MORTALITY ASSOCIATED WITH POSITIVE HEPATITIS C AND B TEST RESULTS

Vera F. Dolan, MSPH, FALU

Robert L. Stout, PhD
Clinical Reference Laboratory
Lenexa, KS

Michael Fulks, MD

Executive Summary *The mortality risk for being hepatitis C (HCV) or hepatitis B (HBV) positive in insurance applicants was studied in a tested applicant population of 513,755 lives followed for a median of 7 years (range 0 to 18 years). The risk with HCV antibody positivity is substantial. Part of this risk is associated with lifestyle and part is from the liver disease. The risk when positive for HBV surface antigen is less than that for HCV and is mainly related to the liver disease itself. The risk associated with either hepatitis is much lower if ALT is <45 U/L. Relative risk is stable over a follow-up of 18 years after testing for both HCV and HBV.*

Hepatitis C virus (HCV) is a single-stranded RNA virus. It was transmitted in the blood supply prior to 1992 at which time blood screening became available. Current transmission is largely limited to sharing needles, with additional cases by contact with or sharing of body fluids. HCV has minimal symptoms as an acute illness, and becomes chronic in 80% of infections when it may progress to end-stage liver disease (cirrhosis or hepatocellular cancer) in up to 20% of cases. However, treatment is improving and may be curative in up to 50% of chronic cases without advanced fibrosis, co-infections or heavy alcohol intake.

HCV is detectable by testing for the antibody. It is found in 1 to 2% of U.S. adults of whom 85% have the virus present. Antibody is highly predictive of active infection unless the titer is low. Confirmation can be performed using a HCV RNA PCR study to detect the virus itself.

About 0.6% of life applicants are antibody positive, with the peak prevalence between ages 40 and 55. Four to five percent of HCV tests are currently positive, mostly tested from the 9% of samples with ALT tests which are greater than 45 U/L. Some HCV positives are missed because about one-third of HCV positive applicants have ALT results between 30 and 45 U/L. However, because 27% of all ALT results are above 30 U/L, there would be three times as many HCV tests required to identify these additional cases.

Hepatitis B virus (HBV) is a double-stranded DNA virus. It can be transmitted by sharing of needles or exposure to body fluids, but the large majority of cases in North America and the rest of the world are vertically transmitted from mother to child, or acquired as an infant from other family members. Only 1 to 5% of adult-onset cases become chronic though the acute illness may be severe. In contrast, 90% of infant cases become chronic. If the infection remains active and chronic, up to 20% of cases may progress to end-stage liver disease. Current treatment is limited and not curative, but HBV can be prevented by vaccination, which has become near universal worldwide. In China (including Taiwan) and other high-risk countries, infant infections have fallen dramatically.

HBV infections have so much circulating virus that we can test for the antigen (parts of the virus) primarily with HBsAg (surface antigen). When active, HBeAg (early antigen) is also present but disappears if the disease becomes less active and enters a "carrier" state which is common. However, HBeAg also becomes negative as the result of mutations in the viral DNA which occur regularly (about 1 to 3% of cases per year), so many active cases of HBV may be negative for HBeAg. Since a lower risk carrier state is demonstrated by both ALT normalization and negative HBeAg, it may be that ALT levels alone are

sufficient to discriminate risk in applicants. However, those with elevated ALT but a negative HBeAg may still be at higher risk.

Only 0.3 to 0.5% of U.S. adults are HBsAg positive, and over half of those are foreign born. Prevalence in insurance applicants is also very low except for companies active in markets with large numbers of Asian immigrants. With little transmission in the U.S. and comprehensive worldwide vaccination programs, the prevalence will continue to decline.

In general, factors that modify the mortality risk associated with HCV and HBV infection include smoking, disease severity, co-infections and heavy alcohol use.[1] Elevations of AST or GGT (usually in addition to ALT) are associated with more fibrosis and poorer response of the HCV infection to therapy.

How the Study Was Done

Clinical Reference Laboratory (CRL) analyzed the mortality of applicants tested for HCV antibody and HBsAg between 1991 and 2005 and followed to 2009. Testing for HCV and HBsAg was done for 513,755 applicants between ages 20 and 79, with 24,987 testing positive for HCV and 3,984 testing positive for HBsAg. After a median of 7 years follow-up (range 0 to 18 years), there were 1,571 deaths among those testing positive for HCV and 130 deaths among those testing positive for HBsAg.

Discussion of our approach and methods can be found in our previous mortality studies published in *ON THE RISK*.[3,4] When possible, applicant mortality is split by sex and by age group. Other variables (smoking, age) are included in our Cox regression analyses for each age-sex band. Cox regression analyses of the entire group include sex as well as smoking and age as other variables. These analyses generate hazard ratios, which in our study are simple mortality ratios between those who test positive and those who test negative.

Since most testing is driven by an ALT >45 U/L, the primary analysis was limited to those actually tested for HCV or HBV. Additional analyses comparing those who test negative and those not tested (reflex trigger not met) indicate no additional risk in those tested and negative except for younger women. For this group, ALT >45 is actually highly abnormal and likely to be associated with AST, GGT or alkaline phosphatase elevations which do have additional mortality risk. See our article on liver function tests for additional information.[5]

What the Study Found

HCV mortality ratios in applicants by age group and sex are shown in Table 1 (below) and corresponding HBV mortality ratios are shown in Table 2 (next page) along with the 95% confidence intervals for both. Some age-sex bands for HBV have insufficient deaths to provide a reliable ratio.

HCV antibody positive applicants have a mortality ratio of around 2.5 (250%) except in younger men where the ratio is 3.9 (390%) relative to those testing negative. These results are consistent with clinical studies in HCV positive younger urban dwellers[6] (MR =300%) which find a higher mortality ratio vs. those in stable rural settings[7] (MR =170%). Excess mortality in the young urban males is caused not just by the liver disease but also by activities associated with acquiring the virus, especially drug use. Many deaths are traumatic in this group. It is likely the relatively higher mortality in this age-sex band of insurance applicants has a similar cause.

We also studied HCV mortality where the ALT reflex trigger was only >30 U/L rather than >45. The mortality ratio for those with ALT <=45 was 1.7 (170%) and for those with ALT >45, it was 2.7 (270%). This is consistent with community studies which find that those who are HCV antibody positive but with persistently "normal" ALTs have very low relative risk.[8]

Table 1. HCV Mortality in Applicants by Age and Sex Using Cox Regression

Females				Males			
Age Group	Mortality Ratio	Lower 95% CI	Upper 95% CI	Age Group	Mortality Ratio	Lower 95% CI	Upper 95% CI
20-39	2.2	1.3	3.7	20-39	3.9	3.2	4.7
40-59	2.3	1.9	2.7	40-59	2.8	2.6	3.0
60-69	2.5	1.9	3.2	60-69	2.0	1.7	2.4
70+	1.6	1.1	2.3	70+	1.8	1.4	2.4

Table 2. HBV Mortality in Applicants by Age and Sex Using Cox Regression

Females				Males			
Age Group	Mortality Ratio	Lower 95% CI	Upper 95% CI	Age Group	Mortality Ratio	Lower 95% CI	Upper 95% CI
20-39	*			20-39	**2.3**	1.4	3.6
40-59	**1.6**	0.9	2.8	40-59	**1.8**	1.4	2.4
60-69	**2.2**	1.1	4.7	60-69	**1.5**	0.9	2.4
70+	*			70+	*		

* Insufficient number of deaths to calculate.

Figure 1 (below left) shows HCV mortality over 18 years after testing when age, sex and smoking are accounted for in a Cox regression model. The mortality ratio remains stable over this period, showing that mortality does not improve or worsen with long-term follow-up.

HBsAg positive applicants have a mortality ratio around 2 (200%) or less. Mortality for younger men is little different from other age-sex bands, reflecting that most of these cases likely represent mother-child transmission and are not associated with risky behavior. Earlier modeling studies using mainly Asian data find mortality ratios only slightly lower than our results.[9,10] No comparable studies of HBV appear to show worse results.

HBV mortality was also studied where the ALT reflex trigger was only >30 U/L rather than >45. The mortality ratio for those with ALT <=45 in men was 0.8 (80%) and for those with ALT >45 it was 2.4 (240%). This is consistent with blood donor studies which find that those who are HBsAg positive with persistently "normal" ALTs have very low risk.[11,12]

Figure 2 (below right) shows HBV mortality over 18 years after testing done in a similar manner to HCV. The mortality ratio remains stable over this period, so mortality does not improve or worsen for the group over longer exposure.

With regard to the mortality risk in smokers who are HCV or HBV positive, we found that the excess risk associated with HCV and HBV is approximately half as much in smokers as nonsmokers. These findings illustrate that some of the risk from hepatitis infection is already accounted for in the higher mortality associated with other risk-taking behaviors including smoking.

To determine whether ALT alone or a combination of ALT and AST was best as a reflex trigger, we evaluated a subset of data from insurers who used elevations of either LFT to reflex to both HCV and HBV. ALT alone would identify 93.4% of HCV positives with either ALT or AST elevation. AST adds just 6.6%. ALT alone would identify 88.1% of HBV positives with either ALT or AST elevation. AST adds just 11.9%.

Figure 1. HCV Mortality by Duration Using Cox Regression

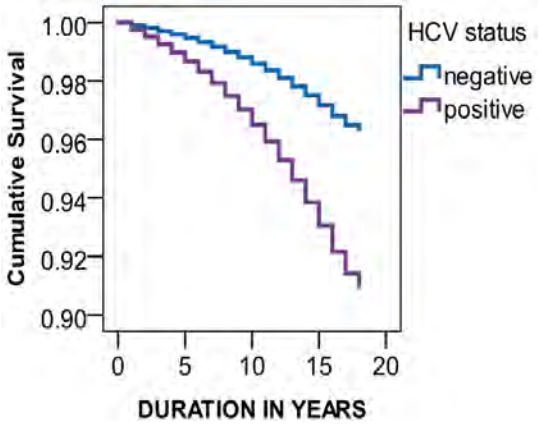
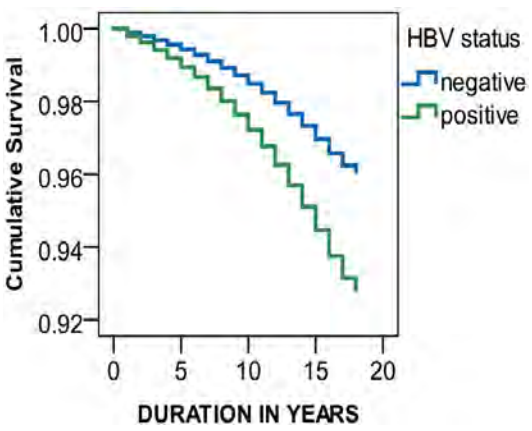


Figure 2. HBV Mortality by Duration Using Cox Regression



What Do the Study Results Contribute to Risk Assessment?

The risk associated with HCV antibody positivity is substantial. Part of this risk is associated with lifestyle and part based on the severity of liver disease. Underwriting should be able to at least partly determine the likelihood of associated risk behaviors, the activity of the hepatitis and degree of fibrosis, either directly or with the benefit of a clinical evaluation of the applicant. The risk in favorable applicants with elevated ALT is still likely to be increased even after favorable evaluation.

The mortality risk for being HCV positive with a normal ALT is much reduced, and the number of tests needed to detect a positive HCV case is increased. It is uncertain whether testing below an ALT of 45 U/L or adding other reflex triggers such as AST in addition to ALT is cost-effective for insurers with typical disease prevalence. The cost of additional testing may exceed the limited risk avoided in those with disease but having an ALT <45.

The risk associated with HBsAg positivity is less than that for HCV and is mainly related to the liver disease itself. Underwriting or clinical evaluation can be of value in determining if advanced fibrosis may be present, but there are fewer behavioral risk factors with which HBV can be underwritten than for HCV. Risk associated with being HBsAg positive with a normal ALT is very low. It is uncertain whether HBeAg adds to risk discrimination because many active cases now are HBeAg negative.

The cost-benefit for HBsAg testing (even when ALT is elevated) is dependent on having more than the industry's average level of positivity, and that in turn is dependent largely on the percentage of Asian immigrants in an insurer's applicant pool.

There is no evidence that HCV or HBV relative mortality risk changes over a follow-up of 18 years. Risk appears to be stable for this group as a whole rather than deteriorating over many years after testing.

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About the Authors

Vera F. Dolan, MSPH, FALU, *Research Associate at Clinical Reference Laboratory, is a consultant specializing in underwriting research and product development. At CRL Vera assists with the analysis and publication of CRL's mortality study data. In her consulting practice, Vera develops risk assessment tools for underwriters, including underwriting manuals, as automated risk assessment systems and underwriter training. Vera provides litigation support for misrepresentation and other underwriting issues, as well as life expectancy calculations for use during litigation.*

Robert L. Stout, PhD, *is President and Director of the Clinical Reference Laboratory based in Lenexa, Kansas. He completed undergraduate studies at California State University (Fullerton) and obtained a PhD in Biological Chemistry from UCLA School of Medicine. Since 1978 he has been directly responsible for introducing many of the new tests and procedures used in risk assessment such as urine and saliva HIV. Dr. Stout has produced nine patents over the last decade.*

Michael Fulks, MD, *Consulting Medical Director, analyzes, interprets and writes up CRL's mortality study results. Dr. Fulks is a graduate of the University of California at Davis, completing his residency at the University of Wisconsin and practicing for 8 years before joining Allmerica in 1987. He became VP & Medical Director of Phoenix Life in 1989, working with its direct and reinsurance areas, group health and disability. Moving to Merrill Lynch in 1997, he developed an underwriting approach for its older age clientele. In 2001, he joined MassMutual, creating its first electronic underwriting manual and updating its requirements, preferred programs and ratings. He moved home to northern California in 2005 and now mixes ranch work with consulting, including ongoing research work for CRL.*