



Bilirubin: Risk Impact of the “Other” LFT

Objective Define the value of bilirubin for life insurance testing. This is CRL proprietary information for internal use at your company.

Background Bilirubin results from the breakdown of hemoglobin, and is transported to the liver loosely attached to albumin. In the liver it is conjugated (attached) to glucuronic acid and becomes water soluble. In a second step, bilirubin is excreted into the bile and then passed into the gut for further disposal. Interference with either step can elevate serum bilirubin levels as can increased turnover of red blood cells.

Gilbert’s disease (which is present in at least 5% of the population) reduces conjugation and results in variable isolated increases in (unconjugated) bilirubin levels of no concern to life underwriting. Other liver diseases, such as hepatitis or cirrhosis, may also cause bilirubin elevations usually by reducing excretion into the bile; they are typically associated with other LFT elevations.

Most companies allow considerable isolated bilirubin elevation without underwriting action, assuming it is likely to be Gilbert’s disease and of no mortality concern. Conversely, elevations of bilirubin in conjunction with other elevated LFTs are usually considered to be a major concern far more than just elevations of the other LFTs. This approach reflects our understanding of bilirubin metabolism but has limited validation from previous population mortality studies.

Facts CRL has analyzed the mortality of applicants tested for bilirubin between 1993 and 1997 and followed for at least 10 years. Mortality among these applicants was determined by use of the Social Security Death Master File, also known as the Social Security Death Index or SSDI. This study comprised about 2 million tested applicants and over 50,000 deaths, allowing the data to be analyzed in an age, sex and LFT-specific manner never before possible. This report is limited to addressing mortality associated with isolated bilirubin and bilirubin elevations in conjunction with other LFT elevations.

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+”). These groups showed different mortality or distribution patterns from each other. After exploring other variables as possible additional grouping criteria, we found that these three age/sex groups were sufficient to define the mortality risk associated with bilirubin.

We divided all bilirubin results into ranges defined by their percentile distributions within each of the three age/sex groups. The distribution of bilirubin values by percentile group is listed in **Table 1**. A mortality ratio (MR) of 100% was assigned to the 25th to 74th percentile as the “reference” mortality

compared to lower and higher bilirubin 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. Data points with <8 deaths are excluded. Data points with 8-29 deaths are shown with open centers.

Our analyses included the relative risks associated with bilirubin in the absence of other LFT elevations shown in **Figure 1**. Even extending the division of results to the 99.75 percentile of distribution produced cut-off values of only 1.9, 2.1 and 2.6 mg/dL, which are values lower than those often clinically accepted as abnormal for bilirubin. Using cut-off values higher than these yielded too few deaths for valid analysis. However, as can be seen, increasing values of bilirubin are not accompanied by any increase in mortality. We have no reason to think this would change for even higher values in the absence of any other LFT elevation based on our data and based on the physiology involved. In the presence of markedly elevated bilirubin, some other LFT should be abnormal in the presence of inflammatory or destructive liver disease.

Interestingly, relative risk increases at low levels of bilirubin, most prominently in males younger than 60 years. This association has been previously noted by others and is linked to higher levels of smoking, hypertension and cardiovascular risk factors.¹ If smokers are excluded from our data, this increase flattens markedly (data not shown). Using low bilirubin as a mortality predictor is likely not warranted since we already evaluate smoking, hypertension and cardiovascular risk factors during underwriting.

We also looked at the mortality of each LFT in the presence of elevated (95th percentile or higher) values of bilirubin. An example of this analysis for alkaline phosphatase (AP) is shown in **Figure 2**. GGT has more and AST has less increased relative risk, but the trends were similar to those found for AP. The excess relative risk is very small until the risk associated with the other LFT approaches 200% total risk relative to the 25th to 74th percentile, when it may increase to a level of an additional 50% excess relative risk (250% total risk). This increase in relative risk is less than many would expect; it also emphasizes the need to be alert to AST, GGT and AP elevations with or without bilirubin elevations.

A rule of thumb for bilirubin elevations higher than 1.2 mg/dL (around 95th percentile for all age/sex groups) in conjunction with AST, GGT or AP might be:

- IF highest other LFT elevation has an extra risk of 0-50%, add nothing.
- IF highest other LFT elevation has an extra risk of 75-100%, add an additional 25% to risk.
- IF highest other LFT elevation has an extra risk of >100%, add an additional 50% to risk.

Conclusions

1. **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, females less than 60 years, and all those age 60 and over. We found that the differences in relative risk for each gender among applicants age 60 and over were small enough to justify combining that group.
2. **Isolated bilirubin elevation** appears to have little mortality impact.
3. **Bilirubin elevation in conjunction with other LFT elevations** is a surprisingly small predictor of extra risk. As the risk for the other LFT elevation grows, so does the impact of the elevated bilirubin but it never amounts to more than half of the excess relative risk of the other LFT elevation; at lower LFT elevations, the effect of elevated bilirubin is much less.

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

Range of Bilirubin Values (mg/dL)			
Percentile	Females <60	Males <60	All 60+
<5	<.2	<.3	<.2
5 to 9	.2-<.3	.3-<.4	.2-<.3
10 to 24	.3-<.31	.4-<.5	.3-<.4
25 to 74 (reference)	.31-<.6	.5-<.8	.4-<.7
75 to 89	.6-<.8	.8-<1.1	.7-<.9
90 to 94	.8-<1.0	1.1-<1.3	.9-<1.1
95 to 97.4	1.0-<1.2	1.3-<1.6	1.1-<1.3
97.5 to 98	1.2-<1.5	1.6-<2.0	1.3-<1.6
99 to 99.4	1.5-<1.7	2.0-<2.3	1.6-<1.9
99.5 to 99.74	1.7-<1.9	2.3-<2.6	1.9-<2.1
99.75+	1.9+	2.6+	2.1+

Figure 2. Mortality Ratios for Alkaline Phosphatase for all cases and just cases with abnormal bilirubin (dashed lines)

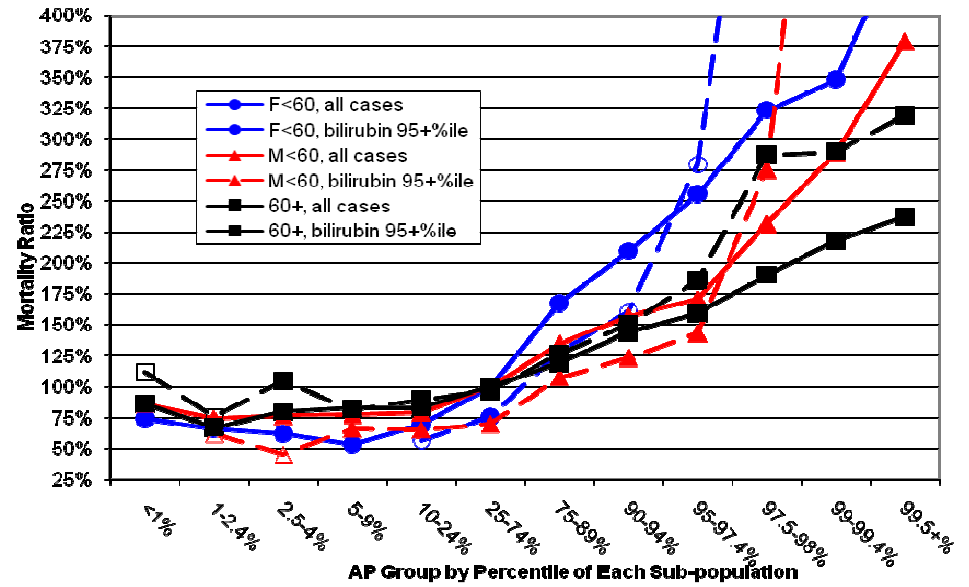
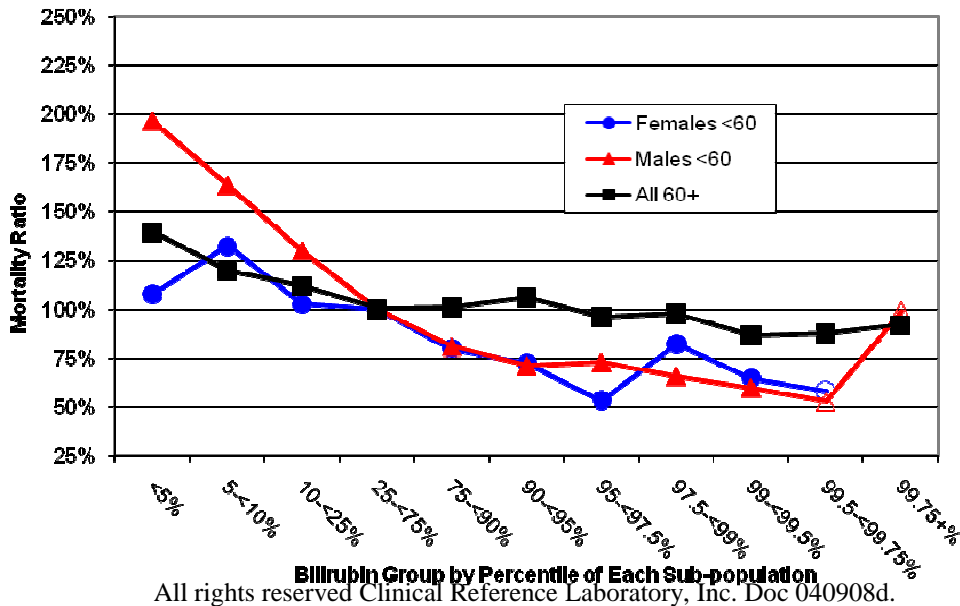


Figure 1. Mortality Ratios for Bilirubin without other Abnormal LFTs



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References

1. Endler G, et al “Is Low Serum Bilirubin an Independent Risk Factor for Coronary Artery Disease in Men but Not in Women?” Clin Chem 2003;49:1201-4