Mortality Impact of Indirect Alcohol Biomarkers

CDT, MCV, HDL, and their relationship to AST/ALT ratio and GGT

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Abstract

This study examines the mortality implications of three indirect biomarkers of alcohol use – carbohydrate-deficient transferrin (CDT), mean corpuscular volume (MCV), and high-density lipoprotein (HDL) cholesterol – with particular emphasis on their relationship to two traditional biomarkers: gamma-glutamyl transferase (GGT) and the aspartate aminotransferase-to-alanine aminotransferase (AST/ALT) ratio. This includes a review of the biologic relevance of these markers, as well as findings from RGA's evidence-based mortality experience analyses. The objectives are to clarify the relationships among these biomarkers and their associations with mortality, thereby improving assessment of alcohol-related risk at the time of underwriting.

CDT and mortality risk

CDT is among the more alcohol-specific blood biomarkers for sustained heavy drinking.[1,2] Compared with conventional markers such as GGT and aminotransferases, its interpretation is often less affected by many non-alcohol-related conditions, although assay method and clinical context remain important.[1,2]

CDT is not generally interpreted as a direct predictor of death; rather, it is best understood as a marker of sustained hazardous alcohol exposure.[2,3] Accordingly, elevated CDT may identify a pattern of drinking associated with increased long-term risk of adverse alcohol-related outcomes, including liver disease and excess mortality, particularly when accompanied by other evidence of organ injury.[3,4]

RGA performed a mortality experience analysis using a dataset of approximately 188,000 life insurance applicants with available CDT results and concurrent traditional alcohol biomarker data – including GGT, HDL, and the AST/ALT ratio – obtained at the time of insurance application (1999–2010). Applicants were followed for an average of nearly five years (with mortality experience up to the end of 2010), during which 3,529 deaths were identified through the Social Security Master Index. Mortality was assessed using the actual-to-expected (A/E) ratio, with expected mortality derived from the 2001 VBT Distinct Smoker table. The observed mortality (AE) in this cohort was 168%.

The mortality impact of elevated CDT (>2.2% vs. ≤2.2%) was first evaluated in a univariate analysis. Without adjusting for other biomarkers, elevated CDT was associated with an approximately 6% increase in mortality, with A/E rising from 1.60 to 1.70. The magnitude of this association increased when higher CDT cut-offs were applied, suggesting a continuous positive relationship between CDT level and mortality risk.

The analysis then examined the association between CDT and mortality within the strata of GGT and the AST/ALT ratio, as shown in Tables 1 and 2. Among applicants with GGT at or below the upper limit of normal (ULN), elevated CDT was associated with an approximately 19% increase in mortality, with A/E increasing from 1.05 to 1.25. In contrast, among those with elevated GGT, the incremental mortality associated with elevated CDT was reduced to approximately 8%, corresponding to an increase in A/E from 1.83 to 1.98.

A similar pattern was observed across AST/ALT ratio strata: Elevated CDT was associated with higher mortality when the AST/ALT ratio was ≤1, but as the AST/ALT ratio increased, overall mortality rose substantially while the additional mortality associated with elevated CDT diminished. Collectively, these findings suggest that although elevated CDT is associated with excess mortality, its incremental prognostic value decreases in the presence of elevated GGT or a higher AST/ALT ratio.

Table 1: Mortality (AE) across GGT and CDT

GGT (ULN)	CDT (%)	Deaths	A/E
≤1	≤ 2.2	157	1.05
≤1	>2.2	757	1.25
>1	≤2.2	658	1.83
>1	>2.2	1,957	1.98

Table 2: Mortality (AE) across AST/ALT ratio and CDT

AST/ALT ratio	CDT (%)	Deaths	A/E
≤1	≤ 2.2	498	1.29
≤1	>2.2	1,570	1.40
1-2	≤2.2	286	2.50
1-2	>2.2	1,008	2.27
>2	≤2.2	31	4.00
>2	>2.2	136	3.77

MCV and mortality risk

Macrocytosis – typically reflected by an elevated mean corpuscular volume (MCV) – serves as an indirect biomarker of chronic heavy alcohol use.[5,6] Its interpretation is less specific than CDT because MCV may also increase in vitamin B12 or folate deficiency, hypothyroidism, liver disease, medication effects, and primary bone marrow disorders.[5,7] An elevated MCV may be clinically relevant from a mortality perspective because it can reflect prolonged toxic exposure, nutritional deficiency, or chronic hepatic injury – each of which has been associated with adverse outcomes.[6,7]

MCV also changes relatively slowly over time and may therefore capture a more sustained history of harmful alcohol exposure versus recent intake alone.[5,6] Accordingly, when MCV remains elevated together with abnormal liver enzymes, the overall laboratory pattern may suggest a more entrenched alcohol-related phenotype and a higher-risk clinical state than an isolated abnormality would imply.[5,6]

RGA conducted a separate mortality experience analysis using RGA internal mortality data. Pre-underwriting MCV, AST, and ALT values were obtained from linked electronic medical records. Because GGT data was sparse in this dataset, it could not be meaningfully included in the stratified analyses. Owing to contractual restrictions on use of the dataset, only the conclusions are presented in this report.

MCV showed a consistent U-shaped association with mortality across all AST/ALT strata and in univariate analyses without AST/ALT adjustment. Unlike CDT, the mortality association of elevated MCV did not weaken as the AST/ALT ratio increased. These findings suggest that elevated MCV may be more strongly and persistently associated with mortality than CDT. However, because MCV can also be elevated in conditions unrelated to alcohol use, including nutritional deficiencies and other systemic disorders, it should be interpreted cautiously and in clinical context.

HDL and mortality risk

HDL concentrations frequently increase with regular alcohol consumption, a pattern that historically contributed to the hypothesis that alcohol might confer cardiovascular benefit.[8,9] More recent evidence, however, supports a more cautious interpretation, particularly because very high HDL concentrations do not uniformly translate into lower mortality risk and may, in some settings, be associated with adverse outcomes.[10]

In individuals with suspected heavy alcohol use, elevated HDL should not be interpreted as evidence of reduced mortality risk. Rather, within an alcohol-biomarker framework, HDL is best regarded as a nonspecific but potentially informative indicator of sustained alcohol exposure.[8,9] Its prognostic significance remains highly context dependent. When elevated HDL occurs in conjunction with other alcohol-related laboratory abnormalities, it may strengthen the inference of chronic alcohol use, but it should not be construed as offsetting concurrent hepatic, metabolic, neurologic, or cardiovascular risk.[8,9,10]

A mortality analysis comparable to the CDT study was conducted in a substantially larger cohort of 4.2 million life insurance applicants with available HDL, GGT, AST, and ALT measurements at the time of underwriting. During follow-up, 43,810 deaths were identified. The observed mortality in this cohort was 110% of AE. The corresponding results are presented in Tables 3, 4, and 5.

Table 3: Mortality (AE) across HDL (univariate analysis)

HDL (mg/dL)	Deaths	A/E
<40	10,956	1.34
40-60	22,579	1.07
>60	10,275	1.02

Table 4: Mortality (AE) across GGT and HDL

GGT (ULN)	HDL (mg/dL)	Deaths	A/E
	<40	9,426	1.26
≤1	40-60	19,815	1.01
	>60	8,685	0.93
	<40	1,530	2.15
>1	40-60	2,764	1.74
	>60	1,590	2.10

GGT is expressed as ratio of upper limit of normal (ULN), ≤1 means normal and >1 means elevated above normal.

Table 5: Mortality (AE) across AST/ALT ratio and HDL

AST/ALT ratio	HDL (mg/dL)	Deaths	A/E
	<40	6,592	1.18
≤1	40-60	11,253	0.96
	>60	3,435	0.92
	<40	4,060	1.64
1-2	40-60	10,625	1.18
	>60	6,306	1.04
	40	304	2.97
>2	40-60	701	1.86
	>60	534	1.73

As shown in Tables 3–5, lower HDL concentrations were consistently associated with higher mortality, likely reflecting their broader adverse cardiovascular implications. In contrast, the mortality signal associated with elevated HDL as a potential marker of alcohol use was observed only when GGT was elevated. Specifically, among applicants with GGT above the upper limit of normal, HDL concentrations >60 mg/dL were associated with an approximate 21% increase in mortality compared with the reference group of 40–60 mg/dL, reflected by an increase in A/E from 1.74 to 2.10.

By comparison, elevated HDL was not associated with increased mortality within any AST/ALT ratio stratum. Relative to CDT and MCV, elevated HDL showed the weakest association with mortality. Detail analysis (results not shown in the tables) indicates that the mortality association of high HDL became more apparent at higher HDL cut-offs.

Taken together, these findings support the view that CDT, MCV, and HDL capture different biologic dimensions of alcohol exposure and its consequences: CDT is relatively more specific for sustained heavy drinking, MCV reflects longer-term hematologic and nutritional effects, and HDL may reflect a metabolic pattern associated with regular alcohol consumption.

Summary: Mortality assessment with CDT, MCV, and HDL

Mortality experience studies indicate that these three indirect alcohol biomarkers have different relationships with mortality, depending on whether traditional biomarkers such as the AST/ALT ratio and GGT are included in the assessment. In analyses that do not account for traditional biomarkers, CDT, MCV, and HDL each show an independent association with mortality, with MCV showing the strongest relationship and HDL displaying the weakest, although the estimated effect size may vary with the biomarker cut-off used. When traditional biomarkers are incorporated, MCV continues to contribute independently to mortality risk, whereas the associations for CDT and HDL are substantially weakened.

All indirect alcohol biomarkers contribute, in varying degrees, to the identification of alcohol use. When several biomarkers are consistent with alcohol exposure, confidence in that assessment increases; however, their effects on mortality risk are not necessarily additive. A more integrated evaluation that considers interactions among biomarkers may improve overall risk assessment.

In underwriting focused on alcohol-related risk, traditional liver biomarkers – such as the AST/ALT ratio and GGT – appear to carry the greatest mortality information. After these markers are taken into account, the overall contribution of indirect biomarkers is substantially reduced. However, MCV appears to retain an independent association with mortality, likely in part because it also reflects non-alcohol-related mechanisms. When traditional biomarkers are unavailable, indirect biomarkers can still inform risk assessments, with MCV contributing the most and HDL the least.

Overall, the findings from this study help illustrate how these biomarkers interact in relation to mortality risk and underscore the importance of experience-based risk assessment in developing underwriting guidelines.

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