

The Significance of Liver Enzyme Elevations

Paper I. Hepatitis C Prevalence in the Insurance Population

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Introduction

Laboratory testing of blood, urine and saliva samples from insurance applicants is performed to detect illness and risk factors that raise mortality risk sufficiently to warrant a rating or declination of a policy. Next to misrepresentation of tobacco use, interpretation of liver enzyme elevations represents the greatest challenge for the underwriter. The liver associated enzymes, alanine aminotransferase (ALT), aspartate aminotransferase (AST), and gamma glutamyl peptidyl transferase (GGT) are indirect measures of liver homeostasis (well being). While they have a relatively high concentration in the cells of the liver, they are also present in other tissues of the body. If the liver is damaged or the normal flow of blood or bile is obstructed, the cellular contents leak or are secreted into the blood that bathes the organ. One enzyme, GGT, is inducible. Increases in the concentration of GGT may occur in response to the presence of certain drugs, even in the absence of tissue damage. This is especially problematic, because GGT elevations are occasionally due to minor insults such as the use of Tylenol.

Any agent that damages the liver may cause elevations of the liver enzymes. Obesity (fatty deposits in liver cells), over-the-counter medications, prescription medications, alcohol, viral hepatitis, systemic or local infection, traumatic injury, excessively high temperature in the hot tub, hemolysis, environmental toxins of biologic or organic origin, food contaminants, fungal or bacteria toxins and /or heavy metals may cause liver damage. Liver enzyme elevations are often idiopathic (of unknown cause).

Liver enzymes are detected in bodily fluids using specific substrates and their relative concentrations are reported as units per liter. The type of enzyme(s) present is dependent on the tissue, the degree of damage or obstruction and the type of cell injured. In general, enzyme levels during acute hepatitis are usually extremely high, with concentrations into the thousands. The highest enzyme levels are seen in cases of drug induced hepatitis with concentrations into the tens of thousands. By contrast, in chronic viral hepatitis, serum enzyme concentration may not always reflect the degree of tissue damage and levels may vary between normal to hundreds of units per liter. As a further complication, serum enzyme concentration(s) may vary considerably over short periods of time reflecting dynamic changes occurring in the liver.

Enzyme elevations may be either acute or chronic. The greatest challenge for the underwriter is the differentiation of the serious from the benign when reviewing applicants with high enzyme(s) levels. In the absence of a known cause for the elevation, the case is normally classified based on a worst-case scenario. Due to marketing pressure and the cost of re-testing of applicants, the availability of additional tests to differentiate the serious from the more benign becomes important.

A variable lexicon of different viruses may cause viral hepatitis. These include both DNA and RNA viruses. Hepatitis A, E, and G cause only acute hepatitis and pose only a short-term risk. In contrast, Hepatitis B and Hepatitis C may cause chronic infections (1-4). Approximately 1.2 million Americans are HBV carriers. Of greater concern is the RNA virus Hepatitis C.

In 1985, 185,000 new cases of non-A, non-B hepatitis occurred; most were HCV infections. With the introduction of testing for Hepatitis C in 1991, the number of annual cases of non-A, non-B hepatitis has declined to 30,000. Only 20- 30% of these cases are ever diagnosed. The virus, while present in circulation, is at very low levels and is only directly detectable by polymerase chain reaction (PCR) or a similar method. Chronic hepatitis may develop in 85% of patients positive for Hepatitis C antibody (2-4). Liver associated enzymes are elevated in 29%-85% of Hepatitis C antibody positive patients (2-7). Serum enzyme levels fluctuate widely from normal to moderately abnormal, with values rarely into the high hundreds (1,2,6). This paper reviews the relationship between serum liver enzyme elevations and presence of HCV antibody in the insurance applicant population.

HCV is an RNA virus that has been completely sequenced. The test for HCV is based on detection of patient antibody to the virus. The targets for the antibody test are both structural and non-structural proteins. A linear

schematic of the virus is shown in Diagram I. The individual boxes represent gene sequences for the core, envelope and RNA/DNA binding nuclear proteins.

Diagram I. HCV RNA Gene Sequence:

C	E1	E2/NS1	NS2	NS3	NS4A	NS4B	NS5A	NS5AB
<i>Core</i>		<i>Envelope</i>		<i>Nuclear proteins</i>				

The two available commercial tests for detecting patient anti-HCV antibody use a combination of three different antigens to assay for antibody to HCV. Most laboratories will use only one or the other of these two tests. At Clinical Reference Laboratory, applicant samples are first screened with the Abbott Laboratories HCV EIA 2.0 (recombinant antigen c100-3, HC-31, and HC-34) test. Reactive sera and their companion plasma are tested with the Ortho HCV version 3.0 ELISA (recombinant antigen c22-3, c200, and NS4) assay. Only samples reactive in both assays, and for both serum and plasma, are reported as reactive. The use of two different tests was chosen to reduce the number of potential false positives that would result from the use of a single test.

Before studying the relationship between liver enzymes and HCV antibody, it is important to determine the prevalence of the agent in the insurance population. In a random sampling of the insurance applicants, 1.8% of were reactive for antibody to HCV.

Table I. Hepatitis C Antibody Prevalence in the Insurance Population and in Applicants with Elevated Liver Enzymes.

	Number Tested	Number Positive	Prevalence
General Population	1008	18	1.8%
High Enzyme Population:	5961	457	7.7%

By comparison, liver enzyme elevations are far more common. In the same population, liver enzyme elevations occur in 14% of samples. When applicants with elevated liver enzymes were tested for antibody to HCV, 7.7% were positive (Table I). This supports the original argument that liver enzyme elevations should help identify a subgroup of applicants with a high probability of being HCV antibody positive. When the pattern of enzyme elevation is studied, a distinct pattern develops. One enzyme, ALT, is elevated far more often than the other two (see Table II).

Of HCV antibody positive applicants, 95.4% had an elevated ALT. In comparison, AST was elevated in the fewest number applicants but had the highest relative percent positive with 315/2030 (15.3%).

Table II. Prevalence of the Liver Enzyme Elevations and Hepatitis C Positivity

	Number Elevated	Positive HCV	Percent of Positives
ALT	5082 (85.2%)	436 (8.6%)	95.4%
AST	2030 (34.0%)	315 (15.%)	68.9%
GGT	2967 (49.8%)	240 (8.0%)	52.5%
Total	5961	457 (7.7%)	100%

Note: The sum in each column is greater than the actual total due to double counting of samples that are positive for more than a single enzyme.

In this population 56.7% of HCV antibody positive applicants have an ALT elevation of less than two times the upper level of normal. If GGT is chosen as the primary reflex marker 59.3% of HCV positive samples have an enzyme elevation of less than 2 times the upper level of normal. However, the percent of positive samples drops to 43% if all three enzymes have elevations of less than 2 times the upper limit of normal. With almost half of the HCV positive population having an enzyme elevation of less than two times the upper level of normal, any elevation should be tested for antibody to HCV.

HCV antibodies are present in 1.8% of a random group of insurance applicants. As such, HCV represents the most prevalent, serious infectious agent in this population. The specificity of the third generation test is reported to be 99.9%. This would mean that 1 applicant per 1000 would be a false positive. With a prevalence of 18 cases per 1000, 1 additional positive would cause 1/19 (5%) false positives. The use of two separate screening tests, Abbott and ORTHO™, with similar specificity reduces the error to less than 0.25%. While this is infrequent, there will be

some applicants that are not confirmed positive by HCV PCR testing. Unfortunately, a single negative HCV PCR does not prove that the applicant is not viremic. The sensitivity of the PCR test is 95% in-patients with liver enzyme elevations. Therefore, initially reactive applicants that are PCR HCV RNA negative should be assayed again in 3-6 months. If the applicant is negative on two separate occasions, they should be considered as false positive by the antibody test.

HCV represents a major identifiable risk for insurance carriers. The mortality ratio for HCV infected patients is approximately 250% to 315% as compared to the general population (8,9). While the infection may be asymptomatic for 10 to 20 years, progressive changes are occurring in the liver. Seventy (70%) to eighty-five percent (85%) of HCV positive patients develop chronic hepatitis (1,2, 6). For the HCV positive applicant, the most prudent approach may be a very careful evaluation of the risk

The general public health risk due to HCV infection has recently been reviewed by a NIH expert panel (10). The group was convened to determine treatment and public health recommendations. In summary, 8,000-10,000 Americans die per year from HCV. With no effective treatment and a large pool of infected, but symptom-free individuals, that number is expected to triple during the next two decades. Interferon therapy is effective in only 10-20% of patients (11). The number of patients classified as sustained responders may increase to 20-30% if the treatment period is extended to 12 months. The severity of liver damage does not correlate with either the level of enzyme elevation or the amount of HCV RNA present in serum (blood) (12). While there is a tendency for the poorest prognosis to be associated with highest HCV RNA levels, the correlation is not absolute. In some patients with a low number of viral particles present in blood, biopsy proven cirrhosis was present. In addition, the correlation between HCV positivity and the level of enzyme elevation is weak. In many patients, enzyme levels will fluctuate between normal and slightly abnormal.

Underwriting:

- ✓ For insurance applicants, when ALT is elevated, the risk of being HCV positive is 8.6%.
- ✓ If ALT, GGT and AST are high, the risk exceeds 16%.
- ✓ 43% of HCV antibody positive applicants have liver enzyme elevations of less than 2 times the upper level of normal.
- ✓ There is no clear relationship between the degree of enzyme elevation and the extent of liver disease.
- ✓ HCV hepatitis may be a symptom-free illness for 15 to 20 years. In retrospect, for 50% of cases no apparent cause for the infection can be identified.
- ✓ The expected excess mortality is 250-315%.
- ✓ The specificity of the double assay test is greater than 99.9%.
- ✓ Most HCV positive applicants are unaware that they are infected.

The above data suggests that all applicants with elevated liver enzymes should be evaluated for HCV. Consult with your laboratory about the best selection criteria for your population.

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