



Liver Enzymes: Controlling the Mortality Risk at All Ages

Objective Define the value of ALT, AST, GGT, and alkaline phosphatase (AP) for life insurance testing. This is CRL proprietary information for internal use at your company.

Background Liver enzymes, often called liver function tests (LFTs), have been used in risk selection for life insurance applicants and in clinical screening since they first became available in a chemistry panel. Many felt that ALT was the most predictive of mortality risk, as it is the LFT most strongly linked with hepatic inflammation. GGT and AST were regarded as nonspecific and less predictive, and AP was seen as important only at older ages and higher values. None were typically used for preferred selection.

Combinations of LFT elevations were usually viewed as indicating a higher risk than individual LFT elevations, but there was little agreement as to how much higher. Some companies have begun relaxing their LFT cut-off values for underwriting action to some high multiple of the statistical normal range, since the mortality risk was uncertain but competitive pressure was very clear.

Until now, what the life insurance and clinical communities have lacked is population data which would indicate the mortality risk associated with LFT elevations found during the screening of an apparently healthy population. This has become even more problematic as ALT values have increased as a result of obesity and fatty liver. The prevalence of “abnormal” ALT values at CRL has increased 3-fold to around 9% within the past 10 to 15 years.

Facts CRL has analyzed the mortality of applicants tested for LFTs between 1993 and 1997 and followed for at least 10 years. See the “Using CRL Risk-based Laboratory Bulletins to Improve Risk Selection” for additional details.

This report is limited to addressing mortality associated with ALT, AST, GGT and AP, their combinations with each other, and combinations with albumin. Subsequent reports will look at the value of reflex tests from LFT results (including HBV, HCV and CDT) and at bilirubin-associated mortality.

The study population was split for analysis purposes into three age/sex groups: females below age 60 (“females <60”), males below age 60 (“males <60”), and age 60 years old and over (“all 60+”) based on differences in mortality and distribution patterns. The distribution of LFT values are listed for GGT in **Table 1**, for AP in **Table 2**, for AST in **Table 3**, and for ALT in **Table 4**. A mortality ratio (MR) of 100% was assigned to the 25th-74th percentile as the “reference” mortality compared to lower and higher LFT results. This band represents the middle 50% of the population. “Relative risk” is an alternate term for MR, since the mortality for any group is

relative to the mortality of the reference group. For some LFTs, we found MRs below 100% for some values, which may be useful in developing preferred criteria.

Data points with <8 deaths aren't shown on the graphs; data points with 8 to 29 deaths have blank centered markers. Typically, empty points or blank centers appear at the extremes. 95% confidence intervals for values on representative graphs are included in the Appendix providing you additional information regarding the credibility of the data.

In evaluating the relative risk curves from the analysis, LFTs which have a steeper slope (higher or lower MR for a given percentile of the population) are more useful for mortality risk discrimination. LFTs where that steep slope persists into favorable LFT values (usually low values) are useful for identifying preferred risks. LFTs with flat relative risk curves at low values are not useful in selecting a preferred population from an average risk population.

Our analyses included the relative risks associated with each LFT in the absence of other LFT elevations. **Figure 1** shows GGT, AP and AST MRs in the absence of other LFT elevations for females <60; **Figure 2** shows the same for males <60, and **Figure 3**, all 60+. The purpose of this was to approximate the relative risk attributable to each LFT. Frequently we found that cases with very high elevations of an individual LFT, with all other LFTs being normal, were rare (because they are unphysiologic) and thus produced highly variable and often flattened or decreasing MRs. We believe that the "real" mortality associated with each LFT simply increases steadily rather than falling off.

Excess relative risks stratified by specific values of GGT, AST and AP are shown in **Tables 5, 6 and 7**. A "0" excess relative risk represents the risk found in the 25th to 74th percentile LFT reference group. If a broader band of risk (such as up to 95th percentile) is desired by an insurer to represent a different base (reference) risk category, the excess relative risks from our tables can simply be added on a frequency-weighted basis, and new excess relative risks can be calculated for those groups outside the new base risk group. "<0" indicates a relative risk below "0" but if risk is to be accepted up to the 95th percentile, then all those currently falling into "<0" or "0" should be considered as having low mortality risk. A risk > than the maximum value indicates the point where the MR begins to fall off or data is insufficient as we discussed above. It is felt risk will increase as an extension of the MR line on the graph. The excess relative risks in Tables 5 through 7 are derived from Figures 1 through 3 and Tables 1 through 3. These excess relative risks are meant to provide only a general guide to facilitate analysis by each insurer.

We also looked at the mortality of each LFT in the presence of abnormal values of other LFTs (for this we defined "other abnormal" as 95th percentile value or higher for each sub-group evaluated). This allowed us to develop a possible approach to combining the risk associated with multiple LFT elevations. This data is included as graphs in the **Appendix**. Though the MRs are often highly variable due to small numbers, the trends we observed were consistent across the LFTs studied and appears to simply be additive. Just add the isolated risk of any LFT to the risk associated with any other or multiple other elevated LFTs.

Albumin is actually another LFT measuring the ability of the liver to synthesize necessary proteins. Our study results (see **Appendix**) indicate that a normal albumin does not decrease the risk of an elevation of AST, GGT or AP. The excess relative risk of both an abnormal albumin and abnormal LFT is approximated by simply adding the risks of both.

At this point, no attempt has been made to sort out other associated abnormalities and impairments such as known HCV, obesity, or prior “normal” evaluation, all of which impact the risk assessment. Since our study includes all applicants tested by CRL during 1993 through 1997, it is possible that an applicant with an LFT elevation but an otherwise clean history and examination will have a lower relative risk than suggested by our results. Additional studies will be performed by CRL as time allows that define some of these factors, including viral hepatitis.

Conclusions

- ◆ **Need to split by age and sex.** Because the reference ranges are lower in women for the LFTs studied, and because mortality impact varies by age and sex, assigning risk for these LFTs should be split into males less than 60 years, female less than 60 years, and all those age 60 and over. For any specific elevated LFT value, risk tends to be higher for younger women than for older women or men of any age.
- ◆ **GGT and AP** are strong linear mortality predictors across the entire risk range at younger ages, and remain important predictors at age 60+. They show a relatively steep and consistent mortality impact as values increase. Even moderate elevations of either GGT or AP (still falling within the traditional statistical normal ranges) may be associated with substantial increased relative risk for some groups. How much influence alcohol abuse has on the GGT findings is a subject of future research at CRL. The slope persists for low values of GGT and AP so they may be useful for preferred selection.
- ◆ **AST** is a moderate predictor of mortality at elevated values. Low values of AST also present increased relative risk among men younger than 60 and all those age 60+. The reasons for this are not clear, but low transaminases can be associated with poor nutrition which may not always be recognizable from other studies. Be cautious when underwriting low AST values, especially in males.
- ◆ **ALT** was a big surprise. We found that there was no elevated mortality at elevated values in any of the three age/sex groups, indicating that ALT elevations have very little predictive value. This can be seen in **Figure 4**. We believe these findings may be partly due to the current high prevalence of obesity and fatty liver, which impact ALT values but have little effect on other LFTs or mortality. Relative risk increases for low values of ALT, similar to what was found for AST.

ALT remains the most sensitive LFT for hepatitis screening, but otherwise does not appear useful for risk selection. Elevated ALT values have little impact on mortality. Since AST identifies a similar increased relative risk at low values, use of ALT for risk selection beyond triggering reflex testing may not be of value.

- ◆ **Combinations of AST, GGT, AP and Albumin.** In applicants with multiple LFT abnormalities, there was considerable variability in part because of small numbers observed for some combinations. However, the overall impact of multiple abnormal LFTs appears to be additive. We believe excess risk attributable to any LFT elevation can simply be added to the risk associated with any other LFT elevation. The same applies to albumin. Excess risk for each LFT based on this study’s results is available in **Tables 5, 6 and 7**. More information about the combinations of LFTs (including ALT and albumin) is available from CRL in the **Appendix** to this report. Bilirubin data is available in its own bulletin.

Table 1. Range of GGT Values Within Group-Specific Percentiles

Range of GGT Values (U/L)			
Percentile	Females <60	Males <60	All 60+
<1	<6	<10	<8
1 to 2.4	6 - <7	10 - <11	8 - <10
2.5 to 4	7 - <8	11 - <13	10 - <11
5 to 9	8 - <9	13 - <15	11 - <13
10 to 24	9 - <12	15 - <19	13 - <17
25 to 74 (reference)	12 - <23	19 - <41	17 - <35
75 to 89	23 - <37	41 - <67	35 - <55
90 to 94	37 - <53	67 - <95	55 - <80
95 to 97.4	53 - <75	95 - <134	80 - <115
97.5 to 98	75 - <118	134 - <203	115 - <185
99 to 99.4	118 - <167	203 - <271	185 - <265
99.5+	167+	271+	265+

Table 2. Range of Alkaline Phosphatase Values Within Group-Specific Percentiles

Range of Alkaline Phosphatase Values (U/L)			
Percentile	Females <60	Males <60	All 60+
<1	<34	<41	<41
1 to 2.4	34 - <38.72	41 - <46	41 - <47
2.5 to 4	38.72 - <42	46 - <51	47 - <51
5 to 9	42 - <47	51 - <56	51 - <57
10 to 24	47 - <57	56 - <65	57 - <67
25 to 74 (reference)	57 - <86	65 - <92	67 - <96
75 to 89	86 - <105	92 - <108	96 - <115
90 to 94	105 - <119	108 - <119	115 - <128
95 to 97.4	119 - <134	119 - <131	128 - <144
97.5 to 98	134 - <157	131 - <149	144 - <170
99 to 99.4	157 - <179.98	149 - <166	170 - <197.35
99.5+	179.98+	166+	197.35+

Table 3. Range of AST Values Within Group-Specific Percentiles

Range of AST Values (U/L)			
Percentile	Females <60	Males <60	All 60+
<1	<9	<11	<11
1 to 2.4	9 - <11	11 - <13	11 - <12
2.5 to 4	11	13 - <14	12 - <13
5 to 9	12 - <13	14 - <15	13 - <15
10 to 24	13 - <15	15 - <18	15 - <17
25 to 74 (reference)	15 - <21	18 - <26	17 - <24
75 to 89	21 - <26	26 - <33	24 - <30
90 to 94	26 - <31	33 - <40	30 - <36
95 to 97.4	31 - <38	40 - <50	36 - <44
97.5 to 98	38 - <52	50 - <69	44 - <59
99 to 99.4	52 - <67	69 - <90	59 - <75
99.5+	67+	90+	75+

Table 4. Range of ALT Values Within Group-Specific Percentiles

Range of ALT Values (U/L)			
Percentile	Females <60	Males <60	All 60+
<1	<5	<8	<7
1 to 2.4	5 - <6	8 - <10	7 - <8
2.5 to 4	6 - <7	10 - <12	8 - <10
5 to 9	7 - <9	12 - <14	10 - <11
10 to 24	9 - <11	14 - <18	11 - <14
25 to 74 (reference)	11 - <19	18 - <34	14 - <24
75 to 89	19 - <27	34 - <49	24 - <33
90 to 94	27 - <36	49 - <63	33 - <41
95 to 97.4	36 - <48	63 - <81	41 - <51
97.5 to 98	48 - <69	81 - <110	51 - <69
99 to 99.4	69 - <89	110 - <142	69 - <87
99.5+	89+	142+	87+

Figure 1. AST, GGT and AP, no other abnormal LFTs, Females <60

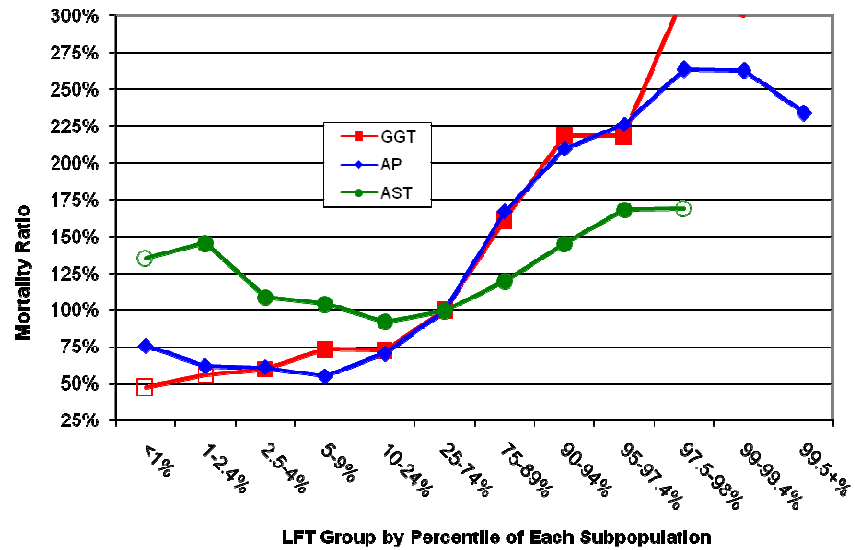


Figure 2. AST, GGT and AP, no other abnormal LFTs, Males <60

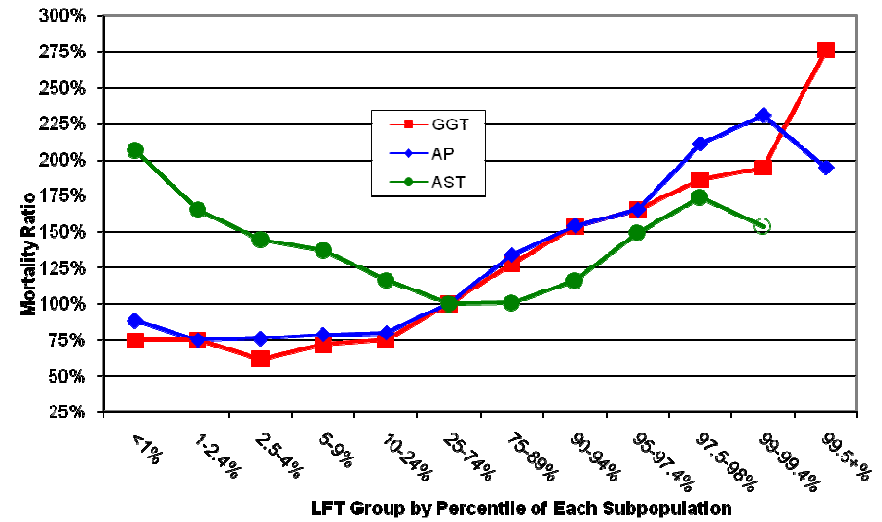


Figure 3. AST, GGT and AP, no other abnormal LFTs, All 60+

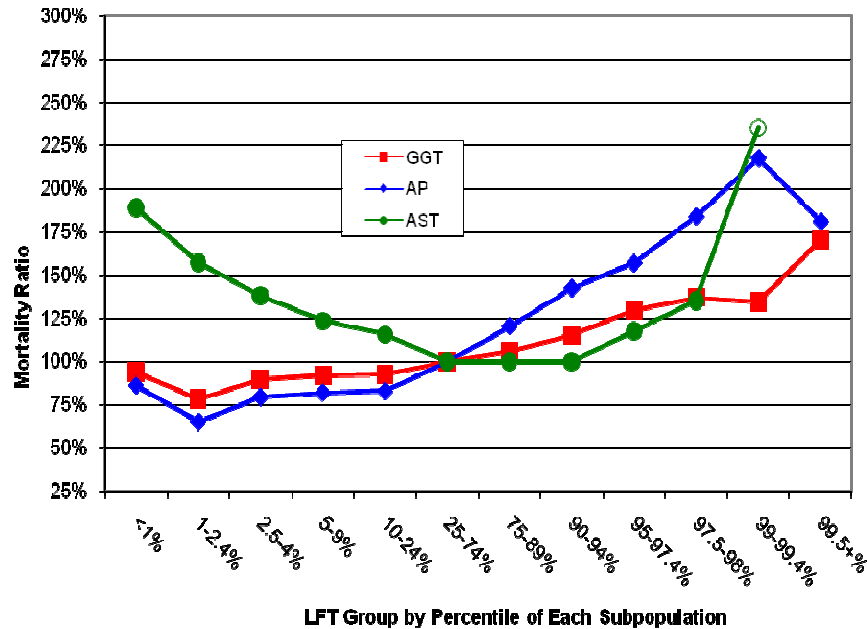


Figure 4. ALT only, no other abnormal LFTs, by age/sex group

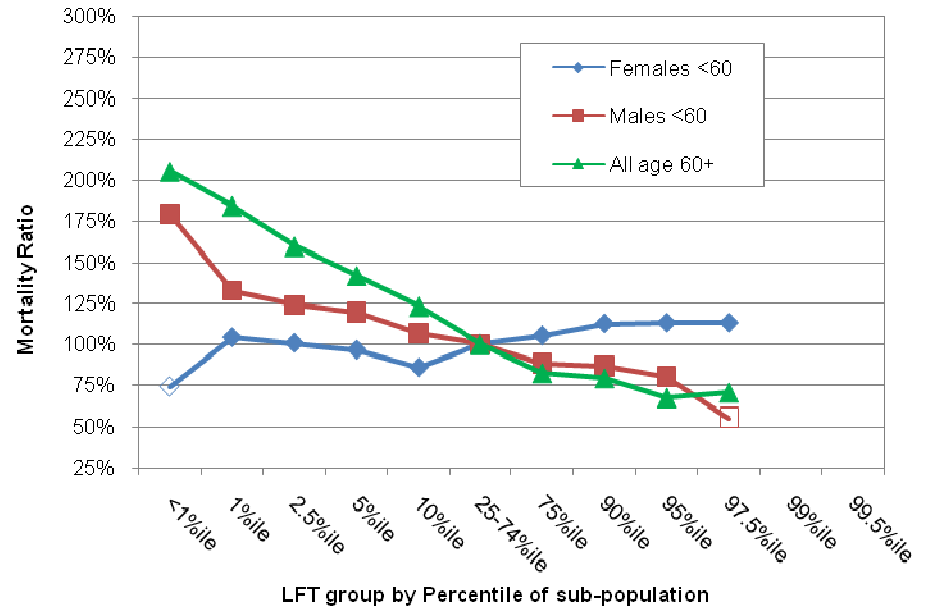


Table 5. Excess Relative Risk for GGT

GGT			
Lab Values	Excess Relative Risk (%)		
U/L	Females <60	Males <60	All 60+
1-10	<0	<0	<0
11-12	<0	<0	0
13-25	0	<0	0
26-35	50	0	0
36-45	100	25	0
46-55	100	25	0
56-75	125	50	25
76-120	150	50	25
121-160	175	75	25
>160	175	150	50
Excess relative risk = MR – 100%			

Table 6. Excess Relative Risk for AST

AST			
Lab Values	Excess Relative Risk (%)		
U/L	Females <60	Males <60	All 60+
1-10	25	50	50
11-20	0	25	25
21-25	25	0	0
26-30	25	0	0
31-35	50	0	0
36-40	50	0	0
41-45	50	0	25
46-55	75	25	25
56-65	75	50	50
>65	75	75	75
Excess relative risk = MR – 100%			

Table 7. Excess Relative Risk for Alkaline Phosphatase

AP			
Lab Values	Excess Relative Risk (%)		
U/L	Females<60	Males <60	All 60+
1-60	<0	<0	<0
61-85	0	0	0
86-105	50	25	25
106-120	100	50	50
121-135	125	50	50
136-150	150	100	75
>150	150	125	125
Excess relative risk = MR– 100%			