performed in this year the effectiveness may occur in the next 10 or 20 years. And many confounding factors may effect in this 10-20 years causing the effectiveness may be lower than the expectation from the model for example effect of weight reduction and its sustainability for more than 10 years.

5.2 Strength of study

This is the first economic evaluation of ultrasonography screening for NAFLD with weight reduction in the very high risk group. We believe that our findings are highly valid and contextually relevant due to three main reasons.

First, the hepatologist and radiologist specialists were involved throughout the process of conducting our cost-effectiveness analysis.

Second, we used as much local data as possible in our analysis. We directly collected the prevalence of NAFLD and the ratio of each degree of fibrosis state in Thai metabolic syndrome patients' data from Siriraj Hospital, which were further categorized into each age interval. This had made our results more reliable in Thai context. The primary data in Thai metabolic syndrome patients were from the most recent report and was quite higher than the previous reports. And all cost data were retrieved from reliable local sources i.e. hospital databases, National data from Ministry of Public Health (MOPH), Drugs and Medical Supplies MOPH, and the reference prices published by standard cost lists for health technology assessment, Health Intervention and Technology Assessment (HITAP), Ministry of Public Health

(Riewpaiboon, 2011). Moreover, the cost data of treatment of cirrhotic and HCC health state, we had used from previous studies in Thailand.

Third, the data of natural history of NAFLD and utilities used in the model were collected from the most recently systematic review, meta-analysis, or other large randomized controlled trials (RCT). Moreover, comprehensive literature search was added to identify data for probabilities, costs, and utilities, such that the model's estimates have incorporated the majority of data currently available for NAFLD.

5.3 Limitation of study

Our model has identified the paucity of data in many areas required for comprehensive economic modeling in NAFLD, and therefore our study has a number of limitations.

Although ultrasonography is the standard test for diagnosis of NAFLD because of easiness of the procedure, better accessibility, and relatively low cost, it had several limitations including low sensitivity to mild fatty change of the liver, operator dependency, subjective interpretation, and some limited ability to quantify the severity of fat infiltration, which have raised concerns. Within the NAFLD spectrum, fat can both occur separately and coexist with inflammation and/or fibrosis but ultrasonography could not identify the different between degree of fat, inflammation, and fibrosis. In this study, we used the NAFLD Fibrosis Score that is the widely investigated non-invasive tool to cross-sectional predicts advanced fibrosis and prognosis in NAFLD (Angulo et al., 2007) better than the degree of fat by ultrasonography in order to increase the accuracy of the model.

Second, even ultrasonography is the simple test in rural areas of Thailand, there is no radiologist or subspecialty in every community hospitals. If our results are considered for implementation in the national health policy, community hospitals should raise concerns due to human resource limitations. This screening program could disturb the queue for patients who need ultrasonography for early diagnosis and treatment in more serious condition. And the accuracy of the test, in case of ultrasonography performed by general practitioners, should also be considered as another issue.

Third, the risk reduction of weight reduction is the important parameter in the model. For this data, we used from the most recent study published in 2015 in Cuba because there was no data in Thailand and this is the first large prospective study conducted in real-world clinical practice that explores the potential benefit of a 12-month of lifestyle intervention on histologic NASH-related features. Patients with favorable risk factors (e.g. absence of diabetes or impaired fasting glucose, male sex, BMI less than 35, and few ballooned cells), modest weight losses produce important benefits on NAFLD activity score in patients with favorable risk factors. Conversely, a weight loss >10% is required to produce maximum beneficial effects in presence of unfavorable risk factors. Highest rates of resolution of steatohepatitis were seen in patients reaching weight losses >10%, and the benefits were consistent across all patient subgroups. Although these results are important, there needs to be a better understanding of the factors that influence changes in histologic outcomes, including weight loss, physical activity degree, and baseline factors. Although weight loss through lifestyle changes improved histologic features of NASH, only a small proportion of patients (25%) achieved resolution of steatohepatitis in the overall cohort. Unfortunately, <50% of patients achieve the necessary weight loss goal of >7% to 10% in the trial setting, and many have questioned the sustainability of this kind of intervention (Franz et al., 2007). The success of these interventions is attributable to the intensive and multidisciplinary support during the lifestyle modification period, but implementing these changes in clinical practice can be difficult (Wadden, Webb, Moran, & Bailer, 2012). We sought to overcome this obstacle by using a practical, low-cost intervention for overweight and obese NASH patients that was applicable in clinical practice. In our study, overall histologic changes at the end of intervention were modest and clearly related to modest changes in weight loss, a pattern that also was seen in other studies performed in the normal outpatient setting. Intensive dietary counseling or extensive exercise programs, for example, might be too expensive; however, there is consistent evidence that those who significantly reduce weight have subsequent health-related beneficial effects. Therefore, in the real world, intensive lifestyle counseling must be offered to all NASH patients, even though the applicability of these interventions depends largely on their availability and real-world adherence to these programs. Another important issue is not only whether larger weight losses produce greater improvements in NASH related features, but also whether larger weight losses are more or less well retained with subsequent changes in histologic outcomes. This study did not examine effects of maintenance of weight loss after 12 months and its relationship to histologic changes. Additional trials should focus on this important aspect. This findings support the current recommendation for weight loss using lifestyle modification as the first step in the management of patients with NASH with long term sustainability.

However, in our study, all patients were diagnosed of metabolic syndrome which is very high risk group and in the real world, the fewer ratios of the patients can achieve weight loss more than 10% and sustained weight reduction is very difficult in the long term. In our Markov model, we assumed that the risk reduction of weight reduction was the same in every year cycle but in the real world, most of patients may not sustain their weight and life style modification. And weight reduction depended on many confounding factors that could affect the regression of fibrosis in the long term. The effectiveness may less than the expectation in the model or its effects may reverse when they are discontinued.

Fourth, the indirect costs and intangible costs should be added on the cost calculation but we did not include these costs because of no available data in Thailand.

Last, lack of HRQoL data from people with NASH may introduce bias. The utility data were obtained from other countries and other chronic liver diseases. Despite feeling reasonable to assume that quality of life at end stage liver disease is similar regardless of the cause, the validity of this assumption has not been tested or brought into question. As a solution, we have included a wide range for utility estimates derived from meta-analysis and other literature; nevertheless, there is a need for preference-based quality of life studies in the NAFLD with using local data. Nevertheless, the sensitivity analyses indicated that the results were not sensitive to change by the utility data in our model.

Whereas our findings showed cost-effectiveness results in base case analysis with low sensitive, the policy maker should interpret and use as supportive evidence for their decisions. However, in general, most of the decision making cannot be made based solely on a cost-effectiveness analysis. Budget impact analysis should be done in order to estimate the total budget required that government should prepare when implementing this program. And weight reduction itself is sufficient for decrease of disease progression, for example, the government may have a campaign of weight reduction for all obese patients without ultrasonography screening for other benefits including controlled risk factors and prevent cardiovascular disease, of these the government may not pay more budgets for screening but they also get the same benefits. On the other hands, ultrasonography may be helpful for alarming to the patients when compared with metabolic syndrome patients who do not know that they have NAFLD or not. In this screening group, they may get more benefits from screening because the patient may have more awareness and more weight reduction than general metabolic syndrome patients.

Conversely, the screening program would be not efficient or very small effectiveness if metabolic syndrome patients lack of health awareness and do not modify their life style including lose their weight according to physician advice even NAFLD was diagnosed after screening by ultrasonography.

CHAPTER VI

CONCLUSIONS AND RECOMMENDATIONS

6.1 Conclusions

Non-alcoholic fatty liver disease is the condition that fat infiltrate in the liver without other causes of liver disease. It is an emerging problem worldwide. Metabolic syndrome is well known as a major risk factor for NAFLD. The prevalence of NAFLD in Thai metabolic syndrome population had increased up to 67 percent even in the non-obesity. NAFLD may lead to liver cirrhosis, HCC, liver failure, and death. NAFLD increases overall mortality when compared with general population.

Currently, liver biopsy is the gold standard for diagnosis and staging of NAFLD but since the procedure is highly invasive, it cannot be applied to population-based studies. For early diagnosis of NAFLD, there were many non-invasive modalities. Serum ALT alone cannot be used to rule out significant chronic liver disease in patients suspected with NAFLD because a large number of patients with NAFLD had normal ALT. Liver ultrasonography is the most common test used to evaluate the fatty change of the liver in clinical practice and population-based researches because of its non-invasiveness, inexpensiveness, and accessibility. However, it had several limitations including low sensitivity, operator dependency, subjective interpretations, and limited ability to quantify the severity of fat infiltration.

In metabolic syndrome patients who had early detection of NAFLD, there were many effective strategies to slow progression of the disease such as life style modification, control of risk factors, and specific drugs whereas the patients who had late detection will face with the serious and high cost complications.

Health Technology Assessment (HTA) has been used around the world including Asia Pacific region for health policy decision making. In Thailand, the ICER of 160,000 THB or less per 1 QALY gained considered as cost-effective. In the present day, the cost-effectiveness of ultrasonography screening especially in metabolic syndrome patients did not have been reported whereas the prevalence of NAFLD was rapidly increased and the cost of ultrasonography screening is quite cheap in Thailand. Health policy makers may consider this information for their decision making of including ultrasonography screening in health-benefit package if this study proves the high probability of cost-effective.

This study aimed to evaluate the cost-effectiveness analysis and cost-utility analysis of ultrasonography screening with weight reduction in metabolic syndrome patients. It used primary data from a descriptive cross-sectional study that reported the prevalence of NAFLD in metabolic syndrome patients at internal medicine out-patient department of Siriraj Hospital between November 2011 and October 2013. The NAFLD Fibrosis Score was used to distinguish between advanced fibrosis and no advanced fibrosis patients because the presence of advanced fibrosis is strong predictors of worse hepatic outcomes than the degree of fat.

A hybrid model consisting of decision tree and Markov models was used to estimate relevant costs and health outcomes compared between screening with weight reduction and no screening. This model was classified into 4 subgroups; true positive, false positive, false negative, and true negative due to limitations of ultrasonography in order to improve the accuracy of the model. Our model was developed to mimic the natural history of NAFLD. The lifetime horizon was chosen in this study since NAFLD could be a life-long condition. Prevalence of NAFLD, sensitivity, specificity of ultrasonography, annual transitional probabilities, costs, and utilities were filled in the Markov models as input parameters. These parameters were obtained from a data set of Siriraj Hospital and systematic literature reviews (local and international publications) which were the most applicable with Thai population.

The all costs data were obtained from data in Thailand. All costs were converted in 2014 THB and using the consumer price index (CPI). All future costs were discounted at a rate of 3%. These costs were retrieved using the reference prices published by standard cost lists of Thailand HTA. The health outcome consisted of clinical outcomes such as number of cases prevented from cirrhosis, HCC, death and additional costs per 1 LY saved and additional costs per 1 QALY gained.

All data were analyzed by using the cost-effectiveness analysis and cost-utility analysis. The total costs and the effectiveness of ultrasonography screening with weight reduction and no screening were compared in terms of ICER. We used the start screening-age at 50 years to be the base case for prevention benefit. In clinical practice, we should screen for the disease approximately 10 years before the disease occurs. However, we also analyzed the ICER and sensitivity analyses of start screening-age at 40 and 60 years for comparing with the base case.

The clinical-related health outcomes for the base case of 50 years showed that at ten years after screening and weight reduction, the number of cases prevented from cirrhosis, HCC, and death were 1094.0, 53.2, and 129.5 per 100,000 screening, respectively. At twenty years after screening and intervention, the number of cases prevented from cirrhosis, HCC, and death were 1538.7, 101.8, and 874.7 per 100,000 screening, respectively. For patients, who had received first ultrasonography screening with weight reduction at 40 years, were better clinical health outcomes than start screening-age at 60 years. And our base-case analysis, ultrasonography screening with weight reduction had an incremental cost per QALY gained of 19,706 THB/QALY gained when compared to no screening. Moreover, the ICER showed cost-saving in start screening-age before 47 years and the ICER showed cost-effective in any screening age before 65 years.

For the sensitivity analyses, the most influential variables for the starting screening-age at the base case of 50 years were the annual probability of no advanced fibrosis progression to advanced fibrosis, the annual probability of advanced fibrosis progression to compensated cirrhosis, and risk reduction of weight reduction. Nevertheless, according to the cut-off cost-effective ICER of 160,000 THB, sensitivity analysis indicated that ultrasonography screening with weight reduction remained cost-effective for these probabilities, costs, and utilities even others parameters were changed. For the start screening-age at 60 years, the annual probability of indeterminate fibrosis progression to advanced fibrosis, the annual probability of advanced fibrosis progression to compensated cirrhosis, and risk reduction of weight reduction, the prevalence of NAFLD, and the utility of NAFLD were sensitive and ICERs were not cost-effective in some ranges of these variables. The results of probabilistic sensitivity analysis of start screening-age at 40, 50, and 60 years showed that ultrasonography screening with weight reduction were 70%, 67%, and 55% of being cost-effective when compared to no screening. Although ultrasonography had limitation in sensitivity, specificity, and accuracy, for our sensitivity analyses, the sensitivity and specificity of ultrasonography were not sensitive in one way sensitivity analyses of start screening-age at 40, 50, and 60 years.

To our knowledge, this study is the first study that has determined the cost-effectiveness of ultrasonography screening for NAFLD with weight reduction in metabolic syndrome patients. It has contributed new knowledge that could be implemented as a policy in clinical practice and national level. This recommendation for clinicians and policy makers was based on cost utility analysis. The decision of screening with weight reduction was cost-effective in metabolic syndrome patients in Thailand with low sensitive. The high risk patients should receive the appropriate screening. These patients should be early diagnosed and treated to prevent further higher costs and more serious complications such as cirrhosis, HCC, and death. Policy makers may consider our findings as part of information for their decision making. Our study had many of strengths. First, the hepatologists and radiologists involved in the process of conducting cost-effectiveness analysis. Second, we used as much local data as possible and all cost data were acquired from reliable local sources and the reference prices published by standard cost lists for Thailand HTA guideline. Third, the data of natural history of NAFLD and utilities used in the model were collected from the most recently systematic review, meta-analysis, or other large RCT.

This study had a number of limitations. First, ultrasonography had limitations including low sensitivity, operator dependency, subjective interpretation, and some limited ability to quantify the severity of fat infiltration. Second, there is no radiologist in every community hospitals. If our results are considered for implementation in the national health policy, community hospitals should raise concerns due to human resource limitations. And the accuracy of the test should also be considered. Third, risk reduction of weight reduction is the important parameter in the model. We used data from the most recent study in Cuba because there was no data in Thailand. In our study, all metabolic syndrome patients were very high risk and in the real world, the fewer ratios of the patients can achieve weight loss more than 10% with sustainability in the long term. These analyses did not examine effects of maintenance of weight loss after 12 months and its relationship to histologic changes. In our Markov model, we assumed that the risk reduction of weight reduction was the same in every year cycle but in the real world, most of patients may not sustain their weight reduction for the long period. Fourth, the indirect costs and intangible costs for the patient perspective should be added on the cost calculation but we did not include these costs because of no available data in Thailand. Last, lack of HRQoL data specifically derived from NAFLD patients because the utility were obtained from other countries and other chronic liver diseases.

Whereas our findings showed cost-effectiveness results in base case analysis with low sensitive, the policy maker should interpret and use as supportive information for their decisions. However, the decision makers should not only be made decisions based on a cost-effectiveness analysis. Budget impact analysis should also be done for evaluate the total budget required that government should prepare when implementing this program. In addition, the screening program would be not efficient if metabolic syndrome patients lack of health awareness and do not change life style according to physician advice.

6.2 Recommendations and policy implications

1. Early ultrasonography screening for Non-alcoholic fatty liver disease with weight reduction in metabolic syndrome patients is possibly a cost-effective screening in Thailand

2. Policy makers may consider this information for their decision making of including ultrasonography screening in health-benefit package process due to the high probability of cost-effective.
3. Relevant information including budget impact analysis, public health impact and human resource limitation should be considered as part of final decision making.

6.3 Suggestion for future study

1. For our results, although, the results determined ultrasonography screening was cost-effective, the budget of this program was quite high because of the large number of metabolic syndrome in Thailand. If we can develop a scoring system to predict and select to screen ultrasonography only in the sub-particular group, it may decrease burden of government budget and be more cost-effective.

2. For the risk reduction of weight reduction parameter, we used data from the recent study in Cuba because there was no available data in Thailand. If we conduct the study in long term effectiveness and sustainability of weight reduction in Thailand, it will be useful for the the model accuracy.

3. In this study, the indirect costs and intangible costs should be added on the cost calculation but we did not include these costs because of no available data in Thailand. If we conduct the study related with indirect cost and intangible cost calculation of Thai patients, it will be useful and appropriate with Thailand context.

4. Because we lack of HRQoL data specifically derived from NAFLD, we used the utility data from other countries and other chronic liver diseases. However, there is a need for preference-based quality of life studies in the NAFLD population with using local data in Thailand.

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