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Cost of Illness of Chronic Hepatitis B Infection in Vietnam

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ABSTRACT

Objectives: To estimate the total financial burden of chronic hepatitis B virus (HBV) infection for Vietnam by quantifying the direct medical, the direct nonmedical, and indirect costs among patients with various stages of chronic HBV infection. **Methods:** Direct medical cost data were retrieved retrospectively from medical histories of inpatients and outpatients in 2008 from a large referral hospital in Hanoi, Vietnam. Direct nonmedical and indirect costs data were obtained from face-to-face interviews of outpatients from the same hospital. The treatment cost per patient per chronic HBV infection stage was multiplied by the total estimated patients in Vietnam to get the total cost of illness for the nation. **Results:** Nationally, the total cost attributable to chronic HBV infection and its complications in 2008 was estimated to be approximately US \$4.4 billion, with the direct medical cost accounting for about 70% of that estimate. The cost of antivirals was the major cost driver in treating chronic HBV infection. The per-patient total annual direct medical cost increased with the severity of the disease, with the

estimated costs for chronic HBV infection and hepatocellular carcinoma as US \$450.35 and US \$1883.05, respectively. When compared with the 2008 per-capita gross domestic product of ~US \$1024, the financial burden of treating chronic HBV infection is very high in Vietnam. **Conclusions:** This study confirmed that chronic HBV infection poses a significant financial burden for the average patient and that lacking treatment would become a social issue in Vietnam. Although HBV vaccination has been universally implemented, more health care investment and the greater availability of affordable medications are still needed to attain equity in proper treatment for patients with HBV infection.

Keywords: chronic hepatitis B, cost of illness, direct medical cost, indirect cost.

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Introduction

Hepatitis B virus (HBV) is one of the most prevalent blood-borne viruses worldwide, with chronic HBV infection afflicting more than 350 million people [1]. Major clinical consequences of HBV infection include liver failure, cirrhosis, and hepatocellular carcinoma (HCC) [2,3]. These complications lead to more than 1 million deaths each year [3–5]. Thus, HBV infection is an important public health problem, especially for developing countries where the endemicity is often either intermediate or high.

Vietnam is a high-endemic country for HBV infection [6]. Population surveys from the two biggest cities, Hanoi and Ho Chi Minh City, have shown a positive hepatitis B surface antigen (HBsAg+) rate of 9% to 14% [7,8]. High HBsAg+ prevalence in Vietnam is supported by another small survey of children in rural regions. In this survey, the HBsAg+ rate was 19.5% [9]. While very little data exist

in Vietnam on the proportion of patients who were HBsAg+ and have chronic HBV infection, cirrhosis, or HCC, the international literature has reported that 75% to 80% of patients with chronic HBV infection, 34% of patients with cirrhosis, and 72% of patients with HCC were also HBsAg+ [10]. Hence, chronic HBV infection and the resulting liver diseases would pose a heavy burden for the Vietnamese health care system.

At the per-capita gross domestic product of US \$1024 [11], the cost of treatment for diseases stemming from HBV infection is significant for the average Vietnamese patient. Moreover, antiviral drugs remain expensive. Comprehensive analyses of the financial burden of HBV infection in Vietnam, however, are very limited. In view of this, we conducted a cost-of-illness study of HBV infection by using data from one major referral hospital in Vietnam and extrapolated the results nationally. Our analyses should provide the Vietnamese decision makers some guidance on resource allocation for health, particularly for HBV-related conditions.

Conflicts of interest: The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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Methods

The study contains two parts: 1) quantification of the direct medical cost and 2) quantification of the direct nonmedical cost and the indirect cost of HBV infection. The financial burden to the Vietnamese society is represented by the total cost (direct medical, direct nonmedical, and indirect costs) multiplied by the estimated number of infected subjects in Vietnam. The study protocol was approved by the Director of Bach Mai Hospital in Hanoi, where the study was carried out. Bach Mai Hospital, a 1400-bed hospital, is among the largest hospitals in Vietnam. It is a highly specialized multidisciplinary medical facility with a focus on internal medicine and the most active in treating hepatitis B patients in Hanoi. In the cost analysis, the study followed the bottom-up approach [12]. Direct medical costs were estimated from retrospective analysis. Direct nonmedical and indirect costs were obtained from patient interviews.

Part 1: Measurement of direct medical cost

Data were collected from medical and financial records of Bach Mai Hospital from January 1 to December 31, 2008. The records for all inpatients treated at the Department of Infectious Diseases and all outpatients treated at the Infectious Diseases Unit of the Outpatient Department were included.

By using the codes established by the *International Statistical Classification of Diseases, 10th Revision*, we identified and retrieved information on HBV patients classified under B18 (chronic HBV infection patients), K74 (compensated cirrhosis [CC] and decompensated cirrhosis [DC]), and C22 (HCC). Patients coded with K74 were subsequently differentiated as either CC or DC through clinical diagnosis from patient case notes.

Cost consideration

The total direct medical cost related to the treatment of chronic HBV infection and associated complications included clinic visit cost (outpatient visits and hospitalizations), investigation cost (laboratory tests and procedures), and drug costs (antiviral drugs and other medicines) and other services (bed costs, meals, etc.).

The study assessed resource utilization based on hospital charges in 2008 and was expressed in US \$ (US \$1 = VND17,803) [13]. Because Bach Mai Hospital is a public nonprofit health care institution with most service charges based on cost recovery, the use of charge for the estimation of costs would be the most appropriate approach [14].

Calculation of direct medical cost

The total annual direct medical cost per patient from each category of chronic HBV infection was calculated by the following formulae:

$$\text{Annual cost/patient} = \text{Cost/visit} \times \text{Visits/year} + \text{Cost/admission} \\ \times \text{Admissions/year}$$

where visits/year = aggregated visits of observed patient cases/aggregated observed patient cases, and admissions/year = aggregated admissions of observed patient cases/aggregated observed patient cases.

Part 2: Measurement of direct nonmedical and indirect costs

Estimations of direct nonmedical (expenses on travel, accommodation, and meals) and indirect costs (medical leave, time off, and productivity loss) were collected through interviews of outpatients after informed consents were obtained. In the cases where no consenting subject for a particular category of clinical diagnosis

(described above) was available, physicians were interviewed as surrogates for their opinions on the likely costs to the patient.

For the working group, medical leave and time off were the components for the indirect cost. The annual cost of day offs for medical leave was calculated by multiplying the days taken for medical leave by the average daily-wage rate. The annual time-off cost for outpatient visits was calculated by multiplying the total time off by the average hourly earnings. For daily and hourly wage calculation, a 5-day workweek and an 8-hour workday were assumed.

For the nonworking group, productivity loss was used as the indicator of indirect cost and was calculated by assuming that the minimum wage was the monthly wage [15].

Estimation of prevalence

To estimate numbers of HBV carriers and cirrhosis cases, data were extrapolated from the study on HBV infections and HBV-related cirrhosis in Vietnam in 2005, which were estimated at 10.05% and 481 per 100,000, respectively [16]. Assuming the same prevalence rate as in 2005 and extrapolating to the 2008 population of 86,084,547 in Vietnam [17], the estimated HBV carriers and patients with cirrhosis were 8,651,497 and 414,067, respectively. No official data on the ratio of CC to DC cases were available in Vietnam. By using the ratio of CC to DC (8:1) at Bach Mai Hospital as a guide, it would translate to approximately 368,059 CC and 46,007 DC cases.

The prevalence of HCC was calculated by multiplying the HCC incidence rate (estimated at 0.019% in 2005 [16]) with the average duration of HCC (estimation of 1 year [18–20]); HCC cases in Vietnam in 2008 were 16,356.

Subtracting the cirrhosis and HCC cases from total chronic HBV carriers, the number of chronic HBV infection cases was estimated to be 8,221,074.

Sensitivity analysis

For the direct medical cost, two one-way sensitivity analyses were performed. In the first sensitivity analysis, the lower and upper limits of the direct medical cost (95% confidence interval) were tested. In the second sensitivity analysis, the number of patients in different chronic HBV disease stages was varied as follows:

1. Using the prevalence rate of HBV-infected patients of 8% to 16% [7–9,21] as the lower and upper limits, respectively, for estimating the number of chronic HBV carriers;
2. Using survival times from 5 months to 16 months [22–24] as the lower and upper limits, respectively, for estimating the prevalence of HCC subjects; and
3. Applying the base-case ratio (4.79%) between cirrhosis cases and chronic HBV carriers [16] to the lower and upper limits of chronic HBV carriers to estimate the lower and upper limits for liver cirrhosis cases.

For direct nonmedical and indirect costs, two one-way sensitivity analyses were also performed. In the first analysis, the 25th and 75th percentiles of the indirect cost were tested. In the second analysis, the number of patients in each disease stage was varied as for the direct medical cost.

Two-way sensitivity analyses (best- and worst-case scenarios) were conducted to test the combined effects of varying both the number of subjects and the treatment costs.

Results

Direct medical cost

A total of 904 patient cases (470 outpatients and 434 inpatients) were included for analysis, consisting of 226 chronic HBV infec-

Table 1 – Annual outpatient visits and hospitalizations for patients with chronic HBV infection by disease stages in Vietnam in 2008*.

| | Chronic hepatitis B | Compensated cirrhosis | Decompensated cirrhosis | Hepatocellular carcinoma |
|----------------------------------------------------------------------|---------------------|-----------------------|-------------------------|--------------------------|
| Outpatient visits | | | | |
| Per person per year | 3.84 (3.02–4.66) | 4.31 (2.65–5.97) | 5.7 (3.79–7.61) | 5 (3.09–6.91) |
| No. of hospitalizations | | | | |
| Per person per year | 0.17 (0.12–0.22) | 0.27 (0.21–0.48) | 0.51 (0.37–0.65) | 2.34 (2.11–4.45) |
| Length of stay | | | | |
| Per admission (d) | 2.35 (2.11–2.59) | 2.50 (2.02–2.98) | 13.54 (9.87–17.20) | 12.76 (10.87–14.65) |
| HBV, hepatitis B virus. | | | | |
| * Liver transplant program was not established at Bach Mai Hospital. | | | | |

tion, 203 CC, 117 DC, and 358 HCC cases. The mean age of the inpatient cases and the outpatient cases was 46.4 years (range 13–83 years) and 39.4 years (range 15–61 years), respectively.

The results show that the annual direct medical cost of the treatment increased with disease progression, with drug costs accounting for the largest part of the direct medical cost. Details on annual health care utilization and the estimated average annual treatment cost per patient for each disease stage are listed in Tables 1 and 2, respectively.

Lamivudine was the most frequently used antiviral agent in our study, likely because it is currently the only agent reimbursed by the health insurance of Vietnam.

In 2008, the total estimated direct medical cost associated with different chronic HBV infection stages was US \$4 billion (Table 3A).

Results of the first and second one-way sensitivity analyses were between US \$2.8 and 5.5 billion and between US \$3.2 and 6.4 billion, respectively (Table 3B). The two-way sensitivity analyses, however, resulted in a range of US \$2.2 to 8.8 billion (Table 3B).

Direct nonmedical and indirect costs

Fifty-one patients with chronic HBV infection (mean age 36.12 [range 16–59 years] years) participated in the study.

Because the cost distribution was skewed, the median values were used to calculate indirect costs. Details on direct nonmedical and indirect costs are shown in Table 4. The base-case estimation for total direct nonmedical and indirect costs for all HBV disease stages in Vietnam was roughly US \$375 million (Table 5A). Results of one-way sensitivity and two-way sensitivity analyses for esti-

imating direct nonmedical and indirect costs are summarized in Table 5B.

Cost of illness for chronic HBV infection estimation

Table 6 shows that the cost of illness for chronic HBV infection in Vietnam in 2008 was estimated at US \$4.4 billion, with chronic HBV infection as the most costly component.

Discussion

To the best of our knowledge, this is the first cost-of-illness study for chronic HBV infections in Vietnam. Our results clearly showed that chronic HBV infection and its complications impose a significant financial burden on the Vietnamese society and health care system. If all patients with chronic HBV infection and its various disease stages were treated in hospitals, the total annual cost would amount to ~US \$4.4 billion, which is ~5% of the gross domestic product of Vietnam in 2008.

In reality, the Vietnamese government's expenditure on health accounted for only a quarter of the total national health expenditure with the remainder coming from patients' out-of-pocket payment [25,26]. At the current per-capita gross domestic product of US \$1024 [11], the treatment costs of chronic HBV infections would be a significant financial burden for the average Vietnamese patient. This might imply that a substantial number of patients with HBV infections who cannot bear these costs may be undertreated or untreated.

Table 2 – Average annual direct medical cost (in US \$) per patient of chronic HBV infection by disease stages and cost compositions in Vietnam in 2008.

| | Chronic hepatitis B | Compensated cirrhosis | Decompensated cirrhosis | Hepatocellular carcinoma |
|------------------------------------------------------------|------------------------|-------------------------|--------------------------|---------------------------|
| Total cost (US \$) | 450.35 (319.73–599.66) | 690.43 (376.05–1234.37) | 1114.50 (642.45–1723.78) | 1883.05 (1228.03–3870.65) |
| Outpatient cost | 439.85 (313.87–582.88) | 658.18 (361.52–1147.15) | 795.60 (505.41–1110.13) | 697.90 (412.17–1007.95) |
| Inpatient cost | 10.49 (5.87–16.78) | 32.25 (14.53–87.23) | 318.90 (137.04–613.65) | 1185.15 (815.85–2862.70) |
| Cost composition (%) | | | | |
| Antiviral drugs* | 14.85 | 23.97 | 27.06 | 1.69 |
| Other medications* | 54.28 | 46.59 | 40.73 | 45.11 |
| Examination/laboratory tests, procedures,† other services‡ | 29.22 | 28.03 | 29.90 | 43.97 |
| Consultations | 1.65 | 1.41 | 2.32 | 9.22 |
| Total | 100.00 | 100.00 | 100.00 | 100.00 |

HBV, hepatitis B virus.

* Cost of medications = $\Sigma(\text{Medication price}_i \times \text{amount}_i)$.

† Cost of examinations and laboratory tests = $\Sigma(\text{Unit cost}_i \times \text{Utilization frequency}_i)$.

‡ Other services include bed cost and meals.

Table 3 – (A) Base-case estimates and (B) sensitivity analyses of total direct medical cost of chronic HBV infection by disease stages in Vietnam in 2008.

| A. Base-case estimates | | | | |
|-------------------------|---------------------------------------|----------------------------------------------|-----------------------------------------------------------|------------------------------------------------------------|
| Disease category | Number of patients | Mean direct medical cost per patient (US \$) | Total direct medical cost per year (US \$) | |
| CHB | 8,221,074.00 | 450.35 | 3,702,344,156.83 | |
| CC | 368,059.00 | 690.43 | 254,118,890.27 | |
| DC | 46,007.00 | 1,114.50 | 51,274,910.42 | |
| HCC | 16,356.00 | 1,883.05 | 30,799,174.35 | |
| Total | 8,651,497.00 | 4,138.33 | 4,038,537,131.88 | |
| B. Sensitivity analysis | | | | |
| Disease category | Range of estimated number of patients | Range of estimated direct medical cost | First one-way sensitivity analysis (US \$) | Second one-way sensitivity analysis (US \$) |
| CHB | 6,533,015–13,058,282 | 319.73–599.66 | 2,628,542,811–4,929,838,419 | 2,942,130,126–5,880,771,131 |
| CC | 308,322–616,644 | 376.05–1,234.37 | 138,409,271–454,322,691 | 212,874,616–425,749,232 |
| DC | 38,540–77,080 | 642.45–1,723.78 | 29,557,257–79,306,656 | 42,953,185–85,906,371 |
| HCC | 6,887–21,521 | 1,228.03–3,870.65 | 20,085,706–63,308,668 | 12,968,124–40,525,388 |
| Total | 6,886,764–13,773,528 | 2,566.26–7,428.47 | 2,816,595,045–5,526,776,434 | 3,210,926,051–6,432,952,122 |
| Disease category | Range of estimated number of patients | Range of estimated direct medical cost | Two-way sensitivity analysis (best-case scenario) (US \$) | Two-way sensitivity analysis (worst-case scenario) (US \$) |
| CHB | 6,533,015–13,058,282 | 319.73–599.66 | 2,088,815,738 | 7,830,512,048 |
| CC | 308,322–616,644 | 376.05–1,234.37 | 115,944,939 | 761,168,906 |
| DC | 38,540–77,080 | 642.45–1,723.78 | 24,760,006 | 132,869,790 |
| HCC | 6,887–21,521 | 1,228.03–3,870.65 | 8,457,139 | 83,300,879 |
| Total | 6,886,764–13,773,528 | 2,566.26–7,428.47 | 2,237,977,823 | 8,807,851,623 |

CC, compensated cirrhosis; CHB, chronic hepatitis B; DC, decompensated cirrhosis; HCC, hepatocellular carcinoma.

As a consequence of these costs, many patients turned to traditional medicines as an alternative. From interviews with physicians from Bach Mai Hospital, it appeared that only 1% of patients with chronic HBV infection and other complications received hospital treatment.

In our study, resource utilization pattern for the direct medical costs was consistent with other published studies, with direct medical costs increasing with disease progression [27–29]. Expenses on medications were the largest cost driver for the direct treatment cost for chronic HBV infection, CC, and DD, accounting for more than 70% of the total direct medical cost. This might be explained by the high drug prices in Vietnam.

Indeed, the prices of nucleosides are still very costly in Vietnam and antiviral therapy is affordable for only a small proportion of HBV-infected patients. This problem is exacerbated by the higher drug prices in public pharmacies [30], where many patients with

chronic HBV infections would purchase their medications. It was estimated that for chronic diseases, 1-month treatment cost might be equivalent to 22-day minimum wages for generic drug and up to 50-day wages for an innovator brand [30]. Thus, if more generic drugs could either be manufactured domestically at a lower cost or imported at a lower price, the affordability of chronic HBV infection treatment would increase.

Because many patients with chronic HBV infection reside outside of Hanoi, direct nonmedical and indirect cost appeared to be a substantial part of cost in Vietnam.

Our study also has several limitations. First is the issue of representativeness of the patient sample. Ideally, inpatients after discharge would have to return for follow-up assessment and therapy. This does not, however, happen in Vietnam. Many patients with chronic HBV infections live in provinces distant from Hanoi and are agricultural workers with very low income, thus making it

Table 4 – Annual direct nonmedical and indirect costs (US \$) of chronic HBV infection by disease stages per patient in Vietnam in 2008.

| Disease category | Medical leave and time off | Productivity loss* | Transportation, meals, accommodation | Annual direct nonmedical and indirect costs |
|------------------|----------------------------|--------------------|--------------------------------------|---------------------------------------------|
| CHB | 1.04 | 15.32 | 22.62 | 38.98 |
| CC | 1.73 | 25.53 | 148.85 | 176.11 |
| DC | 17.63 | 71.49 | 154.11 | 243.23 |
| HCC | 76.19 | 80.27 | 153.12 | 309.58 |
| Total | 96.59 | 192.61 | 478.70 | 767.90 |

CC, compensated cirrhosis; CHB, chronic hepatitis B; DC, decompensated cirrhosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

* Monthly cost of reduced productivity = Reported loss of productivity × monthly wage rate, where Reported loss of productivity = number of sick days due to HBV/total number working days of a month.

Table 5 – (A) Base-case estimates and (B) sensitivity analyses of total direct nonmedical and indirect costs of chronic HBV infection by disease stages in Vietnam in 2008.

| A. Base-case estimates | | | | |
|-------------------------|---------------------------------------|--------------------------------------------------------------|------------------------------------------------------------|------------------------------------------------------------|
| Disease category | Number of patients | Mean direct nonmedical and indirect cost per patient (US \$) | Total direct nonmedical and indirect cost per year (US \$) | |
| CHB | 8,221,074.00 | 38.98 | 320,429,256 | |
| CC | 368,059.00 | 176.11 | 44,846,050 | |
| DC | 46,007.00 | 243.23 | 7,756,533 | |
| HCC | 16,356.00 | 309.58 | 2,417,703 | |
| Total | 8,651,497.00 | 767.90 | 375,449,542 | |
| B. Sensitivity analysis | | | | |
| Disease category | Range of estimated number of patients | Range of estimated direct nonmedical and indirect cost | First one-way sensitivity analysis (US \$)* | Second one-way sensitivity analysis (US \$)† |
| CHB | 6,533,015–13,058,282 | 15.01–100.15 | 123,363,341–823,309,245 | 254,634,496–508,967,017 |
| CC | 308,322–616,644 | 62.30–244.91 | 22,931,607–90,141,550 | 37,567,371–75,134,743 |
| DC | 38,540–77,080 | 113.90–250.86 | 5,240,034–11,541,475 | 6,497,619–12,995,238 |
| HCC | 6,887–21,521 | 130.25–238.14 | 2,130,329–3,894,954 | 1,017,980–3,181,189 |
| Total | 6,886,764–13,773,528 | 321.45–834.05 | 153,665,312–928,887,224 | 299,717,467–600,278,186 |
| Disease category | Range of estimated number of patients | Range of estimated direct nonmedical and indirect cost | Two-way sensitivity analysis (best-case scenario) (US \$) | Two-way sensitivity analysis (worst-case scenario) (US \$) |
| CHB | 6,533,015–13,058,282 | 15.01–100.15 | 98,032,753 | 1,307,737,174 |
| CC | 308,322–616,644 | 62.30–244.91 | 19,209,723 | 151,022,492 |
| DC | 38,540–77,080 | 113.90–250.86 | 4,389,558 | 19,336,503 |
| HCC | 6,887–21,521 | 130.25–238.14 | 896,981 | 5,124,939 |
| Total | 6,886,764–13,773,528 | 321.45–834.05 | 122,529,015 | 1,483,221,108 |

CC, compensated cirrhosis; CHB, chronic hepatitis B; DC, decompensated cirrhosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

* Lower and upper limits of the cost components (95% confidence interval) from the direct medical cost calculation were tested and the number of patients was unchanged.

† Cost components remained constant and the number of patients per disease stage was varied.

difficult to travel to the hospital for regular outpatient visits. Hence, our outpatient samples were from those who attended the outpatient clinic and may not be truly representative as evident that formal care was not required by any of the participants.

In addition, we collected data only from one central hospital, albeit the biggest in the north, and not from other two regions of the country (central and the south). However, as medications accounted for ~70% of the total cost in our study and there is little variation in drug prices across Vietnam, this would allow an extrapolation to the whole country. Likewise, the minimum wage was applied in estimating medical leave and time off for the indirect cost, and there would not be much deviation of these costs when our results are extrapolated to different regions in Vietnam.

Extrapolation of treatment cost collected from one hospital to the national level, however, could be prone to overestimating the

treatment cost of chronic HBV infection in Vietnam. Nonetheless, in lieu of any cost information in Vietnam, our results could be viewed as a potential scenario that provides an estimation of what “might be” the quantum of the cost to fill in an existing information gap.

Even with these potential limitations, this first and only cost-of-illness study on chronic HBV infection in Vietnam still provides valuable information for health care decision makers in resource allocation and planning. Given the high prevalence of HBV infection in Vietnam, it is imperative that steps be taken such as the continuation of universal HBV vaccination of newborns, a reconsideration of Vietnamese policies on drug pricing, treatment of chronic HBV infection, and other initiatives for the prevention of infection.

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Table 6 – Direct medical cost, direct nonmedical and indirect costs, and total cost of illness for different stages of chronic HBV infection in Vietnam in 2008 (US \$).

| Disease category | Direct medical cost | Direct nonmedical and indirect costs | Cost of illness | Ratio of direct medical cost to direct nonmedical and indirect costs |
|------------------|---------------------|--------------------------------------|-----------------|----------------------------------------------------------------------|
| CHB | 3,702,344,157 | 320,429,256 | 4,022,773,413 | 11.6:1 |
| CC | 254,118,890 | 44,846,050 | 298,964,940 | 5.7:1 |
| DC | 51,274,910 | 7,756,533 | 59,031,443 | 6.6:1 |
| HCC | 30,799,174 | 2,417,703 | 33,216,878 | 12.7:1 |
| Total | 4,038,537,132 | 375,449,542 | 4,413,986,674 | |

CC, compensated cirrhosis; CHB, chronic hepatitis B; DC, decompensated cirrhosis; HBV, hepatitis B virus; HCC, hepatocellular carcinoma.

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