MEDICAL AND ECONOMIC BURDEN OF CHRONIC HEPATITIS B PATIENTS AT QUEEN SAVANG VADHANA MEMORIAL HOSPITAL

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ABSTRACT

This is a prospective study conducted among CHB patients at Queen Savang Vadhana Memorial Hospital. The purpose is to assess 1) the medical burden of CHB by using the EuroQOL-5D (EQ-5D), and the Chronic Liver Disease Questionnaire (CLDQ), and 2) the economic burden in a societal perspective by looking at direct medical cost, direct non-medical cost, and indirect cost. A total of 152, 140, and 129 CHB patients at D0, M6 and M12 were enrolled. The median (IQR) age was 39.0 (32.0-49.0) years. More than half (84 of 152 or 55.3%) treated with ARV were in the median (IQR) month of treatment 21.0 (9.0-31.0).

Overall, mean (SD) CLDQ score increased from 5.48 (0.89) at D0, to 5.79 (0.87) at M6, to 5.98 (0.88) at M12 (full score = 7 scores). At D0, the most common sequences of EQ-5D quality of life dimensions where patients reported moderate or severe health impairments were pain/comfort (54.6%), anxiety (51.3%), mobility (13.2%), activity (13.2%), and self care (3.9%). The group classed as experiencing a severe medical burden (CLDQ score < 5) reported moderate or severe health impairments in all EQ-5D dimensions, and described a significantly increased work impairment compared to the group experiencing mild medical burden (CLDQ score ≥ 5).

Out of159 patients, 129 (84.9%) completed a 12 month follow up. The total cost, direct medical cost, direct non-medical cost and indirect cost from work productivity loss were 5,879,645.20, 4,142,839.80, 585,553.00, and 1,169,252.40 Baht/year, respectively. The mean (SD) of these costs were 45,719.12 (64,647.43), 32,115.04 (54,259.40), 4,539.17 (6,353.99), and 9,063.97 (19,068.75) Baht/patient/year. Direct medical cost, direct non-medical cost, and indirect cost accounted for 70.25%, 9.93%, and 19.82% of total cost, respectively. Mean (SD) total cost of those with severe medical burden (CLDQ score < 5) was 57,494.83 (45,405.94) Baht/patient/year, compared to 41,671.22 (69,798.64) for those with mild medical burden (CLDQ score ≥ 5). There was no difference between total cost and direct medical cost between CLDQ < 5 scores and CLDQ ≥ 5 scores. However, the CLDQ < 5 scores group had on average a higher (SD) direct non-medical cost and indirect cost from work productivity loss than the CLDQ ≥ 5 scores group.

KEY WORDS: MEDICAL BURDEN/ECONOMIC BURDEN/
CHRONIC HEPATITIS B

203 pages

ภาระทางการแพทย์และทางเศรษฐกิจของผู้ป่วยโรคไวรัสตับอักเสบบีที่รับการรักษาที่โรงพยาบาลสมเด็จพระบรมราชเทวี ณ ศรีราชา

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บทคัดย่อ

การศึกษานี้เป็นการศึกษาแบบไปข้างหน้า โดยทำการศึกษาผู้ป่วยโรคไวรัสตับอักเสบบีเรื้อรังที่โรงพยาบาลสมเด็จพระบรมราชเทวี ณ ศรีราชา มีวัตถุประสงค์เพื่อประเมินภาระทางการแพทย์ โดยใช้แบบสอบถามคุณภาพชีวิต EQ-5D (EuroQol-5D: EQ-5D) และแบบสำรวจสุขภาพตับ (CLDQ) ภาระทางเศรษฐกิจประเมินในมุมมองของสังคม ประกอบด้วย ต้นทุนทางตรงทางการแพทย์ ต้นทุนทางตรงที่ไม่ใช่ต้นทุนทางการแพทย์ และต้นทุนทางอ้อม ผู้ป่วยโรคไวรัสตับอักเสบบีเรื้อรังที่ศึกษามีจำนวน 152 ราย ในวันแรก 140 ราย ในเดือนที่ 6 และ 129 ราย ในเดือนที่ 12 ผู้ป่วยส่วนใหญ่อายุ 39 ปี หรือระหว่าง 32 – 49 ปี มีผู้ป่วยที่ได้รับการรักษาด้วยยาต้านไวรัสจำนวน 84 รายจาก 152 ราย คิดเป็นร้อยละ 55.3 มีระยะเวลารักษาส่วนใหญ่เป็นเวลา 21 เดือน หรือระหว่าง 9 - 31 เดือน ผู้ป่วยโดยรวม มีค่าเฉลี่ย (ค่าเบี่ยงเบนมาตรฐาน) ของคะแนนความรุนแรงของโรคตับที่ใช้แบบสำรวจสุขภาพตับ (คะแนนเต็ม 7 คะแนน) มากขึ้นจาก 5.48 (0.89) คะแนน ในวันแรกเป็น 5.79 (0.87) คะแนน ในเดือนที่ 6 และเป็น 5.98 (0.88) คะแนน ในเดือนที่ 12 คุณภาพชีวิตที่ประเมินโดยใช้แบบสอบถามคุณภาพชีวิต EQ-5D ในวันแรก พบผู้ป่วยให้ข้อมูลว่ามีการสูญเสียสมรรถภาพด้านสุขภาพในระดับปานกลางหรือมาก ในมิติด้านความปวด/ความสุขสบาย ร้อยละ 54.6 ความวิตกกังวล ร้อยละ 51.3 การเคลื่อนไหว ร้อยละ 13.2 การทำกิจกรรม ร้อยละ 13.2 และการดูแลตนเอง ร้อยละ 3.9 ตามลำดับ กลุ่มผู้ป่วยที่มีความรุนแรงของโรคตับมากโดยมีคะแนนสำรวจสุขภาพตับน้อยกว่า 5 คะแนน ให้ข้อมูลว่ามีการสูญเสียสมรรถภาพด้านสุขภาพในระดับปานกลางหรือมากโดยใช้แบบสอบถามคุณภาพชีวิต EQ-5D มากกว่ากลุ่มผู้ป่วยที่มีความรุนแรงของโรคตับน้อยโดยมีคะแนนสำรวจสุขภาพตับมากกว่าหรือเท่ากับ 5 คะแนน อย่างมีนัยสำคัญ ในทุกมิติ

ผู้ป่วยทั้งหมด 159 ราย มีการมาตรวจตามนัดครบ 12 เดือน จำนวน 129 ราย คิดเป็นร้อยละ 84.9 มีต้นทุนรวม 5,879,645.20 บาท/ปี ต้นทุนทางตรงทางการแพทย์ 4,142,839.80 บาท/ปี ต้นทุนทางตรงที่ไม่ใช่ต้นทุนทางการแพทย์ 585,553.00 บาท/ปี และต้นทุนทางอ้อม 1,169,252.40 บาท/ปี โดยมีค่าเฉลี่ย (ค่าเบี่ยงเบนมาตรฐาน) เท่ากับ 45,719.12 (64,647.43) บาท/ราย/ปี 32,115.04 (54,259.40) บาท/ราย/ปี 4,539.17 (6,353.99) บาท/ราย/ปี และ 9,063.97 (19,068.75) บาท/ราย/ปี ตามลำดับ ต้นทุนทางตรงทางการแพทย์ ต้นทุนทางตรงที่ไม่ใช่ต้นทุนทางการแพทย์ และต้นทุนทางอ้อม คิดเป็นร้อยละ 70.25, 9.93, 19.82 ของต้นทุนรวม ต้นทุนรวมของกลุ่มผู้ป่วยที่มีความรุนแรงของโรคตับมากโดยมีคะแนนสำรวจสุขภาพตับน้อยกว่า 5 คะแนนและกลุ่มผู้ป่วยที่มีความรุนแรงของโรคตับน้อยโดยมีคะแนนสำรวจสุขภาพตับมากกว่าหรือเท่ากับ 5 คะแนนมีค่าเฉลี่ย (ค่าเบี่ยงเบนมาตรฐาน) เท่ากับ 57,494.83 (45,405.94) และ 41,671.22 (69,798.64) บาทต่อรายต่อปี โดยมีต้นทุนรวมและต้นทุนทางตรงทางการแพทย์ไม่แตกต่างกัน อย่างไรก็ตาม กลุ่มผู้ป่วยที่มีคะแนนสำรวจสุขภาพตับน้อยกว่า 5 คะแนน มีต้นทุนทางตรงที่ไม่ใช่ต้นทุนทางการแพทย์ และต้นทุนทางอ้อมมากกว่ากลุ่มผู้ป่วยที่มีคะแนนสำรวจสุขภาพตับมากกว่าหรือเท่ากับ 5 คะแนน อย่างมีนัยสำคัญ

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LIST OF ABBREVIATIONS

Abbreviations	Term
AASLD	American Association for the Study of Liver Diseases
AB	Abdominal domain of Chronic Liver Disease Questionnaire
AC	Activity domain of Chronic Liver Disease Questionnaire
ADV	Adefovir
ALT	Alanine aminotransferase
APASL	Asia-pacific consensus statement of the liver
AUD	Australia Dollar
CLDQ	Chronic Liver Disease Questionnaire
CLDQM	Average CLDQ score
CPI	Customer Price Index
CHB	Chronic hepatitis B
CRF	Case Record Form
CTP	Child-Turcotte-Pugh score
D0	Day zero
EASL	European Association for the Study of Liver
EM	Emotion domain of CLDQ
EQ-5D	EuroQol-5D
ETV	Entecavir
FA	Fatigue domain of CLDQ
HbeAg	Hepatitis B envelope antigen
HBsAg	Hepatitis B surface antigen
HCC	Hepatocellular carcinoma
HBV	Hepatitis B virus
HBV DNA	Hepatitis B virus deoxyribonucleic acid
HIS	Hospital Information System

LIST OF ABBREVIATIONS (cont.)

HIV	Human immunodeficiency virus
ICER	Incremental cost-effectiveness ratio
IFN-α	Interferon alpha
INR	International normalized ratio
IQR	Interquatile range
KASL	Korean Association for the Study of the liver
LAM	Lamivudine
M6	The sixth month of follow up
M12	The twelfth month of follow up
PT	Prothrombin time
QALY	Quality-adjusted life-year
QOL	Quality of life
RSC	Routine service cost
SD	Standard deviation
SF-36	Medical outcomes study short-form 36
SY	Systematic symptom domain of CLDQ
TEF	Transport expense form
TBV	Telbivudine
TNV	Tenofovir
ULN	Upper limit of normal
US algorithm	Treatment algorithm in the United States
USD	United States Dollars
VAS	Visual analog scale
WHO	World Health Organization
WO	Worry domain of CLDQ
WPAI	Work Productivity and Activity Impairment questionnaire

CHAPTER I
INTRODUCTION

1.1 Background and Significant of the study

Hepatitis B virus (HBV) is the most common type of hepatitis virus causing chronic liver infection in humans worldwide. Therefore, it represents a major global public health problem (Lavanchy, 2005). Approximately one third of the world's populations have been exposed to the virus with an estimated 350 million chronically infected individuals (World Health Organization (WHO), 2004; Lavanchy, 2004). This is due to occurrence of frequent new infections and presence of a large reservoir of chronically infected individuals, which may develop severe and fetal complications of chronic liver disease (Lavanchy, 2005). HBV infections result in 600,000 to 1.2 billion deaths per year due to chronic hepatitis B (CHB), cirrhosis, and hepatocellular carcinoma (HCC) (WHO, 1997; Lavanchy, 2005) ranking CHB as the tenth leading cause of death worldwide (Lee, 1997; Mahoney, 1999; De Franchis, 2002). To date, hepatitis B infection remains a major health problem. There is a need for more information on its burden and impact on individuals.

HBV is a highly contagious disease that is easily transmitted through sexual activity, and associated with increased risk of morbidity and mortality (Brown *et al*, 2004; Lok & McMahon, 2007; Hoofnagle *et al*, 2007; Idris *et al*, 2008; Lavanchy, 2008; Walter, 2011). It is also much more resistant to heat and germicidal agents and maintains the capacity to infect via contaminated surfaces hundreds of times longer than human immunodeficiency virus (HIV). Compared to HIV, HBV is 50-100 times more contagious than HIV (Center for Disease Control and Prevention (CDC), 2010). Moreover, HBV has been classified by the International Agency for Research on Cancer as carcinogenic to humans (Parkin *et al*, 2001) causing 60-80% of the world's HCC, one of the major three causes of death in Africa, Asia and the Pacific Rim. Overall, approximately 15-40% of infected patients will develop cirrhosis, liver failure, or HCC (Lok & McMahon, 2007; Fattovich *et al*, 1995; Liaw *et*

al, 2009). It is estimated that 25% of carriers will develop serious HBV-related complications (Yang, Kim, & Kim, 2004). Elimination of HBV transmission along with acute and chronic infections is a feasible goal (Lavanchy, 2005). HBV infections could be prevented by vaccination. In adults, the vaccine is usually given as a series of three injections over a period of six months. Complete vaccination is needed for long-term protection. However, coverage rate with the three-dose regimen is low suggesting less public awareness of the long-term complications of CHB infections.

Despite effective universal hepatitis B immunization programs, there remains a large reservoir of people infected with HBV (Lavanchy, 2008) requiring CHB clinical management. Although a safe and effective vaccine can prevent CHB, HBV remains an important disease in endemic and non-endemic areas (Dusheiko, 2009). Hepatitis B immunization of infants are operational in 169 (88%) of the 191 member states of WHO (CDC, 2008), an estimated 32% of children younger than 1 year were fully vaccinated with three-dose hepatitis B series worldwide (Te & Jensen, 2010). Consequently, prevalence of hepatitis B surface antigen (HBsAg)-positive individuals, a marker indicating hepatitis B infection, decreased in relation to immunization. However, HBsAg positive individuals increased from 223 million to 240 million in 1990 and 2005, respectively with 8.6% HBsAg prevalence in East Asia (Ott *et al*, 2012). It takes approximately 40 years after implementation of universal newborn/infant immunization to impact the natural history of HBV because the incidence of HCC and cirrhosis does not begin to rise substantially until those infected reach their late 30s and early 40s (McMahon, 2004). A dramatic drop in HBV-related liver disease will not be seen for several decades (McMahon, 2004) and significant CHB-related morbidity will continue to occur for the next 15 to 30 years until the benefits of vaccination programs take effect (Yang, Kim, & Kim, 2004). Therefore, chronically infected individuals and those with new infections may cause disease transmission and develop severe fetal complications of chronic liver disease.

Being a ‘silent’ disease, the contribution of chronic HBV infection to global morbidity and mortality is often highly underestimated (Lavanchy, 2008). The number of reported cases is much lower because many infected people do not consult a doctor because they do not have symptoms (McBrien, 2013). A survey showed that diagnostic rate of HBV was 56% in Australia (MacLachlan *et al*, 2013), 25% in

United States of America (USA), 18% in Europe and even lower (4%) in Asia except Japan (13%) (Liaw, 2009). Of the estimated 2 million Americans with chronic HBV infection, only 300,000 were screened and 50,000 received treatment (Do, 2009). Asian patients with chronic HBV infection usually have long immune tolerant phase whereas this phase is not apparent or very short in patients in Western countries or those who acquired HBV infection during adulthood (Chu & Liaw, 2004). An HCC surveillance report estimated that there might be triple the number of people with operable tumors at diagnosis compared with no surveillance (Thompson Coon *et al*, 2008). Hence, the burden of CHB may be greater than previously recognized in a number of undiagnosed patients as well as untreated asymptomatic individuals.

Remission and complications of HBV-related liver disease can be prevented by inhibition and prevention of virus replication (Idris *et al*, 2008; Chen *et al*, 2006; Liaw *et al*, 2004; European Association for the Study of Liver (EASL) 2009; Momeja-Marin *et al*, 2003). However, its implication in clinical practice setting needs to be evaluated. Currently, seven therapeutic agents including five antiviral therapies (ARV) have been approved for treatment of adults with CHB (EASL, 2009; Mercillin *et al*, 2008; Chang *et al*, 2006; Lai *et al*, 2007; Peter *et al*, 2004; Lai *et al*, 2006). Assessment of changes in the clinical course of liver disease during and/or after ARV is one of the key points for the management of CHB (Di Macro, 2009) with proposed international CHB guidelines and treatment algorithms (Lok & McMahon, 2007; De Franchis *et al*, 2003; Liaw *et al*, 2005; Alberi *et al*, 2005; National Institutes of Health, 2002; Choi & Yoo, 2010; Liver Society (Thailand), 2009). However, ARV has limitations which include no possible cure (Lavanchy, 2008), absence of direct head-to-head trial comparison (Rajendra &Wong, 2007), problem of HBV drug development (Dusheiko, 2009; Khungar & Han, 2010), and selection of patients for treatment varies among physician (Lok, 2009; Freeman *et al*, 2003; Amin *et al*, 2006). Besides, persons with chronic HBV must have lifelong treatment with ARV and regular monitoring that will incur considerable healthcare resources (McMahon, 2004). Therefore, assessment of economic burden and benefits of medical outcome from treatment of CHB is important.

Several studies have shown that CHB patients have a number of physical and psychological burdens from complications of the disease. About 16.4% and 5.5%

of CHB carriers had asthenia and anorexia, respectively (Victoria *et al*, 2008). In addition, they also experienced pain (93.3%) (Awan *et al*, 2012), fatigue/loss of energy (90%) (Heidarzadeh *et al*, 2007; Hann *et al*, 2008), and loss of appetite (79%) (Hann *et al*, 2008). Patients with cirrhosis could develop ascites, fatigue and muscle cramps (Zuberi *et al*, 2007). Mental health problems of CHB patients include depression (94.4%), feelings of having problems and sleep dissatisfaction (49.2%) (Awan *et al*, 2012). Moreover, psychological surveys indicated that 90% of CHB patients considered themselves as sufferers (Lok, 1985), and 30.2% had psychiatric disorders (Atesci *et al*, 2005). Therefore, infections with HBV can cause significant medical burden. However, medical burden of Thai CHB patients has not been well described.

The health burden of chronic liver disease is quantified by its impact on the patient's quality of life (QOL) from a range of physical, psychological, and social stressors resulting from the disease and its treatment (Marchesini *et al*, 2001; Kanwal *et al*, 2004; Zuberi *et al*, 2007). The concept of QOL conforms to definition of health by the WHO as being not only the absence of disease and disability but also the presence of physical, mental and social well-being (WHO, 1952). QOL determines the effect of disease on patient's life through the patient's perspective. Its outcomes provide important information regarding the complex circumstances of hepatitis B related disease, which has been shown to translate into improved treatment adherence and greater patient satisfaction (Gutteling *et al*, 2007). Thus, a full understanding of not only survival benefit but of QOL benefit will guide us towards improved patient care (Jay *et al*, 2009) specifically in CHB patient. In addition, previous studies revealed different QOL of CHB patients from none to that with most impact such as CHB infection had similar QOL as normal control (Foster, Goldin & Thomas, 1998; Bondini *et al*, 2007; Ong *et al*, 2008), CHB infection had a negative impact on QOL (Lam *et al*, 2009). There is currently no study on QOL in Thai CHB patients. In this study, QOL was assessed using the EuroQol-5D (EQ-5D) and the Chronic Liver Disease Questionnaire (CLDQ) because the use of both generic and disease-specific questionnaires in clinical research is encouraged to gain substantial information (Younossi & Guyatt, 1998).

HBV infections impose a substantial economic burden on patients, families and the society, and the actual indirect cost might be higher than recognized. Evidence from economic studies contributes to understanding of potential benefits to society from allocating more resources to prevention and treatment of HBV infections in highly endemic countries such as China, Korea, Hong Kong, and Singapore (Lu *et al*, 2013; Hu & Chen, 2009; Liang *et al*, 2010; Yang, Kim, and Kim, 2004; Li *et al*, 2004). As disease progresses, the annual cost of medical care significantly increase. In China, the average annual direct medical costs per case was United States Dollar (USD) 1,636-4,552 in CHB, 2,722-6,936 in decompensated cirrhosis, and 4,611-7,400 in compensated cirrhosis (Hu & Chen, 2009; Lu *et al*, 2013), and the costs ranged from 31% - 298% of the average annual household income (Lu *et al*, 2013; Liang *et al*, 2010). The intangible cost accounted for 53% of the total cost, much more than the proportion of direct and indirect costs (38.5% and 8.5%, respectively) (Ma *et al*, 2011). Indirect costs exceeded 40% of the patient's disposable household income in Shandong, China (Lu *et al*, 2013). Furthermore, an assessment of the total economic burden of CHB-related diseases in Beijing and Guangzhou in China indicated that patients and family members had an average of 1.5 to 3.5 sick-leaves and 1.0 to 4.5 leave days per month (Hu & Chen, 2009). These evidences indicated a large magnitude of economic burden of HBV infections in highly endemic countries that have important policy implications for reducing the burden of catastrophic disease for their citizens. However, the economic burden of CHB in Thai population has not been investigated.

Recent developments in CHB management have heightened the need for economic evaluation in different countries. In an era of increasing healthcare budget, understanding the economics of medical care has become another requirement for the practice of medicine (Rajendra & Wong, 2007). Current guidelines generally share the ultimate goal of ARV in CHB; durable long-term viral suppression by drugs with potent viral suppression and high genetic barrier to resistance, despite some differences in recommendations (Choi & Yoo, 2010). It is proven that antiviral treatment compared with no treatment had incremental cost-effectiveness ratio ranging from 7,600 to 44,300 USD/Quality Adjusted Life Year (QALY) (Dan, Aung & Lim, 2008). However, the cost and long-duration of treatment with ARV and ARV drugs

resistance can be a financial burden to patients and their families. Consequently, clinicians are being asked to consider the economic consequences of their treatment choices (Lok & McMahon, 2007; Liaw *et al*, 2005) in which the guidelines do not take into consideration particularly treatment costs or monitoring of therapy (Buti *et al*, 2009). It was recommended that economic studies of CHB patient be performed to enable countries to prioritize their public health preventive measures, and to make the most appropriate use of available resources (Lavanchy, 2008). Therefore, in an endemic area especially Thailand, an economic study of HBV infections is important to evaluate treatment outcomes, cost impact, and the benefit of investigations.

Previous economic analysis pointed to strategies by prevention and early treatment in CHB management. However, various perspectives from these studies could not be used in Thai population as they referred to their own countries' point of view. They were prevention and disease costs (Yang *et al*, 2001), direct and indirect costs (Yang *et al*, 2001; Ong, Lim & Li, 2009; Yang *et al*, 2010), evaluation of HCC surveillance (Paul *et al*, 2008; Thompson Coon *et al*, 2008), and an average annual direct medical cost in each health states of six CHB-related diseases in which most of the studies were retrospective analysis and using a simulation model (Lee *et al*, 2004; Gagnon *et al*, 2004; Yang *et al*, 2004; Zhiqiang *et al*, 2004; Li *et al*, 2004; Castelo *et al*, 2007; Hu & Chen, 2009). The differences in countries in which the study was conducted, the year horizon, cost, benefit and transition estimates, as well as the simulation model make comparison between various studies impossible (Dan, Aung & Lim, 2008). Most of economic evaluation studies on drug treatment options for patients with CHB were analyzed based on the perspectives of a health care system or a third party payer, which considered only direct medical costs (Tantai *et al*, 2010). It was suggested that country-specific economic evaluation of hepatitis B infections were required to confirm findings (Lacey & Gane, 2007). Consequently, study of economic burden in Thai CHB patients will demonstrate a magnitude of CHB health impairments, and provide basic economic data to estimate cost-effectiveness of CHB management in Thailand.

Lost productivity should be added to assess the level of indirect costs relative to hepatitis B infections as some CHB patients maybe asymptomatic resulting to underestimated health burden. The previous study suggested that approximately

32% of working adults have chronic illnesses that interfere with their job performance (Lerner *et al*, 2000). Measuring health-related work productivity is a key to understand health burden and cost associated with work-related disorders (Escorpizo, 2007). Its measure of work loss could be translated into a monetary figure that could support business decision-making (Loeppke *et al*, 2007; Thavorncharoensap *et al*, 2010; Jayathunge *et al*, 2010). It was suggested that health-related productivity costs were more than four times greater than medical and pharmacy costs (Loeppke *et al*, 2007). Additionally, CHB is a chronic liver disease affecting a working person therefore causing loss in work productivity. As mention earlier, the cost study in China indicated that CHB patients and family members had an average of 1.5 to 3.5 sick leave and 1.0 to 4.5 leave days per month (Hu & Chen, 2009). Therefore, measuring the indirect cost from loss of work productivity in a CHB patient is necessary to determine the economic burden of hepatitis B infections.

In Thailand, hepatitis B infection is one of the most common causes of cirrhosis. Introduced in 1985, the universal hepatitis B vaccination program had coverage of more than 80% for the past 20 years. However, a study in 2004 reported that in children aged between 6 months and 18 years, 74.5% had received hepatitis B vaccine, 5.1% had never received the vaccine and 20.4% could not provide information (Chongsrisawat *et al*, 2006). Moreover, the study indicated that most adolescents and young adults born before the program were susceptible to HBV infection (Chongsrisawat *et al*, 2006). Also, the prevalence of HBsAg is approximately 2-7% of Thai adults in 2005 (Ott *et al*, 2012) or an estimated 1.3-4.5 from 65 million Thais are a potential source of infection through parenteral, sexual and perinatal routes with high HBV transmission rates (Kidd-Ljunggren *et al*, 1995). Of these infected people, one third of them or 1.1-1.5 million Thais will develop cirrhosis and HCC (McMahon, 2004). Also, the incidence rate was high as 8.60 to 10.43 per 100,000 populations among people aged 15-54 years (Bureau of Epidemiology; Ministry of Public Health, 2007) with an estimated 5,595 to 6,786 new CHB cases each year. The CHB guidelines and treatment algorithms recommended ARV for treatment of hepatitis B infection in Thailand (Liver Society (Thailand), 2009). However, the implications in clinical practice have not been demonstrated. As a result,

hepatitis B infection causes considerable health problems to Thai people and therefore needs evaluation.

Results from this study will contribute new information on the medical and economic burden of Thai CHB patients. Also, the use of EQ-5D and CLDQ to assess the medical burden on CHB patients will be useful for physician and healthcare providers in evaluating the clinical problems of this group of patients and improving clinical management. Indirect medical costs, direct non-medical costs and indirect cost of each CHB patient per year could be used to estimate the magnitude of economic burden of overall CHB infection in Thailand. In addition, data obtained from this study will help in the deciding trade-off between costs and benefits of CHB treatment and medical outcomes. QOL assessment can be used for estimation of QALYs of CHB patients in cost effectiveness or cost utility studies (Lam *et al*, 2009). The work productivity loss measurement will present indirect cost of hepatitis B infections that could be applied to other chronic diseases in Thailand.

1.2 Conceptual Framework of the study

Medical burden and economic burden in this study are shown in Figure 1.1.

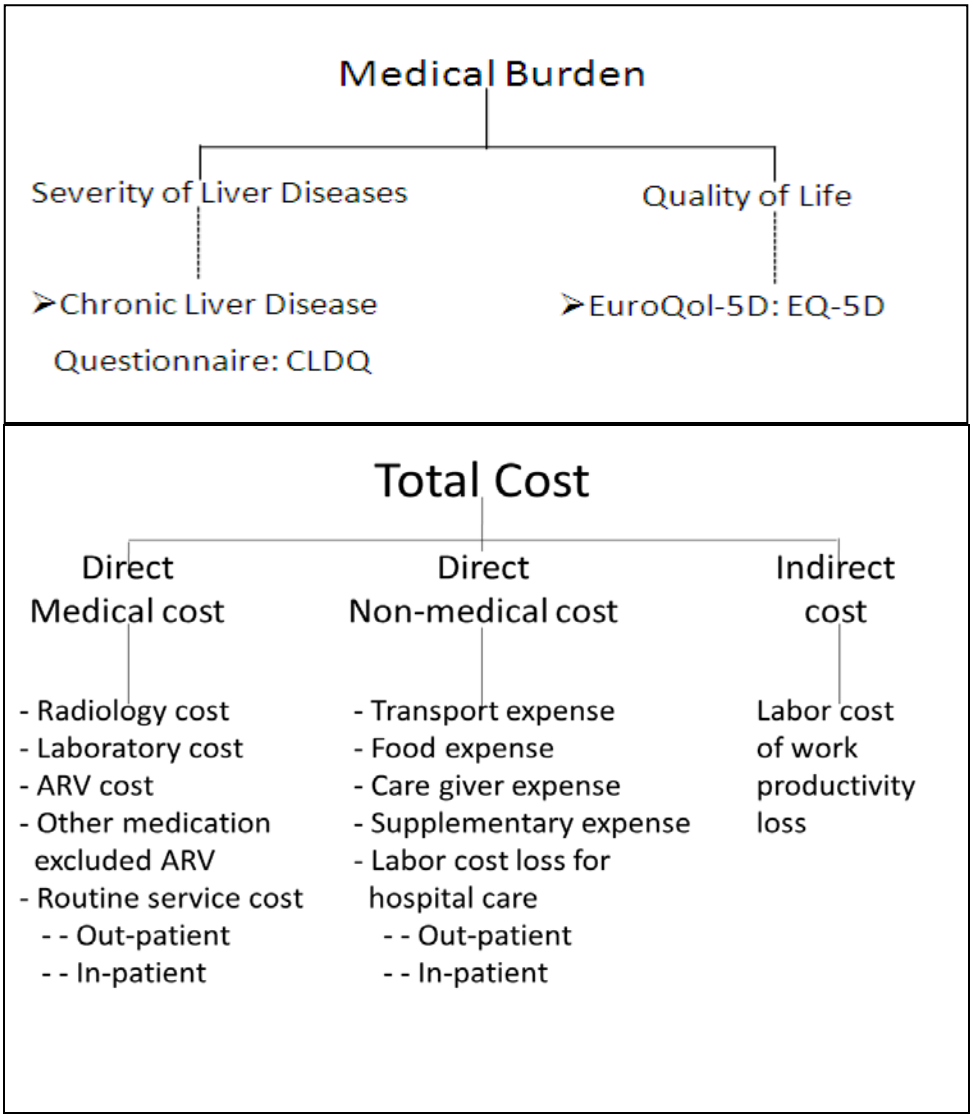


Figure 1.1 Medical burden and economic burden in this study

CHAPTER II
OBJECTIVES

Primary objective

To assess the medical and economic burden of chronic hepatitis B (CHB) patients at Queen Savang Vadhana Memorial Hospital.

Secondary objectives

1. To compare the economic burden between CHB patients with mild and severe medical burden.

2. To assess the clinical manifestation of CHB patients.

CHAPTER III
LITERATURE REVIEW

The present study aimed to assess the medical and economic burden of CHB patients. In this chapter, related literature and research are reviewed in the following topics:

3.1 Definition of medical burden and economic burden

3.2 Epidemiology and burden of chronic hepatitis B virus

2.1 Burden of chronic hepatitis B infection worldwide

2.2 Burden of chronic hepatitis B infection in Thailand

3.3 Natural history of chronic hepatitis B infection

3.3.1 The structure and life cycle of hepatitis B virus

3.3.2 Transmission

3.3.3 Stages of Hepatitis B virus infection

3.3.4 Hepatitis B virus genotypes and liver disease progression

3.4 Guidelines of CHB therapy

3.5 Treatment of CHB patients

3.6 Child-Turcotte-Pugh score (CTP)

3.7 Quality of life of CHB focusing on the EuroQol-5D (EQ-5D), and the Chronic Liver Disease Questionnaire (CLDQ).

3.8 Measuring health-related work productivity

3.9 Basic principle of health economic

3.10 Cost of CHB

3.1 Definition of medical and economic burden in CHB

A review of literature showed that different terms were used to define burden of CHB infections such as number, prevalence and incidence of disease (Lavanchy, 2004; Lavanchy, 2005), economic analysis (Rajendra & Wong, 2007), cost (Lacey & Gane, 2007), cost-effectiveness (Yang *et al*, 2001; Kanwal *et al*, 2005; Wong, 2006; Shepherd *et al*, 2006; Dusheiko, 2009), cost-utility (Veenstra *et al*, 2007; Spackman & Veenstra, 2008; Arnold *et al*, 2008), and quality of life (QOL) (Marchesini *et al*, 2001; Kanwal *et al*, 2004; Zuberi *et al*, 2007).

However, regardless of terms used, the burden of CHB may be physical, psychological, and financial as well as loss of productivity and quality of life of patients and their families.

According to the English dictionary, the term “burden” is defined as an onerous or difficult concern for "the burden of responsibility" or weight to be borne or conveyed. The WHO (1952) defined “health” as the absence of disease and disability and presence of physical, mental and social well-being. In addition, Jay *et al* (2009) described that health care outcomes can be divided into three fundamental categories as follows: survival (how long people live), cost (how much the intervention costs), and quality of life (how well people live).

Several investigators have defined the term “burden of CHB”. Lavancy (2005) defined “burden” as number, prevalence and incidence of disease and suggested that economic burden should also reflect the loss of productivity due to acute and chronic disease.

Lacey and Gane (2007) conducted an economic evaluation of CHB using direct healthcare costs, and recommended that indirect costs should be taken into account including productivity loss for time off from work due to CHB-related illness. Kanwal *et al* (2004) defined health economic burden of cirrhosis as being amplified by its impact on QOL resulting from a range of physical, psychological, and social stressors due to disease and its treatment.

Zuberi *et al* (2007) noted that QOL is important in measuring the impact or burden of a chronic disease like liver cirrhosis.

Therefore, medical burden of CHB refers to physical burden from severity of disease and its progression, and psychological burden from loss of social role that

could be assessed by quality of life. Economic burden refers to treatment costs and productivity loss for both patient and caregiver.

3.2 Epidemiology and burden of CHB virus

HBV is the most common type of hepatitis virus causing chronic human infections of the liver and representing a global public health problem (Lavanchy, 2005). It can be prevented by hepatitis B vaccination, and so, elimination of HBV transmission and acute and chronic infections is a feasible goal (Lavanchy, 2005). Despite effective programs, a large reservoir of people infected with HBV remains prior to implementation of immunization programs (Lavanchy 2008). This is due to continuing occurrence of frequent new infections and presence of a large reservoir of chronically infected individuals, which may develop severe and fetal complications of chronic liver disease (Lavanchy, 2005).

Hepatitis B immunization of infant is operational in 88% (169/191) member states of WHO (CDC, 2008). An estimated 32% of children younger than 1 year were vaccinated fully with 3-dose hepatitis B vaccination series worldwide (Te & Jensen, 2010). The incidence of HBV infection and patterns of transmission vary greatly throughout the world in different population subgroups (WHO, 1996; Lavanchy, 2005). The highest rates of HBsAg carrier rates are found in developing countries with primitive or limited medical facilities (Mahoney & Kane, 1999). In developed countries, the prevalence is higher among immigrants from countries with high or intermediate prevalence rates, and those with high-risk behaviors (Lavanchy, 2004).

3.2.1 Burden of chronic hepatitis B virus in worldwide

Infection with hepatitis B virus varies in different geographical regions but it is endemic in all countries and highly endemic in many parts of the world (Lavanchy, 2008). Affected regions can be divided into three areas where prevalence of chronic HBV infection is high, intermediate, and low (≥8%, 2-7%, and <2%, respectively) (Mahoney & Kane, 1999; Viral Hepatitis Prevention Board, 1998). The prevalence of CHB infection in 2006 is shown in Figure 3.1.

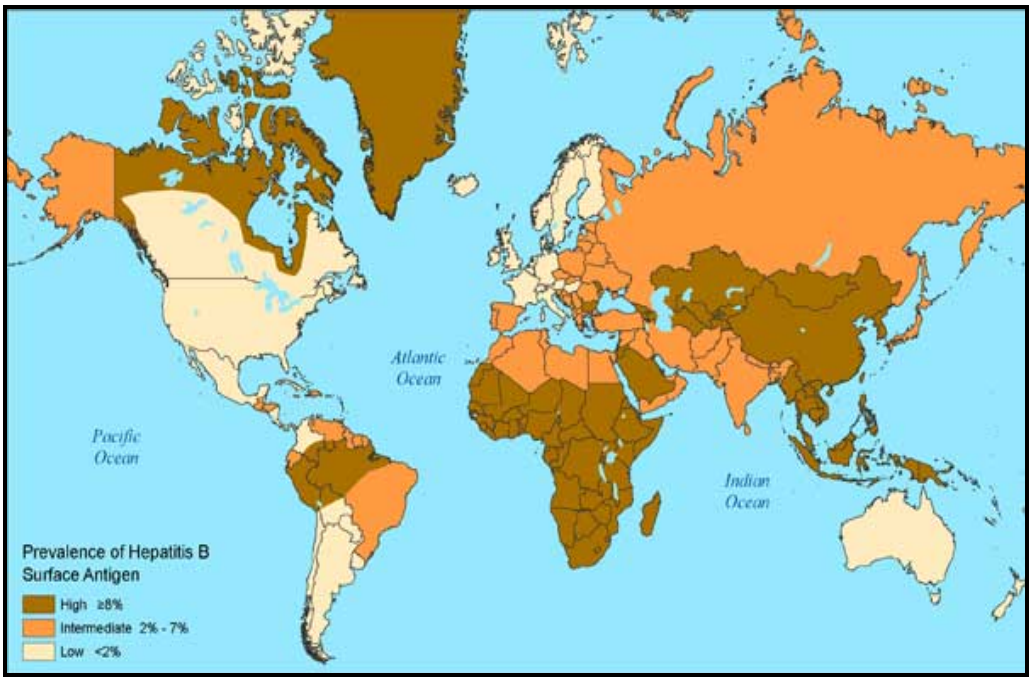


Figure 3.1 Prevalence of chronic HBV infection in 2006 (Center for Disease Control, 2008)

Of approximately 2 billion infected people (Lavanchy, 2008), more than 75% of them come from endemic areas in the Asia-Pacific region (Lesmana *et al*, 2006). Although most carriers will not develop hepatic complications from CHB, 15% to 40% will develop serious sequelae during their lifetime (Bosch *et al*, 2005) resulting in about 320,000 deaths per year (WHO, 1997; Lavanchy, 2005). CHB is the tenth leading cause of death worldwide (Lee, 1997; Mahoney, 1999; De Franchis, 2002).

Being a 'silent' disease, the contribution of chronic HBV infection to global morbidity and mortality is often highly underestimated (Lavanchy, 2008). Asian patients with CHB infections typically have a long immune tolerant phase (Chu & Liaw, 2004). A survey showed that diagnostic rate of HBV was only 25% in USA, approximately 18% in Europe and even lower (4%) in Asia except Japan (13%) (Liaw, 2009). Of the estimated 2 million individuals with CHB infection in the USA, only 300,000 have been screened and 50,000 receive treatment (Do, 2009).

In Western countries, the prevalence of chronic HBV infection is relatively low and infection is acquired primarily in adulthood. In contrast, the prevalence is high in Asia and most of Africa, and hepatitis B infection is usually acquired perinatally (vertical infection) or in early childhood (horizontal infection) (Lavanchy, 2008; Liaw & Chu, 2009).

In highly endemic Asia-Pacific region, there are 300 million affected individuals and can be as high as 20% (Lesmana *et al*, 2006). The prevalence of CHB infection varies among Asian countries (Liaw, 2009). Countries with high-prevalence include China, Korea, Philippines, Taiwan, Thailand, Vietnam, and South Pacific island nations. Regions with intermediate-prevalence include central Asia, Indian continent, Indonesia, Malaysia and Singapore. Countries with low prevalence include Australia and New Zealand but in recent years, immigrants from high-prevalence Asian countries have led to increased burden of disease in these countries (Weinbaum *et al*, 2008).

CHB infection is a serious problem in Asia (Liaw, 2009). WHO estimated HBsAg prevalence in South East Asia was 1% to 10% in 1997, with about 130 million carriers (Custer *et al*, 2004). Although universal HBV vaccination in newborns has been implemented in Asian countries since 1984, these vaccination programs have reduced the prevalence of hepatitis B in people younger than 20 years (Chen *et al*, 1987). It will take approximately 40 years after implementation of universal newborn/infant immunization to impact the natural history of HBV in persons living in endemic countries, because the incidence of HCC and cirrhosis does not begin to rise substantially until patients have reached their late 30s and early 40s. Thus, a dramatic drop in HBV-related liver disease will not be seen for several decades (McMahon, 2004) and a significant CHB-related morbidity will continue to occur for the next 15 to 30 years until the benefits of vaccination programs take effect (Yang, Kim, & Kim, 2004). Consequently, there are still large numbers of chronically infected individuals with HBV in Asia (Liaw, 2009).

Data on decrease of prevalence of HBV markers are accumulating in countries where routine hepatitis B vaccination programs were implemented (Lavanchy, 2005). Proofs of the decreasing incidence of acute hepatitis B after vaccination are available in Europe for Italy (Stroffolini *et al*, 2000) and in Asia for

Taiwan (Ni *et al*, 2001; Chang, *et al*, 1997). In Taiwan, the HBsAg prevalence in children aged less than 15 years decreased from 9.8% to 0.7% in 1984 and 1999, respectively and to 0.5% in 2004, 20 years after implementation of universal HBV vaccination with coverage of 97% (Ni *et al*, 2007). However, a survey from 1996 to 2005 in 157,720 adults aged ≥18 years old from Taiwan showed that the overall prevalence of HBsAg was 17.3%, not much less than the prevalence in studies conducted before 1984 (Chen *et al*, 1987).

3.2.2 Burden of CHB virus in Thailand

For the last two decades, Thailand was a highly endemic area for HBV infection with prevalence of HBsAg in general population ranging from 5-10% (Pramoolsinsup, 1986). When prevalence was compared before and after the HBV vaccine program, the rate of HBsAg was 0.7% among the group born after initiation of the program and 4.3% in those born before the vaccine program (Chongsrisawat *et al*, 2006). In non-risk group, the prevalence of HBsAg was 5-7% in adult Thai people (Ott *et al*, 2012), 4.2% among workers (Srisupanant and Wiwanitkit, 2008), 2.6% to 4.7% in pregnant women in Southern Thailand (Pradutkanchana *et al*, 2005), 2.6% in new blood donors (Chimparlee *et al*, 2011). In the risk group, the prevalence of HBsAg was 4.3% in Thai males over 40 years old (Luksamijarulkul, Drph, & Triamchisri, 2007), 8.2-8.7% in HIV (Chotiprasitsakul *et al*, 2010; Sungkanuparph *et al*, 2004), 9.0% in HIV-TB patients (Sirinak *et al*, 2008), and around 5.0% in injecting drug users (WHO, 2010). Thailand is currently classified as an intermediate endemic area (2-7%) (Mohamed *et al*, 2004). The prevalence of HBsAg was high in patients who born before HBV vaccine and in the high-risk group.

CHB is one of the most popular communicable diseases in Thailand. As an endemic area, hepatitis B vaccination program was introduced since 1985 with 88.3-96.0% coverage from 1996-2006 (Ministry of Public Health, 2008), and it could be used to prevent neonatal infection by vertical transmission from HBV carrier mothers (Poovorawan *et al*, 2011). However, the incidence rates were high as 8.60 to 10.43 per 100,000 populations among people aged between 15-54 years old in 2007 (Bureau of Epidemiology; Ministry of Public Health, 2007). Also, the current study have shown that prevalence of HBsAg is approximately 5-7% of adult Thai people (Ott *et al*, 2012)

or estimated 3.2-4.5 million from 65 million Thais are a potential source of infection and there will be 3,706 to 4,494 newly CHB diagnosed cases each year. Of these infected people, one third of them or 1.1-1.5 million Thais will develop cirrhosis and HCC. Moreover, it was confirmed that HBV was associated with the development of HCC among Thais and prevalence of HBV in HCC was 65%, four times that of HCV (17%) (Tangkijvanich *et al*, 1999). Thus, CHB can cause high impact health problems to Thai people.

3.3. Natural history of CHB virus

3.3.1 The structure and the life cycle of hepatitis virus B

HBV is a DNA virus that infects only humans. It is highly contagious; 50-100 times more than hepatitis C virus (HCV) or human immunodeficiency virus (HIV) (Te & Jensen, 2010; CDC, 2010). The structure and life cycle of HBV are shown in Figure 3.2 and Figure 3.3.

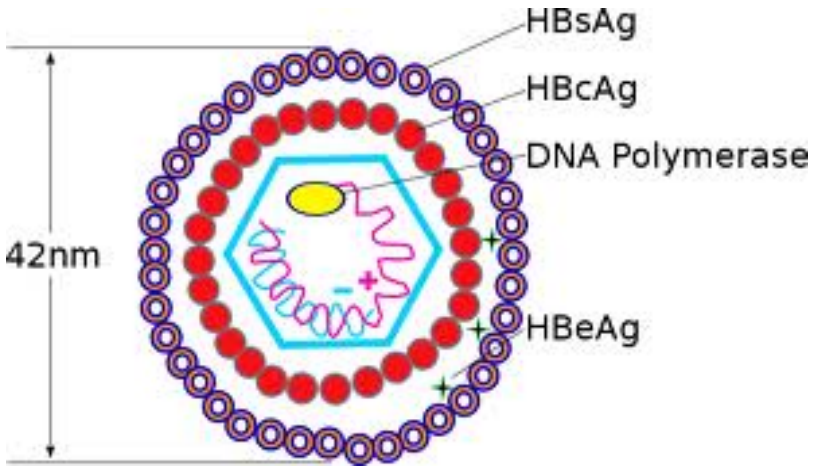


Figure 3.2 Structure of hepatitis B virus
(Available at: wikimedia.org/wiki/File:...s_v2.png. Accessed August 15, 2010)

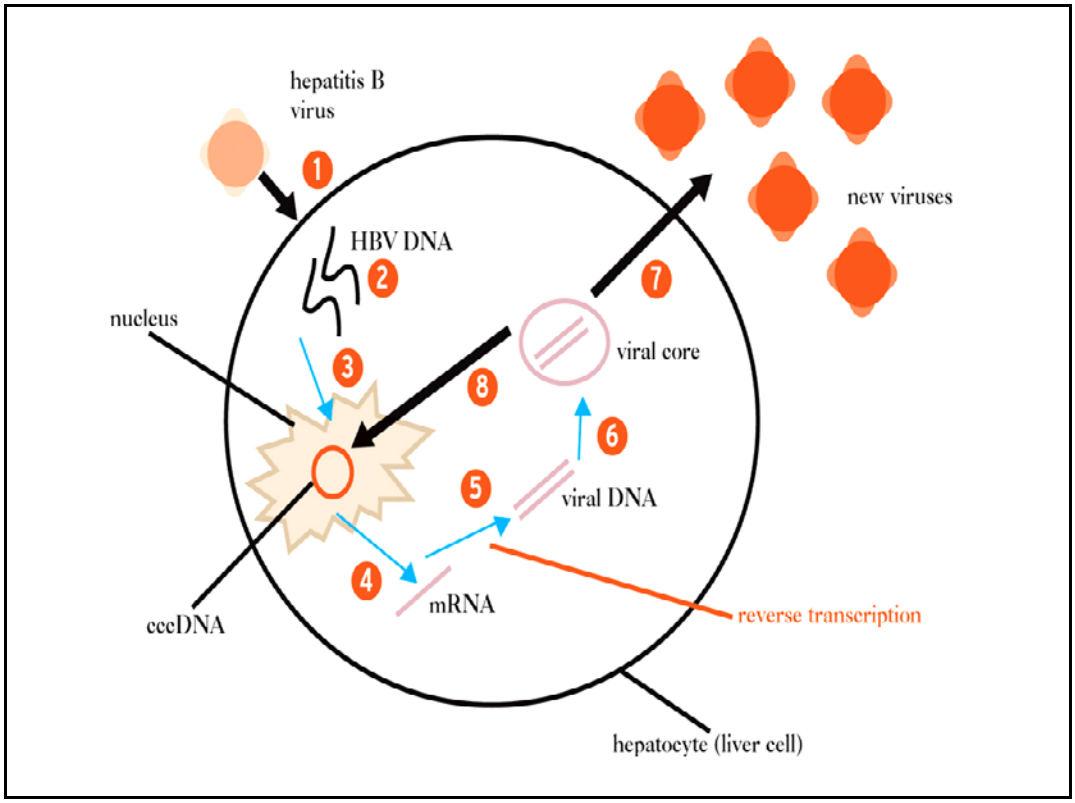


Figure 3.3 Life cycle of Hepatitis B virus
(Available at: www.plusve.org/data/usercontentr...5201.asp. Accessed August 15, 2010)

3.3.2 Transmission

HBV is transmitted by perinatal, percutaneous, and sexual exposure, as well as by close person-to-person contact presumably by open cuts and sores, especially among children in high endemic areas (Mast *et al*, 2005). There is a very high probability (70-90%) of developing CHB if the infection is acquired perinatally or in the pre-school years (Chen, Wang & Yu, 2000). The practice of unsafe injections and percutaneous procedure is a huge public health problem in developing countries (Simonsen *et al*, 1999). Blood transfusions were once a common route of transmission, but improved diagnostic tests and progressively larger screening of blood and blood products for HBV infection, has dramatically reduced the risk of acquiring HBV infection through transfusion (Schmunios *et al*, 2001).

For the last two decades, contaminated medical devices such as needles and syringes caused 8-16 million new HBV infections each year (Kane *et al*, 1999; Hutin *et al*, 1999). Other sources of infection are contaminated multi-dose vials, surgical instruments and donor organs. Healthcare workers, dentists, and others who have frequent contact with infected blood or blood products are at highest risk (Hutin *et al*, 1999). Before immunization of health care workers with hepatitis B vaccine, hepatitis B used to be the most frequent professionally acquired infection in health care workers (Hadler *et al*, 1985). Table 3.1 shows the recommendations for infected persons regarding prevention of transmission of HBV to others (Lok & McMahon, 2007). Table 3.2 shows the groups at high risk for HBV infection that should be screened (Mast *et al*, 2005).

Table 3.1 Recommendations for infected persons regarding prevention of transmission of HBV to others (Lok & McMahon, 2007)

Recommendations for infected persons regarding prevention of transmission of HBV to others
Persons who are HBsAg-positive should • Have sexual contacts vaccinated • Use barrier protection during sexual intercourse if partner is not vaccinated or naturally immune • Do not share toothbrush or razors • Cover open cuts and scratches • Clean blood spills with detergent or bleach • Do not donate blood, organs or sperms
Children and adults who are HBsAg-positive: • Can participate in all activities including contact sports • Should not be excluded from daycare or school participation and should not be isolated from other children • Can share food, utensils or kiss others

Table 3.2 Groups at high risk for HBV infection who should be screened (Mast *et al*, 2005)

Groups at high risk for HBV infection who should be screened
Individuals born in areas of high[#] and intermediate prevalence rate[†] for HBV including immigrants and adopted children^*
- South Asia (except Sri Lanka)
- Africa
- South Pacific Island
- Middle East (except Cyprus)
- European Mediteranean: Greece, Italy, Malta, Portugral and Spain
- The Arctic (indigenous populations)
- South America: Argentina, Bolivia, Brazil, Ecuador, Guyana, Suriname, Venezuela and Amazon region of Colombia and Peru
- Independent states of former Soviet Union
- Eastern Europe, including Russia, except Hungary
- Caribbean: Antigua and Barbuda, Dominica, Dominican Republic, Granada, Haiti, Jamica, Puerto Rico, St. Kitts and Nevis, St. Lucia, St. Vincent and Grenadines, Trinidad and Tobago and Turks and Caicos.
Other high risk groups recommended for screening
- Household and sexual contacts of HBsAg-positive person*
- Persons who have ever injected drugs*
- Persons with multiple sexual partners or history of sexually transmitted disease*
- Men who have sex with men*
- Inmates of correctional facilities*
- Individuals with chronically elevated ALT or AST*
- Individuals infected with HCV or HIV*
- Patients undergoing renal dialysis*
- All pregnant women

^If HBsAg-positive persons are found in the first generation, subsequent generations should be tested

[#] HBsAg prevalence >8%

[†] HBsAg prevalence 2%-7%

*Those who are seronegative should receive hepatitis B vaccine

3.3.3 Stages of Hepatitis B virus infections

HBV infection is a progressive liver disease. Late stage of the disease is associated with an increased risk of morbidity and mortality resulting to considerable health care costs (Brown *et al*, 2004; Lok & McMahon, 2007; Hoofnagle *et al*, 2007; Idris *et al*, 2008) and a substantial burden to society (Lavanchy, 2008). HBV causes 60-80% of the world's HCC, one of the major three causes of death in Africa, Asia and the Pacific Rim. HBV has been classified by the International Agency for Research on Cancer as carcinogenic to humans (Parkin *et al*, 2001). Overall, approximately 15-40% of infected patients will develop cirrhosis, liver failure, or HCC (Fattovich *et al*, 1995; Liaw *et al*, 1988). It is estimated that 25% of carriers will develop serious HBV-related complications (Yang, Kim, & Kim, 2004), 50% of male carriers and 14% of female carriers will eventually die of complications of cirrhosis and HCC (Beasley, 1982).

In Western Europe, the incidence of HCC associated with HBV ranges from 16% to 60% in Italy and Greece, respectively (Stroffolini *et al*, 1998; Kuper *et al*, 2000). In comparison, the results of a European-wide multi centre study found that about 20% of European patients with HCC showed HBV infection (Brechot *et al*, 1998). Among indigenous people in Alaska where HBV infection is highly endemic, HCC is the most common complication, with a reported incidence of 1.9 per 1000 (2.3 and 1.2 in men and women, respectively) (McMahon *et al*, 2001). In the high endemic Asia-Pacific region, it is associated with up to 80-90% of HCC cases in China, India, Korea, Singapore and Vietnam (Lemon *et al*, 2000; Pokoski & Ohlmer, 2001). Demographic, social, and environment risk factors associated with the development of HCC and/or cirrhosis in persons with CHB virus infection were male sex, increasing age >40 years, family history of HCC, and aflatoxin (McMahon, 2004). In Thailand, HCC and cirrhosis represent the most common form of malignant tumor (Tangkijvanich, *et al*, 1999; Pramoolsinsup, Pukrittayakamee & Desakorn, 1986; Sooklim *et al*, 2003; Tangkijvanich, Suwangool & Mahachai, 2003).

The glossary of clinical terms used in HBV infection is shown in Table 3.3.

Table 3.3 Glossary of clinical terms used in HBV infection (Lok & McMahon, 2007)

Glossary of clinical terms used in HBV infection
Definition
CHB
Chronic necroinflammatory disease of the liver caused by persistent infection with hepatitis B virus. Chronic hepatitis B can be subdivided into HBeAg positive and HBeAg negative chronic hepatitis B.
Inactive HBsAg carrier state
Persistent HBV infection of the liver without significant ongoing necroinflammatory disease
Resolved hepatitis
Previous HBV infection without further virologic, biochemical or histological evidence of active virus infection or disease
Acute exacerbation or flare up of hepatitis B
Intermittent elevation of aminotransferase activity to more than 0 times the upper limit of normal and more than twice the baseline value
Reactivation of hepatitis B
Reappearance of active necroinflammatory disease of the liver in a person known to have inactive HBsAg carrier state or resolved hepatitis B
HBeAg clearance
Loss of HBeAg in a person who was previously HBeAg positive
HBeAg seroconversion
Loss of HBeAg and detection of anti-HBe in a person who was previously HBeAg positive and anti-HBe negative
HBeAg reversion
Reappearance of HBeAg in a person who was previously HBeAg negative, anti-HBe positive

#Very low levels may be detectable using sensitive PCR assays

The National Institutes of Health identified 4 phases of HBV infection namely immune-tolerent phase, the immune-active phase, the inactive phase, and HBsAg clearance phase (McMahon, 2004) as shown in Table 3.4 and Figure 3.4.

Table 3.4 Phase of CHB infection (McMahon, 2004)

HBV Phase	HBeAg	HBV DNA level	Liver Biopsy Inflammation and Fibrosis
Immune tolerant	Positive	>200,000 IU/ml	None to minimal
Immune active	Positive or negative	>20,000 IU/ml	Mild to severe
Inactive	Negative	<2,000 IU/ml	None to mild[a]
HBsAg clearance	Negative	<2,000 IU/ml	None to mild[b]

[a] Immune active phase may occasionally occur in persons with HBV DNA between 2000 and 20,000 IU/ml
[b] May have moderate or severe fibrosis that may take years to resolve.

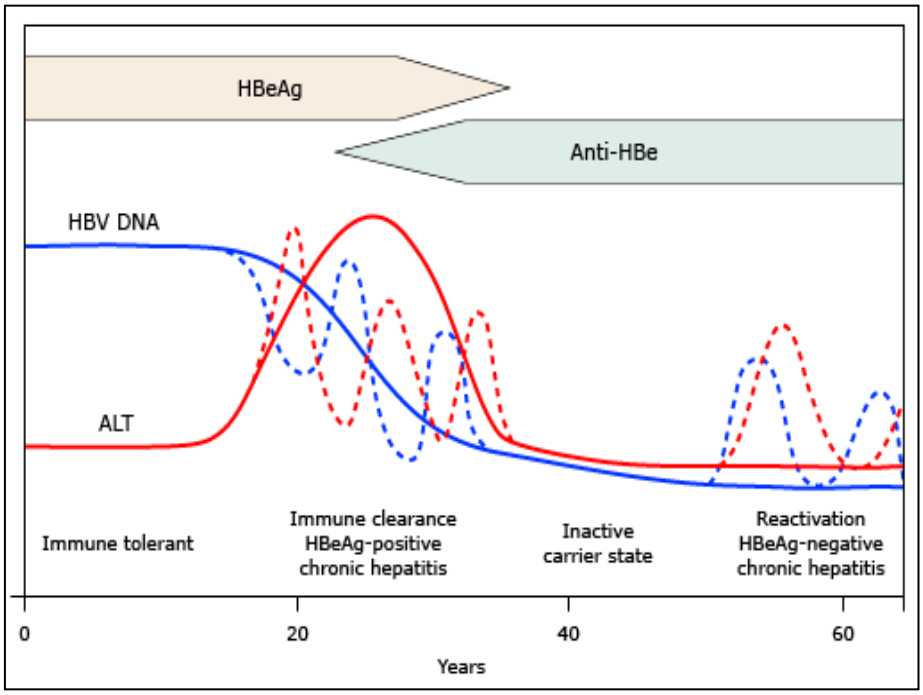


Figure 3.4 The course of chronic HBV infection (Yim & Lok, 2006)

In conclusion, the natural history of HBV is complicated and nonlinear. Many infected persons go from a state of high viral load and no or minimal liver disease to one of active liver inflammation followed by a phase of low viral load and inactive liver disease (McMahon, 2004). However, some persons can revert back from inactive to active disease at any time (McMahon, 2004). Thus, persons with chronic HBV must have lifelong, regular monitoring to access disease activity and identity any period where antiviral intervention might be needed (McMahon, 2004). A schematic algorithm to display the evolution of progression through the phases of hepatitis B virus infection was shown in Figure 3.6.

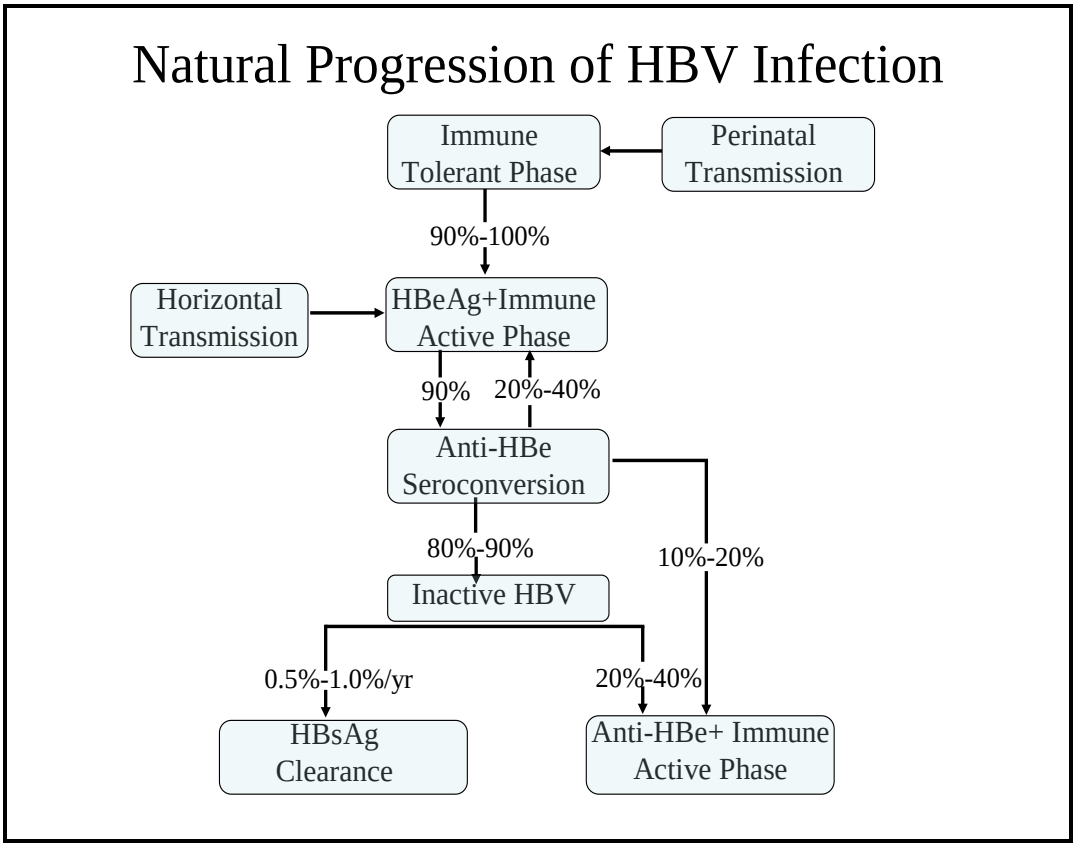


Figure 3.5 A schematic algorithm to display the evolution of progression through the phases of hepatitis B virus infection. (McMahon, 2004; Goldstein *et al*, 2005)

3.3.4 Hepatitis B virus genotypes

There are distinct ethnogeographic variations for the distribution of various HBV genotypes as well as pathogenic and therapeutic differences. Of the eight genotypes (A-H) that have been identified, genotype B and C are the major genotypes in most East and Southeast Asian countries (Liaw, 2009). In general, genotype B infection has a relatively better prognosis than genotype C, which is associated with high rates of HCC and cirrhosis (McMahon, 2004). Genotype B is most prevalent in Taiwan, genotype C is most prevalent in Korea, Japan and China, and genotype D is most prevalent in India, central Asia, and Mongolis (Kao, 2007; Ryan & Tran, 2008; Yurdaydin *et al*, 2008; Pan *et al*, 2008; Han *et al*, 2008). In Thailand, genotype C and B were reported as the major genotyped with 50.0-68.6% of asymptomatic carriers (Theamboonlers *et al*, 1998; Theamboonlers *et al*, 1999). Genotype C was reported in 89.3% of blood donors in northern Thailand (Jutavijittum *et al*, 2006). The hepatitis B virus genotype/subgenotypes and geographic regions and liver-related disease association are shown in Table 3.9.

The viral factors associated with increased risk of development of HCC and/or cirrhosis in persons with CHB virus infection was shown in Table 3.5. Patients with HBV who are co-infected with HIV, HCV, or hepatitis D virus are at an increased risk of developing adverse outcomes to chronic HBV infection. Co-infection with HIV is found in 6% to 15% of individuals with HBV (McMahon, 2004).

Two important mutations in HBV virus have been associated with outcome, the basal core promoter mutation and the pre-core mutation. Although more common mutation occurs in persons who have inactive liver inflammation, the mutation also occurs frequently in persons who have inactive hepatitis.

Table 3.5 Viral factors associated with increased risk of development of HCC and/or cirrhosis in persons with CHB virus infection (McMahon, 2004)

	Increased risk of HCC	Increased risk of cirrhosis
HBV genotype		
Genotype C	3+	2+
Genotype F	2+	No evidence to date
HBV DNA >20,000 IU/mL in persons >40 years	3+	3+
BCP mutation	3+	+
Co-infecting viruses		
HBV/HIV	+	2+
HBV/HCV	3+	2+
HBV/HDV	+	3+

3.4 Guidelines of CHB therapy

Hepatitis B has been a major foci for international consensus and guidelines (Lok & McMahon, 2007; De Franchis *et al*, 2003; Liaw *et al*, 2005; Alberi *et al*, 2005; National Institutes of Health, 2002; Choi & Yoo, 2010; Liver Society (Thailand), 2009). Other groups have proposed additional treatment algorithms (ACT-HBV Asia-Pacific Steering Committee Members, 2006; Keeffe *et al*, 2006). Standardized definition of primary non-response, breakthrough and relapse were also proposed (Lok & McMahon 2007). Several studies have shown that inhibition of virus replication is associated with remission of liver disease and prevention of HBV-related complication (Idris *et al*, 2008; Chen *et al*, 2006; Momeja-Marin *et al*, 2003; Liaw *et al*, 2004; EASL 2009). Table 3.6 shows current guidelines for the management of CHB (modified from Choi & Yoo, 2010).

Table 3.6 Current guidelines for management of CHB (modified from Choi & Yoo, 2010)

Year	Guidelines
2007	Korean Association for the Study of the liver (KASL) guideline (Lee & Kim, 2007)
2008	Asia-Pacific consensus statement (APASL guideline) (Liaw *et al*, 2008)
2008	Treatment algorithm in the United States (US algorithm) (Keefe *et al*, 2008)
2009	European Association for the Study of Liver (EASL) guideline (EASL, 2009)
2009	American Association for the Study of Liver Diseases (AASLD) guideline (Lok & McMahon, 2009)
2009	Thailand Consensus Recommendations for Management of Chronic Hepatitis B and C 2009 (Liver Society (Thailand))

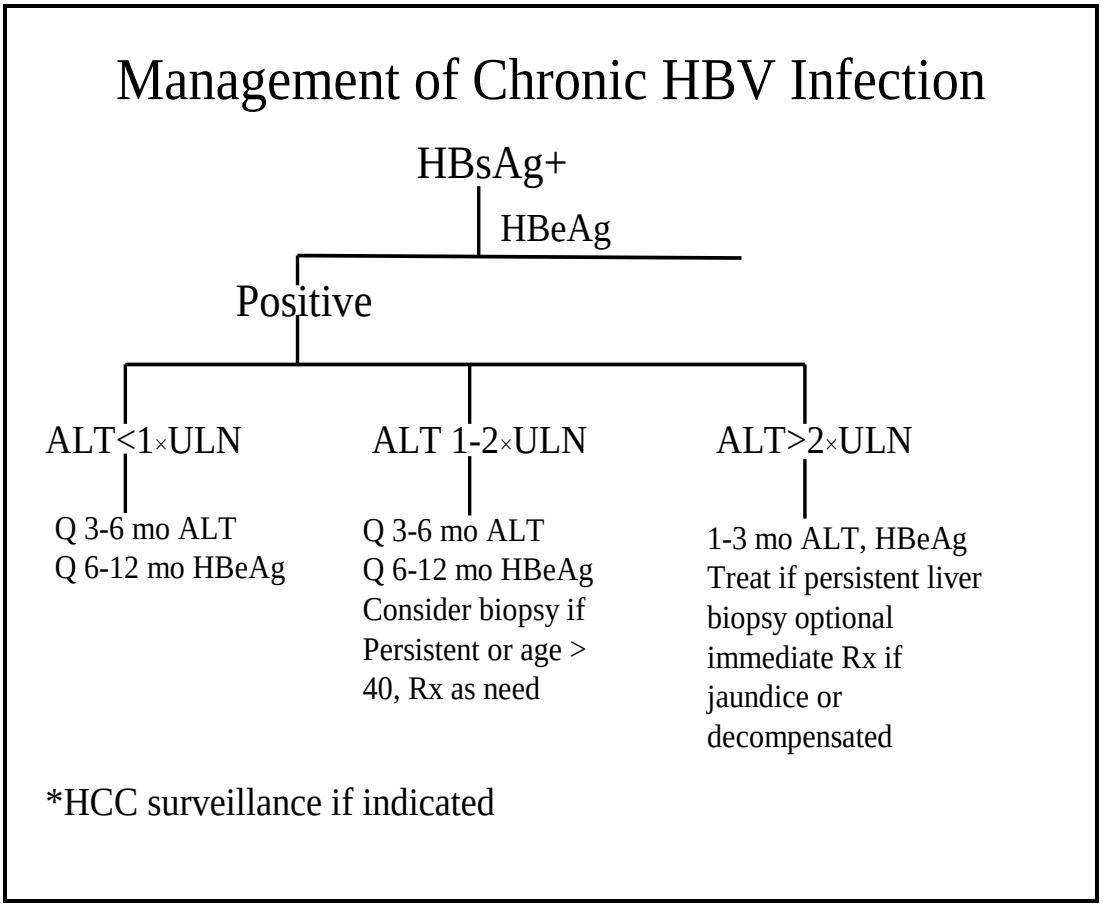
Treatment for CHB aims to prevent or reduce morbidity and mortality associated with cirrhosis, HCC and hepatic failure (Buti, Brosa & Casado 2009; Lok & McMahon, 2007). These goals can be achieved with the eradication of HBV infection, or clearance of serum HBsAg. The current guidelines recommend considering treatment for HBeAg-positive CHB if HBV DNA ≥ 20,000 IU/mL with elevated ALT, HBeAg negative CHB if HBV DNA ≥ 2,000 IU/mL with elevated ALT, and compensated cirrhosis with HBV DNA ≥ 2,000 IU/mL and recommended antiviral therapy (ARV) with referring for liver transplantation in decompensated cirrhosis.

The current guidelines recommend drugs for initial therapy of CHB including interferon base (KPSL 2007, APASL 2008 AASLD 2009 and Thailand Consensus Recommendations for Management of Chronic Hepatitis B and C 2009), and nucleos(t)ide analogue (US algorithm 2008 and EASL 2009). For cirrhosis, they were interferon base (KPSL 2007 and EASL 2009), and nucleos(t)ide analogue (APASL 2008, US algorithm 2008 AASLD 2009 and Thailand Consensus

Recommendations for Management of Chronic Hepatitis B and C 2009) For initial therapy of decompensated cirrhosis; KPSL 2007 recommended lamivudine, US algorithm 2008 recommended lamivudine combination with entecavir plus tenofovier, APASL 2008 and EASL 2009 recommended entecavir, and AASLD 2009 recommended lamivudine or telbevudine plus adefovir or tenofovier.

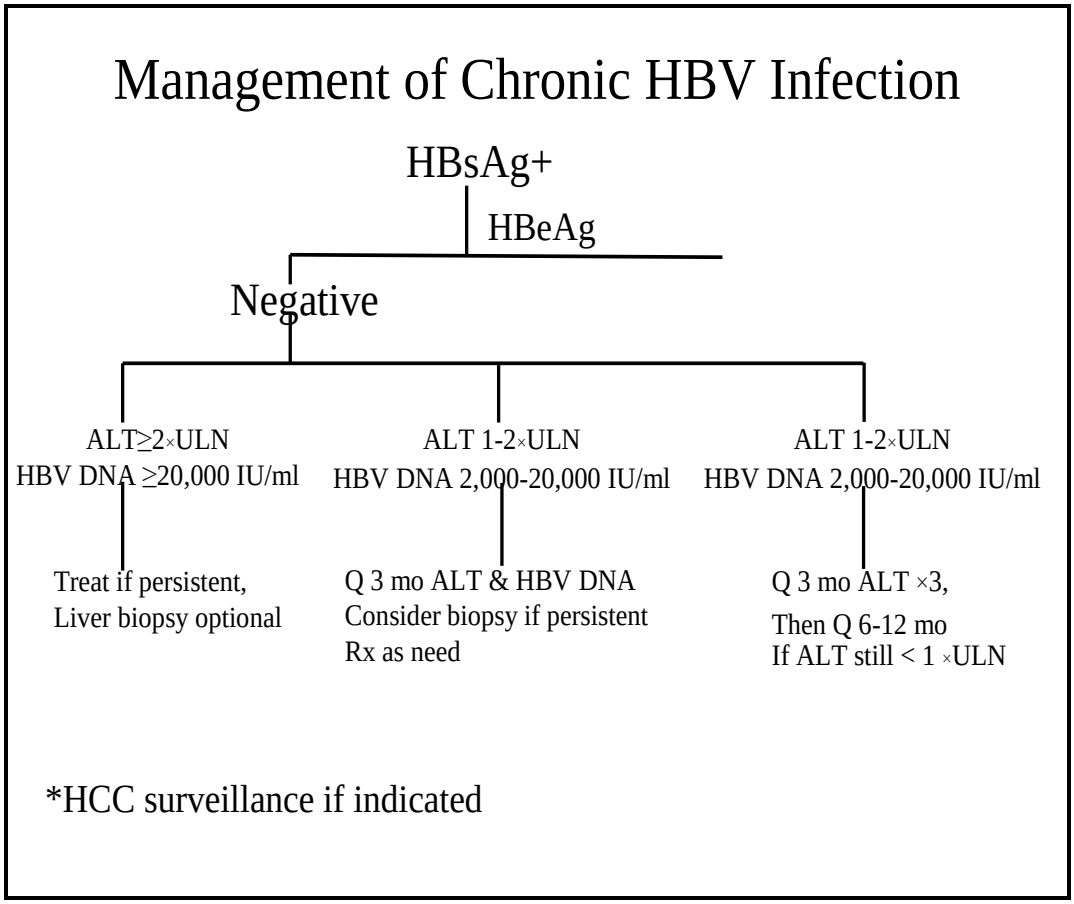
Parameters that are most widely used as end points of therapy are reduction of Hepatitis B virus deoxyribonucleic acid (HBV DNA) to undetectable levels, loss of hepatitis B early antigen (HBeAg) with or without the appearance of anti-HBe (serologic response), normalization of alanine transaminase (ALT), and improvement of liver histology (Lok & McMahon, 2007). Several studies have shown that reduction of HBV DNA to a level of 300-400 copies/mL as possible, ideally below the lower limit of detection for real-time polymerase chain reaction assays, will lead to biochemical remission, histological improvement and prevention of HBV-related complications and is associated with a decrease risk of HBV drug resistance (Momeja-Marin *et al*, 2003; Liaw *et al*, 2004; EASL, 2009).

Algorithms for follow-up of HBV carriers who are HBeAg-positive and negative are shown in Figure 3.7 and Figure 3.8.



Abbreviation; ALT, alanine aminotransferase; ULN, upper limit of normal; Rx, treat; HCC, hepatocellular carcinoma

Figure 3.6 Algorithm for follow-up of hepatitis B virus carriers who are HBeAg-positive (Lok & McMahon, 2007)



Abbreviation; ALT, alanine aminotransferase; ULN, upper limit of normal; Rx, treat; HCC, hepatocellular carcinoma

Figure 3.7 Algorithm for follow-up of hepatitis B virus carriers who are HBeAg-negative (Lok & McMahon, 2007)

3.5 Treatment of CHB patient

For more than 350 million patients with chronic HBV infection, only antiviral treatment can provide help (Lavanchy, 2005). The adequate and appropriate antiviral treatment of chronic HBV infection has been shown to prevent or improve the consequences associated the chronic liver disease (Lavanchy, 2008). Permanent and complete suppression of viral replication is the main treatment goal of antiviral therapy with nucleos(t)ide analogues (NAs) (Chen *et al*, 2007; Iloeje *et al*, 2006; EASL, 2009; Buti, Brosa & Casado 2009). Early guidelines generally agreed that antiviral treatment could be recommended for CHB patients especially those without

liver cirrhosis and/or with serum HBV DNA level above 10^5 copies/mL (20,000 IU/mL) and ALT level greater than two times the normal (Choi & Yoo, 2010).

The five oral antiviral drugs approved by United States Food and Drug Administration (FDA) for the treatment of adults with CHB were lamivudine (LAM), adefovir (ADV), entecavir (ETV), telbivudine (TBV) and tenofovir (TNV) as shown in Table 3.7 (Khungar & Han, 2010). NAs have fast and potent inhibitory effects on hepatitis B virus polymerase and reverse transcriptase activity, and are safe and effective for HBV DNA suppression, ALT normalization, and histological improvement (Liaw & Chu, 2009). These drugs may also rescue patients with decompensated cirrhosis by increasing serum albumin concentrations, and stabilizing bilirubin values and prothrombin time, removing the need for transplantation and prolonging survival (Liaw & Chu, 2009). NAs at least in the short to medium term are generally safe drugs, given once daily, orally, usually with minimal toxicity (Dusheiko, 2009).

Table 3.7 FDA-approved oral antiviral drugs for CHB (Khungar &Han, 2010)

	Lamivudine	**ADV**	**Entecavir**	**Telbivudine**	**Tenofovir**
Year of approval	1998	2002	2005	2006	2008
Abbreviation	LAM	ADV	ETV	TBV	TNV
Mechanism of action	Blocks HBV reverse transcriptase	Blocks HBV reverse transcriptase	Inhibit HBV DNA polymerase	Inhibit HBV DNA polymerase	Inhibit HBV DNA polymerase
Clearance	Renal	Renal	Renal	Renal	Renal
Dose	100 mg/d	10 mg/d	0.5 mg/d	600 mg/d	300 mg/d
Renal and dialysis adjusted dose	50 mg/d	10 mg/d	0.25 mg/d or 0.50 mg every other day	600 mg every other day	300 mg every other day
Common side effects	Occasional myopathy, neuropathy, pancreatitis	Nephrotoxicity, pancreatitis	Negligible	Myopathy	Nephroto-xicity
Pregnancy category	C	C	C	B	B

Development of antiviral resistance is a major limitation to long-term efficacy of NAs (Jannssen & Reijnders, 2009). Prolonged therapy may enhance

chances of HBeAg and HBsAg seroconversion (Sonneveld & Janssen, 2010) but also increases the chance of emergence of viral mutants resistant to current NAs and NA-related side effects (Fontana, 2009). It leads to reversion of virologic and histological improvement, and enhances the rate of disease progression (Liaw *et al*, 2004). A combination of two or more antiviral drugs, as HIV therapy, reduce drug resistance but does not enhance efficacy (Lau *et al*, 2005; Marcellin *et al*, 2004; Lai *et al*, 2005; Sung *et al*, 2008). Nonetheless, CHB is a prolonged illness, and long-term efficacy and toxicity of oral NAs remains unknown (Dusheiko, 2009). The benefit of long-term therapy should be weighed against possible drug resistance and durability of treatment response (Liaw & Chu, 2009). If long term therapy is anticipated, the drug with the lowest rate of resistance is preferable, although cost may affect choice (Liaw & Chu, 2009).

Drug therapy is not usually recommended for children and women of childbearing age-unless there is an absolute indication such as ensuing or overt hepatic decompensation because of potential problems associated with long-term therapy (Liaw *et al*, 2008). Women who become pregnant while receiving oral antiviral agents can continue treatment with telbivudine or tenofovir, which are category B agents (Liaw *et al*, 2008; Hoofnagle *et al*, 2007).

Interferon-based therapy is preferred in patients with compensated liver disease-particularly in young patients, women of childbearing age, and those with low ALT values because of the finite duration of treatment, sustained response, and long term benefits including prevention of HCC (Liaw *et al*, 2008; Lau, Marcillin & Peters, 2007).

Non-eligible patients or non-responders to pegylated interferon should be treated with the most potent NAs, but long-term or indefinite therapy is often necessary, posing considerable risk of viral resistance and long-term side effects (Sonneveld & Janssen, 2010).

In patients with concurrent hepatitis C or D virus infection, the dominant virus should be determined and treated accordingly. In patients with HIV coinfection, ADV or interferon (if CD4 is greater than 500) is preferred if HIV infection does not need treatment. If HIV treatment is required, tenofovir or combination lamivudine and

tenofovir should be included in the active antiretroviral therapy (Lok & McMahon, 2007; Liaw *et al*, 2008).

Pros and cons and response rates of PEG versus NAs were reviewed and are shown in Table 3.8.

Table 3.8 Pros and cons of PEG-IFN versus NAs (Sonneveld & Janssen, 2010)

PEG-IFN	Nucleos(t)ide analogues
Pros	**Pros**
Finite duration of therapy	Daily oral dosing
Absence of viral resistance	Potent HBV DNA suppression
Response durable post-therapy	Minimal side effects in the short term
Proven effect in general patient population	Proven effect in patients with advanced liver disease
Increase in HBsAg seroconversion rate	Less expensive during first year, possibly equally or more costly after long-term therapy
Cons	**Cons**
Frequent side effects	Risk of resistance
Weekly subcutaneous injection	Limited increase in HBsAg seroconversion rate
Less effective HBV DNA suppression	Response less durable post-therapy
Expensive	Long-term or indefinite therapy may be required

3.5.1 Interferon and PEG-IFN

Interferon-alpha therapy showed a beneficial effect on short- and long-term virological outcomes only in those with a lower pretreatment serum HBV-DNA level. For young CHB patients in Taiwan with infection occurring perinatally or in early childhood, the real advantage of IFN-alpha therapy was not observed (Hsu *et al*, 2008).

3.5.2 Lamivudine (LAM)

LAM was the first oral nucleoside analogue approved for the treatment of CHB, at a dose of 100 mg daily. It is the negative enantiomer of 2'-3' dideoxy-3'-thiacytidine. Incorporation of 3TC-TP into growing deoxyribonucleic acid (DNA) results in premature chain termination inhibiting HBV DNA syntesis.

After 1 year of LAM treatment, HBeAg seroconversion was achieved in more than half of patients with ALT values more than five times upper limit of normal, but only 5% of patients with ALT values less than twice the upper limit of normal. Thus, patients with a stronger endogenous immune response to the hepatitis B virus might have an improved chance of reducing cccDNA and HBeAg translation (Liaw & Chu, 2009; Chien, Liaw & Atkins, 1999; Perrillo *et al*, 2002).

LAM was approved in 1998 for the treatment of CHB in adults and in 2001 for children. It was thought to have a safety profile similar to placebo in registration trials (Lai *et al*, 1998). With prolonged use in postmarketting surveillance, it was noted that genotypic resistance can be detected in 14% to 32% after 1 year of lamivudine treatment and up to 70% after 5 years of treatment (Lok & McMahon, 2009).

LAM has been studied extensively and has a well-documented adverse event of liver disease flares due to the emergence of lamivudine-resistant HBV (Khungar & Han, 2010). Rare cases of neuropathy, pancreatitis, Fanconi syndrome, and reversible myopathy have been reported in patients coinfected with HBV and HIV (Lai *et al*, 1998). Virologic breakthrough in those with LAM-resistant virus was usually followed by biochemical breakthrough, with increase in serum ALT, followed by acute exacerbations of liver disease and even hepatic decompensation and death. Mutation in tyrosine-methionine-aspartate motif occurs frequently and confers genotypic resistance to LAM. LAM is now considered second-line therapy for treatment naïve patients due to this resistance pattern.

3.5.3 Adefovir (ADV)

ADV is a nucleotide analogue without cross-resistance to LAM, but a recent study reported an increase in resistance to ADV from 0% to 2% at 1 and 2 years, respectively, to 18% after 4 years in HBeAg–negative patients (Locarnini & Arterburn, 2005). ADV was developed as an antiretroviral for HIV infection but due

to nephrotoxicity at high dose, it was not developed for this indication (Lok & McMahon, 2009). Adefovir dipivoxil is the orally bioavailable pro-drug of ADV, it inhibits reverse transcriptase and DNA polymerase and cause HBV chain termination.

For CHB, it was approved at a dose of 10 mg daily in 2002. It was approved for children 12 to 17 years of age in 2008. The two most common side effects observed with ADV therapy are dose-dependent but reversible nephrotoxicity and antiviral resistance (Lok & McMahon, 2009). Further long-term follow-up in patients are needed to determine adverse events associated with ADV (Khungar & Han, 2010).

Initiating patients with ADV therapy has the clinical advantage of a lower risk of resistance emerging, especially in the early stages of treatment, where LAM has a lower acquisition drug cost for those patients of more modest means who need to pay out of pocket for their medication (Lacey & Gane, 2007).

3.5.4 Entecavir (ETV)

ETV is a nucleoside analogue of 2'deoxyguanosine and inhibits HBV replication at three steps: priming of HBV DNA polymerase, reverse transcription of the negative-strand HBV DNA (Lok & McMahon, 2009). ETV is generally well tolerated even in patients with advanced fibrosis and cirrhosis (Khungar & Han, 2010).

In 2005, it was approved for treatment-naïve CHB patients at a dose of 0.5 mg/d and for LAM-resistant patients at 1.0 mg/d. In animal studies, there has been a higher incidence of solid tumors; long-term human studies are underway (Khungar & Han, 2010). Resistance is rare with ETV in nucleoside treatment naïve patients and when it does occur, it tends to happen in those patients who already have LAM resistance (Khungar & Han, 2010). ETV has been proven effective against CHB, but continued surveillance is necessary to determine its long-term safety (Khungar & Han, 2010). No entecavir-treated patients discontinued therapy due to adverse events (Schiff *et al*, 2008).

ETV is approved with greater antiviral potency than LAM in large comparative trials in 48-week trials in treatment-naive patients, no resistance has been demonstrated. However, its potency is diminished in the presence of LAM-resistant HBV infection. Only 22% of LAM-refractory patient experienced complete

suppression of HBV DNA (by PCR) compared with 83% of treatment-naive patients. In addition, the presence of preexisting lamivudine-induced mutations has been associated with the emergence of several additional signature mutations in patients receiving entecavir therapy, resulting in still further loss of potency (Dienstag *et al*, 2006).

3.5.5 Telbivudine (TBV)

TBV is a potent L-nucleoside analogue approved for the treatment of CHB in 2006 at a dose of 600 mg/d. It is more potent than LAM in suppressing HBV replication, but it is associated with a high rate of viral resistance, reflecting mutations cross-resistant with LAM, so monotherapy is limited (Lok & McMahon, 2009). The safety profile of TBV looked similar to that of LAM in registration trials, but at 2 years, significant adverse effects were noted (Lai *et al*, 2005; Lai *et al*, 2007).

Creatine phosphokinase (CPK) elevations greater than 7 times the upper limit of normal were noted more frequently in patients on TBV at 2 years as compared to patients on LAM (12.9% with TBV compared to 4.1% with LAM treated patients, $p<0.001$) (89 Liaw *et al*, 2009). Reports exist of moderately severe peripheral neuropathy in 17% of patients treated with TBV and peginterferon alfa-2a (United States Food and Drug Administration, 2008). TBV is not recommended for use in combination with PEG at this time (Khungar & Han, 2010). TBV in combination with ADV and TNV is currently being studied (Khungar & Han, 2010).

3.5.6 Tenofovir (TNV)

Tenofovir disoproxil formurate is a nucleotide analogue that was approved for HIV infection as Viread (tenofovir alone) or Truvada (tenofovir plus emtricitabine as a single pill). It was approved for CHB at a dose of 300 mg/d in 2008. It is structurally similar to ADV, but is less nephrotoxic, so higher doses can be used, conferring better antiviral activity in clinical studies (Lok & McMahon, 2009; Leemans *et al*, 2008; Marcellin *et al*, 2008).

TNV is currently recommended as part of the nucleos(t)ide reverse transcriptase inhibitor (NRTI) backbone in combination with non- nucleoside reverse transcriptase inhibitor (NNRTI) or protease inhibitor as first line highly active

antiretroviral therapy, which makes it an excellent choice for therapy in coinfected individuals (Tan, Gilleece & Mandalia, 2009). To date, neither phenotypic nor genotypic resistance to CHB has been identified with tenofovir (Khungar & Han, 2010). It is effective against lamivudine-resistant strains of CHB (Khungar & Han, 2010).

A 4% rate of nephrotoxicity is reported in HIV patients taking tenofovir, but most were able to continue tenofovir at reduced doses. It is recommended that serum creatinine, phosphate levels, and urinalysis be monitored every 3 months in patients taking tenofovir, because nephrotoxicity from this drug is thought to be reversible with dose reduction or discontinuation. Decreased bone density and osteomalacia have also been described in HIV patients taking tenofovir. Bone density measurements and calcium and vitamin D supplementation are recommended in patients taking TNV for HIV. The experience with TNV in CHB is still in its early stages, and long-term data regarding nephrotoxicity, decrease bone density, and osteomalacia in patients with CHB has not been determined (Khungar & Han, 2010).

3.5.7 Comparison of the NAs used in CHB

Liaw and Chu (2009) reviewed and compared the drugs in treatment-naïve patients with HBeAg-positive and -negative CHB. Results from cross-trial 1-year treatment data suggested that ETV is the most potent drug, followed by TNV, TBV, LAM, and ADV. However, the antiviral potency of these drugs does not result in an increase in HBeAg seroconversion which was seen at a rate of around 20% after 1 year of treatment-and HBsAg loss is very rare (Liaw & Chu 2009; Marcellin *et al*, 2003; Hadziyannis *et al*, 2003; Lai *et al*, 2006; Gish *et al*, 2007; Lai *et al*, 2007). The results were shown in Table 3.9 and Table 3.10.

Table 3.9 Comparison of the drugs used in treatment-naïve patients with HBeAg-positive CHB (Liaw & Chu, 2009)

	Pegylated interferon alfa-2a	Lamivudine	Adefovir	Entecavir	Telbivudine	Tenofovir
Dose/route	180 μg/wk subcuta-neous	10 mg/ day orally	10 mg/ day orally	0-5 mg/ day orally	600 mg/ day orally	300 mg/ day orally
Cost (USD/year per person)*	18,480	2,482	6,647	8,694	5,924	5,811
HBV-DNA (PCR)						
Log reduction at year 1†	4.5	5.4	3.6 (1.0)	6.9	5.7	4.5
Undetectable at year 1†	25%	40%	21% (0%)	67%	60%	25%
HBeAg seroconversion at year 1†	32%	20%	12% (6%)	21%	23%	32%
Drug resistance						
Year 1	0	11-14%	0%	0%	5%	0
Year 2	-	40%	..	0%	25%	0
Year 3	-	56%	..	~1%	..	..
Year 5	-	69%	20%	1.2%	..	..
Other side-effect	Various, unpleasant	Negligible	Creatinine increase	Negligible	Increase in CK	Negligible

Abbreviation: CK, Cretinine kinase; HBeAg, hepatitis B e antigen; -, not applicable; †, Data in brackets refer to untreated controls.

Table 3.10 Comparison of drugs used in treatment-naïve patients with HBeAg-negative CHB (Liaw & Chu, 2009)

	Pegylated interferon alfa-2a	Lamivudine	Adefovir	Entecavir	Telbivudine	Tenofovir
Dose/route	180 μg/wk subcuta-neous	10 mg/ day orally	10 mg/ day orally	0-5 mg/ day orally	600 mg/ day orally	300 mg/ day orally
Cost (USD/year per person)*	18,480	2,482	6,647	8,694	5,924	5,811
HBV-DNA (PCR)						
Log reduction at year 1†	4.1	4.5	3.7 (1.4)	5.0	4.4	4.1
Undetectable at year 1†	63%	72%	61% (0%)	90%	88%	63%
HBeAg seroconversion at year 1†	-	-	-	-	-	-
Drug resistance						
Year 1	0	6-27%	0%	0%	2%	0
Year 2	-	26-54%	3%	0%	11%	0
Year 3	-	57%	11%	~1%	..	..
Year 5	-	65%	29%	1.2%	..	..
Other side-effect	Variuos, unpleasant	Negligible	Creatinine increase	Negligible	Increase in CK	Negligible

Abbreviation: CK, Cretinine kinase; HBeAg, hepatitis B e antigen; -, not applicable; †, Data in brackets refer to untreated controls.

3.5.8 Limitations of antiviral therapy in CHB

The limitations of antiviral therapy in CHB included a possibility of no cure (Lavanchy, 2008), absence of direct head-to-head trial comparison (Rajendra &Wong, 2007), problem of HBV drug development (Dusheiko, 2009; Khungar & Han, 2010), and selection of patients for treatment varies among physicians (Lok, 2009; Freeman *et al*, 2003; Amin *et al*, 2006). Another problem is that it is often difficult to ascertain whether an adverse effect is from the study drug or the natural

progression of the disease as some analogues have activities against human mitrochondrial DNA polymerase gamma and can lead to mitochondrial dysfunction (Khungar & Han, 2010). Mitochondrial toxicity can manifest clinically as one or more of the following: myopathy, neuropathy, hepatic steatosis, pancreatitis, macrocytosis, hyperlactemia, lactic acidosis, and nephrotoxicity (Khungar & Han, 2010).

3.6 Child-Turcotte-Pugh score

In gastroenterology, the Child-Pugh score or the Child-Turcotte-Pugh score is used to assess the prognosis of chronic liver disease, mainly cirrhosis. Although it was originally used to predict mortality during surgery, it is now used to determine the prognosis, as well as the required strength of treatment and the necessity of liver transplantation. It was introduced in 1964. Child and Turcotte published a classification to assess the operative risk in cirrhotic patients. The score employs five clinical measures of liver disease including severity of ascites, encephalopathy, nutritional status and serum level of bilirubin and albumin. It classifies patients in class A, B or C in relation to best (A), moderate (B), or worse (C) prognosis (Child & Turcotte, 1964).

In 1973, Pugh *et al* (1973) used a modified version of this classification for patients undergoing surgical transaction for oesophageal varices. They replaced nutritional status with prothrombin time (PT) and assigned a score ranging from 1 to 3 to each variable, with 3 indicating most severe derangement (Pugh, Murray-lyon & Dawson, 1973). This classification was used to predict the outcome of surgery in cirrhotic patients in general, and more recently, to stratified patients on the waiting listed for liver transplantation (Samiullah *et al*, 2009). Indeed, creatinine serum levels proved to be independent predictors of survival in cirrhotic patients during natural course of the disease as well as during acute complications (Angermayr *et al*, 2003). Table 3.11 demonstrates clinical measures of Child and Turcotte classification.

Table 3.11 Clinical measures of Child and Turcotte classification (Child & Turcotte, 1964)

Measure	1 point	2 points	3 points	units
Bilirubin (total)	<34 (<2)	34-50 (2-3)	>50 (>3)	μmol/l (mg/dl)
Serum albumin	>35	28-35	<28	g/l
International normalized ratio (INR)	<1.7	1.71-2.20	>2.20	No unit
Ascites	None	Mild	Severe	No unit
Hepatic encephalopathy	None	Grade I-II (or suppressed with medication)	Grade III-IV (or refractory)	No unit

In primary sclerosing cholangitis and primary biliary cirrhosis, the bilirubin references are changed to reflect the fact that these diseases feature high conjugated bilirubin levels. The upper limit for 1 point is 68 μmol/l (4 mg/dl) and the upper limit for 2 points is 170 μmol/l (10 mg/dl). Table 3.12 shows the interpretation of Child and Turcotte classification score.

Table 3.12 Interpretation of Child and Turcotte classification score in relation to best (A), moderate (B), or worse (C) prognosis (Child & Turcotte, 1964)

Points	Class	One year survival	Two year survival
5-6	A	100%	85%
7-9	B	81%	57%
10-15	C	45%	35%

Previous studies have used CTP scores to assess the severity of cirrhosis (Samiullah *et al*, 2009; Zuberi *et al*, 2007). In Pakistan, the proportion of 222 decompensated cirrhosis patients using the creatinine-modified CTP score were 7 (3.2%), 28 (12.6%) and 187 (59.0%) patients in grade A, B, and C respectively

(Samiullah *et al*, 2009). In Karachi, the proportion of 109 cirrhosis in grade A, B, and C were 30 (27.5%), 38 (34.9%) and 41 (37.6%), respectively (Zuberi *et al*, 2007). Ascites was found to be the most common presentation of patients with 3.6% in mild, 56.0% in moderate, 57.7% in severe and 13.5% in refractory ascites group respectively. About 19% of cirrhosis patients presented with history of encephalopathy whereas 48.6% presented with history of hematemesis (Samiullah *et al*, 2009). The creatinine-modified CTP can better predict encephalopathy than original CTP but has marginal advantage over the original CTP in predicting other cirrhosis related complications such as ascites and haematemesis. The predicting ability of both creatinine-modified CTP and original CTP for short-term prognosis of the patient is the same (Samiullah *et al*, 2009).

3.7 Quality of life in CHB patients

The concept of quality of life (QOL) conforms to a definition of health as not only the absence of disease and disability but also the presence of physical, mental and social well-being (WHO, 1952). Also, health care outcomes can be divided into three fundamental categories: survival (how long people live), cost (how much the intervention costs), and quality of life (how well people live) (Jay *et al*, 2009). This part of review focuses on the concept of QOL in CHB patients.

The QOL measurement examines how patients experience and perceive, and might help clinicians address functioning and well-being issues beyond the scope of usual care (Kanwal *et al*, 2009). It has the capacity to obtain “a full appreciation of the impact of illness and treatment” (Cella & Nowinski, 2002) given its reliance on the patient’s perspective (Jay *et al*, 2009). Its results provide basis for holistic view of the patient and complements the organic outcomes (Sobhonslidsuk *et al*, 2004).

Several studies revealed that QOL outcomes provide important information regarding the complex circumstances of hepatitis B related disease which has been shown to translate into improved treatment adherence and greater patient satisfaction (Cella & Tulsky, 1990; Gutteling *et al*, 2007; Fallowfield *et al*, 2001; Laine *et al*, 1996). Its assessments might complement objective measures of disease severity not only to accurately and comprehensively assess health status but also to better risk

stratify patients with advanced liver disease (Kanwal *et al*, 2009). The results can be used for the estimation of quality adjusted life years (QALYs) for CHB patients in cost effectiveness or cost utility studies (Lam *et al*, 2009). Thus, a full understanding of not only survival benefit but of QOL benefit will guide us towards improved patients care (Jay *et al*, 2009) and more adherence and greater patient satisfaction.

It is encouraged to use both instruments the generic and disease-specific questionnaires in clinical research to gain substantial information (Younossi & Guyatt, 1998). In this study, the QOL assessment focuses on the EuroQol-5D (EQ-5D) and Chronic Liver Disease Questionnaire (CLDQ).

3.7.1 Generic health status measurements and EuroQol-5D (EQ-5D)

The generic instruments enable researchers to make comparisons between patients with chronic liver disease and the general public. Initial validation studies of the generic health status instruments reported strong psychometric properties. A systematic review found that majority of generic instruments that the studies used was the Medical Outcomes Study Short-Form 36 (SF-36), and other commonly used include the Hospital Anxiety and Depression Scale, the Beck Depression Inventory, the EQ-5D, and the Sickness Impact Profile. In addition, a particular advantage of the SF-36 and the EQ-5D is the ability of these instruments to obtain a utility index score. Utility measures are important for the determination of QALYs used in cost-effectiveness studies (Jay *et al*, 2009), and provide valuable information for comparing new treatment options (Levy *et al*, 2008). Table 3.13 demonstrates the most commonly used measurements to assess QOL in adult liver transplant population from Jay *et al* (2009).

Table 3.13 Characteristics of generic health status measurements (Jay *et al*, 2009)

	Medical outcomes study Short Form-36 (SF-36)	Hospital Anxiety and Depression Scale (HADS)	Beck Depression Inventory (BDI)	EuroQOL 5D (EQ-5D)	Sickness Impact Profile (SIP)
Authors	Ware, 1992	Zigmond, 1993	Beck, 1961	EuroQol group, 1990	Bergner, 1981
Burden: # items	36	14	21	6	136
Subscales	8	2	1	5	12
Domains (subscales)	Physical functioning Role-physical Role-emotional Mental health Vitality Bodily pain General health Social functioning	Anxiety Depression	Depression	Mobility Self-care Usual activities Pain/discomfort Anxiety/depression	Ambulation, Body care/movement Mobility, Social interaction Alertness behavior Emotional behavior Communication Sleep/rest, Eating, Work, Home management Recreation
Summary scores	Yes (2) (physical/mental)	-	-	Yes	Yes (2) (physical/psychosocial)
Internal Consistency[a]	>0.73 (0.77-0.94)[b]	>0.80	0.86	Not applicable[c]	0.84-0.94
Test-retest reliability[a]	0.60-0.81	>0.84	-	0.70-0.85	0.85-0.92
Utility measure (for QALY)	Yes	No	No	Yes	No
Cultural/language adaptations	Yes	Yes	Yes	Yes	Yes

[a] Values are reported from original validation studies (not in liver disease or transplant population).
[b] In chronic liver disease population being evaluated for transplant.
[c] Non-applicable due to one item per domain.

EQ-5D has the reliability testing range from 0.70 to 0.85 by test-retested method (Jay *et al*, 2009), and has construct validity at 0.80 by Spearman correlation with Hospital Utility Index-3 (HUI3) and 0.70 with SF-6D (Gutteling *et al*, 2007). For discriminant validity, it is able to discriminate between mildly, moderately, severely and very severely disabled patients (Gutteling *et al*, 2007). The measure of EQ-5D gives both a utility value that range from 0 to 1.00, with 0 corresponding with state of death and 1.00 corresponding with full health based on a five dimensions and a visual analog scale (VAS). Five dimensions include mobility, self-care, usual activity, pain

or discomfort, and anxiety or depression. Each dimension has three levels of severity: no problem or level 1; some health impairments or level 2; and severe health impairments or level 3. VAS asks patients to rate their health on scale of 0 to 100 from the worst possible to the best possible health. Also, the EQ-5D has been frequently used for the computation of QALYs (Günther *et al*, 2008; Scuffham *et al*, 2008).

3.7.2 Liver disease-targeted health status measurements and Chronic Liver Disease Questionnaire (CLDQ)

QOL measurement by disease-targeted or disease specific might tap into aspects of underlying risk or illness severity that are not fully captured by laboratory and clinical parameters. The most frequently applied targeted instruments included the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) Quality of Life questionnaire, the Liver Disease Quality of Life questionnaire, and the CLDQ. The CLDQ and LDQOL were both designed to measure symptoms specific to chronic liver disease patients (Jay *et al*, 2009). Higher QOL as measured by a liver disease-targeted QOL instrument is associated with lower mortality in patients with advanced liver disease (Kanwal *et al*, 2009). The results from CLDQ could reflect a markedly decreased QOL in advanced stages of chronic liver disease (Sobhonslidsuk *et al*, 2004). Table 3.14 demonstrates the characteristics of liver disease-targeted health status instruments.

Table 3.14 Characteristics of liver disease-targeted health status measurements (Jay *et al*, 2009)

	NIDDK Liver Transplant Database QOL questionnaire	Liver Disease Quality of Life questionnaire (LDQOL)	Chronic Liver Disease questionnaire
Authors	Belle, 1995	Gralnek, 2000	Younossi, 1999
Burden: # items	63	112	29
Subscales	6	20	6
Summary scores	Yes (for 21 disease-specific items)	Yes (SF-36 PCS/MCS & disease-specific)	Yes
Internal consistency[a]	0.62-0.99	0.62-0.95	>0.79
Test-retest reliability[a]	0.87-0.94	0.59	-
Domain (subscales)	General health Role function Psychological status Personal function Measures of liver disease	8 SF-36 domains Symtom of liver disease Effects of liver disease Concentration Memory Sexual functioning Sexual health impairments Sleep Loneliness	Fatigue Activity Emotional function Abdominal symptoms Systemic symptoms Worry
	NIDDK Liver Transplant Database QOL questionnaire	Liver Disease Quality of Life questionnaire (LDQOL) Hopelessness Quality of social interaction Health distress Stigma of liver disease	Chronic Liver Disease questionnaire
Cultural/language adaptations	Yes	Yes	Yes

[a] From studies done in liver disease/liver transplant population.

3.7.3 Quality of life of CHB patients

From the literature review, none of the study has demonstrates QOL in Thai CHB patients. Previous studies in China revealed different QOL of CHB patients from none to the most impact such as CHB infection had similar QOL as normal control (Foster, Goldin & Thomas, 1998; Bondini *et al*, 2007; Ong *et al*, 2008), CHB infection had a negative impact on QOL (Lam *et al*, 2009), 95% of them reported symptoms of differing severity in the 12 months prior to the survey (Hann *et al*, 2008). The most common symptoms included fatigue/loss of energy (90%) and loss of appetite (79%). Cirrhosis had significant impact on QOL (Levy *et al*, 2008) especially depression (Hauser, Holtmann & Grant, 2004; Gallegos-Oroaco *et al*, 2003). Decompensated cirrhosis and HCC had a stronger impact on QOL (Levy *et al*, 2008). Patients undergoing therapy with interferon were also affected (Atiq, Gill & Khokhar, 2004). Finally, QOL could be improved from decreased progression rates of a disease from antiviral therapy by diminishing the morbid and expensive complications and a progressive decrease in health preference values (Gold *et al*, 1996; Petitti, 2000).

A cross sectional study in Karachi found that the mean CLDQ score of 109 cirrhosis patients was 89.5±30.4. However, 74 (67.9%) and 28 (25.7%) were anti HCV positive and HBsAg positive, respectively (Zuberi *et al*, 2007). According to Child class, the score for A, B and C were 123.8±30.1, 84.5±19.3, and 69.1±12.6, respectively , (Zuberi *et al*, 2007). The correlation of CLDQ score with Child class by Kruskall-Wallis test gave a highly significant correlation. The internal validity by Conbach's alpha test was found to be highly valid at 0.98. The most effected domain of CLDQ was activity with a score of 8.4±3.8 and the least effected was emotional function with the score of 24.4±8.2 (Zuberi *et al*, 2007).

In Thailand, the CLDQ was translated into Thai language with permission. A total of 200 subjects were recruited into the study, of which 150 had chronic liver disease and 50 were normal subjects. The number of chronic hepatitis: cirrhosis was 76: 74, and the ratio of cirrhotic patients classified as Child A: B: C was 37 (50%): 26 (35%): 11 (15%) (Sobhonslidsuk *et al*, 2004). Cronbach's alpha of the overall CLDQ scores was 0.96 and of all domain were higher than 0.93. Item-total correlation was more than 0.45. Test-retest reliability done at 1 to 4 week apart was 0.88 for the average CLDQ score and from 0.68 to 0.90 for domain scores. The CLDQ was found

to have discriminant validity. The highest score of CLDQ domains were in the normal group and lowest in the decompensated group. A significant correlation between domains of the CLDQ and SF-36 was found (Sobhonslidsuk *et al*, 2004).

The validated CLDQ is found to be a satisfactory tool for future research of QOL in Thais. The CLDQ domains correlated significantly with every domain of SF-36. The strongest correlation was seen in the relationship between the average CLDQ score and the general health domain of SF-36 (Sobhonslidsuk *et al*, 2004).

3.8 Measuring health-related work productivity

Measuring health-related work productivity is a key to understand health burden and cost associated with work-related disorders (Escorpizo, 2007). They characterize the impact of an illness in the workplace (Prasad *et al*, 2004), and the results allow a more comprehensive assessment of treatment on productivity (Burton *et al*, 2004; Prasad *et al*, 2004). In addition, as treatments for various conditions continue to advance, individuals will be able to better manage their illnesses while remaining employed (Prasad *et al*, 2004).

Health impairment often leads to work impairment in the form of both absenteeism and presenteeism or reduced productivity while at work (Prasad *et al*, 2004; Lerner *et al*, 2000). Indeed, approximately 32% of working adults have chronic illnesses that interfere with their job performance (Lerner *et al*, 2000). However, studies of health-related employee productivity are few, in part due to the intricacies of measuring indirect costs (Prasad *et al*, 2004).

In medicine, pharmaceutical and other medical interventions have traditionally been evaluated in terms of two health-focused criteria: medical efficacy and safety (Johns, 2010). However, in recent years, the increasing cost of health care, combined with the provision by employers of employee health plans, has led to a third criterion of interest, economic impact (Johns, 2010).

The contents of this part are; 1) definition of health-related work productivity; 2) method for measuring health-related work productivity; 3) instruments for measuring health-related work productivity; 4) Work Productivity and Activity

Impairment (WPAI)–General Health Questionnaire; 5) WPAI in clinical studies; 6) WPAI studies in hepatitis; 7) WPAI studies in Thailand.

3.8.1 Definition of health-related work productivity

Reilly *et al* (2004) defined that health-related work productivity loss includes time lost from work (absenteeism) and reduced on-the-job effectiveness (presenteeism).

Escorpizo (2007) explicated the two components of work productivity, which are perceived and observed and between absenteeism and presenteeism as sub-components of work productivity.

Burton *et al* (2004) explained that productivity loss was expressed by three different measures: work limitation; work loss; and work disability. Work limitation is synonymous with presenteeism, defined as time lost because of a diminished capacity while at work and work loss is synonymous with absenteeism, defined as time off work.

Prasad *et al* (2004) explained that illness at the workplace often results in absence from work, time off because of disability, and reduced productivity at work, all of which create a financial burden to the employer.

Loeppke *et al* (2007) specified that both absenteeism and presenteeism time loss are components of productivity loss.

Huang (2008) indicated that most productivity studies measure the amount of work loss incurred by employees in the form of absenteeism and presenteeism**.**

Mattke *et al* (2007) identified that the effect of ill health on productivity because of absence from work (absenteeism) or because of reduced performance while at work (presenteeism).

3.8.2 Method for measuring health-related work productivity

Prasad *et al* (2004) discussed two major approaches to measuring work productivity through the employee's self-report and through more "objective" means. However, Trotter (2008) concluded that there are 3 methods for measuring health-related work productivity. These methods are:

1) Employee self-report instruments, such as the WPAI-GH in which utilize the employee's perspective regarding his/her lost work productivity. The subjective nature of these instruments is their major limitation.

2) Objective measures such as payroll record measures of absenteeism; however, these objective records can be expensive to obtain and inappropriate for many employment settings.

3) Employer ratings.

Most productivity studies measure the amount of work loss incurred by employees in the form of absenteeism and presenteeism (Huang, 2008). Although inferior to objective measures, self-report work measures can be extremely useful when objective measures are unavailable (Kessler *et al*, 2003). When the self-report measures are calibrated against objective measures, the scores can be meaningfully interpreted (Kessler *et al*, 2003). In addition, self-reported workforce surveys are the only practical method that can be used in a variety of settings and job functions to measure workforce productivity (Huang, 2008).

There is no gold standard of workforce productivity (Huang, 2008). Loeppke *et al* (2007) explained that time-loss results are converted into days by dividing the sum of hours by 8 and reported by health condition relative to other workers without those health conditions. The lost time for employees with chronic conditions is above and beyond the time for employees without these conditions (Loeppke *et al*, 2007). Thus, lost time must be monetized so that it can accurately represent the financial loss suffered by the organization and, thus, be made meaningful to senior financial executives (Loeppke *et al*, 2007).

3.8.3 Instruments for measuring health-related work productivity

Recognizing the need for such data, a number of health services researchers have developed self-report measurement tools to collect data in employee surveys on untreated health impairments and work performance (Kessler *et al*, 2003). These instruments focus on the following modes of conceiving presenteeism: 1) assessment of perceived impairment, 2) comparative productivity, performance, and efficiency (with those of others and with one's norm), and 3) estimation of

unproductive time while at work (Mattke *et al*, 2007). It was suggested that the instruments vary substantially in length (range, 3-44 questions) (Mattke *et al*, 2007)

There were twenty-one different instruments for measuring health-related work productivity which had been identified form two systematic review studies (Prasad *et al*, 2004; Mattke *et al*, 2007) and a dissertation (Huang, 2008). Prasad *et al* (2004) identified six generic and six disease-specific productivity from articles published in English between January 1990 to and June 2002. Mattke *et al* (2007) identified seventeen survey instruments through searches of the published and unpublished literature and governmental and corporate communications from 1995 to 2005. Huang (2008) found 16 instruments in his review of literature.

An instrument can support business decision-making if the measure of work loss could be translated into monetary figure. Five of the general health-related work productivity instruments have met most of the criteria: Employer Health Coalition of Tampa Assessment Instrument (EHC); Health and Performance Questionnaire (HPQ); Stanford Presenteeism Scale (SPS-6); Work Limitations Questionnaire (WLQ); and Work Productivity and Activity Impairment Questionnaire (WPAI) (Loeppke *et al*, 2003).

Table 3.15 demonstrates general summary of productivity instruments. Table 3.16 explains descriptive summary of productivity instruments. Of these self-report productivity instruments, WPAI is a well-validated instrument that measures impairments in work and activities, and has few questions (6 questions) with one-week recall period. It assesses both absenteenism and presenteenism (Zhang *et al*, 2010), and has also been adapted frequently for populations with specific diseases and different disease severity levels (Prasad *et al*, 2004; Zhang *et al*, 2010).

Table 3.15 General summary of productivity instruments (Modified from Prasad, *et al* (2004); Mattke *et al* (2007); Huang, 2008)

Name (Research/Funding Sponsor)	Abbrevia-tion	Description of Question Set	Recall Period
American Productivity Audit and Work and Health Interview (American Productivity Audit (APA))	APA-WHI	6 questions	2 weeks
Angina-Related Limitations at Work Questionnaire (New England Medical Center/Merck)	ALWQ	17 item questionnaire and appendix of 7 other questions; paper, self-administered	4 weeks
Employer Health Coalition Healthy People/Productive Community Survey (Employer Health Coalition)	EHC	Phase 1: 200 general questions; Phase 2: 150 disease specific questions; 5 minute completion time	1 month
Endicott Work Productivity Scale (NY State Psychiatric Institute/Pfizer)	EWPS	25 item self-scored questionnaire; paper, self-administered; 5 minute completion time	1 week
Health and Productivity Questionnaire	-	44 questions	1, 4 weeks
Health and Labor Questionnaire (Erasmus University Rotterdam Institute for Medical Technology)	HLQ	23-item instrument; paper, self-administered; 10-15 minute completion time	2 weeks
Health-Related Productivity Questionnaire Diary	HRPQ-D	9 questions	1 week
Health and Work Performance Questionnaire (WHO, Harvard Medical School - Department of Health Care Policy/John D. and Catherine T. MacArthur Foundation)	HPQ	30 item questionnaire; 20-minute completion time via telephone	1 week and 4 weeks
Health and Work Questionnaire (GlaxoSmithKline)	HWQ	27 questions in 6 sub-scales; paper, self-administered	1 week
Migraine Disability Assessment Questionnaire	MIDAS	7 Open-ended responses	3 months
Migraine Work and Productivity Loss Questionnaire (New England Medical Center/Merck)	MWPLQ	23 questions; paper, self-administered	most recent episode
Osterhaus Technique (GlaxoSmithKline)	OT	12 questions; paper, self-administered	4 weeks
Quantity and Quality Instrument	QQ	5 questions	1 day
Stanford Presenteeism Scale (American Health Association)	SPS	32 questions (SPS-32) or 6 questions (SPS-6); self-administered	4 weeks
Unnamed Hepatitis Instrument	UHI	3 questions; self-administered	4 weeks

Table 3.15 General summary of productivity instruments (Modified from Prasad, *et al* (2004); Mattke *et al* (2007); Huang, 2008) (Continue)

Name (Research/Funding Sponsor)	Abbreviation	Description of Question Set	Recall Period
American Productivity Audit - Work and Health Interview (Caremark)	WHI	46 questions via computer-assisted phone; 15 minute completion time	2 weeks
Work Limitations Questionnaire (New England Medical Center)	WLQ	25 questions; self-administered	2 weeks, 4 weeks
Work Productivity and Activity Impairment Questionnaire – General Health (Reilly Associates, UT Medical Branch at Galveston, Sanofi-Aventis)	WPAI	6 questions (general), 9 questions (specific); paper, self-administered, interview administered	1 week
Work Productivity and Activity Impairment Questionnaire – Specific Health Problem	WPAI-GH/SHP	9 questions (specific); Same as WPAI-GH	1 week
Work Productivity and Activity Impairment Questionnaire - Allergic rhinitis	WPAI-AS	9 questions (specific); Same as WPAI-GH	1 week
Work Productivity and Activity Impairment Questionnaire - Gastro-Esophageal Reflux Disease	WPAI-GERD*	6 questions (specific); Same as WPAI-GH	1 week
Work Productivity and Activity Impairment Questionnaire – Chronic Hand Dermatitis	WPAI-ChHD	6 questions (specific); WPAI Likert scale was adapted to a visual analogue scale ranging from 0 to 100% with anchors at every 10%	1 week
Work Productivity and Activity Impairment Questionnaire – Hepatitis C	WPAI-Hepatitis C	6 questions (specific); Same as WPAI-GH	1 week
Worker Productivity Index (BankOne)	WPI	Same as WPAI-GH	N/A
Work Productivity Short Inventory (Institute for Health and Productivity Studies at Cornell)	WPSI	22-item questionnaire, 66 questions at maximum	12 months, 3 months, 4 weeks, and 2 weeks

Table 3.16 Descriptive summary of productivity instruments (Prasad *et al*, 2004)

Instrument	Pub Year	$ fig	Diseases Assessed	Productivity metrics	Availability
ALWQ	1998	No	Specific (Angina)	Absenteeism, presenteeism	Public Domain
EHC	2000	Yes	General	Absenteeism, presenteeism	Questions are proprietary and not available for purchase
EWPS	1997	No	General, but intended to be sensitive to the effects of depression and anxiety disorders	Absenteeism, presenteeism	Copyrighted, fee per user for commercial use; purchased a copy
HLQ	1995	Yes	General	Absenteeism, presenteeism, unpaid production, work impediments	Rights are reserved; purchased a copy
HPQ	2003	Yes	General	Absenteeism, presenteeism, critical event information	Public Domain
HWQ	2001	No	General	Absenteeism, presenteeism, work performance	Public Domain
MWPLQ	1999	Yes	Specific (Migraine)	Absenteeism, presenteeism	Public Domain
OT	1992	Yes	Specific (Migraine)	Absenteeism, presenteeism	Selected questions available only
QQ	1999	No	General	Presenteeism	Public Domain
SPS	2002	No	General	Presenteeism	Public Domain
UHI	2001	No	Specific (Hepatitis)	Absenteeism, presenteeism	Public Domain
WHI	2003	No	General	Absenteeism, presenteeism	Proprietary
WLQ	2001	No	General	Presenteeism	Free to non-commercial users but requires a licensing agreement to use
WPAI	1993	Yes	General	Absenteeism, presenteeism	Public Domain
WPI	1999	Yes	General	Absenteeism, presenteeism	Public Domain (Formula)
WPSI	2003	Yes	General	Absenteeism, presenteeism, care giver demands	Copyrighted but 12-month version has been published

To clarify the detail of the instruments, Table 3.17 explicates summary of actual psychometric properties of subjective productivity instruments.

Table 3.17 Summary of actual psychometric properties of subjective productivity instruments (Prasad *et al*, 2004)

Instru-ment	Recall Period	Construct validity	Internal consistency reliability	Test-retest reliability	Respon-siveness	Adminis-trator/respondent burden[a]	Gener-allisa-bility[a]	Applica-bility for economic valuation[a]
EWPS	1 week	Established	Established	Established	NA	Low	NA	No
HLQ	2 weeks	NA	NA	NA	NA	Low/ moderate	NA	Yes
HPQ	4 weeks	NA	NA	NA	NA	Low/ moderate	High	Yes
HWQ	1 week	NA	Established	NA	NA	Low/ moderate	NA	NA
WLQ	2/4 weeks	Established	Established	NA	NA	Low	NA	Yes
WPAI-GH	1 week	Established	Not applicable	Established	NA	Low	High	Yes
WPAI-GH/SHP	1 week	NA	Not applicable	NA	NA	Low	High	Yes
WPAI-AS	1 week	Established	Not applicable	Established	Establis hed	Low	High	Yes
WPAI-GERD	1 week	Established	Not applicable	NA	NA	Low	High	Yes
WPAI-ChHD	1 week	Established	Not applicable	Established	Establis hed	Low	High	Yes
MIDAS	3 months	Established	Established	Established	NA	Low	Not applicable	Yes
MWPLQ	Most recent episode	Established	Established	NA	NA	Low	Not applicable	No

[a] Evaluation made based on perceived property, not on formal tests.
[b] Established according to reviewed articles.
[c] Employer version. The clinical trial version is available using either a 1- or 4-week recall period.
Abbreviations: AS, Allergic rhinitis; ChHD, Chronic Hand Dermatitis; EWPS, Endicott Work Productivity Scale; GERD, Gastro-Esophageal Reflux Disease; GH, General Health; HLQ, Health and Labor Questionnaire; HPQ, Health and Work Performance Questionnaire; HWQ, Health and Work Questionnaire;, MIDAS, Migraine Disability Assessment Questionnaire; MWPLQ, Migraine Work and Productivity Loss Questionnaire; NA, insufficient information available; SHP, Specific Health Problem, WLQ; Work Limitation Questionnaire, WPAI; Work Productivity and Activity Impairment Questionnaire.

3.8.4 Work Productivity and Activity Impairment (WPAI)–General Health Questionnaire

Work Productivity and Activity Impairment (WPAI) questionnaire was developed in 1993 to measure the effect of overall health and specific symptoms on productivity at work and outside work (Reilly *et al*, 1993). The questionnaire is available at: http://www.reillyassociates.net/WPAI_SHP.html. It measures work time missed and work and activity impairment because of a specified health problem during the past 7 days. The validity of the WPAI has been established in a number of diseases including allergies, angina, arthritis, alzheimer's disease, benign prostatic hyperplasia, bronchitis, cancer, claudication, Crohn's disease, congestive heart failure, dermatological conditions, diabetes, hypertension, irritable bowel syndrome, urinary incontinence, renal disease. WPAI has been proven to be a useful tool that measures the relative difference between treatment groups in clinical trials and in subjects with and without disease.

A systematic review study pointed out that WPAI had sufficient reproducibility (test-retest reliability), with correlation coefficients ranging from 0.71 to 0.87 for overall productivity at work and outside of it. Construct validity and test-retest reliability of the self- and the interviewer-administered WPAI-GH were assessed by analyzing the extent to which the instruments correlated with several domains of the Medical Outcomes Study Short Form 36-item health survey (SF-36) general health perceptions, role-physical, role-emotional, pain, symptom severity, and global measures of work and interference with regular activities (Chirban *et al*, 1997). Data gathered by the interviewer had higher construct validity than those collected via self-administration (Prasad *et al*, 2004). Because the WPAI does not ask questions specific to the type of illness or type of employment, the instrument is generalisable across occupations and disease areas.

After the employment status of the respondent is identified, three open-ended questions are asked: (1) hours absent from work due to health impairments; (2) hours absent from work due to other reasons; and (3) hours actually worked. Two additional questions are included that ask about the impact of health impairments on productivity. One question is focused on productivity at work, while the other asks about daily activities other than work. Overall reductions in productivity are derived

from the respondent's answers. As seen in the instrument's validity testing, the questions can also be applied to non-work daily activities. Scores are calculated for four domain areas: percent of work time missed due to health, percent impairment while working due to health, overall work impairment due to health, and percent activity impairment due to health.

3.8.5 WPAI in clinical studies

WPAI was used in clinical studies that determine a valid, reliable and responsive for assessing work productivity in patients with chronic disease such as Crohn's disease (Reilly *et al*, 2008), ankylosing spondylitis (Reilly *et al*, 2010), and rheumatoid arthritis (Zhang *et al*, 2010). Also, in Thailand, the WPAI-GH was used to assess reduced productivity in the economic costs of alcohol consumption study (Thavorncharoensap, *et al*, 2010) and HIV-infected women (Jayathunge *et al*, 2010).

In 2008, Reilly *et al* (2008) used WPAI to determine its validity, reliability, and responsiveness in 662 Crohn's disease (CD) patients. Patients with CD of the worst severity (CDAI > median) showed significantly higher impairment in work (+10.5%) and activities (+10.4%) versus patients with "best health" (no health impairments) (both, $p<$ or $= 0.001$). Patients with "worst" Inflammatory Bowel Disease Questionnaire (IBDQ), Short Form-36 physical component summary (PCS), and mental health component summary (MCS) scores, and EQ-5D VAS also showed significantly higher impairments in work (IBDQ, VAS -24.2%; PCS, -24.1%; MCS, -15.9%; EQ-5D VAS, -16.5%) and activities (IBDQ, -23.3%; PCS, -21.8%; MCS, -16.5%; EQ-5D VAS, -17.2%) versus "best" scores (all, $p < 0.05$).

In 2010, Reilly *et al* (2010) used WPAI: SpA to determine its validity, reliability and responsiveness in 205 ankylosing spondylitis (AS) patients. Patients with more severe Bath AS Disease Activity Index (BASDAI > median) showed significantly greater impairment in work and daily activities than patients with lesser disease severity ($p < 0.001$). This trend was consistent for AS Quality of Life Questionnaire (ASQOL), SF-36 PCS, SF-36 MCS and Health Utilities Index Mark 3 (HUI-3).

Zhang *et al* (2010) conducted a study to evaluate the construct validity of the WPAI-general health version among 150 rheumatoid arthritis (RA) patients and its

ability to differentiate between RA patients with varying health status. The authors noted that of the 137 patients who were working for pay, 26 reported missing works in the past week due to health problems, accounting for 45.5% of their working time (absenteeism). While 123 patients were working, 24% of their work was impaired due to their health problems (presenteeism). In addition, 33% of the patients' regular daily activities (activity impairment) were decreased due to their health impairments. There were moderate correlations between the WPAI absenteeism and function, pain, fatigue, and disease severity (r = 0.34 to 0.39). The WPAI presenteeism and activity impairment were strongly correlated with the health outcomes (0.67 to 0.77). Patients with more severe disease status (for example, low/high functional disability by median) had significantly higher absenteeism (4%/15%), presenteeism (15%/39%), and activity impairment (19%/53%) than those with less severe disease status.

3.8.6 WPAI studies in hepatitis

There were few published studies of WPAI in hepatitis and none of which were in hepatitis B. There were two studies of WPAI in HCV (DiBonaventura *et al*, 2011; Su *et al*, 2010), and two studies of work loss in hepatitis B by the research structured questionnaire (Liang *et al*, 2010; Hu & Chen, 2009). These studies provided evidence that response from WPAI can describe a relationship between hepatitis infection, productivity, and increased absenteeism. However, these researchers suggested that the limitations of these studies include all data that were patient-reported which could be a form of subjective bias. Details of these studies are as follows.

For WPAI studies in HCV, DiBonaventura *et al* (2011) studied the impact of hepatitis C on labor force participation, absenteeism, presenteeism and non-work activities. The researchers used data from the 2009 United States National Health and Wellness Survey, 695 HCV patients were significantly less likely to be in the labor force than controls and reported significantly higher levels of absenteeism (4.88 *vs*. 3.03%), presenteeism (16.69 *vs*. 13.50%), overall work impairment (19.40 *vs*.15.35%), and activity impairment (25.01 *vs*. 21.78%). Su *et al* (2010) conducted a study to compare absenteeism, productivity, and health cost between employees with and without HCV infection in the United States. Databases were assessed for

demographics, salary, healthcare use, work loss, and workers' compensation, which were obtained from employee records of multiple large employers of the Human Capital Management Services Research Reference in the United States. A total of 339,456 subjects were evaluated. Employees with HCV (*n*=1664) had significantly more lost work days per employee than the control cohort (*n*=337,792), including sick leave, short-term disability, and long-term disability. HCV-infected workers had 4.15 more days of absence per employee than the control cohort. Units of work processed per hour measured productivity; employees with HCV processed 7.5% fewer units per hour than employees without HCV ($p>0.05$). All healthcare benefit costs among HCV employees were significantly higher than the same costs among employees without HCV. Overall, the total incremental difference was USD 8,352 per year.

Regarding two studies of work loss in hepatitis B by the research structured questionnaire, Liang *et al* (2010) determined the direct, indirect and intangible costs due to hepatitis B-related diseases and explored main factors associated with the costs in Shenzhen. Health economics-related information was collected using a structured questionnaire. Willing to pay method was used to estimate the intangible costs. The total annual indirect cost per person was 8123.38 Yuan for patients of all hepatitis B-related diseases, while 7134.63 Yuan for caregivers. Corresponding work-loss days were 55.74 days for patients and 19.83 days for caregivers**.** Another study by Hu & Chen (2009) assessed the total economic burden of CHB-related diseases in Beijing and Guangzhou, China. Economic burden of CHB-related diseases (CHB, compensated cirrhosis, decompensated cirrhosis, and hepatocellular carcinoma) were examined. A retrospective cohort of 328 patients in Beijing and 271 in Guangzhou were identified to obtain their socioeconomic status, utilization and costs of treatment, and work loss days due to illness with a structured questionnaire. The results indicated that sick-leave days per month were 1.5±5.5 (mean±standard deviation (SD)) in CHB, 2.5±6.9 in compensated cirrhosis (CC), 3.5±7.0 in decompensated cirrhosis (DC), and 2.5±6.4 in HCC patients (Hu & Chen, 2009). Family member had leave days per month 1.0±4.2 (mean±SD) in CHB, 1.7±5.4 in CC, 4.5±7.5 in DC, and 4.0±5.8 in HCC (55 Hu & Chen, 2009).

3.8.7 WPAI studies in Thailand

In Thailand, two studies of WPAI were found. The target populations of the study were alcohol drinkers (Thavorncharoensap *et al*, 2010), and HIV-infected women (Jayathunge *et al*, 2010). These studies provided evidence that WPAI was used to assess health-related work productivity of Thais including patients with chronic disease. Also, the response from WPAI can demonstrate work productivity loss and could be translated into a monetary figure.

Thavorncharoensap *et al* (2010) conducted a prevalence-based, cost-of-illness study to determine the economic costs of alcohol consumption in Thailand. The estimated costs in this study included both direct and indirect costs. Direct costs included health care costs, costs of law enforcement, and costs of property damage due to road-traffic accidents. Indirect costs included costs of productivity loss due to premature mortality, and costs of reduced productivity due to absenteeism and presenteeism (reduced on-the-job productivity). The WPAI-GH was used to assess reduced productivity. The authors found that the largest cost attributable to alcohol consumption was that of productivity loss due to premature mortality (104,128 million baht/ United States Dollar (USD) 6,422 million per patient), followed by cost of productivity loss due to reduced productivity (45,464.6 million baht/ USD 2,804 million per patient), health care cost (5,491.2 million baht/ USD 339 million per patient), cost of property damage as a result of road traffic accidents (779.4 million baht/ USD 48 million per patient), and cost of law enforcement (242.4 million baht/ USD 15 million per patient), respectively.

Jayathunge *et al* (2010) assessed the psychosocial burden of abnormal pap smears among HIV-infected women at Chon Buri hospital, Thailand. Women with positive (n=73) and negative Pap-smear results (n=317) were assessed for psychosocial burden using 4 questionnaires: Psycho-Social Impact of Abnormal Pap Smears (PEAPS-Q), Hospital Anxiety and Depression Scale (HADS), Work Productivity and Impairment (WPAI) and the EURO-Qol Thermometer. The results showed that HIV infected women with abnormal Pap smears had higher anxiety levels on the HADS questionnaire (p=0.015), and had a significant effect on regular daily activities (p=0.009) per WPAI questionnaire compared to HIV positive women with normal Pap smear.

Although, there were few published studies of WPAI in hepatitis, and none of which were hepatitis B, several studies provided evidences that WPAI was used to assess the health-related work productivity of Thais (Thavorncharoensap *et al*, 2010; Jayathunge *et al*, 2010). Moreover, a relationship between hepatitis infection and productivity (DiBonaventura *et al*, 2011; Su *et al*, 2010) that could be translated into a monetary figure has been described. The WPAI-GH version 2.0-hepatitis C has been translated into Thai.

In this study, the researcher selected WPAI to measure work productivity of CHB patients because of the following reasons:

1) It is a simple instrument with six questions related to the time taken off work, which covers both absenteeism and presenteeism;

2) Data gathered by the interviewer had higher construct validity than those collected via self-administration (Prasad *et al*, 2004);

3) It had sufficient reproducibility (test-retest reliability), with correlation coefficients ranging from 0.71 to 0.87 for overall productivity at work and outside work(Prasad *et al*, 2004);

4) It has low administrator/respondent burden with 6 questions;

5) It can be applicable for economic valuation;

6) It is a well-validated instrument that measures impairment in work and activities and has been used to compare work impairment between treatment groups in clinical studies and trials or between subjects with different disease severity levels (Zhang *et al*, 2010);

7) It has also been modified to measure productivity reductions associated with specific diseases (e.g. allergic rhinitis, gastro-oesophageal reflux disease, and chronic hand dermatitis).

3.9 Basic principle of health economics

Meltzer (2001) described the basic principle of health economics as at least two methods that can be used to assess the economic effect of a health-care intervention, the financial and the economic aspect. The benefits and the costs of using an intervention to prevent or treat a disease may vary depending on the perspective of patients, physicians, health-care payers, and policy makers with respect to the value of using a particular intervention. The differences on which costs are included and excluded with different perspectives are clearly shown in Table 3.18.

Table 3.18 Inclusion and exclusion of costs, depending on perspective for economic analysis (Meltzer, 2001)

	Include (+) or not (--) dependent on perspective[a]				
Examples of costs	Patient[b]	Physician[c]	Hospital	Payer[d]	Society[e]
Direct medical					
Physician time	Yes	Yes	Yes	Yes	Yes
Other medical personnel time (e.g. nurse)	No	Yes	Yes	Yes	Yes
Drugs	Yes	No	Yes	Yes	Yes
Medical devices (e.g. syringes, ultrasound)	No	No	Yes	Yes	Yes
Laboratory tests	No	No	Yes	Yes	Yes
Direct non-medical					
Administration[f]	No	No	Yes	Yes	Yes
Physical facility (e.g. clinic, office)	No	No	Yes	No	Yes
Utilities (e.g. telephone, electricity)	No	No	Yes	No	Yes
Patient's travel costs	Yes	No	No	No	Yes
Temporary hired care-giver[g]	Yes	No	No	No	Yes
Indirect					
Time off from work to visit physician	Yes	No	No	No	Yes
Time off work while ill and recuperating	Yes	No	No	No	Yes
Hire temporary household help while ill[h]	Yes	No	No	No	Yes

a, Inclusion of cost item will depend upon chosen perspective; four perspectives (societal is the sum) do not cover all possible perspectives.
b, Assumes patient is covered by health-care insurance; physician time and drug costs will involve co-payments.
c, Perspective assumed to be that of a physician employed by health-care provider such as hospital.
d, Third-party payer who reimburses physician for services rendered that are covered by an insurance scheme (private or public).
e, Sum of all perspectives.
f, Physician's practice and health insurer might each have separate administration costs.
g, Hired to look after family members while adult visits physician.
h, Might be hired to do household chores and look after family while an adult is ill, or to allow an adult to concentrate on nursing a sick child.

3.9.1 Categorization of costs

Meltzer (2001) described that in economic analyses, costs are typically categorized as “direct medical”; “direct non-medical”; and “indirect costs of lost productivity”. In financial or accounting analyses, costs are classified differently, as “variable” or “fixed”. Variable costs, such as the physician’s time and drugs administered, vary dependent on the numbers of cases treated, whereas fixed costs do not vary in the short-to medium term and are unlikely to change with any fluctuations in the number of cases (e.g., the cost of a building). Some health economists use accountancy terms such as “fixed costs” but this is not a serious problem as long as costs that are included are those appropriate for the perspective chosen and reflect the opportunity costs.

Meltzer (2001) also indicated other key economic factors such as discounting costs over time and discounting non-monetary costs and benefits. Discounting costs over time means that the society places a premium on benefits gained in the present rather than at some time in the future. Discounting non-monetary costs and benefits associate with an intervention, such as future deaths delayed, should be discounted. Society also has a time preference for such non-monetary costs, and will usually value the life of an individual living now more than the value of a birth sometime in the future.

3.9.2 Direct cost of health-related disease

Van Houtven *et al* (2008) explained that direct costs represent the value of goods and services consumed as a result of illness and for which payment is made. These costs include payment for treatment, diagnosis, continuing care, rehabilitation, and terminal care. They are typically measured as costs related to hospital stay, physician services, nursing homes, prescription drugs, and in-home health care services.

Stephenson *et al* (2000) noted that direct costs refer to health sector costs for prevention, diagnosis and treatment of diseases and may include costs for ambulance, inpatient, nursing home, outpatient, rehabilitation, allied health, research, community health and medical services and consumption of pharmaceuticals.

3.9.3 Indirect cost of health-related disease

Van Houtven *et al* (2008) explained that indirect costs represent costs for which no payment changes hands but for which an economic effect is nonetheless observed. These costs include primarily productivity losses associated with illness and premature death, and they are typically measured as the value of lost productivity (labor and household) due to illness.

Stephenson *et al* (2000) indicated that indirect costs measure the value of human life or the lost productivity potential of patients who are too ill to work or die prematurely. Society loses some or all of the productive benefit of an ill person and conversely enjoys that benefit if the illness is prevented or the patient is cured.

There are important and debatable issues in the measurement of indirect costs. Examples include the use of ‘average weekly earnings’ as an appropriate measure of a person’s productive value and the use of an imputed value for non-marketed production such as unpaid household services. Intangible costs are measures of cost to the individual and their family that has an illness in terms of their reduction of quality of life due to such issues as pain, disability, bereavement, anxiety and suffering. Indirect and intangible costs are often omitted from cost of illness studies because they are difficult to measure in dollar terms, although they may be significant outcomes of illness and premature death. These indirect and intangible costs are the essence of quality of life and may have the greatest value in terms of total community welfare.

3.9.4 Assessment of economic costs and benefits

Meltzer (2001) illustrated that the three main methods used to assess the economics of an intervention designed to control and prevent a disease are: cost-benefit analysis (CBA); cost effectiveness analysis (CEA); and cost-utility analysis (CUA) (Table 3.19).

Table 3.19 Three methods of doing an economic analysis of an intervention (Meltzer, 2001)

Method	Costs included[a]		Outcome measure (benefit)
	Direct	Indirect	
Cost-benefit	Yes	Yes	Dollars
Cost-effectiveness	Yes	Often	Health outcome[b]
Cost-utility	Yes	Occasionally	Utility measure[c]

a, All future costs and benefits, monetary and non-monetary, should be discounted to year zero.
b, Example of a health outcome is cases averted.
c, Example of a utility measure is quality-adjusted life years (QALYs).

For many applied economists, CBA is the "gold standard" by which the other methods are judged. In its simplest form, a CBA lists all the costs and benefits that might arise as a result of an intervention up to a pre-specified time. These costs and benefits are discounted to the year zero. If the total discounted benefits are greater than the total discounted costs, the intervention is said to have a positive net present value (NPV).

3.10 Cost of CHB

Because the financial burden of chronic HBV infection is consistently high, mainly due to future costs associated with liver-related complications and liver-related mortality (Brown *et al*, 2004; Idris *et al*, 2008), the attendant loss of economically productive life years for the individual and society (Dan, Aung & Lim, 2008). Additional costs related to specific antiviral drug therapy, more frequent therapy monitoring and the management of HBV drug resistance, often needed long term, should be taken into account (Buti *et al*, 2009). Cost-effective analysis in the specific context of each country is necessary to guide the most cost-effective approach in each of these countries (Liaw *et al*, 2009) to enable countries to prioritize their public health preventive measures and to make the most appropriate use of available resources (Lavanchy, 2008).

3.10.1 Cost analysis studies of CHB

The review found that cost analysis of CHB has varied perspectives. These perspectives include (1) prediagnosis, peridiagnosis, postdiagnosis costs (Metcalf *et al*, 1999) (2) prevention and disease costs (Yang *et al*, 2001) (3) total cost, direct cost and indirect cost (Yang *et al*, 2001; Ong, Lim & Li, 2009; Yang *et al*, 2010) (4) evaluation of HCC surveillance (Paul *et al*, 2008; Thompson Coon *et al*, 2008) and (5) an average annual direct medical cost in each health states of six CHB-related diseases with several studies that compared the results.

Metcalf *et al* (1999) indicated that the prediagnosis cost in the seven months surrounding the appearance of the first diagnostic marker in patients with CHB costs 3.3 times than those of the corresponding control patients. The postdiagnosis cost after the first seven months was 2.9 times per month than those of the control patients. Prediagnosis costs in the laboratory, radiology, office visits, and pharmacy were significantly higher for patients with CHB than for control patients. Except for emergency room costs, postdiagnosis costs per month for patients with CHB were significantly higher than those of the corresponding control patients (Metcalf *et al*, 1999).

Regarding prevention and disease costs, indirect cost accounted for 20.9%. Yang *et al* (2001) found that the prevention costs and indirect costs of HBV-related diseases in 1997 were 142.3 billion (13.2%) Korean Won (KRW) and 225.4 billion (20.9%) KRW, respectively.

For total cost, direct cost, and in direct cost of country, the cost increases over time. In South Korea, the total societal cost of HBV-related disease in 1997 was 1078.3 billion KRW or 959.7 million USD, the direct costs of the HBV disease was 782.2 billion KRW or 696.2 million USD. It was higher in 2005 with 1.937 trillion including direct costs of 474,642 million KRW and indirect costs of 1.463 trillion KRW (Yang *et al*, 2010). In Singapore, the estimated total annual cost of HBV-related disease was 279 million USD, with 58% or 161 million USD attributable to direct costs (Ong, Lim & Li, 2009).

With evaluation of HCC surveillance, it was found that HCC surveillance with alphafetoprotein test every 6 months was cost-effective compared with no surveillance (Paul *et al*, 2008; Thompson Coon *et al*, 2008). Paul *et al* (2008)

conducted a prospective study to estimate the incidence of HCC in 194 cirrhotics. The cost-effectiveness ratio of HCC surveillance program per HCC case detected was estimated at 280 USD from the hospital perspective. From a patient's perspective, the cost was 9,965 USD for outstation and 2,808 USD for local patients. Based on the EASL protocol, the cost-effectiveness ratio for direct medical cost per case of HCC detected by testing alphafetoprotein every 6 months was estimated to be 1,510 USD in the private sector. Also, Thompson Coon *et al* (2008) used a decision-analytic model to evaluate the cost-utility analysis of surveillance for HCC in individuals with cirrhosis. The cheapest strategy employed triage with annual alphafetoprotein (incremental cost-effectiveness ratio (ICER): £20 700 per quality-adjusted life-year (QALY) gained. At a willingness-to-pay threshold of £30 000 per QALY the most cost-effective strategy used triage with 6-monthly alphafoetoprotein (ICER: £27 600 per QALY gained). The addition of ultrasound to this strategy increased the ICER to £60 100 per QALY gained. The model estimates that compared with no surveillance, this strategy may triple the number of people with operable tumours at diagnosis and almost halve the number of people who die from HCC. In the mixed etiology cohort, performing alphafetoprotein test every 6 months plus ultrasound was predicted to be the most effective strategy.

Estimation of the average annual direct medical cost in each health states of six CHB-related diseases proved that as the disease progresses, the cost of medical care increases significantly (Lee *et al*, 2004; Gagnon *et al*, 2004; Yang *et al*, 2004; Zhiqiang *et al* 2004; Li *et al*, 2004; Castelo *et al*, 2007; Hu & Chen, 2009). However, most of these seven studies on economic analysis were retrospective analysis (Lee *et al*, 2004; Zhiqiang *et al* 2004; Hu & Chen, 2009; Li *et al*, 2004), predicted model (Gagnon *et al*, 2004), national health care data base (Castelo *et al*, 2007; Yang *et al*, 2004), and some had reported the costs in their country's currency (Hsieh *et al*, 2004; Brown *et al*, 2004; Butler *et al*, 2004). Table 3.20 shows average annual direct medical costs in each health states of six CHB-related diseases of current studies (in USD).

These studies confirmed that CHB-related diseases imposed a substantial economic burden on patients, families, and the society and its cost related to disease progression (Hu & Chen, 2009; Gagnon *et al*, 2004), which could be prevented. Data provides useful information on cost of treatment and work loss for different disease

states (Hu & Chen, 2009). Medications contributed the largest proportion of costs in CHB and compensated cirrhosis disease states, while hospitalizations were the largest cost (Lee *et al*, 2004; Butler *et al*, 2004). Financial or technical support from international agencies and reduction of price by companies producing anti-HBV drugs or HBV assays would be the most direct and effective measures to improve the situation (Liaw, 2009).

Table 3.20 Average annual direct medical costs (USD) in each health states of six CHB-related disease of current studies

Author, Published year, Location	CHB	Decom-pensated cirrhosis	Compen-sated cirrhosis	Liver-transplant	Transplant follow up	HCC
Lee *et al*, (2004) United States	761	227	11,459	86,552	12,560	7,533
Gagnon *et al*, (2004), Canada	2,191	2,987	11,228	94,328	38,242	13,350
Yang *et al*, (2004) South Korea	248	-	-	67,156	-	-
Zhiqiang *et al*, (2004) China	142	185	1,702	-	-	4,741
Li *et al*, (2004),					-	15 618
Hong Kong	810	1,321	7,490	65,961		
Singapore	410	672	8,794	49,354	-	7,037
Castelo *et al* (2007), Brazil	392	496	8,809	34,948	-	1,905
Hu & Chen (2009)						
China Beijing	1,636	2,722	4,611	-	-	6,615
Guangzhou	1,452	2,065	4,290	-	-	6,054

3.10.2 Cost of CHB treatment

In an era of increasing healthcare budgets, understanding the economics of medical care has become yet another requirement for the practice of medicine (Rajendra & Wong, 2007). Although antiviral treatments incur near-term costs and savings may not occur for many years (Rajendra & Wong, 2007), the cost-effectiveness by Dan, Aung, & Lim (2008) demonstrated that antiviral treatments compared with no treatment had incremental cost-effectiveness ratio range from the least 7,600 to the most 44,300 USD/QALY, but the differences in countries in which the study was conducted in, the year horizon, cost, benefit and transition estimates, as well as the Markov model states make comparison between various studies impossible

(Dan, Aung, & Lim, 2008). A systematic review observed that most economic evaluation studies on drug treatment options for patients with CHB were analyzed based on the perspectives of health care system or third party payer which considered only direct medical costs (Tantai *et al*, 2010). The cost of various drugs and subsidy policies varies significantly between countries as well as impact on the total costs to society, health payer as well to individual patients (Dan, Aung, & Lim, 2008). Country-specific economic evaluation is required to confirm (Lacey & Gane, 2007). Therefore, the study of economic burden in Thai CHB patients is important for implementation of CHB management policy. Table 3.21 demonstrates the cost-effectiveness analysis of CHB by Dan, Aung & Lim (2008).

Table 3.21 Report cost-effectiveness analysis of CHB (Dan, Aung & Lim, 2008)

Treatment	Year of costing	Incremental cost-effectiveness ratio
Compare to no treatment		
IFN	1995	Cost saving – USD 16,000/QALY
	2002 A simulation model, Taiwan patients data base	USD 19,700/QALY
	2005 cost-utility analysis, A systematic review of MEDLINE from 1970-2005	USD 6,337/QALY
LAM	2002 44-A Markov state transition model, A systematic review of 1086 electronic database from 1995-6 to April 2005	Cost-saving – USD 7125
Compare to interferon, LAM, ADV monotherapy		
LAM followed by ADV	2005	USD 8,446/QALY
ADV	A Markov state transition model, A systematic review of 1086 electronic database from 1995-6 to April 2005,	USD14,204/QALY
Compare to regular interferon PEG	2007	USD 32,554/QALY
Compare to LAM	± salvage	
ENT	2007	USD 7,600/QALY
	2008 A cost-utility analysis from an Australian healthcare perspective, A cohort of 1000 antiviral treatment-naïve CHB patients	AUD 5952 in the HBeAg+ve AUD 8003 in the HBeAg-ve
PEG	2007 A Markov state transition model in a cohort of 35-year-old, a US-payer perspective	USD 20,945-35,245/QALY
	2007 A randomized clinical trial of 820 HBeAg-positive CHB patients, a Markov state transition model in a cohort of 32-year-old	USD 12,000/QALY
	2008 A Markov model in a cohort of 40-year-old patients, data were derived from published literature	USD 10,900/QALY
PEG + LAM	2007	USD 28,200/QALY
PEG + LAM + ADV rescue	2007	USD 44,300/QALY
Compare to no treatment in cirrhotic population ADV	2006	USD 19,731/QALY
Compared to ADV in cirrhotic ETV	2006	USD 25,626/QALY

Abbreviation: ADV, adefovir, AUD, Australian dollar, ETV, entecavir, HBeAg, Hepatitis e antigen, IFN, interferon, LAM, lamivudine, PEG, peginterferon, USD, United States Dollar, QALY, Quality Adjusted Life Year

The economic evaluation of CHB patients has many limitations including complicated CHB disease stages and its mortality/morbidity rates (Wong, 2006), likelihood of response to therapy, type of response considered including virologic, serologic, biochemical, or histological, costing method, and estimates of quality of life (Rajendra and Wong, 2007). As patient population differences can confound cross-trial comparisons of efficacy, they can confound the relative cost-effectiveness of alternative treatments in the absence of head-to-head trials (Rajendra & Wong, 2007). Another limitation is that patient adherence during long-term antiviral treatment in a clinical setting may be worse than that in clinical trials (Lacey & Gane, 2007). In addition, the lack of long-term data also makes life cycle projection difficult, as interpretation depends on the assumptions built into the model and is open to errors and manipulations (Dan, Aung and Lim (2008).

CHAPTER IV
MATERIALS AND METHODS

4.1 Study Design

Prospective longitudinal study

4.2 Location of the study

This study was conducted at the outpatient department of Queen Savang Vadhana Memorial Hospital, Chon buri province, Thailand.

4.3 Duration of the study

November 2011 to March 2013

4.4 Study Population

Male and female CHB patients at Queen Savang Vadhana Memorial Hospital, Chon buri province, Thailand.

4.5 Inclusion criteria

- Male or female aged 18 years and over.
- Criteria for diagnosis and/ or treatment bases on Thailand Consensus Recommendations for Management of Chronic Hepatitis B and C 2009.
- Participant's willingness to participate voluntarily.
- Participant is willing and able to provide written informed consent.

4.6 Exclusion criteria

- Severe uncontrolled disease involving other organs (heart, kidney, lung) except the liver
- Participant has any other concurrent medical condition likely to preclude compliance with the schedule of evaluation in the protocol, or likely to confound the efficacy or safety observations of the study.

4.7 Discontinuation criteria

Participant requests withdrawal from the study and will be replaced with a new volunteer.

4.8 Calculation of sample size

The sample size was calculated based on the primary objective, which is to assess medical and economic burden of CHB patients.

The highest prevalence rate of hepatitis B infection is 7%. The formula is $n = z^2 \times p \times (1\text{-}p)/d^2$

$$n = \frac{1.96 \times 0.07 \times (1\text{-}0.07)}{0.05^2} = 51$$

When the sample size was calculated based on a mean CLDQ score of Thai chronic liver diseases patients, the previous study by Sobhonslidsuk *et al* (2004) (165) reported a mean CLDQ of 150 Thai patient with chronic liver diseases as 4.75±1.2 (mean± standard deviation) out of 7 scores. They are 67.86±17.14 scores when adjusted them up as 7 scores is equal to one hundred scores.

The formula is $n = z^2\ SD^2 / d^2$, whereas:

n = sample size

z = 1.96 (95% Confidence Interval)

SD = standard deviation

d = margin of error in estimating mean or effect size

Table 4.1 Effect size and sample size calculated bases on CLDQ score

Effect size (accept within)	Sample size calculated (case)
10 points (68±10 or 58-78 scores)	11 (1.96×1.96×17.14×17.14)/(10×10)
5 points (68±5 or 63-73 scores)	45 (1.96×1.96×17.14×17.14)/(5×5)
1 points (68±1 or 67-69 scores)	1,129 (1.96×1.96×17.14×17.14)/(1×1)

From the formula, 45 participants were needed for a medium effect size or 5 score (63-73 scores). For participant loss compensation, 25% more or 9 participants were added. The sample size based on a mean CLDQ score of Thai CHB patients was 54.

An estimated 150 participants was needed for reliable data analysis. .

4.9 Ethics

This research project was approved by the Ethics Committee of the Faculty of Tropical Medicine, Mahidol University (MUTM 2011-058-01; EC submission number: TMEC 11-047), and Queen Savang Vadhana Memorial Hospital. Participants were aged 18 years and over, and they acknowledged their rights in participant information sheet. All subjects provided written informed consent prior to study participation.

Confidentiality Procedures:

- The researcher explained the process of maintaining confidentiality of records to the participants. The researcher would not collect any direct identifiers such as names or email addresses in either CRF or questionnaires. Only coding was used.
- Source document was used and kept locked at the clinic facility.
- Data was reported in groups. No individual was identified.

Possible risks were answering questionnaires that might make participants uncomfortable and tired of providing response. Therefore, the researcher will ask respondents while waiting for the doctor, and let the participants answer the questionnaires in another room.

Participants received payments of 100 baht for answering questionnaires (EQ-5D and CLDQ).

4.10 Data collecting

Eligible patients' data was collected from hospital information system (HIS), patient's medical records, laboratory report, and medication orders. Three forms were used for data collection: source document, case record form (CRF), transport and expenditure form (TEF). The three questionnaires were CLDQ, EQ-5D and WPAI.

Source document was used to maintain confidentiality. The data consisted of patient identified information: study number patient name, hospital number, registration date, discharge date, date of birth, sex, telephone number, contact address and contact person.

4.10.1 Case record form (CRF)

CRF was used to collect clinical related data, treatment, direct non-medical care cost, other expenses and time consumed per visit. It consists of the following:

- Socio-demographic data
- Presenting symptoms
- Physical examination: phases of CHB, CTP score
- Laboratory investigations: liver investigations, hepatitis B seromarkers, blood test and other laboratory investigation
- Treatment: history of drug allergy, antiretroviral and other drugs recorded in HIS, drug adherence assessment, drug resistance assessment, and adverse drug events

  Note: Drug adherence was assessed as percent of pill count per visit calculated from the number of drugs administered divided by number of drugs received, and multiplied by one hundred. Also, participants were asked for the number of times they forgot to administer antiretroviral drugs per month before that visit.
- Direct medical cost, expenses and times consumed per visit

- Results of treatment at 12th month

4.10.2 Transport and others expenditure form (TEF)

TEF was used to collect transport expense and food expense of patient and care giver and extra health care product expense of patient at D0, M6, and M12.

4.10.3 Questionnaires

Three questionnaires were applied to assess medical and economic burden of CHB patients in this study. These were EuroQOL-5D (EQ-5D), Chronic liver Disease Questionnaire (CLDQ), and Work Productivity and Activity Impairment questionnaire (WPAI), all of which were translated into Thai. For EQ-5D, this study has registered and received permission from the EuroQol Group to apply it. Similarly, CLDQ has been translated to Thai and validated by Sobhonslidsuk *et al* (2004), which was contacted by electronic mail for permission to use the Thai CLDQ. A self-administered hepatitis C version of the WPAI (WPAI: Hepatitis) can be accessed at http://www.reillyassociates.net/WPAI-Hep-C-Thai__Thailand__doc. Permission is not needed to use it.

4.10.3.1 EuroQol-5D (EQ-5D)

The researcher decided on EQ-5D for generic instrument in this study because it has the least items (5 items) with high rate of test-retests. Its outcome can be compared with normal population and other diseases. Also, it can be used in the utility measures, which are important for determining QALYs used in cost-effectiveness studies (Jay *et al*, 2009). EQ-5D has the reliability testing range from 0.70 to 0.85 by test-retested method (Jay *et al*, 2009). Also, it has construct validity at 0.80 by Spearman correlation with HUI3 and 0.70 with SF-6D (Gutteling *et al*, 2007). For discriminant validity, it is able to discriminate between mildly, moderately, severely and very severely disabled patients (Gutteling *et al*, 2007).

The measure of EQ-5D gives both a utility value ranging from 0 to 1.00, with 0 corresponding with state of death and 1.00 corresponding with full health based on a five dimensions and a visual analog scale (VAS). Five dimensions include mobility, self-care, usual activity, pain or discomfort, and anxiety or

depression. Each dimension has three levels of severity: no health impairment or level 1; some health impairments or level 2; and severe health impairments or level 3. EQ-5D VAS asks patients to rate their health on scale of 0 to 100 from the worst possible to the best possible health.

4.10.3.2 Chronic Liver Disease Questionnaire (CLDQ)

The researcher decided on CLDQ to assess medical burden of CHB due to it has the least items with a high rate of internal consistency (>0.79), and it is a self-administered with high responsiveness for liver disease specific questionnaire that is clear and easy to complete in 15 minutes. CLDQ includes 29 items in 6 domains: abdominal symptoms, fatigue, systemic symptoms, activity, emotional function and worry (Younossi *et al*, 1999). The responses of CLDQ result in seven-point Likert scales with one score means “all of the time” or the most impairment to seven scores mean “none of the time” or the least impairment; therefore, the higher score indicates the better QOL. Summary scores for each domain and an overall CLDQ score were calculated based on the mean score, with a range from one to seven.

In Thailand, Sobhonslidsuk *et al* (2004) translated and validated the CLDQ to Thai. The Chronbach’s alpha of the overall Thai CLDQ scores was 0.96, and of all domains were higher than 0.93. Its item-total correlation was 0.88 for the mean CLDQ score and from 0.68 to 0.90 for domain scores. Also, it was found to have discriminant validity.

CLDQ scoring procedure was as following. First, the sum of the corresponding question is taken. This is then divided by the number of items in the domain to get the domain score. To get the overall CLDQ score, the sum of the domains are taken and then divided by the total number of domains.

Abdominal (AB) = Sum of N1 + N5 + N17

Fatigue (FA) = Sum of N2 + N4 + N8 + N11 + N13

Systemic (SY) = Sum of N3 + N6 + N21 + N23 + N27

Activity (AC) = Sum of N7 + N9 + N14

Emotion (EM) = Sum of N10 + N12 + N15 + N16 + N19 + N20 + N24 + N26

Worry (WO) = Sum of N18 + N22 + N25 + N28 + N29

Then,

AB = AB/3

FA = FA/5

SY = SY/5

AC = AC/3

EM = EM/8

WO = WO/5

CLDQM = Sum (of AB, FA, SY, AC, EM, WO) / 6

4.10.3.3 Work Productivity and Activity Impairment questionnaire hepatitis C version (WPAI: Hepatitis)

WPAI is a work productivity loss related health questionnaire. It has 6 items, takes 5 minutes per questionnaire, and determines impairment while working and activity impairment. Patients rated their degree of impairment from the least 0 score to the most 10 scores that were applied to percent. The self- and interviewer-administered versions of the WPAI-GH were tested in 106 employed individuals affected by a health problem (Reilly *et al*, 1993). Construct validity and test-retest reliability of the self- and the interviewer-administered WPAI-GH were assessed by analyzing the extent to which the instruments correlated with several domains of the SF-36 general health perceptions, role-physical, role-emotional, pain, symptom severity, and global measures of work and interference with regular activities (Chirban *et al*, 1997). In addition, data gathered by the interviewer had higher construct validity than those collected via self-administration (Prasad *et al*, 2004). Both WPAI generic and specific versions had sufficient test-retest reliability, with correlation coefficients ranging from 0.71 to 0.87 for overall productivity at work and outside of it (Prasad *et al*, 2004).

4.10.4 Applying the questionnaires

EQ-5D and CLDQ are self-administered questionnaires where the researcher was available to answer any clarifications from study participants. Therefore, if the researcher is not present, these questionnaires will not be applied.

WPAI and TEF are interviewer-administered questionnaires when participants are available.

EQ-5D has 15 items, and takes 10 minutes per questionnaire. CLDQ has 29 items, and takes 15 minutes per questionnaire. WPAI has 6 items, and takes 5 minutes per questionnaire.

4.10.4.1 Process of applying self-administered questionnaires (EQ-5D and CLDQ):

- After signing the consent, the researcher distributed EQ-5D and CLDQ to the participant.
- The participant read the questionnaire.
- The participant answered the questions, researcher was present to answer their questions.
- When the respondents completed the questionnaires, the researcher checked for completeness, clarification wasmade if necessary and thanked the participant.

4.10.4.2 Process of applying interviewer-administered questionnaires (TEF and WPAI):

- The researcher asked permission to interview participant. The interviewer conducted the initial medical examination or inquired if participant is willing to answer questions.
- The researcher interviewed the participant using TEF and WPAI.
- When the interview was finished, the researcher thanked the participant.

4.10.5 Interview timing and frequency

EQ-5D has 15 items, and takes 10 minutes per questionnaire. CLDQ has 29 items, and takes 15 minutes per questionnaire. WPAI was applied to the participants as interviewer-administered questionnaires when participants were available. WPAI has 6 items, and takes 5 minutes per questionnaire.

The study flow chart usually did in D0, M6, M12, and as regular follow up by the physician.

Table 4.2 Study flow chart usually did in D0, M6, M12

		D0	**M6**	**M12**
Screening	Assessment	√		
	Inform consent	√		
	Inclusion criteria	√		
Patient Characteristics	Socio-demographic data	√		
	Presenting symptoms	√		
Current Episode	Physical examination: CTP	√	√	√
	Laboratory investigation	√	√	√
	Treatment: drug adherence assessment	√	√	√
	Cost, Expense and time consumed per visit	√	√	√
	CLDQ	√	√	√
	EQ-5D	√	√	√
	WPAI	√	√	√
	TEF	√	√	√
	Results of treatment at 12^{th} month			√

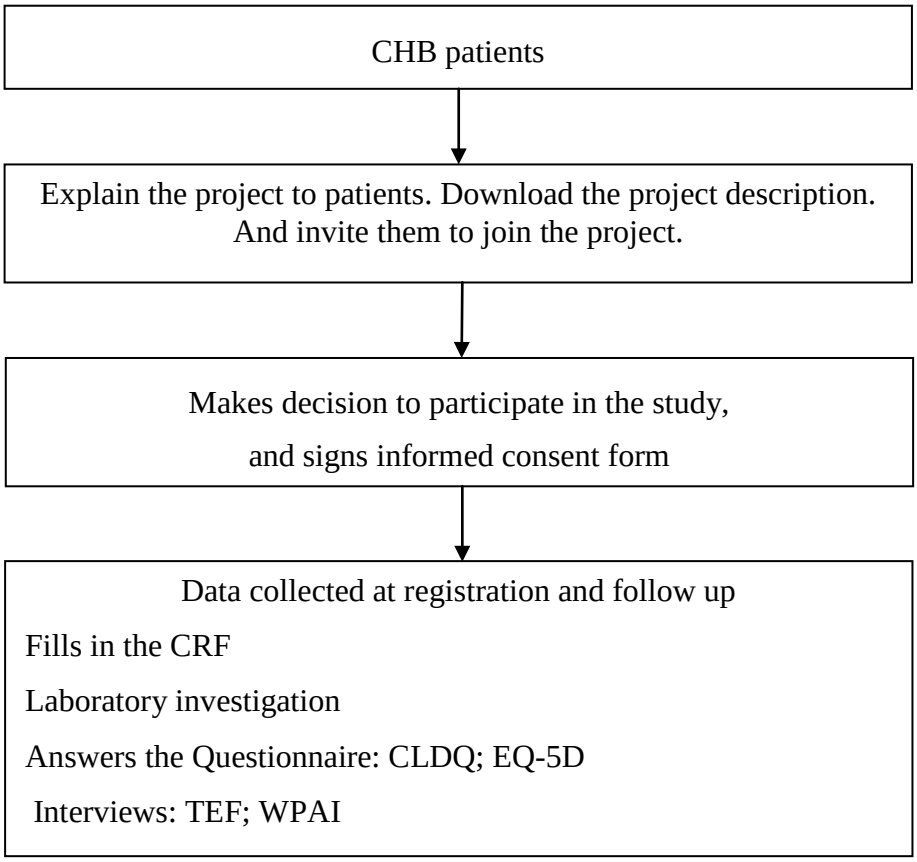


Figure 4.1 Study flow diagram

4.10.6 Cost collecting

4.10.6.1 Schematic diagram of total cost

Schematic diagram of cost is shown in Figure 4.2.

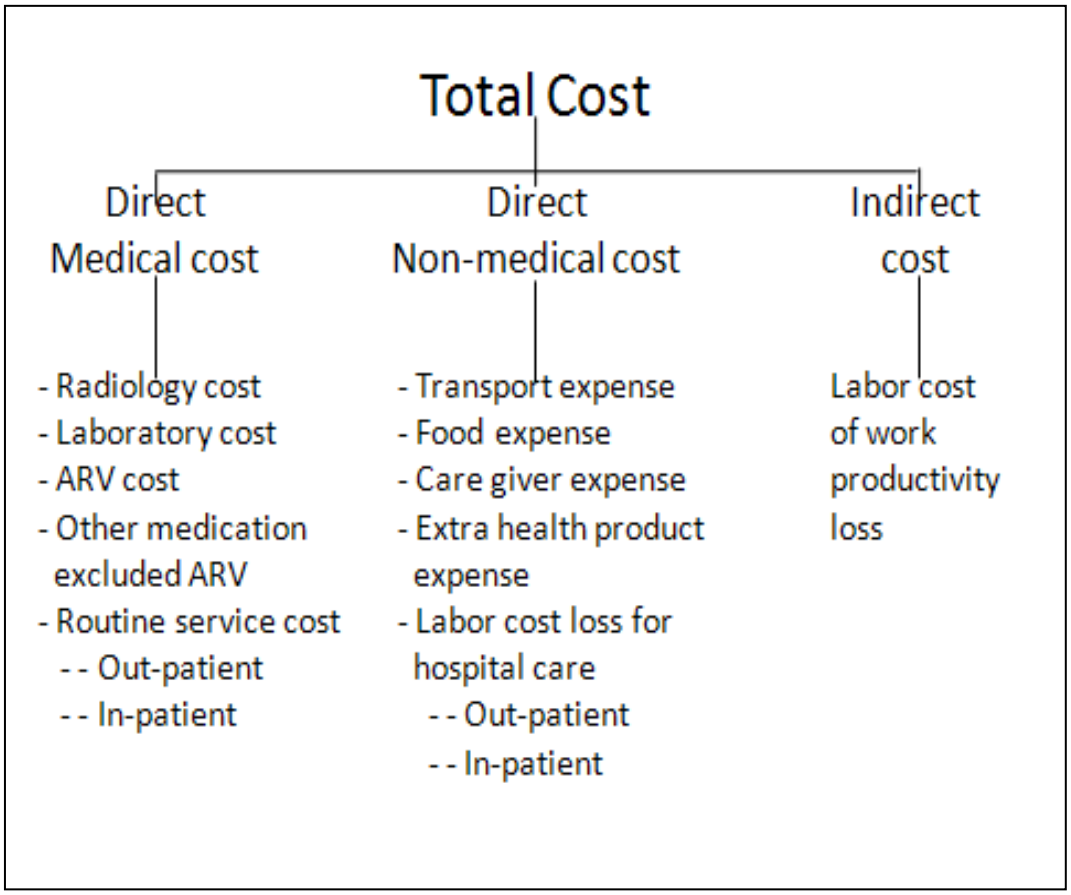


Figure 4.2 Schematic diagram of total cost

4.10.6.2 Source of cost and cost applied to Baht/year

Source of costs and costs applied to Baht/year are shown in Table 4.3. The routine service cost (RSC) of Queen Savang Vadhana Memorial Hospital in 2003 was 321.84 and 2972.63 Baht per OPD visit and per IPD hospital day. Then, they were applied to RSC in 2012 with average customer price index (CPI) 2003 (77.6) and 2012 (103.0) (Ministry of Commerce of the Kingdom of Thailand, 2013) using the formula below.

$$\frac{CPI_{2012}}{CPI_{2003}} \times RSC_{2003}$$

$$\frac{103.0}{77.6} \times 321.84 \text{ for OPD visit or } 2972.63 \text{ for IPD day}$$

= 427.18 for OPD visit

= 3,945.63 for IPD day

Table 4.3 Source of costs and costs applied to Baht/year

Costs	Source	Cost applied to Baht/year
Direct medical cost		
Radiology cost	Patients' history from HIS	Number of each radiology used in each patient (time/year) × cost of each radiology from Standard Cost Lists for Health Technology Assessment (Riewpaiboon, 2011). 2011 price was adjusted to 2012 price with consumer price index.
Laboratory cost	Patients' history from HIS	Number of each laboratory used in each patient (time/year) × cost of each laboratory from Standard Cost Lists for Health Technology Assessment (Riewpaiboon, 2011). 2011 price was adjusted to 2012 price with consumer price index.
ARV cost	Patients' history from HIS	Number of pill patient received each drug in each patient (pill/year) × cost of each drug per pill from Queen Savang Vadhana Memorial Hospital drug list
Other medication cost excluded ARV	Patients' history from HIS	Number of pill patient received each drug in each patient (pill/year) × cost of each drug per pill from Queen Savang Vadhana Memorial Hospital drug list
Routine service cost	Unit cost study, Number of OPD visit/year from HIS, CPI from Ministry of Commerce of the kingdom of Thailand	Routine service costs with capital cost of Queen Savang Vadhana Memorial Hospital in 2003: 321.48 Baht per OPD visit and 2,972.63 Baht per IPD day. These costs were calculated to cost in 2012 using inflation rate from 2003 to 2012 that were 427.18 and 3,945.63 Baht per OPD visit and IPD day.

Table 4.3 Source of costs and costs applied to Baht/year (Continue)

Costs	Source	Cost applied to Baht/year
Direct non-medical cost		
Transport expense	Patient via TEF, Number of OPD visit/year from HIS	(Transport expense of D0, M6, and M12)/3 (Baht/visit) × number of OPD visit/year
Food expense	Patient via TEF	(Food expense of D0, M6, and M12)/3 (Baht/visit) × number of OPD visit/year
Care giver expense	Patient via TEF, each OPD visit took half day	(Care givers' salary/30 day/2) (Baht/visit) × number of OPD visit/year
Supplementary expense	Patient via TEF	Supplementary expense at D0 (Baht/month) × 12
Labor cost loss for hospital care		
- Out patient	Patients' salary via CRF, Number of OPD visit/year from HIS, estimated each OPD visit took half day	(Patients' salary/30 day/2) (Baht/visit) × number of OPD visit/year
- In patient	Patients' salary from CRF, Number of IPD day/year from HIS	(Patients' salary/30 day) (Baht/day) × Number of IPD day/year
Indirect cost		
Labor cost from impairment while working	Patients' salary from CRF, percent impairment while working from WPAI	(Patients' salary per month × percent impairment while working at first 6 months × 6) + (Patients' salary per month × percent impairment while working at second 6 months × 6)

Abbreviation: CPI, customer price index; CRF, case record form; HIS, hospital information system; IPD, in-patient department; OPD, out-patient department; RSC, routine service cost; TEF, transport and other expenditure form; WPAI, Work Productivity and Activity Impairment.

4.11 Operational definition

Medical burden of CHB: Physical burden and psychological burden that could be assessed from severity of liver disease by using CLDQ and from quality of life by using EQ-5D.

Economic burden of CHB: A cost in societal perspective referred to total cost comprising direct medical cost, direct non-medical cost, and indirect cost of both patient and caregiver.

Chronic hepatitis B: A chronic necroinflammatory disease of the liver caused by persistant infection with hepatitis B virus.

Direct medical cost: Patients' costs for hospital care at Queen Savang Vadhana Memorial Hospital including radiology cost, laboratory cost, ARV cost, other medication cost excluded ARV, and routine service cost with capital cost.

Direct non-medical cost: Patients and care givers' costs for health care included transport expense, food expense, care giver expense, supplementary expense, and patients' labor cost loss for hospital care.

Indirect cost: Patients' cost of work productivity loss assessed by WPAI in term of activity impairment while working due to health in patients' perspective that was turn into monetary from patients' salary.

4.12 Data analysis

Data was entered in Microsoft excel worksheet and analysed by SPSS for Windows version 20.0. Qualitative data was shown in frequency and percent. Quantitative data with normal and non-normal distribution were shown in mean with standard deviation and median with interquatile range (IQR). Data were presented in table and figure. A *p* value less than 0.05 was considered as statistically significant.

Baseline socio-demographic and clinical characteristics were analyzed. According to mean (SD) average CLDQ score (CLDQM) of patients at initial D0 was 5.48 (0.89) scores; therefore, a 5 score of CLDQ was used as a cut point. To analyze economic burden related to medical burden, the medical burden of CHB patients was divided into severe medical burden or CLDQ < 5 scores group and mild medical

burden or CLDQ ≥ 5 scores group. Comparison between two groups and within groups among D0, M6, and M12 were done.

As the data on the EQ-5D dimensions was not continuous but ordinal, the information was presented as proportions of the patient reporting level 1 (no health impairments), level 2 (some health impairments) and level 3 (extreme health impairments) per dimension. Because the number of patient reporting severe health impairments was very small, the sum of the proportions of reported level 2 and level 3 health impairments was used. This essentially changed the 3-level EQ-5D dimensions into 2-level dimensions, with categories 'no health impairments' and 'had health impairments'. Finally, the percents of patients reporting moderate or severe health impairments in each EQ-5D dimension were reported. For EQ-5D-VAS, patients rated their health on scale of 0 from the worst possible to 100 the best possible health.

EQ-5D, EQ-5D VAS, CLDQ score, cost, expenses, activity impairment and impairment while working were explored and compared between CLDQ < 5 scores and CLDQ ≥ 5 scores groups, and within group among D0, M6, and M12. The statistics used in comparative groups are shown in Table 4.6.

Table 4.4 Statistics used in comparative groups

Type of data	Statistics used
Comparing between CLDQ<5 scores vs. CLDQ≥5 scores	
Percent	Chi-square (χ^2)
Mean (SD)	Independent t-test (*t*)
Median (IQR)	Mann Whitney U test (Z)
Comparing within group among D0, M6, and M12	
Percent	Friedman K related test (χ^2)
Mean (SD) or median (IQR)	Cochran's Q

Factors affecting QOL measured by EQ-5D VAS and factors affecting severity of liver disease determined by CLDQ were analyzed by correlations and multiple linear regressions. Correlations between baseline socio-demographic, clinical characteristics, and EQ-5D VAS and CLDQ were analyzed. Correlation level was

determined as 0.00-0.19 (no correlation), 0.20-0.49 (little), 0.50-0.79 (fair), 0.80-1.00 (good). *P* value less than 0.05 and 0.01 was considered statistically significant.

For multiple linear regressions, dependent variables in the regression model were EQ-5D VAS (full scores = 100) and CLDQ scores (full scores = 7) that were treated as a continuous variable, and were analyzed separately. The independent socio-demographic variables in the regression model included age more than 35 years, male gender, married status, graduate, employee, monthly household income less than 10000 baht, had health welfare, had family member with hepatitis B, presence of other diseases except liver disease, and independent clinical characteristic variables included treated ARV, month for CHB follow up more than 12, month of treated ARV more than 12, naïve within 6 months, naïve within 12 months, phase I immune tolerant, phase II immune active, phase II inactive, phase IV HBsAg clearance, cirrhosis, HCC, HIV-HBV co-infections, HCV-HBV co-infections, DM, child A, child B, child B, child C, HBeAg-positive were entered as dichotomous variables (1 yes, 0 no). The following variables were constant or had missing correlations and were deleted from the analysis: child A, cirrhosis, phase II immune active, phase III inactive, and phase IV HBsAg clearance. EQ-5D VAS and CLDQ were treated as continuous variables.

In this study, the split-half Cronbach's alpha of the EQ-5D and the CLDQ reliability were 0.76, and 0.82, respectively.

CHAPTER V
RESULTS

This part describes the results as follow:

5.1 Medical burden of CHB patient:

5.1.1 Patients enrolled and study flow,

5.1.2 Baseline socio-demographic and clinical characteristic of CHB patients

5.1.3 Severity of liver disease measured by using Chronic Liver Disease Questionnaire (CLDQ)

5.1.4 Quality of life (QOL) determined by using EuroQol-5D (EQ-5D)

5.1.5 Factors effect to QOL measured by using EuroQol-5D Visual Analog Scale (EQ-5D VAS), average CLDQ score (CLDQM)

5.1.6 Work productivity loss assessed by using WPAI

5.2 Economic burden of CHB patient: direct medical cost, direct non-medical cost, indirect cost

5.1 Medical burden of CHB patient

5.1.1 Patients enrolled and study flow

A total of 152, 140, and 129 CHB patients who visited the OPD of Queen Savang Vadhana Memorial Hospital at D0, M6 and M12, respectively were enrolled. According to mean (SD) CLDQ score (CLDQM) of the patients at initial D0 was 5.48 (0.89) scores, a 5 score of CLDQ was used as a cut point. To compare economic burden between CHB patients with severe and mild medical burden, the medical burden of CHB patients was divided into severe medical burden or CLDQ < 5 scores

group and mild medical burden or CLDQ ≥ 5 scores group. The comparison between two groups and within group betweenD0, M6, and M12 were done.

The percent lost to follow up at M6 and the cumulative percent lost to follow up at M12 were 7.9 and 15.1, respectively. At first 6 month, the CLDQ≥ 5 scores group had 10.5 percent lost to follow up while the CLDQ<5 scores had 0.0%. At second 6 month the CLDQ<5 scores had 13.1% lost to follow up increased from 0.0% at first 6 month. For patients lost to follow up, the registration of Thai people on May 15, 2013 did not report their deaths. Patients enrolled and study flows are shown in Figure 5.1.

For CLDQ < 5 scores group, number of patients at D0, M6, and M12 were 38, 38, and 33, respectively. Their percent loss at M6 and cumulative percent loss at M12 were 0.0 and 13.1, respectively. For CLDQ ≥ 5 scores group, number of patients at D0, M6, and M12 were 114, 102, and 96, respectively. Their percent loss at M6 and cumulative percent loss at M12 were 10.5 and 15.8%, respectively. Regarding death cases, at M6, one case in CLDQ ≥ 5 scores group died, and at M12, two cases of CLDQ ≥5 scores group and one cases of CLDQ < 5 scores group died.

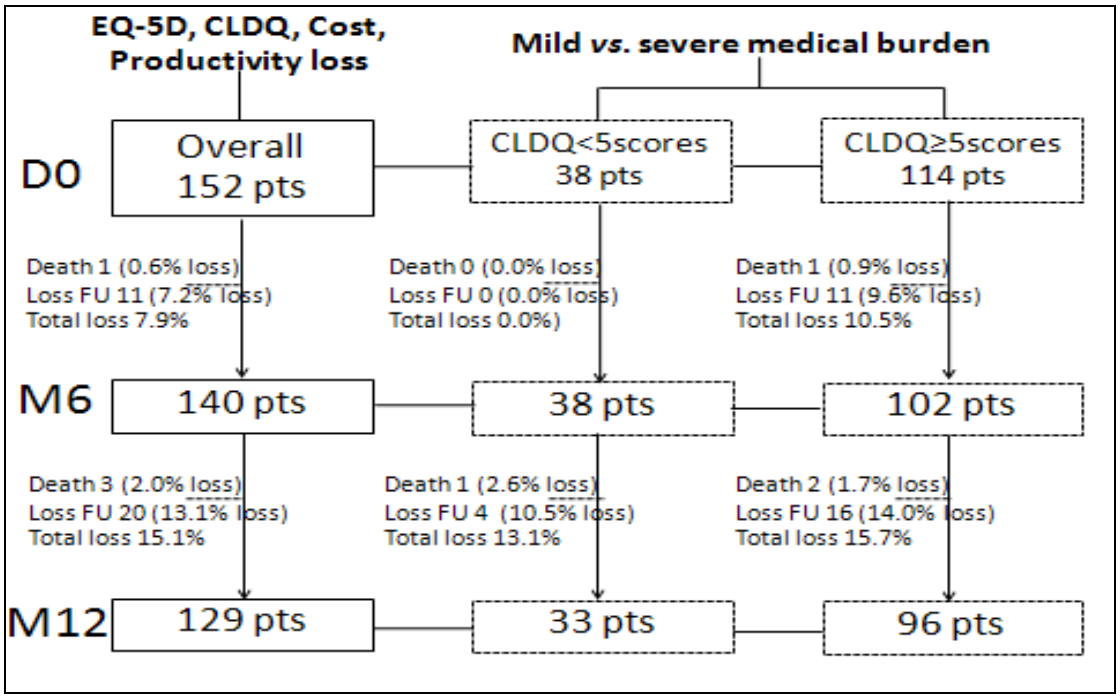


Figure 5.1 Patients enrolled and study flow

Three patients died during the study periodfrom CHB with HCC (2 cases), and Acute Myeloblastic Leukemia (AML) (1 case). The details are as follows.

Case 1: patient no.26: male, age 46 years, diagnosed HCC with CTP 9 scores or child B, phase II or HBeAg positive, treated TDF for 7 months. He lost follow up at M6. Date of death was Feb. 19, 2012. Cause of death was CHB with HCC.

Case 2: patient no.37: male, age 48 years, diagnosed HCC with CTP 5 scores or child A, phase IV or HBeAg negative, treated ETV for 32 months. He was lost to follow up at M12. Cause of death was CHB with HCC. Date of death was May 25, 2012.

Case 3: patient no.147: male, age 60 years, diagnosed HCC with CTP 6 scores or child A, phase IV or HBeAg negative, treated TDF for 22 months. He was lost to follow up at M12. Date of death was March 19, 2013. Cause of death was acute myeloblastic leukemia (AML).

The death cases occurred during the study period as shown in Figure 5.2.

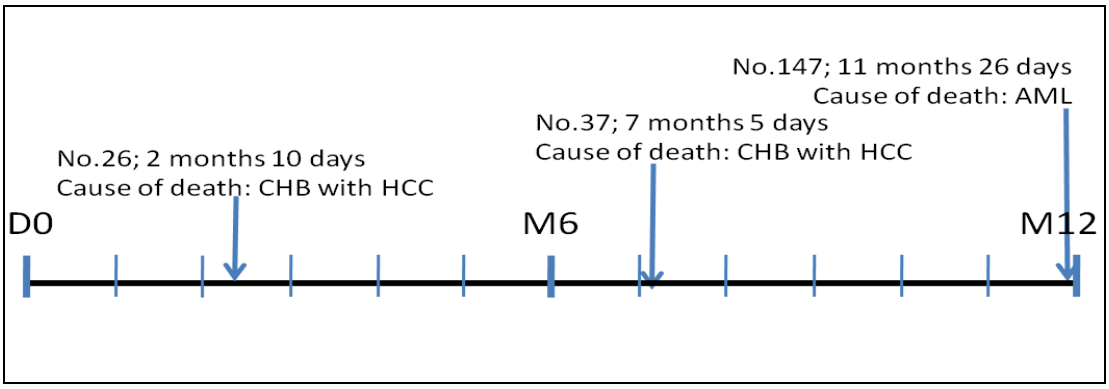


Figure 5.2 Death cases occurred during the study period

5.1.2 Baseline socio-demographic and clinical characteristics of CHB patients and comparison of baseline socio-demographic and clinical characteristics between CLDQ < 5 scores and CLDQ ≥ 5 scores

Baseline socio-demographic and clinical characteristics of CHB patients and comparison of baseline socio-demographic and clinical characteristics between CLDQ < 5 scores and CLDQ ≥ 5 scores are shown in Table 5.1. Median (IQR) age was 39.0 (32.0-49.0) years. Majority were employee (105 of 152 or 69.1%) having median (IQR) income 10000.0 (7500.0-19625.0) baht/month, and had health security (141 of 152 or 92.8%). More than half were male gender (83 of 152 or 54.6%), and married status (96 of 152 or 63.2%). Nearly half were undergraduate or had attended primary school (74 of 152 or 48.7%), had family member as hepatitis B (71 of 152 or 46.7%), and had presence of other diseases except liver disease (64 of 152 or 42.1%). Median (IQR) month for CHB follow up was 16.0 (6.0-24.0). Among CHB four phases, most of patients were phase II immune active (50 patients or 32.9%) and phase IV HBsAg clearance (46 patients or 30.3%), the rest were phase III inactive (33 patients or 21.7%) and phase I immune tolerant (23 patients or 15.1%).

Among patients, 31 or 20.4% and 8 or 5.3% developed to cirrhosis and HCC. Majority had a history of diabetes mellitus (15 of 152 or 9.9%) while the rest were HIV-HBV co-infections (9 of 152 or 5.9%) and HCV-HBV co-infections (3 of 152 or 2.0%). Among cirrhosis patients, majority were child A (27 of 31 or 87.1%), the rest were child B (3 of 31 or 9.7%) and child C (1 of 31 or 3.2%). More than half were HBeAg-negative (80 of 152 or 52.6%). Median (IQR) HBV DNA was 18.5 (10.0-16250.0) IU/ml. Median (IQR) aminotransferase (ALT) and aspartate aminotransferase (AST) were 27.0 (21.0-36.0) and 26.0 (17.0-38.7) IU/ml. Median (IQR) alkaline phosphates and alpha-fetoprotein were 68.0 (54.0-98.5) IU/ml and 2.2 (1.6-3.5) ng/ml. Median (IQR) total bilirubin, albumin and hematocrit were 0.6 (0.5-0.9) mg/dl, 4.3 (4.0-4.5) and 39.0 (35.9-42.8) g%. Median (IQR) International Normalized Ratio (INR) was 1.0 (0.9-1.1).

More than half (84 of 152 or 55.3%) treated ARV for hepatitis B infection having median (IQR) month of treatment 21.0 (9.0-31.0). From 84 treated ARV cases, there were 47 cases of tenofovir (56.0%), 16 cases lamivudine (19.0%), 10 cases entecavir (11.9%), 2 cases adefovir (2.4%), and 9 cases lamivudine and tenofovir

combination (10.7%). For virus co-infections, there were 9 cases of human immune deficiency virus (HIV) with HBV, and 3 cases of hepatitis C virus (HCV) with HBV.

Comparison of baseline socio-demographic and clinical characteristics between CLDQ < 5 scores and CLDQ ≥ 5 scores, the significant differences were median (IQR) age (45 (35-54) *vs.* 38 (31-46) year, p =0.013)), number (%) of cirrhosis (12 (31.6) *vs.* 19 (16.7), p=0.005), median (IQR) albumin (4.0 (3.7-4.4) *vs.* 4.3 (4.1-4.5)) g%, p=0.020), and median (IQR) INR (1.0 (0.9-1.1) *vs.* 1.0 (0.9-1.1)), p=0.048).

Table 5.1 Baseline socio-demographic and clinical characteristics of CHB patients and comparison of baseline socio-demographic and clinical characteristics between CLDQ < 5 scores and CLDQ ≥ 5 scores

Parameters	*n*	Overall	*n*	CLDQ <5 scores	*n*	CLDQ ≥ 5 scores	χ^2/ *Z*	*p*
Baseline socio-demographic								
Age, median (IQR) years	152	39.0 (32.0-49.0)	38	45 (35-54)	114	38 (31-46)	2.48	0.013*
Male gender, number (%)	152	83 (54.6)	38	18 (47.4)	114	65 (57.0)	1.07	0.301
Married status, number (%)	152	96 (63.2)	38	25 (65.8)	114	71 (62.3)	0.15	0.698
Undergraduate, number (%)	152	74 (48.7)	38	14 (36.8)	114	60 (52.6)	2.84	0.092
Employee, number (%)	152	105 (69.1)	38	25 (65.8)	114	80 (70.2)	0.26	0.612
Salary, median (IQR) baht	152	10000 (7500-19625)	38	9500 (5150-20000)	114	10000 (8000-18875)	0.98	0.325
Had health security, number (%)	152	141 (92.8)	38	36 (94.7)	114	105 (92.1)	0.29	0.588
Had family member as hepatitis B, number (%)	152	71 (46.7)	38	15 (39.5)	114	56 (49.1)	1.07	0.302
Had presence of other diseases except liver disease, number (%)	152	64 (42.1)	38	19 (50.0)	114	45 (39.5)	1.29	0.255
Baseline clinical characteristics								
Months for CHB follow up, median (IQR)	152	16 (6-24)	38	18 (7-26)	114	16 (5-22)	0.70	0.483
Phase I immune tolerant, number (%)	152	23 (15.1)	38	4 (10.5)	114	19 (16.7)	0.84	0.360
Phase I immune active, number (%)	152	50 (32.9)	38	13 (34.2)	114	37 (32.5)	0.04	0.842
Phase III inactive, number (%)	152	33 (21.7)	38	9 (23.7)	114	24 (21.1)	0.12	0.733

Table 5.1 Baseline socio-demographic and clinical characteristics of CHB patients and comparison of baseline socio-demographic and clinical characteristics between CLDQ < 5 scores and CLDQ ≥ 5 scores (Continue)

Parameters	*n*	Overall	*n*	CLDQ < 5 scores	*n*	CLDQ ≥ 5 scores	χ^2/ *Z*	*p*
Baseline clinical characteristics (Continue)								
Phase IV HBsAg clearance, number (%)	152	46 (30.3)	38	12 (36.1)	114	34 (29.8)	0.04	0.838
ARV treatment, number (%)	152	84 (55.3)	38	24 (63.2)	114	60 (52.6)	1.28	0.258
Months of treated ARV, median (IQR)	84	21 (10-31)	24	21 (9-29)	60	22 (9-31)	0.14	0.483
Cirrhosis, number (%)	152	31 (20.4)	38	12 (31.6)	114	19 (16.7)	3.90	0.048*
HCC, number (%)	152	8 (5.3)	38	3 (7.9)	114	5 (4.4)	0.70	0.402
HIV-HBV co-infections, number (%)	152	9 (5.9)	38	1 (2.6)	114	8 (7.0)	0.98	0.321
HCV-HBV co-infections number (%)	152	3 (2.0)	38	2 (5.3)	114	1 (0.9)	2.83	0.092
Diabetes Mellitus (DM), number (%)	152	15 (9.9)	38	6 (15.8)	114	9 (7.9)	1.99	0.158
Child-Turcotte-Pugh (CTP) score of cirrhotic, number (%)								
Class A	31	27 (87.1)	12	10 (83.3)	19	17 (89.5)	0.25	0.619
Class B	31	3 (9.7)	12	2 (16.7)	19	1 (5.3)	1.09	0.296
Class C	31	1 (3.2)	12	0 (0.0)	19	1 (5.3)	0.65	0.419
HBV DNA, median (IQR) IU/ml	124	18 (10-16250)	32	32.5 (10-49583)	92	13.5 (10-16250)	0.46	0.645
HBeAg-negative, number (%)	152	80 (52.6)	38	21 (55.3)	114	59 (51.8)	0.14	0.708
ALT/SGOT, median (IQR) U/l	152	27 (21-36)	38	29 (22-39)	114	27 (21-35)	1.00	0.315
AST/SGPT, median (IQR) U/l	152	26 (17-39)	38	24 (16.35)	114	26 (17.39)	0.74	0.460
Alkaline phosphates, median (IQR) U/l	149	68 (54-98)	38	73 (60-109)	111	68 (52-94)	1.66	0.097
Alpha-fetoprotein, median (IQR) ng/ml	136	2.2 (1.6-3.5)	36	2.7 (1.7-5.5)	100	2.1 (1.5-3.1)	1.29	0.197
Total bilirubin, median (IQR) mg/dl	152	0.6 (0.5-0.9)	38	0.6 (0.4-1.0)	114	0.6 (0.4-0.8)	0.34	0.735
Albumin, median (IQR) g%	152	4.3 (4.0-4.5)	38	4.0 (3.7-4.4)	114	4.3 (4.1-4.5)	2.32	0.020*
INR, median (IQR)	152	1.0 (0.9-1.1)	38	1.0 (0.9-1.1)	114	1.0 (0.9-1.1)	1.97	0.048*
Hematocrit, median (IQR) g%	152	39.0 (35.9-42.8)	38	39.0 (34.5-41.9)	114	39.0 (36.5-42.9)	1.32	0.188

*p<0.05, **p<0.01

Abbreviations: ALT, aminotransferase; ARV, antiviral therapy for hepatitis B infection; AST, aspartate aminotransferase; HBeAg, hepatitis B e antigen; HBV-DNA, hepatitis B virus deoxyribonucleic acid; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, International Normalized Ratio; IQR, Interquartile Range; SD, Standard Deviation.

5.1.3 Severity of liver disease measured by using Chronic Liver Disease Questionnaire (CLDQ)

According to CLDQ scoring, the responses of CLDQ result in seven-point Likert scales with meaning of score are listed below; therefore, the higher score indicates the better QOL. Summary scores for each domain and an overall CLDQ score are calculated based on the mean score, with a range from one to seven.

1 = All of the time

2 = Most of the time

3 = A good bit of the time

4 = Some of the time

5 = A little of the time

6 = Hardly any of the time

7 = None of the time

Regarding mean (SD) CLDQM of patients at initial D0 was a little of the time score with 5.48 (0.89) scores, the CHB patients was divided into severe medical burden or CLDQ < 5 scores group and mild medical burden or CLDQ ≥ 5 scores group to analyze economic burden related to medical burden. The comparison between two groups and within group between D0, M6, and M12 were done.

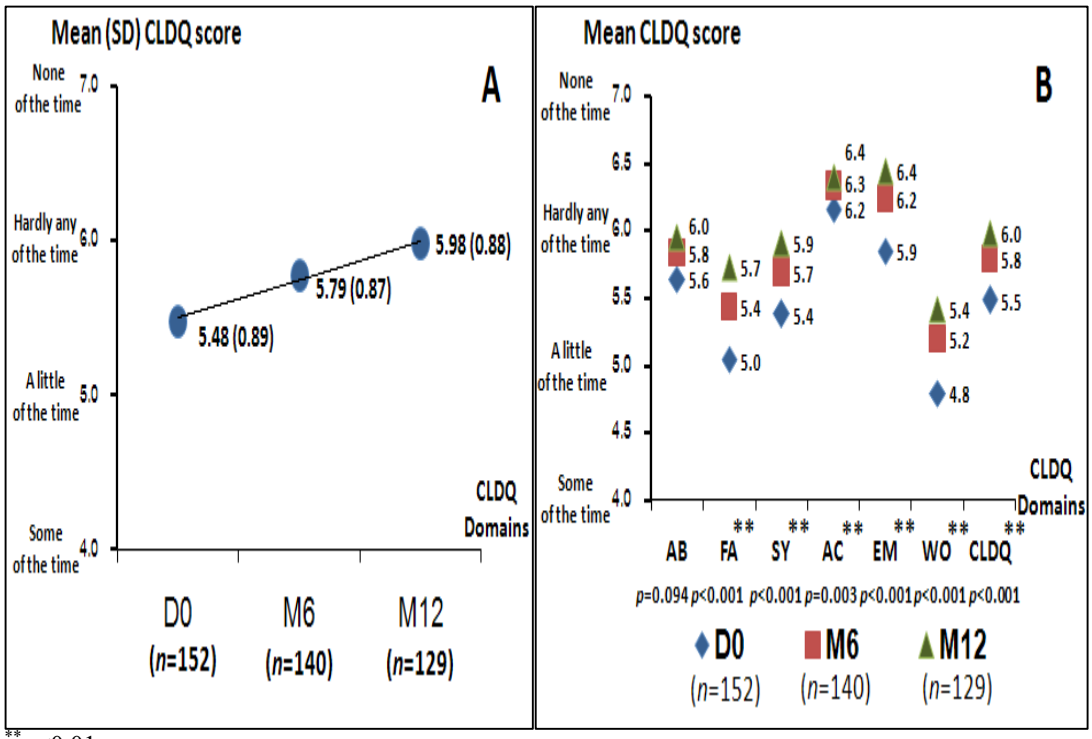
Comparions of mean (SD) CLDQ score within group among D0, M6, and M12 in each CLDQ domain are shown in Table 5.2 and Figure 5.3. Mean (SD) CLDQM increased from a little of the time score with 5.48 (0.89) scores at D0 to hardly any of the time score with 5.79 (0.87) scores at M6 and 5.98 (0.88) scores at M12 (p<0.001). Almost all domains, mean (SD) CLDQ score significantly increased at M6 and M12 except AB. The three domains with the least mean (SD) CLDQ score at D0 were a little of the time score in WO (4.79 (1.24)), FA 5.05 (1.19), and SY (5.38 (1.16)).

Table 5.2 Comparison of mean (SD) CLDQ score within group among D0, M6, and M12 in each CLDQ domain

CLDQ domains	D0 (*n*=152)	M6 (*n*=140)	M12 (*n*=129)	Friedmans' test	*p*
AB	5.64 (1.50)	5.83 (1.35)	5.95 (1.27)	4.74	0.094
FA	5.05 (1.19)	5.43 (1.20)	5.74 (1.16)	45.25	<0.001**
SY	5.38 (1.16)	5.69 (1.07)	5.91 (1.06)	34.21	<0.001**
AC	6.16 (1.00)	6.33 (0.94)	6.40 (1.02)	11.44	0.003**
EM	5.85 (1.00)	6.23 (0.92)	6.45 (0.82)	43.43	<0.001**
WO	4.79 (1.24)	5.19 (1.28)	5.43 (1.09)	32.44	<0.001**
CLDQM	5.48 (0.89)	5.79 (0.87)	5.98 (0.88)	50.87	<0.001**

** $p<0.01$

Abbreviations: AB, abdominal symptoms; AC, activity; CLDQ, Chronic Liver Disease Questionnaire; CLDQM, overall CLDQ score; D0, Day zero; EM, emotional function; FA, fatigue; M6, 6th month of follow up; M12, 12th month of follow up; SD, Standard Deviation; SY, systemic symptoms; WO, worry.



** $p<0.01$

Abbreviations: AB, abdominal symptoms; AC, activity; CLDQ, Chronic Liver Disease Questionnaire; CLDQM, overall CLDQ score; D0, Day zero; EM, emotional function; FA, fatigue; M6, 6th month of follow up; M12, 12th month of follow up; SD, Standard Deviation; SY, systemic symptoms; WO, worry.

Figure 5.3 (A) Mean (SD) CLDQ score (CLDQM) at D0, M6, and M12 (B) Comparison of mean (SD) CLDQ score within group among D0, M6, and M12 in each CLDQ domain

5.1.3.1 Comparison of mean (SD) CLDQ scores between CLDQ < 5 scores and CLDQ ≥ 5 scores at D0, M6, and M12

Mean CLDQ scores between CLDQ < 5 scores and CLDQ ≥ 5 scores groups all domains at D0, M6, and M12 were significant differences. For CLDQ < 5 scores group, mean (SD) CLDQM scores significantly sharply increased from 4.24 (0.67) score at D0 to 4.96 (1.02) score at M6 and 5.18 (1.15) at M12, whereas in CLDQ ≥ 5 scores group, mean (SD) CLDQM scores significantly slowly increased from 5.89 (0.47) at D0 to 6.06 (0.56) at M6 and 6.25 (0.54) at M12. Comparison of mean (SD) CLDQ scores in each domain between CLDQ < 5 scores and CLDQ ≥ 5 scores groups at D0, M6, and M12 are shown in Figure 5.4.

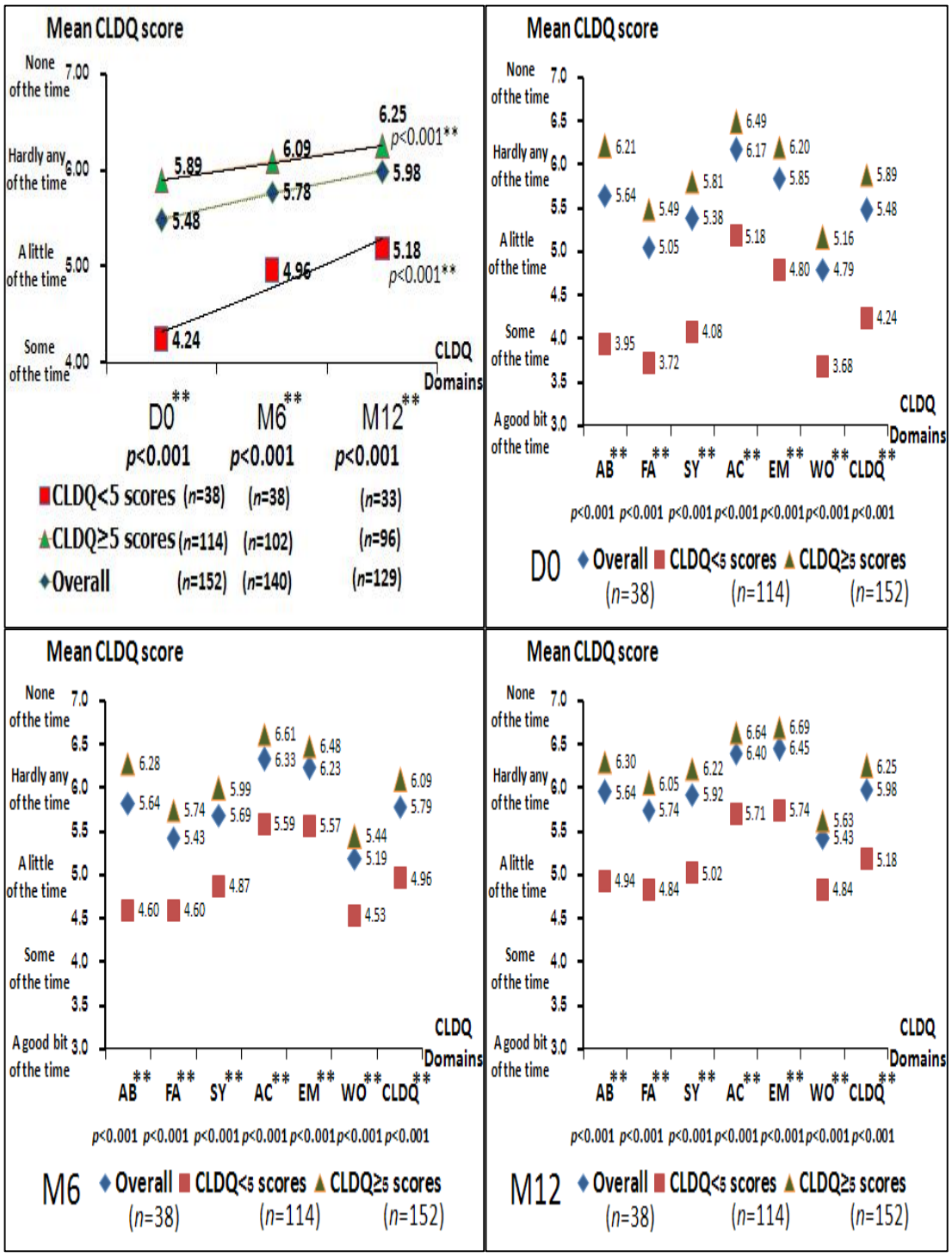


Figure 5.4 Comparison of mean (SD) CLDQ scores in each domain between CLDQ < 5 scores and CLDQ ≥ 5 scores groups at D0, M6, and M12

5.1.3.2 Comparison of CLDQ scores of CLDQ < 5 scores and CLDQ ≥ 5 scores within group among D0, M6, and M12 in each domain

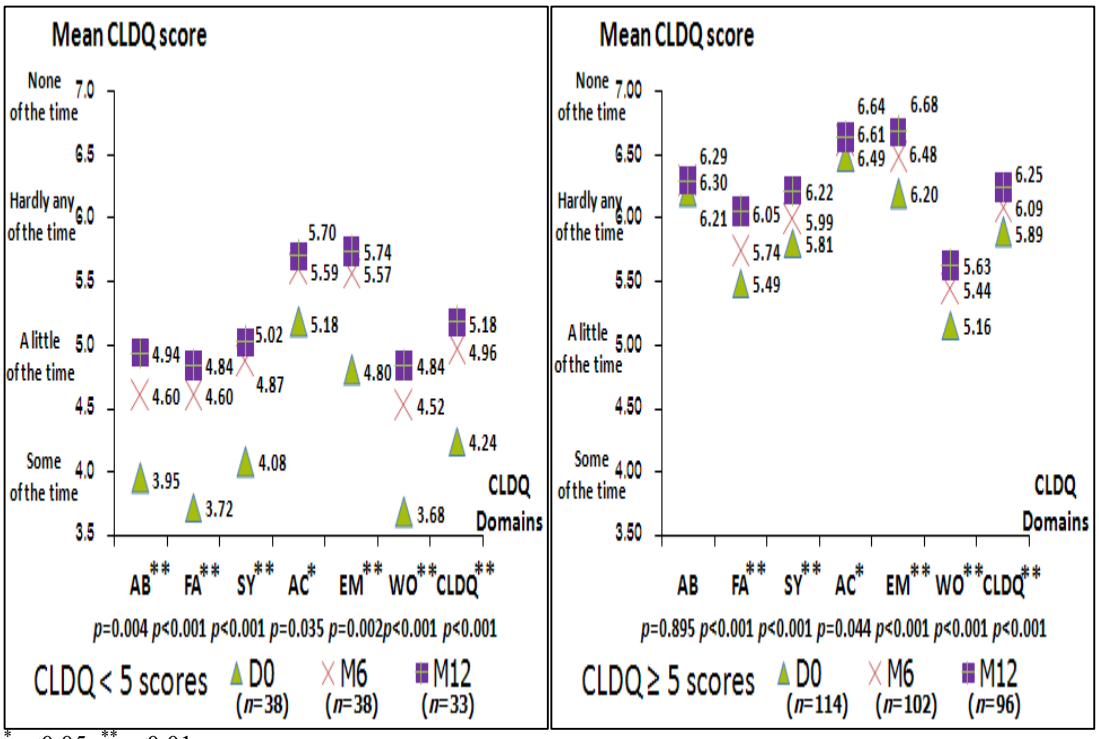
When compared within group of CLDQ < 5 scores and CLDQ ≥ 5 scores among D0, M6, M12, the mean (SD) scores of all domains significantly increased at M6 and M12 excepted AB domain as shown in Table 5.3 and Figure 5.5. At D0, the three domains with the least mean (SD) scores of CLDQ < 5 scores group were a some of the time score in WO (3.68 (1.01)), FA (3.72 (1.05)), and AB (3.95 (1.54), whereas the three domains with the least mean (SD) scores of CLDQ ≥ 5 scores group were a little of the time score in WO (5.16 (1.08)), FA (5.49 (0.86)), SY (5.81 (0.80)).

Table 5.3 Comparison of CLDQ scores of CLDQ < 5 scores and CLDQ ≥ 5 scores within group among D0, M6, and M12 in each domain

CLDQ	**CLDQ < 5 scores**				
Domains	D0 (*n*=38)	M6 (*n*=38)	M12(*n*=33)	Cochran's Q	*p*
AB	3.95 (1.54)	4.60 (1.70)	4.94 (1.60)	10.98	0.004**
FA	3.72 (1.05)	4.60 (1.43)	4.84 (1.45)	23.04	<0.001**
SY	4.08 (1.12)	4.87 (1.32)	5.02 (1.32)	13.29	<0.001**
AC	5.18 (1.20)	5.59 (1.28)	5.70 (1.45)	6.68	0.035*
EM	4.80 (0.94)	5.57 (1.04)	5.74 (1.15)	12.45	0.002**
WO	3.68 (1.01)	4.52 (1.41)	4.84 (1.30)	19.62	<0.001**
CLDQ	4.24 (0.67)	4.96 (1.02)	5.18 (1.15)	21.40	<0.001**
CLDQ	**CLDQ ≥ 5 scores**				
Domains	D0 (*n*=114)	M6 (*n*=102)	M12 (*n*=96)	Cochran's Q	*p*
AB	6.21 (0.97)	6.29 (0.82)	6.30 (0.92)	0.22	0.895
FA	5.49 (0.86)	5.74 (0.94)	6.05 (0.84)	26.30	<0.001**
SY	5.81 (0.80)	5.99 (0.77)	6.22 (0.75)	21.73	<0.001**
AC	6.49 (0.66)	6.61 (0.58)	6.64 (0.68)	6.24	0.044*
EM	6.20 (0.75)	6.48 (0.74)	6.68 (0.48)	31.40	<0.001**
WO	5.16 (1.08)	5.44 (1.14)	5.63 (0.93)	15.88	<0.001**
CLDQ	5.89 (0.47)	6.09 (0.56)	6.25 (0.54)	32.70	<0.001**

*$p<0.05$, **$p<0.01$

Abbreviations: AB, abdominal symptoms; AC, activity; CLDQ, Chronic Liver Disease Questionnaire; CLDQM, overall CLDQ score; D0, Day zero; EM, emotional function; FA, fatigue; M6, 6th month of follow up; M12, 12th month of follow up; SD, Standard Deviation; SY, systemic symptoms; WO, worry



*p<0.05, **p<0.01

Abbreviations: AB, abdominal symptoms; AC, activity; CLDQ, Chronic Liver Disease Questionnaire; CLDQM, overall CLDQ score; D0, Day zero; EM, emotional function; FA, fatigue; M6, 6th month of follow up; M12, 12th month of follow up; SD, Standard Deviation; SY, systemic symptoms; WO, worry

Figure 5.5 Comparison of CLDQ scores of CLDQ < 5 scores and CLDQ ≥ 5 scores within group among D0, M6, and M12 in each domain

5.1.3.3 Number (%) of patients who had CLDQ score changed to another group of CLDQ < 5 scores and CLDQ ≥ 5 scores groups

The number (%) of patients who had CLDQ score changed to another group at M6 and M12were counted, and their comparing within group among D0, M6, and M12 are shown in Table 5.4. The patients in CLDQ < 5 scores group had percent of patients who CLDQ score changed to CLDQ ≥ 5 scores with extremely significantly increasing from 0.0% at D0 to 44.7% at M6 and 57.6% at M12. In contrast, the patients in CLDQ ≥ 5 scores group had CLDQ score changed to CLDQ < 5 scores with percentage increased from 0.0% at D0 to 3.9% at M6 and 5.2% at M12 where half of these patients had cirrhosis (2 out of 4 patients at M6, 3 out of 5 patients at M12).

Table 5.4 Comparison within group among D0, M6, and M12 of number (%) of patients in CLDQ < 5 scores changed to CLDQ ≥ 5 scores and CLDQ ≥ 5 scores changed to CLDQ < 5 scores

	D0	M6	M12
CLDQ < 5 scores changed to CLDQ ≥ 5 scores	0 (0.0%) (*n*=38)	17 (44.7%) (*n*=38)	19 (57.6%) (*n*=33)
CLDQ ≥ 5 scores changed to CLDQ < 5 scores	0 (0.0%) (*n*=114)	4 (3.9%) (*n*=102)	5 (5.2%) (*n*=96)

Abbreviations: CLDQ, Chronic Liver Disease Questionnaire; D0, Day zero; M6, 6th month of follow up; M12, 12th month of follow up.

5.1.4 Quality of life (QOL) determined by EuroQol-5D (EQ-5D)

As the data on the EQ-5D dimensions is not continuous but ordinal, the percentage of patients reporting moderate or severe health impairments in each EQ-5D dimension were reported. For EQ-5D-VAS, patients rated their health on scale of 0 (worst possible) to 100 (best possible health).

Comparison of number (%) of patients reporting moderate or severe health impairments within group among D0, M6, and M12 in each EQ-5D dimension and median (IQR) of EQ-5D VAS are shown in Table 5.5. At initial D0, the most sequences of EQ-5D dimension patients reporting moderate or severe health impairments were pain/comfort (54.6%), anxiety (51.3%), mobility (13.2%), activity (13.2%), 13.2% and self care (3.9%), respectively. Over time, in anxiety dimension, the percentage of patients reporting moderate or severe health impairments significantly decreased from 51.3% at D0 to 33.6% at M6 and 26.9% at M12 (p< 0.001). On the other hand, in self care dimension, the percent of patients reporting moderate or severe health impairments significantly increased from 3.9% at D0 to 9.3% at M6 and 6.9% at M12 (p= 0.047). Median (IQR) EQ-5D VAS among D0, M6 and M12 were significant differences (M12 80.0 (80.0-90.0) < M6 80.0 (71.1-90.0) < D0 80.0 (70.0-88.7), p< 0.001).

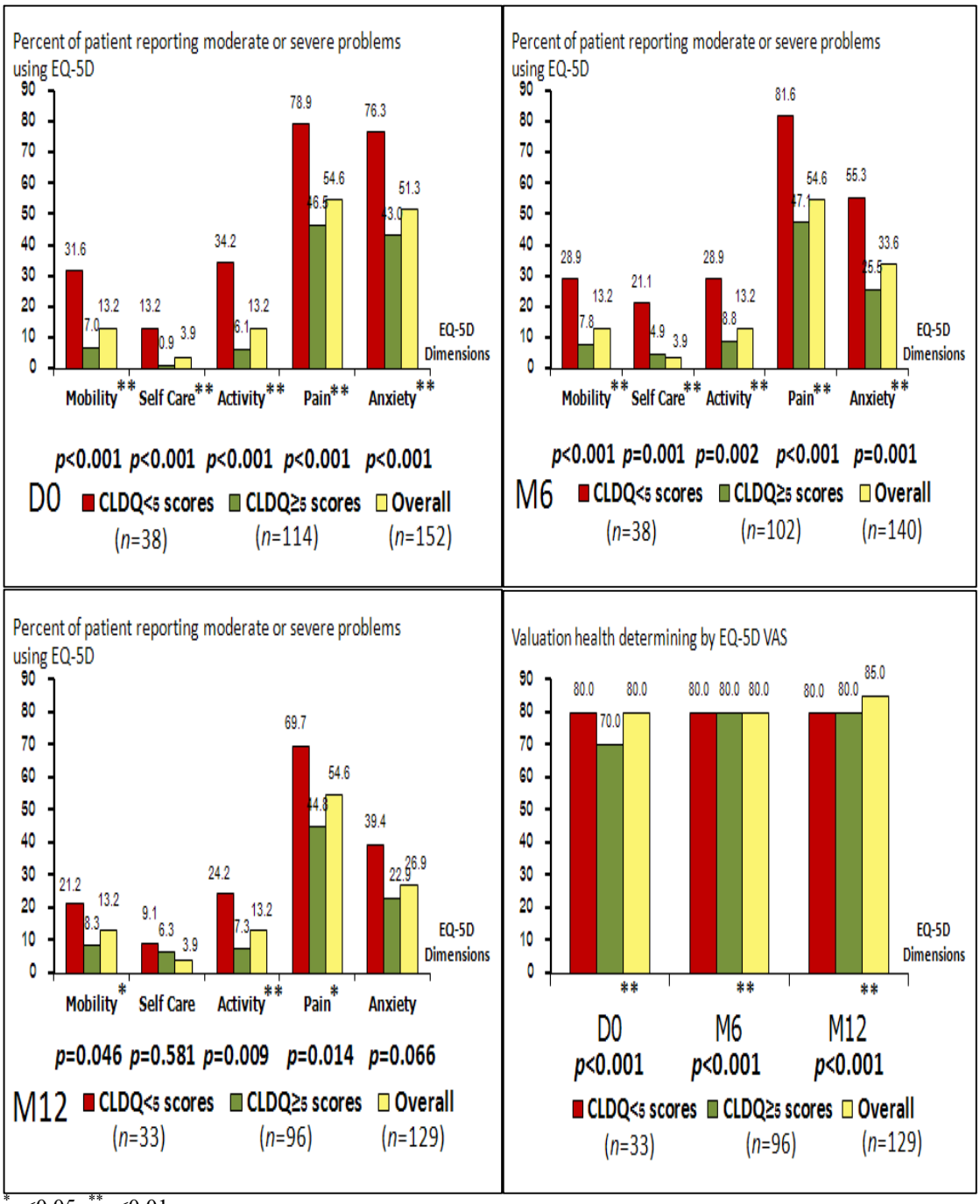
Table 5.5 Number (%) of patient reporting moderate or severe health impairments in each EQ-5D dimension and median (IQR) of EQ-5D VAS at D0, M6, and M12

EQ-5D dimensions	D0 (*n*=152)	M6 (*n*=140)	M12 (*n*=129)	Cochran's Q/ Friedmans'	*p*
Mobility	20 (13.2)	19 (13.6)	12 (11.3)	0.48	0.786
Self care	6 (3.9)	13 (9.3)	9 (6.9)	6.12	0.047*
Activity	20 (13.2)	20 (14.3)	15 (11.5)	0.96	0.619
Pain/comfort	83 (54.6)	79 (56.4)	66 (50.8)	1.39	0.499
Anxiety	78 (51.3)	47 (33.6)	35 (26.9)	16.07	<0.001**
EQ-5D VAS, median (IQR)	80.0 (70.0-88.7)	80.0 (71.1-90.0)	80.0 (80.0-90.0)	15.61	<0.001**

*p<0.05, **p<0.01
Abbreviations: EQ-5D VAS, EuroQol-5D visual analog scale, D0, Day zero; IQR, Interquartile Range; M6, 6th month of follow up; M12, 12th month of follow up.

5.1.4.1 Comparison of number (%) of patients reporting moderate or severe health impairments between CLDQ < 5 scores and CLDQ ≥ 5 scores in each EQ-5D dimension and median (IQR) of EQ-5D VAS at D0, M6, and M12

At D0 and M6, the CLDQ < 5 scores group had of percentage of patients reporting moderate or severe health impairments more than the CLDQ ≥ 5 scores significant differences in all EQ-5D dimension; however, at M12, in self care and anxiety dimensions, percent of patients reporting moderate or severe health impairments between these two groups were not different. For EQ-5D-VAS, the CLDQ < 5 scores group had significant lower median (IQR) scores than the CLDQ ≥ 5 scores group at D0, M6, and M12. Comparison of number (%) of patients reporting moderate or severe health impairments EQ-5D between CLDQ < 5 scores and CLDQ ≥ 5 scores in each EQ-5D dimension and median (IQR) of EQ-5D VAS at D0, M6, and M12 are shown in Figure 5.6.



*p<0.05, **p<0.01

Abbreviations: CLDQ, Chronic Liver Disease Questionnaire; D0, Day zero; EQ-5D VAS, EuroQol-5D visual analog scale; M6, 6th month of follow up; M12, 12th month of follow up.

Figure 5.6 Comparison of number (%) of patients reporting moderate or severe health impairments by using EQ-5D between CLDQ < 5 scores and CLDQ ≥ 5 scores in each EQ-5D dimension and median (IQR) of EQ-5D VAS at D0, M6, and M12

5.1.4.2 Comparison of number (%) of patients reporting moderate or severe health impairments EQ-5D within group among D0, M6, and M12 of CLDQ < 5 scores and CLDQ ≥ 5 scores in each EQ-5D dimension

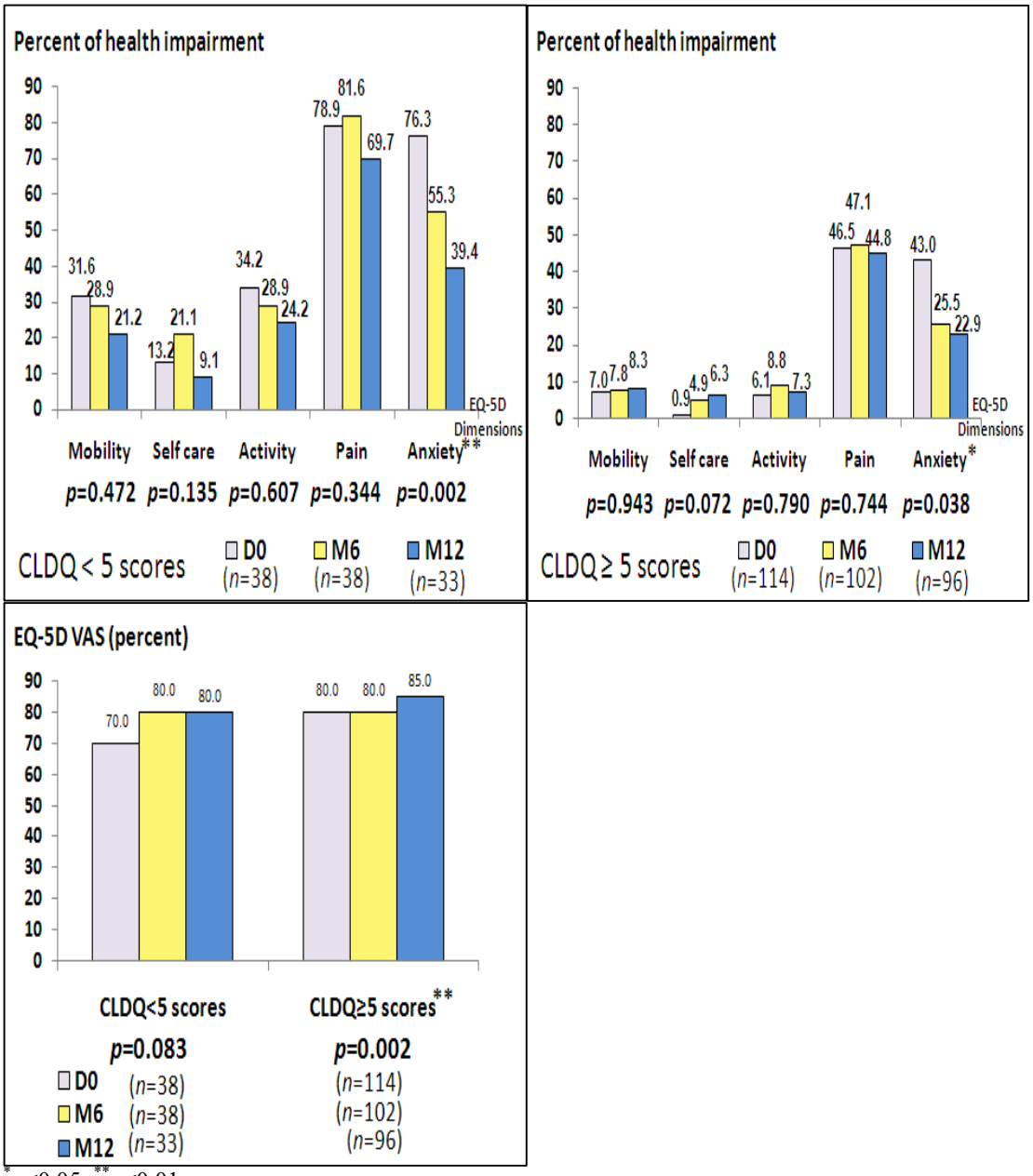
Comparison of number (%) of patients reporting moderate or severe health impairments EQ-5D within group among D0, M6, and M12 of CLDQ < 5 scores and CLDQ ≥ 5 scores in each EQ-5D dimension, in anxiety dimension of both CLDQ < 5 scores and CLDQ ≥ 5 scores groups, number (%) of patients reporting moderate or severe health impairments was significantly greatly decreased from 76.3% at D0 to 55.3% at M6 and 39.4% at M12 in the CLDQ < 5 score group (p=0.002), and from 43.0% at D0 to 25.5% at M6 and 22.9% at M12 in the CLDQ ≥ 5 scores group (p=0.038). For EQ-5D VAS, the CLDQ ≥ 5 scores group had median (IQR) of EQ-5D VAS at M12 more than at M6 and D0 significant differences (M12 85.0 (80.0-90.0)) > M6 80.0 (80.0-90.0) > D0 80.0 (73.7-90.0), p=0.002). Comparison of number (%) of patients reporting moderate or severe health impairments in each EQ-5D dimension within group of CLDQ < 5 scores and CLDQ ≥ 5 scores M12 are shown in Table 5.6 and Figure 5.7.

Table 5.6 Comparison of number (%) of patients reporting moderate or severe health impairments in each EQ-5D dimension within group of CLDQ < 5 scores and CLDQ ≥ 5 scores M12

EQ-5D dimensions	CLDQ < 5 scores				
	D0 (*n*=38)	M6 (*n*=38)	M12 (*n*=33)	Cochran's Q/ Friedmans'	*p*
Mobility, number (%)	12 (31.6)	11 (28.9)	7 (21.2)	1.50	0.472
Self care, number (%)	5 (13.2)	8 (21.1)	3 (9.1)	4.00	0.135
Activity, number (%)	13 (34.2)	11 (28.9)	8 (24.2)	1.00	0.607
Pain/comfort, number (%)	30 (78.9)	31 (81.6)	23 (69.7)	2.13	0.344
Anxiety, number (%)	29 (76.3)	21 (55.3)	13 (39.4)	12.78	0.002**
VAS, median (IQR)	70.0 (70.0-80.0)	80.0 (67.5-80.0)	80.0 (70.0-90.0)	4.98	0.083
EQ-5D dimensions	**CLDQ ≥ 5 scores**				
	D0 (*n*=114)	M6 (*n*=102)	M12 (*n*=96)	Cochran's Q/ Friedmans'	*p*
Mobility, number (%)	8 (7.0)	8 (7.8)	8 (8.3)	0.12	0.943
Self care, number (%)	1 (0.9)	5 (4.9)	6 (6.3)	5.25	0.072
Activity, number (%)	7 (6.1)	9 (8.8)	7 (7.3)	0.47	0.790
Pain/comfort, number (%)	53 (46.5)	48 (47.1)	43 (44.8)	0.59	0.744
Anxiety, number (%)	49 (43.0)	26 (25.5)	22 (22.9)	6.52	0.038*
VAS, median (IQR)	80.0 (73.7-90.0)	80.0 (80.0-90.0)	85.0 (80.0-90.0)	12.59	0.002**

*$p<0.05$, **$p<0.01$

Abbreviations: CLDQ, Chronic Liver Disease Questionnaire; D0, Day zero; EQ-5D VAS, EuroQol-5D visual analog scale, M6, 6th month of follow up; M12, 12th month of follow up.



*p<0.05, **p<0.01

Note: The overall percents were presented.

Abbreviations: CLDQ, Chronic Liver Disease Questionnaire; D0, Day zero; EQ-5D VAS, EuroQol-5D visual analog scale, M6, 6th month of follow up; M12, 12th month of follow up.

Figure 5.7 Comparison of number (%) of patients reporting moderate or severe health impairments in each EQ-5D dimension within group of CLDQ < 5 scores and CLDQ ≥ 5 scores M12

5.1.5 Factors affecting QOL measured by EQ-5D VAS, average CLDQ score (CLDQM)

To determine factors affecting QOL measured by EQ-5D VAS, average CLDQ score (CLDQM), correlations between baseline socio-demographic, clinical characteristics and EQ-5D VAS and CLDQM scores and multiple linear regressions at initial D0 were analyzed.

5.1.5.1Correlations between baseline socio-demographic, clinical characteristics and EQ-5D VAS, CLDQM at D0

The little level correlations between baseline socio-demographic, clinical characteristics and EQ-5D VAS, CLDQM at D0 are shown in Table 5.7.

Table 5.7 Correlations between baseline socio-demographic, clinical characteristics and EQ-5D VAS, CLDQ at D0

Parameters	*r*, *p*	
	EQ-5D VAS	CLDQ
Baseline socio-demographic		
Age (*n*=152)	-0.147, 0.070	-0.231, 0.004**
Male gender (*n*=152)	-0.033, 0.683	0.066, 0.422
Married status (*n*=152)	-0.093, 0.255	-0.023, 0.774
Undergraduate (*n*=152)	0.055, 0.502	0.199, 0.014*
Employee (*n*=152)	0.043, 0.601	0.043, 0.595
Salary (*n*=152)	0.026, 0.746	0.141, 0.083
Had health security (*n*=152)	-0.022, 0.790	-0.044, 0.593
Had family member as hepatitis B (*n*=152)	0.001, 0.989	0.110, 0.178
Had presence of other diseases except liver disease (*n*=152)	-0.102, 0.212	-0.169, 0.037*
Baseline clinical characteristics		
Months for CHB follow up (*n*=152)	-0.033, 0.689	-0.097, 0.234
Months of treated ARV (*n*=84)	0.126, 0.257	0.063, 0.572
Cirrhosis (*n*=152)	-0.104, 0.204	-0.221, 0.006**
Hepatocellular carcinoma (*n*=152)	-0.026, 0.748	-0.100, 0.222
Human immunodeficiency virus (*n*=152)	-0.034, 0.674	0.085, 0.295
HCV (*n*=152)	-0.171, 0.035*	-0.151, 0.063
DM (*n*=152)	-0.045, 0.581	-0.220, 0.006**
CTP score of cirrhotic		
Class A (*n*=31)	-0.225, 0.223	0.129, 0.489
Class B (*n*=31)	0.112, 0.548	-0.220, 0.235
Class C (*n*=31)	0.240, 0.193	0.122, 0.512
HBeAg-negative (*n*=152)	-0.142, 0.081	-0.150, 0.066
HBV DNA level (*n*=124)	-0.037, 0.680	-0.010, 0.916
ALT (*n*=152)	-0.074, 0.367	-0.091, 0.263
AST (*n*=152)	-0.095, 0.244	-0.015, 0.855
Alkaline phosphates (*n*=149)	-0.016, 0.845	-0.065, 0.433
Alpha-fetoprotein (*n*=136)	-0.011, 0.896	-0.007, 0.938
Total billirubin (*n*=152)	-0.003, 0.971	-0.025, 0.757
Albumin (*n*=152)	0.170, 0.037*	0.172, 0.034*
INR (*n*=152)	0.049, 0.549	-0.114, 0.164
Hematocrit (*n*=152)	-0.042, 0.611	0.100, 0.224

*$p<0.05$, **$p<0.01$

Abbreviations: ALT, aminotransferase; ARV, antiviral therapy for hepatitis B infection; AST, Aspartate aminotransferase; CLDQ, Chronic Liver Disease Questionnaire; EQ-5D VAS, EuroQol-5D visual analog scale; HBeAg, hepatitis B e antigen; HBV-DNA, hepatitis B virus deoxyribonucleic acid; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, International Normalized Ratio; *r*, Spearman's correlation.

5.1.5.2 Multiple linear regressions on QOL measured using EQ-5D VAS, average CLDQ score (CLDQM)

For models with dependent variables such as EQ-5D VAS or CLDQM, the following variables were constants of missing correlations: phase III inactive and cirrhosis that would be deleted from the model. The following variables were also excluded: phase II immune active, phase IV HBsAg clearance, and Child B.

The R-squares of models with dependent variables EQ-5D VAS or CLDQM were 0.88 and 0.95, respectively. Significantly, the variable that positively predicted EQ-5D VAS was health security (B = 75.23 (95% CI 39.29-111.17), p=0.001). Significantly, the variables that negatively predict EQ-5D VAS were phase I immune tolerant (B = -49.50 (95% CI -87.31 to -11.69), p=0.017), and months for CHB follow up < 6 (B = -47.12 (95% CI -75.26 to -18.98), p=0.005).

Significantly, the variables that positively predict CLDQM were health security (B = 2.92 (95% CI 1.25-4.59), p=0.004). Multiple linear regressions on QOL measured using EQ-5D VAS, average CLDQ score (CLDQM) are shown in Table 5.8.

From correlation analysis and multiple linear regressions on QOL using EQ-5D VAS or CLDQM and comparison of baseline socio-demographic and clinical characteristics between CLDQ < 5 scores and CLDQ ≥ 5 scores, the CLDQ < 5 scores group had percentage of cirrhosis patients and median (IQR) age more than the CLDQ ≥ 5 scores group (number of cirrhosis patient (%): 12 (31.6) *vs.* 19 (16.7), p=0.005; age (median (IQR)): 45 (35-54) *vs.* 38 (31-46) year, p=0.013)) together with the CLDQ < 5 scores group had median (IQR) albumin less than the CLDQ ≥ 5 scores group (median (IQR) 4.0 (3.7-4.4) *vs.* 4.3 (4.1-4.5)) g%, p=0.020). Therefore, these differences could effect to the worse QOL score in the CLDQ < 5 scores group.

Table 5.8 Multiple linear regressions on QOL measured by using EQ-5D VAS, average CLDQ score (CLDQM) at D0[a]

Parameters	EQ-5D VAS		CLDQM	
	(B (95%CI))	*p*	(B (95%CI))	*p*
Baseline socio-demographic				
Age>35 years old	10.42 (-11.13-93.90)	0.308	-1.04 (-2.07 to -0.02)	0.047*
Male gender	-5.11 (-19.31-9.09)	0.431	1.06 (0.40-1.72)	0.006**
Married status	-2.10 (-17.52-13.32)	0.761	0.43 (-0.29-1.14)	0.205
Undergraduate	4.03 (-14.52-22.59)	0.630	-0.61 (-0.25-1.47)	0.140
Employee	-2.62 (-15.64-10.39)	0.654	-0.16 (-0.77-0.44)	0.546
Salary <10000 Baht/ month	0.75 (-12.00-13.50)	0.896	0.47 (-0.12-1.06)	0.105
Had health security	75.23 (39.29-111.17)	0.001**	2.92 (1.25-4.59)	0.004**
Had family member as hepatitis B	-10.24 (-35.05-14.57)	0.369	-1.09 (-2.24-0.06)	0.061
Had presence of other diseases except liver disease	-1.45 (-18.10-15.19)	0.845	-0.74 (-1.51-0.03)	0.058
Baseline clinical characteristics				
Treated ARV	-17.81 (-50.43-14.82)	0.244	1.06 (-0.46-2.57)	0.146
Months for CHB follow up > 12	-10.05 (-28.99-8.88)	0.256	-0.86 (-1.73-0.02)	0.055
Months of treated ARV > 12	3.33 (-19.59-26.24)	0.747	-0.32 (-1.38-0.74)	0.507
Months for CHB follow up < 6	-47.12 (-75.26 to -18.98)	0.005**	-1.49 (-2.80 to -0.19)	0.030*
Months for CHB follow up < 12	26.54 (-16.65-67.73)	0.194	1.29 (-0.71-3.30)	0.175
Phase I immune tolerant	-49.50 (-87.31 to -11.69)	0.017*	-0.23 (-1.98-1.52)	0.770
Human immunodeficiency virus	1.41 (-20.56-23.38)	0.886	-0.23 (-1.25-0.79)	0.611
HCV	1.60 (21.17-24.38)	0.875	-1.47 (-2.53 to -0.41)	0.012*
DM	-6.24 (-24.43-11.95)	0.452	-0.34 (-1.18-0.50)	0.381
Child A	16.14 (-23.11-55.39)	0.371	-2.82 (-4.64 to -0.99)	0.007**
Child C	22.23 (-45.11-89.58)	0.468	3.27 (-1.55-2.45)	0.042*
HBeAg-negative	-10.09 (-27.50-7.31)	0.218	-0.48 (-0.33-1.28)	0.211
Constant	16.39 (-61.13-93.90)	0.639	2.20 (-1.75-5.39)	0.195
R-square	0.88		0.95	

*p<0.05, **p<0.01

Abbreviations: ALT, aminotransferase; ARV, antiviral therapy for hepatitis B infection; AST, Aspartate aminotransferase; B, constant; CLDQ, Chronic Liver Disease Questionnaire; EQ-5D VAS, EuroQol-5D visual analog scale; HBeAg, hepatitis B e antigen; HBV-DNA, hepatitis B virus deoxyribonucleic acid; HCV, hepatitis C virus; HIV, human immunodeficiency virus; INR, International Normalized Ratio.

[a] Socio-demographic factors include age more than 35 years old, male gender, married status, graduated, employee, salary less than 10000 baht/ month, had health security, had family member as hepatitis B, had presence of other diseases except liver disease, and clinical characteristic variables include treated ARV, month for CHB follow up more than 12, month of treated ARV more than 12, naïve within 6 months, naïve within 12 months, phase I immune tolerant, phase II immune active, phase II inactive, phase IV HBsAg clearance, cirrhosis, HCC, HIV, HCV, DM, child A, child B, child B, child C, HBeAg-positive were entered as independent variables. All of these

independent variables were entered as dichotomous variables (1 yes, 0 no). The following variables were constant or had missing correlations and were deleted from the analysis: child A, cirrhosis, phase II immune active, phase III inactive, and phase IV HBsAg clearance. EQ-5D VAS (full scores = 100) and CLDQM (full scores = 7) were treated as continuous variables.

5.1.6 Percent impairment while working and activity impairment

The mean (SD) percent impairment while working due to health at D0, M6, and M12 were 8.95 (14.88), 8.50 (17.66), and 7.14 (18.51), respectively. The mean (SD) percent activity impairment due to health at D0, M6, and M12 were 5.39 (12.55), 5.21 (13.86), and 3.49 (11.08), respectively

Comparison of mean (SD) percent impairment while working and activity impairment between CLDQ < 5 scores and CLDQ ≥ 5 scores groups, the CLDQ < 5 scores group had mean (SD) percent activity impairment and impairment while working more than the CLDQ ≥ 5 scores group significant differences (impairment while working due to health (D0, 17.73 (17.28) *vs*. 6.20 (12.96), $p< 0.001$; M6 16.40 (23.80) *vs*. 5.81 (14.21), $p=0.004$; M12, 19.83 (30.64) *vs*. 3.22 (10.10), $p< 0.001$; activity impairment due to health (D0, 10.79 (18.36) *vs*. 3.60 (9.32), $p=0.002$; M6 15.53 (21.27) *vs*. 1.37 (6.60), $p<0.001$; M12, 10.30 (18.45) *vs*. 1.15 (5.40), $p< 0.001$) as shown in Table 5.9 and Figure 5.8.

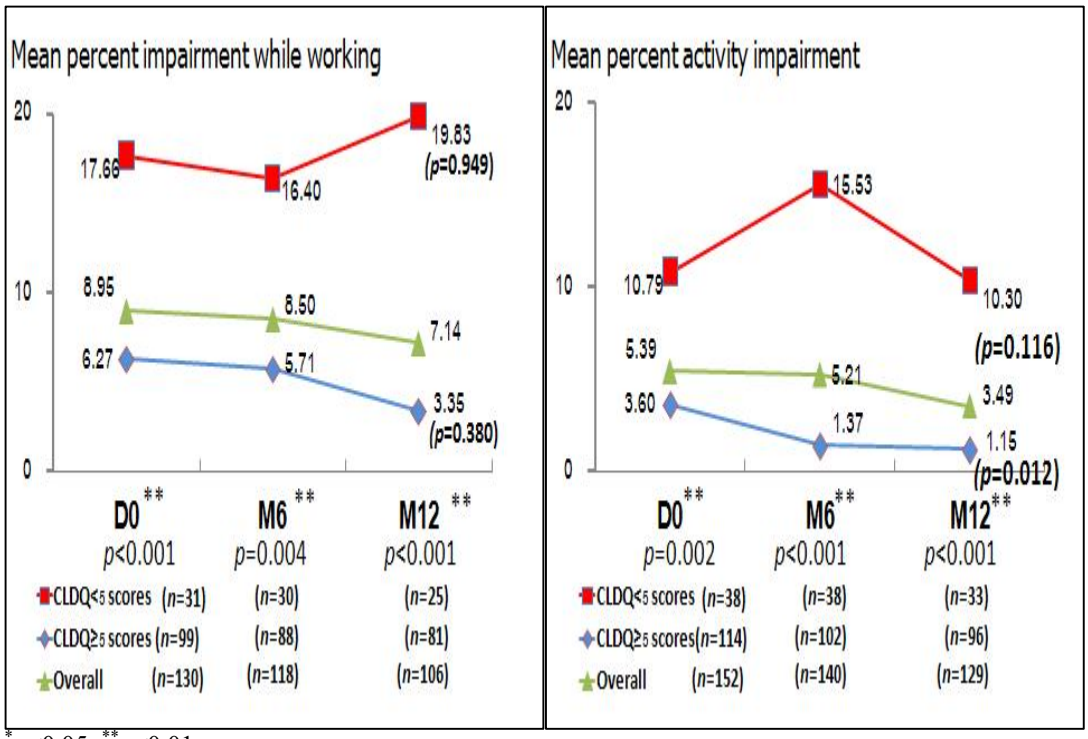
Comparison of within group among D0, M6, and M12 of CLDQ < 5 scores and CLDQ ≥ 5 scores groups, there was no difference of percent impairment while working; however, the CLDQ ≥ 5 scores group had significantly decreased mean (SD) percent activity impairment from 3.60 (9.32) at D0 to 1.37 (6.60) at M6 and 1.15 (5.40) at M12 ($p=0.012$) as shown in Table 5.9 and Figure 5.8.

Table 5.9 Comparison of mean (SD) percent impairment while working and activity impairment between CLDQ < 5 scores and CLDQ ≥ 5 scores groups, and within group among D0, M6, and M12 of CLDQ < 5 scores and CLDQ ≥ 5 scores groups

			Comparison of between group			
		Overall	**CLDQ < 5 scores**	**CLDQ ≥ 5 scores**	***t***	***p***
Mean (SD) percent impairment while working due to health	D0	8.95 (14.88) (*n*=130)	17.73 (17.28) (*n*=31)	6.20 (12.96) (*n*=99)	3.43	0.002**
	M6	8.50 (17.66) (*n*=118)	16.40 (23.80) (*n*=30)	5.81 (14.21) (*n*=88)	10.85	<0.001**
	M12	7.14 (18.51) (*n*=106)	19.83 (30.64) (*n*=25)	3.22 (10.10) (*n*=81)	40.08	<0.001**
Comparison of within group	Cochran's Q	1.20	0.10	1.94		
	p	0.547	0.949	0.380		
Mean (SD) percent activity impairment due to health	D0	5.39 (12.55) (*n*=152)	10.79 (18.36) (*n*=38)	3.60 (9.32) (*n*=114)	27.47	0.002**
	M6	5.21 (13.86) (*n*=140)	15.53 (21.27) (*n*=38)	1.37 (6.60) (*n*=102)	94.97	<0.001**
	M12	3.49 (11.08) (*n*=129)	10.30 (18.45) (*n*=33)	1.15 (5.40) (*n*=96)	72.28	<0.001**
Comparison of within group	Cochran's Q	3.72	4.30	8.86		
	p	0.155	0.116	0.012*		

*$p<0.05$, **$p<0.01$

Abbreviations: CLDQ, Chronic Liver Disease Questionnaire; D0, Day zero; M6, 6th month of follow up; M12, 12th month of follow up.



*p<0.05, **p<0.01
Abbreviations: CLDQ, Chronic Liver Disease Questionnaire; D0, Day zero; M6, 6th month of follow up; M12, 12th month of follow up.

Figure 5.8 Comparison of mean (SD) percent impairment while working and activity impairment between CLDQ < 5 scores and CLDQ ≥ 5 scores groups, and within group among D0, M6, and M12 of CLDQ < 5 scores and CLDQ ≥ 5 scores groups

5.2 Economic burden of CHB patient

The economic burden was assessed in a societal perspective, which consisted of direct medical cost, direct non-medical cost, and indirect medical cost. RSC was included with capital cost. To analyze economic burden correlated to medical burden, comparison of cost between severe medical burden or CLDQ < 5 scores group and mild medical burden or CLDQ ≥ 5 scores group was done.

5.2.1 Total cost

Of 159 patients, 129 (84.9%) patients completed 12 months follow up. Of these, 20 of 129 patients or 15.5% had caregiver expense, and 43 of 129 patients or 33.3% had supplementary expense. For 20 patients who had caregiver expense, 9 cases (45.0%) were CLDQ < 5 scores group and 11 cases (55.0%) were CLDQ ≥ 5 scores group. For 43 patients who had supplementary expense, 30 cases (69.8%) were CLDQ < 5 scores group and 13 cases (30.2%) were CLDQ ≥ 5 scores group.

Mean (SD) and sum total cost comprising direct medical costs, direct non-medical costs and indirect cost per patient per year are shown in Table 5.10. For 129 CHB patients, total cost, direct medical cost, direct non-medical cost and indirect cost from work productivity loss were 5,879,645.20, 4,142,839.80, 585,553.00, and 1,169,252.40 Baht/year, respectively. Mean (SD) of these costs were 45,719.12 (64,647.43), 32,115.04 (54,259.40), 4,539.17 (6,353.99), and 9,063.97 (19,068.75) Baht/patient/year. Direct medical cost, direct non-medical cost and indirect cost accounted for 70.25, 9.93, 19.82 percents of total cost, respectively.

Table 5.10 Mean (SD) and sum total cost, direct medical costs, direct non-medical costs and indirect cost in Thai Baht (*n*=129)

Costs	Mean (SD) (Baht/case/year)	Sum (%)
Total cost	**45,719.12 (64,647.43)**	**5,897,645.20 (100.0)**
- Direct medical cost	32,115.04 (54,259.40)	4,142,839.80 (70.25)
- Direct non-medical cost	4,539.17 (6,353.99)	585,553.00 (9.93)
- Indirect cost	9,063.97 (19,068.75)	1,169,252.40 (19.82)

Total cost, direct non-medical cost, and indirect cost from work productivity lost in Thai Baht between CLDQ < 5 scores and CLDQ ≥ 5 scores are shown in Table 5.11. Mean (SD) total cost of CLDQ < 5 scores and CLDQ ≥ 5 scores groups were 57,494.83 (45,405.94) and 41,671.22 (69,798.64) Baht/patient/year. There was no difference of total cost and direct medical cost between CLDQ < 5 scores and CLDQ ≥ 5 scores. However, the CLDQ < 5 scores group had mean (SD)

direct non-medical cost, and indirect cost from work productivity loss more than the CLDQ ≥ 5 scores group significant differences (direct non-medical cost 7968.54 (9980.18) *vs*. 3992.31 (3992.31) Baht, p=0.004; indirect cost from work productivity loss 17901.60 (24328.96) *vs*. 6026.04 (15940.31) Baht, p=0.002).

Table 5.11 Comparison of mean (SD) total cost, direct non-medical cost, and indirect cost in Thai Baht between CLDQ < 5 scores and CLDQ ≥ 5 scores in Thai Baht

Costs	Overall (*n*=129)	CLDQ < 5 scores (*n*=33)	CLDQ ≥ 5 scores (*n*=96)	*t*	*p*
Total cost	**45,719.12 (64,647.43)**	**57,494.83 (45,405.94)**	**41,671.22 (69,798.64)**	**1.21**	**0.227**
Direct medical cost	32,115.04 (54,259.40)	32,374.77 (34,618.94)	32,060.13 (59,691.35)	0.02	0.984
Direct non-medical cost	4,539.17 (6,353.99)	7,317.29 (8,872.55)	3,584.19 (4,927.28)	3.00	0.003**
Indirect cost	9,063.97 (19,068.75)	17,901.60 (24,328.96)	6,026.04 (15,940.31)	3.19	0.002**

*p<0.05, **p<0.01
Abbreviations: CLDQ, Chronic Liver Disease Questionnaire.

5.2.2 Direct costs

With regard to the subset of direct medical costs and direct non-medical costs, the mean (SD) and sum in Thai Baht are shown in Table 5.12. For direct medical cost, ARV cost, other medication cost excluded ARV, and laboratory cost accounted for 43.35, 22.48, and 16.39%, respectively. Mean (SD) of these costs were 13,921.19 (23,949.18), 7,220.08 (38,133.03), and 5,110.06 (2,964.87) Baht/patient/year. The rest were routine service costs and radiology costs (11.14 and 6.64% , respectively) with mean (SD) 3,578.15 (9,191.76) and 2,071.05 (3,185.44) Baht/patient/year.

For direct non-medical costs, the majority, 43.37 percent, 28.49 percent, and 11.32%were spent on nutritional supplementary expense, productivity loss for hospital care, and productivity loss of caregiver, respectively. Mean (SD) of these

costs were 1,968.74 (5,092.84), 1,293.35 (2,720.68), and 513.75 (1,387.27) Baht/patient/year, respectively. The rest were transport expense, and food expense accounting 10.18% and 6.64%, respectively with mean (SD) 462.14 (441.33) and 301.19 (290.38) Baht/patient/year, respectively. For productivity loss for hospital care, IPD and OPD accounted 28.52 and 2.67.

Table 5.12 Mean (SD) and sum (%) subset of direct medical cost and direct non-medical cost in Thai Baht (*n*=129)

Costs	Mean (SD)	Sum (%)
Direct medical cost	**32,115.04 (54,259.40)**	**4,142,839.80 (100%)**
ARV cost	13,921.19 (23,949.18)	1,795,833.05 (43.35)
Other medication cost excluded ARV	7,220.08 (38,133.03)	931,392.57 (22.48)
Laboratory cost	5,263.36 (3503.81)	678,972.62 (16.39)
Radiology cost	2,133.18 (3,281.00)	275,180.98 (6.64)
Routine service cost	3,578.15 (9,191.76)	461,460.58 (11.14)
- OPD	*1,957.08 (695.60)*	*252,398.37 (6.09)*
- IPD	*1,621.07 (8,844.90)*	*209,062.21 (5.05)*
Direct non-medical care cost	**4,539.17 (6,353.99)**	**585,553.00 (100%)**
Supplementary expense	1,968.74 (5,092.84)	253,968.00 (43.37)
Productivity loss of caregiver	513.75 (1,387.27)	66,274.00 (11.32)
Transport expense	462.14 (441.33)	59,615.70 (10.18)
Food expense	301.19 (290.38)	38,853.17 (6.64)
Productivity loss for hospital care	1,293.35 (2,720.68)	166,842.13 (28.49)
- OPD	*1,172.22 (2,624.44)*	*151,216.80 (25.82)*
- IPD	*121.13 (682.47)*	*15,625.33 (2.67)*

Note: Capital cost was included in routine service cost.
Abbreviations: ARV, antiviral therapy for hepatitis B infection, OPD, out-patient department; IPD, in-patient department.

There was no difference in direct medical cost of the patients with CLDQ < 5 scores and those with CLDQ ≥ 5 scores (Table 5.13). However, the cost of laboratory of the CLDQ < 5 group was significant higher than that of CLDQ ≥ 5 group (6139.5 (3929.64) *vs*. 4756.19 (2479.46) Baht, p=0.020). Similarly, the direct non-medical expense, especially the expense on supplementary expense of these two groups, the CLDQ < 5 group was significantly higher than that of CLDQ ≥ 5 group (3690.91 (6640.09) *vs*. 1376.75 (4325.58) Baht, p=0.024). The greater mean (SD) of other medication excluded ARV in the CLDQ ≥ 5 scores (8146.66 (43852.49)) because one HCC case had other medication cost 395259.60 Baht from rabeprazole

(Pariet), and from 9 cases with other medication cost more than 10000 Baht; 3 cases were cirrhosis/HCC, 2 cases were HIV-HBV co-infections and 4 cases were CHB with gastric ulcer. In detail, the supplementary used were nutrition, vitamin, Ling zhi, tumaric, drumstic tree, and others.

Table 5.13 Mean (SD) subset of direct medical cost and direct non-medical cost in Thai Baht between CLDQ < 5 scores and CLDQ ≥ 5 scores

Costs	Overall (*n*=129)	CLDQ <5 scores (*n*=33)	CLDQ ≥ 5 scores (*n*=96)	*t*	*p*
Direct medical cost	**32,115.04 (54,259.40)**	**32,033.05 (34,531.46)**	**31,853.74 (59,575.66)**	**0.02**	**0.987**
ARV cost	13,921.19 (23,949.18)	15,025.58 (26,390.58)	13,541.55 (23,186.93)	0.31	0.760
Other medication cost excluded ARV	7,220.08 (38,133.03)	4,254.58 (9,869.98)	8,146.66† (43,852.49)	0.47	0.640
Laboratory cost	5,263.36 (3503.81)	6,323.70 (4,047.53)	4,898.87 (2,553.84)	2.35	0.020*
Radiology cost	2,133.18 (3,281.00)	1,975.38 (1,238.35)	2,187.43 (3,738.48)	0.32	0.750
Routine service cost	3,578.15 (9,191.76)	4,426.69 (12,534.26)	3,286.47 (7,783.35)	0.61	0.541
Direct non-medical care cost	**4,539.17 (6,353.99)**	**7,317.29 (8,872.55)**	**3,584.19 (4,927.28)**	**3.00**	**0.003****
Supplementary expense	1,968.74 (5,092.84)	3,690.91 (6,640.09)	1,376.75 (4,325.58)	2.29	0.024**
Caregiver expense	513.75 (1,387.27)	905.42 (1,756.36)	379.11 (1,217.51)	1.89	0.060
Transport expense	462.14 (441.33)	573.13 (502.52)	423.98 (414.26)	1.68	0.094
Food expense	301.19 (290.38)	356.92 (382.52)	282.03 (250.75)	1.28	0.202
Labor cost loss for hospital care	1,293.35 (2,720.68)	1,790.91 (5,039.81)	1,122.31 (1,141.11)	1.22	0.225

*p<0.05, *p<0.01

†There was 1 HCC case with other medication cost 395259.60 Baht, and there were 9 cases cirrhosis/HCC, HIV-HBV co-infections and CHB with gastric ulcer.

Abbreviations: ARV, antiviral therapy for hepatitis B infection; CLDQ, Chronic Liver Disease Questionnaire.

5.2.3 Indirect cost

Indirect cost was assessed in terms of work productivity loss by WPAI consisting of impairment while working and activity impairment due to health. Patients rated their degree of impairment while working from 0 (least score) to 10 (highest score) and applied to percentage.

From percent impairment while working due to health, the labor cost of work productivity loss was calculated from each participant's income multiplied with percent impairment while working divided one hundred. The estimated annual labor cost of work productivity loss each case per year was computed from percent impairment while working each case at the first 6 months and the second 6 months multiplied income per month and multiplied by six.

5.2.3.1 Labor cost of work productivity loss within group among D0, M6, and M12, and mean (SD) annual labor cost of work productivity loss

The mean (SD) labor cost of impairment while working each case at D0, M6, and M12 were 2,110.85 (7,560.71), 1,265.55 (2,718.48), and 664.59 (1,552.42) Baht/month, and there was no difference. The mean (SD) annual labor cost of work productivity loss was 17,058.66 (47,639.18) Baht/patient/year. Comparison mean (SD) labor cost of work productivity loss within group among D0, M6, and M12, and mean (SD) annual labor cost of work productivity loss are shown in Table 5.14.

Table 5.14 Comparison mean (SD) labor cost of work productivity loss within group among D0, M6, and M12, and mean (SD) annual labor cost of work productivity loss

Labor cost of work productivity loss	D0	M6	M12	*t*	*p*
Labor cost of work productivity loss each case per month	2,110.85 (7,560.71) (*n*=109)	1,265.55 (2,718.48) (*n*=108)	664.59 (1,552.42) (*n*=106)	4.07	0.131
Annual labor cost of work productivity loss each case (Baht/patient/year) (*n*=109)	17,058.66 (47,639.18)				
First 6 months	10,701.50 (41,923.09) (*n*=109)				
Second 6 months	6,357.16 (15,176.16) (*n*=108)				

Abbreviations: D0, Day zero; M6, 6th month of follow up; M12, 12th month of follow up.

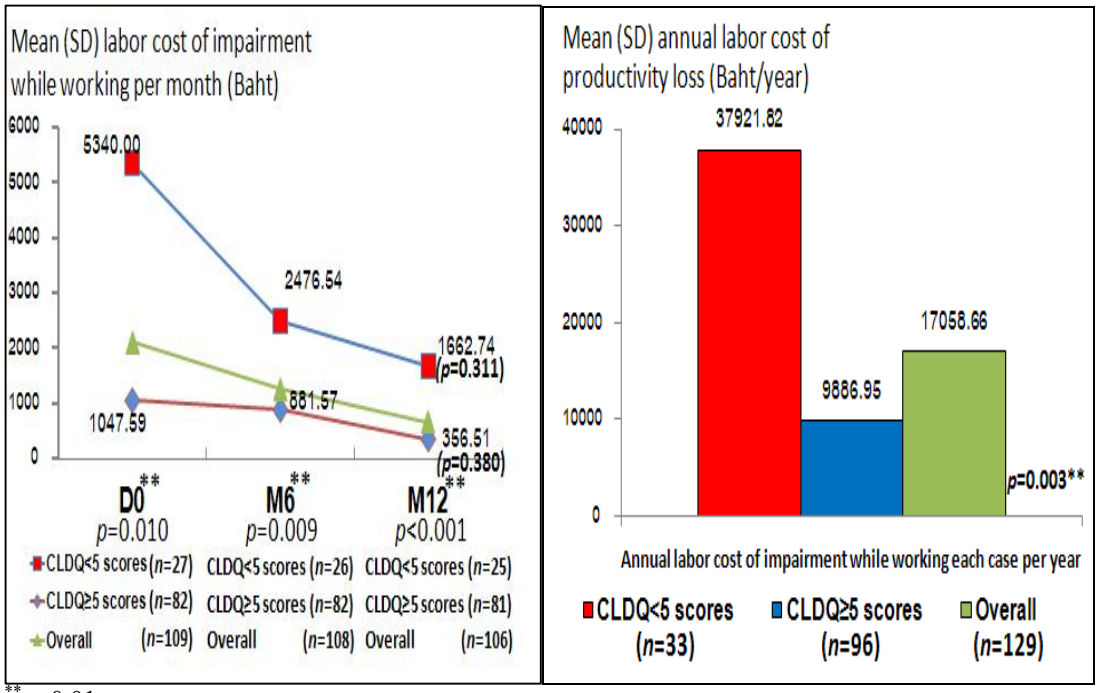
Comparison of mean (SD) labor cost of work productivity loss between CLDQ < 5 scores and CLDQ ≥ 5 scores groups showed that CLDQ < 5 scores had mean (SD) labor cost of work productivity loss at D0, M6, and M12 more than the CLDQ ≥ 5 scores significant differences (D0, 5340.0 (13268.40) *vs*. 1047.59 (3884.44), p=0.010; M6, 2746.54 (3034.26) *vs*. 881.57 (2510.12), p=0.009; M12, 1662.74 (2221.96) *vs*. 356.51 (1128.97) Baht/month, p<0.001). Also, the CLDQ < 5 scores had the mean (SD) of annual labor cost of work productivity loss more than the CLDQ ≥ 5 scores significant difference (37921.82 (75327.09) vs. 9886.95 (30714.28) Baht/month, p=0.003). Comparison of mean (SD) labor cost of work productivity loss between CLDQ < 5 scores and CLDQ ≥ 5 scores are shown in Table 5.15 and Figure 5.9.

Table 5.15 Comparison of mean (SD) labor cost of work productivity loss between CLDQ < 5 scores and CLDQ ≥ 5 scores

Labor cost of impairment while working (Baht/patient/month)	**Overall**	**Comparison of between group**			
		CLDQ < 5 scores	**CLDQ ≥ 5 scores**	***t***	***p***
D0	2,110.85 (7,560.71) (*n*=109)	5,340.00 (13,268.40) (*n*=27)	1,047.59 (3884.44) (*n*=82)	2.63	0.010**
M6	1,265.55 (2,718.48) (*n*=108)	2746.54 (3,034.26) (*n*=26)	881.57 (2,510.12) (*n*=82)	2.68	0.009**
M12	664.59 (1,552.42) (*n*=106)	1662.74 (2,221.96) (*n*=25)	356.51 (1,128.97) (*n*=81)	3.92	<0.001**
Comparison of within group: χ^2	4.07	2.33	1.94		
p	0.131	0.311	0.380		
Annual (Baht/patient/year)	**17,058.66 (47,639.18) (*n*=129)**	**37,921.82 (75,327.09) (*n*=33)**	**9,886.95 (30,714.28) (*n*=96)**	**3.01**	**0.003****
First 6 months	10,701.50 (41,923.09) (*n*=129)	26,214.54 (72,848.89) (*n*=33)	5,368.89 (21,636.11) (*n*=96)	2.51	0.013*
Second 6 months	6,357.16 (15,176.16) (*n*=129)	11,707.27 (17,233.49) (*n*=33)	4,518.06 (14,032.81) (*n*=96)	2.39	0.018*

** p<0.01

Abbreviations: CLDQ, Chronic Liver Disease Questionnaire; D0, Day zero; M6, 6th month of follow up; M12, 12th month of follow up



** $p<0.01$

Abbreviations: CLDQ, Chronic Liver Disease Questionnaire; D0, Day zero; M6, 6th month of follow up; M12, 12th month of follow up; SD, Standard deviation.

Figure 5.9 Comparison of mean (SD) labor cost of impairment while working between CLDQ < 5 scores and CLDQ ≥ 5 scores and within group of CLDQ < 5 scores and CLDQ ≥ 5 scores among D0, M6, and M12

5.2.3.2 Productivity loss of CLDQ < 5 scores with and without ARV

To analyze the effects of ARV treatment on decreasing productivity loss, the case series of CLDQ< 5 score with and without ARV were done. The details of each case including age and CHB disease stages were compared. CHB diseases stages include CHB carrier, uncomplicated CHB, impaired LF, cirrhosis, and HCC those were classified from clinical characteristics at D0. There was no difference of age between the two groups. Majority of patients in CLDQ< 5 score group without ARV were HBsAg carrier (35.7%) and uncomplicated CHB (57.1%) while the patient with ARV were cirrhosis (52.9%), impaired liver function (23.5%) and uncomplicated CHB (23.5%).

Table 5.16 Comparison of mean (SD) age and number (%) of patient classified in CHB disease stage of CLDQ< 5 score group who worked with and without ARV (*n*=31)

Age/ CHB disease stage	Overall	CLDQ< 5 score group		t/χ^2	*p*
		Without ARV (*n*=14)	With ARV (*n*=17)		
Age, year	41.5 (9.6)	39.2 (9.8)	43.6 (9.2)	1.40	0.172
CHB disease stage					
HBsAg carrier	5 (16.1)	5 (35.7)	0 (0.0)	7.24	0.007**
Uncomplicated CHB	12 (38.7)	8 (57.1)	4 (23.5)	3.66	0.056
Impaired liver function	5 (16.1)	1 (7.2)	4 (23.5)	1.52	0.217
Cirrhosis/HCC	9 (29.0)	0 (0.0)	9 (53.0)	10.44	0.001**

** $p<0.01$
Abbreviation: ARV, antiviral therapy for hepatitis B infection, HCC, hepatocellular carcinoma

The case series of productivity loss in CLDQ< 5 score with ARV who worked are shown in Table 5.18. From the case series in the CLDQ< 5 score with ARV group, 9 of 17 cases were cirrhosis and HCC. Of these, two cases could not work, one case was lost to follow up, and one case died. In the CLDQ< 5 score without ARV group, most of the patients were HBsAg carrier and uncomplicated CHB.

Table 5.17 Cases series of productivity loss in CLDQ< 5 score with and without ARV who worked (*n*=31)

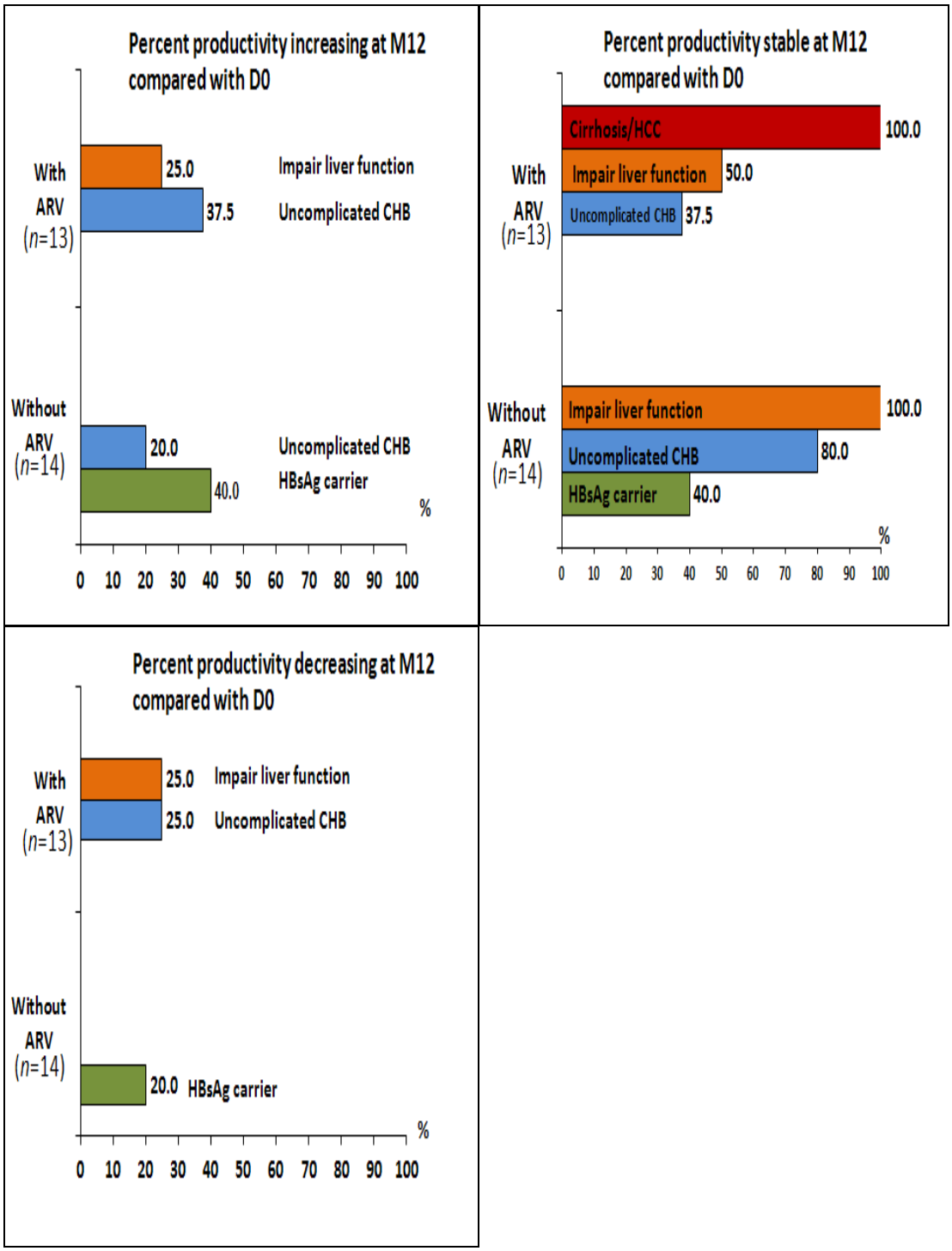
No	Age	CHB stage and other disease	Impairment while working (%)		
			D0	M6	M12
CLDQ< 5 score with ARV (*n*=17)					
1	54	HCC	20.0	90.0	20.0
2	50	HCC	30.0	50.0	Not work
3	51	Cirrhosis	20.0	20.0	20.0
4	51	Cirrhosis	0.0	20.0	Death
5	40	Uncomplicated CHB	20.0	0.0	Loss FU
6	32	Impaired LF	0.0	0.0	0.0
7	33	Uncomplicated CHB	20.0	20.0	20.0
8	62	Cirrhosis	20.0	Not work	Not work
9	37	Impaired LF, DM	0.0	20.0	0.0
10	38	Uncomplicated CHB	20.0	20.0	20.0
11	35	Uncomplicated CHB	0.0	0.0	0.0
12	32	Impaired LF	30.0	20.0	0.0
13	48	Impaired LF	70.0	80.0	60.0
14	49	Uncomplicated CHB	30.0	30.0	0.0
15	54	Cirrhosis	20.0	0.0	0.0
16	37	Uncomplicated CHB, HIV	0.0	0.0	0.0
17	39	Cirrhosis	20.0	10.0	20.0
CLDQ< 5 score without ARV (*n*=14)					
1	34	HBsAg carrier	50.0	40.0	30.0
2	33	HBsAg carrier	40.0	20.0	0.0
3	39	Uncomplicated CHB	0.0	0.0	0.0
4	38	HBsAg carrier	20.0	30.0	60.0
5	35	Uncomplicated CHB	40.0	0.0	0.0
6	48	Uncomplicated CHB, DM	0.0	0.0	0.0
7	49	Uncomplicated CHB	20.0	0.0	0.0
8	32	HBsAg carrier	0.0	0.0	0.0
9	43	Uncomplicated CHB	30.0	10.0	10.0
10	27	Uncomplicated CHB	0.0	0.0	0.0
11	37	Impaired LF	0.0	0.0	0.0
12	22	HBsAg carrier	0.0	0.0	0.0
13	59	Uncomplicated CHB, Gout	20.0	0.0	80.0
14	48	Uncomplicated CHB	20.0	40.0	30.0

Abbreviations: ARV, antiviral therapy for hepatitis B infection, CLDQ, Chronic Liver Disease Questionnaire; D0, Day zero; HCC, hepatocellular carcinoma, M6, 6th month of follow up; M12, 12th month of follow up.

Because two cases could not work, one case was lost to follow up, and one case died at M12, the number of patients in CLDQ< 5 score group with ARV remained at 13 cases.

To determine effects of ARV on decreasing productivity loss, the percent impairment while working at M12 were compared with D0, those results were categorized into percent of patient with increasing productivity, stable, and decreasing. In patient with ARV, cirrhosis and HCC tended to have work loss and died after a while. Of 7 cases, two cases could not work, one case was lost to follow up, and one case died; the rest 3 cases had productivity stable at 100%. Impaired liver function had increasing productivity, stable and decreasing at 25.0%, 50.0% and 25.0%, respectively. Uncomplicated CHB had productivity increasing, stable and decreasing at 37.5%, 37.5% and 25.0%, respectively.

Without ARV, impaired liver function had productivity loss stable at 100.0%. Uncomplicated CHB had productivity loss increasing and stable at 20.0% and 80.0%, respectively. HBsAg carrier had productivity loss increasing, stable, and decreasing at 40.0%, 40.0%, and 20.0%, respectively. Although this study has small sample size, the findings showed benefit of ARV treatment on productivity loss.



Abbreviation: ARV, antiviral therapy for hepatitis B infection, HCC, hepatocellular carcinoma

Figure 5.10 Results of productivity loss of patients with and without ARV of CHB disease stages

5.2.3.3 Costs of CHB with ARV, without ARV, and with cirrhosis/HCC

The mean (SD) total cost among CHB with ARV, without ARV, and with cirrhosis/HCC patients were significantly different (p<0.001), CHB with cirrhosis/HCC had the highest total cost in Baht/patient/year with 81,237.41 (119,037.17), the subsequent were CHB with ARV (54,459.51 (37,392.01), and CHB without ARV (18,872.70 (21,080.42)), respectively.

Table 5.18 Mean (SD) of costs in Thai of CHB with ARV, CHB without ARV, and cirrhosis/HCC

Costs	Overall (n=129)	CHB without ARV (n=52)	CHB with ARV (n=50)	Cirrhosis/ HCC (n=27)	p
Total cost	**45,719.12 (64,647.43)**	**18,872.70 (21,080.42)**	**54,459.51 (37,392.01)**	**81,237.41 (119,037.17)**	**<0.001****
Direct medical cost	**32,115.04 (54,259.40)**	**7,793.06 (6,535.85)**	**41,927.22 (33,716.15)**	**60,786.65 (100,228.83)**	**<0.001****
ARV cost	13,921.19 (23,949.18)	557.59 (4,006.06)	26,944.17 (27,727.66)	15,541.85 (25,636.50)	<0.001**
Other medication cost excluded ARV	7,220.08 (38,133.03)	937.25 (2,947.64)	3,798.46 (8,246.34)	25,656.68 (80,988.51)	0.016*
Laboratory cost	5,263.36 (3503.81)	3,081.48 (2,072.00)	6,140.28 (2,478.88)	7,841.58 (2,829.59)	<0.001**
Radiology cost	2,133.18 (3,281.00)	1,340.31 (524.54)	2,064.76 (2,778.40)	3,786.93 (5,813.99)	0.006**
Routine service cost	3,578.15 (9,191.76)	1,876.90 (1,199.69)	2,980.33 (7,156.76)	7,961.71 (17,034.12)	0.016**
Direct non-medical care cost	**4,539.17 (6,353.99)**	**3,208.78 (4,506.13)**	**4,104.43 (4,517.63)**	**7,906.47 (10,236.67)**	**0.006****
Supplementary expense	1,968.74 (5,092.84)	1,322.31 (3,929.07)	1,862.40 (4,481.62)	3,410.67 (7,519.27)	0.222
Caregiver expense	513.75 (1,387.27)	490.58 (1,411.91)	189.04 (774.68)	1159.70 (1,948.35)	0.012*
Transport expense	462.14 (441.33)	351.61 (337.32)	488.43 (395.18)	626.30 (622.59)	0.026*
Food expense	301.19 (290.38)	273.62 (282.28)	302.17 (315.48)	352.47 (258.94)	0.523
Labor cost loss for hospital care	1,293.35 (2,720.68)	770.66 (597.17)	1,262.40 (1,179.81)	2,357.33 (5,603.08)	0.047*
Indirect cost	9,063.97 (19,068.75)	7,870.38 (18,261.26)	8,427.07 (18,066.88)	12,542.18 (22,464.21)	0.564

*p<0.05, **p<0.01

Abbreviation: ARV, antiviral therapy for hepatitis B infection, HCC, hepatocellular carcinoma

5.3 Outcomes of CHB patient at one-year follow up

The outcomes of CHB patient at one-year follow up include doing well, death, lost to follow up, good adherence of treated ARV, had ARV resistant of treated ARV, HBV DNA < 2000 IU/ml, ALT < 35 U/l, and AST < 40 U/l. Overall, 84.9 % were doing well. Death rate and lost to follow up were 2.0% and 13.2%, respectively. Patient who treated ARV had high percent good adherence (95.2%), and had ARV resistant at 8.3%. For liver biomarker, 87.4% had HBV DNA level less than 2000 IU/ml, 84.9% had ALT less than 35 U/l, and 80.3% had AST less than 40 U/l.

Number (%) of the one-year follows up results between CLDQ < 5 scores and CLDQ ≥ 5 scores are shown in Table 5.19. There was no difference between one-year follow up results of the CLDQ < 5 scores and CLDQ ≥ 5 scores.

Table 5.19 Number (%) of the one-year follows up results between CLDQ < 5 scores and CLDQ ≥ 5 scores at D0

Results	Overall (*n*=152)	CLDQ < 5 scores (*n*=38)	CLDQ ≥ 5 scores (*n*=114)	χ^2/Z	*p*
Doing well	129 (84.9)	33 (86.8)	82 (89.1)	0.15	0.695
Death	3 (2.0)	1 (2.6)	2 (1.8)	0.11	0.736
Lost to follow up	20 (13.2)	4 (10.5)	16 (14.0)	0.31	0.579
Had good adherence of treated ARV	80 (95.2)	23 (95.8)	57 (95.0)	0.03	0.871
Had ARV resistant of treated ARV	7 (8.3)	0 (0.0)	7 (11.7)	3.05	0.081
HBV DNA level < 2000 IU/ml	104 (87.4)	28 (87.5)	76 (87.4)	0.00	0.983
ALT < 35 U/l	129 (84.9)	31 (81.6)	98 (86.0)	0.43	0.514
AST < 40 U/l	122 (80.3)	29 (76.3)	93 (81.6)	0.50	0.480

$^{**}p<0.01$

Abbreviations: ARV antiviral therapy; CLDQ, Chronic Liver Disease Questionnaire; HBV-DNA, hepatitis B virus deoxyribonucleic acid; ALT, aminotransferase; AST, Aspartate aminotransferase.

CHAPTER VI
DISCUSSION

6.1 Baseline socio-demographic and clinical characteristics of CHB patients

In this study, more than half were male (83 of 152 or 54.6%). This was not congruent with previous studies in Thailand and other countries that most of CHB patients were male with a 3:1 male to female ratio among blood donors (Luksamijarulkul, Thammata & Tiloklurs, 2002). In Bangladesh, male CHB was 89.4% (Alam *et al*, 2008), 78.5% in Pakistan (Khan *et al*, 2011), and more than 65.0% in Europe (Berg, *et al*, 2010). However, a nationwide cross-sectional study reported that 45.0% of CHB patients from South East-Asia were male (Fischer *et al*, 2012). The high percentage of female participants in this study may be due to the finding that 15.3% of them were HBsAg-positive at antenatal care and blood donation service unit. The high proportion of females may have an effect to the lesser QOL score of CHB patients in this study because previous studies revealed that females have lower QOL scores than males from worry about their illness (Sobhonslidsuk *et al*, 2006; Gutteling *et al*, 2007; Awan *et al*, 2011), and males showed a better CLDQ score than females (Heidarzadeh *et al* (2007).

In this study, patients with less severity had 10.5% lost follow up during the first 6 months while patients with more severity had 13.1% lost follow up during the second 6 months. In detail, patients with less severity were referred from antenatal care, health check up, and blood donation service to check liver function test without any illness, and most of them had normal laboratory test, so they might not be aware to maintain a regular monitoring or continue hospital care and loss follow up at the first 6 month. For patients with greater severity, it might be that they get better after 6 months without having knowledge and awareness of regular monitoring. It was stressed that one of the most dangerous aspects of the HBV virus is that most people do not realize they have been infected (Wongpaitoon, 2008), and more than 90% of

infected patients were unknown risk factors (McBrien, 2013). There are few symptoms at the time of infection and so patients do not seek medical treatment; the disease continues to progress, and they can spread the virus to others (Wongpaitoon, 2008; McBrien, 2013). Therefore, it should be considered that there must have been those with poorer status who did not know their HBV status, and never received investigations. In addition, during the study, some patients informed that their co-workers have known their HBsAg positive but not recognized from laboratory examinations. Therefore, health promotions for regular monitoring are needed for these patients.

6.2 Medical burden of CHB patient

This is the first study that assessed both EQ-5D and CLDQ at the same time in general practice setting that could visibly reflect physical and psychological burden in CHB patient at over time. With different approaches, EQ-5D is a generic approach whereas CLDQ is a liver disease specific measure. The previous study recommended both disease-specific and generic measures for evaluation of the effect of CHB infection and its treatment on QOL (Lam *et al*, 2009). EQ-5D was found to be generally simpler to use (Theofilou, 2013), preferred for use in the Thai study (Tongsiri, 2009; Kittikraisak *et al*, 2009), and allowed the comparison of CHB patients' health impairments with the variety of populations (Szende & William, 2004). However, it has been criticized as less sensitive than disease-specific measurements resulting in possible overestimation of patients' QQL (Kittikraisak *et al* (2009). CLDQ can determine a comprehensive understanding of some important health impairments specifically among liver disease stages of CHB (Lam *et al*, 2009; Sobhonslidsuk *et al*, 2006). EQ-5D is appropriate for use in the Thai study (Tongsiri, 2009), and CLDQ has discriminant validity for Thai CHB patient. In this study, CLDQ could determine the difference of health related to liver disease between patients with low and high CLDQ scores that advantage for clinical solving. To some extent, both measures may have captured different aspects of health, thus different results may be obtained from the same item. In fact, the findings showed that anxiety or worry did not narrate with any symptoms because these aspects were based on patients' perception

of health and feelings. Data obtained from EQ-5D benefits for cost effectiveness analysis of CHB management in the future. Also, data gained from CLDQ revealed specific liver complications of CHB patients that are useful for general practice setting.

The overall CLDQ scores had significant increase in all domains except abdominal domain. The low CLDQ score group had the lowest score with significant increase over time in this domain which may relate to the patients' physical illness whereas the high CLDQ score group had high score without difference. Because the number of sample in the low score group was less than the high CLDQ score group (38 cases vs. 114 cases), there was no difference of the overall score in abdominal domain at over time.

There are several possible explanations for the high CLDQ score in this study. First, it was assessed from an OPD patient in a rural hospital who might be less severe than in-patient in a secondary and tertiary care setting. Second, some patients in this study were referred for liver function test and were asymptomatic. Third, 55.3% of samples were ARV treated for nearly 2 years and so, the patient's condition was stable. Fourth, 92.8% had health security, which strongly affected positive QOL scores. However, this result showed that CHB patients who received regular monitoring and clinical care could result to better QOL.

Regarding the rest, nearly 10% of patients in this study did not have health security and payment was by cash. It was explained that the study hospital context is a hospital under the Thai Red Cross Society, which provided universal coverage health care to minority of people in its location from the governments' policy. Therefore, some patients who intended to receive health service had to pay for themselves. This situation indicated the limitation of the universal coverage program.

The mean (SD) CLDQ scores assessed in this study was quite high and should be careful when using in general. The high CLDQ score represents less severity of liver disease. They were higher than those reported in the study by Sobhonslidsuk *et al* (2004), lower than those reported in the study by Zhou *et al*, 2013, and almost all dimensions were similar to the study by Lam *et al* (2009) except worry domain which this study had the lowest score as shown in Figure 6.1. One reason for the worse CLDQ score might relate to the high proportion of cirrhosis patients in the sample.

The patients in this study had lower proportion of cirrhosis patient (20.4%) than the study by Sobhonslidsuk *et al* (2004) which half (51.0%) of samples were cirrhosis. Nonetheless, this study had higher proportion of cirrhosis patient compared to the study by Zhou *et al*, 2013 where patients were CHB without cirrhosis. Alternatively, the study by Lam *et al* (2009) did not includ cirrhosis and HCC patients in uncomplicated CHB group. However, it was reported that disease perceptions and treatment attitudes of CHB patients differ between ethnic groups (Hann *et al*, 2008).

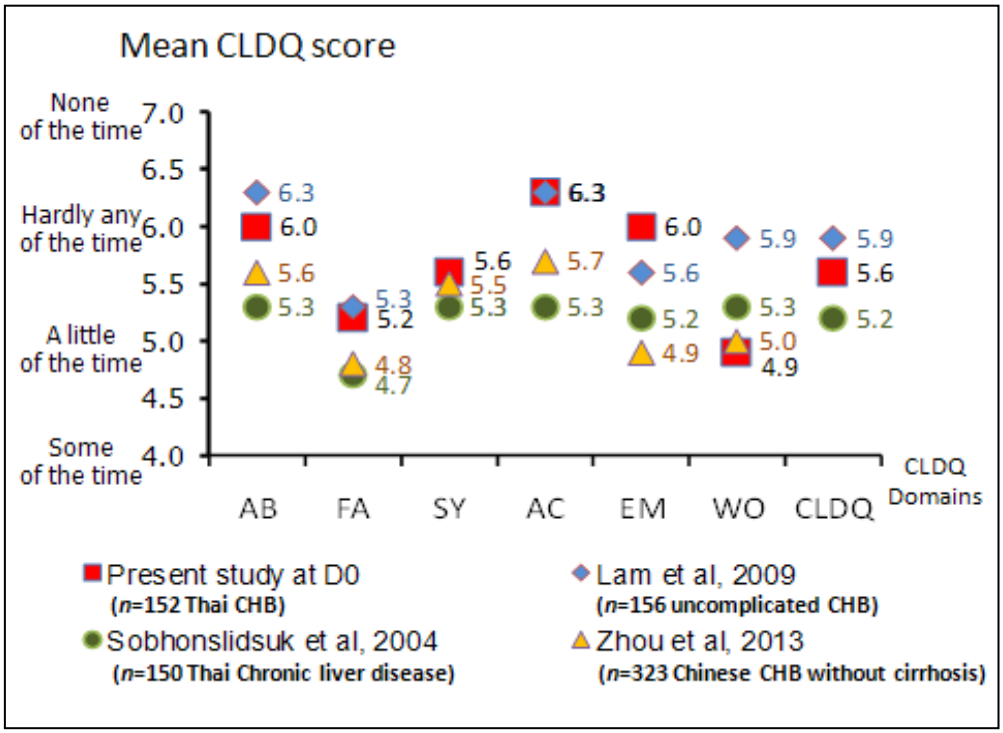


Figure 6.1 Comparison of mean CLDQ score of the present study with other previous studies

CHB patients had health impairments reporting by EQ-5D more than normal population. At initial D0, the most sequences of EQ-5D dimension patients reporting moderate or severe health impairments were pain/discomfort (54.6%), anxiety (51.3%), mobility (13.2%), activity (13.2%), and self care (3.9%), respectively. Because the median (IQR) age of patients in this study overlapped between the period 18-39 years and 40-59 years of the population norm studied by the EuroQol groups (2004), it is difficult to compare the differences of percentage in

health impairments between the studies. However, the percentage of patients reporting health impairments in pain/comfort and anxiety in this study were higher than the population norm in both period (Table 6.1). Previous studies reported that CHB patients had significantly lower QOL scores than the population norm by Short Form 36 (SF-36) (Lam *et al*, 2009; Wu *et al*, 2009), and World Health Organization Quality of Life BREF Questionnaire (WHOQOL-BREF) (Wei *et al*, (2009). However, two studies reported that CHB patients had scores similar to the normal population measured by SF-36 (Bondini *et al*, 2007; Ong *et al*, 2008). In this study, the EQ-5D VAS of CHB patients was not less than the population norm; the CHB patients with stable condition usually rated their health at 80%. In conclusion, this study supported that CHB patients had health impairments reporting by EQ-5D more than population norm.

Compared with other studies, the percentage of CHB patients in this study reporting moderate or severe health impairments in each EQ-5D dimension in this study was lower than the study in Pakistani CHB patients by Ul Haq *et al* (2012), and in Thai tuberculosis patient by Kittikraisak *et al* (2009), but higher than the study in Chinese CHB patients by Ong *et al*, (2008). Ul Haq *et al* (2012) studied QOL in tertiary care hospital where patients were more severe than out-patients in a rural hospital of this study. The difference between this study and the study by Kittikraisak *et al* (2009) might be that half of those Thai tuberculosis patients were in the intensive phase and more prone to disutility whereas the patients in this study were CHB patients who were undertreated ARV for 2 years with stable clinical. Although it is difficult to explain the difference of CHB patients from this study and the study by Ong *et al*, (2008), the findings viewed a comparison of health impairments of CHB patients reporting by EQ-5D with the variety of populations with or without disease.

By using CLDQ, this was observed to confirm the discriminant validity of CLDQ that CHB patients with high severity had higher percentage of health impairment using EQ-5D than patients with low severity. The CLDQ < 5 scores group showed that pain and anxiety dimensions were significantly higher than the CLDQ ≥ 5 scores group (Pain/Comfort at D0, 78.9% *vs*. 4.65%; Anxiety/Depression at D0, 76.3% *vs*. 43.0%). When compared with general Thai adults by Tongsiri (2009) (Table 6.1), the CLDQ < 5 scores group revealed that pain and anxiety at D0 was higher than

general Thai adults (Pain/comfort 78.9% *vs*. 65.9%; Anxiety/depression 76.3% *vs*. 47.4%). This finding ensured that using both EQ-5D and CLDQ could be rechecked, and the severe medical burden group had health impairments more than the mild medical burden group, and Thai adults (Tongsiri, 2009).

Table 6.1 Comparison of percent of patients reporting moderate or severe health impairments in each EQ-5D dimension of present and previous studies

Authors, year, samples	Percent of patients reporting moderate or severe health health impairments					EQ-5D VAS (median (IQR/ mean (SD))
	Mobility	Self care	Activity	Pain/ Comfort	Anxiety/ Depression	
This study, 2012, Thai CHB patient with median (IQR) age 39 (32-49) years (*n*=152)	13.2	3.9	13.2	54.6	51.3	80.0 (70.0-88.7)
EuroQol, 2004, 15 Countries, (*n*=29,000)						
- 18-39 years	5.5	2.0	12.5	25.5	22.0	82.0 (81.0-85.0)
- 40-59 years	16.0	4.0	16.0	43.5	31.0	78.0 (73.0-79.0)
- 60+ years	40.0	14.0	32.5	61.0	34.0	68.0 (62.0-72.0)

CHB patients had many physical impairments measured byEQ-5D and CLDQ. More than half of these CHB patients reported some to severe health impairments in pain/comfort (54.6%) using EQ-5D. Fatigue, abdominal symptoms, and systemic symptoms measured by CLDQ are the most common physical health impairments of severe CHB patients that required clinical management. These findings were consistent with several previous studies indicating that fatigue, abdominal symptom were the main physical health impairments of CHB patient (Sobhonslidsuk *et al* (2004); Lam *et al*, (2009); Heidarzadeh *et al*, 2007; Atiq, Gill & Khokhar, 2008; Chen *et al*, 2010; Hann *et al*, 2008; Nokhodian *et al*, 2009; Mahmood, *et al* 2008). Cirrhosis CHB patients often have symptoms or greater severity such as fatigue, anorexia and weight loss (Lam, *et al*, 2009; Zuberi *et al*, 2007). The other systemic complications of these patients were muscle/joint pain (Hann *et al*, 2008; Awan, *et al*, 2011), nausea, prurience, icter, anorexia, and behavioral changes

(Heidarzadeh *et al*, 2007). This information showed that CHB patients need clinical care to relive physical impairments, regular liver function test monitoring and specific counseling program to solve physical illness, and improve QOL.

CHB patients had psychological health impairments that could affect their daily life, work and social role. These patients reported the highest percentage of health problems in anxiety dimension by EQ-5D together with the lowest score in worry and emotional function domains by CLDQ. This was congruent with Lok *et al*, (1985) described that psychosocial and social impact in CHB patients begin from the moment they are pronounced carriers of the virus and directly affect their QOL. Ong *et al* (2008) indicated that the most anxiety/depression quantified by EQ-5D among CHB patients were HCC (50.0%), followed by post–liver transplantation patients (36.3%), decompensated cirrhosis (30.4%), CHB (27.8%), and compensated cirrhosis (23.0%). The other evidences presented that CHB patients felt loss of self esteem, depression (Awan, *et al*, 2011; Zuberi *et al*, 2007), and 30% to 58% of these patients worried a lot (Hann *et al*, 2008). Anxiety in hepatitis B patients might be due to misinformation about this disease, fear and stigma from social shame or poor support of society (Heidarzadeh, *et al*, 2007; Tan *et al*, 2008), concern regarding prognosis and the need for therapy (Ong *et al*, 2008) or illnesses related cirrhosis or HCC (Lam *et al*, 2009). In this study, the high percentage of anxiety dimension assessed by EQ-5D might be due to patients who were newly diagnosed as HBsAg positive from their health check up and antenatal care, and with the high proportion of females as mentioned before. Also, cirrhosis and HCC displayed anxiety for their illness, which was similar in a previous study by Lam *et al*, (2009). In addition, during the contribution of questionnaires; some CHB patients pointed to the cause of anxiety such as positive HBsAg, which might interfere with their career or cause them to lose a job, they were anxious for the worse laboratory/investigation findings, and they felt burden for the family. Therefore, in clinical practice, there is a need for routine administration of QOL in CHB patients, along with health education and counseling programme dealing with the stigma, and coping skills.

Over time, CHB patients with ARV for hepatitis B infection develop increasing QOL. The findings showed that the overall CLDQ score had increased at M6 and M12 except in abdominal domain that may have been due to greater number

of patient with low severity group (114 cases *vs*. 38 cases) with close high scores between D0, M6, and M12 (6.21-6.30 *vs*. 3.95-4.94 scores). However, it was found that patients with high severity by CLDQ had significantly increasing scores and also nearly half of these patients had changed to the low severity group at M6. This may relate to 63.2% of patients with low CLDQ score who were ARV treated compared with 52.6% of patients with high CLDQ score. They were treated for approximately 2 years with a high percent of good adherence at 95.2% that might be expected to improve clinical conditions. As previous studies reported that ARV treatment improved functional areas of QOL (Lavanchy, 2005; Wang *et al*, 2012; Liaw & Chu, 2009) and patients who not receiving ARV had an impaired QOL (Pojoga *et al*, 2004). As well, it was proved that improvement in HBV treatment had most likely reduced non-HCC liver related mortality (Walter *et al*, 2011). Nonetheless, the finding that CHB patients with cirrhosis had CLDQ score dropped down at one-year follow up with more likely to be stable, although almost of them have been preserved. Likewise, early guidelines generally agreed that ARV could be recommended for CHB patients especially those without liver cirrhosis (Choi & Yoo, 2010). In an ideal setting, every CHB patients should receive the most potent treatment to suppress hepatitis B viral replication (Dan, Aung, & Lim, 2008) to prevent or reduce morbidity and mortality associated with cirrhosis (Buti, Brosa & Casado 2009). In addition, when patients obtained treatment from hospital, the other clinical complications had been solved. Therefore, this finding has important implication for recommending liver function test in all CHB patients with early ARV treatment in CHB patient with low severity that might have good clinical response, and could prevent liver cirrhosis, and also benefit for QOL enhancement.

Cirrhosis had high severity of liver disease determined by using CLDQ. This study found that majority of patients with low CLDQ score or high severity was cirrhosis, and patients' emotional function was affected by their physical illness. Although some of CHB with cirrhosis patients were grouped in a mild medical burden at initial D0, by the liver damage of disease per se, these patients presented the worse QOL eventually. The previous study suggested that cirrhosis might be more a stable condition than CHB (Sobhonslidsuk *et al*, 2006) that caused these patients reported a high QOL. Besides, the evidences presented that cirrhosis patients suffer from

complications or greater severity than other CHB-disease stages especially on physical domain area such as ascites, fatigue, anorexia, weight loss (Lam, *et al*, 2009; Zuberi *et al*, 2007), variceal bleeding, and hepatic encephalopathy (van der Plas SM *et al*, 2003). Moreover, previous studies revealed that cirrhosis associated with increasing health care cost should be prevented (Zhiqiang *et al*, 2004; Hu & Chen, 2009; Liang *et al*, 2010; Gagnon *et al*, 2004; Castelo *et al*, 2007; Yang, Kim, Kim, 2004; Li *et al*, 2004). It could be concluded that cirrhosis had severe medical burden, and cause a substantial economic burden (Dan, Aung, & Lim, 2008) that could be prevented. As a suggestion in clinical practice setting, this study verified that cirrhosis has to be closely monitored by QOL and recommended implication for providing a holistic care in CHB cirrhosis patients and caregiver.

CHB-related diseases could result to productivity loss especially in patients with cirrhosis. This is the first study that measured work-related disorders using WPAI in CHB patients that could express productivity loss with monetary value. In this study, the productivity loss rated in patients' perspective was approximately 10%, and could be more if the disease progress to cirrhosis. This may be related to impairment of physical and psychological function. The case series have shown that patients with cirrhosis and HCC had work loss and died at one-year follow up even if these patients were already treated. This finding emphasized prevention of CHB patient from developing cirrhosis.

In another view related to productivity loss measurement, WPAI could explore work-related disorders in this study was similar to previous studies (Reilly *et al*, 2008; Zhang *et al*, 2010; Thavorncharoensap *et al*, 2010; Jayathunge *et al*, 2010). However, those studies surveyed in other diseases such as Crohn's disease (Reilly *et al*, 2008), rheumatoid arthritis (Zhang *et al*, 2010), and alcohol consumption (Thavorncharoensap *et al*, 2010) and HIV-infected women in Thailand (Jayathunge *et al*, 2010) could not compared with this study. More studies in chronic disease using WPAI in Thai population are proposed.

QOL measured by EQ-5D VAS scores could reflect health impairment of CHB patients obviously from their perspective. It was suggested that QOL should be measured from the patient's perspective (Lam *et al*, 2009). This finding was similar with a study using EQ-5D and EQ-5D VAS measured QOL of tuberculosis patient in

Thailand (Kittikraisak *et al*, 2012). The median (IQR) EQ-5D VAS in this study was the same level as the mean EQ-5D VAS of adult age 30-39 year from 15 countries surveyed by EuroQol Group (2006). In this study, patients usually rated their health as less than 80 out of 100%even if they were healthy similar to Ong *et al* (2008) who noted that while these patients did not feel normal in overall health as they were also mentally affected by their more serious hepatitis B status, this feature could not be classified in any of the dimensions of EQ-5D. Also, the previous study suggested that in liver diseases, physical signs are related to the disease, but social and psychiatric effects are not. Instead, these effects are related to understanding function, knowledge, socioeconomic state, literacy, culture and one's beliefs (Heidarzadeh *et al*, 2007). Therefore, this study suggested that EQ-5D VAS is useful to explore the impact of disease on patients' perspective.

According to variable age, the older age had negative correlation, and age more than 35 years old had negatively predicted average CLDQ discovered in this study. From literature review, previous studies indicated different effect of age on QOL. Several previous studies identified that the older age was associated with poorer QOL in CHB patients and chronic liver disease (Sobhonslidsuk *et al*, 2006; Gutteling *et al*, 2007; Tan *et al*, 2008; Feng Gao *et al*, 2012; Ul Haq *et al*, 2012) whereas the current studies by Lam *et al*, (2009) showed that older age actually had a positive effect on mental QOL. In addition, the fact that cirrhosis usually occurs in older age until persons have reached their late 30s and early 40s (McMahon, 2004), patients suffer from degenerative physical function (Younossi *et al*, 2001) with more comorbidities (Yuen *et al*, 2005) resulting in worse QOL. Finally, this study confirmed that older age results to decrease in QOL.

Apart from variables age, months for CHB follow up less than six had negatively predicted average CLDQ, this finding might be explained by the fact that most of these patients were newly diagnosed with asymptomatic that might feel worry as mentioned before. In addition, anxiety/depression was the major variable on lowering QOL (Serafini *et al*, 2010; Sareen *et al*, 2006; Ul Haq *et al*, 2012). However, in this study, some patients were surprised about being newly diagnosed with HBV cirrhosis in active hepatitis B phase, and some patients had anxiety with their high HBV DNA level without symptoms when checked for the first time. This should be

considered that there must have been those with poorer status who are unrecognized and do not receive investigations. Finally, this finding suggested that newly diagnosed CHB need counseling specifically about CHB disease to decrease anxiety and increase awareness for continuous follow up care.

6.3 Economic burden of CHB patient

One of the strengths of this study is that is the first study to describe the total cost including direct medical cost, direct non-medical cost, and indirect cost of Thai CHB patient together with QOL assessment. There are several advantages of doing a cost study. First, the annual cost including the drug cost, laboratory and radiology cost were collected in each patient form the hospital information database that should be more accurate than an average cost based from the national database or a predicted cost from the model. Unlike, most of the previous studies were retrospective analysis, used a model that may result in gross magnification of errors (Dan, Aung, & Lim, 2008), and most studies were analyzed based on the perspectives of health care system or third party payer which considered only direct medical costs (Tantai *et al*, 2010). Second, the work productivity loss at over time was assessed and it could turn into productivity loss of employer or society. The finding reflects the benefit of CHB caring including ARV, which resulted in an increase in patients' productivity. Third, this is the first prospective study that assessed medical burden and economic burden in the same patients. Finally, information from this study is essential and beneficial for further analysis on economic appraisals for CHB management.

However, the costs in this study had limitations because this economic burden study did not have full economic evaluation. First, the CHB patients in this study were OPD cases and so costs were lower or they were the costs of maintaining service for uncomplicated CHB. Second, CHB patients in this study included HIV-HBV co-infections, HCV-HBV co-infections, and HBV with serious diseases such as diabetes mellitus that could affect costs. Third, non-medical cost was obtained from the patients that could have introduced some subjective biases but it reflected from their perspectives. Another limitation is that some patients had treatment in other hospitals such as chemotherapy, inpatient admission that the researcher could not

follow. So, it may be assumed that this is the lower bound cost of CHB or it is the cost of maintaining service for uncomplicated CHB.

Hepatitis B infection imposes a considerable economic burden on Thai CHB patient and family which have not been ever described. The finding provided that direct non-medical accounted for 10%, which might interfere to loss of income and well-being of these patients. This was consistent with studies in China and Pakistan where patient and family underwent a significant economic pressure because majority of healthcare costs are paid by patients themselves (Hu & Chen, 2009; Ul Haq *et al*, 2012). Although 92.8% of the patients in this study had health security responded to direct medical cost, the direct non-medical cost was a burden to the patients. Also, 43.37% of direct non-medical cost was the nutritional supplementary expense similar to the study by Hu and Chen (2009), this might be that the patients expected to improve or maintain their health condition. However, evidence on effectiveness of these health products should be a part of health education for patients.

ARV treatment in hepatitis B infection benefits for low severity such as uncomplicated and impaired liver function CHB patients, and this study could demonstrate apart from a superior clinical response by enhancing QOL and work productivity over time. As shown before, a CHB patient with low severity measured by CLDQ had greater response to ARV resulting in increasing QOL, ARV cost was less than cost of productivity loss (mean (SD) ARV cost 13,921.19 (23,949.18) *vs*. annual labor cost of impairment while working 17,058.66 (47,639.18) Baht/year). Moreover, there was a decreasing trend of indirect cost from 9,063 (Bath/patient/month) at the beginning of the study to 665 (Bath/patient/month) at the 12^{th} months of follow up. Also, the finding showed that with ARV, 16.7% and 66.7% of CHB patient with cirrhosis/HCC had productivity increasing and stable, 50.0% and 37.5% of impair liver function test had had productivity increasing and stable. Without ARV, 57.5% and 12.5% of uncomplicated CHB had stable and decreasing productivity loss. Besides, ARV was recommended by guidelines for CHB patients especially those without liver cirrhosis (Choi & Yoo, 2010) with permanent and complete suppression of viral replication (Chen *et al*, 2007; Iloeje *et al*, 2006; EASL, 2009; Buti, Brosa & Casado 2009), discontinuing the progress of disease, and reduction transmission of the virus (Lavanchy, 2008; Choi & Yoo, 2010). Previous

economic analyses have shown the cost-effectiveness of ARV in CHB patient (Kanwal *et al*, 2005; Buti *et al*, 2006; Veenstra *et al*, 2007) that tended to save direct medical care cost from progressive liver damages (Hu & Chen, 2009). Hence, this finding emphasized the importance of ARV treatment on medical and economic burden of CHB patient should be considered.

The direct medical cost of CHB patients in this study was quite low with 1,048 USD/patient/year (32,115.04 Baht, 30.63 Baht = 1 USD). The annual direct medical cost of CHB by previous studies was applied different definition and used different database that could not be compared among the studies. However, to view a comparison of cost among the studies, the costs were calculated the inflation rates of USD of their year of study to the year 2012 that are showed in Table 6.2. It seem possible be explained as followings. First, this study is cost approach while others may be charge approach. Second, this study collected data from a rural general hospital while some previous studies used data from secondary to tertiary hospital. Also, the cost of drugs used in this study was quite low because most of drugs were locally made and were in the drug list of Queen Savang Vadhana Memorial hospital. Third, this study was conducted in between treatment, so D0 did not correspond to D0 of treatment. Patients who had impaired LF and active hepatitis were already treated. Also, patients were OPD cases. As a result the cases were less severe.

Table 6.2 Mean (SD) annual direct medical costs (USD) of CHB of present and previous studies

Author (published year), Country	Cost (USD)
This study, (2012), Thailand	1,048*
Lee *et al*, (2004), United States	925
Yang *et al*, (2004), South Korea	301
Zhiqiang *et al*, (2004), China, Beijing	173
Li *et al*, (2004), Hong Kong	984
Li *et al*, (2004), Singapore	498
Castelo *et al*, (2007), Brazil	434
Hu & Chen (2009), China, Beijing	1751
Hu & Chen (2009), China, Guangzhou	1554
Lu *et al*, (2013), China, Shandong	4552

*Calculated to USD from direct medical cost 32,115.04 Baht/ 30.63 Baht/1 USD = 1,048 USD (Bank of Thailand, 2008)

The direct/indirect cost accounted for 4:1 in this study that was less than the ratio of direct/indirect costs in study by Liang *et al*, (2010) with 2:1. The difference of the studies were that indirect cost in this study was estimated from percentage of impairment while working by WPAI while the studies by Hu and Chen (2009), and Liang *et al*, (2010) measured indirect cost from their research structured questionnaire. Liang *et al* (2010) reported that corresponding work-loss days/year from CHB were 55.74 days/year for patients and 19.83 days/year for caregivers. The study by Hu and Chen (2009) informed that average leave day of CHB patients and caregiver were 1.5 (SD 5.5) and 1.0 (SD 4.2) day/month. When compared direct cost in percent of total cost, it was found 42% of total societal cost of HBV-related disease in Singapore (Ong, Lim & Li, 2009) while it was found lesser with 19.8% in this study. The difference is that this study was a cost approach with case by case database while another study was an estimated annual cost. A previous systemic review study presented that the differences of CHB cost analysis including in countries in which the study was conducted in, the year horizon, cost, benefit and transition estimates, as well

as the Markov model states make comparison between various studies impossible (Dan, Aung, & Lim, 2008). Country-specific economic evaluations would be required to confirm (69 Lacey & Gane, 2007). Nonetheless, this study provided understanding a considerable indirect cost of CHB patient to the society with specifically in Thai population.

The cost of the present study could be used to estimate a large magnitude economic burden of all CHB patients over Thailand as shown in Table 6.3. Thailand is currently classified as an intermediate endemic area (2-7%) (Mohamed *et al*, 2004; Pradutkanchana *et al*, 2005; Chongsrisawat *et al*, 2006). The number of the Thai population during 2005-2006 was 65 million (National Statistic Office of Thailand; Ministry of Information and Communication technology, 2009). From the HBsAg prevalence and the number of the Thai population during 2005-2006, the estimated number of Thai CHB patients during 2005-2006 was range from 1.3 to 4.5 million and the cost of CHB was 45,719.12 (64,647.43) Baht/patient/year; therefore, the estimated economic burden from 2-7% of all CHB patients over Thailand will be ranged 59-208 billion Baht/year or 1.9-6.8 billion USD/year. Moreover, one third of these infected people will develop cirrhosis and HCC (McMahon, 2004), or approximately 0.4 to 1.5 million Thai CHB with cirrhosis will occur and incur cost ranged from 24-87 billion Baht/year. From the incidence rate that was high as 8.60 to 10.43 per 100,000 populations among people aged between 15-54 years (Bureau of Epidemiology; Ministry of Public Health, 2007), it was estimated that there would be 5,595 to 6,786 newly diagnosed CHB cases with cost ranging from 255-310 million Baht/year. The cost may save 20-72 billion Baht/year if severe medical burden has been prevented with mild medical burden and 46-161 billion Baht/year if cirrhosis has been prevented with uncomplicated CHB. When compared with cost of CHB in other studies, this cost was greater than the total societal cost of HBV in Korea in 1997 and in Hong Kong in 2003, which were 959.7 million USD (Yang *et al*, 2001) and 279 million USD (Ong, Lim & Li, 2009). Also, this previous study suggested that the cost would be greater in the following year (Yang *et al*, 2001). This finding demonstrated that CHB infection imposes a substantial economic burden on the Thai society and therefore, should be prevented. Evidence from this study also contributed to the understanding of potential

benefits to society from allocating more resources to preventing and treating HBV infection in Thailand.

The more severe CHB disease causes more economic burden that should be prevented including progressive liver damage. The estimated lower bound cost of patients with mild medical burden was less than severe medical burden (54 *vs*.74 billion Baht/year) (Table 6.3). Although, the direct medical cost of the patients between mild and severe medical burden in the present study was not different, the laboratory cost from the more frequencies liver ultrasound and supplementary expense of the severe medical burden group were significant greater than that of mild medical burden group (laboratory 6139.5 (3929.64) *vs*. 4756.19 (2479.46) Baht, p=0.020; supplementary (3690.91 (6640.09) *vs*. 1376.75 (4325.58) Baht, p=0.024). CHB with cirrhosis/HCC had the significant highest cost in Baht/patient/year with 81237.41 (119037.17), the subsequent were CHB with ARV (54459.51 (37392.01), and CHB without ARV (18872.70 (21080.42)), respectively (p<0.001). Besides, the case series demonstrated that CHB patients with cirrhosis and HCC tended to had work loss and died after a while. By the fact that the natural history of HBV are associated with an increased risk of morbidity and mortality (Brown *et al*, 2004; Lok & McMahon, 2007; Hoofnagle *et al*, 2007; Idris *et al*, 2008; Lavanchy, 2008). Several previous evidences supported that cost increase dramatically as the disease progress to more advanced stages (Lee *et al*, 2004; Zhiqiang *et al*, 2004; Hu & Chen, 2009; Liang *et al*, 2010; Gagnon *et al*, 2004; Castelo *et al*, 2007), and suggested that any new therapy over the long term delaying of CHB liver disease progression might reduce cost (Gagnon *et al*, 2004; Castelo *et al*, 2007; Yang *et al*, 2004; Li *et al*, 2004; Rajendra & Wong, 2007). Although the antiviral treatments incur near-term costs and savings may not occur for many years (Rajendra & Wong, 2007) with CHB requires lifelong treatment (Ul Haq *et al*, 2012) that could increase the healthcare costs in CHB patients, the cost-effectiveness study demonstrated that antiviral treatments compared with no treatment had incremental cost-effectiveness ratio range from the least 7,600 to the most 44,300 USD/QALY (Dan, Aung, & Lim, 2008). Moreover, ARV diminishes the morbid and expensive complications and improved QOL from decreasing progression rates of a disease (Gold *et al*, 1996; Petitti, 2000). As well, HCC surveillance by 6 monthly alphafoetoprotein was cost-effectiveness compared with no surveillance

(Paul *et al*, 2008; Thompson Coon *et al*, 2008) with £20 700 per QALY gained (Thompson Coon *et al*, 2008). Therefore, generating treatment in patients with mild medical burden such as uncomplicated and impaired liver function CHB may save cost of cirrhosis treatment, enhance QOL of these patients and also prevent HBV transmission to other people.

Table 6.3 Estimated economic burden of all CHB patients over Thailand

		Number of CHB patient	
Number of Thai population	65,064,077		
Prevalence of HBsAg	2.0-7.0%	1,301,281	4,554,485
One third develop to cirrhosis		433,760	1,518,162
Estimated new CHB case each year	8.6-10.4/100000	5,595	6,786
Estimate cost (Baht)			
All CHB over Thailand	45,719.12 (64,647.43)	59,493,446,881.04	208,227,064,083.66
Mild medical burden by CLDQ ≥ 5 scores	41,671.22 (69,798.64)	54,225,989,335.28	189,790,962,673.48
Severe medical burden by CLDQ < 5 scores	57,494.83 (45,405.94)	24,938,957,460.80	87,286,466,102.46
New CHB case each year	45,719.12 (64,647.43)	255,798,476.40	310,249,948.32
Cirrhosis	81,237.41 (119,037.17)	105,712,741,990.41	369,994,596,966.44
Cost saving			
If severe medical burden had been prevented with mild medical burden	15,823.61	20,590,971,589.16	72,068,400,562.05
If cirrhosis had been prevented with uncomplicated CHB	35,518.29	46,219,295,109.37	161,767,532,882.78

Abbreviations: CLDQ, Chronic Liver Disease Questionnaire, D0, Day zero; M6, 6th month of follow up; M12, 12th month of follow up

The burden of CHB may be greater than recognized, as numerous patients may not have been investigated for CHB or HBV. In this study, asymptomatic CHB usually detectedfrom antenatal care, health check up, blood donation service and pre-operative laboratory while the rest were found in the worse stages such as impaired liver, cirrhosis and HCC when they needed for hospital care. This might point to that there must have been those with unknown HBsAg and/or poorer status who did not receive investigations. As a ‘silent’ disease, the contribution of chronic HBV infection to global morbidity and mortality is often highly underestimated (Lavanchy, 2008).

The number of reported cases is much lower because many infected people do not consult a doctor because they do not have symptoms (McBrien, 2013). In this study, it was interesting to find that some cirrhosis CHB patients knew about their diagnosis of HBV cirrhosis in active hepatitis B phase only recently, and some CHB patients were surprised with their high HBV DNA level despite lack of any significant symptoms during their first health check up. Indeed, a previous survey showed that the diagnostic rate of HBV was only 25% in USA, approximate 18% in Europe and even lower (4%) in Asia except Japan (13%) (Liaw, 2009). Of the estimated 2 million individuals with chronic HBV infection in the United States of America, only 300,000 or 15% have been screened and 50,000 or 2.5% receive treatment (Do, 2009). HCC surveillance may triple the number of people with operable tumours at diagnosis (Thompson Coon *et al*, 2008). With the estimation for the whole country, one assumption is that access to treatment is 100%, but the real number of diagnosedHBV and/or number of treated CHB in Thailand was unknown. Consequently, there is a need for CHB screening with liver investigations and routine monitoring of CHB patients to prevent progressive liver damage.

6.3 Outcome of CHB patient at one-year follow up

In this study, the outcome of CHB patient at one-year follow up seemed to be superior. Overall, 84.9 % were doing well. Death rate and lost to follow up were 2.0% and 13.2%, respectively. Most of the patients who were ARV treated had good adherence (95.2%), and wereARV resistant at 8.3%. For liver biomarker, 87.4% had HBV DNA level less than 2000 IU/ml, 84.9% had ALT less than 35 U/l, and 80.3% had AST less than 40 U/l. Because, this study was conducted based on median (IQR) months for CHB follow up and months for ARV treatment were 16.0 (6.0-24.0) and 21.0 (9.0-31.0). Although there was no significant difference between one-year follow up results of the CLDQ < 5 scores and CLDQ ≥ 5 scores, it was presented by CLDQ and EQ-5D that patients in these two groups had medical burden such as the CLDQ $<$ 5 scores group had fatigue, worry, and systemic symptoms while CLDQ ≥ 5 scores had emotional function, fatigue, and systemic symptoms. This may be because these

patients were already selected, most of them on treatment for nearly 1-2 years. So it automatically excluded the severe cases, non-complaint cases, D0 is not real D0; thus, this outcome is upper-bound outcome.

6.4 Limitation of study

This study had limitations in several ways. First, it was conducted in an out-patient department of a rural hospital where cases were less severe than in-patients in a secondary or tertiary hospital. Second, the patients were already ARV treated for 2 years and the severe and non-compliant cases might not enroll in the study. Third, other costs outside the study hospital for other health services were not included such as cost for hospitalized in private sector or clinic during the study period. Fourth, majority of direct non-medical data were collected from patients' information that might have information bias.

6.5 Benefits of the study and policy recommendation

Information from this study is practical in clinical service. For clinicians, it should be a concern that CHB patients both in active and inactive phases can have psychological burden. QOL could obviously reflect patients sign and symptom of hepatitis and related diseases. Regular liver biomarker monitoring or routine follow up could enhance QOL and prevent cost in severe liver disease stage by reducing anxiety and increasing better clinical condition. A holistic approach in clinical practice, health education and counseling programmed should be used to improve quality of care for CHB patients at outpatient setting. For patients, specific knowledge for CHB self-care is needed in the clinic to relieve symptoms and prevent worsening of the disease such as avoid drinking, adequate rest, and avoid any activity that may spread the infection to other people. Counseling programs should be provided along with QOL assessment to explore the actual health problems. Cirrhosis has severe medical burden and need for complicated holistic care in both patient and caregiver.

For health care policy to reduce burden of HBV in Thai people, the following are recommended. First, screening hepatitis B for all Thai should be promoted because there were some Thai CHB patients who were not screened for hepatitis B infection, unrecognized and at risk for progressing to cirrhosis without appropriate treatment, and transmission prevention. Second, regular liver biomarker monitoring should be provided for all CHB patients with early treatment in impair liver function for superior clinical outcome, cost saving, and productivity increasing. Third, specific CHB disease counseling program should be promoted especially in working personnel and newly hepatitis B infection diagnosis, it is important to enhance knowledge, attitude and awareness including health behavior for prevention, and a continuous follow up through clinical management. Fourth, holistic care should be provided for CHB patient with cirrhosis/HCC.

CHAPTER VII
CONCLUSION

7.1 Medical burden of CHB patients

This is the first study that assessed both EQ-5D and CLDQ at the same time visibly reflecting physical and psychological burden in CHB patients. EQ-5D is appropriate for use in the Thai study and EQ-5D VAS is useful to explore the impact of disease on patients' perspective. CLDQ has discriminant validity for Thai CHB patient. The findings showed a comparison of health problems of CHB patients reporting by EQ-5D with the variety of populations with or without disease. Data obtained from EQ-5D benefits for cost effectiveness analysis of CHB treatment in the future. Also, data gained from CLDQ revealed specific liver complications of CHB patients that are useful in a general practice setting.

A total of 152, 140, and 129 CHB patients who visited the OPD of Queen Savang Vadhana Memorial Hospital at D0, M6 and M12, respectively were enrolled. For CLDQ < 5 scores group, number of patients at D0, M6, and M12 were 38, 38, and 33, respectively. For CLDQ ≥ 5 scores group, number of patients at D0, M6, and M12 were 114, 102, and 96, respectively. The severity of liver disease measured by CLDQ found that mean (SD) average CLDQ score increased from 5.48 (0.89) scores at D0 to 5.79 (0.87) scores at M6 and 5.98 (0.88) scores at M12. At D0, the three domains with the least mean (SD) CLDQ scores were fatigue (5.05 (1.19)), systemic symptom (5.38 (1.16)), and worry (4.79 (1.24)). The three domains with the least mean (SD) scores of the CLDQ < 5 scores group were worry (3.68 (1.01)), fatigue (3.72 (1.05)), and abdominal (3.95 (1.54), whereas in the CLDQ ≥ 5 scores group were worry (5.16(1.08)), fatigue (5.49 (0.86)), systemic symptoms (5.81 (0.80)).

Overall, the quality of life (QOL) determined by EQ-5D and its comparison within group among D0, M6, and M12 were as followings. At initial D0, the most sequences of EQ-5D dimension patients reporting moderate or severe problems were pain/comfort (54.6%), anxiety (51.3%), mobility (13.2%), activity

(13.2%), 13.2% and self care (3.9%), respectively. Over time, in anxiety dimension, the percentage of patients reporting moderate or severe problems significantly decreased from 51.3% at D0 to 33.6% at M6 and 26.9% at M12 ($p< 0.001$). However, in self-care dimension, the percent of patients reporting moderate or severe problems significantly increased from 3.9% at D0 to 9.3% at M6 and 6.9% at M12 ($p= 0.047$). Median (IQR) EQ-5D VAS among D0, M6 and M12 were significantly different (M12 80.0 (80.0-90.0) < M6 80.0 (71.1-90.0) < D0 80.0 (70.0-88.7), $p< 0.001$).

Significantly, HCV-HBV co-infections were negatively correlated to EQ-5D VAS (r=-0.171, p=0.035, n=152), while albumin was significantly positively correlated to EQ-5D VAS (r=0.170, p=0.037, n=152). Variables such as age, presence of other diseases except liver disease, cirrhosis, and DM were significantly negatively correlated to CLDQM (age: r=-0.231, p=0.004; presence of other diseases except liver disease: r=-0.169, p=0.037; cirrhosis: r=-0.221, p=0.006; DM: r=-0.220, p=0.006, (n=152)). Variables such as undergraduate and albumin were significantly positively correlated to CLDQM (undergraduate: r=0.199, p=0.014; albumin: r=0.165, p=0.042, (n=152)).

The R-squares of models with dependent variables EQ-5D VAS or CLDQM were 0.88 and 0.95, respectively. Variable significantly positively predict EQ-5D VAS was having health security (B = 75.23 (95% CI 39.29-111.17), p=0.001). Significantly, variables that negatively predict EQ-5D VAS were phase I immune tolerant (B = -49.50 (95% CI -87.31 to -11.69), p=0.017), and months for CHB follow up < 6 (B = -47.12 (95% CI -75.26 to -18.98), p=0.005). Variables that significantly positively predict CLDQM were male gender (B = 1.06 (95% CI (0.40-1.72), p=0.006), p=0.047), health security (B = 2.92 (95% CI 1.25-4.59), p=0.004), child A (B= 2.82 (95%CI 0.99 to 4.64), p= 0.007), and child C (B= 3.27 (95%CI 0.14 to 6.39), p= 0.042). Variables that significantly and negatively predict CLDQM were age more than 35 years old (B= -1.04 (95%CI -2.07 to -0.02), months for CHB follow up less than six months (B = -1.49 (95% CI -2.80 to -0.19), p=0.030), and HCV (B = -1.47 (95% CI -2.53 to -0.41), p=0.012).

When compared, the percentage of patients reporting moderate or severe problems between the CLDQ < 5 scores and the CLDQ ≥ 5 scores groups, the findings were as follow. At D0 and M6, the CLDQ < 5 scores group, patients reporting

moderate or severe problems were higher than the CLDQ ≥ 5 scores with significant differences in all EQ-5D dimension. However, at M12, in self care and anxiety dimensions, patients reporting moderate or severe problems between these two groups were not different. For EQ-5D-VAS, the CLDQ < 5 scores group had significant lower median (IQR) scores than the CLDQ ≥ 5 scores group. Comparison of number (%) of patients reporting moderate or severe problems EQ-5D within group betweenD0, M6, and M12 of CLDQ < 5 scores and CLDQ ≥ 5 scores in each EQ-5D dimension, in anxiety dimension of both CLDQ < 5 scores and CLDQ ≥ 5 scores groups, number (%) of patients reporting moderate or severe problems were significantly decreased from 76.3% to 55.3% at D0 and M6, respectively and 39.4% at M12 in the CLDQ < 5 score group (p=0.002), and from 43.0%, 25.5% and 22.9% at D0, M6 M12, respectively in the CLDQ ≥ 5 scores group (p=0.038). For EQ-5D VAS, the CLDQ ≥ 5 scores group had median (IQR) of EQ-5D VAS at M12 more than at M6 and D0 significant differences (M12 85.0 (80.0-90.0)) > M6 80.0 (80.0-90.0) > D0 80.0 (73.7-90.0), p=0.002).

According to the work productivity loss assessed by WPAI consisting of impairment while working and activity impairment due to health, the mean (SD) percent impairment while working due to health at D0, M6, and M12 were 8.95 (14.88), 8.50 (17.66), and 7.14 (18.51), respectively. The mean (SD) percent activity impairment due to health at D0, M6, and M12 were 5.39 (12.55), 5.21 (13.86), and 3.49 (11.08), respectively. Comparison of mean (SD) percent impairment while working and activity impairment between CLDQ < 5 scores and CLDQ ≥ 5 scores groups, the CLDQ < 5 scores group had mean (SD) percent activity impairment and impairment while working more than the CLDQ ≥ 5 scores group significant differences (impairment while working due to health (D0, 17.73 (17.28) *vs*. 6.20 (12.96), p< 0.001; M6 16.40 (23.80) *vs*. 5.81 (14.21), p=0.004; M12, 19.83 (30.64) *vs*. 3.22 (10.10), p< 0.001; activity impairment due to health (D0, 10.79 (18.36) *vs*. 3.60 (9.32), p=0.002; M6 15.53 (21.27) *vs*. 1.37 (6.60), p<0.001; M12, 10.30 (18.45) *vs*. 1.15 (5.40), p< 0.001). Comparison within group atD0, M6, and M12 of CLDQ < 5 scores and CLDQ ≥ 5 scores groups showed that there was no difference of impairment while working.; However, the CLDQ ≥ 5 scores group had significantly

decreased mean (SD) percent activity impairment from 3.60 (9.32) at D0 to 1.37 (6.60) at M6 and 1.15 (5.40) at M12 (p=0.012)

CHB patients in this study had health impairments assessed by EQ-5D more than population norm, and the findings showed a comparison with the variety of populations with or without disease. Also, CHB patients had many physical impairments and psychological problems measured by EQ-5D and CLDQ that could effect their daily lives, work and social roles. Fatigue, abdominal symptoms, and systemic symptoms measured by CLDQ are the most common physical problems of CHB patients requiring clinical care. These patients reported a high percentage of health problems in anxiety dimension by EQ-5D and the lowest score in worry and emotional function domains by CLDQ. Over time, the CHB patient with less severity measured by CLDQ had greater response to ARV resulting in increasing QOL, whereas cirrhosis might not. Cirrhosis had high severity of liver disease determined by CLDQ. Based on the results of this study, it is suggested that investigation of liver function in all CHB patients be done in clinical practice and early clinical management by ARV in patients with impaired liver function test to prevent progressive liver damage leading to cirrhosis. Holistic care is needed for both patient and caregiver in cases of CHB cirrhosis. Finally, findings from this study suggested that newly diagnosed CHB needs a counseling program specifically about CHB disease to lessen anxiety and increase awareness in patients and thus maintain compliance in follow up.

7.2 Economic burden of CHB patient

This is the first study to describe total cost including direct medical cost, direct non-medical cost, and indirect cost of Thai CHB patient together with QOL assessment. The present study supported previous economic analyses strategies by prevention and early treatment in CHB management based on the finding that the more severe CHB disease causes more economic burden. It had demonstrated a magnitude of CHB health impairments, and provided basic economic data for estimating cost-effectiveness analysis of CHB management in Thailand. Direct non-medical cost and indirect cost caused a substantial economic burden. Supplementary expense accounted for a considerable proportion of direct non-medical cost. Hepatitis B-related diseases could result to decreased work productivity.

For 129 CHB patients who completed 12 months of follow up, total cost, direct medical cost, direct non-medical cost and indirect cost from work productivity loss were 5,879,645.20, 4,142,839.80, 585,553.00, and 1,169,252.40 Baht/year, respectively. Direct medical cost, direct non-medical cost and indirect cost accounted for 70.25, 9.93, 19.82 percents, respectively. Mean (SD) of these costs were 45,719.12 (64,647.43), 32,115.04 (54,259.40), 4,539.17 (6,353.99), and 9,063.97 (19,068.75) Baht/patient/year. The direct medical cost of CHB patients in this study was quite low at 1,048 USD/patient/year (32,115.04 Baht, 30.63 Baht = 1 USD). This is the lower bound cost of CHB or it is the cost of maintaining services for uncomplicated CHB.

When cost between severe and mild medical burden were compared, the CLDQ < 5 scores group had mean (SD) direct non-medical cost, and indirect cost more than the CLDQ ≥ 5 scores group significant differences (direct non-medical cost 7968.54 (9980.18) *vs*. 3992.31 (3992.31) Baht, p=0.004; indirect cost 17901.60 (24328.96) *vs*. 6026.04 (15940.31) Baht, p=0.002). The laboratory of the CLDQ < 5 group was significant higher than that of CLDQ ≥ 5 group (6139.5 (3929.64) *vs*. 4756.19 (2479.46) Baht, p=0.020). The supplementary expense of the CLDQ < 5 group was significantly higher than that of CLDQ ≥ 5 group (3690.91 (6640.09) *vs*. 1376.75 (4325.58) Baht, p=0.024).

The cost of present study could be used to estimate the large magnitude of economic burden of CHB patient in Thailand. The estimated economic burden of CHB in Thailand ranged from 59,493,446,881.04 (2% prevalence) to 208,227,064,083.66 (7% prevalence) Baht/year. The cost may save 20-72 billion Baht/year if severe medical burden was prevented with mild medical burden and 46-161 billion Baht/year if cirrhosis was prevented with uncomplicated CHB. It is estimated that there will be 5,595 to 6,786 newly diagnosed CHB cases with cost ranging from 255,798,476 to 310,249,948 Baht/year. The finding demonstrated that CHB infection imposed a substantial economic burden to the Thai society that should be prevented. Evidence from this study also contributed to the understanding of potential benefits to society from allocating more resources to preventing and treating HBV infection in Thailand.

The more severe CHB disease causes more economic burden. , The estimated cost of patients with mild medical burden was less than severe medical

burden (Mean (SD) 41,671.22 (69,798.64) *vs*. 57,494.83 (45,405.94), different 15,823.61 Baht/patient/year). The mean (SD) total cost among CHB with ARV, without ARV, and with cirrhosis/HCC patients were significantly different ($p<0.001$), CHB with cirrhosis/HCC had the highest cost in Baht/patient/year with 81237.41 (119037.17), CHB with ARV (54459.51 (37392.01), and CHB without ARV (18872.70 (21080.42)), respectively. Hepatitis B infection imposed a considerable economic burden on patients and their families. Findings from this study showed that the direct non-medical cost exceeded 29.94% of patients' income (mean (SD) 4539.17 (6353.99) from 15160.86 (29264.36) Baht/patient/year). CHB-relate diseases could result to productivity loss related to impairment of physical and psychological function. Evidence on effective health products is required to educate this group of patients. This study pointed to this kind of indirect cost incurring a considerable cost.

Findings from this study emphasized the importance of ARV treatment on medical and economic burden of CHB patients. In-patients with ARV, cirrhosis/HCC had productivity stable at 100.0%. Impaired liver function had productivity increasing, stable and decreasing at 25.0%, 50.0% and 25.0%. Uncomplicated CHB had productivity increasing, stable and decreasing at 37.5%, 37.5% and 25.0%, respectively. Without ARV, impaired liver function had productivity loss stable at 100.0%. Uncomplicated CHB had productivity loss increasing and stable at 20.0% and 80.0%, respectively. HBsAg carrier had productivity loss increasing, stable, and decreasing at 40.0%, 40.0%, and 20.0%, respectively. Although this study had a small sample size, the findings revealed the benefits of ARV treatment on productivity loss.

7.3 Implication of the study and Policy recommendation

Information from this study is practical in clinical service. For the clinician, psychological burden affected CHB patients both in active and inactive phases and therefore, a holistic approach, health education and counseling program are required to improve the quality of care for CHB patients at outpatient setting. For patients, specific knowledge counseling program should be provided along with QOL assessment to explore actual health problems and come up with solutions. Cirrhosis

presents a severe medical burden and needs complicated holistic care for both patient and caregiver.

For health care policy, there should be regular liver biomarker monitoring for all CHB patients and early treatment for CHB patients with impaired liver function at the community hospital. Specific CHB disease counseling program is important to enhance knowledge, attitude and awareness including health behavior for prevention, and a continuous follow up with good compliance for ARV treatment.

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APPENDICIES

APPENDIX A
CASE RECORD FORM

Medical and economic burden of CHB patients at Queen Savang Vadhana Memorial Hospital SN.....

CASE RECORD FORM

1. SOCIO-DEMOGRAPHIC DATA

1.1 เพศ ☐ 1. ชาย ☐ 2. หญิง

1.2 อายุ.....ปี

1.3 สัญชาติ ☐ 1. ไทย ☐ 2. อื่นๆ โปรดระบุ.....

1.4 สถานภาพ ☐ 1. โสด ☐ 2. สมรส ☐ 3. หย่าร้าง ☐ 4. หม้าย

1.5 ระดับการศึกษาสูงสุด ☐ 1. ไม่ได้เรียน ☐ 2. ประถมศึกษา ☐ 3. มัธยมศึกษาตอนต้น/ ปวช
☐ 4. มัธยมศึกษาตอนปลาย/ ปวส ☐ 5. ปริญญาตรี ☐ 6. สูงกว่าปริญญาตรี

1.6 อาชีพ ☐ 1. รับจ้าง ☐ 2. เกษตรกร ☐ 3. ประมง ☐ 4. ค้าขาย ☐ 5. แม่บ้าน
☐ 6. ข้าราชการ/ พนักงานของรัฐ ☐ 7. ไม่ได้ประกอบอาชีพ ☐ 8. อื่นๆ โปรดระบุ.....

1.7 รายได้ที่เกิดจากการทำงาน.....บาท/เดือน .....บาท/ปี

1.8 สิทธิสวัสดิการรักษาพยาบาล
☐ 1. บัตร UC ☐ 2. ประกันสังคม ☐ 3. สิทธิข้าราชการ/รัฐวิสาหกิจ ☐ 4. เจ้าหน้าที่สภากาชาดไทย
☐ 5. ประกันสุขภาพของเอกชน ☐ 6. ชำระเงินเอง ☐ 7. อื่นๆ ระบุ.....

1.9 ประวัติการดื่มอัลกอฮอล์
☐ 1. ไม่เคยดื่ม ☐ 2. เลิกดื่ม.....ปี ☐ 3. ดื่มเป็นครั้งคราว
☐ 4. ดื่มเป็นประจำ.....ปี โปรดระบุชนิด ☐ 1. เบียร์ ☐ 2. เหล้า
ปริมาณที่ดื่ม ☐ 1. ดื่ม 1-2 แก้ว/ วัน ☐ 2. ดื่ม 3-4 แก้ว/ วัน ☐ 3. ดื่ม 5-6 แก้ว/ วัน ☐ 4. ดื่ม 7-9 แก้ว/ วัน
☐ 5. ดื่มมากกว่า 10 แก้ว/ วัน

1.10 ประวัติการใช้สมุนไพร
☐ 1. ไม่เคยใช้ ☐ 2. ใช้ .....ปี (โปรดระบุสมุนไพรที่ใช้.....วิธีใช้.....)
☐ 3. หยุดใช้ .....ปี (โปรดระบุสมุนไพรที่ใช้.....วิธีใช้.....)

1.11 ประวัติการใช้ผลิตภัณฑ์/ อาหารเสริม
☐ 1. ไม่เคยใช้ ☐ 2. ใช้ .....ปี (โปรดระบุผลิตภัณฑ์/ อาหารเสริมที่ใช้.....วิธีใช้.....)
☐ 3. หยุดใช้ .....ปี (โปรดระบุผลิตภัณฑ์/ อาหารเสริมที่ใช้.....วิธีใช้.....)

1.12 ประวัติการสัมผัสไวรัสตับอักเสบบี
☐ 1. ไม่มีคนในครอบครัวหรือเพื่อนร่วมงานเป็นไวรัสตับอักเสบบี
☐ 2. มีคนในครอบครัวเป็นไวรัสตับอักเสบบี ☐ 3. มีเพื่อนร่วมงานเป็นไวรัสตับอักเสบบี
☐ 4. เคยได้รับการให้เลือด ☐ 5. เคยได้รับการสัก
☐ 6. เป็นบุคลากรทางการแพทย์ ☐ 7. เป็นกลุ่มเสี่ยง
☐ 8. ไม่ทราบ ☐ 9. อื่นๆ โปรดระบุ.....

1.13 โรคร่วม ☐ 1. ไม่มีโรคร่วม ☐ 2. มีโรคร่วม โปรดระบุ ICD-10
ICD-10-1..... ICD-10-2..... ICD-10-3..... ICD-10-4.....

ETHICS COMMITTEE
FACULTY OF TROPICAL MEDICINE
MAHIDOL UNIVERSITY
VALID UNTIL: 10 NOV 2012

Medical and economic burden of CHB patients at Queen Savang Vadhana Memorial Hospital SN............

2. PRESENTING SYMPTOMS

2.1 D/M/Y; ....../....../........ at beginning of treatment in hospital.

2.2 HBsAg positive was found for.........years due to

☐ 1. Has presenting symptoms ☐ 2. Health checked

☐ 3. Blood donation ☐ 4. Antenatal care

☐ 5. HIV positive ☐ 6. Other, please specify...

3. PHYSICAL EXAMINATIONS (Physician's Diagnosis)

3.1 Phase of CHB: ☐ 1. Phase 1 ☐ 2. Phase 2 ☐ 3. Phase 3 ☐ 4. Phase 4

3.2 Child-Turcotte-Pugh score (CTP) and present of illness (CTP is assessed every 3 months in cirrhosis)

D/M/Y	At month	CTP		Present of illness
		Score	Class	
..../..../....	1st month		☐1. A ☐2. B ☐3. C	☐ 1. Doing well ☐ 2. Complain
..../..../....	Month........		☐1. A ☐2. B ☐3. C	☐ 1. Doing well ☐ 2. Complain
..../..../....	Month........		☐1. A ☐2. B ☐3. C	☐ 1. Doing well ☐ 2. Complain
..../..../....	Month........		☐1. A ☐2. B ☐3. C	☐ 1. Doing well ☐ 2. Complain
..../..../....	Month........		☐1. A ☐2. B ☐3. C	☐ 1. Doing well ☐ 2. Complain
..../..../....	Month........		☐1. A ☐2. B ☐3. C	☐ 1. Doing well ☐ 2. Complain

4. LABORATORY INVESTIGATIONS

4.1 Liver investigations:

D/M/Y	Investigations	Results	Note
..../..../....	☐ U/S ☐ CT ☐ MRI ☐ EGD ☐ Liver biopsy	☐ Normal ☐ Abnormal	
..../..../....	☐ U/S ☐ CT ☐ MRI ☐ EGD ☐ Liver biopsy	☐ Normal ☐ Abnormal	
..../..../....	☐ U/S ☐ CT ☐ MRI ☐ EGD ☐ Liver biopsy	☐ Normal ☐ Abnormal	
..../..../....	☐ U/S ☐ CT ☐ MRI ☐ EGD ☐ Liver biopsy	☐ Normal ☐ Abnormal	
..../..../....	☐ U/S ☐ CT ☐ MRI ☐ EGD ☐ Liver biopsy	☐ Normal ☐ Abnormal	
..../..../....	☐ U/S ☐ CT ☐ MRI ☐ EGD ☐ Liver biopsy	☐ Normal ☐ Abnormal	

4.2 Hepatitis B seromarkers:

HBeAg				HBV DNA		
D/M/Y	At month	Results		D/M/Y	At month	Results
..../..../....	1st month	☐ Negative ☐ Positive		..../..../....	1st month	
..../..../....	6th month	☐ Negative ☐ Positive		..../..../....	6th month	
..../..../....	12th month	☐ Negative ☐ Positive		..../..../....	12th month	

Medical and economic burden of CHB patients at Queen Savang Vadhana Memorial Hospital SN.....๓๙

4.3 Blood tests (*Please record the results)

Investigation results			VN..... .../.../....	VN..... .../.../....	VN..... .../.../....	VN..... .../.../....	VN..... .../.../....	VN..... .../.../....
Haematology	Hb*	g%						
	Hct*	%						
	WBC	$\times 10^9$/l						
	Neutrophiles	%						
	Lymphocytes	%						
	Eosinophil	%						
	Basophil	%						
	Monocytes	%						
	Platelet-count*	$\times 10^9$/l						
Serology	PT	second						
	INR							
	Anti-HIV*							
	CD4*							
	Other, specify							
Biochemistry	Blood Glucose	mg%						
	Sodium	mmol/l						
	Potassium	mmol/l						
	Chloride	mmol/l						
	HCO_3	mmol/l						
	BUN*	mg/dl						
	Cr*	mg/dl						
	Bilirubin Total*	mg%						
	Direct Bilirubin*	mg%						
	AST*	U/l						
	ALT (SGPT)*	U/l.						
	Alk. Phosphatase*	U/l						
	Total protein*	g%						
	Albumin*	g%						
	Globulin*	g%						
	AFP*							
	Other, specify							

Medical and economic burden of CHB patients at Queen Savang Vadhana Memorial Hospital SN.....

4.4 Other laboratory investigations: (Please identify type and results)

.....

.....

5. TREATMENTS

5.1 History of drug allergy (Please identify drug and symptoms).....

.....

5.2 Antiretroviral and other drugs recorded in HIS (Please do pill counts in ARV)

D/M/Y	Drug	Dose	Pill counts		
			Pill received (pills/month)	Pill administered (pills/month)	Percent of drug received
...../...../.....					
...../...../.....					
...../...../.....					
...../...../.....					
...../...../.....					
...../...../.....					
...../...../.....					
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...../...../.....					
...../...../.....					
...../...../.....					
...../...../.....					

5.3 Adherence assessment: (Please ask patient to estimate times of forgotten per month)

D/M/Y	Forgot to administer	Times of forgot per month
...../...../.....	☐ 1. No ☐ 2. Yes	
...../...../.....	☐ 1. No ☐ 2. Yes	
...../...../.....	☐ 1. No ☐ 2. Yes	
...../...../.....	☐ 1. No ☐ 2. Yes	
...../...../.....	☐ 1. No ☐ 2. Yes	
...../...../.....	☐ 1. No ☐ 2. Yes	

D/M/Y	Forgot to administer	Times of forgot per month
...../...../.....	☐ 1. No ☐ 2. Yes	
...../...../.....	☐ 1. No ☐ 2. Yes	
...../...../.....	☐ 1. No ☐ 2. Yes	
...../...../.....	☐ 1. No ☐ 2. Yes	
...../...../.....	☐ 1. No ☐ 2. Yes	
...../...../.....	☐ 1. No ☐ 2. Yes	

5.4 Drug resistances assessment (Physician assesses): ☐ 1. No ☐ 2. Yes (Please identify D/M/Y of diagnosis, drug, dose and present of illness) .....

.....

5.5 Adverse drug events (Physician assesses): ☐ 1. No ☐ 2. Yes (Please identify D/M/Y of diagnosis, drug, dose and present of illness).....

.....

6. Expenses related to health and times consumed per visit

6.1 Other expenses related to health recorded in HIS; (except drug (5.2), lab. (4.3))

D/M/Y	Department	ICD	DRG	R.W.	Expenses (Type/amount/expense)
...../...../.....	☐ OPD ☐ IPD				
...../...../.....	☐ OPD ☐ IPD				
...../...../.....	☐ OPD ☐ IPD				
...../...../.....	☐ OPD ☐ IPD				
...../...../.....	☐ OPD ☐ IPD				
...../...../.....	☐ OPD ☐ IPD				

6.2 Time consumed per physician visit at OPD (minute)

D/M/Y	Time (minute)	D/M/Y	Time (minute)	D/M/Y	Time (minute)
...../...../.....		...../...../.....		...../...../.....	
...../...../.....		...../...../.....		...../...../.....	
...../...../.....		...../...../.....		...../...../.....	
...../...../.....		...../...../.....		...../...../.....	
...../...../.....		...../...../.....		...../...../.....	
...../...../.....		...../...../.....		...../...../.....	

7. Results of treatment at 12th month: ☐ 1. Doing well ☐ 2. Death ☐ 3. Refer ☐ 4. Loss of follow up

7.1 HBV DNA level: ☐ 1. Lower than normal level ☐ 2. Still at the same level ☐ 3. Greater than normal level

7.2 ALT: ☐ 1. Normal ☐ 2. Greater than normal level

7.3 AST: ☐ 1. Normal ☐ 2. Greater than normal level

7.4 Reactivation: ☐ 1. No ☐ 2. Yes

7.5 Ultrasound result: ☐ 1. Normal ☐ 2. Abnormal

APPENDIX B

TRANSPORT EXPENSE FORM

Medical and economic burden of CHB patients at Queen Savang Vadhana Memorial Hospital SN.....

แบบสัมภาษณ์ค่าใช้จ่ายของการเดินทางและค่าใช้จ่ายอื่นๆ ที่เกี่ยวกับการมารับการรักษาครั้งนี้

(Transport and other expenditure form: TEF)

ชื่อสถาบันวิจัย : รพ.สมเด็จพระบรมราชเทวี ณ ศรีราชา

ชื่อย่ออาสาสมัคร : ☐☐☐ การนัดครั้งที่ :.....

หมายเลขอาสาสมัคร : ☐☐☐ วันที่สัมภาษณ์ :.....

ค่าใช้จ่ายของการเดินทางมารับการรักษาครั้งนี้

1. ระยะทางระหว่างที่อยู่อาศัยและโรงพยาบาล ☐☐☐ กิโลเมตร
2. ระยะเวลาทั้งหมดที่ใช้ในการเดินทาง ☐☐☐ นาที
3. ยานพาหนะหลักที่ใช้ในการเดินทางมารับการรักษาโรคไวรัสตับอักเสบบี
   ☐ 1. เดิน ☐ 2. ยานพาหนะรับจ้าง เช่น มอเตอร์ไซค์ รถสองแถว รถประจำทาง
   ☐ 3. รถจักรยาน ☐ 4. ยานพาหนะส่วนตัว เช่น มอเตอร์ไซค์ รถยนต์ รถปิคอัพ
4. ท่านเดินทางมารับการรักษาด้วยตนเองหรือไม่
   ☐ 1. ใช่ ☐ 2. ไม่ใช่ มีผู้อื่นพามา จำนวน ☐ คน
5. ค่าใช้จ่ายในการเดินทางไป-กลับในการมารับการรักษาโรคไวรัสตับอักเสบบีที่โรงพยาบาล
   ☐ 1. ไม่มีค่าใช้จ่าย ☐ 2. ค่าใช้จ่าย จำนวน ☐☐☐ บาท
6. กรณีที่มีผู้อื่นพามา แต่ละคนมีรายได้ในการทำงานโดยเฉลี่ยต่อวัน เท่าไร *(ถ้ารับเป็นเงินเดือนให้หารด้วย 22)*
   คนที่ 1 ☐ 1. ไม่มีรายได้ ☐ 2. รายได้เฉลี่ยวันละ ☐☐☐☐ บาท ☐ 3. ไม่ทราบ/ไม่ตอบ
   คนที่ 2 ☐ 1. ไม่มีรายได้ ☐ 2. รายได้เฉลี่ยวันละ ☐☐☐☐ บาท ☐ 3. ไม่ทราบ/ไม่ตอบ
   คนที่ 3 ☐ 1. ไม่มีรายได้ ☐ 2. รายได้เฉลี่ยวันละ ☐☐☐☐ บาท ☐ 3. ไม่ทราบ/ไม่ตอบ
7. วันที่ท่านมาโรงพยาบาล เพื่อรับการรักษาโรคไวรัสตับอักเสบบี ท่านได้มารับบริการอื่นด้วยหรือไม่
   ☐ 1. ไม่ มาเพื่อรับการรักษาโรคไวรัสตับอักเสบบีเท่านั้น โดยใช้เวลาในการรักษา ☐☐☐ นาที
   ☐ 2. ใช่ มาเพื่อรับการรักษาโรคไวรัสตับอักเสบบีและตรวจติดตามรักษากับ OPD ด้วย
   โดยส่วนใหญ่ใช้เวลาในการรักษา ☐☐☐ นาที
8. โดยปกติ ท่านใช้เวลาในการมารับการตรวจติดตามรักษากับ OPD ☐☐☐ นาที

ค่าใช้จ่ายอื่นๆที่เกี่ยวกับการมารับการรักษาครั้งนี้

1.ค่าอาหาร.....
2.ค่าอาหารเสริมหรือสมุนไพร.....
3.....
4.....
5.....

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APPENDIX C
EUROQOL-5D

Medical and economic burden of CHB patients at Queen Savang Vadhana Memorial Hospital SN.....

แบบสอบถามด้านคุณภาพชีวิต

(EuroQol-5D: EQ-5D)

ชื่อสถาบันวิจัย : รพ.สมเด็จพระบรมราชเทวี ณ ศรีราชา

ชื่อย่ออาสาสมัคร : □□□ การนัดครั้งที่ :.....

หมายเลขอาสาสมัคร : □□□ วันที่สัมภาษณ์ :.....

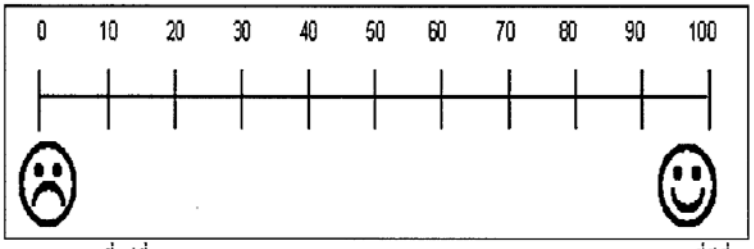
แบบสอบถามด้านคุณภาพชีวิต (ขณะป่วยเป็นโรคไวรัสตับอักเสบบี)	
แบบสอบถามนี้ได้ออกแบบมาเพื่อเก็บข้อมูลภาวะสุขภาพของท่านในช่วงขณะป่วยเป็นโรคไวรัสตับอักเสบบี โปรดเลือกกากบาท (×) ลงในช่องสี่เหลี่ยมที่แสดงถึงภาวะสุขภาพของท่านในช่วงขณะป่วยเป็นโรคไวรัสตับอักเสบ โดยที่แต่ละหัวข้อให้เลือกได้เพียงหนึ่งคำตอบ	
การเคลื่อนไหว	
ฉันไม่มีปัญหาในการเดิน	□
ฉันมีปัญหาในการเดินในบางครั้ง	□
ฉันต้องอยู่แต่บนเตียง	□
การดูแลตนเอง	
ฉันไม่มีปัญหาในการดูแลตนเอง	□
ฉันมีปัญหาในการชำระล้างร่างกายหรือสวมใส่เสื้อผ้าด้วยตนเองในบางครั้ง	□
ฉันมีปัญหาในการชำระล้างร่างกายหรือสวมใส่เสื้อผ้าด้วยตนเองมาก	□
กิจกรรมปกติที่ทำได้ (เช่น การทำงาน การเรียน งานบ้าน กิจกรรมภายในครอบครัว หรือการใช้เวลาว่าง	
ฉันไม่มีปัญหาในการทำกิจกรรมตามปกติ	□
ฉันมีปัญหาในการทำกิจกรรมตามปกติในบางครั้ง	□
ฉันมีปัญหาในการทำกิจกรรมตามปกติมาก	□
อาการปวด/ความไม่สุขสบาย	
ฉันไม่มีอาการปวด/ความไม่สุขสบาย	□
ฉันมีอาการปวด/ความไม่สุขสบายปานกลาง	□
ฉันมีอาการปวด/ความไม่สุขสบายมาก	□
อาการวิตกกังวล/ซึมเศร้า	
ฉันไม่มีอาการวิตกกังวล/ซึมเศร้า	□
ฉันมีอาการวิตกกังวล/ซึมเศร้าปานกลาง	□
ฉันมีอาการวิตกกังวล/ซึมเศร้ามาก	□

EQ-5D June 14, 2011

Medical and economic burden of CHB patients at Queen Savang Vadhana Memorial Hospital SN.....

เส้นแบ่งที่ใช้แสดงถึงภาวะสุขภาพ

เส้นแบ่งข้างล่างนี้ใช้แสดงถึงภาวะสุขภาพ โดยปลายด้านหนึ่งจะแสดงถึงภาวะสุขภาพที่ดีที่สุด และปลายอีกข้างหนึ่งแสดงถึงภาวะสุขภาพที่แย่ที่สุด เราอยากให้ท่านระบุสุขภาพของท่านในช่วง**ขณะป่วย**เป็นโรคไวรัสตับอักเสบบีว่าดีหรือไม่ดีอย่างไร โดยกากบาท (X) ณ จุดใดที่ได้บนเส้นแบ่งข้างล่างที่ตรงกับภาวะสุขภาพของท่านในช่วงขณะป่วยเป็นโรคไวรัสตับอักเสบบี ตามความคิดเห็นของท่าน



ภาวะสุขภาพที่แย่ที่สุด ภาวะสุขภาพที่ดีที่สุด

APPENDIX D
CHRONIC LIVER DISEASE QUESTIONNAIRE

Medical and economic burden of CHB patients at Queen Savang Vadhana Memorial Hospital SN.....

แบบสำรวจสุขภาพตับ

(Chronic Liver Disease Questionnaire: CLDQ)

ชื่อสถาบันวิจัย : รพ.สมเด็จพระบรมราชเทวี ณ ศรีราชา

ชื่อย่ออาสาสมัคร : □□□ การนัดครั้งที่ :.....

หมายเลขอาสาสมัคร : □□□ วันที่สัมภาษณ์ :.....

แบบสำรวจสุขภาพตับ

แบบสอบถามนี้สร้างขึ้นเพื่อสำรวจว่าคุณมีความรู้สึกอย่างไรบ้างในช่วง 2 สัปดาห์ที่ผ่านมา คุณจะได้รับการถามเกี่ยวกับอาการซึ่งสัมพันธ์กับโรคตับของคุณ ว่าอาการนั้นมีผลกระทบต่อกิจกรรมและอารมณ์ของคุณอย่างไรบ้าง **ท่านจะไม่ตอบคำถามข้อใดก็ได้** จะยกเลิกการตอบเมื่อใดก็ได้ และเลือกกากบาท (×) ลงในช่องสี่เหลี่ยมที่แสดงถึงภาวะสุขภาพของท่านในช่วงก่อนป่วยเป็นโรคไวรัสตับอักเสบ โดยที่แต่ละหัวข้อให้เลือกได้เพียงหนึ่งคำตอบ

1. ในช่วง 2 สัปดาห์ที่ผ่านมา **อาการท้องอืด แน่นท้อง** รบกวนคุณ มากเท่าใด
   ☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

2. ในช่วง 2 สัปดาห์ที่ผ่านมา **คุณรู้สึกเหนื่อยและอ่อนเพลีย** มากเท่าใด
   ☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

3. ในช่วง 2 สัปดาห์ที่ผ่านมา **คุณมีอาการเจ็บปวดตามร่างกาย** มากเท่าใด
   ☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

4. ในช่วง 2 สัปดาห์ที่ผ่านมา **คุณรู้สึกง่วงนอนในเวลากลางวัน** บ่อยเพียงใด
   ☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

5. ในช่วง 2 สัปดาห์ที่ผ่านมา **คุณมีอาการปวดท้อง** มากเท่าใด
   ☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

6. ในช่วง 2 สัปดาห์ที่ผ่านมา อาหารหายใจไม่เต็มอิ่มเป็นปัญหาในการทำกิจวัตรประจำวันของคุณมากเท่าใด

☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

7. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณไม่สามารถรับประทานอาหารได้มากเท่าที่คุณอยากรับประทานมากเท่าใด

☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

8. ในช่วง 2 สัปดาห์ที่ผ่านมา ความรู้สึกว่าพละกำลังที่ลดลงเป็นปัญหากับคุณ มากเท่าใด

☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

9. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณมีความยากลำบากในการยกของหรือถือของหนัก บ่อยเพียงใด

☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

10. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณมีความรู้สึกวิตกกังวล บ่อยเพียงใด

☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

11. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณรู้สึกว่ามีกำลังวังชาลดลง บ่อยเพียงใด

☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

12. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณรู้สึกว่าไม่มีความสุข มากเท่าใด

☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

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13. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณรู้สึกง่วงซึม บ่อยเพียงใด
☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

14. ในช่วง 2 สัปดาห์ที่ผ่านมา การจำกัดและควบคุมอาหารเป็นปัญหาลับคุณ มากเท่าใด
☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

15. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณรู้สึกหงุดหงิดหรือไม่สบายใจ บ่อยเพียงใด
☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

16. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณมีปัญหาของการนอนในตอนกลางคืน บ่อยเพียงใด
☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

17. ในช่วง 2 สัปดาห์ที่ผ่านมา ความรู้สึกอึดอัดไม่สบายท้อง รบกวนคุณ มากเท่าใด
☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

18. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณกังวลว่าโรคตับของคุณจะมีผลกระทบต่อครอบครัวของคุณ มากเท่าใด
☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

19. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณมีอารมณ์แปรปรวน มากเท่าใด
☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

20. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณไม่สามารถข่มตาให้หลับได้ในตอนกลางคืน มากเท่าใด
☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

21. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณมีอาการปวดเกร็งกล้ามเนื้อ บ่อยเพียงใด
☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

22. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณมีความกังวลว่าอาการของคุณจะกลายเป็นปัญหาที่ใหญ่โต มากเท่าใด
☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

23. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณมีอาการปากแห้ง มากเท่าใด
☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

24. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณมีความรู้สึกซึมเศร้า มากเท่าใด
☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

25. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณมีความกังวลว่าอาการของคุณจะแย่ลง มากเท่าใด
☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

26. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณมีปัญหาของการขาดสมาธิในขณะทำงาน มากเท่าใด
☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

27. ในช่วง 2 สัปดาห์ที่ผ่านมา อาการคันรบกวนคุณ มากเท่าใด

☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

28. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณมีความกังวลว่าไม่เคยรู้สึกดีขึ้นเลย มากเท่าใด

☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

29. ในช่วง 2 สัปดาห์ที่ผ่านมา คุณกังวลว่าจะมีตับเพื่อนำมาผ่าตัดเปลี่ยนตับหรือไม่ ถ้าถึงเวลาที่คุณจำเป็นต้อง เข้ารับการผ่าตัด

☐ ตลอดเวลา ☐ เกือบตลอดเวลา ☐ บ่อยๆ ☐ บางเวลา ☐ นานๆครั้ง ☐ แทบไม่มีเลย ☐ ไม่มีเลย

APPENDIX C
WORK PRODUCTIVTY AND ACTIVITY IMPAIRMENT QUESTIONNAIRE

Medical and economic burden of CHB patients at Queen Savang Vadhana Memorial Hospital SN.....

แบบสัมภาษณ์เกี่ยวกับอัตราการหยุดงานและการขาดประสิทธิภาพของการทำงาน: โรคไวรัสตับอักเสบบี

(Work Productivity and Activity Impairment Questionnaire (WPAI-Hepatitis B))

ชื่อสถาบันวิจัย : รพ.สมเด็จพระบรมราชเทวี ณ ศรีราชา

ชื่ออาสาสมัคร : □□□ การนัดครั้งที่ :.....

หมายเลขอาสาสมัคร : □□□ วันที่สัมภาษณ์ :.....

คำถามต่อไปนี้ถามเกี่ยวกับผลของโรคไวรัสตับอักเสบบีต่อความสามารถในการทำงาน และในการทำกิจกรรมปกติของท่าน ในที่นี้ ผลของโรคไวรัสตับอักเสบบี หมายถึง ปัญหาหรืออาการใด ๆ ก็ตามทางร่างกาย หรืออารมณ์ ที่เกี่ยวข้องหรือมีผลมาจากโรคไวรัสตับอักเสบบี

1. ปัจจุบันท่านทำงาน (งานที่ได้รับค่าจ้างตอบแทน) หรือไม่ _____ไม่ทำ_____ทำ

   ถ้าไม่ทำ ให้ทำเครื่องหมาย X *ในช่อง "ไม่ทำ" และข้ามไปตอบข้อ 6*

คำถามต่อไปนี้ถามถึงช่วงเจ็ดวันที่ผ่านมา โดยไม่นับรวมวันนี้

2. ในช่วงเจ็ดวันที่ผ่านมา จำนวนชั่วโมงที่ท่านหยุดงานเนื่องจากโรคไวรัสตับอักเสบบี เช่น อ่อนเพลีย ห้องอืด ปวดท้อง

   นับรวมจำนวนชั่วโมงที่ ท่านหยุดงานเนื่องจากอาการป่วย เวลาที่มาทำงานสาย กลับ/เลิกก่อนเวลา หรือสาเหตุอื่นอันเนื่องมาจากโรคไวรัสตับอักเสบบีของท่าน แต่ไม่รวมเวลาที่ท่านหยุดงานเพื่อมาร่วมตอบแบบสอบถามนี้

   _____ชั่วโมง_____นาที

3. ในช่วงเจ็ดวันที่ผ่านมา จำนวนชั่วโมงที่ท่านหยุดงาน เนื่องจากสาเหตุอื่น เช่น ลาพักร้อน ลากิจ หรือไปธุระ

   _____ชั่วโมง_____นาที

4. ในช่วงเจ็ดวันที่ผ่านมา ท่านทำงานจริง ๆ ทั้งหมดกี่ชั่วโมง/นาที _____ชั่วโมง_____นาที

   (ถ้าตอบ "0 ชั่วโมง" ให้ข้ามไปตอบข้อ 6)

5. ในช่วงเจ็ดวันที่ผ่านมา ปัญหาสุขภาพของท่านมีผลทำให้ท่านทำงานได้ไม่เต็มที่มากน้อยเพียงใด

   หากปัญหาสุขภาพเนื่องมาจากโรคไวรัสตับอักเสบบีส่งผลต่อการทำงานของท่านเพียงเล็กน้อย ให้เลือกตัวเลขที่มีค่าน้อย แต่หากปัญหาสุขภาพเนื่องมาจากโรคไวรัสตับอักเสบบีส่งผลกระทบต่อการทำงานของท่านอย่างมาก ให้เลือกตัวเลขที่มีค่ามาก โดย 0 หมายถึงปัญหาสุขภาพไม่มีผลต่อการทำงานของท่านเลย และ 10 หมายถึง ปัญหาสุขภาพทำให้ท่านไม่สามารถทำงานได้เลย

ปัญหาสุขภาพไม่กระทบต่อการทำงานของฉันเลย											ปัญหาสุขภาพทำให้ฉันทำงานไม่ได้เลย
	0	1	2	3	4	5	6	7	8	9	10

วงกลมล้อมรอบตัวเลข 1 ตัว

6. *ในช่วงเจ็ดวันที่ผ่านมา* ปัญหาสุขภาพของท่านมีผลกระทบต่อความสามารถในการทำกิจวัตรประจำวันทั่วไป เช่น การทำงาน บ้าน ดูแลเด็ก ออกกำลังกาย มากน้อยเพียงใด

หากปัญหาสุขภาพเนื่องมาจากโรคไวรัสตับอักเสบบีส่งผลต่อการทำงานของท่านเพียงเล็กน้อย ให้เลือกตัวเลขที่มีค่าน้อย แต่หากปัญหาสุขภาพเนื่องมาจากโรคไวรัสตับอักเสบบีส่งผลกระทบต่อการทำงานของท่านอย่างมาก ให้เลือกตัวเลขที่มีค่ามาก โดย 0 หมายถึงปัญหาสุขภาพไม่มีผลต่อการทำงานของท่านเลย และ 10 หมายถึงปัญหาสุขภาพทำให้ท่านไม่สามารถทำงานได้เลย

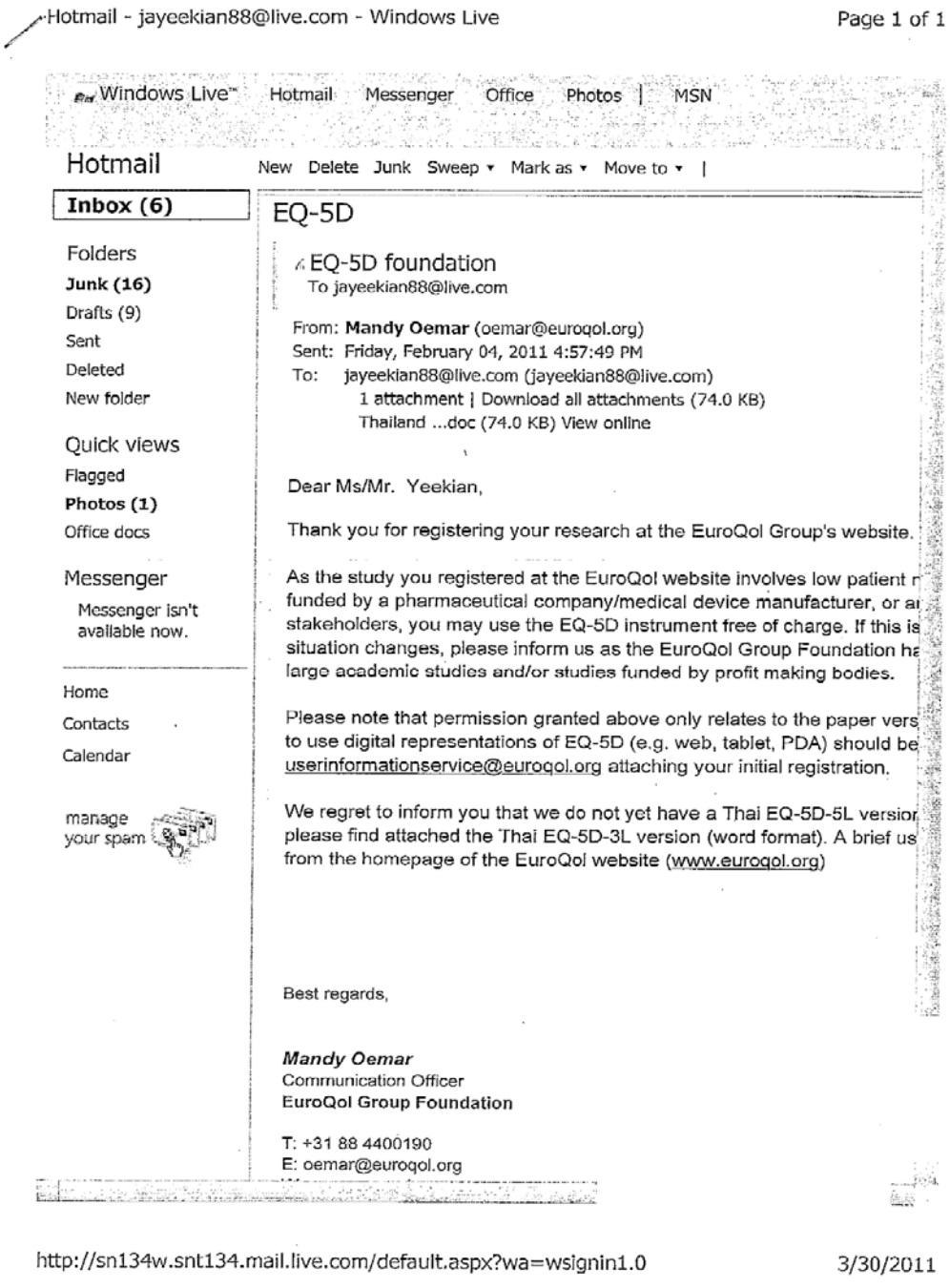
ปัญหาสุขภาพไม่กระทบต่อการทำกิจวัตรประจำวันของฉันเลย	0	1	2	3	4	5	6	7	8	9	10	ปัญหาสุขภาพทำให้ฉันทำกิจวัตรประจำวันของฉันไม่ได้เลย

วงกลมล้อมรอบตัวเลข 1 ตัว

ETHICS COMMITTEE
FACULTY OF TROPICAL MEDICINE
MAHIDOL UNIVERSITY
VALID UNTIL: 10 NOV 2012

APPENDIX E

PERMISSION LETTER TO USE RESEARCH INSTRUMENT



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EQ-5D

EQ-5D foundation
To jayeekian88@live.com

From: **Mandy Oemar** (oemar@euroqol.org)
Sent: Friday, February 04, 2011 4:57:49 PM
To: jayeekian88@live.com (jayeekian88@live.com)
1 attachment | Download all attachments (74.0 KB)
Thailand ...doc (74.0 KB) View online

Dear Ms/Mr. Yeekian,

Thank you for registering your research at the EuroQol Group's website.

As the study you registered at the EuroQol website involves low patient n
funded by a pharmaceutical company/medical device manufacturer, or ai
stakeholders, you may use the EQ-5D instrument free of charge. If this is
situation changes, please inform us as the EuroQol Group Foundation ha
large academic studies and/or studies funded by profit making bodies.

Please note that permission granted above only relates to the paper vers
to use digital representations of EQ-5D (e.g. web, tablet, PDA) should be
userinformationservice@euroqol.org attaching your initial registration.

We regret to inform you that we do not yet have a Thai EQ-5D-5L versior
please find attached the Thai EQ-5D-3L version (word format). A brief us
from the homepage of the EuroQol website (www.euroqol.org)

Best regards,

Mandy Oemar
Communication Officer
EuroQol Group Foundation

T: +31 88 4400190
E: oemar@euroqol.org

http://sn134w.snt134.mail.live.com/default.aspx?wa=wsignin1.0 3/30/2011

Home EQ-5D EuroQol Group News Contact

Home

Register your study

Dear ,

Thank you for registering your study at the EuroQol website. Please allow 3 working

You sent us the following information:

Job title	MEDICAL BURDEN OF CHRONIC HEPATITIS B PATIENTS T
First name	CHUENRUTAI
Surname	YEEKIAN
Organization	QUEEN SAVANG VADHANA MEMORIAL HOSPITAL; THE T
Postal address	290 Jermhompol road, Ampur Sriracha, Chonburi Provi
Postal/Zip code	20110
City	Chonburi
Country	Thailand
Telephone	066-081-862-4534
Telephone 2 (optional)	066-038-372157-9
Fax	066-038-311009
E-mail	jayeekian88@live.com
Work environment	Hospital / Clinical Practice
Other work environment	
Terms of use	I agree with the Terms of use
Title / Description of study / Project	This prospective longitudinal study will be conducted i burden in the new CHB patients treated with antiviral Queen Savang Vadhana Memorial hospital and Chonbu analysis in the community hospital in clinical practice the real medical burden of both patients and their car international agencies to plan the policies or strategie hepatitis B virus treatment and prevention.
Study objective	To assess medical burden and economic burden of chr antiviral therapy at the eighteenth month of follow up
Linked countries	Thailand
Study design	Observational
Other study design	
Clinical area	Liver disease
Other clinical area	
Source of funding	Mahidol University, Queen Savang Vadhana Memorial H
Number of patients	150
Starting date(year only)	2011
Finishing date (year only)	2013
Which version of the EQ-5D would you like to use?	EQ-5D-5L (5 level version)
Which other generic health measures will you be using?	None
Which other disease / condition specific health measures will you be using?	Chronic Liver Disease Questionnaire
Journal articles or other published reports	

Are you prepared to have this information published in any EuroQol reports/surveys regarding usage of EQ-5D?	Yes
Are you prepared to have your details made available to colleagues who are involved in research in a similar area?	Yes

INOVA FAIRFAX HOSPITAL

Center for Liver Diseases
Inova Fairfax Hospital
3300 Gallows Road
Falls Church, Virginia 22042

Tel 703 776-3182
Fax 703 776-4386

July 25, 2011

Chuenrutai Yeekian, M.N.S.
PhD Candidate
Faculty of Tropical Medicine, Mahidol University
Academic Department, Queen Savang Vadhana Memorial
Hospital, Sriracha, Chon buri, Thailand, 20110

Tel: 038-322157-9-3457 Mob: +61 430 147 151
Mob: 081-862-4534
e-mail: jayeekian88@live.com

Dear Chuenrutai Yeekian:

Thank you for your interest in the Chronic Liver Disease Questionnaire (CLDQ).

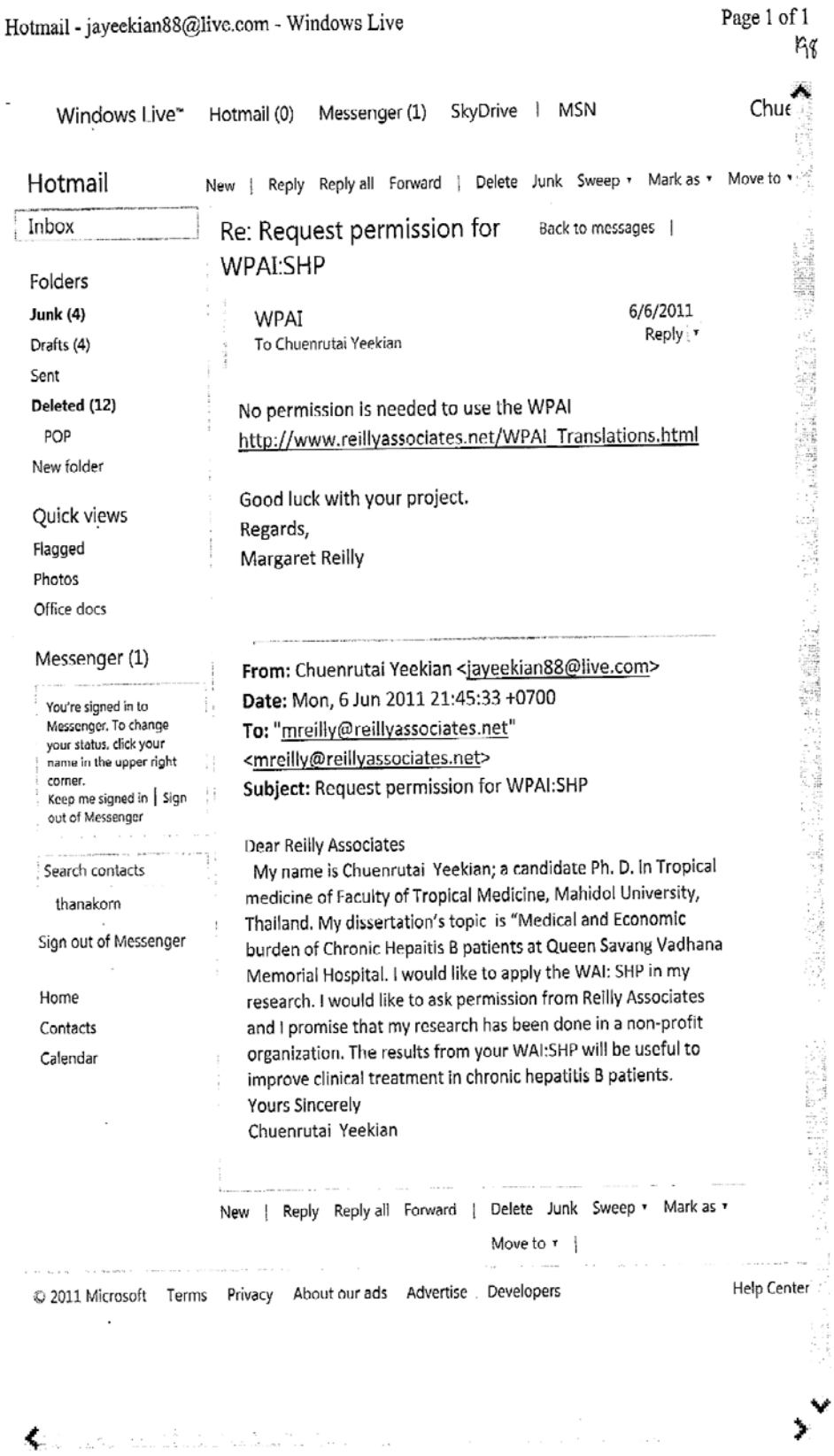
You have indicated that you would like to obtain permission to use of the Chronic Liver Disease Questionnaire (CLDQ), for the study Medical and economic burden of chronic hepatitis B patients at Queen Savang Vadhana Memorial Hospital.

As your study is academic and unfunded, we hereby grant permission for the use of the CLDQ in the study "Medical and economic burden of chronic hepatitis B patients at Queen Savang Vadhana Memorial Hospital". Please note that you are not to share CLDQ or any translations with any other entity without our written permission, and that we maintain all copyrights to the CLDQ including translations. Also, any resulting publication must acknowledge our contribution to your study.

Please do not hesitate to contact us with any questions.

Kind regards,

Zobair M. Younossi, MD, MPH
Director, Center for Liver Disease
Inova Health System



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Junk (4)
Drafts (4)
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POP
New folder

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Flagged
Photos
Office docs

Messenger (1)

You're signed in to Messenger. To change your status, click your name in the upper right corner.
Keep me signed in | Sign out of Messenger

Search contacts
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Sign out of Messenger

Home
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Calendar

Re: Request permission for WPAI:SHP

Back to messages |

WPAI
To Chuenrutai Yeekian

6/6/2011
Reply ▾

No permission is needed to use the WPAI
http://www.reillyassociates.net/WPAI_Translations.html

Good luck with your project.
Regards,
Margaret Reilly

From: Chuenrutai Yeekian <jayeekian88@live.com>
Date: Mon, 6 Jun 2011 21:45:33 +0700
To: "mreilly@reillyassociates.net" <mreilly@reillyassociates.net>
Subject: Request permission for WPAI:SHP

Dear Reilly Associates
My name is Chuenrutai Yeekian; a candidate Ph. D. In Tropical medicine of Faculty of Tropical Medicine, Mahidol University, Thailand. My dissertation's topic is "Medical and Economic burden of Chronic Hepaitis B patients at Queen Savang Vadhana Memorial Hospital. I would like to apply the WAI: SHP in my research. I would like to ask permission from Reilly Associates and I promise that my research has been done in a non-profit organization. The results from your WAI:SHP will be useful to improve clinical treatment in chronic hepatitis B patients.
Yours Sincerely
Chuenrutai Yeekian

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BIOGRAPHY

NAME Chuenrutai Yeekiain

DATE OF BIRTH 8 July 1969

PLACE OF BIRTH Saraburi, Thailand

INSTITUTIONS ATTENDED

2009-2013 Mahidol University,
Tropical Medicine,
Doctor of Philosophy
(Tropical Medicine)

2003-2004 Burapha University
Master of Nursing Science

1986 - 1991 The Thai Red Cross Collage of Nursing,
Bachelor of Science (Nursing)

TRAINING COURSE

2010 Ethics in Human Research,
Mahidol University

2011 Academic writing,
Burapha University

2011 A training Workshop on Introduction to Health Economic Evaluation, Health Intervention and Technology Assessment Program (HITAP)

TRAINING COURSE (cont.)

2011 A training Workshop on Modeling Methods for Health Economic Evaluation, Health Intervention and Technology Assessment Program (HITAP)

2011 Researcher Training Program in Biomedical Science,
Chulalongkorn University

2012 International Standard Course in Clinical Trials,
Chulalongkorn University

2012 Systemic Reviews and Meta-analysis, Thai Cochrane Network and Burapha University

2012 International Standard Course in Clinical Trials,
Chulalongkorn University

2013 Data Analysis and Scientific Writing Workshop,
Chulalongkorn University

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E-mail: jayeekian88@live.com

PUBLICATION

First Author

Yeekian, C., Jesadapornchai, S., Urairong, K., Santibenjakul, S., Suksong, W., Nuchprayoon, C. (2013). Comparison of Maternal Factors and Neonatal Outcomes between Elective Cesarean Section and Spontaneous Vaginal Delivery. *J Med Assoc Thai*, 96 (4), 389-393.

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Other Authors

Ratvongsa, J., Yeekian, C. (2012). Comparison therapeutic effects of treatments between ultrasound treatment and Swedish massage in Trapezius myofascial pain. Thai Journal of Physical Therapy, 34 (2), 112-123.

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PUBLICATION (cont.)

Tangpoonpholwiwat, W., Yeekian, C. (2009). Effect of water drinking on the blood pressure of the intentionally blood donors. *Journal of hematology and transfusion medicine*, 19(4), 271-275.

Jirathunya, S., Yeekian, C. (2009). The blood donation service costs study at Queen Savang Vadhana Memorial Hospita. *Journal of hematology and transfusion medicine*, 19(2), 93-99.

Chunpongthong, S., Yeekian, C. (2008). The surveillance of staffs' dental health at Queen Savang Vadhana Memorial Hospital. *Chula Med J.* 52(5), 357-67.

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Atiprayoon, S., Yeekian, C. (2007). Results of Dome High Tibial Osteotomy among patients younger than sixty years old. *Chonburi Hospital Journal*, 32(3), 183-188.

ORAL PRESENTATION

Chuenrutai Yeekian, Medical and Economic Burden of Chronic Hepatitis B patient at Queen Savang Vadhana Memorial Hospital. December 11-13, 2013, Joint International Tropical Medicine Meeting 2013, Faculty of Tropical Medicine, Mahidol University

Chuenrutai Yeekian, Nursing Information System (NIS) and Data Warehouse (DW) using ICNP: A pilot project implementation at I.C.U. in Thailand, May 18-23, 2013, International Council of Nurse, Melbourne, Australia

Chuenrutai Yeekian, Medical and economic burden of chronic hepatitis B at Queen Savang Vadhana Memorial Hospital, Student Academic Forum, 24-25 November, 2012, Tropical Disease Research, Kanchanaburi, Faculty of Tropical Medicine, Mahidol University

ORAL PRESENTATION (cont.)

Chuenrutai Yeekian and Julalux Baramee, The effects of using the ICNP standard care plan on the data quality of nursing care category in selected diagnosis related group, the 23rd Quadrennial Congress 2009, International Council of Nurses, Durban, South Africa

Chuenrutai Yeekian and Julalux Baramee, Describing nursing practice for the top-ten DRGs at Queen Savang Vadhana Memorial Hospital, the 6th European Conference of ACENDIO: Nursing Communication in Multidisciplinary Practice 19-21 April 2007, Association of Common European Nursing Diagnoses, Interventions and Outcomes, Amsterdam, The Netherlands

Chuenrutai Yeekian and Julalux Baramee, A Study of Nursing Minimum Data Set in Inpatient Department of Queen Sawangwattana Memorial Hospital at Sriracha, the 23rd Quadrennial Congress 2005: Nursing on the move: knowledge, innovation and vitality 21-27 May 2005, International Council of Nurses, Taipei, Taiwan

POSTER PRESENTATION

Chuenrutai Yeekian and Punnee Pitisuttithum, Quality of Life of Chronic Hepatitis B Patients in a Rural Hospital, Queen Sri Savarindira and Prince Mahidol Adulayadej Commemoration Conference and Mahidol University Research Expo 2012, October 31 to November 1, 2012, Faculty of Graduate Studies, Mahidol University

Chuenrutai Yeekian and Julalux Baramee, A Study of Nursing Minimum Data Set in Inpatient Department of Queen Sawangwattana Memorial Hospital at Sriracha, the 6th European Conference of ACENDIO: Nursing Communication in Multidisciplinary Practice 19-21 April 2007, Association of Common European Nursing Diagnoses, Interventions and Outcomes, Amsterdam, The Netherlands