Long-Term Morbidity and Mortality in Chinese Insurance Applicants Infected With the Hepatitis B Virus

Robert J. Pokorski, MD, FACP; Ulrike Ohlmer, DIPL. MATH., DR. RER. POL.

Background.—Worldwide, there are approximately 350 million carriers of the hepatitis B virus (HBV). The protracted course of HBV infection makes it difficult to estimate morbidity and mortality risk in an insured lives population that is chronically infected with HBV because most studies on this topic have been based on older patients with advanced disease who were treated at tertiary centers that specialize in care of patients with liver disease. Data from these reports bias risk estimates toward severe cases and are not appropriate indicators of what might be expected in an insurance context. This article discusses use of a Markov model to estimate long-term morbidity and mortality risk associated with chronic HBV infection in otherwise healthy Chinese insurance applicants.

Results.—The model was validated by comparing results to population data published in Taiwan, Hong Kong, Shanghai, Singapore, and Korea. For males, mortality ratios were in the range of 150–175% for underwriting ages 20, 30, and 40 and slightly lower for age 50. For females, mortality ratios were in the range of 125–150% and slightly higher for age 50. Higher mortality ratios in males were related to the fourfold higher hepatocellular carcinoma (HCC) incidence rate. Mortality ratios varied with the extent of the underwriting evaluation. Liver-related morbidity incidence increased with age at underwriting for males and females. HBeAg (hepatitis B “e” antigen)/anti-HBe status was not a major factor for differentiating risk in an insurance context.

Conclusion.—Morbidity and mortality are within the insurable range for the majority of HBV-infected Chinese applicants. Risk varies with the extent of the underwriting evaluation and the percentage of applicants with significant liver fibrosis or early cirrhosis that are detected during the underwriting process. HBeAg/anti-HBe status is not a major factor for differentiating risk in an insurance context. Morbidity and mortality estimates provided by the model can be generalized to other populations and individuals where HBV infection occurs at birth or during early childhood, although some modification in insurance risk might be required in non-Asian markets.

Worldwide, there are approximately 350 million carriers of the hepatitis B virus (HBV). As many as 1 million of these people develop hepatocellular carcinoma (HCC) each year, and countless others develop end-stage liver disease.1 Prevalence of HBV is highest in China, Southeast Asia, Indonesia, and sub-Saharan Africa, where more than 8% of the
Table 1. Annual Transition Probabilities, Male and Female Unless Otherwise Stated*

<table>
<thead>
<tr>
<th>Transition</th>
<th>Transition Rate (Range)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected death</td>
<td>Per mortality table</td>
<td>7, 8</td>
</tr>
<tr>
<td>HBeAg/HBsAg to anti-HBe/HBsAg</td>
<td>0.034 (0.031–0.034)</td>
<td>9–11</td>
</tr>
<tr>
<td>Anti-HBe/HBsAg to HBsAg negative</td>
<td>0.005 (0.001–0.01)</td>
<td>1, 43, 51–55</td>
</tr>
<tr>
<td>Cirrhosis data</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Overall cirrhosis incidence rate (all ages combined)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Male</td>
<td>0.0074 (0.0074–0.021)</td>
<td>13, 19</td>
</tr>
<tr>
<td>Female</td>
<td>0.25 × male overall cirrhosis incidence rate</td>
<td>—</td>
</tr>
<tr>
<td>Age-adjusted cirrhosis incidence multiplier</td>
<td>Per derived table</td>
<td>13, 19</td>
</tr>
<tr>
<td>HBeAg multiplier</td>
<td>1.73 (1.73–1.8)</td>
<td>13, 19</td>
</tr>
<tr>
<td>Anti-HBe/HBsAg to compensated cirrhosis</td>
<td>Overall cirrhosis incidence rate × age-adjusted cirrhosis incidence multiplier</td>
<td>19</td>
</tr>
<tr>
<td>HBeAg/HBsAg to compensated cirrhosis</td>
<td>HBeAg multiplier × anti-HBe/HBsAg to compensated cirrhosis transition rate</td>
<td>—</td>
</tr>
<tr>
<td>HBsAg negative to compensated cirrhosis</td>
<td>0.01 × anti-HBe/HBsAg to compensated cirrhosis transition rate</td>
<td>22</td>
</tr>
<tr>
<td>Compensated cirrhosis to decompensated cirrhosis</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Males</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ages 20–54</td>
<td>0.023 (0.023–0.05)</td>
<td>3, 16</td>
</tr>
<tr>
<td>Ages 55–70</td>
<td>0.7 × age 20–54 transition rate</td>
<td>—</td>
</tr>
<tr>
<td>Females, all ages</td>
<td>0.023 (0.023–0.05)</td>
<td>3, 16</td>
</tr>
<tr>
<td>Decompensated cirrhosis to cirrhosis death</td>
<td>0.19 (0.19–0.33)</td>
<td>24, 56, 57</td>
</tr>
<tr>
<td>Compensated/decompensated cirrhosis to HCC</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Males</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Ages 20–60</td>
<td>0.028 (0.0083–0.05)</td>
<td>16, 58–64</td>
</tr>
<tr>
<td>Ages 61–70</td>
<td>Per derived values</td>
<td>—</td>
</tr>
<tr>
<td>Females, all ages</td>
<td>0.028 (0.0083–0.05)</td>
<td>—</td>
</tr>
<tr>
<td>HCC mortality rates</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Year 1</td>
<td>0.458</td>
<td>—</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.219</td>
<td>—</td>
</tr>
<tr>
<td>Year 3</td>
<td>0.213</td>
<td>—</td>
</tr>
<tr>
<td>Year 4</td>
<td>0.206</td>
<td>—</td>
</tr>
<tr>
<td>Year 5</td>
<td>0.199</td>
<td>—</td>
</tr>
<tr>
<td>Year 6</td>
<td>0.064</td>
<td>—</td>
</tr>
<tr>
<td>Year 7</td>
<td>0.064</td>
<td>—</td>
</tr>
<tr>
<td>Year 8</td>
<td>0.064</td>
<td>—</td>
</tr>
<tr>
<td>Year 9</td>
<td>0.064</td>
<td>—</td>
</tr>
<tr>
<td>Year 10</td>
<td>0.064</td>
<td>—</td>
</tr>
</tbody>
</table>

* HBeAg, hepatitis B "e" antigen; HBsAg, hepatitis B surface antigen; HCC, hepatocellular carcinoma.

The protracted course of HBV infection makes it difficult to estimate morbidity and mortality risk in an insured lives population that is chronically infected with HBV. Most studies on this topic have been based on older patients with advanced disease who were...
treated at tertiary centers that specialize in care of patients with liver disease. Data from these reports bias risk estimates toward severe cases and are not appropriate indicators of what might be expected in an insurance context.

This article discusses use of a Markov model to estimate long-term morbidity and mortality risk associated with chronic HBV infection in otherwise healthy Chinese insurance applicants. The topic was chosen because chronic HBV infection is one of the most common medical impairments in Asia and there are extensive data in the medical literature regarding the incidence of complications during decades of follow-up. The
A Markov model was created to estimate risk associated with chronic HBV infection (Figure 1). Simplifying assumptions were made that caused the model structure to diverge from a strict interpretation of the HBV pathophysiologic disease process. For example, since HCC arises in a cirrhotic liver in the vast majority of cases, the model assumes that cirrhosis must precede HCC. Though not totally correct from a pathophysiologic standpoint (transitions directly from chronic HBV infection to HCC can occur), errors would be small since cirrhosis usually precedes HCC.

The 10 Markov states are described below.

**DESCRIPTION OF THE MARKOV MODEL**

A Markov model is validated by comparing results to population data published in Taiwan, Hong Kong, Shanghai, Singapore, and Korea.
and gender-specific risk of expected death per the chosen mortality table. For the state HBeAg (hepatitis B "e" antigen)/HBsAg, those who survive expected death move to anti-HBeAg/HBsAg or to compensated cirrhosis or stay in HBeAg/HBsAg and face the same risks during the next cycle. Each cycle of the model represents 1 year.

Anti-HBe/HBsAg.—Subjects who survive expected death move to HBsAg negative or to compensated cirrhosis or stay in anti-HBe/

HBsAg and face the same risks during the next cycle.

HBsAg Negative.—Subjects who survive expected death move to compensated cirrhosis or stay in HBsAg negative and face the same risks during the next cycle.

Compensated Cirrhosis.—Subjects who survive expected death move to decompensated cirrhosis (obvious subjective symptoms of liver failure, jaundice, ascites, hepatic encephalopathy, or blood coagulation disorders) or
Table 2. Percentage of Subjects in Each Markov State at Start of Model, by Age and Percentage of Cirrhosis Cases Detected During Underwriting*†

<table>
<thead>
<tr>
<th>Markov State at Start of Model Calculations</th>
<th>Age 20</th>
<th>Age 30</th>
<th>Age 40</th>
<th>Age 50</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>—</td>
<td>20%</td>
<td>50%</td>
<td>80%</td>
</tr>
<tr>
<td>HBeAg/HBsAg</td>
<td>0.80</td>
<td>0.54</td>
<td>0.55</td>
<td>0.55</td>
</tr>
<tr>
<td>Anti-HBe/HBsAg</td>
<td>0.20</td>
<td>0.44</td>
<td>0.44</td>
<td>0.44</td>
</tr>
<tr>
<td>Compensated cirrhosis</td>
<td>0.00</td>
<td>0.02</td>
<td>0.01</td>
<td>0.01</td>
</tr>
</tbody>
</table>

* HBeAg, hepatitis B “e” antigen; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus.
† For example, for a cohort aged 40, if 50% of HBV-infected applicants with compensated cirrhosis are detected and declined, the remaining subjects are distributed in these Markov states at the start of the model calculations: HBeAg/HBsAg, 0.38; anti-HBe/HBsAg, 0.58; and compensated cirrhosis, 0.04. For age 20, the assumption is that no applicants have cirrhosis.

Figure 6. Male cirrhosis mortality rates calculated by Markov model versus 50% of actual cirrhosis mortality rates, Taiwan (assume 15% hepatitis B virus prevalence rate).

ANNUAL TRANSITION RATES

Transition rates described in this section are summarized in Table 1.
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Figure 7. Female cirrhosis mortality rates calculated by Markov model versus 50% of actual cirrhosis mortality rates, Taiwan (assume 15% hepatitis B virus prevalence rate).

Expected Death

Taiwan mortality tables were used to determine age- and gender-specific population and insured lives mortality rates as described later in this article.

HBeAg/HBsAg to Anti-HBe/HBsAg

Subjects in HBeAg/HBsAg test positive for HBeAg and HBsAg. Those in anti-HBe/HBsAg have developed antibodies to HBe but remain HBsAg positive. For Chinese populations age 20–60, this annual transition probability was reported by Guan and Yu (0.034), Liaw et al (0.031), and Lok et al (0.031). The value used in the model was 0.034. Transitions from HBeAg/HBsAg to anti-HBe/HBsAg were not allowed after age 60 because data indicate that people who are HBeAg positive at older ages remain HBeAg positive.

Anti-HBe/HBsAg to HBsAg Negative

Transition to HBsAg-negative status (essentially, total clearing of HBV) is rare in people infected at birth or during early childhood, with estimates varying from 0.001 to 0.01 per year. The approximate median value of 0.005 was chosen.

Cirrhosis Data

Overall Cirrhosis Incidence Rate (All Ages Combined)

This category refers to the annual rate for the transition from chronic HBV to cirrhosis. Rates quoted in the literature vary depending on characteristics of the study and the population (age, severity of infection, prospective versus retrospective study, etc). The value chosen for this transition (0.0074 per year) was based on data by Yu et al. Investigators in this very large prospective study (1506 patients) used liver ultrasound examinations to exclude patients with preexisting cirrhosis, thereby providing a more accurate estimate of the rate at which cirrhosis develops, and then followed the cohort to determine the incidence of cirrhosis.

Male/Female Differentiation

Population data indicate that fibrosis and cirrhosis are more common in men. The mechanism is related to favorable influences of estrogen (women) on the rate of hepatic fibrosis, a higher frequency of acute exacerbations in males (which accelerate the fibrotic process), and perhaps gender differences in lifestyle and occupational factors.
Because cirrhosis (the final stage of the fibrotic process) is the primary risk factor for HCC, the effect of a higher rate for development of fibrosis in males is to increase the incidence of HCC. Estimates of the male-to-female ratio of HCC incidence in Chinese populations vary from 3.214 to 4.1.17 In this model, the causes of excess morbidity and mortality are HCC and decompensated cirrhosis, and transitions to these Markov states depend on prior transitions from HBeAg/HBsAg, anti-HBe/HBsAg, and HBsAg negative to compensated cirrhosis. Thus, control of transitions to compensated cirrhosis (and effectively, transitions to HCC and decompensated cirrhosis) is handled in the model by using different male and female transitions to compensated cirrhosis. The assumption was that HCC incidence would be four-fold higher in Chinese males. For females, this adjustment was accomplished by multiplying 0.25 times male transition rates from HBeAg/HBsAg to compensated cirrhosis, anti-HBe/HBsAg to compensated cirrhosis, and HBsAg negative to compensated cirrhosis.

**Age-Adjusted Cirrhosis Incidence Multiplier**

Yu et al13 and Liaw et al19 published similar age factors that modify the overall transition rate (all ages combined, above) from chronic hepatitis to compensated cirrhosis. Data by Yu et al13 were fitted to a general linear model to create age-adjusted cirrhosis multipliers for ages 20–70, that is, values that multiply the overall cirrhosis incidence rate to produce age-adjusted transitions to compensated cirrhosis. The importance of this adjustment is that transitions to compensated cirrhosis (and subsequently to HCC and decompensated cirrhosis) become a function of duration of infection, and the model conforms in this regard to clinical observations that indicate that sequelae of HBV are related to age and duration of infection.20,21

**HBeAg Multiplier**

HBeAg-positive patients progress to compensated cirrhosis at a faster rapid rate than anti-HBe patients. The magnitude of this effect has been estimated at 1.7313 and 1.8.19 Yu et al13 reported that HBeAg was associated with an increased risk of cirrhosis, while the relation of HBeAg to HCC was not statistically significant.13 The model assumes that the sole effect of HBeAg is to increase (by a factor of 1.73) the transition rate from HBeAg/HBsAg to compensated cirrhosis.
Anti-HBe/HBsAg to Compensated Cirrhosis

This transition rate is calculated as the overall cirrhosis incidence rate (0.0074) multiplied by the age-adjusted cirrhosis incidence multiplier.

HBeAg/HBsAg to Compensated Cirrhosis

This transition rate is calculated as the HBeAg multiplier (1.73) multiplied by the anti-HBe/HBsAg to compensated cirrhosis transition rate.

HBsAg Negative to Compensated Cirrhosis

This is a rare event. The transition rate was based on data by Wong et al. and was calculated as 0.01 multiplied by the anti-HBe/HBsAg to compensated cirrhosis transition rate.

Compensated Cirrhosis to Decompensated Cirrhosis

Males, Ages 20–54, and Females, All Ages

This transition rate (0.023) was based on data by Liaw et al. in which a cohort with recently diagnosed cirrhosis was followed to determine the annual incidence of HCC.

Males, Ages 55–70

For older males, a transition rate of 0.023 per year yielded a cirrhosis mortality rate (Markov state death (cirrhosis)) that exceeded estimates of HBV-related cirrhosis mortality in Taiwan (below). The fit of the model improved by calculating this transition as 0.7 multiplied by age 20–54 transition rate (0.023).

Decompensated Cirrhosis to Cirrhosis Death

This transition rate (0.19) is the only model value that was not based on data from a Chinese population.

Compensated and Decompensated Cirrhosis to HCC

Males, Age 20–60, and Females, All Ages

The transition rate for compensated or decompensated cirrhosis to HCC (0.028 per year) was based on a prospective study by Liaw et al. in which a cohort with recently diagnosed cirrhosis was followed to determine the annual incidence of HCC.
Figure 10. Estimated mortality ratios for hepatitis B virus-infected Chinese males age 20 at underwriting, by hepatitis B \textit{e} antigen (HBeAg) and anti-HBe status.

Figure 11. Estimated mortality ratios for hepatitis B virus-infected Chinese females age 20 at underwriting, by hepatitis B \textit{e} antigen (HBeAg) and anti-HBe status.

**Males, Ages 61–70**

For older males, a transition rate of 0.028 per year yielded HCC incidence and mortality rates (Markov state death (HCC)) that were less than HBV-related estimates of HCC incidence and mortality in Taiwan (below). The fit of the model improved by multiplying the age 20–60 transition rate (0.028) by a factor, thereby increasing HCC incidence at older ages. These factors are as follows: age 61, 1.05; age 62, 1.10; age 63, 1.15; age 64, 1.20; age 65, 1.25; age 66, 1.30; age 67, 1.35; age 68, 1.40; age 69, 1.45; and age 70, 1.50.

**HCC Mortality Rates**

Determination of these values was problematic. Many sources in the Chinese literature list mortality following diagnosis of HCC, but data generally have one or more deficiencies:
Figure 12. Estimated mortality ratios for hepatitis B virus-infected Chinese males age 30 at underwriting, by percent detection of existing cirrhosis.

Figure 13. Estimated mortality ratios for hepatitis B virus-infected Chinese females age 30 at underwriting, by percent detection of existing cirrhosis.

- Data do not reflect modern surgical and nonsurgical treatments. In these reports, survival after diagnosis of HCC is measured in weeks and months.\textsuperscript{25,26}  
- Survival rates are based on operated cases, thereby biasing the results to show favorable results, that is, patients with disease that is so advanced that it cannot be treated surgically are not included in the statistics.  
- Data do not include recent favorable trends due to early detection via screening with annual or biannual liver ultrasound examinations and/or alpha-fetoprotein (AFP) levels.\textsuperscript{27}  

HCC survival rates were estimated as follows:

- Screening programs are often used in high-risk populations to detect early, asympto-
matic HCC, but even aggressive screening programs often fail to detect early HCC.\textsuperscript{28,29}

- The extent of screening varies with the size of the at-risk population, the amount of resources committed to the project, and the urban/rural distribution of the population. For example, screening would generally be less successful in rural areas with less sophisticated medical facilities and a lower population density.

- The most favorable outcomes that can be achieved with current technologies and an aggressive screening program that targets most of the at-risk population result in detection of (1) one quarter of HCC cases at an early, potentially curable stage; (2) one half at an intermediate stage, where cure is unlikely but possible in a minority of cases; and (3) one quarter at end-stage disease, where survival is less than 1 year.\textsuperscript{30} However, studies of Asian populations indicate that a maximum of 15\% of patients presenting with HCC are curable with surgery.\textsuperscript{31}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure14}
\caption{Estimated mortality ratios for hepatitis B virus-infected Chinese males age 40 at underwriting, by percent detection of existing cirrhosis.}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure15}
\caption{Estimated mortality ratios for hepatitis B virus-infected Chinese females age 40 at underwriting, by percent detection of existing cirrhosis.}
\end{figure}
Figure 16. Estimated mortality ratios for hepatitis B virus-infected Chinese males age 50 at underwriting, by percent detection of existing cirrhosis.

Figure 17. Estimated mortality ratios for hepatitis B virus-infected Chinese females age 50 at underwriting, by percent detection of existing cirrhosis.

- Cumulative 5- and 10-year survival rates for early, potentially curable HCC cases are 60 and 42.7%, respectively, and for intermediate stage disease are 22.2 and 16.1%, respectively. For end-stage disease, survival at 1 year after HCC diagnosis is 0%. Annual transition probabilities from HCC to death (HCC) in a market with an HCC screening program were derived from these cumulative survival rates by weighting the likely stages at diagnosis as follows: early diagnosis, 15%; intermediate diagnosis, 55%; and late (end-stage) diagnosis, 30% (Table 1).
- Sensitivity testing was performed using different weightings for the percentage of cases that would be diagnosed in early, intermediate, and late HCC stages (data not shown). For all scenarios (including a most favorable scenario that detected 25% of HCC cases at an early, potentially curable stage), mortality rates were so high that outcomes calculated by the model did not vary significantly.
VALIDATION

Description of the Validation Process

Two methods were used to validate the model. First, transition probabilities were based exclusively on Chinese data (with the single exception noted earlier\textsuperscript{24}). In cases of conflicting data, preference was given to long-term prospective studies in cohorts that were well characterized with respect to risk factors used in the model. For example, transition probabilities from chronic hepatitis to cirrhosis were based on a cohort examined by liver ultrasound to exclude cases with pre-existing cirrhosis.\textsuperscript{13}

Second, results of the model were compared to real-life population data sets: (1) HCC incidence rates in Taiwan,\textsuperscript{32} Hong Kong,\textsuperscript{33} Shanghai,\textsuperscript{18} Singapore,\textsuperscript{34} and Korea\textsuperscript{35}; (2) HCC mortality rates in Taiwan,\textsuperscript{36} Hong Kong,\textsuperscript{37} and Korea\textsuperscript{38}; and (3) cirrhosis mortality rates in Taiwan.\textsuperscript{39} The validation process was designed as follows:

\begin{itemize}
  \item Expected death rates (data for all nodes identified in Figure 1 as death (expected)) for the validation phase of the model were based on the 1996 Taiwan Life Tables\textsuperscript{7} for the general population. Taiwan mortality rates were used because most of the transition probabilities in the model were derived from Taiwanese cohorts.
  \item All subjects were age 20 at the beginning of the validation phase.
  \item A simplifying assumption was made that cirrhosis prevalence at age 20 was 0%. Studies indicate that 3–5% of 20 year olds with chronic HBV infection already have cirrhosis.\textsuperscript{40,41} These estimates probably overestimate cirrhosis prevalence because of referral bias, that is, clinics specializing in care of HBV-infected children treat patients with more severe disease.
  \item Prevalence of HBeAg at age 20 has been estimated at 80–85\%\textsuperscript{5,9,42} The model assumes an HBeAg prevalence rate at age 20 of 80%.
  \item At the beginning of the model run for age 20, subjects are distributed among the Markov states as follows: HBeAg/HBsAg, 80%; anti-HBe/HBsAg, 20%; HBsAg negative, 0%; compensated cirrhosis, 0%; decompensated cirrhosis, 0%; HCC, 0%; HCC cure, 0%; death (expected), 0%, death (HCC), 0%; and death (cirrhosis), 0%. This distribution indicates that at age 20 all subjects are in Markov states HBeAg/HBsAg (80%) or anti-HBe/HBsAg (20%) and none have cirrhosis or HCC.
  \item Prevalence estimates of chronic HBV infection in East and Southeast Asia among the population age 20 and older range from 8–25\%,\textsuperscript{24,42–46} The model assumes a prevalence rate of 15%. Sensitivity testing (data not shown) indicated that HBV prevalence rates between 10 and 20\% would approximate the real-life population data sets (below), with the best fit achieved for estimates of 15–20\%.
  \item In Taiwan, 87\% of all primary liver cancers are HCC,\textsuperscript{32} that is, most but not all liver cancers are HCC. Estimates in the Chinese literature of the percentage of HCC cases attributable to HBV range from 67 to 85\%,\textsuperscript{5,10,13,17,43,47,48} with most estimates about 80\%. The model assumes that 70\% of all liver cancers are due to HBV (0.87 × 0.80, ie, the percentage of liver cancers that are HCC multiplied by the percentage of HCC cases attributable to HBV). Sensitivity testing (data not shown) indicated that estimates (of the percentage of all liver cancers that are due to HBV) between 50 and 80\% would approximate the real-life data sets (below), with the best fit achieved for estimates of 70\%.
  \item Data were not found for the percentage of cirrhosis deaths attributable to HBV. This value would be less than the percentage of HCC cases attributed to HBV, the reason being that there are more disease processes that might lead to cirrhosis and subsequent death due to liver failure, including heavy alcohol intake, certain liver and biliary tract diseases, and genetic disorders. The model assumes that 50\% of cirrhosis deaths are attributable to HBV. Sensitivity testing (data not shown) indicated that estimates
\end{itemize}
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Figure 18. Estimated incidence of total and permanent disability in hepatitis B virus-infected Chinese males age 20 at underwriting, by cause of disability.

(of the percentage of cirrhosis deaths that are due to HBV) between 40 and 60% would approximate the real-life data sets (below), with the best fit achieved for the estimate of 50%.

- Values for all other transition probabilities were set as described previously.

Outcome of the Validation Process

The output of the model based on these data and assumptions is represented in Figures 2–7.

- Figures 2 and 3 display, respectively, male and female HCC incidence rates calculated by the model compared with 70% of actual HCC incidence rates in Taiwan, Hong Kong, Shanghai, Singapore, and Korea. The calculated male and female incidence curves (Markov model, Taiwan) closely approximate population HCC incidence rates in these 5 markets.

- Figures 4 and 5 display, respectively, male and female HCC mortality rates calculated by the model compared with 70% of actual HCC mortality rates in Taiwan, Hong Kong, and Korea. The calculated male and female mortality curves (Markov model, Taiwan) closely approximate population HCC mortality rates in these 3 markets.

- Figures 6 and 7 display, respectively, male and female cirrhosis mortality rates calculated by the model compared with 50% of actual cirrhosis mortality rates in Taiwan. The calculated male and female mortality curves (Markov model, Taiwan) closely approximate population cirrhosis mortality rates in Taiwan.

DISTRIBUTION AMONG MARKOV STATES BY AGE AT UNDERWRITING

Having demonstrated that the model approximates population HCC incidence rates, HCC mortality rates, and cirrhosis mortality rates in East and Southeastern Asia, the next step is to estimate insured lives morbidity and mortality experience. Expected death rates (data for all nodes identified in Figure 1 as death (expected)) for this phase of the modeling process are based on 90% of the 1989 Taiwan Standard Ordinary (TSO89) insured lives table. Values for other variables were set as described previously.

Markov State Distribution, Age 20

The initial run of the model was for healthy applicants age 20 at underwriting, with the assumption that 80% of subjects were in the HBeAg/HBsAg Markov state and 20% were...
in the anti-HBe/HBsAg state (Table 2). During each 1-year cycle of the model, subjects age 1 year and gradually move into different Markov states as they convert to anti-HBe/HBsAg or to HBsAg negative, develop compensated cirrhosis, decompensated cirrhosis, or HCC, or die.

Markov State Distribution, Ages 30, 40, and 50

Data from the age 20 run of the model were used to estimate the likely Markov state of subjects who might apply for insurance at older ages after they had been redistributed among the various states. Assumptions were as follows regarding the Markov state in which applicants would be found at underwriting ages 30, 40, and 50 (Table 2):

- Applicants age 30, 40, or 50 would not be sold coverage if there was a history of severe HBV-related disease, including decompensated cirrhosis and current or cured HCC, that is, at the time of underwriting, no subjects would begin the model in decompensated cirrhosis, HCC, or HCC cure.
- No subjects would be in any of the three death states at the time of application.
- No subjects would be in the HBsAg negative Markov state, the reason being that this model is concerned with estimating risk in people chronically infected with HBV, not in those who have cleared the virus.
- Thus, all subjects at underwriting ages 30, 40, and 50 would be in 1 of 3 Markov states: HBeAg/HBsAg, anti-HBe/HBsAg, and compensated cirrhosis.
- Distribution among these three states was determined by two factors:
  - the weighted probabilities (weighted so the total sums to 100%) of being located in these states per attained age (30, 40, or 50) as determined during the initial age 20 run of the model, after eliminating subjects who had died, were HBsAg negative, or were in states indicative of severe disease; and
  - the percentage of applicants with compensated cirrhosis that were detected and eliminated from the risk pool during the underwriting process, that is, the effectiveness of the selection process. What percentage of applicants with existing cirrhosis would be detected during underwriting? The likelihood of identifying these higher risk applicants would de-
pend on the extent of the underwriting evaluation, for example, few or no laboratory tests versus a full blood profile and AFP level, insurance examination to detect signs and symptoms of more advanced disease, a physician's statement (very useful for this impairment, particularly if a liver biopsy has been performed), and liver ultrasound to detect cirrhosis and early HCC (especially in large amount cases). Three scenarios were created, which assumed cirrhosis detection rates of 20, 50, and 80% (ie, 20, 50, and 80%, respectively, of applicants with existing cirrhosis would be detected and eliminated from the risk pool during the underwriting process). Three scenarios were created, which assumed cirrhosis detection rates of 20, 50, and 80% (ie, 20, 50, and 80%, respectively, of applicants with existing cirrhosis would be detected and eliminated from the risk pool during the underwriting process). Table 2 summarizes the calculated percentages (per these assumptions) of subjects in each Markov state at the beginning of the model run for ages 20, 30, 40, and 50.

Magnitude and Duration of Selection Process

In addition to detecting existing cirrhosis cases, the underwriting process also decreases the rate at which transitions occur between compensated cirrhosis and both decompensated cirrhosis and HCC, the reason being that severe cases of compensated cirrhosis (which would be more likely to progress to decompensated disease and/or HCC in the first few years after underwriting) are detected and eliminated from the risk pool. There are no HBV-specific data regarding the magnitude or the duration of this selection effect. The model assumes that transitions from compensated cirrhosis to decompensated cirrhosis and from compensated cirrhosis to HCC would decrease (compared with what would be expected without underwriting) per this schedule: year 1, 10% of expected; year 2, 20% of expected; year 3, 33% of expected; year 4, 50% of expected; year 5, 75% of expected, and year 6, 100% of expected (ie, no further effects from the selection process). Shorter or longer select periods would shorten or lengthen, respectively, the period of time between underwriting and claims due to HCC and decompensated cirrhosis.

RESULTS

Mortality Results

Risk Associated With HBeAg Status

Medical studies report a less favorable outcome in patients with HBeAg (HBeAg/HBsAg Markov state), principally because HBeAg is associated with more rapid development of cirrhosis, but the magnitude of
this risk has not been quantified in an insured lives context. Figures 8 and 9, respectively, display estimated mortality ratios for HBV-infected Chinese males and females age 20 at underwriting, by HBeAg and anti-HBe status, based on comparison with 90% of mortality rates in the TSO89 Insured Lives Table. HBeAg100% means all subjects in the model are HBeAg positive and anti-HBe100% means all subjects in the model are anti-HBe positive. As noted earlier, the assumption is that all 20-year-old applicants are healthy and that none have cirrhosis. For males, Figure 8 indicates that estimated mortality ratios are relatively similar for ages 20-30 and 55-70 and are approximately 25 mortality percentage points higher for HBeAg-positive middle-aged adults. A similar pattern is seen for females (Figure 9), but the difference in mortality ratios is only about 10 mortality percentage points. When averaged over a 50-year follow-up (ages 20-70), estimated mortality ratios for HBeAg-positive subjects are approximately 15 mortality percentage points higher for males, and 5 mortality percentage points higher for females.

Age 20 at Underwriting

Insurers in Asia may or may not know HBeAg and anti-HBe status at the time of underwriting. The question then is what the mortality risk of a healthy 20-year-old HBV-infected applicant (1) known to be HBeAg positive (HBeAg100%), (2) known to be anti-HBe positive (anti-HBe100%), and (3) whose HBe status is unknown at the time of underwriting (HBeAg80% anti-HBe20%, ie, the usual HBeAg and anti-HBe distribution for a 20 year old). Figures 10 and 11 display this information for males and females, respectively.

- Mortality ratios for males age 20 at underwriting (Figure 10) increase gradually for the first decade, plateau between ages 40 and 55, and taper gradually at older ages. Peak mortality ratios are as follows: HBeAg100%, 173%; HBeAg80%-anti-HBe20%, 168%; and anti-HBe100%, 150%.
- Mortality ratios for females age 20 at underwriting (Figure 11) demonstrate a similar pattern. Peak mortality ratios are as follows: HBeAg100%, 131%; HBeAg80%-anti-HBe20%, 129%; and anti-HBe100%, 121%.
- Depending on HBeAg/anti-HBe status, mortality ratios for males are 30-40 percentage points higher than for females.

Age 30, 40, and 50 at Underwriting

Subjects that enter the model at age 20 are redistributed among the different Markov...
states after each cycle (1 year) in a manner that fairly closely approximates real-life experience in East and Southeastern Asia. When older people with HBV infection apply for insurance coverage, underwriters usually identify severe risks (decompensated cirrhosis and HCC) and some, but not all of the applicants, with compensated cirrhosis. Thus, estimated mortality ratios for applicants older than age 20 show a steeper increase (compared with age 20) because applicants with existing, undetected cirrhosis progress more rapidly to HCC and/or decompensated cirrhosis.

Figures 12–16 display estimated mortality experience for HBV-infected applicants by age, gender, and assumed percent cirrhosis detection rate. For a given age and gender, mortality ratios are inversely related to the percent cirrhosis detection rate: lower detection rates result in higher mortality ratios because more claims occur in the early policy years.

- Age 30. Mortality ratios for males (Figure 12) increase rapidly during the first decade, plateau between ages 40 and 55 at values that vary with percent cirrhosis detection, and taper gradually thereafter. Peak mortality ratios are detect 20% (172%) and detect 50% (170%). The 80% detection rate is not shown because calculated values are identical to the 50% detection rate per assumptions in Table 2. For females (Figure 13), mortality ratios peak after the first decade, followed by a long plateau. Peak mortality ratios are detect 20% (154%) and detect 50% (137%) (80% detection rate not shown for reasons explained above).

- Age 40. Mortality ratios increase until approximately ages 45–50. For males (Figure 14), peak mortality ratios are detect 20% (176%), detect 50% (170%), and detect 80% (165%). Female peak mortality ratios (Figure 15) are detect 20% (156%), detect 50% (143%), and detect 80% (131%).

- Age 50. Mortality ratios increase until approximately ages 55–60. For males (Figure 16), peak mortality ratios are detect 20% (160%), detect 50% (151%), and detect 80% (143%). Female peak mortality ratios (Figure 17) are detect 20% (167%), detect 50% (149%), and detect 80% (131%).

Morbidity Results

An assumption was made that total and permanent disability (TPD) would occur upon diagnosis of HCC or decompensated cirrhosis. Figures 18 and 19 display estimated incidence rates of TPD for males and females, respectively, age 20 at underwriting according to liver-related causes of disability. HCC is the most significant cause of disability. TPD incidence rates for age 20 at underwriting (both liver-related causes) peak at age 70 at 13.7 per 1000 for males and 6.1 per 1000 for females.

Figures 20 and 21 summarize estimated incidence rates for both liver-related causes of TPD in HBV-infected males and females, respectively, for ages 20–50 at underwriting. Peak TPD incidence rates occur at age 70 for males (18.4 per 1000) and females (7.8 per 1000).

DISCUSSION

Insurability

The model suggests that morbidity and mortality experience would be within insurable ranges for the majority of HBV-infected persons. For males, mortality ratios are in the range of 150–175% for underwriting ages 20, 30, and 40 and slightly lower for age 50. For females, mortality ratios are in the range of 125–150% and slightly higher for age 50. Higher mortality ratios in males are related to the fourfold higher HCC incidence rate.

Risk Varies With Extent of Underwriting Evaluation

Some HBV-infected people have significant liver fibrosis or early cirrhosis when they apply for insurance, and they are closer to the date of HBV-related complications. Cirrhosis detection rates in Figures 12–17 are theoretical illustrations of the inverse relationship be-
between rate of detection and estimated insured lives experience. For example, a detection rate of 20% means that fewer high-risk applicants would be detected and mortality ratios would be higher; if the cirrhosis detection rate were 50%, more high-risk applicants would be detected, with correspondingly lower mortality ratios.

What percentage of higher risk applicants would actually be detected during the underwriting process? There are no specific data that answer this question. In general, the likelihood of identifying applicants at higher risk would depend on the extent of the underwriting evaluation, including:

- few or no laboratory tests versus a full blood profile (e.g., a serum albumin level below the lower limit of normal indicates a poor prognosis) and AFP level;
- insurance examination to detect signs and symptoms of more advanced disease;
- a physician's statement (very useful for this impairment, particularly if a liver biopsy has been performed); and
- liver ultrasound to detect cirrhosis and early HCC (especially in large amount cases).

**HBeAg/Anti-HBe Status Not a Major Factor for Differentiating Risk**

Authors have reported the frequency distribution of HBeAg and anti-HBe by age and the long-term impact of HBeAg versus anti-HBe status. These data were used in the model to approximate real-life population data in Taiwan, Hong Kong, Shanghai, Singapore, and Korea. For subjects age 20 at underwriting, the difference between peak mortality ratios for HBeAg positive versus anti-HBe positive is approximately 25 (males) and 10 (females) mortality percentage points (Figures 8 and 9, respectively). When averaged over a 50-year follow-up (ages 20–70), estimated mortality ratios for HBeAg-positive subjects are approximately 15 mortality percentage points higher for males and 5 mortality percentage points higher for females. Thus, HBeAg/anti-HBe status is not a major factor for differentiating risk in an insurance context.

**HBV Mutations**

HBV often mutates to a form in which active replication persists even though HBeAg is not detectable. These are known as precore and core promoter mutations. Studies involving these mutations were not incorporated in the model because the reported prevalence of the mutation varies a great deal from study to study, there are insufficient data regarding the long-term impact of the core mutation, and real-life data sets could be approximated without further complicating the model.

**Generalization to Other Populations**

The focus of this analysis is on Chinese people infected with HBV. Morbidity and mortality estimates provided by the model can be generalized to other populations and individuals where HBV infection occurs at birth or during early childhood. Some modifications in insurance risk (usually higher risk estimates) might be required in non-Asian markets where few or no HBV-related deaths would be included in insured lives mortality rates.

**Serum Alanine Aminotransferase Levels**

Serum alanine aminotransferase (ALT) levels were not included as a variable in the Markov model because the literature indicated that the correlation between ALT levels and prognosis was weak. The natural history of HBV acquired at birth or during early childhood is such that ALT levels fluctuate during the course of HBV infection, increasing and decreasing depending on host and viral factors, and values at a single point in time are not strongly predictive of outcome. For example, an elevated ALT level at the time of underwriting might indicate seroconversion or attempted seroconversion from HBeAg to anti-HBe (a favorable development), while a normal ALT level could occur...
in an applicant with progressive fibrosis and/or cirrhosis (both unfavorable developments).

One situation where ALT levels might prove useful is in the case of sustained ALT elevation. Yu et al\textsuperscript{13} observed more rapid progression to cirrhosis in patients with sustained elevation of serum ALT for 6 months or longer. These cases could be identified in an insurance setting only via a physician's statement that listed results of prior enzyme levels.

**CONCLUSIONS**

Morbidity and mortality are within the insurable range for the majority of HBV-infected Chinese applicants, with higher male mortality ratios due to the fourfold higher HCC incidence rate. Risk varies with the extent of the underwriting evaluation and the percentage of applicants with significant liver fibrosis or early cirrhosis that are detected during the underwriting process. HBeAg/anti-HBe status is not a major factor for differentiating risk in an insurance context. Morbidity and mortality estimates provided by the model can be generalized to other populations and individuals where HBV infection occurs at birth or during early childhood, although some modification in insurance risk might be required in non-Asian markets.

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