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LABORATORY TESTING

Using Liver Enzymes as Screening Tests to Predict Mortality Risk

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Objective.—Determine the relationship between liver function test results (GGT, alkaline phosphatase, AST, and ALT) and all-cause mortality in life insurance applicants.

Method.—By use of the Social Security Master Death File, mortality was examined in 1,905,664 insurance applicants for whom blood samples were submitted to the Clinical Reference Laboratory. There were 50,174 deaths observed in this study population. Results were stratified by 3 age/sex groups: females, age <60; males, age <60; and all, age 60+. Liver function test values were grouped using percentiles of their distribution in these 3 age/sex groups, as well as ranges of actual values.

Results.—Using the risk of the middle 50% of the population by distribution as a reference, relative mortality observed for GGT and alkaline phosphatase was linear with a steep slope from very low to relatively high values. Relative mortality was increased at lower values for both AST and ALT. ALT did not predict mortality for values above the middle 50% of its distribution.

Conclusion.—GGT and alkaline phosphatase are significant predictors of mortality risk for all values. ALT is still useful for triggering further testing for hepatitis, but AST should be used instead to assess mortality risk linked with transaminases.

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INTRODUCTION

Liver enzymes have been used for preventive screening programs since they became available in chemistry panels, and for life insurance screening since industry blood testing began. The actual value of liver enzyme tests (liver function tests or LFTs) in predicting risk of mortality has been unclear in both environments. Decisions regarding further action or evaluation have been made on a statistical basis (often >2 standard deviations of some reference population) or based on studies that had further investigated selected populations with LFT elevations, including the use of liver biopsy.[1–5]

Based on pathologic findings in various studies and predicted risk from conditions associated with elevated LFTs, authors have projected what the mortality risk might be for LFT elevations in a general population.[6] More recently, studies in Europe and Asia have looked directly at mortality or morbidity associated with elevations of transaminases or GGT in the absence of symptoms.[7–11] A potential role for GGT as a significant predictor of mortality risk was noted.[7,9] Limitations

of these recent studies include relatively small numbers of deaths, and populations not representative of an adult screening population in the United States.

In current clinical or insurance screening utilizing GGT, alkaline phosphatase (AP), AST and ALT, most attention is usually paid to LFTs traditionally felt to be most closely associated with serious liver disease (eg, ALT) and to markedly elevated results that are out of the statistical normal range. Multiple LFT elevations are given more weight than single elevations, but in no consistent manner. Fortunately, it is now possible to measure long term mortality risk associated with LFT values in a large healthy population and provide guidance for the use of LFTs in preventative or risk assessment programs.

Applicants for life insurance are a self-selected group of relatively healthy adults, typically employed or retired with access to health care. They are representative of that portion of the general adult population seen regularly for preventive care screening, providing insights for this group as well.

METHODS

A blood sample is usually obtained as part of the life insurance application process, except for younger ages and lower amounts of insurance. This sample is then sent overnight to one of a small number of laboratories serving the life insurance industry, including Clinical Reference Laboratory (CRL).

We analyzed the data from all insurance applicants tested for GGT, AP, AST and ALT at CRL between 1993 and 1997. Only those applicants with missing identifying data or laboratory results were excluded. The vast majority of these blood samples were from adults applying for individual life insurance products. Mortality was ascertained by use of the Social Security Death Master File (DMF) in 2007, resulting in an exposure of 10 to 14 years with a median follow-up of 12 years. This yielded our study population of 1,905,664 with 50,174 deaths.

The DMF contains almost all deaths for ages 65 and up, but not all the deaths for ages below 65. However, our analysis is based on mortality ratios between groups within the study population defined by demographic factors and bands of laboratory values rather than any external mortality expectation, so it is unaffected by missing deaths. This study is independent of the insurers that ordered LFT tests and any action they may have taken on the test results. Identification information for each applicant in the study was removed before analysis was conducted. All of the authors are either employees of CRL, or have a consulting relationship.

The distribution of values and mortality risk associated with LFTs vary substantially by age and sex, requiring division for analysis purposes into 3 age/sex groups: females, age <60 (females <60); males, age <60 (males <60); and both sexes combined for ages 60+ (all 60+). Further divisions were explored, but findings were not substantially different from the combined groups and resulted in smaller numbers of deaths and wider 95% confidence intervals. To compare the utility of different LFTs in predicting mortality risk, results for each LFT were calculated within each age/sex group by the same percentiles of LFT distribution.

The relative mortality in each LFT percentile band was measured as the mortality ratio (MR) compared to a reference band consisting of the 25^{th} to 74^{th} percentile (middle 50%) for each of the 3 age/sex groups. The MR for the reference band was set to 100%. This allowed the predictive ability of various LFTs to be directly compared, and revealed mortality differences across the full range of LFT values, especially at the low and high extremes. The middle 50% was chosen as the largest reference group that would not mask important relative mortality differences. Using the data displayed in our figures, the mortality ratios may be combined if a broader reference group (up to 90^{th} or 95^{th} percentile) is desired. The relative risk of the

Table 1. Study Population Characteristics

Group	Number Tested	Number of Deaths	Median Age	Median Age for LFT 75th+ Percentile
Females <60	614,361	5947	38	39
Males <60	1,104,294	19,270	40	41
All 60+	187,009	24,957	65	65

remaining bands can be determined by dividing the old MR for that band by the MR of new broader reference band. Analysis by LFT value is also presented. For that, the reference band (MR = 100%) is the band of values representing the highest proportion within the total study population.

Analysis of LFTs in this study was limited to GGT, AP, AST and ALT; results for bilirubin and albumin will be reported separately. Data was not analyzed by the results of other possible tests such as hepatitis B (HBV) or hepatitis C (HCV) antibodies, by the applicants' medical history, or by the applicants' height and weight. During 1993 to 1997, hepatitis testing was not routinely done based on LFT elevations; personal medical history, height and weight were infrequently disclosed on the laboratory intake form.

Data points displayed on the graphs have solid centers if there were 30 or more deaths, and open centers if there were 8 to 29 deaths observed. Data points and their associated trend lines are not displayed where there were less than 8 deaths observed. Ninety-five percent confidence intervals were calculated for the MR at each data point.[12] Analysis was performed with SPSS for Windows, version 16.0.1 (SPSS Inc.).

RESULTS

Table 1 shows the distribution of the study population by age/sex group, the median age for each age/sex group, and the median ages for each age/sex group for those with any LFT value at or above the 75th percentile. When comparing median ages for all applicants in each age/sex group against those with any LFT value at or above the 75th percentile, these median ages differ by a year or less.

When results for those younger than age 20 were excluded from the age <60 groups, distributions of LFT values were nearly identical (data not shown). Results were also examined by smoking status (urine cotinine cut-off < 500 ng/mL). Nonsmokers had GGT and AP values 1 unit less than the combined group, and transaminase values were only 0.2 units higher (data not shown). Because differences based on excluding age <20 or smokers were small and did not impact the mortality ratios other than at a few isolated data points, and because the number of deaths at more data points became too small, only the combined results are presented.

Table 2 shows the distribution of GGT values by percentile band for each age/sex group, Table 3 for AP, Table 4 for AST, and Table 5 for ALT. Note the sometimes large differences in LFT values for the same percentile between the 3 age/sex groups.

To determine the mortality risk associated with each LFT alone, we looked at the relative mortality associated with each LFT in the absence of other LFT elevations (any other LFT at or above the 95th percentile). The relative mortality results for GGT, AP and AST are shown in Figure 1 (females <60), Figure 2 (males <60), and Figure 3 (all 60+). GGT and AP show a fairly linear association, with relative mortality risk proceeding from lowest risk at low values to highest risk at high values. The relative mortality risk trends for AST are more ''U'' shaped. The relative mortality results for ALT alone are shown for all age/sex groups in Figure 4. We show ALT separately because unlike the other LFTs, the relative mortality risk increases at low

Table 2. GGT Values Within Percentile Bands

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 (ref.)	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 4. AST Values Within Percentile Bands

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 (ref.)	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+

values but remains flat from the middle 50% band and higher.

The utility of each LFT in predicting mortality risk is apparent when displayed by percentile of the population, as we show in Figures 1 through 4; the steeper the slope, the better the risk discrimination. The further the slope extends into the low risk areas, the better the LFT is at discriminating risk between the healthiest and those at average risk.

Alternate presentations of our data appear in Figure 5 for GGT, Figure 6 for AP, and Figure 7 for AST. On these graphs, the horizontal axis is divided into ranges of LFT values, a more traditional way to look at laboratory values and associated relative mortality risk. In these graphs, the relative mortality curves diverge from those shown in Figures 1–3, because LFT distributions are so different among the 3 age/sex groups. For example, as can be seen in Table 2 (the percentile distribution for GGT), 4% of females <60, 8% of all 60+, and 12% of males <60 have GGT results higher than 65 IU, the value typically indicated as the upper end of GGT's normal range on laboratory reports.

Additional analyses looked at the relative mortality risk associated with GGT, AP or AST with or without other LFT elevations

Table 3. Alkaline Phosphatase Values Within Percentile Bands

Range of Alkaline Phosphatase Values (U/L)			
Percentile	Females <60	Males <60	All 60+
<1	<34	<41	<41
1 to 2.4	34–<38.7	41–<46	41–<47
2.5 to 4	38.7–<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 (ref.)	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–<180	149–<166	170–<197.4
99.5+	180+	166+	197.4+

Table 5. ALT Values Within Percentile Bands

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 (ref.)	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+

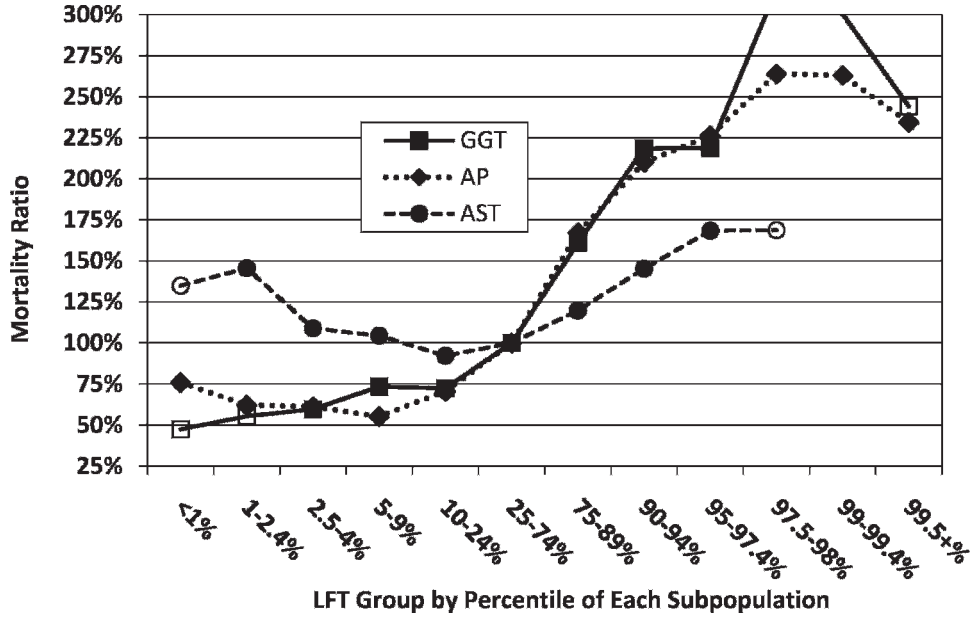

Figure 1. *Females <60: Relative Mortality of Each LFT by Percentile.*

(any other LFT at or above the 95th percentile). The relative mortality risks for the isolated elevation of one LFT, any of the other two also elevated, or both others elevated are shown in Figure 8 (GGT), Figure 9 (AP), and Figure 10 (AST) for males <60. Figure 10 also includes a line for AST combined with elevated ALT, showing no increased risk. Results are similar for the other two age/sex groups, but the data is more limited (data not shown). Relative mortality risk increases for each LFT when any other LFT elevation is present, except for ALT. It goes up further when multiple elevated LFTs are present.

Figure 11 shows the 95% confidence intervals (CI) for isolated LFT elevations, one example from each age/sex group for a different LFT. These are representative of the 95% confidence intervals for the rest of

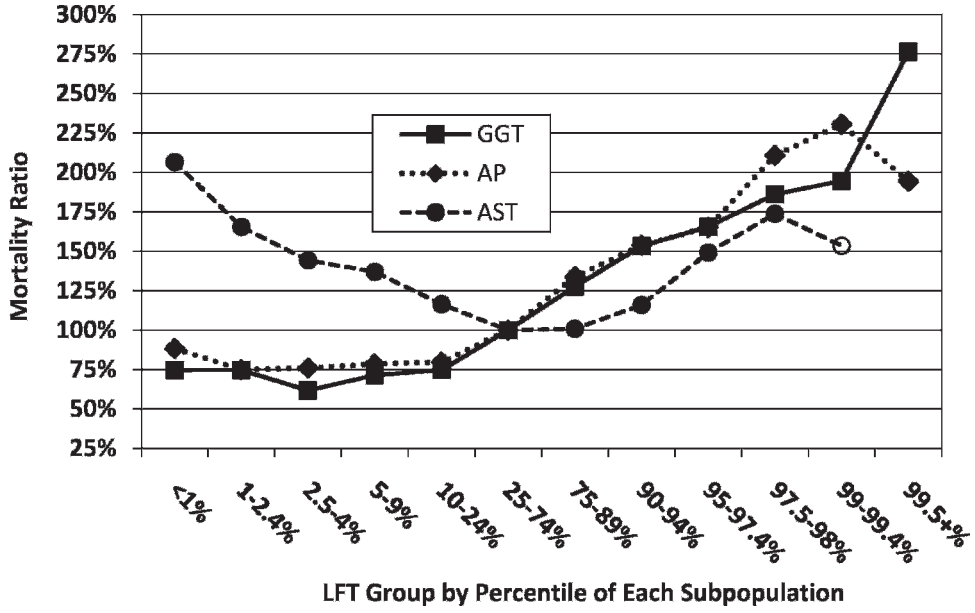

Figure 2. *Males <60: Relative Mortality of Each LFT by Percentile.*

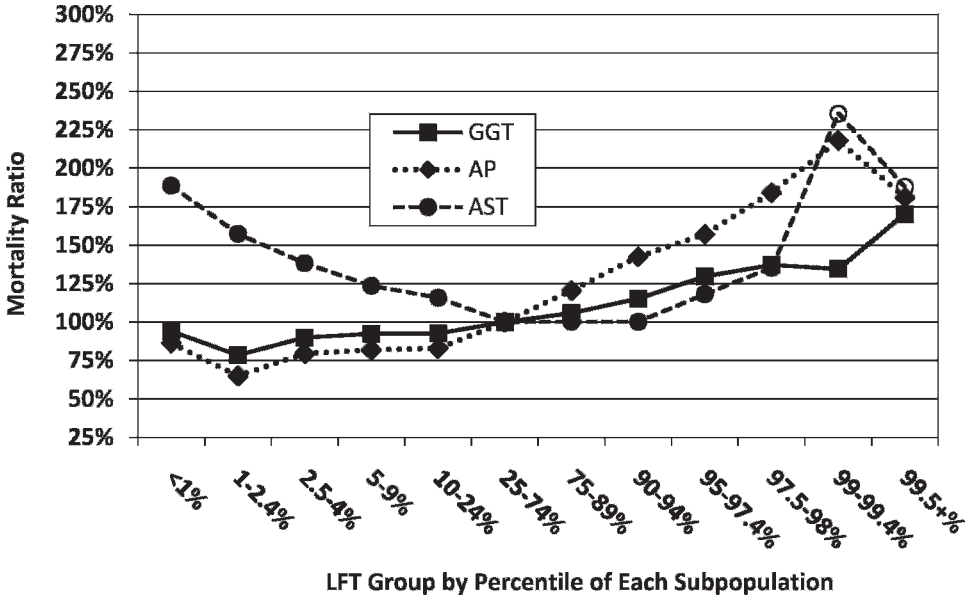

Figure 3. *All 60+: Relative Mortality of Each LFT by Percentile.*

the data since the numbers of lives and deaths are similar (data not shown). Note the width of the 95% CIs where hollow line markers indicate 8 to 29 deaths and where solid line markers indicate 30+ deaths. They are narrow where deaths exceed 29 but become wider where there are fewer deaths, although the trends in mortality risk usually remain readily apparent.

DISCUSSION

GGT, AP and AST are all associated with increased mortality risk as values increase above those present in the middle 50% band of each population. Relative mortality appears to fall off at the highest values (Figures 1–3), but isolated LFT elevations of this magnitude are rare, and we believe

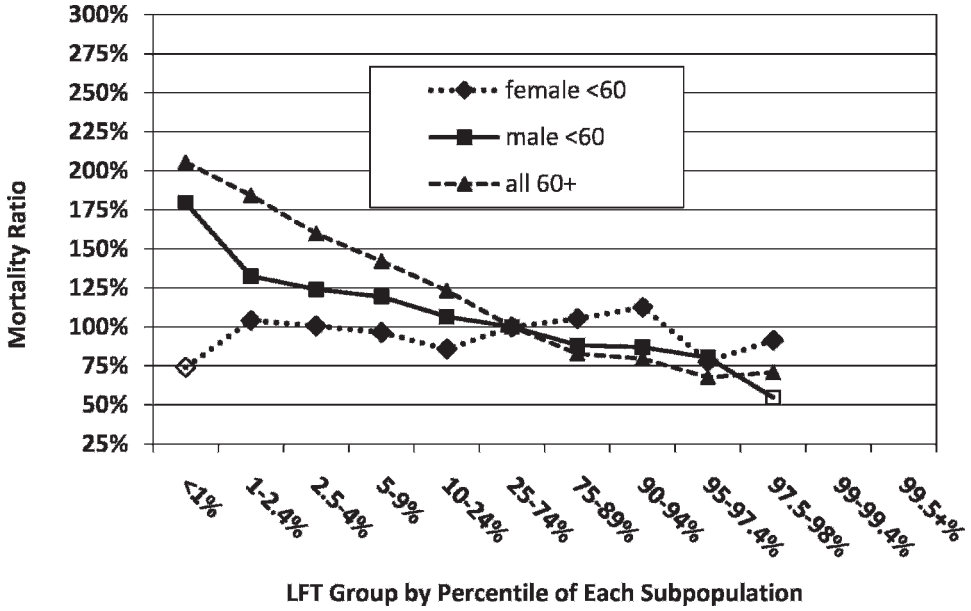

Figure 4. *ALT: Relative Mortality for Each Age/Sex Group by Percentile.*

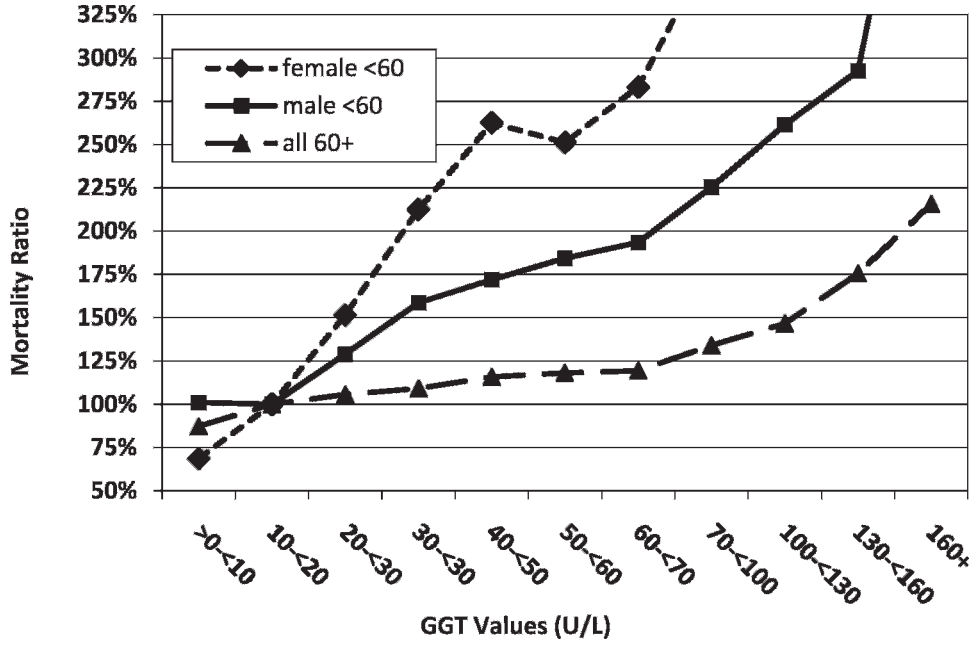

Figure 5. *GGT: Relative Mortality by Value with All Other LFTs <95th Percentile.*

they are associated with conditions that do not present an increased risk. Figures 5–7 provide MRs that are more representative of the risk of each LFT when more than one LFT is elevated. Much of the downturn seen at the highest values for isolated LFTs disappears when other LFT elevations are included. When looking only at the risk of an isolated LFT elevation, use the results in Figures 1–4. When considering the independent contribution of the risk from each LFT, we suggest looking at the trend lines from Figures 5–7, and using this information to adjust the risk estimates at the highest LFT results in Figures 1–4. Risk continues upward when such an adjustment is made for

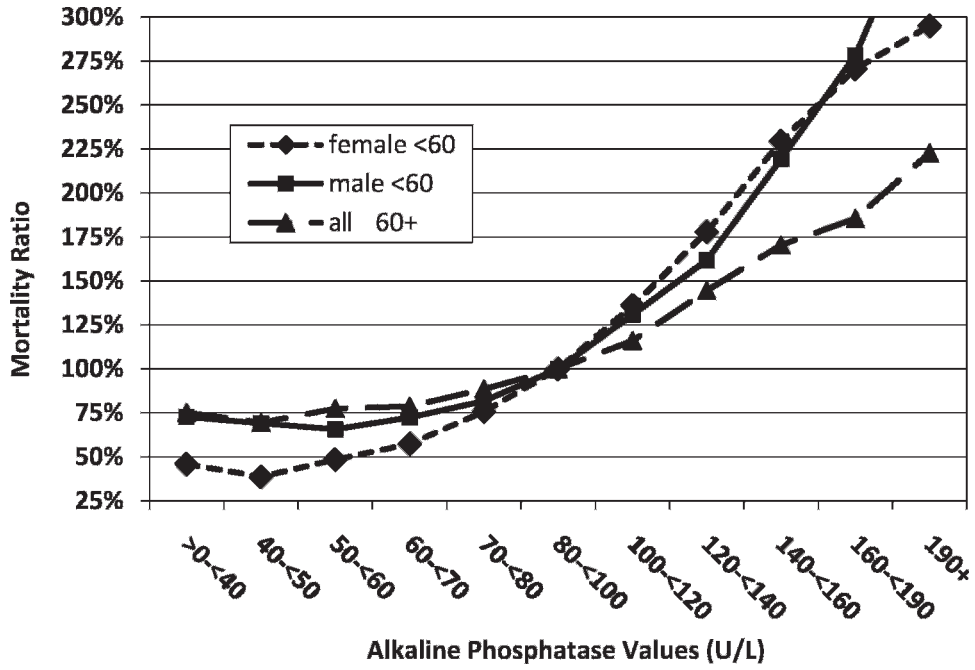

Figure 6. *AP: Relative Mortality by Value with All Other LFTs <95th Percentile.*

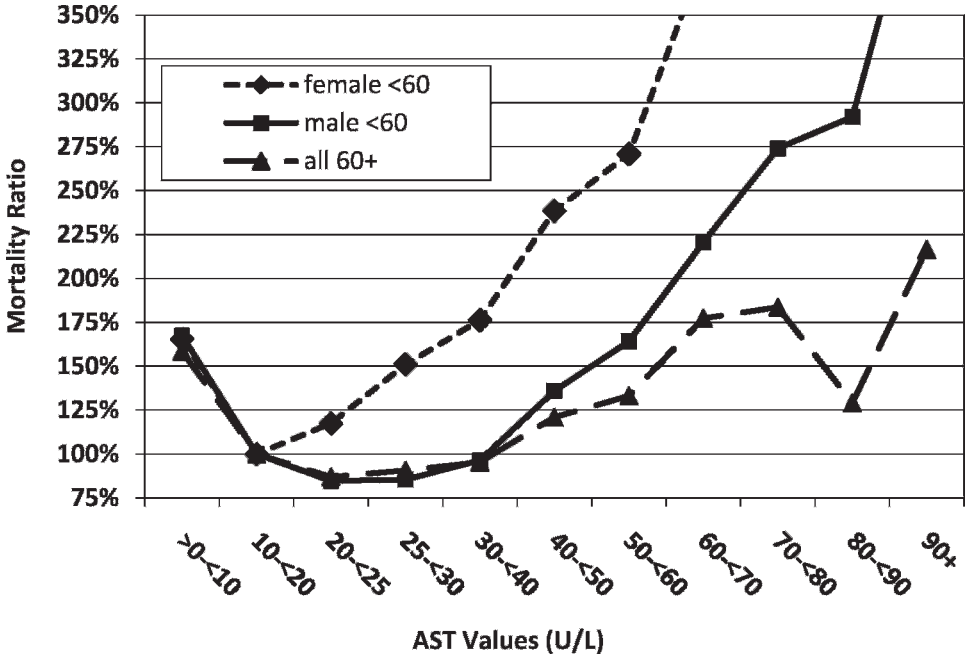

Figure 7. *AST: Relative Mortality by Value with All Other LFTs <95th Percentile.*

the other two age/sex groups as well (data not shown).

Elevated GGT is associated with heavy regular alcohol consumption and with increased cardiovascular risk. It may be that these conditions explain most of the association observed in our study between GGT and mortality risk. Since GGT is produced in many tissues, how much of the increased mortality risk is attributable to higher levels of hepatic GGT is unclear. Until now, both the risk presented by GGT values even mildly higher than those in the middle 50% range and the reduced mortality risk for lower GGT values have not been fully appreciated. These patterns are apparent in all 3 age/sex groups, although they are more prominent at younger ages.

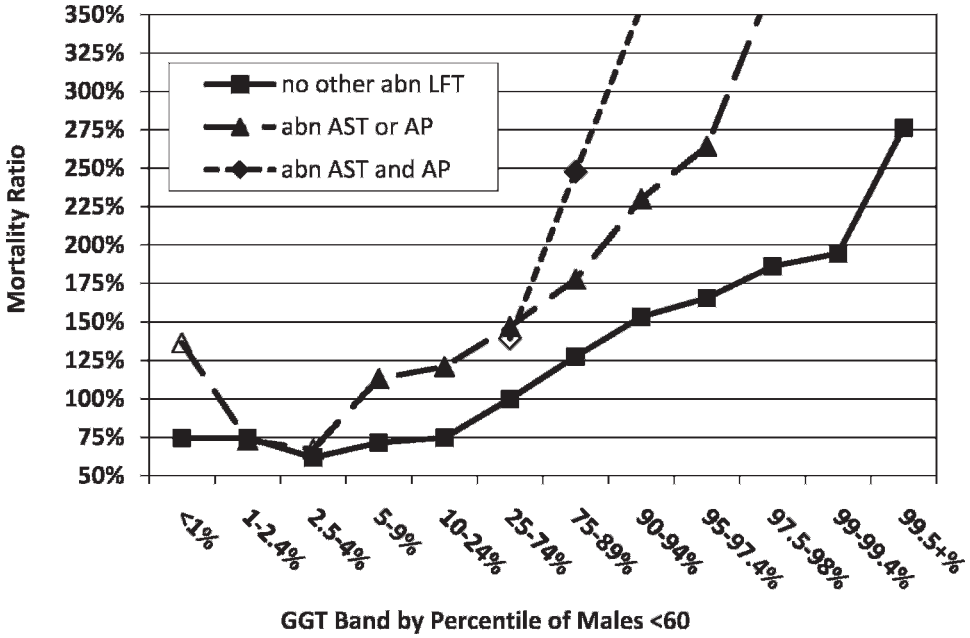

Figure 8. *GGT: Relative Mortality With and Without Other LFTs at 95th+ Percentile.*

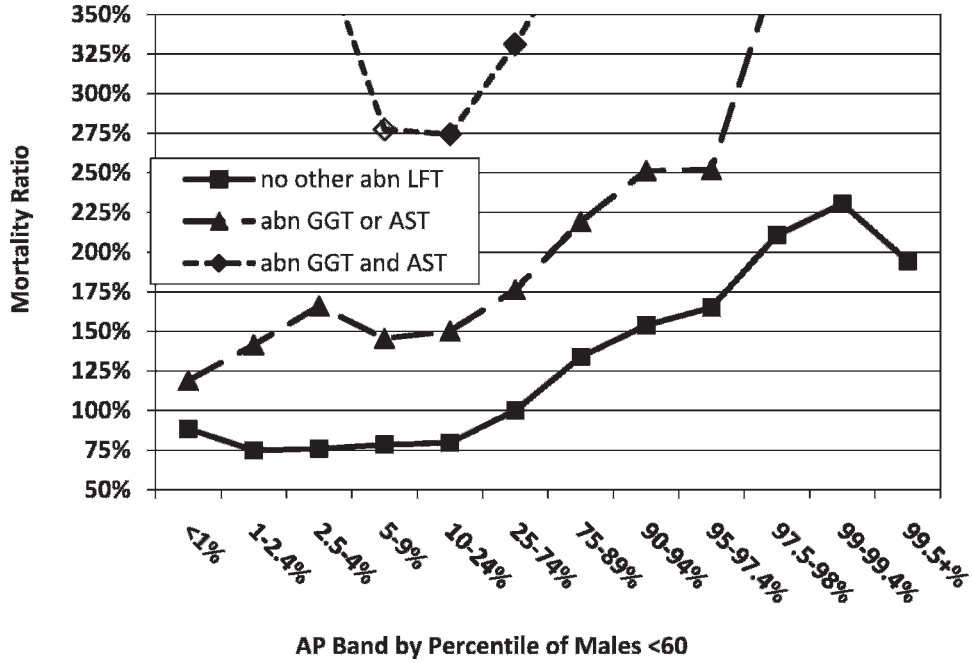

Figure 9. *AP: Relative Mortality With and Without Other LFTs at 95th+ Percentile.*

Alkaline phosphatase is largely of liver or bone origin but is produced by other tissues as well. Many conditions are associated with AP elevation; which of these conditions explains the increased relative mortality risk at high AP values is unclear from our data. What is clear is the extent of mortality risk associated with even modestly higher values of AP, even among those under age 60. As we found for GGT, reduced relative mortality risk is apparent in those with the lowest AP values within all 3 age/sex groups.

AST has a ''U'' shaped mortality curve, ie, elevated relative risk at both low and high values. Most circulating AST is derived from the liver or from muscle. Low values of transaminases are reported in the literature in association with uremia, pregnancy and low

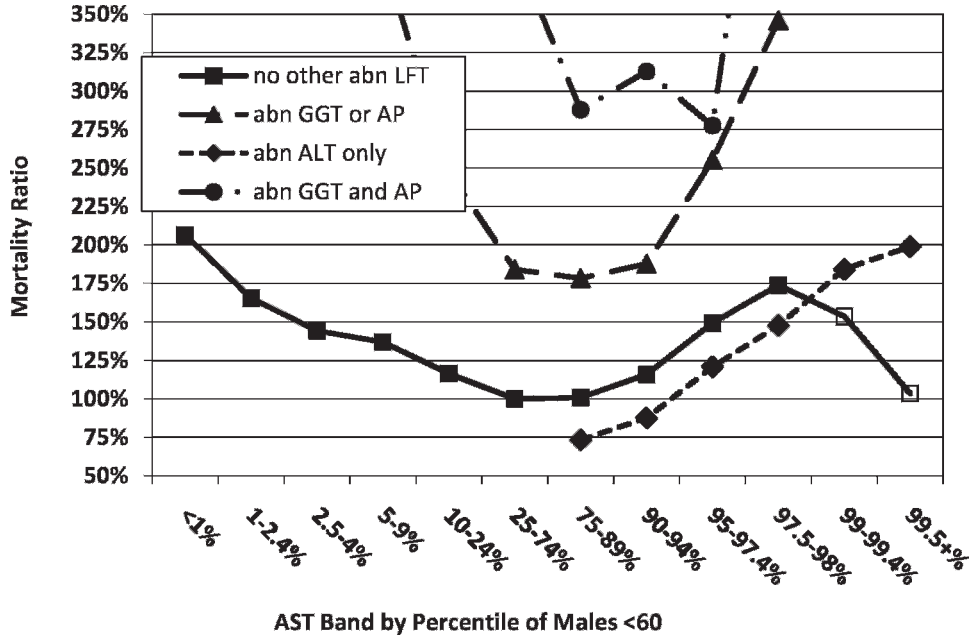

Figure 10. *AST: Relative Mortality With and Without Other LFTs at 95th+ Percentile.*

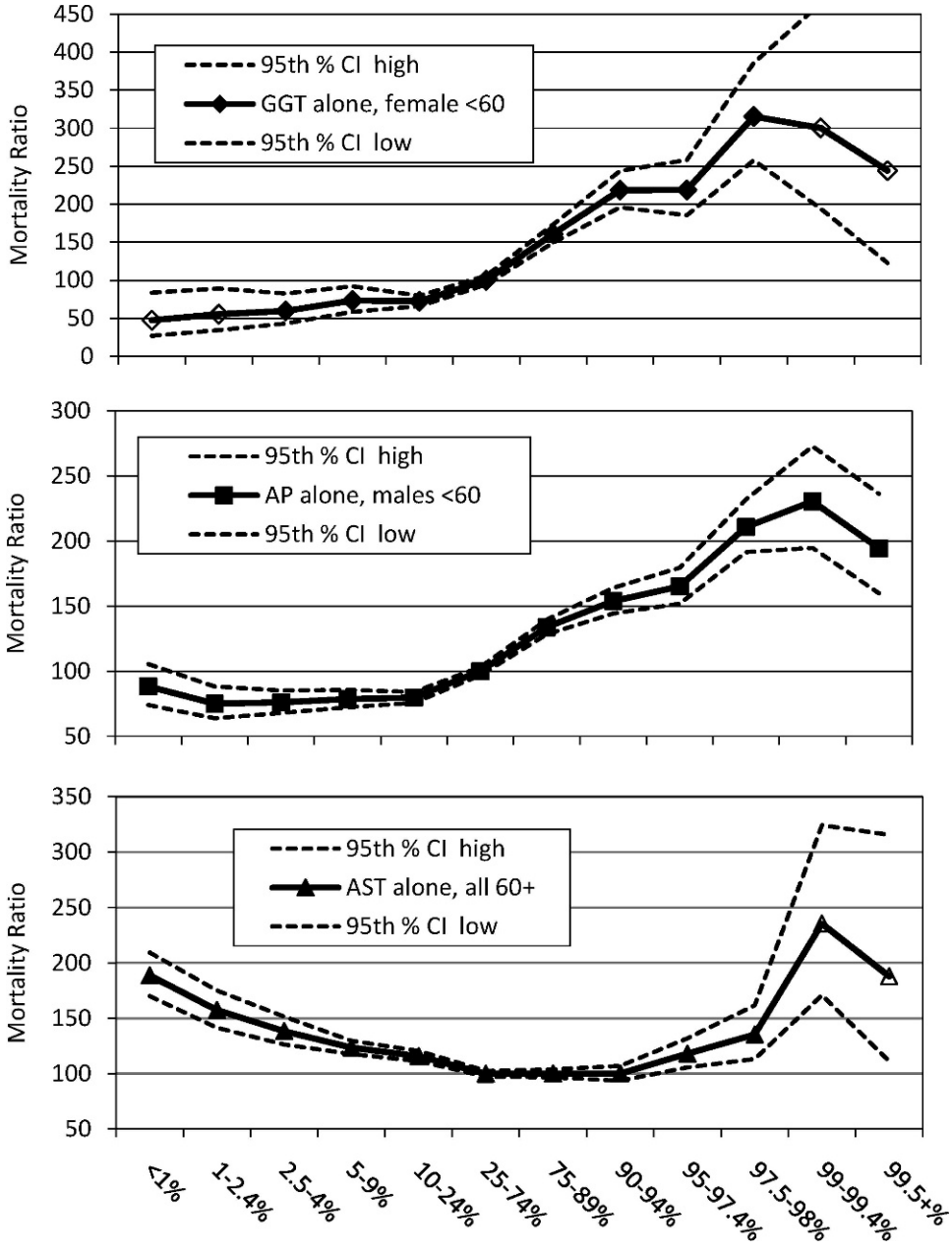

Figure 11. *Confidence Intervals for Selected Representative Mortality Ratios.*

vitamin B levels; in at least one report, low transaminases are associated with increased mortality in men age 70+.[13] The causes of increased mortality associated with AST in our study are not clear, but because we found similar relative risks at low values for both AST and ALT, we believe these are likely related to fatal conditions associated with reduced hepatic production of the transaminases.

Uremia is unusual in an insurance applicant population, and an association is not apparent when eGFR and ALT values are compared (data not shown). Pregnancy, which can raise transaminase levels, is not known to be a mortality risk, and any relationship to poor nutrition is uncertain. In general, relative mortality risk increases with higher values of AST but with a shallower slope than with GGT and AP, making AST a useful yet less effective tool in risk discrimination.

ALT has increased relative mortality associated with low values similar to AST, except in females <60; we assume this is due to

similar underlying physiology. Surprisingly, we found no increase in mortality with increases in ALT values above the middle 50% for any age/sex group. Other studies have shown some increase in mortality as ALT rises; in one study, this occurred only when BMI was below the population median.[10] With the trend of increasing girth in North America, we have seen a corresponding increase over time in ALT values, which is more likely associated with fatty liver rather than with highly lethal diseases. ALT remains the most sensitive test for many forms of hepatitis (including HBV and HCV), but specificity is decreasing because of obesity. Given the low prevalence of HBV and HCV infection in the insurance-buying population, and the fairly low relative mortality (less than 3-fold) from HBV and HCV in insurance applicants (data not shown), the lack of observed increased relative mortality risk associated with ALT is understandable.

As can be seen in Figure 10, elevated ALT does not increase the relative risk associated with AST elevation. Although ALT is a useful test to trigger specific reflex tests for hepatitis, it appears to have no value as an independent predictor of mortality risk when elevated. Because AST shows a similar pattern to ALT at low values, and is more consistent across all 3 age/sex groups, the additional predictive value of ALT in this lower range is minimal.

Risk associated with multiple LFT elevations (Figures 8–10), has a stepwise increase as each LFT (other than ALT) is added. The sum of the risks can be approximated by simple addition of the risk associated with each LFT value.

Our study has many more deaths and a larger age range than any of the references cited in this article; it is also more representative of middle and upper income adults in the United States. When split by age and sex, the wide differences in LFT value distribution and relative mortality risk can be seen. We feel that these differences preclude the use of a universal normal range for LFT risk assessment, as is now commonly done both in clinical settings and for risk stratification of insurance applicants. Not only must risk assessment be based on appropriate age and sex splits, but within the middle 95% of adults (approximately 2 standard deviations) large variations in relative mortality risk must be addressed.

Table or formula-based risk calculators are in use for assessing the mortality risk of ''healthy'' persons, as well as those with specific conditions such as breast or prostate cancer. Rather than using a statistical normal range for each LFT for screening purposes, it may be more effective to assign risk scores for any laboratory value on which actual mortality data is available. Based on the composite risk score of all values, a person's overall mortality risk may be calculated. This approach assumes that the risk score assigned to each laboratory value represents an accurate and independent contribution to overall mortality risk. Reporting on other laboratory values in a similar format will be required before an appropriately-weighted composite risk score for laboratory screening is possible.

This study has limitations. No cause of death was available, and medical history, height and weight information was available for few of these insurance applicants. This information would have been of value in better understanding our results. Some of the mortality risk for an individual would be apparent from other medical history or laboratory findings, and may not be attributable only to LFT status. However, when used in a screening capacity, other medical history or laboratory findings are not always immediately available; we often make judgments regarding the need for further evaluation based solely on LFT screening results. Our study will not change that process, but can help make those judgments more accurate.

Another limitation is the few deaths observed for data points at the extremes of the LFT value ranges, resulting in broader 95% confidence intervals. In our figures, all data points with few deaths and consequently

wider 95% confidence intervals are identified, or simply excluded if there were fewer than 8 deaths. The alternate approach of combining bands of LFT values in these situations was considered; we did not utilize this approach since a sufficient number of deaths were available for all but a few data points, and we did not wish to obscure the trends unique to each LFT value band. The trends are fairly clear based on the available well-populated data points and from age/sex groups where sufficient deaths are available.

A third limitation of our study is the relatively small (typically 2- to 3-fold) elevations of LFT values even at the 99.5th percentile band compared to a typical traditional range with an upper limit of 65 U/L for GGT, 115 U/L for AP, 41 U/L for AST, and 45 U/L for ALT. In this healthy population, isolated elevations beyond the 99.5th percentile are too rare even for our large database to provide sufficient deaths for analysis. This may be of most concern with ALT, which unexpectedly shows no increased mortality risk above the middle 50% of values. We believe that there is no reason to expect even higher isolated elevations of ALT would present increased mortality risk. Liver diseases of concern would be expected to have other LFT abnormalities as well, and those other elevations adequately identify the potential risk. Further refinement of the risk at these levels is more appropriately done via additional efforts toward a specific diagnosis, rather than considering only a single assessment of multiple LFT elevations.

CONCLUSIONS

Our results suggest that changes are needed in the approach toward the results of screening LFTs. GGT and AP are strong linear predictors of relative mortality risk in all 3 age/sex groups. This predictive value extends from the lowest values (healthiest) to the highest values. Above the middle 50% band of the population, AST is less predictive and ALT has very limited predictive value. However, low values of transaminases also predict increased risk. The mortality risk associated with multiple LFT elevations can be approximated by adding the risk of each elevation.

Until now, we have been largely unaware of the elevated mortality risk associated with low values of transaminases, as well as the reduced mortality risk associated with low values of GGT and AP. Because we have been using statistical or traditional normal ranges for LFT values for all demographic groups combined, that practice masked the major differences in mortality risk between males <60, females <60 and all 60+ years for any specific LFT value. Further research is needed to find out why GGT and AP are so predictive of mortality risk, and why low levels of transaminases indicate increased mortality risk.

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