

CDT AND SERUM ALCOHOL: WHAT IS THE RISK?



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Alcohol-related mortality is common. It may take the form of a medical condition such as cirrhosis, gastrointestinal bleeding or diabetes; or as commonly, it may be associated with a traumatic death including accidents, suicide and homicide. The key to risk selection for alcohol is defining who is at increased risk and what tools identify them. Daily alcohol use of 5+ drinks for men and 4+ drinks for women and binge drinking are associated with increased long-term mortality risk.¹⁻⁷ Lesser amounts of alcohol consumption are not associated with excess risk, and in many studies have a lower risk as compared to no alcohol consumption.^{5,7}

Carbohydrate deficient transferrin (CDT) is a marker for chronic alcohol abuse, and has been correlated with mortality noted in heavy regular alcohol users.⁸⁻⁹ The percentage of CDT is increased relative to total transferrin levels in the presence of alcohol, and gives a measure of alcohol consumption over several weeks in a manner analogous to HbA1c for serum glucose. However, since more moderate alcohol consumption is common among applicants and since there is more variability in CDT production as compared to HbA1c, the specificity is slightly lower. When combined with the relatively low prevalence of heavy regular alcohol use in an applicant population (no more than 1%, based on data from a health maintenance organization⁷ and unpublished insurance applicant data), the result is a lower positive predictive value (PPV). Fortunately, the PPV can be improved as discussed below.

The test for CDT is performed at CRL by a commercial kit utilizing highly specific capillary zone electrophoresis (CZE) methodology. The basic CZE methodology was patented by CRL and Mayo Clinic researchers in 1994.

Binge drinking (5+ drinks for men and 4+ drinks for

Executive Summary *Mortality in insurance applicants who are serum alcohol or CDT positive is at least twice as high as that found in applicants who are negative, after accounting for age, sex and tobacco use differences. The presence of serum alcohol identifies many binge drinkers and heavy chronic alcohol users, and is potentially useful at all ages. A positive result for serum alcohol is often associated with tobacco use. CDT identifies heavy chronic alcohol use, and is most valuable at younger and middle ages where relative mortality for heavy users is highest. Relative mortality for both tests appears stable over a period of up to 15 years after testing.*

women at one sitting) is more common than heavy regular consumption among applicants, but harder to identify. Serum alcohol testing to find applicants who drink shortly before a scheduled insurance blood test is an indication of inappropriate alcohol use, which overlaps with both binge and heavy regular abuse. For average-sized individuals, one hour is required to metabolize one standard drink containing alcohol; serum alcohol is thus detectable when the number of drinks minus the number of hours spent drinking or since is >0. Two drinks 3 hours ago would result in a negative serum alcohol, and two drinks 1 hour ago would result in positive serum alcohol, etc.

Any positive serum alcohol (>10 mg/dL) is confirmed at CRL by retesting the sample using gas chromatography (GC) to separate and identify ethanol, methanol, isopropanol and acetone. Therefore, the quantitation and reporting of serum alcohol (ethanol) with GC is unaffected by other topically applied alcohols or acetone.

How the Study Was Done

We analyzed the mortality of life insurance applicants who had CDT or serum alcohol testing performed.

Mortality among these applicants was determined by use of the Social Security Death Master File. This study comprised 1,355,552 applicants tested between 1995 and 2009, with 21,514 deaths on follow-up in 2010. The mean follow-up was 5.5 years (range 0 to 15).

Mortality ratios were calculated by use of Cox regression, usually splitting the groups by sex, tobacco status (a negative tobacco status is indicated by urine cotinine < .2 ng/mL) and age band. CDT or serum alcohol status, as well as age, were included as covariates within each study group. Age bands were 20 to 39, 40 to 59 and 60 to 79 years. If an analysis was not split by tobacco use, that variable was included as a covariate.

What the Study Found

Of those tested for CDT (519,144 applicants), 6% of males and 2.5% of females were positive. When separated by tobacco use, of CDT positive applicants 26% and 74% were respectively non-tobacco and tobacco users. However, CDT testing is usually reflexed from other laboratory test elevations, with the most common being elevated GGT. Since approximately 9% of GGT values are >65 U/L, this means the detected CDT positivity rate among all applicants may be only 0.6% in males and 0.25% in females using this approach. Since there is an estimated 1% prevalence of heavy alcohol users, we are likely identifying about half of heavily drinking applicants in this population. The median age for all those tested for CDT was 44 years, and for those who were CDT positive the median age was 47.

Of those tested for serum alcohol (930,570 applicants), 0.5% of non-tobacco and 2% of tobacco users were positive, with little difference by sex. Of those who were serum alcohol positive (5,570 applicants), 22% had values ≥ 80 mg/dL, which is the typical legal threshold for driving under the influence (DUI). For applicants who were positive for serum alcohol and also tested for CDT (3,376 applicants), 32% were positive for both. This likely overstates the concordance, since testing for CDT was more likely based on other findings which increase pre-test likelihood (such as elevated GGT) rather than alcohol positivity. The median age for those tested for serum alcohol was 41 years, and for those who were serum alcohol positive the median age was 43.

The relative mortality by sex and age band is shown in Table 1 for those who were serum alcohol positive relative to those who were tested and had negative

Group	Age (Years)		
	20 to 39	40 to 59	60 to 79
Male Nonsmokers	2.5	2.6	2
Male Smokers	2.2	2	1.9
All Females	1.4*	1.9	2.3

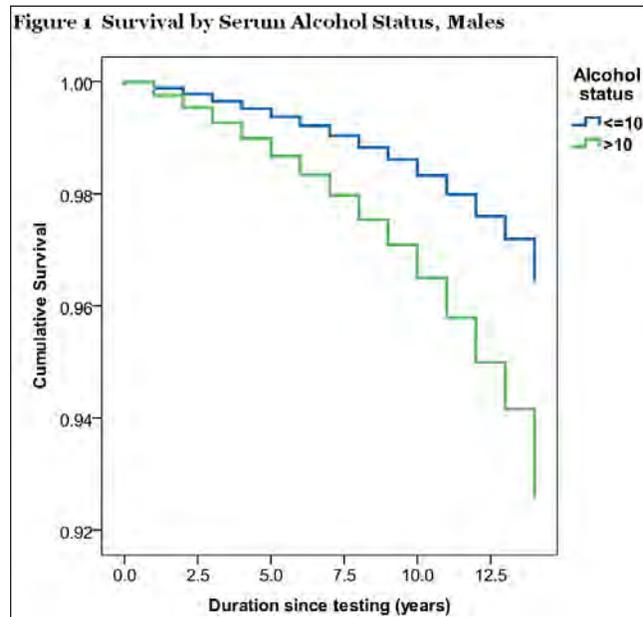
* Fewer deaths with wider 95% confidence intervals

Group	Age (Years)		
	20 to 39	40 to 59	60 to 79
Male Nonsmokers	3.5	1.8	1.1*
Male Smokers	2.2	1.6	1.3
All Females	1.6*	1.5	1.7

* Fewer deaths with wider 95% confidence intervals

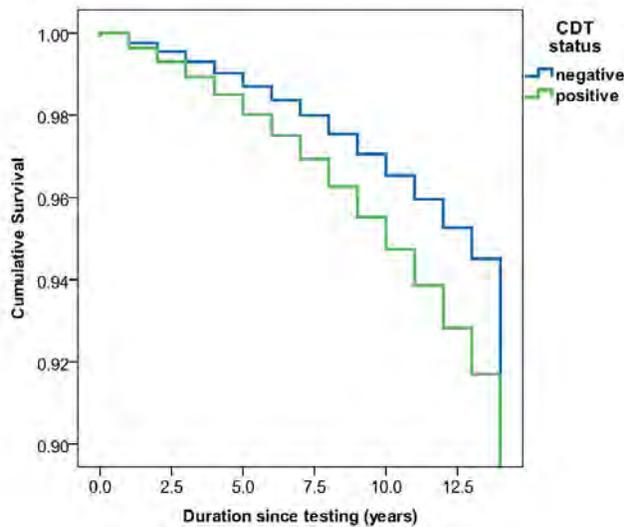
results. There were insufficient deaths to split females by tobacco use, so that factor was included as a covariate. When level of serum alcohol was considered relative to those who tested negative, the mortality ratio was approximately two for values 11 to 79 mg/dL and three for values 80+ mg/dL.

Figure 1 shows the long-term cumulative survival of negative serum alcohol (≤ 10 mg/dL) vs. positive results (> 10 mg/dL) for males, using Cox regression with age and tobacco status as covariates. Similar survival results were found for females; all cumulative survival results appeared stable on follow-up to 15 years.



The relative mortality by sex and age is shown in Table 2 for those who were CDT positive relative to those tested for CDT and negative. There were insufficient deaths to split females by tobacco status, so that factor was included as a covariate. Figure 2 (next page) shows the long-term cumulative survival of negative vs. positive CDT for males, using Cox regression with

Figure 2 Survival by CDT Status, Males



age and tobacco status as covariates. Similar survival was found for females, and all cumulative survival results appeared stable on follow-up to 15 years

For those applicants who were positive for both serum alcohol and CDT, mortality was increased by an additional 50%.

What Do the Study Results Contribute to Risk Assessment?

Both positive CDT and serum alcohol have a similar impact on relative mortality below age 60, although the impact of CDT, while still increased, is reduced at older ages. This may be due partly to the favorable impact of alcohol on HDL and cardiovascular risk, and possibly due to less excess alcohol-related harm among older individuals. The degree of mortality found for CDT positivity is consistent with that noted for heavy regular alcohol use by others.¹⁻⁷ The elevated risk appears to be sustained over the long term, and can be quantified using simple mortality ratios that we found to not vary dramatically by sex or tobacco status.

CDT identifies a substantial portion of heavy regular alcohol users. If used as a screen rather than as a reflex test, the PPV is insufficient to take definitive action without supporting information. Accepting a real-world specificity of 98.5% (published values of 98-100%), sensitivity of 75%, and a heavy alcohol use prevalence in applicants of 0.75%, the PPV is only 0.3. This low PPV would argue against using CDT as a general population screening test.

The alternative approach is to improve predictive

value by requiring the presence of other alcohol-associated findings before testing with CDT. Those findings would include: a GGT >65 U/L, an HDL >50 mg/dL (or higher cut-off) or being a tobacco user. Based on CRL research, GGT elevations triple the pre-test likelihood of heavy alcohol use, HDL >50 doubles it, and positive tobacco may cause a 4-fold increase.^{9 & unpublished}

If any two of these three conditions are present and CDT is positive, we estimate the pre-test likelihood increases sufficiently so that the final positive predictive value is 0.7 or better. This post-test likelihood is at least as high as that of other underwriting information (such as ECG findings) on which action is taken. Used alone as an alert, or used in combination with other tests predictive of heavy alcohol use leading to adverse underwriting action, are the two most common approaches used currently.

Serum alcohol screening identifies a substantially higher risk group that overlaps both heavy regular alcohol use and binge drinking. Tobacco users have a prevalence of elevated serum alcohol that is four times that of non-tobacco applicants. The sensitivity and specificity for recent alcohol use are very high and clearly associated with increased mortality, but the nature of the resulting underwriting action varies. Such actions may include additional review and requirements, or various adverse underwriting actions.

In conclusion, mortality for applicants who are positive for serum alcohol or CDT is at least twice as high as for those who are negative, after accounting for age, sex and tobacco use differences. For CDT, but not serum alcohol, this increased risk decreases as the population ages.

Serum alcohol testing detects some applicants who at the time of a scheduled insurance examination are positive for alcohol; this type of behavior is found in heavy chronic users and some applicants who are likely binge drinkers (for whom short-term risk is as high or higher). The benefits of testing are similar for both sexes and all ages, but are greater for tobacco users than for non-users.

CDT identifies heavy chronic alcohol use and is most valuable at younger and middle ages where relative mortality is highest. Definitive underwriting action likely requires either finding additional supporting information, or use of CDT as a reflex test based on any two of: tobacco use, elevated GGT or high HDL.

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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.