Long-Term Morbidity and Mortality Risk in Japanese Insurance Applicants With Chronic Hepatitis C Virus Infection

Robert J. Pokorski, MD, FACP

Background.—Japan has the highest rate of liver cancer of any industrialized country in the world, and research indicates that hepatitis C virus (HCV) is responsible for 50-76% of these cases. The natural history of chronic HCV infection is difficult to determine because the initial bout of acute infection is usually not recognized and serious complications generally do not develop for at least 3 decades. This article discusses use of a Markov model to estimate long-term morbidity and mortality risk associated with chronic HCV infection in otherwise healthy Japanese insurance applicants. A range of risk estimates is derived based on different assumptions of disease progression.

Results.—Data for this analysis were based on prospective and combined retrospective-prospective studies of populations infected at different ages and followed for durations of up to 25 years. Estimated mortality ratios varied with assumptions regarding rate of progression from active HCV infection to cirrhosis. For males, peak mortality ratios decreased with advancing age at underwriting, from a high of 253% (age 20) to a low of 144% (age 60). A similar age-related pattern was seen for females, from a peak mortality ratio of 222% (age 20) to a low of 156% (age 60). In contrast to the pattern of decreasing relative mortality at older ages, morbidity increased with age at underwriting. Sensitivity analysis indicated that calculations in the model were sensitive to different transition rates from active HCV infection to cirrhosis and from cirrhosis to HCC, but were not sensitive to treatment frequency and success or the percentage of people treated prior to application. A review of the literature also suggested that a favorable prognosis was likely in applicants with persistently normal ALT levels, but prognosis was less certain for those with intermittent or persistent elevation of liver enzymes.

Conclusion.—Morbidity and mortality are within the insurable range for the majority of HCV-infected persons. Risk varies with gender, age at infection, and other variables discussed in the article.

An estimated 3% of the world’s population is chronically infected with hepatitis C virus (HCV). Japan has been greatly affected by this epidemic. Dr Tsukuma of the Japan Society of Hepatology reported that Japan has the highest rate of liver cancer of any
industrialized country in the world. In 1995, hepatocellular carcinoma (HCC) became the third leading cause of cancer death in males and the fourth in females, and the annual liver cancer death rate of 32,000 is expected to rise over the next 10 years. Research indicates that HCV is responsible for 50-76% of these cases.

The natural history of chronic HCV infection is controversial. Some medical experts have suggested that progression to end-stage liver disease is inevitable; others have concluded that progression is restricted to a limited percentage of those who are infected. These opposing views have caused uncertainty among medical underwriters who must assess risk in applicants with this impairment.

Long-term outcome is difficult to determine for several reasons. First, the initial bout of acute HCV infection is usually not recognized because of the paucity or complete absence of symptoms. Second, the chronic phase of infection is usually asymptomatic. Third, serious complications such as decompensated cirrhosis (liver failure) and HCC often develop more than 3 decades after acute infection.

Discordant views about the risk for serious long-term sequelae of HCV infection are related to the different strategies used to study the natural history of infection. Retrospective series of patients with chronic, clinically obvious HCV infection suggest that serious or fatal outcomes are highly likely. (Retrospective studies are based on patients with established HCV-related liver disease, prospective studies follow patients from a known date of acute infection, and combined retrospective-prospective studies involve individuals infected in large numbers in clearly defined situations, eg, infection via contaminated blood or immunoglobulin, who are identified at a later date and are then followed prospectively.) These studies have a strong bias toward selection of the most severe cases because patients are treated at tertiary care and liver transplantation centers and persons who fully recover or have asymptomatic or mild infection are omitted from the study. For example, the oft-quoted landmark article by Kiyosawa et al, which reported a very unfavorable prognosis, was based on a cohort of 231 patients with posttransfusion chronic non-A, non-B hepatitis (almost all cases were chronic HCV infections) evaluated at Shinshu University Hospital. At the initial consultation, all patients were symptomatic, 96 had chronic hepatitis, cirrhosis was present in 81 patients, and HCC had been diagnosed in 54 subjects. As would be expected, the results of the study suggested that HCV was a very serious disease that generally progressed to end-stage liver disease. In contrast, prospective and combined retrospective-prospective studies that begin with acute HCV illness have identified serious complications in a relatively small proportion of infected persons. These reports provide a much better indication of outcome for the typical HCV-infected person, and they represent the principal data source for this analysis.

This article discusses use of a Markov model to estimate long-term morbidity and mortality risk associated with chronic HCV infection in otherwise healthy Japanese insurance applicants. A range of risk estimates is derived based on different assumptions of disease progression. Data for this analysis are based on prospective and combined retrospective-prospective studies of populations infected at different ages and followed for durations of up to 25 years.

**DESCRIPTION OF MODEL**

A Markov model was created to estimate risk associated with chronic HCV infection (Figure 1). Simplifying assumptions were made that caused the model structure to diverge from a strict interpretation of the HCV pathophysiologic disease process. For example, since HCC arises in a fibrotic (scarred) or cirrhotic liver in the vast majority of cases, the model assumes that cirrhosis must precede HCC. Though not totally correct from a pathophysiologic standpoint, errors would be small since transitions directly
from chronic HCV infection to HCC are relatively rare.\textsuperscript{13-15}

The 10 Markov states are described below. 

Active HCV Infection (Prior Treatment Failure).—Active HCV infection (prior treatment failure) means that interferon has been administered in the past but active HCV infection persists as manifested by an elevated alanine aminotransferase (ALT) level and/or detectable serum HCV RNA. For this and all subsequent Markov states (except the 3 death states), subjects are first exposed to the age-and gender-specific risk of expected death in an insured lives population. Expected mortality rates are based on the 1996 "Japan Experience Mortality Table for Males and Females."\textsuperscript{16} Subjects who survive expected death transition to cirrhosis or back to active HCV infection (prior treatment failure) and face the same risks during the next cycle. Each cycle of the model is 1 year in duration.

Interferon is standard treatment for patients with chronic HCV infection,\textsuperscript{17} and almost all affected patients have been treated since interferon became available after 1992 for HCV-related hepatitis under medical insurance in Japan\textsuperscript{18} except for patients who refused treatment, had a history of psychiatric problems, or had decompensated liver cirrhosis or autoimmune disease.\textsuperscript{19} Estimates are that interferon has been administered to more than 250,000 Japanese patients.\textsuperscript{20} Underwriters generally do not know who has or has not been treated. The assumption in the model is that 90% of insurance applicants have already received interferon but treatment has failed, that is, they apply for insurance and ALT levels are elevated and/or serum HCV RNA can

\begin{figure}
\centering
\includegraphics[width=\textwidth]{Markov_model.png}
\caption{Markov model used to estimate long-term morbidity and mortality risk in Japanese insurance applicants infected with the hepatitis C virus.}
\end{figure}
Table 1. Summary of Prospective and Combined Retrospective-Prospective Studies of Progression From Active Hepatitis Virus Infection to Cirrhosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Age at Infection</th>
<th>Gender Distribution</th>
<th>Annual Transition Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vogt et al\textsuperscript{24}</td>
<td>3</td>
<td>49% male</td>
<td>0.000</td>
</tr>
<tr>
<td>Seeff et al\textsuperscript{5}</td>
<td>20</td>
<td>Male</td>
<td>0.003</td>
</tr>
<tr>
<td>Rodger et al\textsuperscript{25}</td>
<td>21</td>
<td>70% male</td>
<td>0.005</td>
</tr>
<tr>
<td>Grønbæk et al\textsuperscript{26}</td>
<td>26</td>
<td>53% male</td>
<td>0.001</td>
</tr>
<tr>
<td>Kenny-Walsh\textsuperscript{23}</td>
<td>28</td>
<td>Female</td>
<td>0.000</td>
</tr>
<tr>
<td>Muller\textsuperscript{27}</td>
<td>Unknown</td>
<td>Female</td>
<td>0.000</td>
</tr>
<tr>
<td>Seeff\textsuperscript{9}</td>
<td>50</td>
<td>50% male</td>
<td>0.011</td>
</tr>
<tr>
<td>Kuboki et al\textsuperscript{33}</td>
<td>≤50</td>
<td>Male</td>
<td>0.010</td>
</tr>
<tr>
<td>Kuboki et al\textsuperscript{33}</td>
<td>≥50</td>
<td>Male</td>
<td>0.011</td>
</tr>
<tr>
<td>Kuboki et al\textsuperscript{33}</td>
<td>&lt;50</td>
<td>Female</td>
<td>0.000</td>
</tr>
<tr>
<td>Kuboki et al\textsuperscript{33}</td>
<td>≥50</td>
<td>Female</td>
<td>0.005</td>
</tr>
</tbody>
</table>

be detected. Thus, 90% of subjects begin the model in this Markov state. Scenario modeling (Table 4, described in the Results) examines the effect of different assumptions regarding percentage of treated applicants.

Active HCV Infection (No Prior Treatment).—Ten percent of applicants begin the model in this Markov state. Subjects who survive expected death are either treated or not treated. Those who are not treated transition to cirrhosis or back to active HCV infection (no prior treatment) and face the same risks during the next cycle. Those who are treated transition to either sustained treatment response or active HCV infection (prior treatment failure), depending on whether treatment succeeds or fails.

Sustained Treatment Response.—Subjects who survive expected death transition to active HCV infection (prior treatment failure) if relapse occurs or back to sustained treatment response and face the same risks during the next cycle.

Cirrhosis.—Subjects who survive expected death transition to HCC, decompensated cirrhosis, or back to cirrhosis and face the same risks during the next cycle.

Decompensated Cirrhosis.—Subjects who survive expected death transition to HCC, death (cirrhosis), or (3) back to decompensated cirrhosis to face the same risks during the next cycle.

HCC.—This is a 10-year tunnel state (an array of temporary Markov states that can be visited only in a fixed sequence\textsuperscript{21}). During each of the 10 years that subjects stay in this state, those who survive expected death transition (1) to death (HCC), (2) back to HCC to face the same risks during the next cycle, or after 10 years, (3) exit the tunnel state to HCC cure.

HCC Cure.—Subjects who survive expected death transition back to HCC cure to face the same risks during the next cycle.

Death (Expected); Death (HCC); Death (Cirrhosis).—There are no transitions from these Markov states.

TRANSITION RATES

Active HCV Infection to Cirrhosis

Each year subjects with chronic HCV infection are at risk for cirrhosis. There are few (if any) long-term prospective or combined retrospective-prospective studies in the English language medical literature that provide these transition rates in Japanese patients. This problem was addressed by (1) finding data for Western patients, (2) adjusting the data for what might be expected in a Japanese cohort, and (3) modeling different scenarios to gauge the sensitivity of calculations to different assumptions.

Western Studies

Probabilities for the transition from active HCV infection to cirrhosis in Western subjects were determined from a review of prospective and combined retrospective-prospective studies that began with acute HCV illness and followed patients with active HCV infection to determine the incidence of complications (Table 1). These data indicate that progression from active HCV infection to cirrhosis is approximately 10 times faster when HCV is acquired at older ages,\textsuperscript{22} ranging from 0.001 (Kenny-Walsh\textsuperscript{23}) to approximately 0.010 (Seeff\textsuperscript{9}).
1. Vogt et al\textsuperscript{24} studied 67 children (33 male and 34 female; mean age at infection, 3 years) who underwent cardiac surgery in Munich, Germany, before 1991. At a mean interval of 19.8 years after surgery, only 3 patients had histologic signs of progressive liver disease and a non-HCV explanation was likely in all cases (congestive heart failure, 2 patients; chronic hepatitis B infection, 1 patient).

2. Seeff et al\textsuperscript{5} observed serious liver disease in 2 of 17 HCV-infected male US army recruits (mean age at infection, 20 years) during a 45-year follow-up. Route of infection was unknown.

3. Rodger et al\textsuperscript{25} reported that 2 of 35 HCV-infected Australian patients (70\% male; mean age at infection, 21) developed cirrhosis after 23 years. Injecting-drug use was the presumed route of infection.

4. Grønbæk et al\textsuperscript{26} found cirrhosis in 16 of 162 HCV-infected Danish patients (53\% male; median age at infection, 26 years) during a 19-year follow-up. Probable route of infection was unknown in 61\%, was injecting-drug use in 36\%, and was transfusion in 3\%.

5. Kenny-Walsh\textsuperscript{23} reported experience of the Irish Hepatology Research Group. Seven cases of cirrhosis were observed in 363 women (mean age at infection, 28 years) during a 17-year follow-up. Infection was via HCV-contaminated anti-D immune globulin.

6. Muller\textsuperscript{27} observed no cases of cirrhosis after a 15-year follow-up in 152 German women infected with HCV via contaminated anti-D immune globulin.

7. Seeff\textsuperscript{9} summarized combined retrospective-prospective posttransfusion studies performed in the United States. Cirrhosis was reported in 15–20\% of US patients (approximately half male and half female; mean age at infection, 50 years) during an 18–20 year follow-up. Of the subjects who had presumably died of liver disease, 71\% were identified as heavy drinkers and many had been hospitalized for alcohol-related problems.

Poynard et al\textsuperscript{28} published the largest series that provided data on relative rates of progression from chronic HCV infection to cirrhosis. Based on their analysis of 3072 European patients with chronic HCV infection, 3 factors were independently associated with an increased progression rate: older age at infection, male gender, and heavy daily alcohol consumption. Age at infection was the main risk factor for fibrosis progression. Rate of progression was extremely low in individuals younger than 20 years, low in those age 21–40 years, intermediate for ages 41–50 years, and highest in those older than 50 years. A possible explanation for higher progression rates at older ages of infection is that immune defense mechanisms are weaker in older people. Male gender was associated with higher rates of progression independently of age at infection and alcohol consumption. The reason for this association is unknown but is perhaps related to favorable influences of estrogen (in women) on the rate of hepatic fibrosis\textsuperscript{29,30} or to the unfavorable effects of elevated testosterone levels in males.\textsuperscript{31} Overall, male fibrosis progression rates were approximately 1.4 times higher than female progression rates. The importance of alcohol intake is discussed later in this article.

\textbf{Japanese Studies}

As noted previously, estimates of long-term morbidity and mortality risk in an insured lives population should be based on prospective and combined retrospective-prospective studies. Two studies are exemplary of the problems that would occur if data for the Markov model were derived from retrospective studies.

- Ikeda et al\textsuperscript{18} reported experience in 1500 subjects with chronic HCV infection. The group was heavily weighted to severe, advanced fibrosis, that is, severe or moderate fibrosis was present in 35\% and 54\%, respectively, of subjects when the study began, two thirds were male (more rapid progression), and 18\% had a history of
heavy alcohol ingestion (more rapid progression).

- Yano et al.\textsuperscript{32} followed 80 patients with chronic HCV infection selected from approximately 2000 patients with chronic liver disease seen at Nagasaki Chuo Hospital, Ohmura, and Toranomon Hospital, Tokyo. Subjects had a mean of 3.9 liver biopsies (range, 2–10).

There is marked selection bias in both of these studies because they included only very sick patients with aggressive disease, effectively "the worst of the worst." The likelihood of progression from active HCV infection to cirrhosis would be greatly overestimated if these data were used to model outcomes in an insured lives group.

The only Japanese study that approximates the prospective and combined retrospective-prospective data cited above was published by Kuboki et al.\textsuperscript{33} The cohort was probably infected during a 1967–72 HCV epidemic in Yamagata Prefecture, Japan. Among patients that were biopsied, cirrhosis was found in 3 of 16 males age 49 or younger at time of biopsy, 8 of 39 males age 50 or older, none of 10 females age 49 or younger, and 4 of 40 females age 50 or older. There was almost certainly an element of selection bias. Liver biopsy was done in only 157 of 2382 subjects, and it would be expected that biopsies would be more likely in patients with clinical or laboratory evidence of aggressive disease (thereby making active HCV to cirrhosis transition rates higher than they would be if all patients were biopsied). Nonetheless, results from this report are in line with Western studies listed in Table 1, with the exception of considerably higher transition rates in males age 49 or younger.

Data by Yoshida et al.\textsuperscript{34} and Ikeda et al.\textsuperscript{18} indicate that progression from active HCV infection to cirrhosis is approximately 2 times faster in males compared with females.

**Estimated Progression Rates by Age and Gender, Western Data**

Based on data in Table 1, the large cohort followed by Poynard et al.\textsuperscript{28} and Japanese studies that compared progression rates in males and females,\textsuperscript{18,34} general heuristic principles were used to estimate age- and gender-specific transition probabilities from active HCV infection to cirrhosis in Western patients (Table 2). Annual transition probabilities from active HCV infection to cirrhosis:

- increase with older age at infection;
- are twice as high for males;
- are fixed at the age of infection, that is, a person of a given attained age retains the transition probability that applies to the age when infection occurred (eg, a 40-year-old infected at age 20 would transition from active HCV infection to cirrhosis at the same rate as someone infected at age 20);
- are approximately 0.001 per year for females age 20 at infection based on data from the relatively large cohorts followed by Kenny-Walsh\textsuperscript{23} and Muller\textsuperscript{27};
- are approximately 0.002 per year for males infected at age 20 (0.002 rather than 0.003 was chosen to give statistical deference to the Poynard et al.\textsuperscript{28} data based on 3072 patients rather than to the 17 subjects reported by Seeff\textsuperscript{5}, ie, assuming that the 0.001 transition rate for females was accurate and that male transition rates average 1.4–2 times those of females, the male transition rate would be closer to 0.002 than to 0.003); and
- are estimated for age 60 based on extrapolation from age 50 values.

<table>
<thead>
<tr>
<th>Age</th>
<th>Western Subjects</th>
<th>Japanese Subjects*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>20</td>
<td>0.002</td>
<td>0.001</td>
</tr>
<tr>
<td>30</td>
<td>0.004</td>
<td>0.002</td>
</tr>
<tr>
<td>40</td>
<td>0.008</td>
<td>0.004</td>
</tr>
<tr>
<td>50</td>
<td>0.016</td>
<td>0.008</td>
</tr>
<tr>
<td>60</td>
<td>0.032</td>
<td>0.016</td>
</tr>
</tbody>
</table>

* The assumption is that Japanese age- and gender-specific transition rates are 2 times those of Western subjects.
Estimated Progression Rates by Age and Gender, Japanese Data

Japan has the world’s highest rate of liver cancer of any industrialized country. Part of the explanation is related to the high rate of infection that occurred in the years following World War II among persons aged 15–25 years, resulting in HCV prevalence rates in some cities as high as 45%. A second phase of HCV dissemination occurred decades later that was associated with commercial blood collections and traditional healing practices that favored transmission of bloodborne pathogens. Other reasons might involve environmental and host factors. The difference is not well explained by genotypic differences because HCC is most often associated with genotype 1b in Japan and other countries, although isolates of genotype 1b in Japan differ from those in European studies.

In the absence of prospective and combined retrospective-prospective studies (with the partial exception of data from Kuboki et al, which are very similar to Western studies except for males age 49 or younger), the model assumes that age- and gender-specific progression rates from active HCV infection to cirrhosis are 2 times higher in Japanese subjects compared with Western subjects (Tables 2 and 3 in the rows entitled “active HCV infection to cirrhosis”).

Treatment of Active HCV Infection

The assumption in the model was that people with active HCV infection would be treated at a rate of 10% per year after they purchased insurance. Given that (1) treatment is recommended for all patients with persistently elevated ALT levels, detectable serum HCV RNA, and evidence of chronic hepatitis on liver biopsy and that (2) interferon is available for HCV-related hepatitis under medical insurance in Japan, most insurance applicants with active HCV infection would be candidates for treatment. Thus, the assumption that 10% of new policyholders would be treated each year after purchasing insurance is probably a conservative estimate.

Sustained Response After Treatment of Active HCV Infection

Successful treatment refers to a sustained response (SR), defined as “persistently normal ALT and negative serum HCV RNA levels 6 months after completion of therapy.” Data in the Japanese literature indicate SR rates of 15–40%. The transition probability used in the model was 0.30 (30% probability of success). The value of 0.30 may understate the favorable effect of treatment because studies indicate that interferon is effective even in patients who do not achieve a SR, yielding significant reductions in viral load and serum ALT levels, improvement in histologic activity, and decreased rates of fibrosis progression compared with the natural history of the disease. The likely mechanism is suppression of hepatic inflammation and the regenerative process.

Relapse After Sustained Response

The probability of relapse after a SR to treatment of active HCV infection ranges from 0.04 to 0.10 per year. A value of 0.05 was chosen for this variable because therapeutic improvements are decreasing the likelihood of relapse.

Cirrhosis to HCC

The Japanese literature cites cirrhosis to HCC transition rates that range from 0.044 to 0.07. These are based on retrospective studies from tertiary treatment centers that specialize in care of patients with liver disease, and many of the subjects had advanced cirrhosis when they entered the study. These transition rates are considerably higher than what would be expected in an insured lives population, which progresses over many years from chronic HCV infection to (1) early cirrhosis (no clinical manifestations, detectable only via liver biopsy), (2) clinical cirrhosis (signs and symptoms of disease but clinically stable), and finally, (3) decompensated cirrhosis. The following are examples of the selection bias in these reports:
Table 3. Annual Transition Probabilities, Male and Female Unless Otherwise Stated*

<table>
<thead>
<tr>
<th>Transitions</th>
<th>Transition Rate (Range)</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expected death</td>
<td>Per mortality table</td>
<td>16</td>
</tr>
<tr>
<td>Active HCV infection to cirrhosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male (by age at infection)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>0.008</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.016</td>
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</tr>
<tr>
<td>50</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>0.064</td>
<td></td>
</tr>
<tr>
<td>Female (by age at infection)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
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<td>0.004</td>
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</tr>
<tr>
<td>40</td>
<td>0.008</td>
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</tr>
<tr>
<td>50</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>60</td>
<td>0.032</td>
<td></td>
</tr>
<tr>
<td>Treatment of active HCV infection</td>
<td>0.10</td>
<td>7, 10, 18</td>
</tr>
<tr>
<td>Sustained response after treatment of active HCV infection</td>
<td>0.30 (0.15–0.40)</td>
<td>17, 19, 34, 40</td>
</tr>
<tr>
<td>Relapse after sustained response</td>
<td>0.05 (0.04–0.10)</td>
<td>42, 45, 46</td>
</tr>
<tr>
<td>Cirrhosis to HCC</td>
<td>0.030 (0.044–0.07)</td>
<td>19, 34, 47–49</td>
</tr>
<tr>
<td>Cirrhosis to decompensated cirrhosis</td>
<td>0.023 (0.023–0.054)</td>
<td>54, 57, 62</td>
</tr>
<tr>
<td>Decompensated cirrhosis to death</td>
<td>0.129</td>
<td>57</td>
</tr>
<tr>
<td>HCC mortality, surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Year 1, male/female</td>
<td>0.551/0.527</td>
<td></td>
</tr>
<tr>
<td>Year 2, male/female</td>
<td>0.311/0.313</td>
<td></td>
</tr>
<tr>
<td>Year 3, male/female</td>
<td>0.300/0.277</td>
<td></td>
</tr>
<tr>
<td>Year 4, male/female</td>
<td>0.217/0.168</td>
<td></td>
</tr>
<tr>
<td>Year 5, male/female</td>
<td>0.253/0.124</td>
<td></td>
</tr>
<tr>
<td>Year 6, male/female</td>
<td>0.206/0.243</td>
<td></td>
</tr>
<tr>
<td>Year 7, male/female</td>
<td>0.154/0.103</td>
<td></td>
</tr>
<tr>
<td>Year 8, male/female</td>
<td>0.180/0.130</td>
<td></td>
</tr>
<tr>
<td>Year 9, male/female</td>
<td>0.136/0.097</td>
<td></td>
</tr>
<tr>
<td>Year 10, male/female</td>
<td>0.178/0.279</td>
<td></td>
</tr>
</tbody>
</table>

* HCV, hepatitis C virus; HCC, hepatocellular carcinoma.

- Tsukada et al\textsuperscript{47} observed cirrhosis to HCC transition rates of 0.044 per year, but some of the cohort had elevated AFP levels when the study began.
- Ikeda et al\textsuperscript{48} reported cirrhosis to HCC transition rates for 795 patients with viral and alcoholic cirrhosis. For the 349 subjects with HCV, mean age was 55 years, 24% were regular, heavy users of alcohol, and 6% already had decompensated cirrhosis (and hence a markedly increased risk of progression to HCC). The cirrhosis to HCC transition rate for the entire cohort was 0.056 per year.
- Sato et al\textsuperscript{49} reported a cirrhosis to HCC transition rate of 0.07 per year on subjects with a mean age of 59 years, a rate that would considerably overstate transition rates for younger ages.

The cirrhosis to HCC transition rate that would apply to an insured lives population cannot be determined, but it must be considerably less than values quoted by these retrospective studies based on highly selected, very sick cohorts. Poynard and Opolon\textsuperscript{50} suggested that the cirrhosis to HCC transition rate might be about 0.03 per year worldwide.
in a general population cohort, and this value was used in the model (Table 3). For purposes of comparison, the cirrhosis to HCC transition rate in Western subjects ranges from 0.0151-54 to 0.0335-60. Thus, the rate of 0.03 used in this model for Japanese subjects is the upper limit of what might be expected in Western insured lives cohorts and represents a further attempt (in addition to doubling Western age- and gender-specific transition rates from active HCV infection to cirrhosis) to adjust the model to allow for a more aggressive course for chronic HCV infection in Japanese subjects.

**Cirrhosis to Decompensated Cirrhosis**

Decompensated cirrhosis is diagnosed when a patient with stable (compensated) cirrhosis develops ascites, jaundice, hepatic encephalopathy, or variceal bleeding.54 It was difficult to find cirrhosis to decompensated cirrhosis transition rates that were applicable to an insured lives population because of the same problem with selection bias that existed when determining cirrhosis to HCC transition rates. For example, Serfaty et al54 reported a transition rate of 0.054 per year (Western data), but up to 10% of the cohort had more advanced cirrhosis when they entered the study61 and thus would have been much more likely to transition from compensated to decompensated cirrhosis. A value of 0.023 was chosen for the transition from cirrhosis to decompensated cirrhosis based on studies of patients with newly diagnosed cirrhosis caused by hepatitis B.62

**HCC Mortality**

Mortality after diagnosis of HCC was based on data presented by Inoue et al63 at the 1998 meeting of the Institute of Actuaries of Japan for subjects hospitalized with a first diagnosis of liver cancer between 1984 and 1996.

Transition rates described in Section 3 are summarized in Table 3.

**RESULTS**

**Age at Infection**

As noted previously, progression from active HCV infection to cirrhosis is related to age at infection,28 not current age. In an insurance context, this means that a 40-year-old man infected with HCV at age 20 or 30 would generally experience the progression rate typical of a 20- or 30-year-old male, respectively. This circumstance poses problems
Figure 3. Estimated mortality ratios for HCV-infected Japanese females age 20 at underwriting, by transition rate from active HCV infection to cirrhosis.

for underwriters, who almost never know age at infection.

Routes of transmission include transfusion of blood products (transfusions during surgery, organ transplant, contaminated immunoglobulins, clotting factors, vaccines), occupational exposure in hospital employees (needlesticks, dialysis units), miscellaneous causes (tattoos), perinatal (mother to infant), sexual contact, and injecting-drug use. Transfusion-related HCV infection decreased markedly from the mid-1980s to the early 1990s. Thus, in the absence of an event known to be associated with HCV transmission (e.g., major surgery in the 1980s or earlier that required blood transfusion or a known needlestick injury in a hospital employee), the strongest associations with HCV infection among persons age 17-59 are injecting-drug use and sexual contact. Thus, in the absence of an event known to be associated with HCV transmission (e.g., major surgery in the 1980s or earlier that required blood transfusion or a known needlestick injury in a hospital employee), the strongest associations with HCV infection among persons age 17-59 are injecting-drug use and sexual contact. These are Western data, which probably apply to young and middle-aged people worldwide with no history of an event associated with HCV infection. Given that these risks are more common in the teenage and young adult ages, the likely date of infection can be estimated relative to current age. For example, middle-aged insurance applicants would generally have been infected 10-20 years earlier, and they would retain the active HCV infection to cirrhosis transition rates characteristic of that age.

The uncertainty regarding actual date of infection is addressed by modeling different rates for the transition from active HCV infection to cirrhosis (below).

Estimated Mortality Experience

Figures 2–13 display estimated mortality ratios for Japanese males and females by age at underwriting according to different transition rates from active HCV infection to cirrhosis. The intent is to provide a range of mortality estimates using multiples of transition rates that have been reported in Western studies.

Males

- Age 20 (Figure 2)—Transition rates from active HCV infection to cirrhosis include 0.002 (Western transition rate per Table 2; peak mortality ratio, 177%), 0.003 (1.5 times Western transition rate; peak mortality ratio, 215%), 0.004 (2 times Western transition rate; peak mortality ratio, 253%), and 0.006 (3 times Western transition rate; peak mortality ratio, 328%). The following male and female data continue this pattern of estimating transition rates for Japanese cohorts according to multiples of Western data (Table 2).
Figure 4. Estimated mortality ratios for HCV-infected Japanese males age 30 at underwriting, by transition rate from active HCV infection to cirrhosis.

Age 30 (Figure 4)—Transition rates include 0.002 (peak mortality ratio, 134%), 0.004 (peak mortality ratio, 168%), 0.006 (peak mortality ratio, 201%), 0.008 (peak mortality ratio, 234%), and 0.010 (peak mortality ratio, 266%). Age 30 marks the beginning of an important trend predicted by the Markov model: with advancing age at underwriting, expected death rates increase more rapidly than HCV-related deaths, the result being that mortality ratios decrease for applicants underwritten at older ages.

Figure 5. Estimated mortality ratios for HCV-infected Japanese females age 30 at underwriting, by transition rate from active HCV infection to cirrhosis.

Age 30 (Figure 5)—Transition rates include 0.001 (peak mortality ratio, 119%), 0.002 (peak mortality ratio, 127%), 0.003 (peak mortality ratio, 154%), 0.004 (peak mortality ratio, 176%), and 0.005 (peak mortality ratio, 204%).

• Age 30 (Figure 4)—Transition rates include 0.002 (peak mortality ratio, 134%), 0.004 (peak mortality ratio, 168%), 0.006 (peak mortality ratio, 201%), 0.008 (peak mortality ratio, 234%), and 0.010 (peak mortality ratio, 266%). Age 30 marks the beginning of an important trend predicted by the Markov model: with advancing age at underwriting, expected death rates increase more rapidly than HCV-related deaths, the result being that mortality ratios decrease for applicants underwritten at older ages.

• Age 40 (Figure 6)—Transition rates include 0.004 (peak mortality ratio, 127%), 0.008 (peak mortality ratio, 154%), 0.016 (peak mortality ratio, 204%), and 0.032 (peak mortality ratio, 297%).

• Age 50 (Figure 7)—Transition rates include 0.002 (peak mortality ratio, 119%), 0.010 (peak mortality ratio, 154%), 0.032 (peak mortality ratio, 204%), and 0.050 (peak mortality ratio, 269%).
mortality ratio, 168%), and 0.064 (peak mortality ratio, 223%).

- Age 60 (Figure 10)—Transition rates include 0.016 (peak mortality ratio, 112%), 0.032 (peak mortality ratio, 124%), 0.064 (peak mortality ratio, 144%), and 0.128 (peak mortality ratio, 177%).

- Maximum estimated mortality ratios for ages 20–60 are summarized in Figure 12. Maximum estimated mortality ratios were determined by assuming that age-specific transition rates from active HCV infection to cirrhosis for Japanese males were 2 times higher than those in Western studies (Table 2).

**Females**

The approach used to estimate mortality ratios for males was used to project female experience. Maximum estimated mortality ratios were determined by assuming that age-specific
transition rates from active HCV infection to cirrhosis for Japanese females were 2 times higher than those in Western studies (Table 2).

- Age 20 (Figure 3)—Maximum estimated mortality ratios are displayed by curve 0.002. Mortality ratios peak at 222%.
- Age 30 (Figure 5)—Maximum estimated mortality ratios are displayed by curve 0.004. Mortality ratios peak at 202%. As with males, estimated mortality ratios decrease for applicants underwritten at older ages.
- Age 40 (Figure 7)—Maximum estimated mortality ratios are displayed by curve 0.008. Mortality ratios peak at 192%.
- Age 50 (Figure 9)—Maximum estimated mortality ratios are displayed by curve 0.016. Mortality ratios peak at 184%.
- Age 60 (Figure 11)—Maximum estimated mortality ratios are displayed by curve 0.032. Mortality ratios peak at 156%.
- Maximum estimated mortality ratios for ages 20–60 are summarized in Figure 13.

### Estimated Morbidity Experience

An assumption was made that total and permanent disability (TPD) would occur upon diagnosis of HCC or decompensated cirrhosis. Figures 14 and 15 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 (all liver-related causes) peak at 3.1 per 1000 for males and 1.7 per 1000 for females.

- Figures 16 and 17 summarize estimated incidence rates for all liver-related causes of TPD in HCV-infected males and females, respectively, for ages 20–60 at underwriting. Incidence rates are higher for males. Peak incidence rates occur in applicants age 60 at underwriting (males, 17.2 per 1000; females, 12.2 per 1000). As predicted by active HCV infection to cirrhosis transition rates in Table 3, the incidence of TPD in HCV-infected applicants increases with age at infection. Higher incidence rates at ages 40, 50, and 60 are based on the assumption that HCV infection occurred shortly before the time of application. If infection had occurred much earlier (eg, if a 50 or 60 year old was infected at age 20), TPD incidence rates at older ages would be closer to those observed for 20- and 30-year-old applicants.

### Sensitivity Testing

Figures 2–11 indicate that calculations are sensitive to different transition rates from ac-
tive HCV infection to cirrhosis, particularly at younger ages.

Sensitivity testing was also performed to gauge the effects of different assumptions regarding (1) frequency and efficacy of treatment for active HCV infection and cirrhosis and (2) transition rates from cirrhosis to HCC. Six scenarios are listed in Table 4 and calculations based on these scenarios are displayed in Figure 18. Scenario 1 is the baseline scenario for an HCV-infected male age 40 at underwriting with a 0.016 annual transition rate from active HCV infection to cirrhosis (curve 0.016 in Figure 6). Boldfaced entries in Table 4 in scenarios 2–6 identify changes relative to scenario 1.

Figure 18 indicates that calculations are not sensitive to variations in treatment of the magnitude that might be expected in the near future. Outcomes were essentially the same if treatment of active HCV infection varied from 10 to 20% (scenario 2), if the ability to achieve a sustained treatment response varied from 30 to 50% (scenario 3), if frequency of relapse after achieving a sustained response varied from 0 to 5% (scenario 4), and if the percentage of applicants treated prior to application varied from 50 to 90% (scenario 5).

Calculations are sensitive to different assumptions regarding cirrhosis to HCC transition rates. An increase in this transition rate from 0.03 to 0.04 results in a maximum increase of 20 mortality percentage points (scenario 6).

**DISCUSSION OF PRINCIPAL FINDINGS**

**Insurability**

The model suggests that morbidity and mortality experience would be within insurable ranges for the majority of HCV-infected persons. Mortality ratios were highest at younger ages at underwriting and were higher in males. The incidence of liver-related TPD increased at older ages, a finding in agreement with most studies worldwide that report more rapid disease progression with older ages at infection.

**Risk Greater Than Projected by Figures 2–18**

Morbidity and mortality risk would be greater and begin somewhat earlier (after underwriting) than projected by Figures 2–18. The model assumes that 90% of subjects are located in the Markov state active HCV infection (prior treatment failure) and 10% are located in active HCV infection (no prior treat-
Figure 10. Estimated mortality ratios for HCV-infected Japanese males age 60 at underwriting, by transition rate from active HCV infection to cirrhosis.

Figure 11. Estimated mortality ratios for HCV-infected Japanese females age 60 at underwriting, by transition rate from active HCV infection to cirrhosis.

ment) at the time of underwriting, with subsequent progression per Figure 1. However, most insurance applicants would have been infected 10 or more years prior to the date of application. Some may have developed significant liver fibrosis and perhaps even early cirrhosis, that is, they may be closer to the date of HCV-related complications. (Applicants with decompensated cirrhosis or HCC within the prior 10 years would either not apply for insurance or would be detected during the underwriting process). What percentage of the applicants with significant fibrosis and/or early cirrhosis would be detected during underwriting? The likelihood of identifying applicants at higher risk would depend 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
Figure 12. Maximum estimated mortality ratios for HCV-infected Japanese males, by age at underwriting.

Figure 13. Maximum estimated mortality ratios for HCV-infected Japanese females, by age at underwriting.

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).

Key Assumptions
The favorable results projected by the model must be interpreted in the context of data limitations and sensitivity to key assumptions.

Japanese Transition Rates
With the partial exception of the report from Kuboki, data from long-term prospective and combined retrospective-prospective studies of chronic HCV infection were not identified in the Japanese literature. Two principal assumptions were made to estimate
outcome in Japanese insurance applicants. First, transition rates from active HCV infection to cirrhosis are greater in Japanese people. How much greater is unknown; multiple scenarios were run based on multiples of Western rates. Second, the transition from cirrhosis to HCC is 0.03. The exact rate for this transition cannot be determined, but it must be considerably less than values quoted by retrospective studies based on highly selected, very sick Japanese cohorts.

**Maximum Estimated Mortality Ratios**

Figures 12 and 13 display maximum estimated mortality ratios for HCV-infected Japanese males and females, respectively, by age at underwriting. The basis for this maximum estimate is that (1) the transition rate from active HCV infection to cirrhosis is 2 times higher than values reported in Western subjects and (2) the cirrhosis to HCC transition rate is 0.03, a rate at the upper limit of what

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**Figure 14.** Maximum estimated incidence of total and permanent disability in HCV-infected Japanese males age 20 at underwriting. Transition rate from active HCV infection to cirrhosis equals 0.004.

**Figure 15.** Maximum estimated incidence of total and permanent disability in HCV-infected Japanese females age 20 at underwriting. Transition rate from active HCV infection to cirrhosis equals 0.002.
might be expected in Western insured lives cohorts. Scenario 6 indicates that peak mortality ratios for a 40-year-old male would increase 20 mortality percentage points if a value of 0.04 were used instead.

Because of uncertainty regarding active HCV to cirrhosis transition rates in Japanese cohorts, maximum estimated mortality ratios were based on the assumption that infection occurred shortly before the time of application. However, natural history studies on Western subjects indicate that these transition rates are fixed at the age of infection, that is, a person of a given attained age retains the transition probability that applies to the age when infection occurred. If this same pattern occurs in Japanese subjects with active HCV infection, mortality ratios would be somewhat lower than indicated in Figures 12 and 13 because progression from active HCV infection to cirrhosis would occur at the lower rates that apply at age of infection (per Table 2), not age at application.

Existing data do not allow a precise determination of maximum mortality ratios that might occur. Accordingly, different assumptions were used to calculate values for Figures 2-18 to allow independent estimations of risk.

**Western Transition Rates From Active HCV Infection to Cirrhosis**

Age- and gender-specific transition rates that are applicable to insured lives populations can only be determined from prospective and combined retrospective-prospective studies that begin with date of infection. Current data in the Western literature are insufficient to precisely determine these rates. In addition, published transition rates were based on small numbers of patients followed for 25 years or less from the date of infection. Longer term studies involving more patients will be needed to confirm rates used in this model.

**HCC Develops Only Via Cirrhosis**

The model assumes that HCC can occur only after cirrhosis has developed. Exceptions to this rule may occur. For example, Miyano et al reported a case of HCC in a 67-year-old man 4.5 years after apparent complete eradication of HCV infection with interferon treatment. The patient had only mild hepatic fibrosis before treatment and the liver showed no evidence of cirrhosis at the time of tumor resection. Nonetheless, this pattern—chronic HCV infection to HCC without intervening cirrhosis—is thought to be uncommon.

**Treatment Frequency and Efficacy**

Calculations in the model are not sensitive to variations in treatment of the magnitude that might be expected in the near future nor are they sensitive to the percentage of people that are treated prior to application.

**Linearity**

The model assumed that progression from chronic HCV to cirrhosis is linear during the third and subsequent decades of infection. Existing data can neither confirm nor refute this hypothesis. One study suggested that progression rates might eventually decrease. If this were the case, prognosis would be more favorable than predicted by the model, which assumes a constant, life-long rate of progression from active HCV infection to cirrhosis, for example, 0.002 per year for 20-year-old females. Another study reported that progression increased with duration of infection. Regardless of whether progression is linear or nonlinear (either decreasing or increasing with time), data in Figures 2-13 suggest a favorable prognosis even if transition rates from active HCV infection to cirrhosis were greater than estimates in Table 3.

**UNDERWRITING CONSIDERATIONS**

Based on recent studies that included measurement of serum HCV RNA, around 15% of people infected with HCV clear the virus and have a full recovery. Eighty-five percent remain chronically infected. There are two patterns of chronic HCV infection: chronic
HCV hepatitis with normal serum ALT and chronic HCV hepatitis with elevated serum ALT.

Chronic HCV Hepatitis With Normal Serum ALT

Approximately 25% of patients with chronic HCV infection have persistently normal ALT levels despite detectable serum HCV RNA. These people are usually asymptomatic and are detected after donating blood or by systematic screening. HCV RNA levels tend to be lower, and HCV genotypes do not differ from those in patients with elevated ALT levels. There is no satisfactory explanation for why ALT levels are normal in the face of ongoing viral replication. It may be that these patients mount a less aggressive immune response to HCV-infected liver cells.

A review of 16 published studies involving 447 cases of chronic HCV infection and normal serum ALT levels indicated that most patients have some degree of histologic abnormality on liver biopsy: normal findings or minimal, nonspecific changes, 24%; mild chronic hepatitis, 54%; and moderate chronic hepatitis, 21%. Fibrosis was usually absent or minimal, and cirrhosis was found in less than 1% of cases. Kuboki et al reported similar findings: liver biopsy indicated only mild hepatitis and no cases of cirrhosis in 43 subjects with detectable HCV RNA and normal ALT levels.

Long-term prognosis is unknown but is generally favorable because progression to cirrhosis is very slow. An exception regards patients with heavy alcohol intake: cirrhosis may occur in alcoholics even with persistently normal ALT levels.

Meaning of Persistently Normal ALT Levels

It is important to understand the meaning of persistently normal ALT levels because underwriting decisions will be based on this parameter. The following factors are important when assessing risk in HCV-infected applicants whose liver enzyme levels are currently normal.

- Are prior enzyme levels available for review? It is common for patients to have normal values for months or even years, followed by increases in enzyme levels. Without information about previous tests, the only possible conclusion is that a favorable prognosis is more likely but not...
POKORSKI—RISK IN JAPANESE INSURANCE APPLICANTS WITH HEPATITIS C

**Figure 17.** Maximum estimated incidence of total and permanent disability (all liver-related causes) in HCV-infected Japanese females, by age at underwriting.

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**Table 4.** Effects of Different Rates of HCV Treatment and Success and a Different Transition Rate From Cirrhosis to HCC, Compared with Baseline Assumptions (Scenario 1) for a 40-Year-Old Japanese Male*\(^*\)

<table>
<thead>
<tr>
<th>Transition</th>
<th>Scenario 1</th>
<th>Scenario 2</th>
<th>Scenario 3</th>
<th>Scenario 4</th>
<th>Scenario 5</th>
<th>Scenario 6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active HCV infection to cirrhosis</td>
<td>0.016</td>
<td>0.016</td>
<td>0.016</td>
<td>0.016</td>
<td>0.016</td>
<td>0.016</td>
</tr>
<tr>
<td>Treated prior to application</td>
<td>0.90</td>
<td>0.90</td>
<td>0.90</td>
<td>0.90</td>
<td>0.50</td>
<td>0.90</td>
</tr>
<tr>
<td>Treatment of active HCV infection</td>
<td>0.10</td>
<td><strong>0.20</strong></td>
<td>0.10</td>
<td>0.10</td>
<td>0.10</td>
<td>0.10</td>
</tr>
<tr>
<td>Sustained response after treatment of active HCV infection</td>
<td>0.30</td>
<td>0.30</td>
<td><strong>0.50</strong></td>
<td>0.30</td>
<td>0.30</td>
<td>0.30</td>
</tr>
<tr>
<td>Relapse after sustained response</td>
<td>0.05</td>
<td>0.05</td>
<td>0.05</td>
<td><strong>0.00</strong></td>
<td>0.05</td>
<td>0.05</td>
</tr>
<tr>
<td>Cirrhosis to HCC</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td><strong>0.04</strong></td>
</tr>
</tbody>
</table>

* HCV, hepatitis C virus; HCC, hepatocellular carcinoma.
\(^*\) Scenario 1 contains the values used to calculate curve 0.016 in Figure 6. Boldface entries in scenarios 2–6 identify changes relative to scenario 1.

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certain. A physician's statement is very beneficial in these situations. The questionnaire should request information about HCV-related symptoms, treatment, and prior enzyme levels.

- How much time should pass before enzyme levels can be considered normal for underwriting purposes?
- What is the mathematical definition of normal? If values start at the lower end of the normal range, a disease flare-up could double the level but enzymes could still remain within the normal range.
- Which liver enzymes are important? The ALT is the best enzyme indicator of disease activity. However, patients with advanced liver disease may have a normal ALT but elevated aspartate aminotransferase (AST) or gamma-glutamyl transferase (GGT) levels.

Given these considerations, persistently normal ALT levels in an applicant with chronic HCV infection might be defined as ALT and AST levels within the normal range on several occasions measured at least 1 month apart over a total period of at least 12 months.\(^*\)
Chronic HCV Hepatitis With Elevated Serum ALT

Seventy-five percent of patients with chronic hepatitis have elevated ALT levels. Prognosis depends on whether or not cirrhosis occurs, which in turn is related to the rate at which liver fibrosis develops. Age at infection and gender (variables used in the Markov model) correlate with disease progression, as does heavy alcohol intake, but there are no other clinical parameters that help underwriters estimate risk. Physical examination is usually normal, and the presence and severity of symptoms do not correlate with rate of fibrosis progression. When all HCV-infected patients with elevated serum ALT levels are viewed as a group, prognosis is generally more favorable if ALT levels are no more than 2 times the upper limit of normal or are abnormal only intermittently. However, on an individual case-by-case basis, ALT levels are not reliable enough to determine rate of disease progression. Specifically, advanced fibrosis or cirrhosis could be present even though ALT levels are less that 2 times normal, and higher elevations do not necessarily indicate more rapid progression. The reason for the lack of correlation between ALT and progression is that prognosis in chronic HCV hepatitis depends on the extent of liver fibrosis (which leads to cirrhosis), not on the severity of liver inflammation, and ALT levels mainly reflect degree of liver inflammation.

The only accurate way to assess the degree of fibrosis and the likely rate of progression is via a liver biopsy. If a biopsy has been performed, risk classification can be greatly enhanced by reviewing the actual biopsy report (not just the attending physician's interpretation of the results).

Risk of HCC After Sustained Treatment Response

Subjects who achieve a sustained remission have a favorable prognosis. However, there is a risk of relapse during the first 5 years. There is also a very small residual risk of HCC. In Japan, a total of 5 HCC cases have been reported after long durations postinterferon therapy (4 cases, 4 years after treatment; 1 case, 6 years after treatment).

Other Risk Factors

Daily alcohol consumption is strongly associated with more rapid progression in Japanese subjects. In Western patients with chronic HCV infection, estimates are that
consumption of more than 40 grams of alcohol per day approximately doubles the relative risk of HCC.\textsuperscript{79,80} Regarding HCV genotype, there is convincing evidence that genotype 1 is associated with a poor response to antiviral therapy.\textsuperscript{81} The association between genotype and severe liver disease is still somewhat controversial; many Japanese authors have found no association between HCV genotype and incidence of HCC.\textsuperscript{19,82-84} Viral load (HCV RNA level) does not significantly influence rate of progression.\textsuperscript{1} Progression is more rapid in patients with immunodeficiency (eg, HIV infection).\textsuperscript{1}

CONCLUSION

Morbidity and mortality are within the insurable range for the majority of HCV-infected persons. Calculations in the model are sensitive to different transition rates from active HCV infection to cirrhosis and from cirrhosis to HCC but are not sensitive to treatment frequency and success or the percentage of people treated prior to application. A favorable prognosis is likely in applicants with persistently normal ALT levels. For applicants with chronic HCV infection and elevated ALT levels, clinical parameters do not provide a clear indication of prognosis and data generated by the model are particularly useful for estimating risk in these cases.

REFERENCES

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