BILIRUBIN

Implications in Life Underwriting

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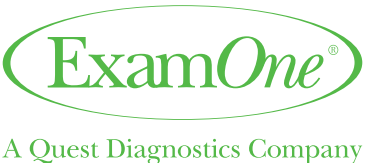

Preface

A great deal of new information has come to light regarding the life underwriting implications of serum bilirubin.

This paper focuses on two questions:

Is low/below normal bilirubin a significantly adverse insurability risk factor?

Is high normal/mild-to-moderately increased bilirubin a notably favorable insurability risk factor in the absence of elevated liver enzymes or other evidence of hepatobiliary disease?

These questions will be considered in the context of a comprehensive review of the clinical/epidemiological literature, as well as several recently insurance industry studies.

To address them, I reviewed 218 articles, studies and study abstracts, 177 of which, having relevant content, are cited in this paper.

The author thanks Brian J. Lansrath (ExamOne) for his gracious (and essential) assistance with certain statistical aspects of this undertaking.

The author also thanks RGA Re and ExamOne for stepping up to cosponsor this project.

Hank George, FALU
March 12, 2015

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Executive Summary

"Support for the beneficial effects of UB [unconjugated bilirubin] is provided by multiple studies showing a negative association between serum bilirubin and various diseases such as coronary artery disease in subjects with normal liver function, as well as in subjects with Gilbert's syndrome."

David G. Levitt and Michael D. Levitt
Department of Integrative Biology and Physiology
University of Minnesota Medical School
Clinical and Experimental Gastroenterology
7(2014):307

"Mild or moderately elevated serum bilirubin seems to be beneficial. Bilirubin is known to be a strong antioxidant and the protective effects of bilirubin on atherogenesis and [carcinogenesis] have been demonstrated in both ***in vitro*** *and* ***in vivo*** *studies."*

Eva Sticova, MD, et al
Institute for Clinical and Experimental Medicine, Prague
World Journal of Gastroenterology
19(2013):6398

Bilirubin, a byproduct of the breakdown of senescent red blood cells, is metabolized in the liver. There are two kinds of bilirubin: unconjugated (indirect) and conjugated (direct). The vast majority of individuals with isolated bilirubin elevations have a genetically mediated condition known as Gilbert syndrome.

Bilirubin is a potent antioxidant and antiinflammatory agent. While bilirubin levels tend to be lower in cigarette smokers, the adverse effects of low/below normal bilirubin impact both smokers and nonsmokers.

High normal/elevated bilirubin has been convincingly linked to a significantly lower risk of circulatory diseases, diabetes and other prevalent medical impairments. Conversely, low normal/below normal bilirubin levels are now a well-established marker for increased risk of these diseases and their complications.

Bilirubin has a strongly negative association with all-cause mortality. In other words, as bilirubin increases, the risk of death decreases. This has been demonstrated in ten clinical studies. The adverse implications of low normal/below normal bilirubin have also been documented in a major insurance industry study.

Based on the weight of evidence cited in this paper, a powerful argument can be made for changing our current approach to underwriting bilirubin in applicants who are free of liver disease and have normal liver enzymes readings.

Applicants with high bilirubin levels and/or Gilbert syndrome deserve consideration for credits in a preferred risk context. On the other hand, those with low normal/below normal bilirubin are ill-suited for preferred risk status. Moreover, applicants with frankly below normal levels are appropriate candidates for mortality risk debits.

Bilirubin Metabolism and Causes of Hyperbilirubinemia

Bilirubin is a byproduct of heme breakdown.

It is reported in mg/dL in the US and in SI units as mmol/L in other countries. The conversion factor from mmol/L to mg/dL is 17.104 (mmol/L ÷ 17.104 = mg/dL).

All bilirubin readings cited in this paper are reported in mg/dL.

Serum bilirubin is routinely reported on both clinical and insurance blood profiles/liver panels.

The basic metabolic pathway of bilirubin is shown in Figure 1 (on the following page).

During the breakdown of senescent red blood cells, the heme portion is further separated into biliverdin, iron (Fe) and carbon monoxide (CO) by the enzyme heme oxygenase. Biliverdin is then transformed into unconjugated (indirect) bilirubin by the enzyme biliverdin transferase.

Unconjugated bilirubin is not water soluble and requires a process called conjugation to become excretable by the body. Conjugation takes place in the liver, mediated by the enzyme UDP-glucuronyl transferase. Then, conjugated bilirubin is excreted via both the intestines (as bile) and the kidneys.

[Dennery, Guillemette, Jemnitz, Kirkby, Kundar]

Bilirubin is typically reported as total bilirubin, which is the sum of the indirect and direct fractions. Unless otherwise stated, “bilirubin” is synonymous with “total bilirubin” in this paper.

The main causes of elevated direct (conjugated) bilirubin are:

- Obstructive/cholestatic jaundice (cancer, bile duct stones, etc.)
- Micro-obstruction of the intrahepatic bile ducts (hepatitis, cirrhosis)
- Dubin-Johnson syndrome
- Rotor syndrome

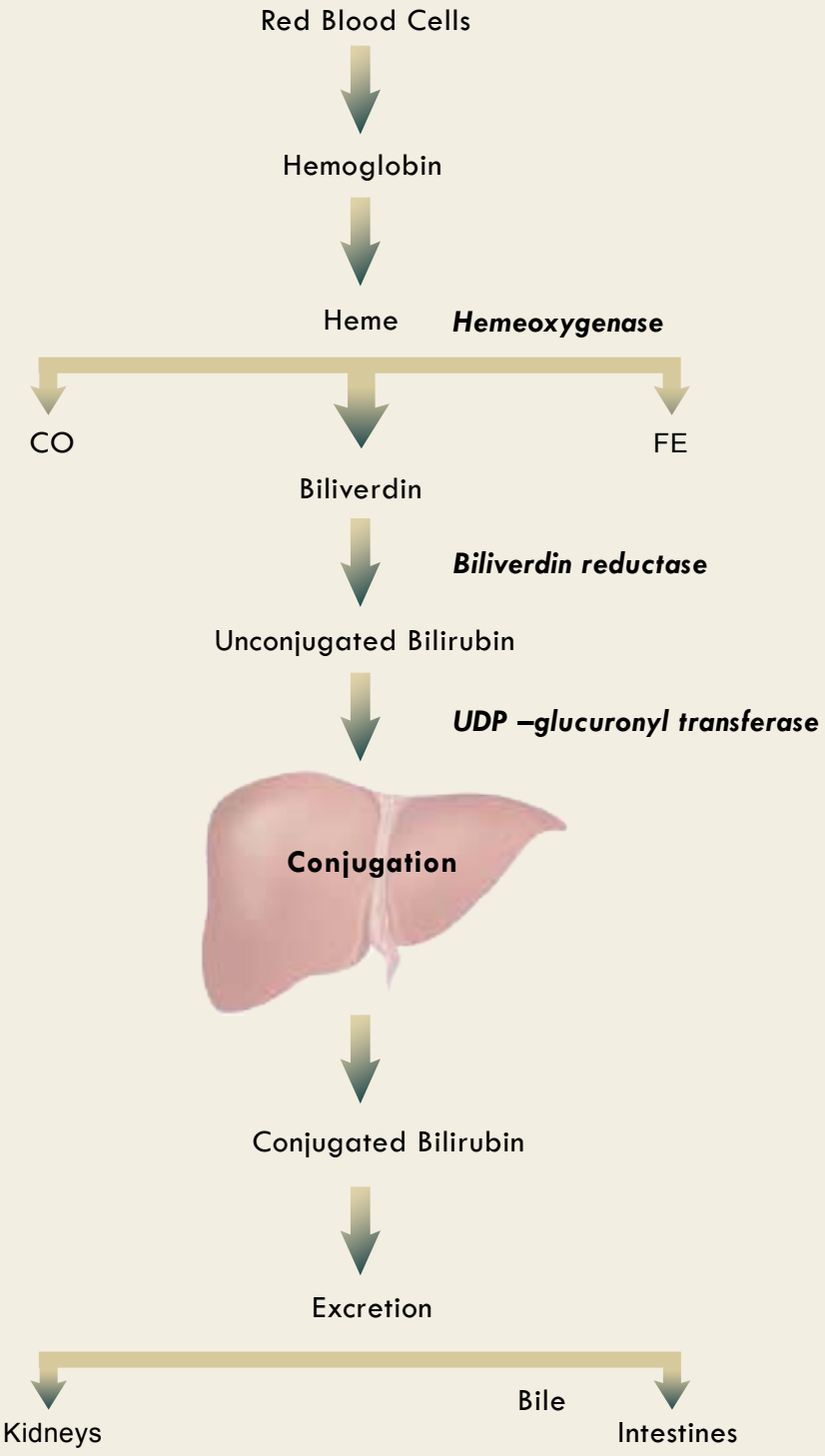
The causes of elevated indirect (unconjugated) bilirubin are:

- Gilbert syndrome
- Hemolytic anemias
- Crigler-Najjar syndromes 1 and 2 (rare)
- Toxic hyperbilirubinemia (rare)
- Neonatal jaundice (neonates only)

[Franchini, Levitt, Sticova]

In order for hemolytic anemia to account for elevated indirect bilirubin, it would have to be severe, reducing red blood cell survival from 120 days to roughly 16 days. Thus, the vast majority of isolated elevations of indirect bilirubin are due to Gilbert syndrome. [Levitt, VanWagner]

Figure 1: Bilirubin Metabolism



Genetics of Hyperbilirubinemia

A metaanalysis and subsequent research have confirmed that the main gene affecting bilirubin is *UGT1A1*. [Johnson, Rodrigues]

While there are other genes involved in this process, they have no significant underwriting implications, and a review of them is beyond the scope of this paper. [Sanna]

Mutations of the *UGT1A1* gene can lead to decreased expression or partial/complete inactivation of the bilirubin conjugating enzyme, UDP-glucuronyl transferase. Various *UGT1A1* mutations affecting unconjugated bilirubin account for neonatal jaundice, the Crigler-Najjar syndromes and Gilbert syndrome. [Lin-1, Sticova]

The *UGT1A1* test costs $75-$100 and is seldom used for diagnostic purposes. [VanWagner]

The *UGT1A1*28* mutation is associated with Gilbert syndrome. While it correlates with cardiovascular risks on a univariate basis, it is no longer significant after adjusting for the bilirubin level. It is unlikely that underwriters will see references to this or other *UGT1A1* mutations in applicants' medical records. [Lin-3, McArdle, Stender]

Gilbert Syndrome

Gilbert syndrome (GS) is a hereditary condition associated with intermittently elevated indirect bilirubin in the absence of liver disease or hemolysis.

The *UGT1A1**28 mutation is found in 35%-40% of Caucasians, but in fewer persons of Asian descent (11%-16%). [Sticova]

GS is present in 5%-10% of individuals of Western European origin, and most are likely unaware of having this condition.

In *UGT1A1*28* homozygotes, GS results in 70% less hepatic bilirubin conjugating activity, and there are lesser decreases (25%-30%) in heterozygotes. Homozygotes have lower levels of bilirubin excretion and increased serum bilirubin levels, primarily in the presence of certain aggravating factors. [Lin-1, Schwertner-3]

The main factor is fasting. Others include stress, menstruation, intercurrent illness, administration of certain pharmaceuticals and a short time interval following strenuous exercise. [Sticova, Swift, Teich]

Fasting alone can raise bilirubin in GS up to 3.0+ mg/dL, and fasting is sometimes used as a diagnostic test for the syndrome. [Levitt, Rodrigues]

Bilirubin is also inverse to BMI, being somewhat higher in underweight individuals. [Rodrigues, Vitek-2]

Mean total bilirubin (TB) levels in GS are typically 3-fold higher than in unaffected individuals. [Marubashi, Vitek-1] Maximum TB in GS is roughly 5 times normal and, in most cases, is ≤ 3 mg/dL. [Skierka]

Given its prevalence, GS accounts for the vast majority of isolated bilirubin levels in otherwise healthy insurance applicants.

Bilirubin, Oxidative Stress and Inflammation

Oxidative stress (excess reactive oxygen species) and inflammation are primary mechanisms in chronic disease. [Morita, Ross]

> ***"During the past few years the concept is emerging that bilirubin is involved in the pathogenesis of several disorders featured by enhanced systemic low-grade inflammation and increased oxidative stress."***
>
> **Petronella E. Deetman, et al**
> **University of Groningen**
> **Cardiovascular Diabetology**
> **12(2013):166**

> ***"Because of its antioxidant, antiinflammatory, and other biological properties, higher bilirubin concentrations could possibly prevent plaque formation and subsequent atherosclerosis."***
>
> **Jing-Ping Lin, MD, et al**
> **National Institutes of Health**
> **Clinical Chemistry**
> **56(2010):1535**

Bilirubin is widely recognized as a powerful antioxidant.

[Alamdari, Bulmer, Franchini, Vitek-1]

- It is more a far more potent antioxidant than vitamin E. [Dennery]
- Its antioxidant effect is minimal in the absence of higher serum bilirubin levels. [McCarty-2]
- LDL-C oxidation accounts for its atherogenicity, and this process is greatly inhibited by high bilirubin levels in Gilbert syndrome. [Berliner, Boon-1, Mayer]
- Bilirubin provides cytoprotection for cardiomyocytes and neurons, and inhibits both nitrate excess and renal damage. [Kirkby]
- Bilirubin levels are inverse to toxic heavy metals such as cadmium. [Pollack]
- Bilirubin also exerts antiapoptotic and antiproliferative effects. [Ollinger]

In a recent literature review, bilirubin was found to reduce the production of inflammatory pro-cytokines. [Kang-2]

Persons with Gilbert syndrome have significantly lower levels of interleukin-6 (a potent marker for inflammation), and bilirubin has modulatory effects on regulatory T-cell differentiation. [Rocuts, Wallner]

In addition, eight studies show a steeply inverse relationship between bilirubin and CRP/hs-CRP both in healthy persons and in those with diabetes, metabolic syndrome and other disorders.

[Deetman, Gullu, Hwang, Sung, Vitek-2, Yoshino, Yu, Zhang]

It is likely that the antioxidant, antiinflammatory and other favorable effects explain the relationships between bilirubin levels, disease risks and mortality.

Bilirubin and Cigarette Smoking

Tobacco smoking is predictive of lower antioxidant levels and is also associated with elevated CRP and other inflammatory markers. [Alberg]

There are conflicting data on the relationship between cigarette smoking and bilirubin levels.

In a study involving 48,040 healthy persons, age 30-87, Jo et al reported multivariate odds ratios for bilirubin being in the lowest quartile based on three cigarette smoking variables:

Cigarette Smoking Category	Odds Ratio
Smoking Amount (cigs/day)	
Never Smoker	1.0
1-9	1.1
10-19	1.5
≥ 20	1.8
Smoking Duration (years)	
Never Smoker	1.0
1-12	1.1
13-21	1.5
≥ 22	1.9
Pack Years	
Never Smoker	1.0
1-6	1.1
7-19	1.4
≥ 20	1.7

The impact of smoking on the likelihood of a low bilirubin level was greatest in those with BMI < 23, as well as in teetotalers and ex-drinkers.

In another study of 10,035 persons, age 25-74:

	Mean TB (mg/dL)
Never smoker	0.48
Ex-Smoker	0.47
Current Smoker	0.41
Non-Filtered	0.38
Filtered	0.43

The differences here are quite narrow, especially when distinguishing between filtered vs. non-filtered cigarettes. [Pascale]

Cigarette smoking status significantly altered the relationship between bilirubin and risk in 6 additional studies.

[Apperly, Ekblom, Frost-Pineda, Perlstein-1, Ryu, Schwertner-1,

On the other hand, bilirubin was independently significant after adjusting for cigarette use in 10 other studies.

[Horsfall-1, Huang-1, Ioannu, Lingenhal, Mashitani, Oda-1, Rantner, Targher, Temme, Troughton, Wang-1]

Quitting cigarettes has now been shown to increase bilirubin levels. [O'Malley]

New data from ExamOne, based on age and gender, consistently show higher percentages of cotinine-negative (vs. cotinine-positive) applicants in the subset with elevated bilirubin readings. [Lansrath, personal communication, January 9, 2015]

Fulks et al made the following observation regarding smokers and bilirubin in the CRL bilirubin mortality study:

"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."

Clearly, cigarette smokers are prone to have lower bilirubin readings than nonusers and ex-smokers. Nevertheless, the impact of cigarette use status does not explain most of the differences in disease and mortality risks associated with bilirubin levels.

Bilirubin and Other Laboratory Tests

Bilirubin levels significantly correlate in a negative manner in these lipid tests:

- Small dense and oxidized LDL-C
- Triglycerides
- Apolipoprotein B
- Remnant lipoprotein cholesterol (RLP-C)

[Dullart, Kamisako, Ocadlik, Oda-2, Tapan, Troughton, Yesilova]

Conversely, they correlate positively with HDL-C, including large particle HDL-C. [Dullart]

When bilirubin is added to the TC:HDL-C ratio, it improves the diagnostic sensitivity from 40.4% to 52.1% in subjects undergoing angiography. [Schwertner-2]

Bilirubin does not correlate with liver enzyme levels in healthy individuals. [Horsfall-2, Kim-3, Li]

Bilirubin decreases with serum albumin in persons with chronic diseases. [Levitt]

Bilirubin is negatively associated with HbA1-c levels in both diabetics and nondiabetics. [Han, Kim-1, Lin-2, Ohnaka, Wang-2]

Bilirubin is inverse to eGFR, and the risk of eGFR < 30 is 3.5-fold greater in the 1st vs. 4th bilirubin quartile. [Kawamoto-2, Mashitani, Tanaka-2, Targher]

Bilirubin is also inverse to urinary albumin excretion. [Fukui-1, Mashitani]

In a 3.2-year follow-up of T2 diabetics, subjects in the 1st bilirubin quartile had a 5.8-fold greater risk of manifesting significant albuminuria, as compared to those in the top quartile. [Okada]

Red blood cell distribution width (RDW) is now a well-established risk factor for many diseases and all-cause mortality. [George]

Bilirubin is inverse to RDW, as well as hemoglobin. [Mashitani, Rodrigues]

The foregoing relationships between bilirubin and commonly used laboratory tests are consistent with the premise that bilirubin is inverse to the risk of major diseases and excess mortality.

There is a great deal of heterogeneity in the studies cited in the following sections of this paper.

They vary widely in terms of adjustments, from age and gender only to encompassing conventional risk factors and inflammatory markers, as well as health habit/demographic variables that we do not use in risk appraisal.

In addition, studies delineating risk based in broader groupings, such as tertiles, do not adequately reflect the true impact of low/below normal and high normal/elevated bilirubin levels.

Bilirubin and Circulatory Diseases

"Increasing evidence has demonstrated that mild to moderate increases in the serum bilirubin concentration, even within the normal range, are associated with a reduced risk of CVD…"

Eun Sook Kim, MD, et al
College of Medicine
Catholic University of Korea
PLoS One
9(2014):e109251

"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 partially explained by smoking."

Fulks, et al
Op. Cit.

Coronary Artery Disease

"The inverse association of serum total bilirubin with coronary artery disease (CAD) suggests that the antiinflammatory and antioxidant properties of bilirubin may offer protection from atherosclerosis."

Todd S. Perlstein, MD, et al
Harvard Medical School
Arteriosclerosis, Thrombosis and Vascular Biology
28(20089):166

The PRIME Study is a prospective assessment of the risk of CAD. Over a 5-year interval, 216 subjects who developed CAD were matched to 216 CAD-free controls. The fully adjusted CAD risk was 30% lower in the 2nd as compared to the 1st quintile, and the risk continued to decline in the remaining quintiles. Bilirubin < 0.33 was an independent risk factor for CAD. [Troughton]

In the PREVEND Study of 7,222 subjects followed for 9 years, there was an independent log-linear inverse relationship between bilirubin and CVD risk in males and a trend in this direction in females (insufficient interim CVD diagnoses).

The authors concluded *"…overall evidence from this study supports the possibility that mildly elevated circulating total bilirubin levels might protect from CVD events in the general population."* [Kunutsor]

The Rotterdam Study did not find a significant association between bilirubin and CAD. However, this study consisted of subjects with a mean age of 70 and was likely impacted by survival bias. [Bosma]

In a small 277-subject study of subjects with premature CAD matched to CAD-free controls (mean age 55), the risk of CAD decreased 10% in males and 25% in females per 0.1 md/dL increase in bilirubin. [Lingenhal]

Among patients with Gilbert syndrome, the prevalence of CAD was 2%, as compared to 12.1% in the general population. The low risk here was largely attributable to their higher bilirubin levels. [Vitek-4]

Five investigations centered on patients undergoing angiography.

In a 2,862-patient cohort of men free of known CAD who underwent CT angiography, the prevalence of significant (≥ 50%) stenosis was 27.9% when bilirubin was ≤ 1.2 vs. 19.9% at higher levels. [Kang-1]

When 1,115 patients had 64-slice CT angiography, bilirubin was significantly lower if they had: [Canpolat]

- Any coronary plaque
- Primarily non-calcified or mixed plaque lesions
- Critical vs. non-critical stenoses

In a Chinese study of 1,320 CAD patients matched to CAD-free controls, there was an inverse association between bilirubin and angiographic CAD in men only. [Endler]

Similar results were reported in two other studies. [Nguyen, Turfan]

Bilirubin and Myocardial Infarction

An 11-study metaanalysis showed a significant difference in MI risk between the 3rd vs. 1st tertile of total bilirubin. The fully adjusted risk was 10% lower in the top tertile. This is an example of where fractionating into tertiles fails to demonstrate the magnitude of the difference in subjects with very low vs. elevated readings. [Stender]

Arguably the best investigation of MI/CV death and bilirubin comes from the Framingham Offspring Study. They followed 4,276 individuals, mean age 38 and free of MI history at baseline, for 22 years. [Djousse] This is what they found in terms of MI/CV death by bilirubin quintiles after multivariate adjustment:

Quintile	Risk Ratio
1	1.00
2	0.65
3	0.55
4	0.81
5	0.61

In 618 patients experiencing a first MI, bilirubin was significantly lower in cases when matched to MI-free controls. This was not significant after adjustment. However, adjustments included iron, TIBC, ferritin, cystatin C and homocysteine. [Ekblom]

Except for a handful of carriers now screening with cystatin C, these other potent markers for oxidative status and MI risk are not used in insurance or adjusted for in most clinical studies, and they likely accounted for the failure of bilirubin to remain significant after adjustment.

Bilirubin post-PCI

In 544 consecutive PCI patients followed for 3 years, all-cause and cardiac deaths were markedly lower in those with higher bilirubin levels:

Bilirubin	All-Cause Deaths	Cardiac Deaths
≤ 0.5	24.9%	15.6%
> 0.5 - ≤ 0.7	17.7%	8.8%
> 0.7	8.2%	4.8%

The odds ratio for the risk of new cardiac events was 11.82 for low vs. high bilirubin and

4.87 for mid-range vs. high readings. [Huang-1]

In 372 PCI patients, the cardiac death rate over 26 months was 10.4% with low bilirubin, as compared to 0.6% when bilirubin was high, leading the researchers to describe bilirubin as a *"predictive marker."* [Kim-2]

A third PCI study showed that the percentage of patients with diabetes was almost twice as high (49%) in those with bilirubin ≤ 0.5 as it was when bilirubin was 0.7 (27%).

In-stent restenosis is a major PCI complication. [Stettler]

After following 1,076 PCI patients for 236 days, the incidence of this high-risk event was 31% in the 1st bilirubin quartile and 16% in the 4th quartile. [Kuwano]

Bilirubin and Coronary Artery Calcium (CAC) Score

Zhang et al performed CT CAC scoring on 3,408 males. Each 0.1 mg/dL increase in bilirubin significantly reduced the risk of a score > 100, and low bilirubin was an independent risk factor for a high CAC score in this large cohort.

In another investigation, a 0.5 mg/dL decrease in bilirubin increased the odds of a CAC score ≥ 400 by 14%. [Tanaka-1]

Sung et al showed that the percentage of subjects with a CAC score > 0 was 11.2% in the 1st bilirubin quartile vs. 8.5% in the 4th quartile.

Bilirubin and Other Cardiac Issues

The odds ratio for a Framingham Risk Score ≥ 10% was steeply inverse to bilirubin readings after full CV risk factor adjustment. [Kim-4]

In 108 consecutive subjects said to have chest pain with normal coronary arteries (cardiac syndrome X), the risk of cardiac events after 5 years was lowest in the top bilirubin tertile. [Huang-2]

In 376 patients with dyslipidemia, bilirubin was an inverse and independent risk factor for CAD and stroke in male smokers. There was a trend of lower risk in nonsmokers, but there were too few nonsmokers with CV consequences for this to attain statistical significance. [Ganotakis]

In persons with familial hypercholesterolemia, bilirubin was inverse to the risk of CV disease. [de Sauvage Nolting]

Patients taking statins for hyperlipidemia were less likely to experience a CV event if their bilirubin was ≥ 0.58, as compared to ≤ 0.29. [Horsfall-4]

Two studies have demonstrated a substantially lower risk of thrombosis because high bilirubin lessened the risks of platelet activation and complement activation, respectively. [Basiglio, Kundar]

Bilirubin and Markers for Subclinical Atherosclerosis

Arterial stiffness is a risk factor for progression of CV disease. Pulse wave velocity (PWV) is reliable measurement of the extent of arterial stiffness. [Laurent]

Three studies have shown a favorable relationship between PWV and high bilirubin in diabetics or survivors of acute coronary events. [Fukui-1, Kim-1, Tanindi]

Arslan et al reported significantly less arterial stiffness based on aortic PWV in persons with Gilbert syndrome.

Caliskan et al found greater aortic stiffness and impaired elasticity in patients with low bilirubin.

Flow-mediated dilatation (FMD) is a marker for endothelial dysfunction. Two investigators reported significantly greater FMD, consistent with superior endothelial function, in Gilbert syndrome subjects; a third study revealed that FMD is 35% less in males and females with low bilirubin. [Erdogan, Marubashi, McArdle]

Coronary flow reserve (CFR) is another marker for endothelial function. Based on transthoracic echocardiography with color Doppler flow mapping, CFR was significantly greater (more favorable) in healthy subjects with bilirubin ≥ 1 mg/dL. [Gullu]

Advanced glycation end products (AGE) are major contributors to atherosclerosis. Gilbert syndrome is associated with lower AGEs after adjustment for possible modifiers. [Kalousova]

Bilirubin and Cerebrovascular Disease

A study of 849 elderly patients, mean age 80, explored the relationship between bilirubin levels and both carotid intima-media thickness (CIMT) and carotid plaque, using ultrasound. These are the findings:

Multivariate Odds Ratios

Bilirubin Quartile	CIMT ≥ 1 mm		Carotid Plaque Present	
	Males	Females	Males	Females
1	1.00	1.00	1.00	1.00
2	0.38	0.40	0.47	0.41
3	0.43	0.61	0.53	0.51
4	0.29	0.43	0.25	0.46

Low bilirubin was a significant predictor of adverse findings using both benchmarks for risk of cerebrovascular events. [Kawamoto-1]

Two more studies affirm this adverse relationship between low bilirubin and CIMT. [Vitek-5, Yang-1]

In 13,214 healthy persons, the risks of stroke and adverse outcomes from cerebrovascular events were 45% less in those with bilirubin in the top tertile. For every 0.1 mg/dL increase in bilirubin, the stroke risk was decreased 9%, after full risk factor adjustment. [Perlstein-2]

In 78,724 healthy persons followed for 14 years, there was a steeply inverse relationship between bilirubin and the risks of ischemic and hemorrhagic stroke. [Kim-3]

Li reported silent cerebral infarctions in 21.3% with bilirubin in the 1st quartile, as compared to 5.4% in the 4th quartile.

Ode showed a 60% decreased stroke risk in 3,375 male subjects with high bilirubin.

Bilirubin and Peripheral Arterial Disease (PAD)

In 7,075 healthy subjects, a 0.1 mg/dL increase in bilirubin correlated with a 6% reduction in the likelihood of PAD. [Perlstein-1].

Four other studies reveal similar associations between bilirubin and the risk of PAD, as well as for predicting disease severity and progression. [Breimer, Krijsman, Rantner, Wang-1]

The inverse relationships between bilirubin levels and the risks of CAD, cardiac events, markers for subclinical atherosclerosis, cerebrovascular disease and PAD have been extensively documented in clinical studies.

Bilirubin and Diabetes Mellitus

Bilirubin and Markers for Glucose Metabolism

Four studies show an inverse relationship between bilirubin and HOMA-IR score. [Deetman, Lin-2, Ryu, Sung]

Ryu et al reported an inverse association between bilirubin and insulin secretion.

Two studies show an inverse relationship between bilirubin and insulin resistance. [Guzek, Wu]

Bilirubin and Risk of Diabetes

After following 15,876 healthy subjects, a 0.6 mg/dL increase in bilirubin was linked to a 20% lower risk of T2 diabetes. [Cheriyath]

Ohnaka et al assessed 12,400 middle-aged/older persons and reported a 27% lower probability of a T2 diabetes diagnosis in the 4th vs. 1st quartile of bilirubin.

Abbasi et al found a similar lessening of the odds of T2 diabetes in 3,381 subjects, age 28-75.

Li et al looked at 2,865 individuals, mean age 50, and showed a 22% prevalence of T2 DM in the 1st bilirubin quartile, as compared to a 5% prevalence in the top quartile.

Jung et al reported a 31% lower risk of T2 DM in the 4th vs. 1st bilirubin quartile.

Bilirubin and Diabetes Complications

Najam et al followed 1,761 subjects ≥ age 40. Those in the 4th quartile (bilirubin > 0.99 mg/dL) had a 45% lesser risk of retinopathic changes than those in the 1st quartile.

Two other studies showed similar findings. [Mashitani, Sekioka]

The odds ratio of chronic kidney disease in diabetics was 12% lower in males in the 5th quintile of bilirubin and 32% lower in females in this quintile. [Han-2]

Mashitani et al found that the risk of nephropathy progression was 57% lower in the top bilirubin quartile vs. the 1st quartile in 2,511 diabetics followed for 504 days.

In another study, the mean bilirubin in patients on hemodialysis was 0.30 vs. 0.74 in those who did not require this end-stage renal disease intervention. [Fukui-2]

In a 2,991-patient T2 DM cohort, the multivariate risk of cardiovascular autonomic neuropathy was 64% lower in the 3rd vs. 1st bilirubin quintile. [Chung]

Chan et al showed that bilirubin levels were a major predictor of the risk of lower limb amputation after adjusting for microvascular complications, smoking, GGT, HbA1-c, etc. There was greater than a 3-fold risk gradient across bilirubin levels, with the highest risk in those with low readings.

Inoguchi et al reported that diabetic patients with Gilbert syndrome had 80% lower prevalences of coronary disease, retinopathy and macroalbuminuria. Mean HbA1-c was

7.10% with GS vs. 7.78% in its absence. The percentages of smokers were the same in both groups.

In a 1,711 T2 DM subject cohort, mean age 57, the risk of a high Framingham Risk Score was 1/3rd lower in the top vs. 1st bilirubin tertile. [Kim-1]

Bilirubin has a multidimensional association with the risk of type 2 diabetes, as well as major parameters defining its insurability.

Bilirubin and Other Prevalent Disorders

Bilirubin and Metabolic Syndrome

One team of researchers stated that low bilirubin is an *"early biomarker indicating asymptomatic individuals at increased risk of developing metabolic syndrome."* [Jenko-Praznikar]

This statement is well supported in the literature.

Choi et al followed 12,342 healthy adults, age 20 and older. High bilirubin in males (0.90) and females (0.71) correlated with a 26% lower incidence of metabolic syndrome diagnoses. Bilirubin was negatively associated with the number of metabolic syndrome criteria present.

Six additional studies affirm the inverse relationship between bilirubin and metabolic syndrome in adolescents and adults. [Guzek, Kwon, Lin-2, Song, Ryu, Wu]

Bilirubin and Liver Diseases

Kwak and coworkers did routine physical examinations on 17,348 persons and included abdominal ultrasound in their assessments.

The risk of apparent nonalcoholic fatty liver disease (NAFLD) was 20% lower in the 4th vs. 1st bilirubin quintile, after adjusting for other NAFLD risk factors.

Salomone et al showed a significantly increased likelihood of both moderate/severe necroinflammatory disease and advanced fibrosis in NAFLD patients with low bilirubin. These pathological findings are consistent with non-alcoholic steatohepatitis (NASH).

Similarly, another study of 641 patients with NAFLD found an inverse association between bilirubin levels and disease severity. [Hjelkrem]

In children with NAFLD, low bilirubin correlated with a high NAFLD activity score, and those with high bilirubin had a 71% lower probability of NASH. [Puri]

Bilirubin has now been shown to have risk implications in chronic hepatitis C.

In 112 patients with genotype 1b chronic HCV, those with advanced fibrosis had a mean indirect bilirubin level of 0.28 vs. 0.44 in patients free of this cirrhosis precursor, after full risk factor adjustment. [Cengiz]

Bilirubin is emerging as a significant risk predictor in the world's most prevalent liver disorder (NAFLD) and may also have implications for chronic hepatitis C.

Bilirubin and Cancer

Follow-up with 68,676 subjects undergoing a routine medical assessment showed the risk of a lung cancer diagnosis was 2.8 times greater if bilirubin was 0.2-0.7 vs. ≥ 1.0. The protective effect of elevated bilirubin was highest in smokers, but was also present in never- and ex-smokers. [Lim]

In a case-control study, every 0.1 mg/dL increase in bilirubin was linked to a 5% lower

lung cancer incidence in smokers only. [Wen]

Ching et al revealed that the likelihood of breast cancer was twice as high in the 1st bilirubin quartile, as compared to the other three quartiles.

Shatalova et al found that subjects with high bilirubin had a 2.6-fold greater probability of having of low (vs. high) grade breast carcinoma.

In 2,425 Caucasian females diagnosed with non-metastatic breast cancer, overall 5-year survival was superior in those with high bilirubin. High levels correlated with a 38% lower risk of death. [Liu]

In the 3rd NHANES study, high bilirubin was associated with a *"markedly decreased prevalence"* of colorectal cancer (hazard ratio 0.257). [Zucker]

Another study showed a 7% reduction in colorectal cancer risk for every 0.58 mg/dL increase in bilirubin. [Jiraskova]

Lacko et al reported that low bilirubin increased the risk of head and neck carcinoma.

Franchini suggested that the reduced risk of cancer in persons with high bilirubin is likely due to bilirubin's inhibiting effects on major carcinogens, such as polycyclic aromatic hydrocarbons, heterocyclic amines and various oxidants.

Evidence to date suggests that bilirubin is an evolving marker for aspects of cancer risk.

Bilirubin and Lung Diseases

Apperly et al looked at COPD disease progression in 4,680 smokers at baseline, followed for 11 years.

> ***"Bilirubin is inversely related to COPD disease severity and progression. Higher bilirubin was associated with a higher FEV_1 and less annual decline in FEV_1. These data support the hypothesis that bilirubin is protective against COPD progression… [and] bilirubin may prove useful as an easily accessible and readily available blood based COPD marker."***
>
> **Scott Apperly, MD, et al**
> **Department of Pulmonary Medicine**
> **University of British Columbia Medical School**
> **Chest**
> **E-published January, 2015**

In this investigation, bilirubin was significant in those who quit smoking, as well as in those who continued indulging their habit.

In another study, high bilirubin was linked to more favorable timed vital capacity and FEF 25-75 midflow rate. [Curjuric]

In a long-term follow-up of a 2,196-subject 1946 UK cohort, those with Gilbert syndrome had higher FVC and FEV_1, and these effects were strongest in heavy smokers. The odds of chronic respiratory disease were 50% less in persons with GS. [Horsfall-3]

Misso et al reported that low bilirubin increased the risk of severe asthma by 31%.

Bilirubin in Additional Disorders

Two studies showed a substantially lower risk of Crohn disease in those with high bilirubin. [Lenicek, de Vries]

In 218 systemic lupus erythematosus (SLE) patients with normal liver function, matched to SLE-free controls, each 0.58 mg/dL decrease in bilirubin increased the risk of systemic lupus 37%. In those with Gilbert syndrome, this risk was decreased 77%. The authors described GS as potentially protective against developing SLE. [Vitek-3]

In another SLE study, bilirubin was inverse to the odds of renal involvement, after adjusting for other prevalent risk factors. [Yang-2]

Fischman et al found that the risk of rheumatoid arthritis was inverse to bilirubin in 8,147 general population subjects.

Cho et al reported low bilirubin levels in 45% of patients with proven osteoporosis.

Qin et al showed that low bilirubin was a significant predictor of Parkinson disease, especially cases diagnosed within 2 years and/or in patients not as yet taking PD pharmacotherapy.

In another study, mildly elevated bilirubin was described as broadly protective against the development of chronic degenerative diseases. [Boon-2]

Functional independence, a critical consideration in elder mortality, has also been linked to bilirubin. In 2,235 subjects, the risk decreased significantly across bilirubin quartiles. [Kao]

Bilirubin and Mortality

There are seven published studies on bilirubin and mortality in the medical literature (excluding insurance industry studies, which will be discussed separately below).

Temme et al looked at 10-year mortality in a cohort of 10,303 Belgians enrolled in a nutrition and health study.

The adjusted (including smoking) hazard ratio for all-cause death was 0.73 in the highest (≥ 0.6) vs. lowest (≤ 0.2) subset. The hazard ratio for cancer mortality was 0.42 between these two bilirubin groupings. CV mortality was not significantly different.

In the largest study comparing Gilbert syndrome to controls, 4,266 GS patients were matched to 21,968 GS-free individuals and followed prospectively for a decade. The adjusted (including smoking) all-cause mortality risk ratio for GS cases was 0.53. [Horsfall-2]

In the Rancho Bernardo study, Boland et al followed 2,364 relatively affluent elderly (mean age 70) Californians for 13.7 years. The mean bilirubin reading in survivors was 0.68 vs. 0.48 in those who died during follow-up. Mortality in the top bilirubin quartile was 13% lower than in the 3rd quartile.

A South Carolina investigation tracked 1,279 healthy subjects, age 30 to 82 at baseline, for 17 years. After adjustments (including treadmill exercise time, abnormal ECG changes and family history), all-cause mortality was 27% lower in the top bilirubin quartile, and CVD mortality was 39% less. [Ajja]

These South Carolinian researchers also looked at the impact of physical fitness on bilirubin-related mortality:

	Bilirubin Quartiles	All-Cause Mortality	CVD Mortality
Low Fitness	Q1-Q3	1.00	1.00
	Q4	0.86	0.72
High Fitness	Q1-Q3	0.70	0.70
	Q4	0.55	0.46

High bilirubin in both low and high fitness contexts was associated with superior mortality in the 4th vs. first three quartiles.

Apperly et al in British Columbia studied the impact of bilirubin on mortality in 4,680 smokers with mild-to-moderate airflow limitation.

The top quintile included bilirubin levels ranging from 0.58 to 2.10; in that subset, all-cause mortality was 17% lower in the 5th vs. 4th quintile.

In a 3-year follow-up of 995 subjects, mean age 76, the mortality hazard ratio in the top bilirubin tertile was 0.64. [Han-1]

In a UK investigation, 130,052 patients on statin Rx were followed prospectively for 43 months. After adjusting for CV risk factors, social deprivation and other demographics, all-cause mortality was 33% higher in those in the 1st decile (bilirubin ≤ 0.3), as compared to the 5th decile.

The authors made the following comment about their findings:

"Serum bilirubin is a cheap and routine test that captures risk information beyond that of conventional CVD risk factors recorded before statin prescription."

Laura J. Horsfall, MD, et al
University College, London
Circulation
126(2013):2556

In these studies, all-cause mortality was consistently highest in those with low bilirubin readings and lowest in those with high bilirubin levels.

Bilirubin: Cause or Marker for Mortality?

> ***"The distinct inverse correlation between serum bilirubin concentrations and CHD risk may have important clinical implications. [It is]… a new reliable marker of cardiovascular risk that can be measured easily in the clinical laboratory and applied in medical practice."***

Massimo Franchini, et al
Department of Pathology and Laboratory Medicine
University of Parma, Italy
Advances in Clinical Chemistry
50(2010):47

Levitt and Levitt argue that *"it will be important to determine if lower serum bilirubin concentrations are a cause or an effect of ill health… low UB [may] simply be a marker of the propensity to develop disease."*

According to Mayer et al *"another possibility is that low bilirubin concentrations per se are not a major causative factor… but rather a reflection of the presence of this ailment (CAD)."*

Kronenberg maintains that additional long-term studies need to be done to assess causality.

Kundar believes that understanding the mechanisms by which Gilbert syndrome favorably influences well-being and longevity *"…could play a crucial role in the development of a therapeutic drug influencing bilirubin concentrations, which could not only prevent CVD, but assist in improving recovery from myocardial infarction."*

Other investigators have also called for research to develop interventional strategies, including gene therapy, because of what is now known about the advantages conferred by both high bilirubin and the Gilbert syndrome. [Hoekstra, McCarty-1, Perlstein-2, Ryter, Vitek-2]

It is clear from the foregoing that clinical medicine is concerned about whether bilirubin's role is causal (vs. being just a marker) because only causation would justify developing treatments to raise low bilirubin in high-risk patients.

The distinction between being a marker vs. a cause has no direct bearing on underwriting. For us, it is sufficient to establish that both low normal/below normal and high normal/elevated bilirubin significantly impact mortality independent of those factors we currently use to assess risk.

Insurance Industry Studies

In 2009, a study titled "Liver Function Tests and Mortality in a Cohort of Life Insurance Applicants" by Pinkham and Krause (Swiss Re) was published in the Journal of Insurance Medicine. [41(2009):170]

It was based on 560,000 insurance applications with blood profiles obtained between 1995 and 2004. Mean age was 42.6 years.

This study is a major contribution to the insurance literature, primarily as it pertains to the implications of elevated ALT, AST and GGT.

Regarding bilirubin, there were 190 deaths among 15,239 applications with readings of 1.6 mg/dL or higher. According to the authors, some of these cases could have had other elevated LFTs.

Elevated bilirubin in this range did not significantly impact mortality after adjustment for multiple variables, including smoking status and liver enzymes. [Krause, personal communication, 2/23/15]

Low normal/below normal bilirubin was not included in their analysis.

A somewhat similar study by Hu and Duncan, titled "Associations between Selected Laboratory Tests and All-Cause Mortality," was published in JIM in 2013. [34(2013):208]

These investigators looked at one insurer's experience, encompassing 311,535 policies and 837 deaths, with an average follow-up of 4.5 years.

They reported the following hazard ratios for quartiles of bilirubin and "abnormally high" (≥ 0.92) and "abnormally low" (≤ 0.83) readings.

These finding are adjusted only for age and gender, and therefore do not account for the impact of other liver test results.

Quartile (Bilirubin Range)	Risk Ratio
1 (0.2-0.4)	1.00
2 (0.41-0.59)	0.88
3 (0.60-0.79)	1.06
4 (0.8-1.20)	0.89
Abnormally High	0.92
Abnormally Low	0.83

The confidence intervals here are quite wide, and these findings are not statistically significant. [Lanzrath, personal communication, 2/6/15]

In terms of bilirubin mortality, the most instructive paper, by Fulks et al, was published in JIM in 2009. [44(2009):49]. It is based on 1,905,664 insurance applicants.

Mortality was roughly 2.6-fold greater for subjects with bilirubin of 0.3, as compared to those with readings between 1.1-1.3.

The authors make this important comment:

"Our results… 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% in all 3 age/sex groups."

This paper affirms the substantial excess

mortality in applicants with low normal/below normal bilirubin.

Bilirubin: Underwriting Implications

The two questions targeted for resolution in this review paper have been answered:

1. High normal/elevated bilirubin and the Gilbert syndrome – absent other elevated liver-related tests and a history of chronic hepatobiliary disease – are associated with significantly lower mortality risk.

2. Low normal/below normal bilirubin confers significantly increased mortality.

The view has been expressed that *"using low bilirubin as a mortality predictor is likely not warranted since we already evaluate smoking, hypertension and cardiovascular risk factors during underwriting."* [CRL bulletin doc. 0409089]

The weight of evidence presented here challenges this perception.

It is clear that low normal/below normal bilirubin independently increases all-cause mortality to the extent that it is necessary to reflect its impact in our underwriting practices.

Based on a bilirubin reference range of 0.3-1.1 mg/dL, this underwriter believes the following practices are consistent with the findings in this review:

1. Applicants with bilirubin ≤ 0.3 should not be eligible for preferred risk coverage. Moreover, it is appropriate to consider assigning debits when readings are ≤ 0.2.
2. Applicants with isolated bilirubin levels between 1.2-3.0 mg/dL and those with Gilbert syndrome should get credits applied against debits for medical preferred risk criteria, as well as for offsetting CV risk factor debits in other appropriate contexts.

To clarify current bilirubin underwriting practices, we asked chief underwriters from 19 companies (having their own life underwriting manuals or internal guidelines for assessing liver tests) to complete a three-question survey. Twelve complied with this request.

This is a brief synopsis of their responses:

1. No respondents give applicants with Gilbert syndrome credits against debits for other CV risk factors.
2. Two carriers rate applicants with bilirubin elevations < 3.0, five rate at 3.0, and the other five have various practices, all of which appear to result in assessing debits for elevated bilirubin between 3.0 and 4.5.
3. Ten companies do not assign debits for low normal or below normal bilirubin. One would be "concerned" about "very low bilirubin" in non-smokers only. The other would "investigate and rate for cause."

Hopefully, this paper will motivate at least some life insurers/reinsurers to rethink their approach to bilirubin underwriting.

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