COST UTILITY ANALYSIS OF ENDOSCOPIC BILIARY STENT IN UNRESECTABLE HILAR CHOLANGIOCARCINOMA: DECISION ANALYTIC MODELING APPROACH

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การวิเคราะห์ต้นทุนอรรถประโยชน์ของการใส่ท่อระบายน้ำดีผ่านกล้องในผู้ป่วยมะเร็งท่อน้ำดีขั้วตับที่ไม่สามารถผ่าตัดได้: วิเคราะห์โดยใช้แบบจำลองการตัดสินใจ

นาย อภิชาติ แสงจันทร์

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต

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Thesis Title	COST UTILITY ANALYSIS OF ENDOSCOPIC BILIARY STENT IN UNRESECTABLE HILAR CHOLANGIOCARCINOMA: DECISION ANALYTIC MODELING APPROACH
By	Mr. Apichat Sangchan
Field of Study	Health Economics and Health Care Management
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อภิชาติ แสงจันทร์ : การวิเคราะห์ต้นทุนอรรถประโยชน์ของการใส่ท่อระบายน้ำดีผ่านกล้องในผู้ป่วยมะเร็งท่อน้ำดีขั้วตับที่ไม่สามารถผ่าตัดได้ : วิเคราะห์โดยใช้แบบจำลองการตัดสินใจ (COST UTILITY ANALYSIS OF ENDOSCOPIC BILIARY STENT IN UNRESECTABLE HILAR CHOLANGIOCARCINOMA: DECISION ANALYTIC MODELING APPROACH) อ.ที่ปรึกษาวิทยานิพนธ์หลัก : รศ.ดร. ศิริเพ็ญ ศุภกาญจนกันติ, อ.ที่ปรึกษาวิทยานิพนธ์ร่วม : รศ.ดร. ณธร ชัยญาคุณาพฤกษ์, 81 หน้า.

การศึกษานี้มีวัตถุประสงค์เพื่อวิเคราะห์ต้นทุนอรรถประโยชน์ของการใส่ท่อระบายน้ำดีโลหะและท่อระบายพลาสติกผ่านกล้องในผู้ป่วยมะเร็งท่อน้ำดีที่ขั้วตับที่ไม่สามารถผ่าตัดได้

การศึกษานี้ใช้แบบจำลองการตัดสินใจมาร์คอฟในการคำนวณค่าใช้จ่ายและจำนวนปีสุขภาวะในการรักษาโรคมะเร็งท่อน้ำดีขั้วตับที่ไม่สามารถผ่าตัดได้ ข้อมูลต้นทุนในมุมมองของผู้ให้บริการมาจากค่ารักษาผู้ป่วยในโรงพยาบาลศรีนครินทร์ในปีพ.ศ. 2551-2553 ข้อมูลอรรถประโยชน์มาจากผู้ป่วยโรงพยาบาลศรีนครินทร์ ข้อมูลความน่าจะเป็นของการเสียชีวิตของผู้ป่วยที่ใส่ท่อระบายน้ำดีและประสิทธิผลของการใส่ท่อระบายน้ำดีผ่านกล้องมาจากการวิจัยแบบทดลองโดยมีการสุ่มและการควบคุมที่กำลังดำเนินการศึกษาในโรงพยาบาลศรีนครินทร์ ข้อมูลความน่าจะเป็นของการเสียชีวิตและประสิทธิผลของการใส่ท่อระบายน้ำดีผ่านผิวหนังมาจากการทบทวนวรรณกรรม วิเคราะห์ผลค่าอ้างอิงและวิเคราะห์ความไวแบบอาศัยความน่าจะเป็นและนำเสนอเป็นอัตราส่วนต้นทุนส่วนเพิ่มต่อ 1 ปีสุขภาวะ

จากผลการวิเคราะห์ค่าอ้างอิงพบว่าท่อระบายน้ำดีโลหะมีประสิทธิผลดีกว่าแต่มีต้นทุนการรักษาโรคตลอดชีวิตผู้ป่วยสูงกว่าท่อพลาสติกโดยมีอัตราส่วนต้นทุนส่วนเพิ่มต่อ 1 ปีสุขภาวะเท่ากับ 192,584 บาท จากผลการวิเคราะห์ความไวโดยใช้ความน่าจะเป็นที่นำเสนอในรูปแสดงระดับความคุ้มค่าที่ยอมรับได้พบว่าที่ระดับความเต็มใจที่จะจ่าย 1 เท่า (158,000 บาท)และ 3 เท่า (474,000 บาท) ของผลิตภัณฑ์มวลรวมภายในประเทศต่อหัวประชากรในปีพ.ศ. 2553 ความน่าจะเป็นที่ท่อระบายโลหะจะคุ้มค่าเมื่อเปรียบเทียบกับท่อพลาสติกเท่ากับร้อยละ 26 และ 99.9 โดยสรุปภายใต้ข้อสมมติของแบบจำลองและข้อจำกัดของการศึกษาพบว่าที่ระดับความเต็มใจที่จะจ่ายระหว่าง 1 ถึง 3 เท่าของผลิตภัณฑ์มวลรวมภายในประเทศต่อหัวประชากรในปีพ.ศ. 2553 การใส่ท่อระบายน้ำดีโลหะผ่านกล้องมีความคุ้มค่าเมื่อเปรียบเทียบกับท่อพลาสติกในผู้ป่วยมะเร็งท่อน้ำดีที่ผ่าตัดไม่ได้ในโรงพยาบาลระดับตติยภูมิ

สาขาวิชา เศรษฐศาสตร์สาธารณสุขและการจัดการบริการสุขภาพ	ลายมือชื่อนิสิต...
การศึกษา 2553	ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์หลัก..................................
	ลายมือชื่อ อ.ที่ปรึกษาวิทยานิพนธ์ร่วม................................

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APICHAT SANGCHAN : COST UTILITY ANALYSIS OF ENDOSCOPIC BILIARY STENT IN UNRESECTABLE HILAR CHOLANGIOCARCINOMA : DECISION ANALYTIC MODELING APPROACH. ADVISOR : ASSOC. PROF. SIRIPEN SUPAKANKUNTI, Ph.D., CO-ADVISOR : ASSOC. PROF. NATHORN CHAIYAKUNAPRUK, Pharm.D., Ph.D., 81 pp.

The objective of this study was to evaluate the cost-utility of metal and plastic stent endoscopic biliary drainage in unresectable hilar cholangiocarcinoma (CCA) patients.

Markov model was used to evaluate cost and quality-adjused life year (QALY) of endoscopic biliary drainage in unresectable hilar CCA. Costs of treatment were calculated from hospital charges at Srinagarind hospital in year 2008-2010 using health care provider perspective. Utilities of hilar CCA patients at Srinagarind hospital were used in this model. Transition probability of death in patients with endoscopic biliary drainage and effectiveness of biliary stent were retrieved from ongoing randomized controlled trial at Srinagarind hospital. Transition probability of death in patients with percutaneous transhepatic biliary drainage (PTBD) and effectiveness of PTBD were retrieved from literature review. Base case analyses and sensitivity analyses were performed and presented in terms of incremental cost per QALY gained.

Under the baseline assumptions, metal stent is more effective but more expensive than plastic stent. An incremental cost per additional QALY gained is 192,584 baht. From probability sensitivity analysis presented in the form of cost-effectiveness acceptability curve, at the willing to pay threshold or decision threshold of 1 time GDP per capita (158,000 baht) and 3 times GDP per capita (474,000 baht) in year 2010, the probability of metal stent being cost-effective are 26% and 99.9% respectively. In conclusion, according to the model assumptions and the limitations of the study, endoscopic biliary drainage using metal stent is cost-effective compared to plastic stent at the willingness to pay threshold between one and three times GDP per capita in tertiary care hospital in Thailand in year 2010.

Field of Study: Health Economics and health Care Management. Student's Signature……….................

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LIST OF ABBREVIATIONS

CBA	Cost-Benefit Analysis
CBD	Common Bile Duct
CCA	Cholangiocarcinoma
CEA	Cost-Effective Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CUA	Cost-Utility Analysis
DSA	Deterministic Sensitivity Analysis
EBD	Endoscopic Biliary Drainage
EQ-5D	EuroQoL 5 Dimensions
GDP	Gross Domestic Product
HUI	Health Utility Index
ICD-9CM	International Classification of Disease 9th revision Clinical Modification
ICD-10	International statistical Classification of Disease and related health problems 10th revision
ITT	Intention to Treat
PostEBD	Post Endoscopic Biliary Drainage
PostPTBD	Post Percutaneous Transhepatic Biliary Drainage
PSA	Probabilistic Sensitivity Analysis
PTBD	Percutaneous Transhepatic Biliary Drainage
QALY	Quality Adjusted Life Year
QWB	Quality of Well-Being
RCT	Randomized Controlled Trial
SF-6D	Short Form 6D
SG	Standard Gamble
TP	Transition Probability
TTO	Time trade-Off
VAS	Visual Analogue Scale

CHAPTER I

INTRODUCTION

1.1 Problems and Its Significance

Cholangiocarcinoma (CCA) is one of the most two common types of primary liver cancer. CCA originates from epithelial lining of biliary tree or bile duct, whereas hepatocellular carcinoma derives from liver cell or hepatocytes. CCA is more common than HCC in the Northeast region of Thailand. The incidence of CCA in this region of Thailand is highest in the world. The incidence per 100,000 in men and women in KhonKaen province was 84.6 and 36.8 respectively.(Parkin, Ohshima, Srivatanakul, and Vatanasapt, 1993)

Tumor at liver hilum can obstruct bile flow and cause symptoms related to bile duct obstruction such as jaundice, pruritus, clay-color stool and dark urine. Some patients may have life threatening complication such as ascending cholangitis.

The treatment of choice of hilar CCA is surgical resection because it can prolong patients' survival. The overall one-year survival of patients with resectable tumor is 68% versus 31% in palliative treatment group.(Launois, Reding, Lebeau, and Buard, 2000) However, only one third of tumors can be removed successfully. Although there is no survival benefit, patients with inoperable tumor managed by palliative drainage therapy will have symptomatic improvement i.e. itching and jaundice. At present, the commonly used palliative drainage techniques are endoscopic biliary drainage, percutaneous transhepatic biliary drainage and bypass surgery.(Singhal, van Gulik, and Gouma, 2005)

Endoscopic biliary drainage using biliary stent in patients with unresectable hilar tumor is as effective as surgical bypass and has fewer early complications compared to surgical bypass.(Smith, Dowsett, Russell, Hatfield, and Cotton, 1994) The target of drainage volume is to drain at least 25% of the liver volume to achieve the goal of palliative drainage e.g. symptom relief, improvement in biochemical parameters and health related quality of life improvement. (Abraham, Barkun, and Barkun, 2002; Dowsett et al., 1989)

The commonly used stents in endoscopic biliary drainage are tubular plastic stent and open-mesh metal stent. Plastic stent is cheaper than metal stent but the weak point of plastic stent is its relatively high occlusion rate, which occurred at a median interval of 3 months after insertion. (De Palma, Galloro, Siciliano, Iovino, and Catanzano, 2001). The other disadvantages of plastic stent are the close tubular structure which might obstruct side branch drainage and its rigidity with a tendency to migrate. (Perdue et al., 2008) In contrast, metal stent has many theoretical advantages: 1) the mesh structure allows side branch drainage and, 2) the larger diameter might provides better drainage and longer patency comparing to plastic stent.(Cheng et al., 2002; De Palma et al., 2003; Freeman and Overby, 2003) In addition, patients with metal stent insertion have substantially lower rate of complication, number of re-interventions compare to patients in plastic stent group.(Perdue, et al., 2008)

Cost-effectiveness of plastic and metal stent in unresectable hilar CCA depends on several factors as follows

1. Effectiveness of biliary stents: Successful drainage rate, patency time of stent, complication after stent insertion;
2. Patient's survival;
3. Cost of stent, endoscopic procedure and its complication.

Because of the previous reasons, it is difficult to conduct single randomized controlled trial to answer this question; in addition, at present, there is no study comparing cost-effectiveness between plastic and metal stent in unresectable hilar CCA. Therefore, we conduct the study to evaluate the cost-utility of metal and plastic endoscopic biliary stent drainage in unresectable complex hilar CCA using decisional analytic modeling approach.

1.2 Research Question

Is endoscopic metal stent drainage cost effective compared with plastic stent in patients with unresectable complex hilar cholangiocarcinoma at Srinagarind Hospital?

1.3 Objectives of the Study

1.3.1 General objective

To evaluate the cost effectiveness of endoscopic metal stent drainage compared with plastic stent in patients with unresectable complex hilar CCA at Srinigarind hospital.

1.3.2 Specific objectives

1.3.2.1 To measure the total cost of treatment by endoscopic biliary drainage using plastic and metal stent in unresectable complex hilar CCA at Srinagarind hospital.

1.3.2.2 To determine the effectiveness of endoscopic biliary drainage using plastic and metal stent in unresectable complex hilar CCA at Srinagarind hospital.

1.3.2.3 To measure the additional cost per additional quality adjusted life year (QALY) gained from endoscopic metal stent drainage compared with plastic stent in unresectable complex hilar CCA at Srinagarind hospital.

1.4 Scope of the Study

This research studied the cost utility of endoscopic biliary drainage at Srinagarind Hospital. The effectiveness of endoscopic stent drainage, cost of treatment and utility of each disease stage were based on data from Srinagarind hospital. Effectiveness of percutaneous transhepatic biliary drainage was reviewed from literature.

1.5 Hypothesis

Endoscopic metal stent is cost effective compared with plastic stent in patients with unresectable complex hilar cholangiocarcinoma at Srinagarind Hospital.

1.6 Benefit of the Study

This study used decision analytic model, Markov model, to measure the incremental cost per additional QALY gained between metal and plastic stent in unresectable hilar CCA. The result of this study can provide the evidences to support the decision making of the physicians in palliative care of patients with unresectable complex hilar CCA. In addition, policy maker may use these evidences to support the decision to provide metal stent for the palliative endoscopic drainage of unresectable complex hilar CCA patients in Universal Coverage Scheme and Social Security Scheme.

CHAPTER II

LITERATURE REVIEW

2.1 Cholangiocarcinoma

Primary liver cancer is the leading cancer in Thai male. The incidence of liver cancer in Thai male was 38.6/100,000 population in year 2003. For female, incidence of this disease was in the third rank, ASR 14.6/100,000 population, in the same year. (Khuhaprema, 2010) Cholangiocarcinoma (CCA) is one of two major type of primary liver cancer, CCA and hepatocellular carcinoma. CCA originates from epithelial lining of biliary tree or bile duct. (de Groen, Gores, LaRusso, Gunderson, and Nagorney, 1999; Kanno et al., 2011) In general, hepatocellular carcinoma is more common than CCA, but in Northeast region of Thailand CCA is more common. (Figure 2.1) Furthermore, incidence of CCA in this region of Thailand is highest in the world. The incidences of CCA in men and women in KhonKaen province were 84.6 and 36.8 per 100,000 population respectively. (Parkin, et al., 1993)

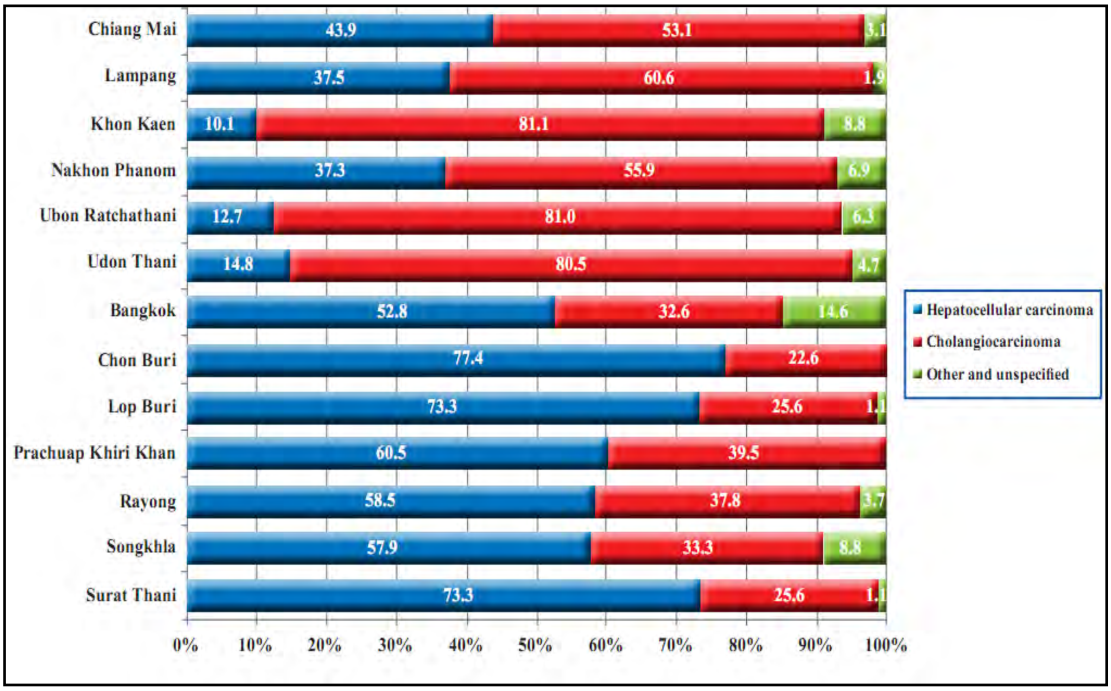


Figure 2.1 Type of liver cancer in Thai male, 2001-2003. (Khuhaprema, 2010)

In western countries, the most common risk factor of CCA is primary sclerosing cholangitis (PSC) and the other risk factors are intrahepatic biliary stone, congenital biliary cystic diseases, liver cirrhosis, viral infection and chemical agent i.e. thorium dioxide. (Aljiffry et al., 2009) In contrast, risk factor of CCA in Thailand is liver fluke, *Opisthorchis viverini*. (Sripa and Pairojkul, 2008) People acquire this parasite by eating raw fresh water fish infected by metacercariae of the fluke. Accordingly, CCA results from chronic inflammation of bile duct induced by mechanical injury and fluke metabolic product. (Sripa et al., 2007)

CCA was classified into two types according to its location.

1. Intrahepatic CCA or peripheral type CCA originated from intrahepatic bile duct which is located in liver parenchyma.
2. Extrahepatic CCA originated from bile duct within hepatoduodenal ligament. Extrahepatic CCA is subdivided into hilar and distal CCA. (Aljiffry, Walsh, and Molinari, 2009) Hilar CCA is located in hepatic hilum or hepatic duct bifurcation. It is also known as Klatskin tumor.

Tumor at liver hilum can obstruct bile flow and cause symptoms related to bile duct obstruction such as jaundice, itching, clay-color stool and dark urine. Some patients may have life threatening complication, specifically ascending cholangitis, from bacterial infection in the obstructed bile duct segment. (Sripa and Pairojkul, 2008)

The treatment of choice of hilar CCA is surgical resection because it could prolong survival of the patients. However, only one third of the patients had successful operation. The overall one-year survival of patients with resectable tumor is higher than palliative treatment group, 68% versus 31%. (Launois, et al., 2000)

The following criteria are the criteria for unresectable tumor. (Jarnagin et al., 2001)

Patients factors
- -Medical unfit
- -Cirrhosis

Local factors

-Bismuth type IV tumor. (Figure 2.2)

-Encasement or occlusion of main portal vein (PV) proximal to its bifurcation

-Atrophy of 1 hepatic lobe with contralateral PV branch encasement or occlusion

-Atrophy of 1 hepatic lobe with contralateral sectional bile ducts involvement

-Unilateral tumor extension to sectional bile ducts with contralateral PV branch encasement or occlusion

-Metastases to lymph node groups beyond the hepatoduodenal ligament

-Lung, liver or peritoneal metastasis

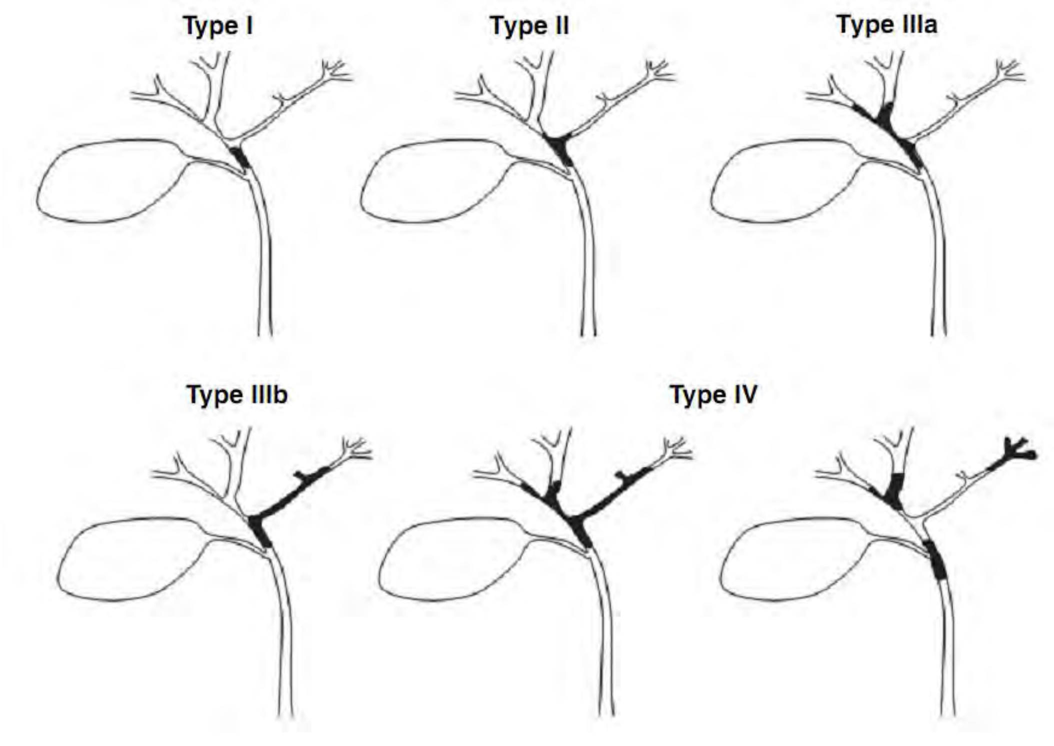


Figure 2.2 Bismuth classification of hilar CCA. Type I affects the common hepatic duct. Type II affects the confluence of the right and left hepatic ducts. Type IIIa and IIIb affects the confluence and right hepatic duct or left hepatic duct respectively. Type IV involves secondary branch of right and left hepatic duct or multifocal CCA. (Malhi and Gores, 2006)

In general, the average life expectancy of advanced stage hilar CCA is less than 1 year; hence, the aim of treatment is to relieve symptom of biliary tract obstruction and improve quality of life of the patient. Patients with unresectable tumor could be treated by palliative drainage therapy to correct obstructive symptoms i.e. jaundice, pruritus. At present, the commonly used palliative drainage techniques are endoscopic biliary drainage (EBD), percutaneous transhepatic biliary drainage (PTBD) and bypass surgery.

EBD using biliary stent in patients with unresectable hilar tumor is as effective as surgical bypass and has fewer early complications compared to surgery. (Smith, et al., 1994) The target volume of biliary drainage is to drain at least 25% of the liver volume to achieve adequate palliation e.g. symptom relief, improvement in biochemical parameters, biliary decompression as demonstrated by ultrasonography and improvement in health related quality of life. (Abraham, et al., 2002; Dowsett, et al., 1989) EBD is the most frequently use technique for palliative drainage because it is less invasive compared to surgical bypass and it causes less discomfort compared to PTBD.

2.2 Types and effectiveness of biliary stent

There are two types of biliary stents which are routinely used in EBD. The first one is plastic stent which is made from polyethylene or polyvinyl. Plastic stent has small diameter compared to metal stent. The commonly use sizes are 7, 8.5 and 10 Fr. The main drawback of the plastic stent is the relatively high occlusion rate, which occurs at a median interval of 3 months after insertion (De Palma, et al., 2001) but its advantage is the lower cost compared to metal stent (1,000-2,000 baht vs. 25,000-40,000 baht respectively). The advantage of metal stent in hilar CCA are the open mesh design which allow drainage of the side branch of bile duct and its larger diameter (10 mm.) which may provide better drainage. Moreover, metal stent has longer patency (3-9 months) before occlusion. (Cheng, et al., 2002; De Palma, et al., 2003; Freeman and Overby, 2003)

Endoscopic insertion of unilateral plastic stent provides good palliation of proximal malignant biliary obstruction caused by unresectable hilar malignancy in 41-81% of patients (De Palma, et al., 2001; Hintze et al., 2001; Liu, Lo, Lai, and Fan, 1998; Polydorou et al., 1991) and also avoids the risk of further procedure-related complications compared to bilateral endoscopic hepatic duct drainage. (De Palma, et al., 2001) Therefore, unilateral metallic stent insertion is safe, feasible and achieves adequate drainage in 77-96.7% of patients with a malignant hilar obstruction. Nevertheless, all of the trials are not randomized controlled trial.(De Palma, et al., 2003; Freeman and Overby, 2003)

However, there was a small randomized controlled trial of bilateral metallic versus plastic stents drainage using the combination of endoscopic and percutaneous drainage technique. (Wagner, Knyrim, Vakil, and Klose, 1993) The researchers found that patients in metallic stent group had substantially lower rate of cholangitis, number of re-interventions, and days in hospital compare to patients in plastic stent group, but there was no information about the efficacy of stent in terms of adequacy of biliary drainage. In addition, the patients included in this study is quite small, only 20 patients and only nine of them were diagnosed CCA. Recently, there was non-randomized controlled study comparing metal and plastic stent in hilar CCA. Patients with metal stent insertion had substantially lower rate of complication, number of re-interventions compare to patients in plastic stent group.(Perdue, et al., 2008)

2.3 Cost-effectiveness study

To choose type of stent in endoscopic biliary drainage, not only the effectiveness of stents which included successful drainage, patency time and complications are considered but also the cost of treatment is concerned. Until now, there is no study about cost effectiveness of plastic and metal stent in patients with hilar CCA.

There are four studies of economics evaluation of plastic and metal stents in malignant obstruction of common bile duct (CBD). The first study is a cost-minimization study. The results revealed that the cost of treatment of each alternative strategy depends on the expected survival time of patients. Cost of treatment in plastic stent group is less than metal stent group in patients with short survival time such as patients with metastatic liver disease. (Kaassis et al., 2003) The result of this study confirm the result of another study using decision analytic modeling approach which revealed that plastic stents is preferable in malignant CBD obstruction patients who had survival less than 4 months. (Yeoh, Zimmerman, Cunningham, and Cotton, 1999)

In other two cost-effective studies, the result of the first study reveals that metal stent is more cost-effective than plastic stent in terms of cost per number of endoscopic procedures needed for each treatment strategy. (Katsinelos et al., 2006) but the result of the second study that evaluates the effectiveness of biliary stent drainage in terms of jaundice resolution shows that there is no difference in mean cost per jaundice resolution between the patients in metal and plastic stent groups. (Yoon et al., 2009) The results of these two studies are different because of the different in effectiveness measurement unit which is the weakness of cost-effectiveness analysis that use the different effectiveness unit and cannot compare across the studies.

Although, there are a few articles studied about the cost-effectiveness of plastic and metal stents in malignant obstruction of common bile duct (CBD) but the results could not be applied to patients with hilar CCA because the anatomy at obstructive sites are different.

2.4 Concept of economic evaluation.

Economic evaluation compares the costs and consequences of two or more alternatives treatments or interventions; thus, it helps efficiently allocating limited health care resources. In other words, it helps improving the value for money from investment in health care and welfare. (Fox-Rushby, 2005)

We can classify economic evaluation according to the consequences of the programs or sources of data used in the study.

2.4.1 Type of economic evaluation classified according to consequences of the programs.

2.4.1.1 Cost-effective analysis. (CEA)

CEA is the commonly used type of economic evaluation. The outcomes are measured in natural unit which are vary upon diseases or programs of interest. Thus, it is difficult to compare the results across programs.

2.4.1.2 Cost-utility analysis. (CUA)

CUA is the economic evaluation that measures outcome in terms of utility which can easily be compared across programs.

2.4.1.3 Cost-benefit analysis. (CBA)

CBA measures outcome in terms of money which is easy to be compared across studies. However, it is difficult to measure health outcome in money unit.

2.4.2 Type of economic evaluation classified according to sources of data used.

2.4.2.1 Economic evaluation along clinical trials.(patient-level data)

Although, economic evaluation along-side the clinical trials have high internal validity because of its prospective data collection as part of the trial. However, there are some limitations e.g. the problems of protocol-driven costs and outcoes, inadequate patients follow-up and issue of intermediate versus final outcome. (Drummond, 2005)

2.4.2.2 Decision analytic model.(Secondary data)

Decision analytic model use mathematical relationships to evaluate the outcomes of the alternative programs of interest.(Briggs, 2006) Model can simulate the pattern of management in the real clinical practice. We can compare the relevant treatment options and extrapolate the result over the appropriate time horizon of the evaluation. In addition, model allows us to use the information from systematic review of the available literatures which might have different values and we can combine them together by meta-analysis; therefore, the result of the study is a representative of all relevant evidences or inputs. Finally, the model also allows us to use sensitivity analysis to deal with uncertainty relating to model structure and input parameters. (Drummond, 2005; Fox-Rushby, 2005)

2.5 Markov Model

Markov model is a commonly used decision analytic model which can handle complex processes that repeated over time. It consists of finite numbers of health states. Patients in the model will move from one health sate to another according to the transitional probabilities. Besides, costs is incorporated into the model and multiplied by the numbers of patients in each state. The outcomes of Markov model are accumulative cost and life years. If the life years are weighted by the value of health status such as utility score or health preference which is measured on cardinal scale between 0 (death) and 1 (full health), the outcome will be quality-adjusted life year (QALY). (Briggs, 2006) Therefore, the important input variables in the model are transitional probability, utility and cost.

2.5.1 Transition probability (Briggs, 2006)

The proper choice of probabilities is important issue in decision analytic model because it directly affects the result of decision analytic model. To collect the information to fill transition probabilities, there are three important issues to be considered. First, the information should be systematic searching to identify the best available information. Second, if there are several sources of information, the rationale of selection should be given. Meta-analysis is a favorite method to pool the results. Finally, if the primary source of information is used to estimate probabilities, the methods of data collection should be described in detail. Another aspect to consider is using the source which is the representative of population to be generalized. (Petitti, 2000)

In some conditions, the transition probabilities may change according to time in model, for example, the probability of death increases with time in advanced stage cancer patients. In this case, if patient level data were available, we can use survival analysis to calculate the time-dependent probabilities.

Survival analysis is frequently used in medical field to handle the censored data that usually found in time to event data or survival data. The commonly uses survival model is Cox proportional hazards model which is the semiparametric survival model. In this model, the baseline hazard, risk of an event over time, is not specified but fixed. Therefore, it cannot use to implement time-dependency in Markov model. In this purpose, the useful model is parametric survival models. In these models, the baseline hazard rate is specified. The frequetly used model are Weibull model and exponential model. In Weibull model, the baseline hazard rate is decreased or increased overtime, whereas baseline hazard rate is constant in exponential model.

There are two parameters in Weibull model.

1. Lambda (λ) parameter represents the scale of the distribution.
2. Gamma (γ) parameter or ancillary parameter defines the shape of hazard rate over time.
   a. If $0 < \gamma < 1$, hazard rate decreases over time
   b. If $\gamma > 1$, hazard rate increases over time

We can calculate transition probability between time-points t-u and t or $tp(t_u)$ from the results of Weibull regression by the following equation.

$$tp(t_u) = 1 - \exp(\lambda * [(t-u)^{\gamma} - t^{\gamma}])$$

u = cycle length of the model

λ = scale parameter

γ = shape parameter or ancillary parameter

If the ancillary parameter or gamma (γ) is equal to 1, the baseline hazard is constant overtime. This special case of Weibull regression is exponential regression. In this case the transition probability is constant over time and we can calculate the transition probability from the results of exponential regression by the following formula.

$$tp = 1 - \exp(-\lambda * u)$$

u = cycle length of the model

λ = scale parameter

2.5.2 Utility

Quality-adjusted life year(QALY) is the value or worth placed on a level of health status, as measure by the preferences of individual or society.(Drummond, 2005) The QALY can be calculated by multiplying life expectancy and utility score which is measured on cardinal scale between 0 (death) and 1 (full health). There are two methods to measure utility, directly measured utility methods and multi-attribute health status classification system.

The directly measure utility or preference elicitation techniques consist of three techniques as follows. (Brazier, 2007)

1. Visual analogue scale (VAS)

   VAS is rating scale which the distance between interval on the scale reflects the difference in utilities. One end of the scale is zero or death and the other end of scale is 100 or full health. VAS is easy to measure but it does not include the concept of choice and uncertainty

2. Time trade-off (TTO)

   TTO is conceptually equivalent to QALY. The subject is questioned to trade-off number of year in disease state and number of year in full health. In TTO, respondents need to make a decision to choose a choice which is based on the concept of expected utility theory but it does not include the uncertainty concept.

3. Standard gamble (SG)

   SG is fit the axiom of expected utility theory because the respondent need to make a choice under uncertainty. The respondent has to choose between living in disease state and living in full health with risk of immediate death. The disadvantage of SG is its complex procedure and it is difficult for the respondent to understand.

The second method of utility measurement is multi-attribute health status classification system or indirectly measured utility method. The commonly used instruments are EuroQoL EQ-5D (EQ-5D), Quality of Well-Being (QWB), Health Utilities Index (HUI), and Short Form-6D (SF-6D). The steps in using these questionnaires are as follows.

1. Respondents rate the level of multi-attribute health state in questionnaire.
2. The answers are mapped into utility score.

The choice of instrument might depend on theory, ease of use, or empirical relationships between the different scores. In general there is no different in performance of these instruments. Many recommendations are based on the theories but from the review, there is no strong conclusions about which methods are best for health preference measurement (Glick, 2007).

In Thailand, the validated official Thai version of EQ-5D is available to use. The answer from Thai version of EQ-5D questionnaire can convert into 0-1 utility score by Thai preference score for EQ-5D health state (Tongsiri, 2009). Because of its practicality and accepted reliability, EQ-5D is the recommended utility measurement method in Thailand (Sakthong, 2008). The other advantage of EQ-5D is that it is easy for patients to answer the questionnaires rather than make a decision in preference elicitation techniques.

2.5.3 Cost

Cost is the key parameter of economic evaluation and the perspective of the study is important issue because it affects the process of resources used identification for cost calculation. The commonly used study perspectives are societal perspective, provider perspective, payer perspective and patient perspective.

Because costing take substantial time and effort, it is important for researcher to know the precision of costing in the study. There are several levels of precision in hospital costing from most precise to least precise as follows; micro-costing, case-mix group, disease-specific per diem, average per diem and cost to charge ratio.

Cost to charge ratio is used to convert hospital charges to cost by multiplying charges to cost to charge ratio. Conversion of hospital charge to costs is a reasonable trade-off between accuracy and the resources used for costing. (Drummond, 2005)

In Thailand, the cost to charge ratio of 0.8 is derived from the general administration information of hospital in Thailand (Kasemsap, n.d.). However, cost to charge ratios of each service in hospital are different. In Phramongkutklao hospital which is a teaching hospital, cost to charge ratios for drugs and medical supply is 0.8:1 but cost to charge ration for services is 1.25:1 (Werayingyong, 2006).

2.6 Uncertainty and sensitivity analyses

There are two type of uncertainty. The first one is model or structure uncertainty. This uncertainty results from the internal structure of model. The second is parameter uncertainty which is the uncertainty of the true value of parameters used in the model. (Briggs, 2006)

Sensitivity analysis is a tool that examines the effect of input data and model uncertainties on the results of the model. There are two important type of sensitivity analysis.

2.6.1 Deterministic sensitivity analysis (DSA)

The common type of DSA is one-way sensitivity analysis which one parameter is varied in reasonable range such as standard deviation, 95% confidence interval, whereas the other variables are fixed. Then the results are calculated.

Tornado diagram is the alternative presentation of one-way sensitivity analysis. It provides the information about the magnitude of influence of the parameters on incremental cost-effectiveness ratio in the same diagram. The length of the horizontal bar of Tornado diagram reflected the sensitivity of study results to the variation of each parameter. The most influential parameter is at the top of diagram and the least influential parameter is at the bottom of diagram. (Limwattananon, 2008)

2.6.2 Probabilistic sensitivity analysis (PSA)

PSA determines the effect of change of all parameters in the reasonable range such as standard error at the same time. It is accepted as a standard test to handle parameter uncertainty. Monte Carlo simulation is the popular method to handle PSA. The computer will randomly draw the value of all parameters according to their distribution at the same time and calculated the result. This process is repeated for a large number of times i.e. 1,000 or 10,000 times (Drummond, 2005)

CHAPTER III

RESEARCH METHODOLOGY

3.1 Research Design

This study used decision analytic model to compare cost utility of endoscopic biliary drainage using metal and plastic stent in patients with unresectable complex hilar CCA. The target populations of this study were patients with unresectable complex hilar CCA who were the candidates for palliative treatment by endoscopic biliary drainage.

The following figure is the conceptual framework of this study.

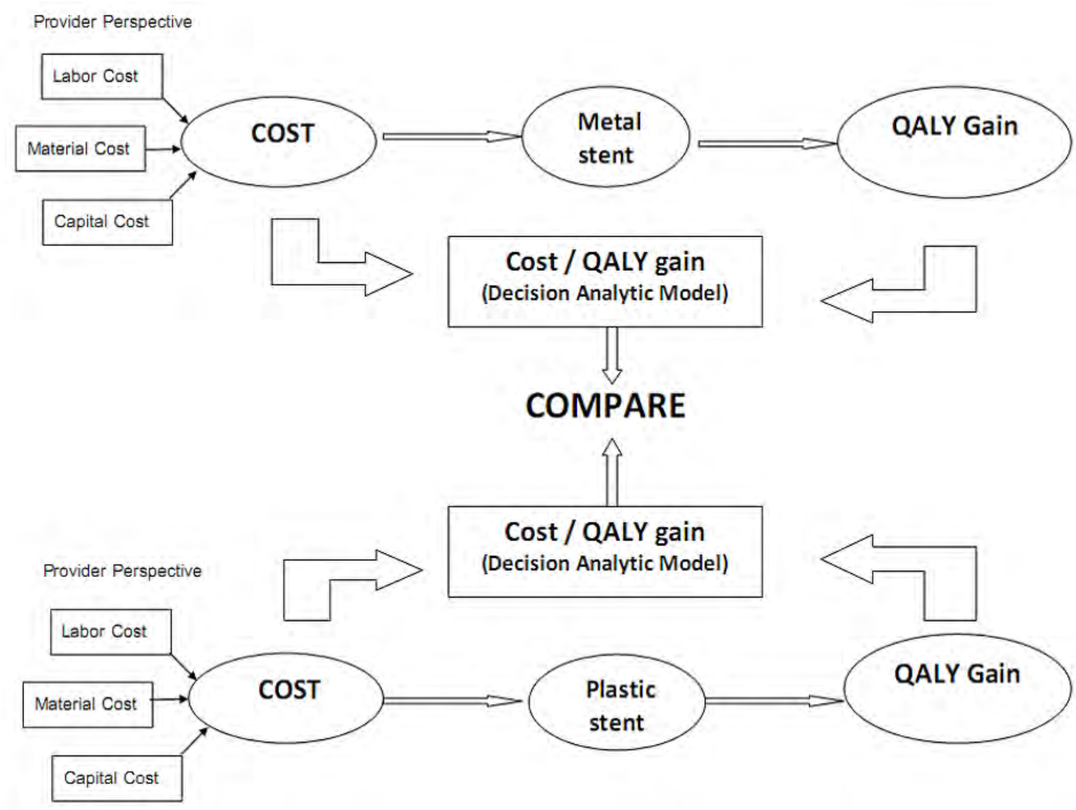


Figure 3.1 The conceptual framework.

3.2 Perspective

The provider perspective is used in this study to estimate the costs incurred by treatment of this particular disease.

3.3 Decision analytic model

Markov model was used to simulate the treatment of unresectable hilar CCA using endoscopic biliary drainage. The cohorts of patients who decided to have palliative treatment by EBD will enter Markov model. Markov model is used in this study because along the treatment process, some events such EBD, PTBD could occur repeatedly over time. The health states or Markov states in the model were determined according to the natural history of patients with unresectable CCA treated by palliative treatment in Thailand as in Figure 3.2.(National Health Security Office, 2006)

Cycle length of 2 weeks was chosen because it was close to the shortest time frame that could capture the natural progression and resolution of disease states in this model.

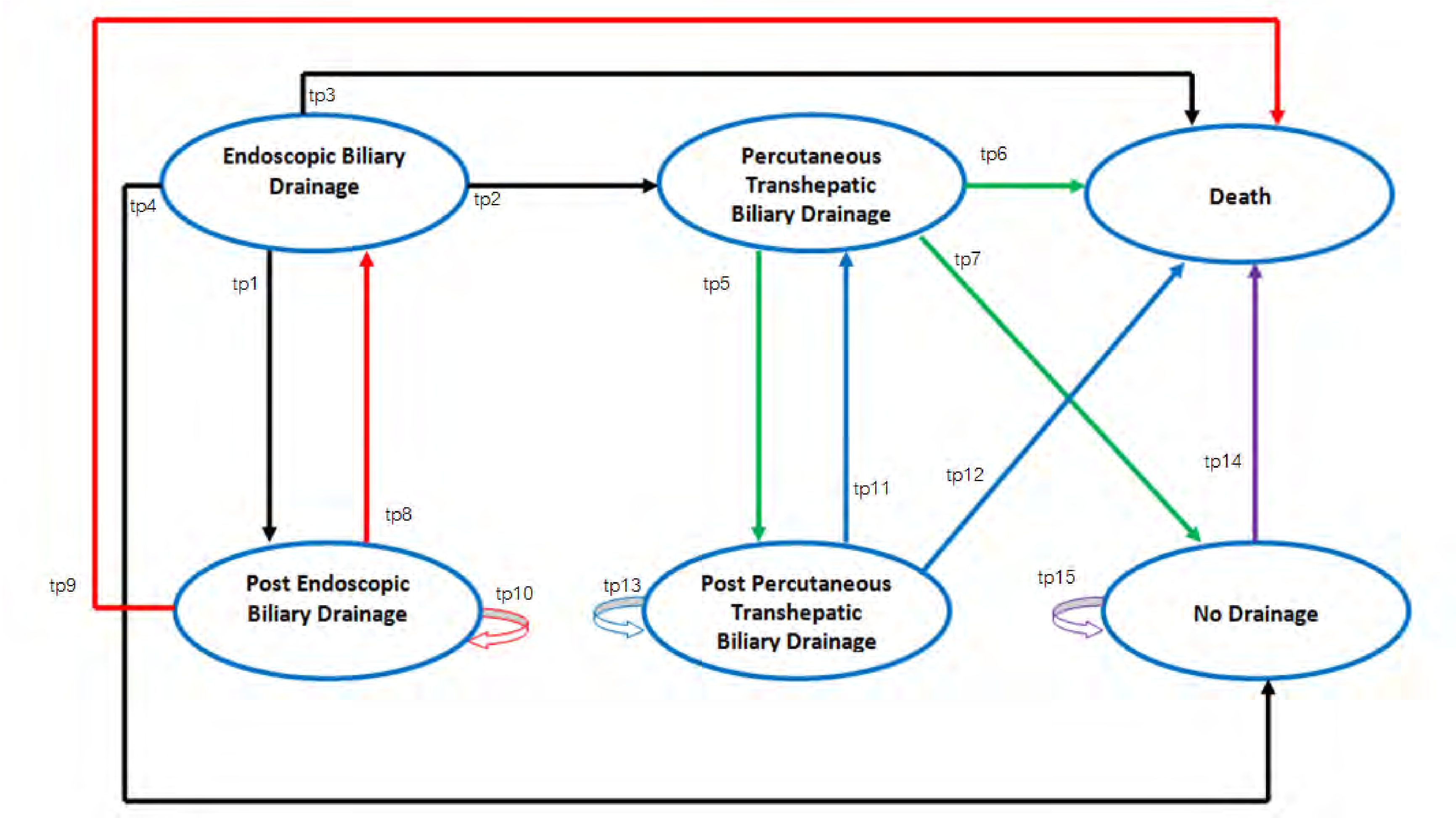
Time horizon in this study is the time from stent insertion until death because most of patients with advanced stage CCA will die within 6 months to 1 year from disease progression.

The transitional probabilities of each disease state were attached to model to determine the probability to move from one state to other states and the summation of transition probabilities from each Markov state is equal to 1. Besides, the value of health status or utilities and costs are also attached to each disease state. Then, models are run to simulate the clinical course of disease. As a result, disease outcomes and costs will be accruing during model running and finally, we receive the accumulate utilities and costs of the cohorts at the end of simulation.

3.4 Markov state

Figure 3.2 demonstrated six health states in Markov model and the details of each disease state are as follows.

Figure 3.2 Markov model disease states for the treatment of complex unresectable hilar CCA.



3.4.1 Endoscopic Biliary Drainage state (EBD)

EBD state is the state that represents CCA patients with obstructive symptoms who received endoscopic biliary drainage using plastic or metal stent. Patients with endoscopic complication are also included in this state.

3.4.2 Percutaneous Transhepatic Biliary Drainage state (PTBD)

PTBD state is the state that represents CCA patients who failed EBD and were rescued by PTBD.

3.4.3 Post-Endoscopic Biliary Drainage state (PostEBD)

PostEBD state is the state that represents CCA patients with successful EBD. These patients are followed up at out-patient clinic. PostEBD state also included patients who have complications during followed up and need hospital admission but do not need endoscopic treatment procedure.

3.4.4 Post-Percutaneous Transhepatic Biliary Drainage state (PostPTBD)

PostPTBD state is the state that represents patients with successful PTBD who are followed up at out-patient clinic. The patients who have complications during followed up and need hospital admission but do not need PTBD catheter exchange also included in this state.

3.4.5 No drainage state

No drainage state is that state that represents patients who failed both drainage procedures and patients who do not want further drainage procedure.

3.4.6 Death state

Death state is the state that includes all the patients who died from other states.

3.5 Transition probabilities

The transition probabilities were derived from 2 main sources. The first source was the ongoing randomized controlled trial (RCT) at Srinagarind hospital, KhonKaen University,“Efficacy and Cost Analysis of Plastic Stent Compare to Metallic Stent in Hilar Cholangiocarcinoma” (ClinicalTrials.gov Identifier: NCT00721175). The second source of transition probabilities was from literature review.

The ongoing RCT at Srinagarind hospital which was in data analysis phase evaluated the efficacy of unilateral plastic and metal stent in unresectable hilar CCA Bismuth type II-IV. The 7-10 Fr plastic stent or metallic stent was inserted into the left or right hepatic duct which shown largest intercommunicating ductal segment on computed tomography (CT) or magnetic resonance cholangiopancreatography (MRCP) imaging. The efficacy of drainage was assessed 2 weeks after intervention and the criteria of successful drainage were 1) lack of jaundice by physical examination or, 2) decreasing in bilirubin level less than 30% of baseline at 2nd weeks or 50% of baseline at 4th week. In case of failed drainage, PTBD was offered as soon as possible. The exclusion criteria in this study are 1) patients with ASA physical status classification class 4 or 5; 2) patients with liver failure; and 3) patients unable to comply with follow-up.

Table3.1 summarized the transition probabilities and regression parameters in this study. Details of the sources and how to calculate transition probabilities are as follows.

Table3.1 Summary of means and standard error (SE) of transition probability

Parameters	Mean	SE	Parameter distribution	Data source
14-day transition probabilities				
1st cycle from EBD to PostEBD plastic (tp1_1p)	0.462	0.068	Beta	NCT00721175
1st cycle from EBD to PostEBD metal (tp1_1m)	0.704	0.063	Beta	NCT00721175
Other cycle from EBD to PostEBD plastic (tp1_2p)	0.532	0.074	Beta	NCT00721175
Other cycle from EBD to PostEBD metal (tp1_2m)	0.818	0.059	Beta	NCT00721175
From EBD to PTBD plastic (tp2p)	0.034	0.034	Beta	NCT00721175
From EBD to PTBD metal (tp2m)	0.063	0.061	Beta	NCT00721175
From EBD to Dead (tp3_1p)	0.204	0.055	Beta	NCT00721175
From EBD to Dead (tp3_1m)	0.074	0.036	Beta	NCT00721175
From EBD to Dead (tp3_2p)	0.176	-	Beta	NCT00721175
From EBD to Dead (tp3_2m)	0.038	-	Beta	NCT00721175
From PTBD to PostPTBD (tp5)	0.939	0.029	Beta	Lee (2007)
From PTBD to Dead (tp6)	0.007	0.007	Beta	Lee (2007)
From PostPTBD to PTBD (tp11)	0.180	0.062	Beta	Lee (2007)
From PostPTBD to Dead (tp12)	0.112	0.085	Beta	Wongkonkitsin (2006)
Regression parameters				
From EBD to Dead (tp3_2)				NCT00721175
Constant value	-6.502	0.762	Log normal	
Stent coefficient	-1.600	0.721	Log normal	
Bilirubin coefficient	0.080	0.028	Log normal	
From PostEBD to EBD (tp8)				NCT00721175
Constant value	-7.812	1.221	Log normal	
Stent coefficient	-1.925	0.552	Log normal	
Gamma	1.623	0.263	Log normal	
From PostEBD to Dead (tp9)				NCT00721175
Constant value	-4.766	0.204	Log normal	
Stent coefficient	-0.701	0.270	Log normal	
From No drainage to Dead (tp14)				NCT00721175
Constant value	-3.976	0.639	Log normal	
Bilirubin coefficient	0.025	0.012	Log normal	
Gamma	0.792	0.090	Log normal	

NCT00721175, ClinicalTrials.gov identifier of ongoing trial evaluating efficacy and cost analysis of plastic stent compare to metallic stent in hilar cholangiocarcinoma at Srinagarind hospital.

3.5.1 Transitional probability from EBD to PostEBD state (tp1)

This probability was derived from the effectiveness of endoscopic plastic and metal biliary drainage from the ongoing RCT at Srinagarind hospital (ClinicalTrials.gov Identifier: NCT00721175). This study was in the process of data analysis. We selected this study because it was the only RCT that compares the effectiveness of plastic and metal stent in unresectable complex hilar CCA.

tp1 in the first cycle were calculated from the efficacy of drainage of plastic and metal stent after the first endoscopic procedure. From intention to treat analysis, the efficacy of plastic and metal stent drainage are equal to 46.3 % and 70.4% respectively. Therefore, tp1 of plastic and metal stent in 1st cycle (tp1_1p and tp1_1m) and its standard error (se) are equal to 0.463 (0.068) and 0.704 (0.063) respectively.

tp1 from the 2nd-104th cycle were derived from the effectiveness of drainage of plastic and metal stent using per protocol analysis because patients in these cycle used to have successful stent insertion in the previous cycle. tp1 of plastic (tp1_2p) and metal (tp1_2m) stent in 2nd-104th cycle and their standard error (se) are equal to 0.532(0.074) and 0.818(0.059) respectively.

3.5.2 Transitional probability from EBD to PTBD state (tp2)

tp2 were calculated from the proportion of patients who were managed by PTBD after failed EBD in the ongoing RCT at Srinagarind hospital.

tp2 of plastic (tp2p) and metal stent (tp2m) and their standard errors are equal to 0.034 (0.034) and 0.063 (0.061) respectively.

3.5.3 Transitional probability from EBD to Death state (tp3)

These probabilities were calculated from data of patient with unsuccessful stent drainage group from the ongoing RCT at Srinagarind hospital.

tp3 in the first cycle were derived from probability of death in the first 14 days from trail database using intention to treat (ITT) analysis. The major components of these probabilities were probability of death from disease and intervention related mortality rate. tp3 of plastic (tp3_1p) and metal stent (tp3_1m) in 1st cycle and their standard errors are equal to 0.204 (0.055) and 0.074(0.036) respectively.

tp3 from the 2nd-104th cycle were derived from probability of death of patients with unsuccessful stent drainage group using per protocol analysis because patients in these cycle used to have successful stent insertion in the previous cycle. Probability of death in these periods mainly related to disease related mortality and late complication. Because the risk of death might change over time, the probability should be calculated from base line hazard rate (λ) and ancillary parameter (γ) that predicted by Weibull regression (parametric survival regression) of trial database by the following equation

$$P = 1 - \exp(\lambda * [(t-u)^{\gamma} - t^{\gamma}])$$

In this case, the ancillary parameter or gamma (γ) is not different from 1, then the exponential regression (parametric survival regression) was used and the probability of death could be calculated from the following equation.

$$P = 1 - \exp(-\lambda * u)$$

From the results of exponential regression in table 3.1, we can calculate λ of each stent type by the following equation.

λ = exp(constant value + stent coefficient * stent type + bilirubin coefficient * mean serum bilirubin)

Mean serum bilirubin in this group is 27.66 mg/dl. Stent type is equal to 1 for metal stent and 0 for plastic stent. Cycle length (u) is 14 days. Therefore, tp3 of plastic (tp3_2p) and metal stent (tp3_2m) from 2nd to 104th cycle are 0.176 and 0.038 respectively.

To incorporate uncertainty into the estimation of the transition probability from the survival model, we used the Cholesky decomposition of the covariance matrix to provide correlated draws from a multivariate normal distribution. The example of values drawn from the multivariate normal distribution for calculating tp3_2 was shown in Appendix C.

3.5.4 Transitional probability from EBD to No drainage state (tp4)

This probability was calculated by one subtract by the Transitional probability from EBD to PostEBD, Transitional probability from EBD to PTBD, and Transitional probability from EBD to Death. (tp4 = 1- tp1 – tp2 – tp3)

3.5.5 Transitional probability from PTBD to PostPTBD state. (tp5)

This probability was derived from systematic review of the clinical trials which study about the effectiveness of PTBD in unresectable hilar CCA patient. PubMed database was searched with the following keywords: cholangiocarcinoma OR klatskin* OR hilar OR bismuth AND "biliary drainage" AND percutaneous AND (effect* OR efficacy)

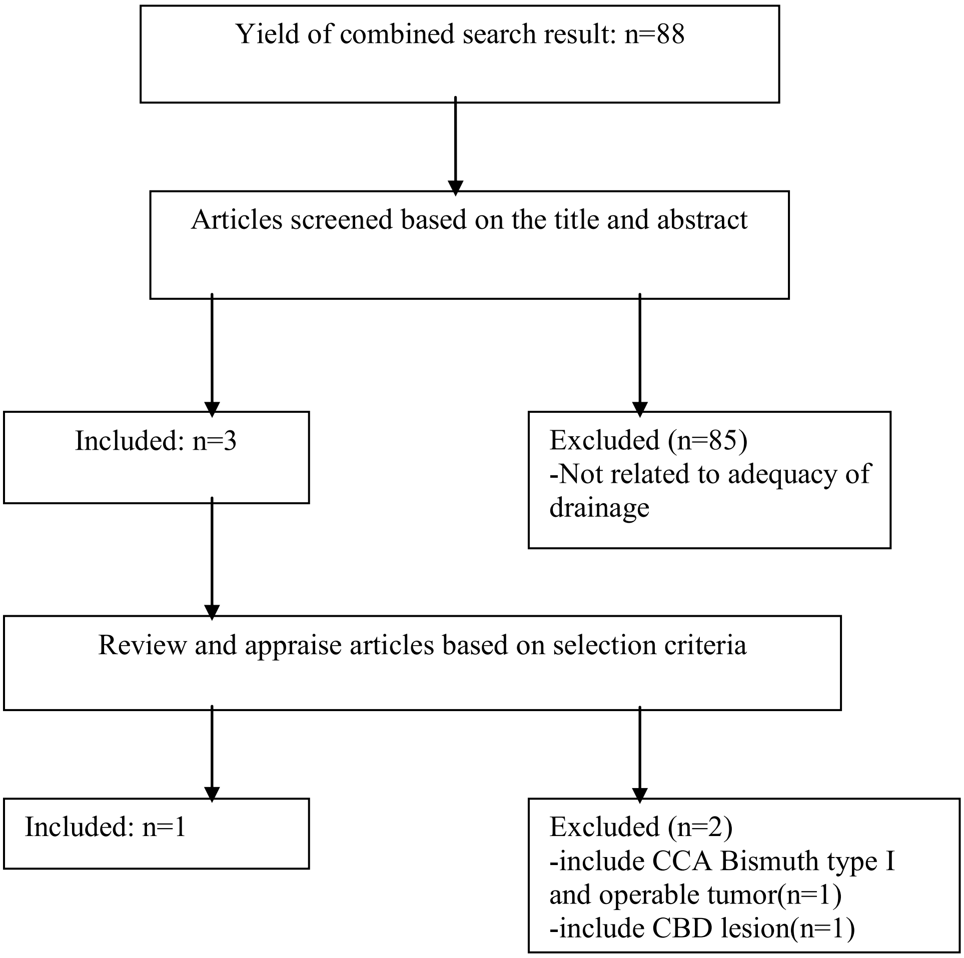


Figure 3.3 Identification of eligible studies for investigating the effectiveness of PTBD.

Inclusion criteria

1. Prospective or retrospective study evaluating the effectiveness of biliary drainage of PTBD in terms of adequacy of drainage or jaundice resolution in unresectable hilar CCA Bismuth type II, III, IV.

2. Studies from Asian country which cause of CCA originated from liver fluke.

Exclusion criteria

1. Studies that included patients with malignant hilar obstruction from other diseases.

The search results showed one study that reported the adequacy of biliary drainage in Bismuth II-IV hilar CCA in Asian country.(Lee et al., 2007). Sixty two out of 66 patients had adequate drainage after PTBD catheter insertion. tp5 and its standard error are equal to 0.939 and 0.029.

The standard error was calculated from the following formula

$$\text{Standard error} = \sqrt{p(1-p)/n}$$

n = size of sample　　　　p = proportion

3.5.6 Transitional probability from PTBD to Death state (tp6)

This probability was derived from systematic review of the clinical trials which study about the mortality rate of unresectable hilar CCA patient with PTBD.

PubMed database was searched with the following keywords: cholangiocarcinoma OR klatskin* OR hilar OR bismuth AND "biliary drainage" AND percutaneous AND (survival OR mortality OR dead)

Inclusion criteria

1. Prospective or retrospective study evaluating mortality rate related to PTBD procedure in unresectable hilar CCA Bismuth type II, III, IV;
2. Studies from Asian country which cause of CCA originated from liver fluke;
3. Provide sufficient data of deviation from median.

Exclusion criteria

1. Studies that included patients with malignant hilar obstruction from other diseases.

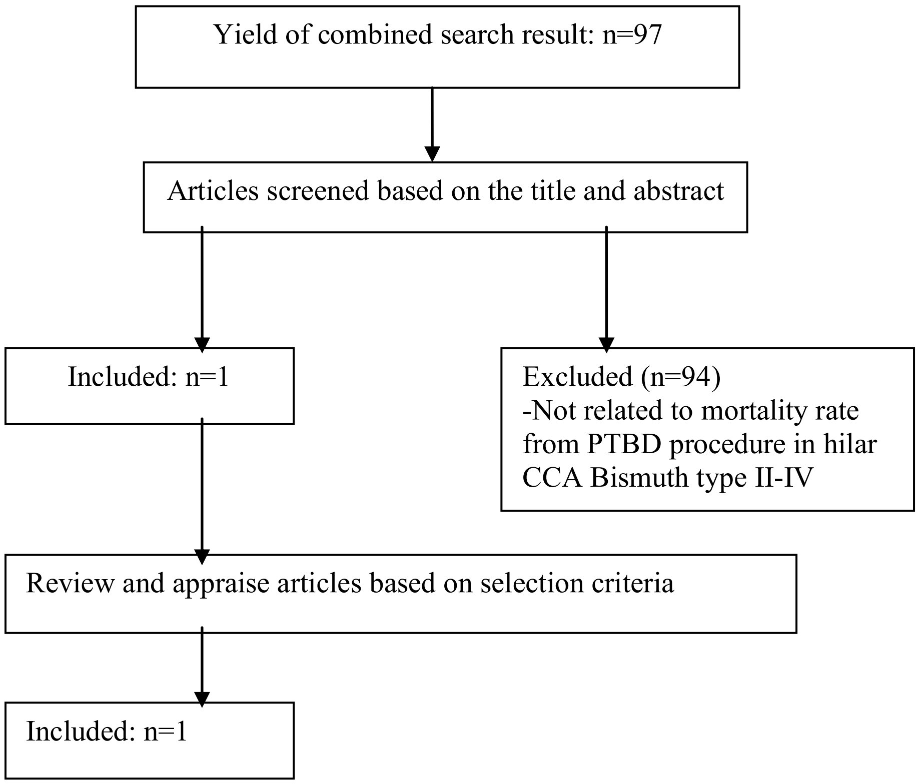


Figure 3.4 Identification of eligible studies for investigating mortality rate of PTBD procedure.

The search results showed one study that reported short term or 30-day probability of death which is equal to 1.515% (1 out of 66 patients) in Bismuth type II-IV CCA with PTBD procedure. (Lee, et al., 2007). Its standard error is equal to 0.015036.

tp6 or 14-day probability of death was calculated by the following formula.

$tp_1 = 1 - (1\text{-}tp_t)^{1/t}$

The following section demonstrated how to calculate transition probability for specific cycle length and its standard error.

tp6 =1- ((1-0.01515)^(1/(30/14))) = 0.007099 tp6 (lower bound) =1-((1- 0.000115)^(1/(30/14))) = 0.000054 (different from median=0.007045)

tp6 (upper bound) =1-((1- 0.030188)^(1/(30/14))) = 0.0142 (different from median=0.007101)

The larger standard error of probability of death, 0.007101, was used in probability sensitivity analysis.

3.5.7 Transitional probability from PTBD to No drainage state (tp7)

This probability was calculated by one subtract by the Transitional probability from PTBD to PostPTBD, and Transitional probability from PTBD to Death. (tp7 = 1-tp5-tp6)

3.5.8 Transitional probability from PostEBD to EBD state (tp8)

This probability was calculated from data from ongoing RCT at Srinagarind hospital. Because the risk of stent occlusion might change over time, the probability could be calculated from base line hazard rate (λ) and ancillary parameter (γ) that predicted by Weibull regression of trial database by the following equation

$$P = 1 - \exp(\lambda*[(t-u)^{\gamma}-t^{\gamma}])$$

From the results of Weibull regression in table 3.1, we can calculate λ of each stent type by the following equation.

$$\lambda = \exp(\text{constant value} + \text{stent coefficient} * \text{stent type})$$

Stent type is equal to 1 for metal stent and 0 for plastic stent. Then we can calculate the transition probability. In this case the transition probability will increase every cycle because ancillary parameter is greater than 1.

To incorporate uncertainty into the estimation of the transition probability from the survival model, we used the Cholesky decomposition of the covariance matrix to provide correlated draws from a multivariate normal distribution. The example of values drawn from the multivariate normal distribution for calculating tp8 was showed in Appendix C.

3.5.9 Transitional probability from PostEBD to Death state (tp9)

This probability was calculated from data of patient with successful stent drainage group from the ongoing RCT at Srinagarind hospital. Because the risk of death might change over time, the probability could be calculated from base line hazard rate (λ) and ancillary parameter (γ) that predicted by Weibull regression of trial database by the following equation

$$P = 1 - \exp(\lambda * [(t-u)^{\gamma} - t^{\gamma}])$$

In this case, the ancillary parameter or gamma (γ) is not different from 1. Then the exponential regression was used and the probability of death could be calculate as the following equation

$$P = 1 - \exp(-\lambda * u)$$

From the results of the exponential regression in table 3.1, we can calculate λ of each stent type by the following equation.

$$\lambda = \exp(\text{constant value} + \text{stent coefficient} * \text{stent type})$$

Stent type is equal to 1 for metal stent and 0 for plastic stent. Cycle length (u) is 14 days. In this case the transition probability is constant over time. tp9 of plastic (tp9p) and metal stent (tp9m) are equal to 0.112 and 0.057 respectively.

To incorporate uncertainty into the estimation of the transition probability from the survival model, we used the Cholesky decomposition of the covariance matrix to provide correlated draws from a multivariate normal distribution. The example of values drawn from the multivariate normal distribution for calculating tp9 was showed in Appendix C.

3.5.10 Transitional probability of staying in PostEBD state (tp10)

This probability was calculated by one subtract by Transitional probability from PostEBD to EBD, and Transitional probability from PostEBD to Death. (tp10 = 1 – tp8 – tp9)

3.5.11 Transitional probability from PostPTBD to PTBD state (tp11)

This probability was derived from systematic review of the clinical trials which study about the effectiveness of PTBD in terms of occlusion rate in unresectable hilar CCA patient.

PubMed database was searched with the following keywords: cholangiocarcinoma OR klatskin* OR hilar OR bismuth AND "biliary drainage" AND percutaneous AND (patency OR occlu*)

Inclusion criteria

1. Prospective or retrospective study evaluating the effectiveness of PTBD in terms of patency time in unresectable hilar CCA Bismuth type II, III, IV;
2. Studies from Asian country which cause of CCA originated from liver fluke;
3. Provide sufficient data of deviation from median patency time.

Exclusion criteria

1. Studies that included patients with malignant hilar obstruction from other diseases.

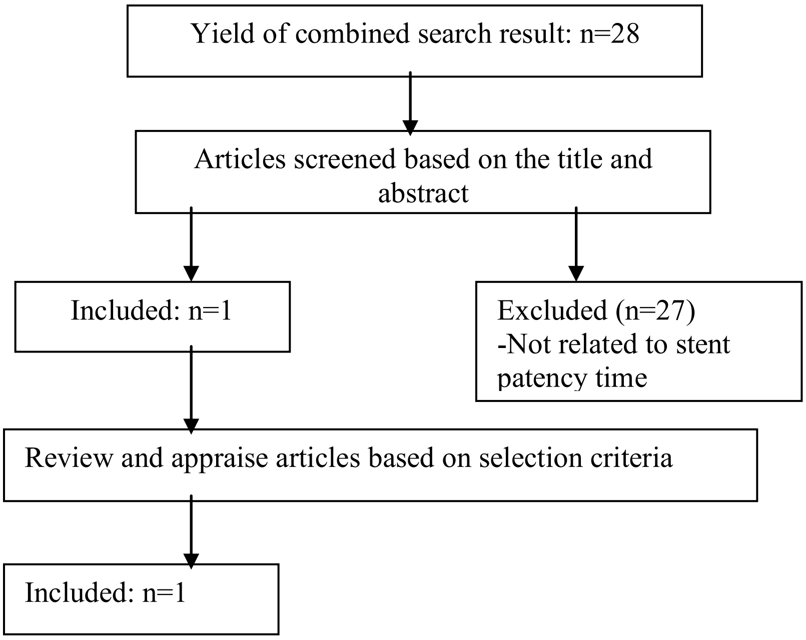


Figure 3.5 Identification of eligible studies for investigating PTBD occlusion rate.

Lee et al.(2007) reported median patency time equal to 49 days (range 27-71days). Probability of PTBD occlusion during14 days could be calculated by the following equation.

$tp_1 = 1 - (1-tp_t)^{1/t}$

The following section demonstrated how to calculate transition probability for specific cycle length and its standard error.

tp11 =1-((1-0.5)^(1/(49/14))) =0.179664644

tp11 (lower bound) =1-((1-0.5)^(1/(27/14))) = 0.301911679 (different from median=0.1222)

tp11 (upper bound) =1-((1-0.5)^(1/(71/14))) =0.127748002 (different from median=0.052)

Standard error is approximately 0.1222/1.96 or 0.062.

3.5.12 Transitional probability from PostPTBD to Death state (tp12)

This probability was derived from systematic review of the clinical trials which study about the mortality rate of unresectable hilar CCA patients with PTBD. The inclusion and exclusion criteria of studies are as follows.

PubMed database was searched with the following keywords: cholangiocarcinoma OR klatskin* OR hilar OR bismuth AND "biliary drainage" AND percutaneous AND (survival OR mortality OR dead)

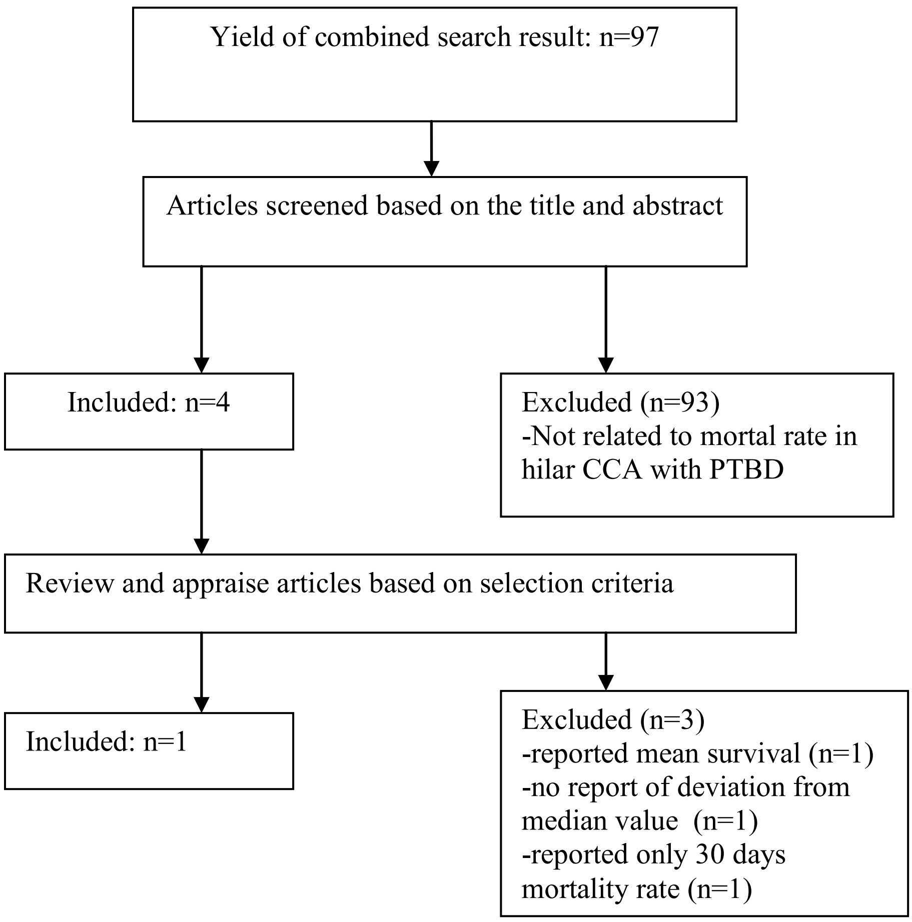


Figure 3.6 Identification of eligible studies for investigating mortality rate in patients with PTBD**.**

Inclusion criteria

1. Prospective or retrospective study evaluating survival or mortality rate of unresectable hilar CCA patients with PTBD;
2. Studies from Asian country which cause of CCA originated from liver fluke;
3. Provide sufficient data of deviation from median survival.

Exclusion criteria

1 Studies that included patients with malignant hilar obstruction from other diseases.

The search results showed one study that reported median survival time of unresectable hilar CCA patients with PTBD. The median time of the patients in this study was 94 days and 95% CI was between 29.76 and 134.24 days. (Wongkonkitsin, Phugkhem, Jenwitheesuk, Saeseow, and Bhudhisawasdi, 2006). We could calculate 14-day probability of death by the following formula.

$$tp_1 = 1 - (1\text{-}tp_t)^{1/t}$$

The following section demonstrated how to calculate transition probability for specific cycle length and its standard error.

tp12 =1-((1-0.5)^(1/(82/14))) = 0.1116080

tp12 (lower bound) =1-((1-0.5)^(1/(29.76/14))) =0.2782506 (different from median=0.1666)

tp12 (upper bound) =1-((1-0.5)^(1/(134.24/14))) =0.0697378 (different from median=0.0419)

Standard error is equal to 0.1666/1.96 = 0.085

3.5.13 Transitional probability of staying in PostPTBD state (tp13)

This probability was calculated by one subtract by Transitional probability from PostPTBD to PTBD, and Transitional probability from PostPTBD to Death (tp13 = 1- tp11 –tp12).

3.5.14 Transitional probability from No drainage to Death state (tp14)

This probability was calculated from data of patient with unsuccessful stent drainage group from the randomized controlled trial in Srinagarind hospital (ClinicalTrials.gov Identifier: NCT00721175). Because the risk of death might change over time, the probability should be calculated from base line hazard rate (λ) and ancillary parameter (γ) that predicted by Weibull regression of trial database by the following equation

$$P = 1 - \exp(\lambda * [(t-u)^{\gamma} - t^{\gamma}])$$

From the results of Weibull regression in table 3.1, we can calculate λ by the following equation.

$$\lambda = \exp(\text{constant value} + \text{bilirubin coefficient} * \text{mean serum bilirubin})$$

Mean serum bilirubin of patients in this group is equal to 28.92 mg/dl. Then we can calculate the transition probability. In this case the transition probability will decrease every cycle because ancillary parameter is less than 1.

To incorporate uncertainty into the estimation of the transition probability from the survival model, we used the Cholesky decomposition of the covariance matrix to provide correlated draws from a multivariate normal distribution. The example of values drawn from the multivariate normal distribution for calculating tp14 was showed in Appendix C.

3.5.15 Transitional probability of staying in No drainage state (tp15)

This probability is calculated by one minus Transitional probability from No drainage to Death. (tp15 = 1-tp14)

Table 3.2 demonstrated matrix of transition probabilities in this study. The transition probabilities in the model control the speed and direction of transitions between disease states.

Table 3.2 Matrix of transition probabilities.

	EBD	PostEBD	PTBD	PostPTBD	ND	Death
EBD	0	tp1	tp2	0	tp4 = 1-tp1-tp2-tp3	tp3
PostEBD	tp8	tp10 = 1-tp8-tp9	0	0	0	tp9
PTBD	0	0	0	tp5	tp7 = 1-tp5-tp6	tp6
PostPTBD	0	0	tp11	tp13=1-tp11-tp12	0	tp12
ND	0	0	0	0	tp15 = 1-tp14	tp14
Death	0	0	0	0	0	1

The values of transition probabilities of plastic stent in the first cycle and 2nd -104th cycle and transition probabilities of metal stent in the first cycle and 2nd -104th cycle were shown in Table 3.3 to table 3.6 respectively.

Table 3.3 Transition matrix for plastic stent in first cycle

	EBD	PostEBD	PTBD	PostPTBD	ND	Death
EBD	0	0.462	0.034	0	0.3	0.204
PostEBD	0.029	0.859	0	0	0	0.112
PTBD	0	0	0	0.939	0.054	0.007
PostPTBD	0	0	0.180	0.708	0	0.112
ND	0	0	0	0	0.733	0.267
Death	0	0	0	0	0	1

Table 3.4 Transition matrix for plastic stent in 2^{nd} -104^{th} cycle

	EBD	PostEBD	PTBD	PostPTBD	ND	Death
EBD	0	0.532	0.034	0	0.258	0.176
PostEBD	1 – exp (0.0004* $[(t-14)^{1.623}-t^{1.623}]$) (tp8)	1-0.112-tp8	0	0	0	0.112
PTBD	0	0	0	0.939	0.054	0.007
PostPTBD	0	0	0.180	0.708	0	0.112
ND	0	0	0	0	1-tp14	1 – exp(0.038* $[(t-14)^{0.792}-t^{0.792}]$) (tp14)
Death	0	0	0	0	0	1

Table 3.5 Transition matrix for metal stent in first cycle

	EBD	PostEBD	PTBD	PostPTBD	ND	Death
EBD	0	0.704	0.063	0	0.159	0.074
PostEBD	0.004	0.939	0	0	0	0.057
PTBD	0	0	0	0.939	0.054	0.007
PostPTBD	0	0	0.180	0.708	0	0.112
ND	0	0	0	0	0.733	0.267
Death	0	0	0	0	0	1

Table 3.6 Transition matrix for metal stent in 2^{nd} -104^{th} cycle

	EBD	PostEBD	PTBD	PostPTBD	ND	Death
EBD	0	0.818	0.063	0	0.081	0.038
PostEBD	$1 - \exp(0.00006*[(t-14)^{1.623}-t^{1.623}])$ (tp8)	1-0.057-tp8	0	0	0	0.057
PTBD	0	0	0	0.939	0.054	0.007
PostPTBD	0	0	0.180	0.708	0	0.112
ND	0	0	0	0	1-tp14	$1 - \exp(0.038*[(t-14)^{0.792}-t^{0.792}])$ (tp14)
Death	0	0	0	0	0	1

3.6 Health outcome measurement

In this study, the utilities of patients in each Markov state were measured by indirect method using the validated Official Thai version of EQ-5D. The answer from EQ-5D questionnaire could be converted into 0-1 utility score by Thai preference score for EQ-5D health state which is in the appendices B (Tongsiri, 2009).

The utilities of patients in the model were derived from 2 main sources. The first source was the unpublished trial evaluating quality of life in patients with unresectable hilar cholangiocarcinoma on palliative metallic stent versus plastic stent at Srinagarind hospital. (ClinicalTrials.gov Identifier: NCT00746538). This study evaluates the quality of life of unresectable hilar CCA patients before and after biliary plastic/metal stent drainage using the Functional Assessment of Cancer Therapy–Hepatobiliary (FACT-Hep) and EQ-5D questionnaire. The second source of utilities in this study was from data collection during Febuary 7, to March 7, 2011 at Srinagarind hospital. In this data collection, unresectable hilar CCA patients who had undergone PTBD for palliation of inoperable hilar CCA were identified at out-patient clinic, Surgical department, Srinagarind hospital. The patients were interviewed by Thai version EQ-5D questionnaire; in addition, serum bilirubin level of the patients before and after PTBD procedure were recorded. Case record form is in appendix A. Table3.7 summarized the utility of each disease state.

3.6.1 EBD and PTBD state

Utility of EBD state and PTBD state which were assumed to be equal to EBD state were retrieved from database of the trial "Quality of Life in Patients With Unresectable Hilar Cholangiocarcinoma on Palliative Metallic Stent Versus Plastic Stent" (ClinicalTrials.gov Identifier: NCT00746538). EQ-5D questionnaire was used to interview unresectable hilar CCA patients before drainage procedures were done.

Table 3.7 Summary of means and standard error (se) of utility parameters

Markov state	N	Mean	SE	Parameter distribution	Data source
EBD, PTBD	34	0.488	0.047	Beta	NCT00746538
Post-EBD	32	0.574	0.058	Beta	NCT00746538
Post-PTBD	14	0.494	0.031	Beta	*
No drainage	15	0.099	0.096	Gamma for utility decrement (D)	* and NCT00746538

NCT00746538, ClinicalTrials.gov identifier of unpublished trial evaluating quality of life in patients with unresectable hilar cholangiocarcinoma on palliative metallic stent versus plastic stent at Srinagarind hospital; *patients at Srinagarind hospital during Febuary 7, to March 7, 2011.

Details and sources of utilities of each disease states are as follows.

3.6.2 PostEBD state

Utility of postEBD state was also retrieved from database of the trial "Quality of Life in Patients With Unresectable Hilar Cholangiocarcinoma on Palliative Metallic Stent Versus Plastic Stent". EQ-5D questionnaire was used to interview unresectable hilar CCA patients who had successful EBD. The criteria of successful drainage were lack of jaundice or serum total bilirubin level less than 50% of baseline level within 2 weeks or 75% of baseline level within 4 weeks after EBD.

3.6.3 No drainage state

Utility of No drainage state is retrieved from

1. Database of the trial "Quality of Life in Patients With Unresectable Hilar Cholangiocarcinoma on Palliative Metallic Stent Versus Plastic Stent". Patients who had inadequate drainage after EBD plus PTBD or EBD alone and refused to had further drainage procedure were interviewed by EQ-5D

questionnaire. Data of six patients were retrieved from this database.

2. Nine unresectable hilar CCA patients who failed PTBD were identified and interviewed by EQ-5D questionnaire during Febuary 7, 2011 – March 7, 2011 at Department of Surgery, Srinagarind hospital.

3.6.4 Post PTBD state

Utility of PostPTBD state was collected by EQ-5D questionnaire during Febuary 7, 2011 – March 7, 2011 at Department of Surgery, Srinagarind hospital. The inclusion criteria of patients enrollment are as follows.

1 Patients with previously documented successful PTBD indicated by the lack of jaundice or TB less than 30% of baseline within 2 weeks or 50% of baseline within 4 weeks after PTBD.

2 Newly conducted as successful PTBD indicated by the lack of jaundice or TB less than 30% of baseline within 2 weeks or less than 50% of baseline within 4 weeks after PTBD.

3 Patients without fever (temperature less than 37.8^{o}C)

3.7 Cost data

This study used health care provider perspective; thus, direct medical costs were used in cost calculation of each alternative. The cost of treatment of each disease state in year 2008-2010 at Srinagarind hospital were calculated from the treatment charge of unresectable hilar CCA patients with endoscopic stent / PTBD insertion, patient with successful drainage from stent or PTBD and patients who failed drainage. Table3.8 summarized the charges of each disease state and the components of charge of each Markov state are as follows.

3.7.1 EBD state

Charge of EBD state consisted of charge of patients with ICD-10 C22.1 (Intrahepatic bile duct carcinoma; Cholangiocarcinoma) and ICD-9CM 51.10 (Endoscopic retrograde cholangiopancreatography; ERCP) and 51.11 (Endoscopic retrograde cholangiography; ERC) which were retrieved from Srinagarind hospital database in year 2008-2010. The patients were classified into metal and plastic stent group by the information from registration database at endoscopic unit, Srinagarind hospital.

Table 3.8 Summary of means and standard error (se) of cost of each disease state.

Markov state	N	Mean	SE	Parameter distribution	Data source
EBD with metal stent	32	44,203	3,369	Gamma	Database
EBD with plastic stent	84	28,968	2,852	Gamma	Database
Post-EBD with metal stent	20	2,309	508	Gamma	Database
Post-EBD with plastic stent	19	1,916	781	Gamma	Database
PTBD	151	29,867	1,996	Gamma	Database
Post-PTBD	68	2,759	733	Gamma	Database
No drainage	14	5,762	1,569	Gamma	Database

Database, Data were average charges calculated from patients in each Markov state in Srinagarind hospital in year 2009-2010; EBD, endoscopic biliary drainage; PTBD, percutaneous transhepatic biliary drainage.

3.7.2 PTBD state

Charge of PTBD state consisted of charge of patients with ICD-10 C22.1 and ICD-9CM 51.98 (Other percutaneous procedures on biliary tract) in combination with 87.51 (Percutaneous hepatic cholangiogram). Data were retrieved from Srinagarind hospital database in year 2008-2010.

3.7.3 PostEBD state

Charge of PostEBD state were retrieved from charge of patients with EBD who were followed-up at out-patient department or admitted in hospital because of complication of EBD and CCA at Srinagarind hospital. Data were retrieved from Srinagarind hospital database in year 2008-2010.

3.7.4 PostPTBD

Charge of PostPTBD state consisted of charge of patients with ICD-10 C22.1 and ICD-9CM 51.98 in combination with 87.51 who had palliative medication and routine laboratory examination at out-patient department or admitted in hospital because of complication of PTBD and CCA at Srinagarind hospital. Data were retrieved from Srinagarind hospital database in year 2008-2010.

3.7.5 No drainage

Charge of No drainage state consisted of charge of patients with ICD-10 C22.1 who failed EBD and/or PTBD drainage and received palliative treatment at out-patient department or admitted in hospital because of disease complication at Srinagarind hospital. Data were retrieved from Srinagarind hospital database in year 2008-2010

3.7.6 Death

Charge of Death state was assumed to be zero.

In this study, cost to charge ratio of 0.8 was used to convert treatment charges of unresectable hilar CCA in each disease state into costs (Kasemsap, n.d.; Werayingyong, 2006). Cost of treatment in year 2008 and 2009 are changed into cost in year 2010 by medical care Consumer Price Index (CPI). Thai medical care CPI in year 2008, 2009 and 2010 were 100.5, 100.9 and 101.06 respectively (Bureau of Trade and Economic Indices, 2010).

3.8 Model assumptions.

The following statements are the assumptions of Markov model in this study.

1. All patients with complex, Bismuth II, III and IV, unresectable hilar CCA who decided to have endoscopic biliary stent drainage were enrolled into the model.
2. Patients were assessed at 2^{nd} week after stent and PTBD catheter insertion to determine the effectiveness of drainage.
3. In successful biliary drainage groups, stent or PTBD catheter exchange will be done in case of stent / catheter occlusion.
4. Utility of patients in EBD, PTBD state were assumed to be equal to utility of unresectable hilar CCA patients before biliary drainage procedure.
5. Cost of procedure and disease complications such as cholangitis were included in the related disease states.
6. Cost of death state was assumed to be zero.

3.9 Cost-utility Analysis

The incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in total costs between metal and plastic stent groups by the difference in the QALYs gained between metal and plastic stent groups. ICER is the value of additional costs per one additional QALY gained from metal stent relative to plastic stent.

The ICER was calculated by the follow equation.

$$ICER = \frac{Cost_{plastic\ stent} - Cost_{metal\ stent}}{QALYs_{metal\ stent} - QALYs_{plastic\ stent}}$$

3.10 Dealing with uncertainty

Deterministic sensitivity analysis (DSA) and probabilistic sensitivity analysis (PSA) were used in this study. In one-way sensitivity analysis, one parameter was varied according to its 95% CI and the incremental cost-effectiveness ratio was calculated. The results of one-way sensitivity analyses were presented in form of Tornado diagram.

In PSA, all parameters were randomly varied along its standard error at the same time. Then incremental cost-effective ratios were calculated. These are the steps of PSA.

1. Define the point estimate (mean value) and standard error of input parameters.

2. Assign distribution for input parameters

2.1 Gamma distribution for cost.

Gamma distribution is in the interval between 0 to positive infinity and it can be skewed to reflect the characteristic of the cost data.

2.2 Beta distribution for probabilities, utilities

Beta distribution constrained on the interval between 0 and 1 which is suitable for probability and utility data.

2.3 Multivariate normal distribution for transitional probabilities that calculated from the parameters of parametric survival regression (Weibull regression and exponential regression).

The multivariate normal distribution is derived from Cholesky decomposition of covariance matrix. The Cholesky decomposition method begins with variance-covariance matrix (matrix V) which we got from the regression. Then matrix T or Cholesky decomposition of matrix V is calculated from this matrix. (matrix T multiplied by its transpose is covariance matrix, V. In this technique, the Cholesky decomposition of matrix V is the lower triangular matrix. Then vector of correlated variable (vector x) that we want to used in PSA is generated by the following formula (Briggs, 2006).

$$x = y + Tz$$

y = vactor of parameter mean values

z = vector of independent standard normal variate

Vector x that derived from covariance matrix of Weibull regression are the random value of constant coefficient, parameter coefficient(s) and ln γ that drawn from multivariate normal distribution. Likewise, vector x that derived from covariance matrix of exponential regression are the random value of constant coefficient and parameter coefficient(s) that drawn from multivariate normal distribution.

2.4 In no drainage state, the health state utility is close to zero and the value less than zero is possible. Therefore, binomial distribution is not appropriate in this setting. To solve this problem, the utility decrement (D) is used instead. D is calculated from the following equation

$$D = 1 - U$$

U = utility score

Now the values of D are in the range of zero to positive number; therefore, we can use gamma distribution for utility decrement in PSA. After the process of randomly drawn was complete, D was converted back to U again.

3. Perform PSA by computer-based second order Monte Carlo simulation.
4. Present the result in the form of scatter plot of incremental cost and incremental effectiveness, and Cost-effectiveness acceptability curve. (CEAC)

3.11 Discounting

All costs and consequences that occur beyond 1 year will be discounted into the present value of base year by the following formula. (Permsuwan, Guntawongwan, and Buddhawongsa, 2008)

$$PV = FV *(1 / (1 + r)^t)$$

PV=present value FV=future value

r=discount rate t=the duration or time at year t

Discount rate of 3% per year is used in calculation of both cost and consequence in base case analysis and the discount rates of 0% and 6% are used in one-way sensitivity analysis.

3.12 Programming software

Microsoft Excel 2007® was used to calculate costs and outcomes of the model in based-case analysis and sensitivity analyses.

CHAPTER IV

RESULTS AND DISCUSSION

This chapter provides the empirical results and discussion of the results of the study as follows.

4.1 Results

The results of the study were retrieved from base-case analyses and sensitivity analyses. Base-case analyses used the mean value of the input parameters to calculate the results. In sensitivity analysis, the resulted were calculated using the value of input parameters that varied in reasonable ranges.

4.1.1 Base-case analyses

Using the health care provider perspective, the total costs and quality adjusted life years (QALYs) gained from endoscopic plastic and metal stent drainage in unresectable complex hilar CCA are showed in Table 4.1

Table 4.1 Cost-effectiveness results of base-case analysis

	Plastic stent	Metal stent
Total lifetime cost (baht)	62,938	98,799
Total life expectancy (years)	0.27	0.56
Total QALYs (years)	0.10	0.29
Incremental cost per life expectancy (bath per life year gained)		124,635
Incremental cost per QALY (bath per QALY gained)		192,584

QALY, Quality adjusted life year

Under the baseline assumptions, the total lifetime cost of endoscopic biliary drainage by metal stent in unresectable complex hilar CCA is 98,799 baht. The average life expectancy and the average QALYs are 0.56 and 0.29 years/patient respectively. Besides, the total lifetime cost of endoscopic biliary drainage by plastic stent is 62,938 baht. The average life expectancy and the average QALYs are 0.27 and 0.10 years/patients respectively.

The life expectancy and quality-adjusted life expectancy of the patients in metal stent group are longer than those in plastic stent group. However, the total costs of treatment of patients in metal stent group are higher than the total cost of patients in plastic stent group. From incremental cost-effectiveness result, we have to pay 124,635 baht and 192,584 baht for one life year gained and one additional QALY gained from using metal stent relative to plastic stent.

4.1.2 Sensitivity Analyses

A probabilistic sensitivity analysis was done using a second order Monte Carlo simulation. The scatter plots of one thousand simulation processes of incremental cost and incremental effective in terms of incremental QALY are illustrated in Figure 4.1.

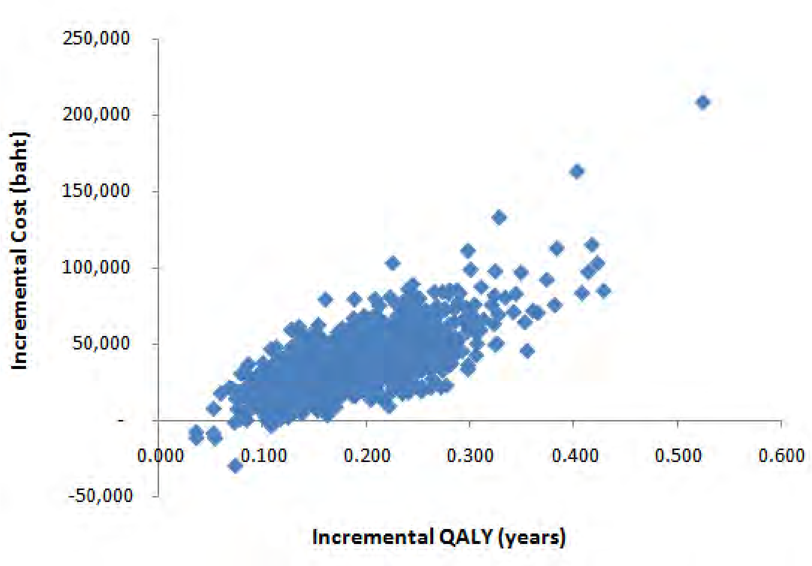


Figure 4.1. The incremental cost and incremental QALYs scatter plot.

From Figure 4.1, most of incremental cost-effectiveness ratio scatter plots were in the right-upper quadrant which means that endoscopic metal stent drainage has higher cost compared to plastic stent and it is more effective than plastic stent.

The result of probabilistic sensitivity analysis in the form of cost-effectiveness acceptability curve (CEAC) is presented in Figure 4.2.

CEAC demonstrated the probability of cost-effectiveness of each type of stent for any particular willingness to pay or decision threshold. From figure 4.2, metal stent is preferable if the willingness to pay or decision threshold is higher than 210,000 baht. The 95% uncertainty intervals on cost-effectiveness of metal stent are approximately 50,000 baht to 350,000 baht.

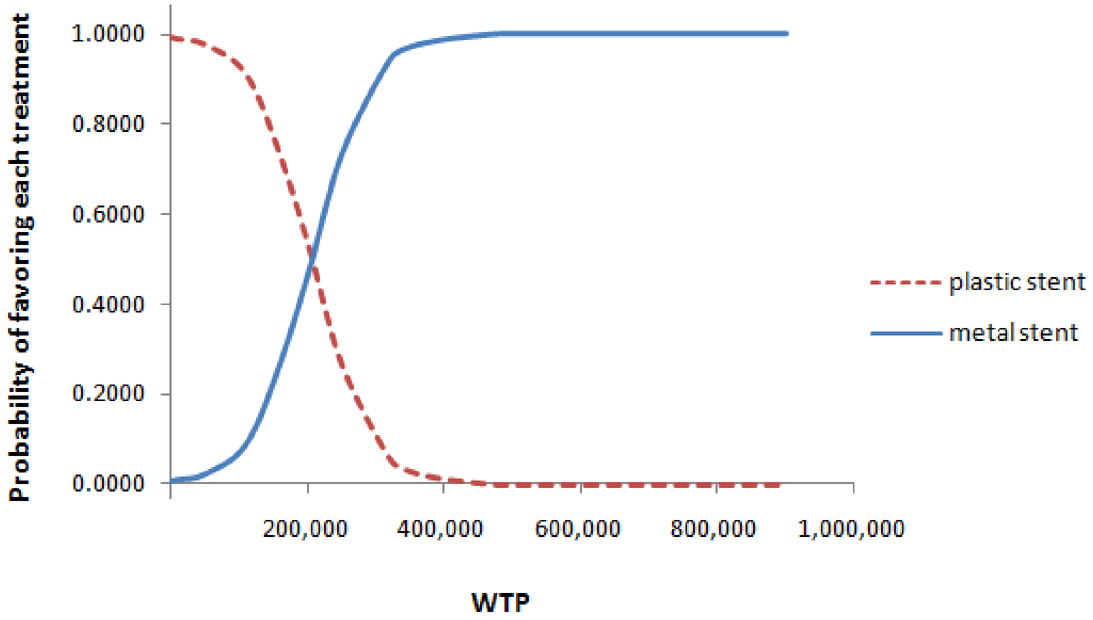


Figure 4.2. The cost-effectiveness acceptability curve.

At the willingness to pay threshold of 158,000 and 474,000 baht or one and three times GDP per capita in year 2010 (Bank of Thailand, 2011), the probabilities of metal stent being cost-effective are 26% and 99.9% respectively.

In one-way sensitivity analyses, the value of input parameter was varied one by one in the range of its 95% confidence interval then the lower bound and upper bound ICER were calculated. Table 4.2 demonstrated results of one-way sensitivity analysis of each parameter and Figure 4.3 demonstrated the results of one-way sensitivity analysis in the form of tornado diagram.

Table 4.2 Results of one-way sensitivity analysis

Parameters	Base-case value	95% Confidence Interval	Minimum and Maximum ICER (Baht)	Differences in ICER (Baht)
Ebd Utility	0.488	0.580-0.395	192,446 - 192,722	277
Ptbd Utility	0.488	0.580-0.395	192,239 - 192,930	691
Discounting	3%	6% - 0%	192,131 - 193,067	936
Post-Ptbd Utility	0.494	0.555-0.433	191,854 - 193,319	1,465
Efficacy of plastic stent_PP	0.532	0.387-0.667	189,860 - 196,145	6,284
Late MR of EBD_metal	0.038	0.148-0.009	182,969 - 195,082	12,113
Efficacy of metal stent_PP	0.818	0.993-0.702	184,963 - 200,077	15,114
No Drainage Utility	0.096	-0.089-0.287	183,818 - 202,227	18,409
Early MR of EBD_metal	0.074	0.144-0.004	180,850 - 204,112	23,262
Efficacy of plastic stent_ITT	0.462	0.329-0.595	181,281 - 206,196	24,915
Early MR of EBD_plastic	0.204	0.096-0.312	174,325 - 210,351	36,026
Late MR of EBD_plastic	0.176	0.043-0.578	183,256 - 219,896	36,640
Cost PostEBD_plastic (baht)	1,916	3,447-385	170,419 - 214,746	44,327
Efficacy of metal stent_ITT	0.704	0.827-0.581	171,012 - 226,638	55,626
Post-Ebd Utility	0.574	0.688-0.460	161,259 - 239,011	77,752
Cost of EBD_plastic (baht)	28,968	34,557-23,378	152,371 - 232,795	80,424
Cost of EBD_metal (baht)	44,203	37,599-50,806	143,741 - 241,425	97,684
Cost PostEBD_metal (baht)	2,309	1,043-3,045	133,916 - 251,252	117,336
Cost to charge ratio	0.8	0.7-1.25	168,511 - 300,912	132,401
Baseline hazard of plastic stent occlusion	0.0004	0.00444-0.00004	110,613 - 270,031	159,418
Baseline hazard of metal stent occlusion	0.00006	0.00002-0.00017	126,955 - 345,491	218,536

ITT, intention to treat analysis; MR, mortality rate; PP, per protocol analysis.

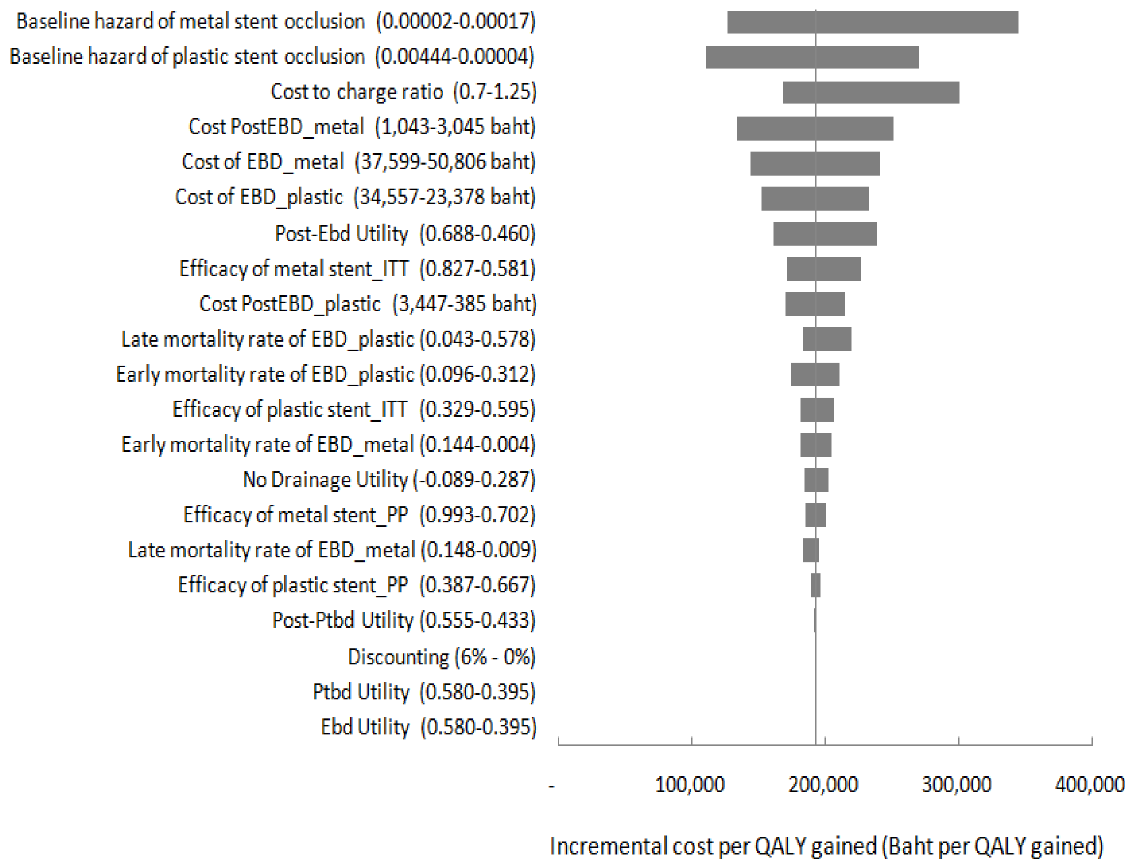


Figure 4.3 Tornado diagram of one-way sensitivity analyses.

From table 4.2 and figure 4.3, the two most influential variables are baseline hazard rate of metal stent and plastic stent occlusion. When baseline hazard of metal stent occlusion or probability of metal stent occlusion is changed, the incremental cost per QALY is changed in the same direction. In case of plastic stent, the effects of baseline hazard of stent occlusion on the incremental cost per QALY is in the opposite direction.

The next four parameters that affect incremental cost per QALY gained are cost parameters: cost to charge ratio, cost of treatment after metal stent insertion (PostEBD_metal state), cost of metal stent insertion and its complication (cost of EBD_metal state), and cost of plastic stent insertion and its complication. (EBD_plastic state)

Among the utilities of each disease state, utility of PostEBD state has the greatest impact on incremental cost-effectiveness ratio compared to the others. Discount rate has little impact on the result of the study.

4.2 Discussion

Until now there is no study about cost-effectiveness or cost-utility analysis of plastic and metal stent drainage in patients with unresectable hilar CCA. Although there were a few cost-effectiveness studies comparing plastic and metal stent in patients with obstructive jaundice from malignant CBD obstruction, the results from those studies can not apply to unresectable hilar CCA directly. The treatment outcome of CBD obstruction and hilar obstruction may be different because of the difference in anatomy of bile duct. Hilar lesion is far from the ampulla of Vater, bile duct openning; therefore, it needs longer stent compared to CBD lesion; in addition, it requires stent that have ability to drain bile from the side branches of biliary tree because it locates at hepatic duct bifurcation and it is close to secondary branch of bile duct. (Perdue, et al., 2008)

This study is the first cost-effectiveness study compared plastic and metal stent drainage in unresectable complex hilar cholangiocarcinoma using Markov model. In the evaluation of cancer treatment, not only the effectiveness of treatment but also the quality of life of patients during treatment is important. These are the reasons why we used cost-utility analysis in this study. In addition cost-utility analysis can address the issue of the opportunity cost of funding the new program and its result could be compared across different programs. (Drummond, 2005)

Effectiveness data in this study are derived from RCT conducted in our country; therefore, it is reasonable to generalize the result of this study to other hospitals, which have the similar cost structure and service level to Srinagarind hospital. In addition, patient-level data from this RCT are available for calculating transition probabilities. Thus, we can calculate time-dependent transition probabilities, which are more similar to the natural history of disease than fixed transition probabilities, from Weibull survival regression.

According to the threshold value of cost-effectiveness recommended by World Health Organization, the value between one and three times GDP per capital is cost-effective (World Health Organization, The Commission on Macroeconomics and Health, 2001). The results of base-case analyses showed that endoscopic biliary drainage by metal stent is cost-effective compared to plastic stent in management of unresectable complex hilar cholangiocarcinoma patients in Srinagarind hospital. From CEAC, at the upper bound of willingness to pay (three times GDP per capita) which was approximately 474,000 baht in 2010, the probability of metal stent being cost-effective is 99.9% compared to plastic stent.

The reasons why metal stent is cost-effective relative to plastic stent in this study are as follows.

1. Metal stent has higher efficacy in biliary drainage.
2. The utility or quality of life of patients with adequate biliary drainage is higher than patients who failed drainage.
3. The metal stent occlusion rate is lower than plastic stent.
4. The survival of the patients in metal stent group is longer than patients in plastic stent group.

From these reasons, patients in metal stent group have high tendency to stay in the cheap and high utility Post-EBD state. The chance of re-entering into the expensive EBD state is low because of its low occlusion rate. Consequently, metal stent is cost-effective relative to plastic stent in patients with unresectable complex hilar CCA.

From tornado diagram, the two most important parameters that affect the incremental cost-effectiveness ratio are baseline hazard of metal and plastic stent occlusion which derived from stent patency time. When the metal stent patency time increased, the incremental cost-effectiveness ratio will decrease because the cost related to repeating endoscopic procedure is decreased. The effect of baseline hazard of plastic stent occlusion is in the opposite direction of metal stent patency time.

Incremental cost-effective ratio is also sensitive to cost of EBD state which includes cost of stent insertion and cost of management of its complication, and cost of Post-EBD state which includes cost of follow-up therapy after stent insertion, cost of disease complication and stent related complication. These costs are important because they directly affect the cost of management in each treatment strategy. From table 3.1, 3.7 and 3.8, the transition probabilities of re-entering into expensive, low utility EBD state and staying in cheap and high utility Post-EBD state are substantially different between two treatment strategies. This reason can explain why the incremental cost-effective ratio sensitive to cost of EBD and Post-EBD state. Another factor that might explain this result is the high variance of costs data.

Among utilities of each disease state, utility of Post-EBD state had the greatest impact on incremental cost-effectiveness ratio because this state has the highest utility scores and the chance of staying in this state is substantially different between two treatment strategies due to the difference in occlusion rate of each type of stent and the difference in mortality rate of patient in each group.

Discount rate had little impact in this study because the majority of patients died in the first year; therefore, most of the costs and outcomes were measured in the first year without discounting.

It is well known that the clinical and economic analyses should be interpreted within the context of parameters in the study. Therefore, the result of this study should be generalized within the clinical context of randomized controlled trial that used in this study and within the setting of tertiary care hospital that have similar cost structure and service level to Srinagarind hospital.

Despite the limitations, this study provided the evidence that endoscopic metal stent drainage is cost-effective relative to plastic stent in palliative care of unresectable complex hilar CCA patients at tertiary care hospital setting.

CHAPTER V

SUMMARY AND RECOMMENDATIONS

5.1 Summary

CCA is the most common biliary tract cancer in Thailand especially in the Northeast region of Thailand. Hilar CCA, CCA at liver hilum, can obstruct bile flow and cause symptoms related to bile duct obstruction such as jaundice, pruritus, clay-color stool and dark urine. Some patients may have life threatening complication such as ascending cholangitis. The treatment of choice of early stage hilar CCA is surgical resection. However, the patients usually present in advanced stage; therefore most of them require palliative drainage therapy.

Although the patients did not have survival benefit from palliative drainage, it could alleviate obstructive symptoms and improve their quality of life. At the present time, the commonly used palliative drainage techniques are EBD, PTBD and bypass surgery. However, EBD using biliary stent is the most frequently used treatment modality compared to PTBD or biliary bypass surgery in patients with unresectable hilar cholangiocarcinoma because EBD is less invasive than bypass surgery and it has fewer early complications. Compared to patients with PTBD who has external drainage catheter and bag outside the body, patients with EBD has less discomfort because the biliary stent is inside the body.

In clinical practice, there are two types of biliary stents, tubular plastic and open-mesh metal stent. Metal stent is more expensive than plastic stent but it has low occlusion rate and low number of re-intervention. In addition, patients with metal stent insertion had substantially lower rate of complication compared to patients in plastic stent group. However, to choose stent in EBD procedure, not only the effectiveness of stents which included successful drainage, patency time and complications are considered but also the cost of treatment is concerned. Nevertheless, until now, there is no cost-effectiveness study of plastic and metal stent in hilar CCA patients. Although, there are a few cost-effectiveness studies of plastic and metal stents in malignant obstruction of common bile duct (CBD) but the results could not be directly applied to hilar CCA patients because the anatomy of bile duct at obstructive sites are different. Therefore, we conducted this study to evaluate the cost effectiveness of endoscopic metal and plastic stent drainage in terms of incremental cost per additional QALY in patients with unresectable hilar CCA at Srinigarind hospital.

Decision analytic model, Markov model, was used to compare cost-utility of endoscopic biliary drainage using metal and plastic stent in patients with unresectable hilar CCA. Markov model was used in this study because it could simulate the natural course of disease that some events could occur repeatedly over time such as endoscopic procedure or PTBD. The Markov states or disease states in this study consisted of EBD, PTBD, PostEBD, PostPTBD, No drainage and Death state. These disease states were determined according to the natural history of disease and clinical practice guideline of CCA in Thailand.

The cohorts of patients who decided to have palliative treatment by endoscopic biliary drainage entered the model at EBD state and moved to other Markov states according to its relationship with other states and the transition probability of moving to or staying in each disease state. The cycle length of 2 weeks was chosen because it was close to the shortest time frame that could capture the clinical courses of disease in this model. In addition, the time horizon in this study is the whole life time of the patients after stent insertion because most of them will die within 6 months to 1 year from advanced stage cancer.

The transitional probabilities of each disease state were attached to model to determine the probability of moving from one state to another state. Most of transition probabilities were based on the ongoing RCT at Srinagarind hospital, KhonKaen University,“Efficacy and Cost Analysis of Plastic Stent Compare to Metallic Stent in Hilar Cholangiocarcinoma” (ClinicalTrials.gov Identifier: NCT00721175). This study is selected because it is the only RCT that compared the effectiveness of metal and plastic stent in unresectable hilar CCA. This study is in the data analytic process. The rest of transition probabilities were reviewed from literature. Table 3.1 summarized the transition probabilities of each disease state in this study. The transition probabilities derived from survival data of patients in RCTs at Srinagarind hospital such as transition probability from EBD to Dead, transition probability from PostEBD to EBD, transition probability from PostEBD to Dead and transition probability from No drainage to Dead were calculated from the parameters of parametric survival regression (exponential regression or Weibull regression) of the patients in this RCT.

The value of health status or utilities was also attached to the model. The utilities of unresectable hilar CCA patients at Srinagarind hospital were used in this study (Table 3.2). Patients in each Markov state were interviewed by the validated Official Thai version EQ-5D questionnaire. Then the answers from questionnaires were converted into 0-1 utility score by Thai preference score for EQ-5D health state.

Finally, costs were attached to the model. The treatment cost of each disease state is calculated from the treatment charge of unresectable hilar CCA patients at Srinagarind hospital in 2008-2010. Costs of treatment in year 2008-2009 were converted into year 2010 by Thai Medical Care Consumer Price Index. Table3.3 summarized the costs of each disease state. Health care provider perspective was used to estimate cost of treatment in this study.

The assumptions of the model in this study are as follows.

1. All patients with complex, Bismuth II, III and IV, unresectable hilar CCA who decide to have endoscopic biliary stent drainage are enrolled into the model.
2. Patients are assessed at 2nd week after stent and PTBD catheter insertion to determine the effectiveness of drainage.
3. In successful biliary drainage groups, stent or PTBD catheter exchange will be done in case of stent / catheter occlusion.
4. Utility of patients in EBD, PTBD state are assumed to be equal to utility of unresectable hilar CCA patients before biliary drainage procedure.
5. Cost of procedure and disease complications such as cholangitis are included in the related disease states.
6. Cost of death state is assumed to be zero.

The results of Markov Model, both base-case analyses and PSA were calculated by Microsoft Excel 2007®. In base-case analysis, result was presented in terms of incremental cost-effectiveness ratio or incremental cost per additional QALY. The discount rate of 3% was used to discount both costs and consequences.

To handle the uncertainty of the results, one-way sensitivity analysis and PSA were used. The result of one-way sensitivity analysis was presented in the form of Tornado diagram. In PSA, all parameters are randomly varied along its standard error at the same time. Then the incremental cost-effective ratios were calculated. This process was repeated one thousand times. (second order Monte Carlo simulation) The results of PSA were presented in the form of scatter plot of incremental cost and incremental effectiveness, and Cost-effectiveness acceptability curve.

The results of base-case analysis showed that incremental cost-effectiveness ratio is equal to 192,584 baht per additional QALY. The results of PSA revealed that most of incremental cost-effectiveness ratio scatter plot were in the right upper quadrant. The results from base-case analysis and PSA, scatter plot, confirmed that endoscopic metal stent drainage has higher cost compared to plastic stent and it is more effective than plastic stent. The results of PSA which presented in the form of CEAC indicated that metal stent is preferable when the willingness to pay is above 210,000 baht/QALY. At the willing to pay level of one and three times GDP per capita, the probabilities of metal stent being cost-effective are 26% and 99.9% respectively.

In conclusions, according to model assumptions and the limitations of the study, endoscopic biliary drainage using metal stent compared to plastic stent is cost-effective at the willingness to pay threshold or decision threshold between one and three times GDP per capita in unresectable complex hilar CCA patients in year 2010.

5.2 Limitations of the Study

The limitations of this study are as follows.

1. Costs of treatment were retrieved from database of Srinagarind hospital which is the tertiary referral hospital; therefore, it is difficult to generalize cost from one hospital to the others because of the difference in cost structure and pattern of clinical practice or level of services.

2. Cost to charge ratio of Srinagarind hospital is not available; therefore cost to charge ratio of 0.8 which derived from the general administration information of hospital in Thailand is used in this study.

3. The effectiveness of metal and plastic stent in this study were retrieved from the ongoing randomized controlled trial: Efficacy and Cost Analysis of Plastic Stent Compare to Metallic Stent in Hilar Cholangiocarcinoma (ClinicalTrials.gov Identifier: NCT00721175), at Srinagarind hospital, KhonKaen University. Therefore, we should take the clinical context of this randomized controlled trial into account when interpreting the results of this study.

5.3 Policy Implications

From the results of base case analysis and PSA in this study, at the willingness to pay one to three times GDP per capita in year 2010, metal stent is cost-effective compared to plastic stent in unresectable hilar CCA.

In 2010, National Health Security Office (NHSO) included metal biliary stent in benefit package of Universal Coverage Scheme (UCS). Meanwhile, this study was conducted during 2010 to 2011. The result from this study is the evidence supported the decision of NHSO regarding the use of metal stent in unresectable CCA patients in UCS.

Currently, patients in Social Security Scheme (SSS) cannot reimburse the cost of metal stent in treatment of unresectable CCA. According to the result of this study which shown that metal stent is cost effective compared to plastic stent in unresectable hilar CCA, Social Security Office should consider to include metal biliary stent in the benefit package of SSS for treatment of these patients.

5.4 Recommendations for Further Researchers

Apart from endoscopic biliary stent, palliative biliary drainage in hilar CCA could be performed by other techniques such as surgical bypass, PTBD and percutaneous transhepatic biliary stent insertion. Surgical bypass and PTBD have been practiced for a long time; however, there is no cost-effectiveness study comparing these techniques with endoscopic biliary drainage in hilar CCA. Besides, percutaneous transhepatic biliary stent insertion has been practiced for some time by interventional radiologist. The successful biliary decompression rate in percutaneous treanshepatic metal stent was significantly higher than endoscopic metal stent and the overall procedure related complications were similar in both groups (Paik et al., 2009). However, the cost-effective study comparing percutaneous and endoscopic metal stent drainage in hilar CCA is not available.

Therefore, the cost-effectiveness of these techniques including surgical bypass, endoscopic biliary stent, PTBD and percutaneous biliary stent should be studied to guide the policy makers and physicians in selecting the cost-effective modalities in management of unresectable hilar CCA patients in the future.

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APPENDICES

APPENDIX A

Case Record Form

CASE RECORD FORM

COST UTILITY ANALYSIS OF ENDOSCOPIC BILIARY STENT IN UNRESECTABLE HILAR CHOLANGIOCARCINOMA: DECISION ANALYTIC MODELING APPROACH

ID………………………… Date………………………

Sex [0] female [1] male Age ……… years

ภูมิลำเนาจังหวัด...

PTBD date……………………………….. Revision…………….. times.

Symptom & Sign

Pruritus	[1] yes	[2] no
Jaundice	[1] yes	[2] no
Fever	[1] yes	[2] no
RUQ pain	[1] yes	[2] no

Lab: before PTBD**:** date………………

Albumin………. TB……………… DB…………… ALP…………

Lab: Day of interview

Albumin………. TB……………… DB………….. ALP…………

EQ-5D questionnaire: Thai version

Part 1 The Thai EQ-5D questionnaire

กรุณาทำเครื่องหมาย X ในช่องสี่เหลี่ยม (☐) ของคำถามแต่ละข้อที่ตรงกับสภาวะสุขภาพของท่านในวันนี้มากที่สุด

1. **การเคลื่อนไหว**

ข้าพเจ้าไม่มีปัญหาในการเดิน ☐

ข้าพเจ้ามีปัญหาในการเดินบ้าง ☐

ข้าพเจ้าไม่สามารถไปไหนได้ และจำเป็นต้องอยู่บนเตียง ☐

2. **การดูแลตนเอง**

ข้าพเจ้าไม่มีปัญหาในการดูแลตนเอง ☐

ข้าพเจ้ามีปัญหาในการอาบน้ำหรือแต่งตัวบ้าง ☐

ข้าพเจ้าไม่สามารถอาบน้ำหรือแต่งตัวด้วยตนเองได้ ☐

3. **กิจกรรมที่ทำเป็นประจำ (เช่น การทำงาน การเรียนหนังสือ การทำงานบ้าน การทำกิจกรรมในครอบครัว หรือการทำกิจกรรมยามว่าง)**

ข้าพเจ้าไม่มีปัญหาในการทำกิจกรรมที่ทำเป็นประจำ ☐

ข้าพเจ้ามีปัญหาในการทำกิจกรรมที่ทำเป็นประจำอยู่บ้าง ☐

ข้าพเจ้าไม่สามารถทำกิจกรรมที่ทำเป็นประจำได้ ☐

4. **ความเจ็บปวด ไม่สุขสบาย**

ข้าพเจ้าไม่มีอาการเจ็บปวดหรืออาการไม่สุขสบาย ☐

ข้าพเจ้ามีอาการเจ็บปวดหรืออาการไม่สุขสบายปานกลาง ☐

ข้าพเจ้ามีอาการเจ็บปวดหรืออาการไม่สุขสบายมากที่สุด ☐

5. **ความวิตกกังวล ซึมเศร้า**

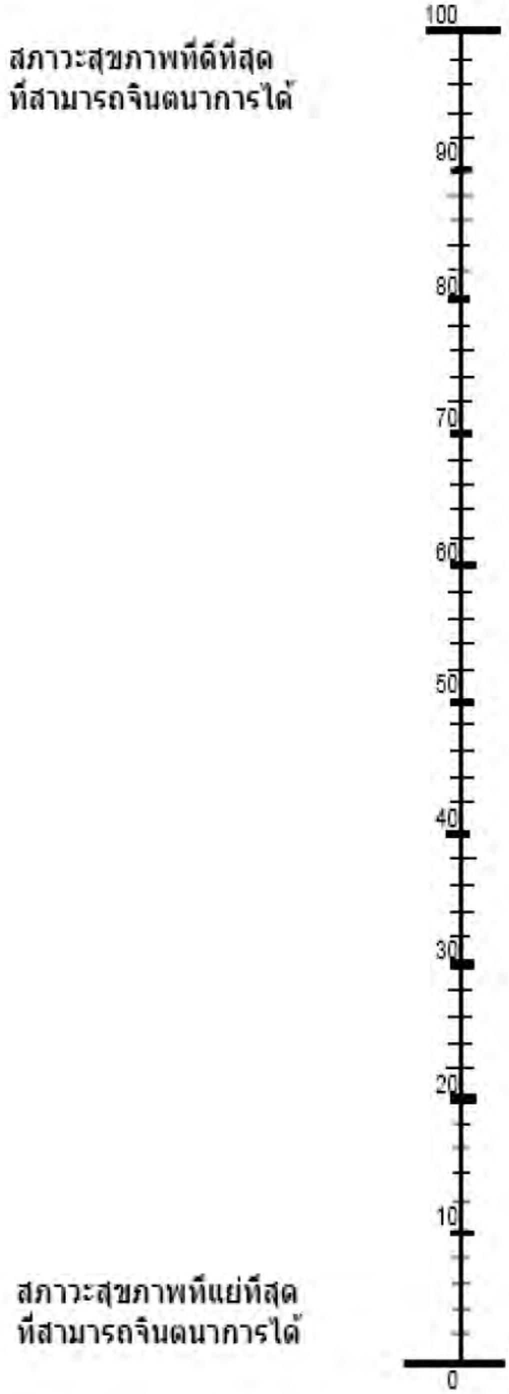
ข้าพเจ้าไม่รู้สึกวิตกกังวลหรือซึมเศร้า ☐

ข้าพเจ้ารู้สึกวิตกกังวลหรือซึมเศร้าปานกลาง ☐

ข้าพเจ้ารู้สึกวิตกกังวลหรือซึมเศร้ามากที่สุด ☐

EQ-5D visual analogue scale: Thai version

Part 2 Thermometer scale “Own health state”



APPENDIX B

General Data

Thai preference scores for EQ-5D health states.

EQ-5D state	Score	EQ-5D state	Score	EQ-5D state	Score
1 1 1 1 1	1.000	1 2 2 2 2	0.513	1 3 3 3 3	-0.022
1 1 1 1 2	0.766	1 2 2 2 3	0.295	2 1 1 1 1	0.677
1 1 1 1 3	0.548	1 2 2 3 1	0.269	2 1 1 1 2	0.645
1 1 1 2 1	0.726	1 2 2 3 2	0.237	2 1 1 1 3	0.427
1 1 1 2 2	0.693	1 2 2 3 3	0.158	2 1 1 2 1	0.605
1 1 1 2 3	0.475	1 2 3 1 1	0.419	2 1 1 2 2	0.573
1 1 1 3 1	0.449	1 2 3 1 2	0.387	2 1 1 2 3	0.355
1 1 1 3 2	0.417	1 2 3 1 3	0.309	2 1 1 3 1	0.328
1 1 1 3 3	0.338	1 2 3 2 1	0.347	2 1 1 3 2	0.296
1 1 2 1 1	0.739	1 2 3 2 2	0.315	2 1 1 3 3	0.217
1 1 2 1 2	0.707	1 2 3 2 3	0.236	2 1 2 1 1	0.618
1 1 2 1 3	0.489	1 2 3 3 1	0.210	2 1 2 1 2	0.586
1 1 2 2 1	0.666	1 2 3 3 2	0.178	2 1 2 1 3	0.368
1 1 2 2 2	0.634	1 2 3 3 3	0.099	2 1 2 2 1	0.546
1 1 2 2 3	0.416	1 3 1 1 1	0.417	2 1 2 2 2	0.513
1 1 2 3 1	0.390	1 3 1 1 2	0.384	2 1 2 2 3	0.295
1 1 2 3 2	0.358	1 3 1 1 3	0.306	2 1 2 3 1	0.269
1 1 2 3 3	0.279	1 3 1 2 1	0.344	2 1 2 3 2	0.237
1 1 3 1 1	0.540	1 3 1 2 2	0.312	2 1 2 3 3	0.158
1 1 3 1 2	0.508	1 3 1 2 3	0.234	2 1 3 1 1	0.419
1 1 3 1 3	0.430	1 3 1 3 1	0.207	2 1 3 1 2	0.387
1 1 3 2 1	0.468	1 3 1 3 2	0.175	2 1 3 1 3	0.309
1 1 3 2 2	0.436	1 3 1 3 3	0.096	2 1 3 2 1	0.347
1 1 3 2 3	0.357	1 3 2 1 1	0.357	2 1 3 2 2	0.315
1 1 3 3 1	0.331	1 3 2 1 2	0.325	2 1 3 2 3	0.236
1 1 3 3 2	0.299	1 3 2 1 3	0.247	2 1 3 3 1	0.210
1 1 3 3 3	0.220	1 3 2 2 1	0.285	2 1 3 3 2	0.178
1 2 1 1 1	0.677	1 3 2 2 2	0.253	2 1 3 3 3	0.099
1 2 1 1 2	0.645	1 3 2 2 3	0.174	2 2 1 1 1	0.556
1 2 1 1 3	0.427	1 3 2 3 1	0.148	2 2 1 1 2	0.524
1 2 1 2 1	0.605	1 3 2 3 2	0.116	2 2 1 1 3	0.306
1 2 1 2 2	0.572	1 3 2 3 3	0.037	2 2 1 2 1	0.484
1 2 1 2 3	0.354	1 3 3 1 1	0.298	2 2 1 2 2	0.452
1 2 1 3 1	0.328	1 3 3 1 2	0.266	2 2 1 2 3	0.234
1 2 1 3 2	0.296	1 3 3 1 3	0.188	2 2 1 3 1	0.207
1 2 1 3 3	0.217	1 3 3 2 1	0.226	2 2 1 3 2	0.175
1 2 2 1 1	0.618	1 3 3 2 2	0.194	2 2 1 3 3	0.096
1 2 2 1 2	0.586	1 3 3 2 3	0.115	2 2 2 1 1	0.497
1 2 2 1 3	0.368	1 3 3 3 1	0.089	2 2 2 1 2	0.465
1 2 2 2 1	0.546	1 3 3 3 2	0.057	2 2 2 1 3	0.247

EQ-5D state	Score	EQ-5D state	Score	EQ-5D state	Score
2 2 2 2 1	0.425	2 3 3 3 2	-0.064	3 2 2 2 1	-0.026
2 2 2 2 2	0.392	2 3 3 3 3	-0.143	3 2 2 2 2	-0.058
2 2 2 2 3	0.175	3 1 1 1 1	0.226	3 2 2 2 3	-0.137
2 2 2 3 1	0.148	3 1 1 1 2	0.194	3 2 2 3 1	-0.163
2 2 2 3 2	0.116	3 1 1 1 3	0.116	3 2 2 3 2	-0.195
2 2 2 3 3	0.037	3 1 1 2 1	0.154	3 2 2 3 3	-0.274
2 2 3 1 1	0.299	3 1 1 2 2	0.122	3 2 3 1 1	-0.013
2 2 3 1 2	0.266	3 1 1 2 3	0.043	3 2 3 1 2	-0.045
2 2 3 1 3	0.188	3 1 1 3 1	0.017	3 2 3 1 3	-0.124
2 2 3 2 1	0.226	3 1 1 3 2	-0.015	3 2 3 2 1	-0.085
2 2 3 2 2	0.194	3 1 1 3 3	-0.094	3 2 3 2 2	-0.117
2 2 3 2 3	0.115	3 1 2 1 1	0.167	3 2 3 2 3	-0.196
2 2 3 3 1	0.089	3 1 2 1 2	0.135	3 2 3 3 1	-0.222
2 2 3 3 2	0.057	3 1 2 1 3	0.057	3 2 3 3 2	-0.254
2 2 3 3 3	-0.022	3 1 2 2 1	0.095	3 2 3 3 3	-0.333
2 3 1 1 1	0.296	3 1 2 2 2	0.063	3 3 1 1 1	-0.015
2 3 1 1 2	0.264	3 1 2 2 3	-0.016	3 3 1 1 2	-0.048
2 3 1 1 3	0.185	3 1 2 3 1	-0.042	3 3 1 1 3	-0.126
2 3 1 2 1	0.223	3 1 2 3 2	-0.074	3 3 1 2 1	-0.088
2 3 1 2 2	0.191	3 1 2 3 3	-0.153	3 3 1 2 2	-0.120
2 3 1 2 3	0.113	3 1 3 1 1	0.108	3 3 1 2 3	-0.199
2 3 1 3 1	0.086	3 1 3 1 2	0.076	3 3 1 3 1	-0.225
2 3 1 3 2	0.054	3 1 3 1 3	-0.003	3 3 1 3 2	-0.257
2 3 1 3 3	-0.025	3 1 3 2 1	0.036	3 3 1 3 3	-0.336
2 3 2 1 1	0.237	3 1 3 2 2	0.004	3 3 2 1 1	-0.075
2 3 2 1 2	0.204	3 1 3 2 3	-0.075	3 3 2 1 2	-0.107
2 3 2 1 3	0.126	3 1 3 3 1	-0.101	3 3 2 1 3	-0.185
2 3 2 2 1	0.164	3 1 3 3 2	-0.133	3 3 2 2 1	-0.147
2 3 2 2 2	0.132	3 1 3 3 3	-0.212	3 3 2 2 2	-0.179
2 3 2 2 3	0.054	3 2 1 1 1	0.105	3 3 2 2 3	-0.258
2 3 2 3 1	0.027	3 2 1 1 2	0.073	3 3 2 3 1	-0.284
2 3 2 3 2	-0.005	3 2 1 1 3	-0.005	3 3 2 3 2	-0.316
2 3 2 3 3	-0.084	3 2 1 2 1	0.033	3 3 2 3 3	-0.395
2 3 3 1 1	0.178	3 2 1 2 2	0.001	3 3 3 1 1	-0.134
2 3 3 1 2	0.145	3 2 1 2 3	-0.078	3 3 3 1 2	-0.166
2 3 3 1 3	0.067	3 2 1 3 1	-0.104	3 3 3 1 3	-0.244
2 3 3 2 1	0.105	3 2 1 3 2	-0.136	3 3 3 2 1	-0.206
2 3 3 2 2	0.073	3 2 1 3 3	-0.215	3 3 3 2 2	-0.238
2 3 3 2 3	-0.006	3 2 2 1 1	0.046	3 3 3 2 3	-0.317
2 3 3 3 1	-0.032	3 2 2 1 2	0.014	3 3 3 3 1	-0.343
		3 2 2 1 3	-0.064	3 3 3 3 2	-0.375
				3 3 3 3 3	-0.454

Thailand's Macro Economic Indicators (Bank of Thailand, 2011)

	2010 p	2009	2008	2007	2006
1. Population (Million persons)	63.88	63.53	63.39	63.04	62.83
2. GDP					
2.1 GDP at constant 1988 price (Billions of Baht)	4,595.8	4,263.1	4,364.8	4,259.0	4,054.5
(% change)	7.8	-2.3	2.5	5.0	5.1
2.1.1 Agriculture (Billions of Baht) 2/	381.5	390.3	385.2	369.7	365.4
(% change)	-2.2	1.3	4.2	1.2	5.0
2.1.2 Non-agriculture (Billions of Baht) 2/	4,214.2	3,872.7	3,979.6	3,889.2	3,689.0
(% change)	8.8	-2.7	2.3	5.4	5.1
2.2 GDP at current price (Billions of Baht)	10,102.9	9,041.5	9,080.4	8,525.2	7,844.9
(% change)	11.7	-0.4	6.5	8.7	10.6
2.3 GNP per capita (Baht : Person)	143,612.5	129,875.1	131,717.8	124,377.1	114,803.5

GDP per capita year 2010 = GDP year 2010 / population year 2010

= 158,154 Baht / person

APPENDIX C

Analysis Result

Example of PSA value of regression coefficient for calculating transition probability from EBD to Dead 2nd -104th cycle (tp3_2)

Explanatory var.	coefficient	se	
cons	-6.502	0.762	
stentpp	-1.600	0.721	
bilirubin	0.080	0.028	

Covariance matrix

	cons	stentpp	biliru1
cons	0.5811		
stentpp	0.1436	0.5201	
bilirubin	-0.0196	-0.0089	0.0008

Cholesky decomposition

	cons	stentpp	biliru1
cons	0.7623		
stentpp	0.1883	0.6962	
bilirubin	-0.0257	-0.0059	0.0087

Random variables

	z	Tz	mu + Tz
cons	-1.4442	-1.1009	-7.6032
stentpp	1.7780	0.9658	-0.6340
bilirubin	-2.2430	0.0071	0.0874

Example of PSA value of regression coefficient for calculating transition probability from PostEBD to EBD (tp8)

Explanatory var.	coefficient	se
lngamma	0.48	0.16
cons	-7.81	1.22
stentpp	-1.92	0.55

Covariance matrix

	lngamma	cons	stentpp
lngamma	0.0263		
cons	-0.1905185	1.4915	
stentpp	-0.0520198	0.2658	0.3049

Cholesky decomposition

	lngamma	cons	stentpp
lngamma	0.1622		
cons	-1.1749	0.3333	
stentpp	-0.3208	-0.3333	0.3015

Random variables

	z	Tz	mu + Tz
lngamma	0.2714	0.0440	0.5281
cons	-1.6792	-0.8785	-8.6903
stentpp	-0.0703	0.4515	-1.4730

Example of PSA value of regression coefficient for calculating transition probability from PostEBD to Dead (tp9)

Explanatory var.	**coefficient**	**se**
cons	-4.77	0.20
stentpp	-0.70	0.27

Covariance matrix

	cons	stentpp
cons	0.0417	
stentpp	-0.0417	0.07292

Cholesky decomposition

	cons	stentpp
cons	0.2041	
stentpp	-0.2041	0.1768

Random variables

	z	Tz	mu + Tz
cons	-0.4873	-0.0995	-4.8652
stentpp	0.4141	0.1727	-0.5281

Example of PSA value of regression coefficient for calculating transition probability from No Drainage to Dead (tp14)

Explanatory var.	coefficient	se
lngamma	-0.23	0.11
cons	-3.98	0.64
Bilirubin	0.02	0.01

Covariance matrix

	lngamma	cons	biliru1
lngamma	0.0128		
cons	-0.059978	0.4079	
bilirubin	0.000451	-0.0058	0.0001

Cholesky decomposition

	lngamma	cons	biliru1
lngamma	0.1132		
cons	-0.5300	0.3563	
bilirubin	0.0040	-0.0102	0.0049

Random variables

	z	Tz	mu + Tz
lngamma	1.1115	0.1258	-0.1074
cons	0.7306	-0.3288	-4.3053
bilirubin	-1.4856	-0.0103	0.0145

BIOGRAPHY

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