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Association of Serum Bilirubin with SYNTAX Score and Future Cardiovascular Events in Patients Undergoing Coronary Intervention

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Background: Bilirubin has emerged as an important endogenous antioxidant molecule, and increasing evidence shows that bilirubin may protect against atherosclerosis. The SYNTAX score has been developed to assess the severity and complexity of coronary artery disease. The aim of this study was to evaluate whether serum bilirubin levels are associated with SYNTAX scores and whether they could be used to predict future cardiovascular events in patients undergoing coronary intervention.

Methods: Serum bilirubin levels and other blood parameters in patients with at least 12-h fasting states were determined. The primary endpoint was any composite cardiovascular event within 1 year, including death, nonfatal myocardial infarction, and target-vessel revascularization.

Results: In total, 250 consecutive patients with stable coronary artery disease (mean age 70 ± 13) who had received coronary intervention were enrolled. All study subjects were divided into two groups: group 1 was defined as high SYNTAX score (> 22), and group 2 was defined as low SYNTAX score (≤ 22). Total bilirubin levels were significantly lower in the high SYNTAX score group than in the low SYNTAX score group (0.51 ± 0.22 vs. 0.72 ± 0.29 mg/dl, $p < 0.001$). By multivariate analysis, serum total bilirubin levels were identified as an independent predictor for high SYNTAX score (adjusted odds ratio: 0.28, 95% confidence interval 0.04-0.42; $p = 0.004$). Use of the Kaplan-Meier analysis demonstrated a significant difference in 1-year cardiovascular events between high (> 0.8 mg/dl), medium (> 0.5, ≤ 0.8 mg/dl), and low (≤ 0.5 mg/dl) bilirubin levels (log-rank test $p = 0.011$).

Conclusions: Serum bilirubin level is associated with SYNTAX score and predicts future cardiovascular events in patients undergoing coronary intervention.

Key Words: Cardiovascular events • Serum bilirubin • SYNTAX score

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INTRODUCTION

Oxidative stress plays an important role in atherosclerosis.[1-3] Bilirubin, once considered simply the metabolic end-product of heme degradation by heme-oxygenase, has proven to be a potent antioxidant by inhibiting both lipid and protein oxidation.[4-6] A growing body of evidence has confirmed the relationship between bilirubin and peripheral artery disease and carotid intima-media thickness.[7-9] Several studies have noted an inverse relationship between coronary artery disease and circulatory total bilirubin.[10,11] Bilirubin has also been

proven to act against plaque formation in coronary artery disease.[12]

The SYNTAX score is a comprehensive anatomic scoring system based on the coronary angiogram. SYNTAX score represents lesion complexity, and has been shown to be a useful tool for decision-making and for estimating prognoses among patients who have undergone coronary revascularization.[13-15] Given the remarkable antioxidant and anti-inflammatory properties of bilirubin, and the critical role of oxidative stress in the pathogenesis of coronary artery disease, we have investigated whether serum bilirubin level is associated with the SYNTAX score levels and whether it can be used to predict future cardiovascular events among patients with stable coronary artery disease undergoing coronary intervention.

METHODS

Study participants

From January 2009 through December 2011, we consecutively recruited 250 patients who were referred to the Catheterization Center of Taipei Veterans General Hospital for coronary angiography on account of angina and/or suspected coronary artery disease (CAD). Patients were excluded if they had acute coronary syndrome including acute myocardial infarction or unstable angina during hospitalization, uncontrolled decompensated heart failure, unstable hemodynamic status, chronic liver disease, end-stage renal disease, chronic systemic inflammatory disease, or malignancy with an expected life span of less than 1 year. Baseline demographic data were recorded at the time of recruitment, and all patients were enrolled by the same physician to minimize inter-observer variations. The study was approved by the research ethics committee of Taipei Veterans General Hospital, and all participants provided written informed consent.

Clinical evaluation

Medical history, including cardiovascular risk factors, previous and present cardiovascular events, and current medication regimen, was obtained during a personal interview and from medical files. All the measurements were made at the medical center after an overnight fast of at least 8 hours. Weight, height, and waist circumference were measured and BMI was calculated. Brachial blood pressure was measured by a physician with a mercury sphygmomanometer after patients sat for 15 minutes or longer. The average of 3 SBP measurements was used for the analysis.

Laboratory measurements

Venous blood samples were collected from all patients for measurement after 8 hours of overnight fasting. The plasma and serum samples were stored at -80 °C until use. Biochemical parameters including total bilirubin, total cholesterol, triglyceride, low-density lipoprotein-cholesterol (LDL) and high-density lipoprotein-cholesterol (HDL), fasting blood glucose, creatinine, and uric acid were determined using commercial kits and a Hitachi 7600 autoanalyzer (Roche Modular; Hitachi Ltd, Tokyo, Japan). Each standard and plasma sample was analyzed twice, and the mean value was used in all subsequent analyses. The intra-assay and inter-assay variation coefficients of the tests were < 10%.

SYNTAX score calculation

Two expert angiographers, who were unaware of the patients' clinical and laboratory data, independently reviewed the coronary angiographies. Each coronary lesion with a diameter stenosis of at least 50%, in vessels of at least 1.5 mm, was scored. The latest updated version of the algorithm found online was used for the calculation of the SYNTAX scores (http://www.Syntaxscore.com). The patients were then divided into different groups according to their SYNTAX score.

Prospective follow-up and study end-points

After the baseline investigation, patients were followed prospectively until the study endpoints or the observation period ended on December 31, 2012. The end point of the study was the occurrence of major adverse cardiovascular events (MACE), including death, nonfatal MI, target vessel revascularization and ischemic stroke during the follow-up period.

Statistical analysis

The analysis was performed on the complete data set, and results were expressed as mean ± SD or as percent frequency. Comparisons between two groups were

made by unpaired Students t-test, Mann-Whitney U test, or Chi square test, as appropriate. Comparisons of continuous variables among the 3 groups were performed by analysis of variance (ANOVA), and subgroup comparisons of categorical variables were assessed by Chi square or Fisher's exact test. The Cox proportional hazards model was used to examine the association of baseline variables with high SYNTAX score. Multivariate Cox regression analysis was performed to evaluate the independent contribution of bilirubin levels to the risk of high SYNTAX score, adjusting for significant variables in univariate analysis ($p < 0.100$). The Kaplan-Meier technique (log-rank test) was applied to survival analysis. To ascertain study end-points, observations were concluded at the end of the study or the date that patients died, whichever occurred first. The accumulated data were analyzed using SPSS software (version 20, SPSS, Chicago, Illinois, USA); a p-value of less than 0.05 was considered to indicate statistical significance.

RESULTS

Patient characteristics

During a 12-month follow-up period to December 2012, 250 patients (183 men and 67 women; mean age 70 ± 13 years) were enrolled for analysis in our study. Based on coronary angiography, 174 patients were found to have significant CAD (the presence of ≥ 50% stenosis in at least one major coronary artery), 52 had insignificant CAD (the presence of < 50% but ≥ 20% stenosis in at least one major coronary artery), and 24 had normal coronary arteries (< 20% stenosis at all major coronary arteries). Among the 174 patients who had significant CAD, 107 patients (61%) were treated with angiography-guided percutaneous coronary intervention, 21 patients (12%) were treated with coronary artery bypass surgery, and 46 patients (27%) only received standard medical treatment for CAD.

Correlation between serum bilirubin and CAD severity

All study subjects were divided into 2 groups (see Table 1). Group 1 was defined as patients with a high SYNTAX score (> 22), and group 2 was defined as low SYNTAX score (≤ 22). Patients with high SYNTAX score were significantly older and had more comorbidities (diabetes, dyslipidemia and smoking). Total bilirubin levels were significantly lower in the high SYNTAX score group than in the low SYNTAX score group (0.51 ± 0.22 vs. 0.72 ± 0.29 mg/dl, $p < 0.001$) (Figure 1).

Table 1. Baseline characteristics of patients with high and low SYNTAX score

	High SYNTAX score (> 22) (n = 66)	Low SYNTAX score (≤ 22) (n = 184)	p value
Age (years)	75.2 ± 12.0	67.5 ± 13.9	< 0.001
Male	52 (78.8%)	131 (71.2%)	0.232
Current smoker	41 (62%)	81 (44%)	0.012
Hypertension	55 (83%)	147 (80%)	0.542
Diabetes mellitus	43 (65%)	72 (39%)	< 0.001
Dyslipidemia	44 (67%)	90 (49%)	0.013
CKD	36 (55%)	75 (41%)	0.053
Lipid profiles (mg/dl)			
Triglycerides	119.6 ± 66.0	118.3 ± 75.4	0.930
Total cholesterol	174.8 ± 41.5	160.6 ± 42.3	0.080
High-density lipoprotein	38.2 ± 11.1	44.9 ± 13.8	0.010
Low-density lipoprotein	108.1 ± 35.3	92.5 ± 33.8	0.073
Fasting glucose (mg/dl)	155.3 ± 62.6	133.3 ± 67.5	0.099
Creatinine (mg/dl)	1.66 ± 2.06	1.60 ± 0.97	0.855
Total bilirubin (mg/dl)	0.51 ± 0.22	0.72 ± 0.29	< 0.001
AST (U/L)	33.8 ± 37.1	25.9 ± 30.0	0.228
ALT (U/L)	31.5 ± 39.0	26.8 ± 30.0	0.456
SYNTAX score	29.4 ± 7.0	9.4 ± 7.1	< 0.001
hsCRP (mg/dl)	1.86 ± 2.70	1.40 ± 2.35	0.325

Values are mean ± SD or n (%).
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CKD, chronic kidney disease; hsCRP, high-sensitivity C-reactive protein.

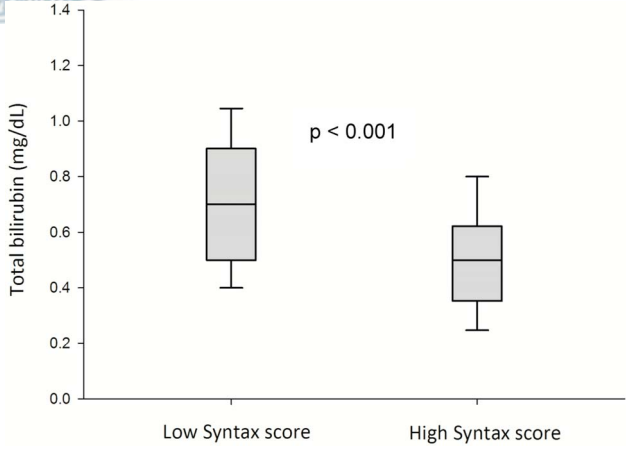

Figure 1. *Total bilirubin levels between low and high SYNTAX score groups.*

As shown in Table 2, patients in the high bilirubin group had a lower prevalence of hypertension, diabetes, chronic kidney disease, and had lower SYNTAX score than patients in the low bilirubin group (10 ± 10 vs. 20 ± 12, p < 0.001).

By multivariate analysis, serum total bilirubin levels were identified as an independent predictor for high SYNTAX score (adjusted odds ratio: 0.28, 95% confidence interval 0.04-0.42; p = 0.004) (Table 3).

Independent correlates of serum bilirubin and predictors of MACE

The Kaplan-Meier analysis demonstrated a significant difference in 1-year cardiovascular events between high (> 0.8 mg/dl), medium (> 0.5, ≤ 0.8 mg/dl), and low (≤ 0.5 mg/dl) bilirubin levels (log rank test p = 0.011). Patients in the high bilirubin group had a significantly higher MACE-free survival rate (Figure 2).

In order to investigate the independent predictors

Table 2. Baseline characteristics among three bilirubin groups

	Low-bilirubin (N = 83) (≤ 0.5 mg/dl)	Medium-bilirubin (N = 83) (> 0.5, ≤ 0.8 mg/dl)	High-bilirubin (N = 84) (> 0.8 mg/dl)	p value
Age (years)	71.8 ± 13.5	70.5 ± 13.8	66.9 ± 13.8	0.078
Male	58 (70)	64 (77)	61 (73)	0.569
Current smoker	37 (45)	40 (48)	44 (52)	0.601
Hypertension	72 (87)	71 (86)	59 (70)	0.010
Diabetes mellitus	47 (57)	38 (46)	30 (36)	0.025
Dyslipidemia	47 (57)	45 (54)	42 (50)	0.685
CKD	45 (54)	42 (51)	24 (29)	0.001
Lipid profiles (mg/dl)				
Triglycerides	129.2 ± 78.7	120.3 ± 70.6	107.0 ± 69.3	0.319
Total cholesterol	174.5 ± 38.6	173.8 ± 44.6	175.2 ± 42.8	0.703
HDL-cholesterol	42.2 ± 13.2	44.1 ± 13.3	43.6 ± 14.1	0.783
LDL-cholesterol	106.4 ± 29.4	110.1 ± 38.6	108.4 ± 36.3	0.447
Fasting glucose (mg/dl)	142.4 ± 72.0	141.2 ± 62.4	132.7 ± 66.1	0.753
Creatinine (mg/dl)	2.09 ± 2.52	1.86 ± 1.86	1.06 ± 0.40	0.011
Total bilirubin (mg/dl)	0.37 ± 0.11	0.64 ± 0.08	0.97 ± 0.22	< 0.001
AST (U/L)	21.2 ± 11.9	27.8 ± 21.9	34.4 ± 48.0	0.144
ALT (U/L)	21.5 ± 12.7	30.1 ± 35.2	32.7 ± 41.8	0.192
hsCRP (mg/dl)	1.90 ± 3.07	1.65 ± 2.51	1.03 ± 1.48	0.176
Coronary angiography				
1-vessel disease	10 (12)	11 (13)	22 (26)	0.001
2-vessel disease	18 (22)	23 (28)	15 (18)	
3-vessel disease	38 (46)	24 (29)	13 (16)	
PCI	40 (61)	37 (64)	30 (60)	0.905
CABG	8 (12)	7 (12)	6 (12)	0.984
SYNTAX score	20.0 ± 12.3	15.7 ± 9.8	10.0 ± 10.0	< 0.001
Medications				
ACEI	8 (10)	17 (21)	16 (19)	0.110
ARB	29 (35)	23 (28)	20 (24)	0.282
CCB	19 (23)	17 (21)	18 (21)	0.953
Beta-blockers	29 (35)	32 (40)	26 (31)	0.515
Statin	47 (57)	49 (61)	39 (46)	0.171
Aspirin	58 (70)	59 (73)	65 (77)	0.543
Clopidogrel	56 (68)	49 (61)	35 (42)	0.002

Values are mean ± SD or n (%).

ACEI, angiotensin-converting enzyme inhibitor; ALT, alanine aminotransferase; ARB, angiotensin II receptor blocker; AST, aspartate aminotransferase; CAG, coronary angiography; CABG, coronary artery bypass grafting; CCB, calcium channel blocker; CKD, chronic kidney disease; hsCRP, high-sensitivity C-reactive protein; PCI, percutaneous coronary intervention.

Table 3. Effects of various variables on high SYNTAX score in univariate and multivariate logistic regression analyses

Variables	Unadjusted OR	95% CI	p value	Adjusted* OR	95% CI	p value
Age: per 1 year	1.05	1.02-1.08	< 0.001	1.04	1.00-1.08	0.05
Male: male vs. female	1.50	0.77-2.94	0.234			
Smoking: smoker vs. non-smoker	2.10	0.98-4.50	0.055	3.48	1.37-8.80	0.009
Hypertension: hypertension vs. non-hypertension	1.31	0.49-3.50	0.596			
Diabetes: diabetes vs. non-diabetes	2.94	1.36-6.36	0.006	3.69	1.42-9.55	0.007
CKD: CKD vs. non-CKD	1.71	0.81-3.62	0.158			
hsCRP: per 1 mg/L	1.07	0.93-1.23	0.329			
Serum bilirubin: per 1 mg/dL	0.17	0.08-0.37	< 0.001	0.28	0.04-0.42	0.004

CI, confidence interval; CKD, chronic kidney disease; hsCRP, high-sensitivity C-reactive protein; OR, odds ratio.
* Adjusted for age, gender, medical history (smoking, hypertension, diabetes), and serum bilirubin levels.

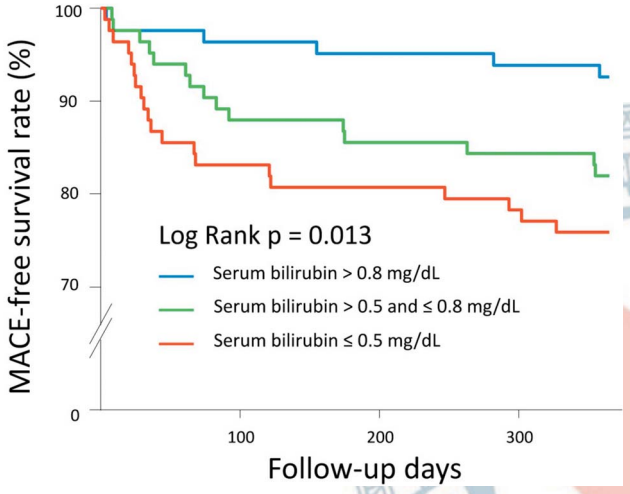

Figure 2. *Kaplan-Meier survival curves stratified by the serum bilirubin levels. The MACE-free survival rate was significantly reduced in patients with lower serum bilirubin levels (p = 0.013 by log-rank test).*

of 1-year MACE, multivariate Cox regression analysis was performed with factors including age, gender, medical history (hypertension, diabetes, CKD, and smoking), serum high-sensitivity C-reactive protein concentration, total cholesterol concentration, serum bilirubin level and SYNTAX score. As shown in Table 4, serum bilirubin level was an independent predictor of 1-year MACE in patients with stable coronary artery disease undergoing coronary intervention (adjusted odds ratio: 0.23, 95% confidence interval 0.06-0.86; p = 0.039).

DISCUSSION

The present study revealed that serum bilirubin level is independently associated with SYNTAX score and can predict cardiovascular events in patients with stable coronary artery disease undergoing coronary intervention. Our results confirm a potential protective role of bilirubin in cardiovascular disease.

SYNTAX score and CAD

The development of the SYNTAX score has provided useful information on angiographic coronary anatomy. Evidence has been accumulating about the importance of the SYNTAX score, wherein a substantially elevated SYNTAX score predicts adverse outcomes after percutaneous coronary intervention (PCI) in patients with coronary artery disease who have undergone revascularization.[13] The SYNTAX score predicts clinical outcomes after PCI or CABG in patients with multivessel and/or left main coronary artery disease.[16] The SYNTAX score reflects the lesion complexity and the level of technical difficulty in coronary intervention.

The link between serum bilirubin and CAD

Several image studies have demonstrated the association of the serum bilirubin level with cardiovascular disease. Sung et al. investigated the relation between serum conjugated bilirubin level and coronary artery calcium score.[17] The study found there to be a strong inverse and independent relation between conjugated bilirubin level and coronary artery calcium score calculated by cardiac computed tomographic scan. Another population-based cohort study also confirmed the relationship between conjugated bilirubin and coronary artery calcium score.[18] Coronary artery calcium scoring is a sensitive method used to detect the presence of preclinical atherosclerosis and to identify those at an increased

Table 4. Effects of various variables on major adverse cardiovascular events in univariate and multivariate COX regression analyses

Variables	Crude HR	95% CI	p value	Adjusted* HR	95% CI	p value
Age: per 1 year	1.02	1.00-1.04	0.011	1.02	0.98-1.04	0.333
Male: male vs. female	1.11	0.57-2.17	0.766			
Smoking: smoker vs. non-smoker	1.03	0.53-2.00	0.928			
Hypertension: hypertension vs. non-hypertension	1.96	0.69-5.56	0.204			
Diabetes: diabetes vs. non-diabetes	4.29	2.01-9.18	< 0.001	2.39	1.05-5.44	0.037
Cholesterol: per 1 mg/dL	1.01	1.00-1.02	0.013	1.01	1.00-1.02	0.057
CKD: CKD vs. non-CKD	3.12	1.52-6.37	0.002	2.38	1.05-5.42	0.038
hsCRP: per 1 mg/L	1.23	1.15-1.32	< 0.001	1.17	1.07-1.27	< 0.001
SYNTAX score: per +1 score	1.03	1.01-1.06	0.008	1.03	1.00-1.06	0.041
Serum bilirubin: per 1 mg/dL	0.16	0.05-0.56	0.004	0.23	0.06-0.86	0.039

CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein.
* Adjusted for age, gender, medical history (smoking, hypertension, diabetes, CKD), serum cholesterol levels, serum hsCRP levels, SYNTAX score, and serum bilirubin levels.

risk of cardiovascular disease.[19] The pathophysiological mechanism for these findings remains uncertain. Several mechanisms have been postulated by which increased concentrations of bilirubin could mediate decreased risk of cardiovascular disease. Bilirubin has been proven to be an effective antioxidant[20-22] and has been shown to suppress the oxidation of lipids and lipoproteins, especially LDL cholesterol. In addition, the association of unconjugated bilirubin with cardiovascular risk has also been investigated. Patients with Gilbert syndrome were found to have slight elevations in serum unconjugated bilirubin concentrations while the cardiovascular risk was reduced remarkably.[22] A basic study conducted by Öllinger et al. showed bilirubin inhibits proliferation of vascular smooth muscle cell in cells and in animal models.[23] The study result represents bilirubin might have a potentially therapeutic effect in vascular proliferative disorders and explains the association of high-normal levels of bilirubin in humans with less atherosclerotic disease.

A role of heme oxygenase-1 (HO-1) and a heme-bilirubin-carbon monoxide pathway in atherosclerosis has been proposed.[24-26] HO-1 removes heme which has pro-oxidative and pro-atherosclerotic properties, and produces biliverdin and carbon monoxide which appear to have antiatherosclerotic properties. HO-1 therefore plays an important role in the protective properties of bilirubin with regard to cardiovascular disease.

Serum bilirubin and cardiovascular events

Our study has demonstrated that patients with stable coronary artery disease and higher serum bilirubin level have lower SYNTAX score than those with lower bilirubin level. Higher serum bilirubin level was an independent predictor of 1-year MACE. Growing evidence has also confirmed the predictive value of serum bilirubin for long term outcomes in patients with stable coronary artery disease.[27] Further large prospective studies are required to confirm our findings.

Nevertheless, in acute conditions, such as acute coronary syndrome, bilirubin levels increase due to stress induced HO-1 enzyme. Sahin et al.[28] found that high bilirubin levels are independently associated with high SYNTAX score in patients with ST elevation myocardial infarction. In another study, Glu et al.[29] demonstrated that high bilirubin level is one of the independent predictors of in-hospital cardiovascular morbidity and mortality in STEMI patients. It has been showed in vivo and in vitro that HO-1 enzyme activity is markedly increased in the myocardium in response to acute infarction.[30,31] These studies have revealed that the role of serum bilirubin level is quite opposite in stable coronary artery disease and in acute coronary syndrome. It remains to be clarified whether bilirubin was responsible for the prognostic properties or if it was just acting in concert with other main factors such as HO-1.

Limitations of the present study

There are some possible limitations to our study. First, this study was a single-center experience and involves only a small number of patients. Second, we did not follow up the biochemical parameters including to-

tal bilirubin, total cholesterol, low-density lipoprotein-cholesterol and hsCRP in the current study. The significance of the serial change of total bilirubin level should be investigated further. Third, we did not measure HO-1 enzyme activity, therefore we couldn't clarify the association between HO-1 enzyme activity, serum bilirubin level and the risk of cardiovascular disease. Further large-scale study using bilirubin and HO-1 enzyme levels at follow-up would be beneficial to assess the long-term outcome and to investigate the prognostic properties of bilirubin in cardiovascular disease.

CONCLUSIONS

In conclusion, serum bilirubin level is associated with SYNTAX score and predicts future cardiovascular events in patients with stable coronary artery disease undergoing coronary intervention.

CONFLICTS OF INTEREST DISCLOSURES

None.

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