Long-Term Insured Lives Morbidity and Mortality Risk Associated With Chronic Hepatitis C Virus Infection

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Background.—Hepatitis C virus (HCV) infects 170 million people worldwide. 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 added to the uncertainty faced by underwriters who must assess risk in applicants infected with HCV. This article discusses use of a Markov model to estimate risk associated with chronic HCV infection in otherwise healthy applicants for life and critical illness insurance.

Results.—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 209% (age 20) to a low of 122% (age 60). A similar age-related pattern was seen for females, from a peak mortality ratio of 184% (age 20) to a low of 128% (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 hepatocellular carcinoma (HCC) but not sensitive to treatment frequency and success. A review of the literature also suggested that a favorable prognosis was likely in applicants with persistently normal alanine aminotransferase (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). 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 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 ab-
sence of symptoms. Second, the chronic phase of infection is usually asymptomatic. Third, serious complications such as decompensated cirrhosis (liver failure) and hepatocellular carcinoma (HCC) often develop more than 3 decades after acute infection.2

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. 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.3,4 (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 then followed prospectively.) For example, the oft-quoted article by Tong et al,5 which reported a very unfavorable prognosis, was based on a cohort evaluated at a major liver referral center; at the initial consultation, all patients were symptomatic, three fourths had liver enlargement, half had cirrhosis, and 5% had HCC. In contrast, prospective and combined retrospective-prospective studies have identified serious complications in a relatively small proportion of infected persons.6,7 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 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,1,8,9 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.10-12

The 13 Markov states are described below and are listed as the left-hand column in figure 1.

Active HCV Infection (No Prior Treatment).—All subjects begin the model in this Markov state. Each cycle of the model is 1 year in duration. Active HCV infection (no prior treatment) means that HCV RNA can be detected, the alanine aminotransferase (ALT) level is elevated or has been elevated in the recent past, and no anti-HCV treatment has been given. For this and all subsequent Markov states (except the three death states), subjects are first exposed to the age-specific risk of expected death. Expected mortality rates are based on 55% of the United States 1975-80 “Select and Ultimate Aggregate Table for Males and Females.”13 Subjects who survive expected death are either treated or not treated. Those who are not treated transition to cirrhosis (no prior treatment) 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 (treatment failure), depending on whether treatment succeeds or fails.

Sustained Treatment Response.—Subjects who
Figure 1. Markov model used to estimate long-term mortality and morbidity in insurance applicants infected with the hepatitis C virus.
survive expected death transition to active HCV infection (treatment failure) if relapse occurs or back to sustained treatment response and face the same risks during the next cycle.

Active HCV Infection (Treatment Failure).—Subjects who survive expected death transition to cirrhosis (treatment failure) or back to active HCV infection (treatment failure) and face the same risks during the next cycle.

Cirrhosis (No Prior Treatment).—These subjects have never been treated with anti-HCV therapy. Subjects who survive expected death are now either treated or not treated. Those who are not treated transition to (1) HCC, which can be treated with surgery or other traditional therapies (HCC treatment surgery) or with liver transplantation (HCC treatment, liver transplant), (2) decompensated cirrhosis (decompensated cirrhosis), or (3) back to cirrhosis (no prior treatment) to face the same risks during the next cycle. Those who are treated transition to either cirrhosis (treatment success) or cirrhosis (treatment failure), depending on whether treatment succeeds or fails.

Cirrhosis (Treatment Success).—Subjects who survive expected death transition to (1) HCC (above), (2) decompensated cirrhosis (above), or (3) back to cirrhosis (treatment success) to face the same risks during the next cycle.

Cirrhosis (Treatment Failure).—Subjects who survive expected death transition to (1) HCC (above), (2) decompensated cirrhosis (above), or (3) back to cirrhosis (treatment failure) to face the same risks during the next cycle.

 Decompensated Cirrhosis.—Subjects who survive expected death transition to (1) HCC (above), (2) death (cirrhosis), or (3) back to decompensated cirrhosis to face the same risks during the next cycle.

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

HCC Treatment (Liver Transplant).—This is a 10-year tunnel state. During each of the 10 years that subjects stay in this state, those who survive expected death transition to (1) death (HCC), (2) back to HCC treatment (liver transplant) 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

Transition rates described in this section are summarized in Table 1.

Active HCV Infection to Cirrhosis

Overview of Cited Studies

Probabilities for the transition from active HCV infection to cirrhosis 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 2). These data indicate that progression from active HCV infection to cirrhosis is approximately 10 times faster when HCV is acquired at older ages. 

1. Vogt et al 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 observed serious liver disease in 2 of 17 HCV-infected male US army re-
cruits (mean age at infection, 20 years) during 45-year follow-up. Route of infection was unknown.
3. Rodger et al\textsuperscript{17} 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{18} 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{19} 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{20} 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{6} 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 a 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.

**Estimated Progression Rates by Age and Gender**

Poynard et al\textsuperscript{21} 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
<table>
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<tr>
<th>Transitions</th>
<th>Transition Rate (Range)</th>
<th>References</th>
</tr>
</thead>
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<tr>
<td>Expected death</td>
<td>0.55 × mortality table rates</td>
<td>13</td>
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<tr>
<td>Active HCV infection to cirrhosis</td>
<td>—</td>
<td>2, 6, 16–21</td>
</tr>
<tr>
<td>Male (by age at infection)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>20</td>
<td>0.002</td>
<td>—</td>
</tr>
<tr>
<td>30</td>
<td>0.005</td>
<td>—</td>
</tr>
<tr>
<td>40</td>
<td>0.008</td>
<td>—</td>
</tr>
<tr>
<td>50 and older</td>
<td>0.012</td>
<td>—</td>
</tr>
<tr>
<td>Female (by age at infection)</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>20</td>
<td>0.001</td>
<td>—</td>
</tr>
<tr>
<td>30</td>
<td>0.002</td>
<td>—</td>
</tr>
<tr>
<td>40</td>
<td>0.004</td>
<td>—</td>
</tr>
<tr>
<td>50 and older</td>
<td>0.008</td>
<td>—</td>
</tr>
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<td>Treatment of active HCV infection</td>
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<td>7</td>
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<tr>
<td>Sustained response after treatment of active HCV infection</td>
<td>0.30 (0.20–0.40)</td>
<td>7, 46, 67</td>
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<tr>
<td>Relapse after sustained response</td>
<td>0.05 (0.04–0.10)</td>
<td>7, 28, 30, 31, 46, 62</td>
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<tr>
<td>Treatment of cirrhosis</td>
<td>0.20</td>
<td>—</td>
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<tr>
<td>Sustained response after treatment of cirrhosis</td>
<td>0.15 (0.07–0.30)</td>
<td>32, 33, 35</td>
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<tr>
<td>Cirrhosis to HCC</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Treatment success</td>
<td>0.010 (0.0–0.011)</td>
<td>34, 36–38</td>
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<tr>
<td>Treatment failure</td>
<td>0.030 (0.030–0.033)</td>
<td>36, 39–44</td>
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<tr>
<td>Cirrhosis to decompensated cirrhosis</td>
<td>—</td>
<td>—</td>
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<tr>
<td>Successful treatment</td>
<td>0.3 × treatment failure rate</td>
<td>—</td>
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<tr>
<td>Treatment failure</td>
<td>0.023 (0.023–0.054)</td>
<td>38, 41, 45</td>
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<td>Decompensated cirrhosis to death</td>
<td>0.129</td>
<td>41</td>
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<td>Surgery after HCC diagnosis</td>
<td>0.969</td>
<td>—</td>
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<td>HCC mortality, surgery</td>
<td>—</td>
<td>48</td>
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<td>Year 1</td>
<td>0.817</td>
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<td>Year 2</td>
<td>0.457</td>
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<tr>
<td>Year 3</td>
<td>0.269</td>
<td>—</td>
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<tr>
<td>Year 4</td>
<td>0.187</td>
<td>—</td>
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<tr>
<td>Year 5</td>
<td>0.172</td>
<td>—</td>
</tr>
<tr>
<td>Year 6</td>
<td>0.081</td>
<td>—</td>
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<tr>
<td>Year 7</td>
<td>0.079</td>
<td>—</td>
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<td>Year 8</td>
<td>0.059</td>
<td>—</td>
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<tr>
<td>Year 9</td>
<td>0.054</td>
<td>—</td>
</tr>
<tr>
<td>Year 10</td>
<td>0.020</td>
<td>—</td>
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<tr>
<td>Liver transplant after HCC diagnosis</td>
<td>0.031</td>
<td>47</td>
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<td>HCC mortality, transplant</td>
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<td>50</td>
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<tr>
<td>Year 1</td>
<td>0.370</td>
<td>—</td>
</tr>
<tr>
<td>Year 2</td>
<td>0.175</td>
<td>—</td>
</tr>
<tr>
<td>Year 3</td>
<td>0.173</td>
<td>—</td>
</tr>
<tr>
<td>Year 4</td>
<td>0.186</td>
<td>—</td>
</tr>
<tr>
<td>Year 5</td>
<td>0.057</td>
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<tr>
<td>Year 6</td>
<td>0.057</td>
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<tr>
<td>Year 7</td>
<td>0.057</td>
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<tr>
<td>Year 8</td>
<td>0.057</td>
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<tr>
<td>Year 9</td>
<td>0.057</td>
<td>—</td>
</tr>
<tr>
<td>Year 10</td>
<td>0.057</td>
<td>—</td>
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* HCV, hepatitis C virus; HCC, hepatocellular carcinoma.
Table 2. Summary of Prospective and Combined Retrospective-Prospective Studies of Progression from Active Hepatitis C 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 16</td>
<td>3</td>
<td>49% male</td>
<td>0.000</td>
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<tr>
<td>Seeff et al 2</td>
<td>20</td>
<td>Male</td>
<td>0.003</td>
</tr>
<tr>
<td>Rodger et al 17</td>
<td>21</td>
<td>70% male</td>
<td>0.003</td>
</tr>
<tr>
<td>Grønbæk et al 18</td>
<td>26</td>
<td>53% male</td>
<td>0.005</td>
</tr>
<tr>
<td>Kenny-Walsh 19</td>
<td>28</td>
<td>Female</td>
<td>0.001</td>
</tr>
<tr>
<td>Muller 20</td>
<td>Unknown</td>
<td>Female</td>
<td>0.000</td>
</tr>
<tr>
<td>Seeff 6</td>
<td>50</td>
<td>50% male</td>
<td>0.008–0.011</td>
</tr>
</tbody>
</table>

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 or to the unfavorable effects of elevated testosterone levels in males. 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.

Based on data in Table 2 and from the large cohort followed by Poynard, general heuristic principles were used to estimate age- and gender-specific transition probabilities from active HCV infection to cirrhosis (summarized in Table 1, active HCV infection to cirrhosis, male and female). Annual transition probabilities from active HCV infection to cirrhosis:

- Increase with older age at infection;
- 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 (e.g., 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 always higher for males;
- Are approximately 0.001 per year for females age 20 at infection based on data from the relatively large cohorts followed by Kenny-Walsh and Muller;
- 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 data based on 3072 patients rather than to the 17 subjects reported by Seeff, that is, assuming that the 0.001 transition rate for females was accurate and that male transition rates average 1.4 times those of females, the male transition rate would be closer to 0.002 than to 0.003); and
- Peak at age 50 per the Seeff posttransfusion data at approximately 0.010 per year.

Figure 3. Estimated mortality ratios for hepatitis C virus-infected females age 20 at underwriting, by transition rate from active hepatitis C virus infection to cirrhosis.
Figure 4. Estimated mortality ratios for hepatitis C virus-infected males age 30 at underwriting, by transition rate from active hepatitis C virus infection to cirrhosis.

with a male/female difference that reflects the 1.4 times faster progression rate in males, that is, a progression rate for 50-year males and females of 0.012 and 0.008, respectively.

**Treatment of Active HCV Infection**

Treatment varies from country to country according to factors such as established medical practice, prevalence of infection, and cost. 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 treatment is recommended for all patients with persistently elevated ALT levels, detectable serum HCV RNA, and evidence of chronic hepatitis on liver biopsy, 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. Recent studies in 1744 previously untreated patients found that a SR can be achieved in up to 41% of cases. The transition probability used in the model was 0.30 (30% probability of success), which represents the average response for a cohort with different HCV genotypes (refer to later discussion of variation in treatment response by genotype). 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 disease.

**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.

**Treatment of Cirrhosis**

Cirrhosis is a more serious disease than active HCV infection, and it is likely that pa-
Figure 5. Estimated mortality ratios for hepatitis C virus-infected females age 30 at underwriting, by transition rate from active hepatitis C virus infection to cirrhosis.

Figure 6. Estimated mortality ratios for hepatitis C virus-infected males age 40 at underwriting, by transition rate from active hepatitis C virus infection to cirrhosis.

Sustained Response After Treatment of Cirrhosis

Studies report SR rates in cirrhotic patients that range from 7 to 24%, and newer regimens have induced remissions in up to 30% of HCV patients with cirrhosis. An assumption was made that a SR could be achieved in cirrhotics half as often as a SR in patients with active HCV infection (without cirrhosis).

Cirrhosis to HCC

Successful treatment of HCV-related cirrhosis reduces the likelihood that HCC will develop. The transition probabilities selected for treated and untreated patients, respective-
Figure 7. Estimated mortality ratios for hepatitis C virus-infected females age 40 at underwriting, by transition rate from active hepatitis C virus infection to cirrhosis.

Figure 8. Estimated mortality ratios for hepatitis C virus-infected males age 50 at underwriting, by transition rate from active hepatitis C virus infection to cirrhosis.

ly, were 0.010 and 0.030. These values may overstate transitions (an unfavorable bias) for both treated and untreated cases compared with values expected in an insured lives population. The reason is because data for these transitions were derived from studies at tertiary treatment centers that specialize in care of patients with liver disease, and some of the patients had more advanced cirrhosis when they entered the study.

Cirrhosis to Decompensated Cirrhosis

 Decompensated cirrhosis is diagnosed when a patient with stable (compensated) cirrhosis develops ascites, jaundice, hepatic encephalopathy, or variceal bleeding. It was difficult to find cirrhosis to decompensated cirrhosis transition rates that were applicable to an insured lives population because of the same problem that existed when determining
Figure 9. Estimated mortality ratios for hepatitis C virus-infected females age 50 at underwriting, by transition rate from active hepatitis C virus infection to cirrhosis.

Figure 10. Estimated mortality ratios for hepatitis C virus-infected males age 60 at underwriting, by transition rate from active hepatitis C virus infection to cirrhosis.

rates for cirrhosis to HCC transition rates. For example, Serfaty et al.\textsuperscript{38} reported a transition rate of 0.054 per year, but up to 10% of the cohort had more advanced cirrhosis when they entered the study\textsuperscript{35} and thus would have been much more likely to transition from compensated to decompensated cirrhosis. For subjects who are not treated after cirrhosis develops, 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.\textsuperscript{45}

Data are more uncertain for treated patients. Does a SR in a patient with cirrhosis imply that the transition from cirrhosis to decompensated cirrhosis is zero (subject to cases that relapse)? Data by Marcellin et al.\textsuperscript{46} support this possibility. They reported a zero incidence of decompensated cirrhosis in 5 pa-
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Figure 11. Estimated mortality ratios for hepatitis C virus-infected females age 60 at underwriting, by transition rate from active hepatitis C virus infection to cirrhosis.

patients with cirrhosis who achieved a SR with anti-HCV therapy. Other series also found lower cirrhosis to decompensated cirrhosis transition rates in treated patients.\textsuperscript{37,38} Given the uncertainty, a conservative assumption was made that progression from cirrhosis to decompensated cirrhosis among subjects who achieved a SR was 0.3 times that of untreated patients.

Surgery or Liver Transplant After HCC Diagnosis

HCC can be treated by surgery or other traditional means and by liver transplant. The number of liver transplants is limited by donor availability. Transitions to HCC treatment (liver transplant) and HCC treatment (surgery) were set at 0.031\textsuperscript{47} and 0.969 (1–0.031) per year, respectively.

HCC Mortality, Surgery

Transitions from HCC treatment (surgery) to death (HCC) were determined from the most recent database published by the US Department of Health and Human Services.\textsuperscript{49} The high mortality rates in Table 1 attest to the severity of this cancer. Mortality rates are high even in countries that conduct annual examinations of patients with chronic HCV to detect HCC at an early stage.\textsuperscript{42}

HCC Mortality, Transplant

Survival after liver transplantation for HCC varies widely depending on the transplant center and the criteria for inclusion or exclusion (eg, stage of HCC, severity of underlying cirrhosis).\textsuperscript{40} Transitions from HCC treatment (liver transplant) to death (HCC) were based on results from the European Transplant Registry for 2783 patients with liver cancer operated between 1988 and 1998.\textsuperscript{50} Data in the Registry were provided for the first 5 years posttransplant. The year-5 value of 0.057 was used for years 6–10.

RESULTS

As noted previously, progression from active HCV infection to cirrhosis is related to age at infection, not current age.\textsuperscript{21} 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 for underwriters who almost never know age at infection.
Figure 12. Estimated mortality ratios projected according to most likely transition rates for hepatitis C virus-infected males, by age at underwriting. Transition rate for age 20, 0.002; age 30, 0.002; age 40, 0.005; age 50, 0.008; age 60, 0.012.

Figure 13. Estimated mortality ratios projected according to most likely transition rates for hepatitis C virus-infected females, by age at underwriting. Transition rate for age 20, 0.001; age 30, 0.001; age 40, 0.002; age 50, 0.004; age 60, 0.008.

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 (eg, 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. 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 transition rates. Table 1 lists most likely transition rates from active HCV infection to cirrhosis by gender and age at infection. These rates were varied to derive a range of mortality ratios and morbidity incidence rates (Figures 2–12).

**Estimated Mortality Experience**

Figures 2–12 display estimated mortality ratios for males and females by age at underwriting according to different transition rates from active HCV infection to cirrhosis.

**Males**

- Age 20 (Figure 2)—The curve labeled 0.002 is the most likely outcome; mortality ratios peak at 209%. Curve 0.003 represents projected outcome if the transition rate were 1.5 times higher, with a peak mortality ratio of 262%.

- Age 30 (Figure 4)—For ages 30 and older, the most likely outcome was determined by assuming that HCV infection would have occurred at least 1 or 2 decades earlier, that is, infection would have occurred in teenage or young adult ages, and the transition rate from active HCV infection to cirrhosis would be that of an applicant 1 or 2 decades younger. Accordingly, the curve labeled 0.002 is the most likely outcome for a 30-year-old applicant, based on the assumption that infection occurred at around age 20; mortality ratios peak at 157%. Curve 0.005 represents projected outcome if the transition rate were that of a 30-year-old male, that is, if infection occurred shortly before application, with a peak mortality ratio of 242%. Prior comments related the difficulty in choosing age-specific transition rates from the limited data available. If the transition rate for a newly infected 30-year-old male were 0.004, the corresponding mortality ratios would be between those in curves 0.002 and 0.005.

- Age 40 (Figure 6)—The curve labeled 0.005 is the most likely outcome; mortality ratios peak at 150%. Curve 0.008 represents projected outcome if infection occurred shortly before application, with a peak mortality ratio of 180%. Curve 0.012 indicates pro-
Figure 15. Estimated incidence of total and permanent disability in hepatitis C virus-infected females age 20 at underwriting. Transition rate from active hepatitis C virus infection to cirrhosis equals 0.001.

Figure 16. Estimated incidence of total and permanent disability (all liver-related causes) in hepatitis C virus-infected males, by age at underwriting. Transition rate for age 20, 0.002; age 30, 0.002; age 40, 0.005; age 50, 0.008; age 60, 0.012.

Age 40 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 50 (Figure 8)—The curve labeled 0.008 is the most likely outcome; mortality ratios peak at 135%. Curve 0.012 represents projected outcome if the transition rate were that of a 50-year-old (peak mortality ratio, 219%). Age 40 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 50 (Figure 8)—The curve labeled 0.008 is the most likely outcome; mortality ratios peak at 135%. Curve 0.012 represents projected outcome if infection occurred shortly before application, with a peak mortality ratio of 152%. Curve 0.024 indicates projected outcome if the transition rate were 2 times that of a 50-year-old (peak mortality ratio, 201%).

- Age 60 (Figure 10)—The curve labeled 0.012 is the most likely outcome; mortality ratios peak at 122%. Data are limited for transition rates when infection occurs at older ages. Curves 0.024 and 0.036 represent projected outcomes if transition rates
POKORSKI—RISK ASSOCIATED WITH HEPATITIS C INFECTION

Figure 17. Estimated incidence of total and permanent disability (all liver-related causes) in hepatitis C virus-infected females, by age at underwriting. Transition rate for age 20, 0.001; age 30, 0.001; age 40, 0.002; age 50, 0.004; age 60, 0.008.

Table 3. Effects of Different Rates of HCV Treatment and Success, and Different Transition Rates from Cirrhosis to HCC Compared with Baseline Assumptions (Scenario 1)*†

<table>
<thead>
<tr>
<th>Probability</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>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
<td>0.001</td>
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<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>0.40</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>Treatment of cirrhosis</td>
<td>0.20</td>
<td><strong>0.40</strong></td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
</tr>
<tr>
<td>Sustained response after treatment of cirrhosis</td>
<td>0.15</td>
<td>0.15</td>
<td><strong>0.20</strong></td>
<td>0.15</td>
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</tr>
<tr>
<td>Cirrhosis to HCC, treatment success</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td>0.01</td>
<td><strong>0.015</strong></td>
<td><strong>0.02</strong></td>
</tr>
<tr>
<td>Cirrhosis to HCC, treatment failure</td>
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<td>0.03</td>
<td>0.03</td>
<td>0.03</td>
<td><strong>0.045</strong></td>
<td><strong>0.06</strong></td>
</tr>
</tbody>
</table>

* HCV, hepatitis C virus; HCC, hepatocellular carcinoma.
† Scenario 1 contains the values used to calculate curve 0.001 in Figure 3. Bold entries in scenarios 2–6 identify changes relative to scenario 1.

were 2 times (peak mortality ratio, 144%) and 3 times (peak mortality ratio, 164%) higher, respectively, than those of a 50-year-old.
- Projected outcomes for ages 20–60 are summarized in Figure 12. Most likely transition rate refers to the transition rate cited in Table 1 for an individual 10 years younger than age at application.

Females

The approach used to estimate mortality ratios for males was used to project female experience. Most likely outcomes were determined by assuming that HCV infection occurred at least 1 or 2 decades prior to the date of application (depending on current age relative to teenage and young adult ages), and some outcomes were based on a multiple of female transition rates in Table 1.

- Age 20 (Figure 3)—The curve labeled 0.001 is the most likely outcome. Mortality ratios peak at 184%.
- Age 30 (Figure 5)—The curve labeled 0.001 is the most likely outcome. Mortality ratios peak at 134%.
Figure 18. Estimated mortality ratios for hepatitis C virus-infected females age 20 at underwriting, by scenario.

Figure 19. Estimated mortality ratios for hepatitis C virus-infected females age 20 at underwriting, by scenario.

- Age 40 (Figure 7)—The curve labeled 0.002 is the most likely outcome. Mortality ratios peak at 128%.
- Age 50 (Figure 9)—The curve labeled 0.004 is the most likely outcome. Mortality ratios peak at 127%.
- Age 60 (Figure 11)—The curve labeled 0.008 is the most likely outcome. Mortality ratios peak at 128%.
- Projected outcomes for ages 20–60 for most likely transition rates are summarized in Figure 13. As with males, projected mortality ratios decreased with advancing age at underwriting.

**Estimated Morbidity Experience**

An assumption was made that total and permanent disability (TPD) would occur upon diagnosis of HCC, decompensated cirrhosis, or liver transplant. 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, followed by decompensated cirrhosis. Liver transplant is an insignificant contributor to disability incidence, reflecting the limited number of transplants that could be performed due to a shortage of donor livers. TPD incidence rates for age 20 at underwriting (all liver-related causes) peak at 1.5 per 1000 for males and 0.8 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 slightly higher for males. Peak incidence rates occur in applicants age 60 at underwriting (males, 4.4 per 1000; females, 3.5 per 1000). As predicted by active HCV infection to cirrhosis transition rates in Table 1, 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 approximately 1 decade earlier. 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 active 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 3. Scenario 1 is the baseline scenario for an HCV-infected female age 20 at underwriting with a 0.001 transition rate from active HCV infection to cirrhosis (curve 0.001 in Figure 3). Bold entries (Table 3) 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. For example, outcomes were essentially the same if treatment of active HCV infection varied from 10–20% per year and if treatment of cirrhosis varied from 20–40% per year (scenario 2). Outcomes were also not sensitive to variation in treatment efficacy (scenario 3) and frequency of relapse after achieving a SR (scenario 4).

Figure 19 indicates that calculations are sensitive to different assumptions regarding cirrhosis to HCC transition rates. Increases in these transition rates result in higher mortality ratios compared with scenario 1. However, even doubling transition rates (scenario 1 versus scenario 6, last two rows of Table 3) causes a maximum increase of only 44 mortality percentage points.

DISCUSSION OF PRINCIPAL FINDINGS

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 higher in males by approximately 25 mortality percentage points. 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.

Morbidity and mortality risk would be greater and begin somewhat earlier (after underwriting) than projected by Figures 2–19. The model assumes that all subjects are located in the first Markov state, HCV infection (no prior treatment) 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 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.

Transition 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 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.

The intent of modeling different rates for the transition from active HCV infection to cirrhosis in Figures 2–13 was to gauge the sensitivity of calculations to variations in these rates (eg, Figure 6, 0.002 versus 0.005 versus 0.008 versus 0.012). These data suggest that mortality and morbidity would remain within the insurable range even if transition rates were considerably higher than the most likely rates listed in Table 1.

Transition From Cirrhosis to HCC and From Cirrhosis to Decompensated Cirrhosis

These rates were derived from series at tertiary medical centers that specialize in care of patients with liver disease; some of the patients had more severe and/or advanced disease when the study began. Use of these data in the model might add an unfavorable bias to the results, that is, it is possible that outcomes would be more favorable if these transition rates were based on an average cohort of patients with HCV-related cirrhosis. Figure 19 indicates that calculations are sensitive to different assumptions regarding cirrhosis to HCC transition rates, but even significant increases in transition rates (compared with baseline assumptions) result in comparatively modest increases in mortality ratios. Calculations were also sensitive to different assumptions regarding cirrhosis to decompensated cirrhosis transition rates (data not shown).

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.

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.15 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, 0.001 per year for 20-year-old females. Another study reported that progression increased with duration of infection.15 Regardless of whether progression is linear or nonlinear (either decreasing or increasing with time), data in Figures 2–11 suggest a favorable prognosis even if transition rates from active HCV infection to cir-
rhosis were greater than the most likely estimates in Table 1.

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.1

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.1 Kuboki et al56 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.1,15,57 An exception regards patients with heavy alcohol intake: cirrhosis may occur in alcoholics even with persistently normal ALT levels.58

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:57

- 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.59 Without information about previous tests, the only possible conclusion is that a favorable prognosis is more likely but not 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.57
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 two 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 than two 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.


REFERENCES

Daily alcohol consumption is strongly associated with more rapid progression. Estimates are that consumption of more than 40 g of alcohol per day approximately doubles the relative risk of HCC in patients with HCV. Regarding HCV genotype, there is convincing evidence that genotype 1 is associated with a poor response to antiviral therapy. The association between genotype and severe liver disease is still controversial; some studies reported more rapid progression with genotype 1b, and others found no association between HCV genotype and incidence of HCC. Viral load (HCV RNA level) does not significantly influence rate of progression. Progression is more rapid in patients with immunodeficiency (eg, HIV infection).

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. A favorable prognosis is likely in applicants with persistently normal 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.
40. Bruno S, Silini E, Crosignani A, et al. Hepatitis C virus genotypes and risk of hepatocellular carci-


