# Cost-effectiveness of Early Detection of Inactive and Treatment of Active Cases in a High Endemic Chronic Hepatitis B Region

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## Abstract

**Background:** Persons with chronic hepatitis B (CHB) infection are at risk of developing cirrhosis and hepatocellular carcinoma (HCC). Early detection of active CHB through monitoring and treatment of eligible patients have the potential to prevent these diseases.

**Aims:** We aimed to predict the disease progression in our baseline patient cohort by using risk prediction tools, and estimate the cost-effectiveness of a monitor and treat (M&T) strategy.

**Methods:** The REVEAL-HBV study team has developed nomograms for predicting liver cirrhosis and HCC risk in patients with CHB. Baseline data such as gender, birth date, HBVDNA, ALT, HBeAg status, stage of liver disease, genotype, family history of HCC, and alcohol consumption were taken for 668 CHB patients. The cohort was divided into three subgroups according to the eligibility for treatment under the APASL guidelines; ineligible, borderline and eligible, and each were scored according to the REVEAL nomogram tools.

**Results:** In the ineligible group, if inactive cases are being monitored and treated upon transition to active, the number of new cirrhotic and HCC cases will be reduced by 30% and 40%, respectively. For the borderline group, cirrhosis and HCC will be reduced by 63% and 72%, and for the eligible group, by 84% and 95%, respectively. If we were to implement the M&T strategy, the US$ per QALY gained, compared to do nothing strategy, for sub-groups eligible, borderline, and ineligible are $1,131, $500 and $97, respectively.

**Conclusions:** To reduce the risk of cirrhosis and HCC, a monitor and treat strategy is cost-effective in all-subgroups.

**Keywords:** Hepatitis B; Cost-effectiveness; Treatment; Monitor; Disease progression

## Introduction

Approximately 80% of hepatocellular carcinoma (HCC) is due to chronic hepatitis B (CHB) infection [1]. Adults with CHB infection that was acquired through mother-to-infant transmission, which is the case in China, develop HCC at a rate of about 5-10% per decade, which is approximately 100-fold higher than the rate among uninfected persons [2]. In comparison to HIV, which affects 600,000 Chinese, HBV has chronically infected an estimated 130 million Chinese, making it the most prevalent life threatening infection in China [2].

Antiviral therapy is the only option to control and prevent progression of disease in patients with active CHB, which is defined as HBV DNA >$10^4$ copies/mL, and ALT 2xULN. It is unclear whether patients with mild liver disease, borderline elevated HBV DNA, and mildly elevated ALT levels should be treated at all [3]. In patients with HBV DNA <$10^4$ copies/mL, the impact of antiviral treatment on clinical outcomes and whether treatment would actually reduce the risk of HCC are still unknown.

The Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus (REVEAL-HBV) study team has developed easy-to-use nomograms for predicting liver cirrhosis and hepatocellular carcinoma risk in patients with CHB infection, based on sex, age, family history of HCC, alcohol consumption, serum ALT level, HBeAg status, serum HBV DNA level, and HBV genotype [4,5]. This scoring system estimates the risk of developing HCC and cirrhosis at 5 and 10 years in adult chronic hepatitis B patients. In the present

study we aimed to apply these nomograms to predict the disease progression to cirrhosis and HCC in our baseline patient cohort, by dividing the groups according to the eligibility for treatment under the Asian-Pacific Association for the Study of the Liver (APASL) guidelines [6], and estimate, by implementing the predicted disease progression risks to cirrhosis and HCC in a Markov model, the cost and effects of a monitor and treat scenario for each sub-group.

## Methods

### Cohort

Between May 2011 and October 2012, a total of 1010 chronic hepatitis B patients who had mono-HBV infection were identified at the infectious diseases department of the Zhoushan hospital, Zhejiang. Baseline patient data such as gender, date of birth, baseline HBV DNA level, baseline ALT level, HBeAg status, stage of liver disease (cirrhosis,

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HCC or liver failure), genotype, family history of HCC, and alcohol consumption were taken. Alcohol consumption habit was defined as drinking alcohol at least 4 days a week for at least 1 year. All patients were treatment naïve when baseline measurements were taken. We excluded patients with HCC (n=96) and cirrhosis (n=246), and the data of the remaining 668 CHB patients at baseline were used for our study.

The CHB cohort was divided into three subgroups; ineligible, borderline and eligible, according to the 2012 APASL treatment guidelines [6] the eligibility requirements include; HBeAg-positive patients: HBV DNA ≥ 10$^5$ copies/mL and ALT ≥ 2×ULN, HBeAg-negative patients: HBV DNA ≥ 10$^4$ copies /mL and ALT ≥ 2×ULN. Borderline group was defined as; HBV DNA high or low and ALT < 2×ULN.

The CHB cohort was scored according to the REVEAL nomogram tools for risk of liver cirrhosis and HCC. For example, a 45 year old man, with family history of HCC and alcohol consumption habit, serum ALT level of 80 (U/L), HBeAg-negative, HBV DNA of 10$^5$ copies/mL and genotype C, will have a total risk score of 18 for predicting cirrhosis and a score of 15 for predicting HCC. According to the REVEAL-HBV studies risk of end stage liver diseases [7], his predicted 5- and 10-year risk was 24.85% and 54.87%, respectively, for cirrhosis; and 23.44% and 52.62%, respectively, for HCC. We calculated the 5- and 10-year risk for cirrhosis and HCC for each individual case in our CHB cohort, and have calculated the arithmetic mean for disease progression. Each subgroup was scored and the 5 and 10 year risks for liver cirrhosis and HCC were calculated. The sub-group specific 5- and 10-year risks were calculated into annual rates using the formula: $r=-(1/t))*(LN(1-P))$, and were then transformed into annual probabilities using a standard formula : $P=1-e^{-rxt}$, where $P$ is the probability, $e$ is the base of natural logarithm, $r$ is the event rate, and $t$ is the time interval, which were used as disease progression probabilities in a Markov model.

## Markov model

To compare the incremental clinical and economic outcomes of monitoring and subsequent treatment of eligible CHB patients, we used a Markov model that describes disease progression and assesses the long-term morbidity and mortality of a cohort of patients during follow-up. The structure of the model and the estimates used have been described in detail in our previous modeling study [8] and are included in supplementary Tables 1 and 2.

## Assumptions

Our model assumes continued antiviral therapy for active HBeAg-positive and negative patients. We assumed that eligible patients receive treatment with entecavir, an antiviral drug with a low resistance profile [9,10], this also according to a recent cost-effectiveness study in China on antiviral therapy concludes that entecavir is cost-effective to treat CHB compared to other antivirals [11].

## Strategies

**Natural History:** The cohort follows the natural history of disease (no antiviral treatment), with the calculated cirrhosis and HCC disease progression risk for each subgroup (Table 2), and other health states, such as death and liver transplantation (supplementary Table 1).

**Monitor & Treat:** Patients start in the inactive health state (ineligible and borderline sub-groups), and are being monitored 2x annually, when they transition to the active state, they are being treated

with entecavir. The treatment eligible group starts in the treatment model.

## Sensitivity analysis

To study the effect of uncertainty of the robustness of our results we performed a sensitivity analysis on the lower and upper bounds for the arithmetic mean of the disease progression estimates (Table 2). In addition, we tested drug (entecavir) price reduction by 5% and 50%.

## Results

### Clinical and economic outcomes

Of the 668 chronic hepatitis B patients, approximately 63% (n=425) were eligible for treatment on the basis of the APASL guideline (Figure 1). Characteristics and risk scores for the CHB cohort is summarized in Table 1. The male gender dominated (73%) and about 43% of patients were HBeAg-positive with genotype C.

| Characteristics | Risk score for liver cirrhosis* | Risk score for HCC* | Chronic hepatitis B patients N=668 |
|---|---|---|---|
| **Gender** | | | |
| Female | 0 | 0 | 180 (27%) |
| Male | 3 | 2 | 488 (73%) |
| **Age (years)** | | | |
| 30-34 | 0 | 0 | 259 (38.8%) |
| 35-39 | 1 | 1 | 76 (11.4%) |
| 40-44 | 2 | 2 | 84 (12.6%) |
| 45-49 | 3 | 3 | 80 (12%) |
| 50-54 | 4 | 4 | 82 (12.2%) |
| 55-59 | 5 | 5 | 44 (6.6%) |
| 60-64 | 6 | 6 | 43 (6.4%) |
| **Family history of HCC** | | | |
| No | - | 0 | 604 (90%) |
| Yes | - | 2 | 64 (10%) |
| **Alcohol consumption habit‡** | | | |
| No | - | 0 | 583 (87%) |
| Yes | - | 2 | 85 (13%) |
| **Serum ALT level (U/L)** | | | |
| <15 | 0 | 0 | 2 (0.3%) |
| 15-44 | 0 | 1 | 60 (9 %) |
| ≥45 | 2 | 1 | 606 (90.7%) |
| **HBeAg/HBV DNA (copies/mL)/genotype** | | | |
| Negative/<300 (undetectable)/- | 0 | 0 | 64 (9.6%) |
| Negative/300-9999/- | 2 | 1 | 41 (6.1%) |
| Negative/10 000-99 999/B or B + C | 4 | 3 | 14 (2.1%) |
| Negative/10 000-99 999/C | 3 | 4 | 34 (5.1%) |
| Negative/100 000-999 999/B or B + C | 6 | 3 | 9 (1.3%) |
| Negative/100 000-999 999/C | 10 | 7 | 40 (6%) |
| Negative/≥ 10$^6$/B or B + C | 6 | 4 | 21 (3.1%) |
| Negative/≥ 10$^6$/C | 12 | 7 | 62 (9.3%) |
| Positive/B or B + C | 6 | 6 | 95 (14.2%) |
| Positive/C | 9 | 6 | 288 (43.1%) |

*Risk scores assigned to risk predictors of liver cirrhosis and HCC from the REVEAL-study [7]‡Alcohol consumption habit was defined as drinking alcohol at least 4 days a week for at least 1 year [5]

**Table 1:** Patient characteristics and the risk scores.

Table 2 presents the estimated disease progression risks for cirrhosis and HCC in each sub-group. In a 10-year period, the disease progression for (total cohort) cirrhosis and HCC is 24.42%, and 11.40%, respectively. If we look at sub-group specific disease progression, a high HCC disease progression is noted in the borderline group.

The average lifetime costs, QALYs gained, and US$ per QALY gained (Incremental Cost Effectiveness Ratio (ICER)) in the natural history and monitor & treat scenario for each sub-group, are presented in Table 3. The highest amount of QALYs gained in the treatment eligible group if monitor & treat scenario is applied, is 9.09, followed by the borderline group 7.54, and 3.30 in the ineligible group, compared to the natural history. The US$ per QALY gained for sub-groups treatment, borderline, and no treatment are $1,131, $500 and $97, respectively. The ICER was the lowest ($97) in the no treatment group.

A reduction in the development of cirrhosis and HCC was observed in our model projections when the monitor & treatment scenario was applied. In the ineligible group, if inactive cases are being monitored and treated upon transition to active, the number of new cirrhotic and HCC cases will be reduced by 30% and 40%, respectively. For the borderline group, cirrhosis and HCC will be reduced by 63% and 72%, and for the treatment group, by 84% and 95%, respectively. Compared to the natural history (do nothing) scenario, for sub-groups ineligible, borderline and eligible, the monitor & treat scenario has a gain of 7, 14 and 23 life years, respectively.

### Program costs for monitoring inactive and treating eligible patients

In addition to the cost and QALY gained per patient, we calculated the total program costs if the CHB patients are identified, monitored and treated. The Zhoushan Island has a population of approximately 500,000. If we modestly assume that the prevalence of HBsAg is 10% on the island, meaning 50,000 HBsAg-positive cases. If we further categorize these patients into sub-groups, we will have 15,000 (30%) in no-treatment, 3,500 (7%) in borderline and 31,500 (63%) in the treatment group. The total costs for a monitor & treat program in sub-groups no-treatment, borderline and treatment, are $323 million,

$129 million and $1.3 billion, respectively. In return, we gain a total of 290,000 QALYs, and 105,000 LYs for no-treatment group; a total of 69,720 QALYs, and 49,000 LYs for borderline group; and a total of 671,895 QALYs and 724,500 LYs for the treatment group.

### Sensitivity analysis

When the upper boundary the disease progression estimates were assumed, the ICER in each subgroup decreased by 72%, 77% and 12% for the ineligible, borderline and eligible groups, respectively, compared to the base case results. When the lower boundary disease progression estimates were assumed, the ICER increased by 49%, 30% and 11% for the ineligible, borderline, and eligible groups, respectively (Figure 2). When 50 % price reduction is applied to entecavir, the monitor & treat scenario becomes cost-saving in all sub-groups, by cost-saving meaning that the cost is lower and the QALY higher compared to the natural history. Even if the entecavir price is reduced by 5%, it will be a cost saving scenario in the ineligible group, and higher ICERs compared to the base case price in the monitor & treat scenario (Table 3).

### Discussion

Chronic hepatitis B is an asymptomatic disease, meaning that persons that are infected are often not aware, and generally not detected. The cases that are detected are usually not followed-up for reasons such as high costs, and not taking the disease seriously, either by the patient or the health care specialist. If the already detected active and inactive cases follow a so called "monitor & treat" program, the reduction in cirrhosis and HCC will be substantial, compared to the high disease progression which we calculated using the REVEAL nomograms. The monitor & treat program will be cost-effective in all sub-groups, and even cost-saving if the price for the low resistant profile drug is reduced by 5%.

The height of the threshold value is of great influence on decisions in the reimbursement process and intervention policy. The World Health Organization defines the threshold value for intervention cost-effectiveness as 1-3x the gross domestic product per capita for a country [12]. For China this value is between $5,545 and $16,635, which makes

| Disease progression risk, % (95% CI) | | | | |
|---|---|---|---|---|
| | **Cirrhosis** | | **HCC** | |
| Sub-group | 5-year | 10-year | 5-year | 10-year |
| Ineligible (n=198) | 5.86 (4.9-6.8) | 14.51 (12.5-16.5) | 3.22 (2.5-4.0) | 8.04 (6.3-9.8) |
| Borderline (n=45) | 13.63 (8.6-18.6) | 27.95 (19.5-36.4) | 9.48 (4.2-14.7) | 18.42 (10.3-26.5) |
| Eligible (n=425) | 12.86 (11.6-14.0) | 28.67 (26.5-30.7) | 5.20 (4.4-6.0) | 12.23 (10.6-13.9) |
| Total cohort (n=668) | 10.84 (9.9-11.7) | 24.42 (22.8-26.0) | 4.90 (4.2-5.6) | 11.40 (10.1-12.7) |

arithmetic mean was taken for the disease progression rates

**Table 2:** Cirrhosis and HCC progression rates in each sub-group.

| Strategy | **Ineligible group** | | | **Borderline group** | | | **Eligible group*** | | |
|---|---|---|---|---|---|---|---|---|---|
| | Total cost per patient ($) | Total QALYs per patient | ICER* | Total cost per patient ($) | Total QALYs per patient | ICER* | Total cost per patient ($) | Total QALYs per patient | ICER* |
| Natural history | 21,229 | 16.06 | - | 33,280 | 12.38 | - | 32,430 | 12.24 | - |
| Monitor & Treat | 21,550 | 19.36 | 97 | 37,043 | 19.92 | 500 | 42,711 | 21.33 | 1,131 |
| Reduction in ETV price by 5% | 20,752 | 19.36 | cost saving | 35,196 | 19.92 | 254 | 40,243 | 21.33 | 860 |
| Reduction in ETV price by 50% | 14,794 | 19.36 | cost saving | 21,622 | 19.92 | cost saving | 22,164 | 21.33 | cost saving |

US$ per QALY gained
*Patients eligible under the APASL treatment guideline

**Table 3:** Average life-time costs and QALYs per patient for each sub-group.

our calculated ICERs very appealing, because for each sub-group the values are lower than the given threshold. If we manage to lower drug costs by about 50%, we will be saving money and lives compared to doing nothing, and this will be the case by only reducing the price by 5% for the no-treatment group.

The disease progression risk to HCC in the borderline group was the highest. This could suggest the following: the REVEAL study takes factors such as age, HBeAg, HCC family history, genotype and alcohol consumption into consideration. When APASL is preparing treatment guidelines, they look at ALT and HBV DNA values, and take HBeAg as a co-factor when looking at ALT and HBV DNA. In our borderline sub-group, patients have a family history of HCC that increases the risk, which could explain the high rate of disease progression in this group. Therefore if family history of HCC and alcohol consumption is known, which can play a major factor in the progression of disease; this should be taken in consideration including the already used indicators for treatment eligibility such as HBV DNA and ALT levels.

Studies have found that a noticeable proportions of patients with borderline normal and/or mildly elevated ALT to have substantial histologic disease and thus to be at risk of liver related mortality [13-15]. Especially in Asian patients, liver damage is more deceptive, leading to a long term and severe complications even with ALT levels 1-2xULN [16]. Patients with normal ALT who are not considered treatment eligible according to the treatment guidelines, are still at risk to have serious disease activity [15,17]. Tong et al. [18] provides insight into the effect of current treatment guidelines in which their study reports that 30-53% of patients who later developed HCC or died of liver related causes were not found to be eligible for treatment on the basis of either the US Panel or AASLD guidelines.

Nguyen et al. [19] studied the treatment eligibility during follow-up of patients that were initially ineligible for treatment, a cohort that consisted primarily of Asian patients, under the US Panel and the AASLD guidelines. In this study, the cumulative rates of patients meeting treatment criteria was 6% at year 1, 18% at 2 years, and 29% at 3 years of follow up, which emphasize the importance of regular follow-up of CHB patients to assess disease status and treatment conditions.

Results from a recent meta-analysis [20] report that HBV genotype C doubles the risk of developing HCC compared with other major HBV genotypes. This finding can support to implement screening for high-risk patients in order to provide intensive HCC surveillance for patients infected with genotype C. The predominant genotype found in our patients was genotype C, which is in accordance with a recent genotype study on a CHB patient population in the Zhoushan Islands [21]. Most Asian patients acquire HBV infection through vertical or early horizontal transmission and are often diagnosed during the immuno-tolerant phase, when serum HBV DNA levels are high but ALT values are persistently normal [22]. Sarin and Kumar [23] propose that patients with normal ALT should be considered for treatment based on the HBV DNA levels and histological injury.
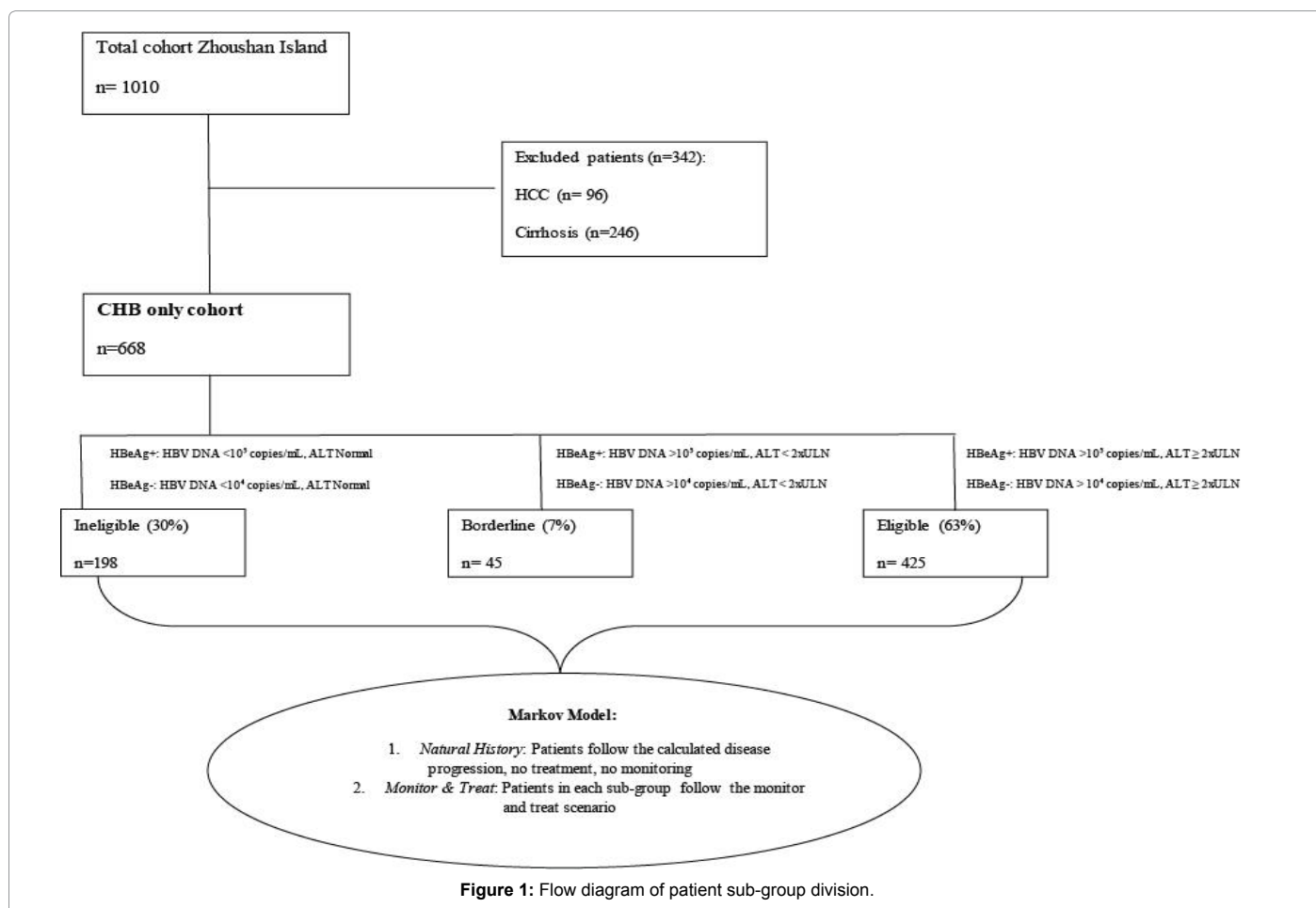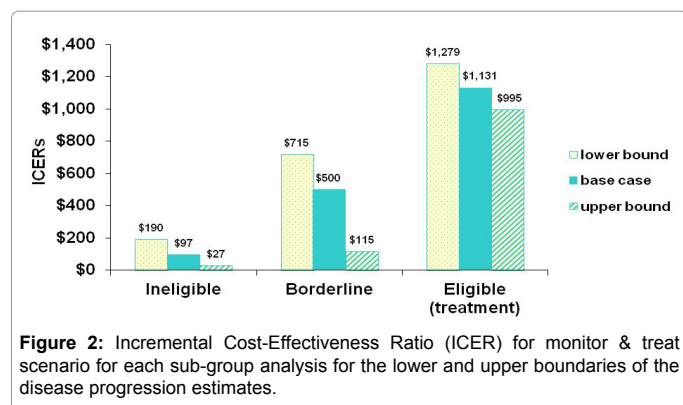


**Figure 1:** Flow diagram of patient sub-group division.

**Figure 2:** Incremental Cost-Effectiveness Ratio (ICER) for monitor & treat scenario for each sub-group analysis for the lower and upper boundaries of the disease progression estimates.

Patients should be regularly monitored to detect active disease as effective treatment is available. Many patients with CHB do not receive routine monitoring, treatment or follow-up, which could have several reasons; lack of knowledge about the disease and the need for treatment, uncertainty about how to treat, insufficient knowledge on the severity of the disease, and lack of resources to diagnose and subsequently treat [24]. In a recent survey study by Chao et al. [25], of the 250 highly educated health care and public health professionals, 34% did not know that CHB is often asymptomatic, and 29% did not know that CHB confers a high risk of cirrhosis, liver cancer, and premature death.

In Asia, the cost of therapy and cost-effectiveness analyses from the patient's perspective is heavily influenced by reimbursement policies of countries. There are three basic types of policies: full reimbursement where the patient pays no direct costs as the costs are borne by the tax payer, partial reimbursement where only part of the costs are reimbursed and the balance is paid directly by the patient, and no reimbursement where the patient pays for everything [26]. A recent study by Lu et al. [27] estimated the direct out of pocket cost of all HBV-related diseases. In their study population 95% were insurance, but concluded that patients with severe hepatitis B or primary cancer suffered a high economic burden even after insurance reimbursement, spending 137.5% and 149.5%, respectively, of their household annual income.

A limitation in our study is that our patient data is a hospital based cohort, and it is possible that the proportion of patients in the treatment eligible group is high. Although, our results are in accordance with a large population of Chinese CHB patient study by Fung et al. of which, 64% of their study population was eligible for treatment under the APASL guidelines.

Hepatitis B virus vaccines created the first breakthrough in HBV prevention. The next breakthrough came with therapy for CHB, which has the potential to prevent progression to cirrhosis, reverse cirrhosis scares [28], and possibly prevent liver cancer. But treatment is only effective if the people who are eligible for treatment are identified. Screening not only identifies persons who may be HBV carriers, and need to be monitored, and/or treated to prevent liver cancer, but it also identifies non-carriers so they can be vaccinated, and thus prevented. So if we do detect HBsAg-positive cases, it should be possible to apply a monitor & treat if eligible strategy, in a high endemic area. The next step is to find out how much a screening program will cost, and whether it is cost-effective in combination with our proposed "monitor & treat" strategy.

## References

1. El-Serag HB (2012) Epidemiology of viral hepatitis and hepatocellular carcinoma. Gastroenterology 142: 1264-1273.

2. Liu J, Fan D (2007) Hepatitis B in China. Lancet 369: 1582-1583.

3. Liaw YF (2009) On-treatment outcome prediction and adjustment during chronic hepatitis B therapy: now and future. Antivir Ther 14: 13-22.

4. Yang HI, Sherman M, Su J, Chen PJ, Liaw YF, et al. (2010) Nomograms for risk of hepatocellular carcinoma in patients with chronic hepatitis B virus infection. J Clin Oncol 28: 2437-2444.

5. Yang HI, Yuen MF, Chan HL, Han KH, Chen PJ, et al. (2011) Risk estimation for hepatocellular carcinoma in chronic hepatitis B (REACH-B): development and validation of a predictive score. Lancet Oncol 12: 568-574.

6. Liaw YF, Leung N, Kao JH, Piratvisuth T, Gane E, et al. (2008) Asian-Pacific consensus statement on the management of chronic hepatitis B: a 2008 update. Hepatol Int 2: 263-283.

7. Chen CJ, Yang HI (2011) Natural history of chronic hepatitis B REVEALed. J Gastroenterol Hepatol 26: 628-638.

8. Toy M (2013) Population health impact and cost-effectiveness of monitoring inactive chronic hepatitis B and treating eligible patients in Shanghai, China. Hepatology in press.

9. Woo G, Tomlinson G, Nishikawa Y, Kowgier M, Sherman M, et al. (2010) Tenofovir and entecavir are the most effective antiviral agents for chronic hepatitis B: a systematic review and Bayesian meta-analyses. Gastroenterology 139: 1218-1229.

10. Wong GL, Chan HL, Mak CW, Lee SK, Ip ZM, et al. (2013) Entecavir treatment reduces hepatic events and deaths in chronic hepatitis B patients With liver cirrhosis. Hepatology .

11. Wu B, Li T, Chen H, Shen J (2010) Cost-effectiveness of nucleoside analog therapy for hepatitis B in China: a Markov analysis. Value Health 13: 592-600.

12. Iloeje UH, Yang HI, Chen CJ (2012) Natural history of chronic hepatitis B: what exactly has REVEAL revealed? Liver Int 32: 1333-1341.

13. Tsang PSY, Trinh H, Garcia RT, Phan JT, Ha NB, et al. (2008) Significant prevalence of histologic disease in patients with chronic hepatitis B and mildly elevated serum alanine aminotransferase levels. Clin Gastroenterol Hepatol 6: 569-574.

14. Kim HC, Nam CM, Jee SH, Han KH, Oh DK, et al. (2004) Normal serum aminotransferase concentration and risk of mortality from liver diseases: prospective cohort study. BMJ 328: 983.

15. Lai M, Hyatt BJ, Nasser I, Curry M, Afdhal NH (2007) The clinical significance of persistently normal ALT in chronic hepatitis B infection. J Hepatol 47: 760-767.

16. Yuen MF, Yuan HJ, Wong DK, Yuen JC, Wong WM, et al. (2005) Prognostic determinants for chronic hepatitis B in Asians: therapeutic implications. Gut 54: 1610-1614.

17. Kumar M, Sarin SK, Hissar S, Pande C, Sakhuja P, et al. (2008) Virologic and histologic features of chronic hepatitis B virus-infected asymptomatic patients with persistently normal ALT. Gastroenterology 134: 1376-1384.

18. Tong MJ, Hsien C, Hsu L, Sun HE, Blatt LM (2008) Treatment recommendations for chronic hepatitis B: an evaluation of current guidelines based on a natural history study in the United States. Hepatology 48: 1070-1078.

19. Nguyen NH, Nguyen V, Trinh HN, Lin B, Nguyen MH (2013) Treatment eligibility of patients with chronic hepatitis B initially ineligible for therapy. Clin Gastroenterol Hepatol 11: 565-571.

20. Wong GL, Chan HL, Yiu KK, Lai JW, Chan VK, et al. (2013) Meta-analysis: The association of hepatitis B virus genotypes and hepatocellular carcinoma. Aliment Pharmacol Ther 37: 517-526.

21. Li SB, Lin ZY, Ding XJ, Li YW, Li SZ, et al. (2007) [The relationship between the genotype of hepatitis B virus and clinical and liver pathological features of infected patients in the Zhoushan Islands, China]. Zhonghua Gan Zang Bing Za Zhi 15: 179-183.

22. Chu CM, Liaw YF (2007) Chronic hepatitis B virus infection acquired in childhood: special emphasis on prognostic and therapeutic implication of delayed HBeAg seroconversion. J Viral Hepat 14: 147-152.

23. Sarin SK, Kumar M (2008) Should chronic HBV infected patients with normal ALT treated: debate. Hepatol Int 2: 179-184.

24. Lau G, Marcellin P, Peters M (2007) Chronic hepatitis B: a global health problem requiring coherent worldwide treatment strategies. Hepatol Int 1: 316-325.

25. Chao J, Chang ET, So SKS (2010) Hepatitis B and liver cancer knowledge and practices among healthcare and public health professionals in China: a cross-sectional study. BMC Public Health 10: 98.

26. Dan YY, Aung MO, Lim SG (2008) The economics of treating chronic hepatitis B in Asia. Hepatol Int 2: 284-295.

27. Lu J, Xu A, Wang J, Zhang L, Song L, et al. (2013) Direct economic burden of hepatitis B virus related diseases: evidence from Shandong, China. BMC Health Serv Res 13: 37.

28. Marcellin P, Gane E, Buti M, Afdhal N, Sievert W, et al. (2013) Regression of cirrhosis during treatment with tenofovir disoproxil fumarate for chronic hepatitis B: a 5-year open-label follow-up study. Lancet 381: 468-475.