LOW ALT
RED FLAG in Elderly Applicants

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Background

Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) – previously called SGPT and SGOT (transaminases) – are liver enzymes. They are used routinely in clinical and underwriting screening.

Both tests elevate in the presence of virtually all hepatocellular disorders. In addition, elevated ALT is often seen with central obesity, diabetes and the metabolic syndrome, mainly due to comorbid nonalcoholic fatty liver disease (NAFLD).

Even though it is seldom acknowledged in laboratory test reference books, ALT also increases from intensive exercise as well as skeletal muscle injury. [Foran, Nathwani, Pettersson]

Reference (normal) ranges for ALT vary widely. We have seen them reported as anywhere from 0-35 to 0-70. While most begin with 0 there are some that have reference range lower limits between 2 and 10.

Age-specific ALT reference ranges are rarely if ever cited in clinical lab reports. In healthy persons, mean ALT levels decrease somewhat with aging. [Dong]

The American College of Gastroenterology 2017 liver chemistry guidelines do not address low normal/below normal ALT and we have not seen this mentioned in laboratory test handbooks for clinicians. [Kwo]

ALT is reported in international units (IU) worldwide. Therefore, we will refrain from adding "IU" when we cite ALT test results in this paper.

The purpose of this paper is to discuss the insurability implications of low normal/below normal ALT in the elderly… in the hope that insurers will consider adding appropriate guidelines for this finding at older ages.

Low ALT and Frailty

Ramsay and coworkers used data from the British Regional Heart Study to determine if there is an association between ALT and physical frailty. Their cohort consisted of 1622 males, ages 71 to 92 at the time of 30-year followup of this longstanding study.

Comparing those in the first vs. fourth ALT quintile, the odds ratio (OR) for frailty was 1.87 in subjects with ALT in the bottom 25% (≤ 13). The OR increased to 2.32 in those free of cardiovascular disease.

Gringuz et al followed 490 hip fracture patients, mean age 83, after discharge from rehabilitation. Persons with elevated ALT were excluded.

They found that subjects with ALT >10 had significantly more favorable scores on measures assessing both cognitive function and independent lifestyle, as compared to those with ALT ≤ 10.

ALT and AST differ in their relationship to physical frailty.

In the British Regional Heart Study and others, ALT is inverse to frailty, decreasing with the magnitude of physical function impairment.

Conversely, AST has been shown to be lower in moderately health individuals when compared to peers satisfying criteria for frailty. [Edvardsson]

Frailty was also a factor in low ALT mortality in several of the studies we cite further on.

Low ALT and Cardiovascular Events

Williams et al in a 2016 fenofibrate trial assessed the links between ALT and the risks of a CV event (MI, stroke, etc.) and mortality. Their study cohort consisted of 9795 men and women with type 2 diabetes, mean age 62.

They excluded persons with known liver disease, CV event within the past 3 months, recent history of alcohol abuse and/or ALT > twice the upper limit of the reference range.

Their reference ranges for ALT were 9-59 in males and 8-41 in females. Thus, one could have a below normal ALT in this study.

These researchers found that ALT had an inverse relationship with the risk of a CV event. The risk was 23% for below normal ALT, 13% with normal ALT and just 9% when ALT was elevated.

More significantly from our perspective, 40% of the below normal ALT events were deaths, compared to 17% with normal ALT and 8% when ALT was elevated.

The adjusted hazard ratio for events with low vs. normal ALT was 1.56.

Low ALT and All-Cause Mortality

We found 11 individual studies and a metaanalysis reporting on all-cause mortality in elders with low normal/below normal ALT.

The incidence of these investigations has been increasing in recent years undoubtedly propelled by the findings from earlier research.

We will cite the individual studies chronologically after reporting on the metaanalysis.

Liu and coworkers (2014) conducted a literature review and metaanalysis comparing the all-cause mortality implications of highest vs. lowest subsets of ALT at older ages.

Their review consisted of 12 prospective cohort studies encompassing 206,678 subjects.

Under age 70, high vs. low ALT was insignificant (HR 0.99).

At ages 70 and older, high ALT has notably lower mortality risk (HR 0.75) than low ALT.

Elinav (2006)

Israeli physicians looked at low ALT in 455 ambulatory subjects, age 70 and followed for 12 years. Median ALT was 13 in men and 11 in women.

They found that ALT below the median was an independent predictor of mortality in men only. After adjustment for common risk factors, below-median all-cause mortality was 2.4-fold greater for low ALT than in men with readings above the median level.

They concluded that low ALT was a "strong and independent surrogate marker" for mortality in community dwelling elderly men.

Le Couteur (2010)

Researchers in the Concord Health and Aging in Men (CHAMPS) Study followed 1673 male subjects ≥ 70 for 5 years.

They reported these odds ratios in subjects with ALT below the median at baseline:

	Odds Ratio
Frailty	3.54
All-Cause Mortality	2.10

All-cause mortality was no longer significant after adjusting for the most widely used criteria defining physical frailty (Cardiovascular Health Study criteria).

Thus, frailty associated with low ALT was the driver of mortality risk.

Ford (2011)

A team of 13 Scottish, Irish and Dutch epidemiologists assessed the relationship between ALT and mortality based on findings in 3 earlier investigations:

- West of Scotland Coronary Prevention Study (Group 1), consisting of 6595 men and women ages 45-64 (mean 55) followed for almost 15 years
- Prospective Study of Pravastatin in the Elderly at Risk (Group 2), consisting of 5804 men and women, ages 70-82 (mean 75) followed for 3.2 years
- Leiden 85-Plus Study (Group 3), consisting of 561 men and women ≥ age 85 followed for 10 years

These are the all-cause mortality hazard ratios by ALT quartile and on a continuous log basis:

	Hazard Ratios		
ALT Quartile	**Group 1**	**Group 2**	**Group 3**
1	1.00	1.00	1.00
2	0.78	0.90	0.76
3	0.68	0.76	0.67
4	0.64	0.86	0.66
Continuous Log ALT	0.85	0.91	0.87

ALT in the first quartile had significantly greater mortality than readings in the higher quartiles and continuous log ALT was also statistically significant in all 3 studies.

Schooling (2012)

Three epidemiologists at the CUNY School of Public Health (Hunter College, New York) followed 16,865 adults for 13 years. Mean age of subjects in the 1st ALT quartile was 50 at baseline.

Low ALT was 0-13 in men and 0-9 in women vs. ≥21 and ≥ 15 in the 3rd tertile.

All-cause mortality was 27% lower in the 2nd tertile and 16% less in the 3rd tertile as compared to those in the 1st tertile of ALT readings.

Excluding deaths related to diabetes, mortality was 32% lower in the 3rd vs. 1st tertile.

Ruhl (2013)

Ruhl and Everhart followed 14,950 viral-hepatitis-negative subjects for 14.5 years. Mean and median ages decreased progressively across deciles of ALT.

There was little difference in all-cause mortality between the 4th and 9th declines in subjects that were ≥ age 60 at baseline.

ALT Decile	Adjusted All-Cause Mortality Hazard Ratios
1	1.66*
2	1.34*
3	1.24*
4-9	1.00
10	1.16

* Significant

Low ALT was also linked to greater CVD, cancer and non-CVD/non-cancer mortality.

Ramaty (2014)

Ramaty et al did a historical prospective cohort analysis of 23,506 adults mean age 48, for a median of 8.6 years. All subjects had ALT levels within the reference range.

ALT ≤ 17 had an all-cause mortality ratio of 1.6 and remained statistically significant after adjustment for age, gender and medical history.

This study is interesting because it reflects the impact of lower ALT levels on mortality even in late middle-aged subjects.

Koehler (2014)

Dutch investigators assessed all-cause mortality in a cohort of 5186 community residing subjects, ≥ age 55 (mean age 70). They were followed for 19.5 years.

The highest mortality was in subjects with ALT < 13 in men and < 12 in women. While the mortality curve was J-shaped, subjects in the 95th percentile had 8% lower mortality risk than those in < 25th percentile.

AST had a similarly shaped mortality curve but the risk was greater in those with high vs. lower (< 25th percentile) readings.

Deetman (2015)

Deetman et al did a prospective 11.1-year mortality study of 1187 type 2 diabetics. Mean age was 67.

ALT was inverse to mortality risk (hazard ratio 0.81). The impact of low ALT was greater for non-CV vs. cardiovascular deaths.

Oh (2016)

A team of Korean physicians evaluated all-cause mortality in 313,252 subjects ≥ age 20 enrolled in the national health insurance system.

They excluded individuals with known liver disease as well as deaths within the first 6 months; then, they followed this group for 6 years.

ALT mortality was U-shaped in older subjects:

ALT	All-Cause Mortality HR Subjects ≥ Age 60
≤ 10	1.37
21-30	1.00
≥ 40	1.32

There were 225 deaths per 100,000 person-years when ALT was 10 or lower as compared to 150/100,000 PY with ALT ≥ 40.

In subjects under age 60, mortality increased linearly across ALT level subsets.

Peitz-Sinvani (2016)

This study was confined to individuals with stable coronary artery disease (CAD), participating in the Bezafibrate Infarction Prevention Registry. All 6575 subjects were free of known liver pathology and they were followed for 22.5 years.

Cumulative mortality was 65.6% in those with low ALT (< 17) versus 58.4% in subjects with higher ALT levels. The adjusted hazard ratio was 1.11 and it was statistically significant.

Vespasiani-Gentilucci (2017)

Researchers at Bio-Medico University in Rome used data on 765 subjects > age 65 from the InChianti Study to determine the implications of low ALT in the elderly.

All subjects had ALT within their reference range of 10-40. They were free of malignancy, chronic liver disease and self-reported heavy drinking.

Those in the 2 lowest quintiles (< 14, 14-16) had a 2.1-fold increased risk of frailty.

Death rates decreased across ALT quintiles.

ALT Quintile	% Deceased
1	30.8%
2	23.3%
3	12.9%
4	10.0%
5	9.6%

They calculated adjusted all-cause and CVD mortality hazard ratios:

	Adjusted Mortality Hazard Ratios ALT Quintiles 1 and 2 vs. 4*	
	All-Cause Mortality	CVD Mortality
Quintile 4	1.0	1.0
Quintile 1	4.3	5.5
Quintile 2	2.3	2.7

*The authors used the 4th quintile for comparative purposes. Adjusted all-cause mortality was reported as insignificantly increased in the 5th quintile (ALT ≥ 24) but specific numerical data were not cited in the paper.

Pathological Factors Accounting for These Findings

Two credible potential mechanisms were advanced as potential explanations for higher mortality in low normal/below normal ALT.

First, the prevalence of frailty was greatest at lower ALT levels, including loss of skeletal mass (sarcopenia) in some but not all of these studies. Frailty has been consistently linked to significant excess mortality in the elderly. [Dong, Ford]

Secondly, aging is associated with decreasing liver cell turnover and a corresponding diminution in the liver's capacity to synthesize proteins and protect against the adverse effects of toxins. One reflection of this is declining or low normal/ below normal serum albumin, a common finding in low ALT cases, [Dong, Ford, Vespasiani-Gentilucci]

Comments

Based on the studies cited here, the weight of evidence strongly suggests that low normal/below normal – or perhaps more conveniently, single digit – is a significant insurability issue in elderly life insurance applicants.

Typical underwriting practices assess debits for ALT at some magnitude of elevation but do not specifically address low normal/below normal readings.

Those accountable for life underwriting guidelines should consider adding debits for low normal/below normal ALT at age 65 or 70 and over.

ALT should also be recognized as a major risk factor for premature frailty and thus cited along with unexplained weight loss and many others.

References

Deetman. European Journal of Clinical Investigation. 45(2015):807
Dong. Clinical Gastroenterology and Hepatology. 10(2012):285
Edvardsson. Clinical Chemistry and Laboratory Medicine. 56(2008):571
Elinav. Journal of the American Geriatrics Society. 54(2006):1719
Foran. Laboratory Medicine. 10(2003):736
Ford. International Journal of Epidemiology. 40(2011):1530
Gringauz. International Journal of Rehabilitation Research. E-published 10/24/17
Koehler. Liver International. 34(2014):296
Kwo. American Journal of Gastroenterology. 112(2017):18
Le Couteur. Journal of Gerontology A: Biological Science and Medical Science. 65(2010):712
Liu. PLoS One. 9(2014):e91410
Nathwani. Hepatology. 41(2005):380
Oh. Liver International. 36(2016):126
Peitz-Sinvani. Journal of General Internal Medicine. 31(2016):209
Pettersson. British Journal of Clinical Pharmacology. 65(2007):253
Ramaty. European Journal of Internal Medicine. 25(2014):919
Ramsay. Heart. 101(2015):616
Ruhl. American Journal of Epidemiology. 178(2013):1702
Schooling. Annals of Epidemiology. 22(2012):789
Vespasiani-Gentilucci. Journal of Gerontology A: Biological Science and Medical Science. E-published 6/19/17
Williams. Diabetes Medicine. 33(2016):356