

Journal of Insurance Medicine

Official Journal of the American Academy of Insurance Medicine

Mortality Associated with Bilirubin Levels in Insurance Applicants

Michael Fulks, MD; Robert L. Stout, PhD; Vera F. Dolan, MSPH



LABORATORY TESTING

Mortality Associated with Bilirubin Levels in Insurance Applicants

Michael Fulks, MD; Robert L. Stout, PhD; Vera F. Dolan, MSPH

Objective.—Determine the relationship between bilirubin levels with and without other liver function test (LFT) elevations and relative mortality in life insurance applicants.

Method.—By use of the Social Security Death Master File, mortality was determined 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+. The median follow-up was 12 years.

Results.—Relative mortality increased as bilirubin decreased below bilirubin levels seen for the middle 50% of the population. The known association of smoking with lower bilirubin values explained only part of the additional elevated risk at low bilirubin levels. In the absence of other LFT elevations, relative mortality remained unchanged as bilirubin increased beyond levels seen for the middle 50% of the population. When a bilirubin elevation was combined with other LFT elevations, mortality further increased only at the highest elevations of other LFTs, seen only in <2.5% of applicants.

Conclusion.—Isolated elevations of bilirubin in this healthy screening population were not associated with excess mortality but values below the midpoint were. Other investigations have suggested a cardiovascular cause may underlie the excess mortality associated with low bilirubin. In association with other LFT elevations, bilirubin elevation further increases the mortality risk only at the highest elevations of other LFTs.

Address: Vera F. Dolan, MSPH, Clinical Reference Laboratory, 601 North State Street, Suite 2000, Ukiah, California 95482; ph: 707-463-3200; fax: 707-463-3209; e-mail: dolanvp@consultancy.com.

Correspondent: Vera F. Dolan, MSPH, Research Associate, Clinical Reference Laboratory, Ukiah, CA.

Author affiliation: Fulks, Medical Director, Clinical Reference Laboratory, Jackson, CA; Stout, President, Clinical Reference Laboratory, Lenexa, KS; Dolan, Research Associate, Clinical Reference Laboratory, Ukiah, CA.

Key words: Bilirubin, liver enzymes, liver function tests, mortality, life insurance.

Received: October 24, 2008

Accepted: December 12, 2008

INTRODUCTION

Mild elevations (>1.2 mg/dL) of total bilirubin are not uncommon on a screening chemistry panel with or without other liver enzyme (liver function test or LFT) elevations. However, information as to the actual mortality risk associated with bilirubin elevations and when additional action is needed is difficult to find. An online search of the

US National Library of Medicine's PubMed and several medical reference texts revealed only information on bilirubin values for specific conditions, rather than information on the mortality risk presented by bilirubin elevations in the absence of a diagnosis or obvious evidence of disease. In contrast, recent bilirubin research appears to focus on the association of low bilirubin levels with increased cardiovascular risk.^{1–4}

When bilirubin is tested as part of a blood screen for individual life or disability insurance, the issue of risk is magnified since an initial business decision regarding the applicant must be made prior to any follow-up or clinical evaluation of the laboratory results. We know that isolated bilirubin elevations are noted with Gilbert syndrome (no known risk), other more serious enzyme defects, and with conditions having increased red cell turnover or disordered red cell production. Bilirubin elevations, typically associated with other LFT elevations, occur with liver inflammation or biliary obstruction. What we don't know is the relative mortality risk associated with bilirubin elevation (either by itself or in combination with other elevated LFTs) in the absence of a clear diagnosis.

Our investigation utilizing serum from unselected adult insurance applicants is designed to answer questions about the relative mortality risk attributable to elevated bilirubin, and further explore possible increased risk at low bilirubin values. This study adds information on the use of bilirubin in risk evaluation to the information on the use of ALT, AST, GGT and alkaline phosphatase (AP) from our article on mortality risk and LFTs published in a previous issue of this journal.⁵

METHODS

The population studied for this article is the same as that analyzed for our study of mortality risk and LFTs, and is described in depth in that article.⁵ Briefly, 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 after a median follow-up of 12 years (range 10 to 14 years).

Results were stratified by 3 age/sex groups: females, age <60 (females <60); males, age <60 (males <60); and both sexes combined, age 60+ (all 60+). Bilirubin values

Table 1. 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+ |

were grouped using percentiles of their distribution within these three age/sex groups. The middle 50% band of each subpopulation (25th to 74th percentile) was assigned a mortality ratio of 100%. Mortality results in other percentile bands for bilirubin were compared to this reference mortality.

All mortality ratios in the tables or figures based on fewer than 8 deaths are omitted. All mortality ratios based on 8 to 29 deaths are indicated by italics in the tables, or by a blank-centered marker in the figures. Representative 95% confidence intervals for mortality ratios were presented in our previous publication on mortality and LFTs.⁵ Analysis was performed with SPSS for Windows, version 16.0.1 (SPSS Inc.).

RESULTS

Table 1 provides a distribution of bilirubin values by percentile band within each of the 3 age/sex subpopulations. There are differences in bilirubin values between these 3 groups, although they are less dramatic than the differences found among the other LFTs. One notable finding is that even at the 99.75% band, the bilirubin level is only 2.6 mg/dL for males <60, 1.9 mg/dL for females <60, and 2.1 mg/dL for all 60+.

Figure 1 looks at the relative mortality associated with bilirubin for all cases without elevated LFTs. Elevated LFTs are AST, AP or

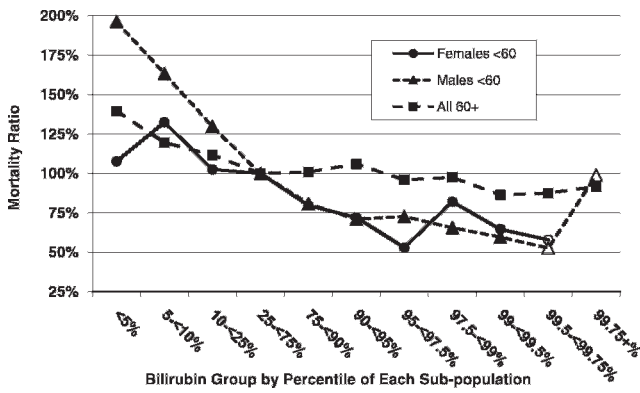


Figure 1. Mortality Ratios for All Cases with All Other LFTs Normal (<95th percentile).

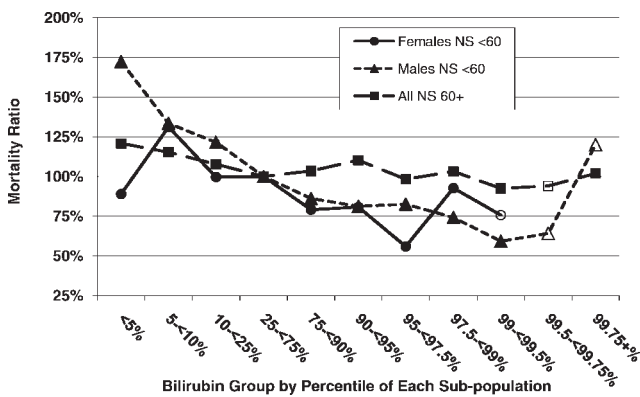


Figure 2. Mortality Ratios for Nonsmokers with All Other LFTs Normal (<95th percentile).

GGT values at or above the 95th percentile for each age/sex subpopulation. ALT is not included for analysis in this study, due to our previous finding that ALT did not predict mortality risk by itself or in conjunction with other LFTs.⁵ From Figure 1, even at

the >99.75th percentile band of isolated bilirubin elevation, there is no increase in relative risk. Instead, relative mortality increases as bilirubin level decreases, a finding previously noted by others.¹⁻⁴

Figure 2 looks at relative mortality associated with bilirubin in nonsmokers only (identified by a urine cotinine <200 ng/mL) without elevated LFTs. Relative mortality is still increased for lower bilirubin levels, but the increase is slightly less than observed in Figure 1 where smokers also are included. Median bilirubin values are lower for smokers than for nonsmokers: for females <60, the median bilirubin value is 0.40 in smokers vs 0.45 mg/dL in nonsmokers; for males <60, it is 0.52 vs 0.61 mg/dL, and for all 60+, it is 0.50 vs 0.54 mg/dL.

Mortality ratios for cases based on other LFTs (either with bilirubin elevated to the 95th percentile, or higher or with any bilirubin values) are shown in Table 2 (AST), Table 3 (AP), and Table 4 (GGT). For all mortality ratios, the 100% reference band is defined as the 25th to 74th percentile of the other LFT analyzed without regard to bilirubin level. LFT values for each percentile band were presented in our previous publication on mortality and LFTs.⁵ Adding an elevated bilirubin to another LFT elevation increases relative mortality risk, but only at the highest levels of the other LFT analyzed. The mortality ratios for the AST, AP or GGT elevations regardless of any bilirubin eleva-

Table 2. Mortality Ratios for All AST Elevations vs Joint AST/Bilirubin Elevations

| AST Percentile (%) | Females <60 | | Males <60 | | All 60+ | |
|----------------------|-------------|-------------------|-----------|-------------------|---------|-------------------|
| | All AST | AST and bilirubin | All AST | AST and bilirubin | All AST | AST and bilirubin |
| 25 to 74 (reference) | 100% | 66% | 100% | 71% | 100% | 94% |
| 75 to 89 | 123% | 94% | 104% | 72% | 100% | 104% |
| 90 to 94 | 156% | 126% | 119% | 106% | 102% | 109% |
| 95 to 97.4 | 189% | 168% | 160% | 134% | 124% | 154% |
| 97.5 to 98 | 208% | 191% | 213% | 288% | 145% | 167% |
| 99-99.4 | 334% | 420% | 326% | 449% | 198% | 280% |
| 99.5+ | 506% | 1109% | 524% | 978% | 212% | 269% |

Note: Numbers in italics indicate ratios based on 8 to 29 deaths.

Table 3. Mortality Ratios for All AP Elevations vs Joint AP/Bilirubin Elevations

| AP Percentile (%) | Females <60 | | Males <60 | | All 60+ | |
|----------------------|---------------|-------------------------|---------------|-------------------------|---------------|-------------------------|
| | <i>All AP</i> | <i>AP and bilirubin</i> | <i>All AP</i> | <i>AP and bilirubin</i> | <i>All AP</i> | <i>AP and bilirubin</i> |
| 25 to 74 (reference) | 100% | 76% | 100% | 70% | 100% | 97% |
| 75 to 89 | 167% | 127% | 135% | 107% | 119% | 127% |
| 90 to 94 | 210% | 161% | 157% | 123% | 144% | 151% |
| 95 to 97.4 | 255% | 280% | 171% | 143% | 160% | 186% |
| 97.5 to 98 | 323% | 658% | 232% | 275% | 191% | 288% |
| 99-99.4 | 348% | ---- | 289% | 736% | 218% | 290% |
| 99.5+ | 470% | 1536% | 379% | 1008% | 238% | 320% |

Note: Numbers in italics indicate ratios based on 8 to 29 deaths. Missing ratios have 8 or fewer deaths.

tion (shown in Tables 2, 3 and 4) and the ratios for those LFT elevations with normal bilirubin (data not shown) are nearly identical. LFT values for each percentile band are found in our prior article.⁵

DISCUSSION

Our results in Figure 1 are surprising, not because they show no increased relative risk as bilirubin level increases, but because of the clearly increased mortality risk associated with the lowest half of values extending down from the middle 50% of all 3 age/sex groups. Relative mortality starting from the 75th percentile remains at or lower than 100% all the way up to the >97.5th percentile band. Although some increase in mortality risk beyond this point is possible, it is not

anticipated since isolated bilirubin elevations of this magnitude in a healthy adult likely preclude any liver disease associated with increased mortality.

This trend of stable rather than increasing mortality risk when an elevation is limited to only one LFT was apparent to a lesser extent in our study of the other LFTs.⁵ In a clinical situation, GGT results may not be available, so a finding of a truly isolated elevation of bilirubin may not be certain. However, in the practice of insurance screening, AST, AP and GGT are all routinely obtained in addition to albumin, a measure of the synthetic function of the liver.

The trend of increasing relative risk as bilirubin declines is apparent for all 3 age/sex groups, but has the greatest magnitude for younger men. This inverse relationship

Table 4. Mortality Ratios for All GGT Elevations vs Joint GGT/Bilirubin Elevations

| GGT Percentile (%) | Females <60 | | Males <60 | | All 60+ | |
|----------------------|----------------|--------------------------|----------------|--------------------------|----------------|--------------------------|
| | <i>All GGT</i> | <i>GGT and bilirubin</i> | <i>All GGT</i> | <i>GGT and bilirubin</i> | <i>All GGT</i> | <i>GGT and bilirubin</i> |
| 25 to 74 (reference) | 100% | 69% | 100% | 67% | 100% | 91% |
| 75 to 89 | 167% | 106% | 129% | 95% | 106% | 100% |
| 90 to 94 | 225% | 224% | 160% | 145% | 117% | 119% |
| 95 to 97.4 | 253% | 347% | 183% | 203% | 136% | 190% |
| 97.5 to 98 | 359% | 500% | 251% | 392% | 164% | 249% |
| 99-99.4 | 416% | ---- | 291% | 405% | 169% | 250% |
| 99.5+ | 725% | 1637% | 541% | 1014% | 248% | 309% |

Note: Numbers in italics indicate ratios based on 8 to 29 deaths. Missing ratios have 8 or fewer deaths.

has been noted previously, and the association of bilirubin with atherosclerosis is summarized in a meta-analysis from Novotny et al.² Endler et al looked at the association of bilirubin with cardiovascular risk factors and found that only the smoking risk factor was associated with lower bilirubin values.³

When we removed smokers from the cases studied, the increase in relative risk was reduced by about 25%, so smoking can explain some (but not all) of the increase in mortality risk associated with lower bilirubin values. Lin et al found that lower bilirubin levels, cardiovascular disease, and their consequent excess mortality are all associated with the UGT1A1*28 allele.⁴ Other investigators have suggested that bilirubin may act directly as an antioxidant.² It is unclear why smokers from all of the 3 age/sex groups have lower median bilirubin values though oxidants present in cigarette smoke may play a role.⁶ It is also unclear why there is an association of low bilirubin with increased cardiovascular risk. However, based on results from our very large study population, the association of low bilirubin values with excess mortality appears to be consistent, real and only partly explained by smoking.

Tables 2–4 reveal that bilirubin elevations at the 95th percentile or higher do not increase the mortality risk associated with “normal” or mildly elevated AST, AP or GGT values. In fact, relative mortality is actually decreased for reasons discussed above in association with Figure 1. Only after the 95th or 97.5th percentile level is reached does the elevated bilirubin begin to contribute additional mortality risk, and that additional risk is small. At the 99th percentile level of AST, AP or GGT, concurrent bilirubin elevations add substantially to the mortality risk, but at that point the relative risk associated with the elevated AST, AP or GGT is already quite high (most often >200% compared to the reference band).

For the screening situation, overall mortality risk is better identified by summing the risks associated with AST, AP and GGT. Once that is done, the bilirubin level will not contribute to the decision of whether further action or evaluation is needed.

CONCLUSIONS

Bilirubin elevation as an isolated finding is not associated with increased mortality risk in this healthy screening population. In combination with other LFT elevations, relative risk may be increased by bilirubin elevations, but only beyond the point where other LFT elevations already indicate a doubling of risk compared to the middle 50% of the population.

Low values of bilirubin are associated with increased cardiovascular and mortality risk. That association is attenuated (but not eliminated) by excluding smokers who, as a group, have a lower median value of bilirubin.

REFERENCES

1. Breimer L, Wannamethee G, Ebrahim S, Shaper A. Serum bilirubin and the risk of ischemic heart disease in middle-aged British men. *Clin Chem.* 1995;41:1504–1508.
2. Novotny L, Vitek L. Inverse relationship between serum bilirubin and atherosclerosis in men: a meta-analysis of published studies. *Exp Biol Med.* 2003;228:568–571.
3. Endler G, Hamwi A, Sunder-Plassmann R, et al. Is low serum bilirubin an independent risk factor for coronary artery disease in men but not in women? *Clin Chem.* 2003;49:1201–1204.
4. Lin J, O'Donnell C, Schwaiger J, et al. Association between the UGT1A1*28 allele, bilirubin levels, and coronary heart disease in the Framingham heart study. *Circulation.* 2006;114:1476–1481.
5. Fulks M, Stout RL, Dolan VF. Using liver enzymes as screening tests to predict mortality risk. *J Insur Med.* 2008;40:191–203.
6. Frei B, Forte TM, Ames BN, Cross CE. Gas phase oxidants of cigarette smoke induce lipid peroxidation and changes in lipoprotein properties in human blood plasma. *Biochem J.* 1991;277:133–138.