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Serum total bilirubin and long-term outcome in patients undergoing percutaneous coronary intervention

Abstract

Purpose: The purpose of this study was to investigate the associated between serum total bilirubin (STB) levels and long-term outcomes in patients with acute coronary syndrome (ACS) after percutaneous coronary intervention (PCI).

Methods: A total of 1,273 consecutive patients were enrolled. Patients were grouped according to their baseline STB levels: Group 1 (STB < 3.4 $\mu\text{mol/L}$), Group 2 (3.4 $\mu\text{mol/L}$ $\leq$ STB $\leq$ 10.3 $\mu\text{mol/L}$), Group 3 (10.3 $\mu\text{mol/L}$ < STB $\leq$ 17.1 $\mu\text{mol/L}$), and Group 4 (STB > 17.1 $\mu\text{mol/L}$) and the rate of major adverse cardiovascular events (MACE) was determined

Results: A total of 1,152 patients were successfully followed up (90.5%) for a mean period of 30 ± 5 months, including 187 patients experiencing a major adverse cardiovascular event (MACE: death from any cause, myocardial infarction, repeat revascularization or readmission). The MACE rate in Groups 3 and 4 was lower than in Groups 1 and 2 ($P < 0.01$). After adjusted the confounding factors with Cox regression analysis, the MACE rates in Groups 2-4 were still lower than in Group 1 (Group 2, RR=0.293, 95% CI 0.167-0.517, $P < 0.01$; Group 3, RR=0.142, 95% CI 0.065-0.312, $P < 0.01$; Group 4, RR=0.134, 95% CI 0.071-0.252, $P < 0.01$). The cumulative survival rates of Groups 3 and 4 were higher than that of Groups 1 and 2 ($P < 0.01$).

Conclusions: High STB concentration is associated with lower MACE in patients with ACS after PCI.

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Acute coronary syndrome (ACS) is a common and potentially fatal cardiovascular disease and its morbidity continues to rise [1]. One of the most effective treatments for ACS, which has been shown to reduce mortality and improve the quality of life, is elective or emergency percutaneous coronary intervention (PCI) [2]; however, several risk factors are associated with repeat revascularization and other adverse events after PCI [3]. Several biomarkers, such as C-reactive protein, creatine kinase (CK), CK-MB, hyperuricemia, serum total bilirubin (STB), and troponin-T, have been shown to predict adverse cardiac events after PCI [4, 5, 6].

For decades, STB was believed to be merely a waste product of erythrocytes, but in recent years a large number of studies have consistently shown that STB is also an antioxidant [7,8] able to scavenge oxygen-free radicals, inhibit complement-mediated inflammatory responses, and prevent atherosclerosis [9,10]. Furthermore, low serum concentrations of STB are associated with endothelial dysfunction and an increased risk of atherosclerotic disease [11,12,13], hypertension [14], diabetes mellitus [15] and metabolic syndrome [16]. Although it is well known that there is a prominent relationship between coronary artery disease and STB [12, 17, 18], to our knowledge there has been very little published on the effects of STB in patients with ACS after PCI. The aim of this study was to assess the relationship between STB levels and the prognosis of ACS patients after PCI.

Materials and Methods

Study Population

This was a descriptive study of consecutive patients with ACS admitted to the First Affiliated Hospital of Zhengzhou University for PCI between June 2009 and December 2010. A total of 1,273 Chinese patients with ACS, defined as ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), or unstable angina pectoris, were selected for this study.

Patients who met one or more of the following conditions were excluded from this study: (1) severe hepatic injury (alanine aminotransferase (ALT) > 80 U/L); (2) severe anemia (hemoglobin < 90 g/L); (3) malignancy; (4) hemolytic anemia; (5) cholecystitis or cholelithiasis; (6) chronic pulmonary diseases; (7) connective tissue disease; (8) congenital heart disease; (10) valvular heart disease; and, (11) cardiomyopathy.

Patients with ACS were treated according to the guidelines for the management of ACS published by the American College of Cardiology/American Heart Association [19]. For

patients with STEMI, the primary PCI procedure was performed in the first 6 h after the onset of symptoms. Patients with NSTEMI or unstable angina pectoris underwent PCI 3–6 days after the onset of symptoms. All patients usually received 100 to 300 mg of aspirin and 300 mg of clopidogrel before the procedure. In addition, 5,000–10,000 IU of unfractionated heparin were administered subcutaneously before the procedure. Coronary angiography was performed through the radial artery. Drug-coated stents were used in patients with stenotic or totally occluded lesions. All procedures were carried out by experienced surgeons performing, on average, 200 procedures per year in the last five years. Coronary blood flow after stent implantation was determined according to the thrombolysis in myocardial infarction classification. After PCI, patients received 100 mg of aspirin per day indefinitely, as well as 75 mg of clopidogrel per day for at least 12 months. Other pharmacological treatments included β -blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin II receptor blockers (ARB), and statins.

Data Collection

Basic information such as gender, age, height, weight, previous history and smoking habits was recorded for each patient. Weight and height were measured using a standard measurement, and used to calculate the body mass index (BMI), which was equal to the weight (kg) divided by the square of the height (m). Resting blood pressure was measured in the morning using a mercury sphygmomanometer.

Biochemical measurements were taken before PCI. Blood samples were taken from the antecubital vein of all patients after 12 h of fasting. ALT, triglyceride (TG), total cholesterol (TC), serum high density lipoprotein (HDL), serum low density lipoprotein (LDL), STB, conjugated bilirubin, unconjugated bilirubin, C-reactive protein, serum creatinine and blood urea nitrogen (BUN) were measured. Normal reference values of STB ranged from 3.4 to 17.1 $\mu\text{mol/L}$. Patients were divided into four groups according to STB levels, as follows: lower than the normal level (G1: STB < 3.4 $\mu\text{mol/L}$), low-normal STB group (G2: 3.4 $\mu\text{mol/L}$ $\leq$ STB $\leq$ 10.3 $\mu\text{mol/L}$), high-normal STB group (G3: 10.3 $\mu\text{mol/L}$ < STB $\leq$ 17.1 $\mu\text{mol/L}$) and higher than the normal level (G4: STB > 17.1 $\mu\text{mol/L}$).

Follow Up

All follow ups were conducted between August 2012 and November 2012 by telephone or in our outpatient clinics. Data on medication compliance after discharge and occurrence of endpoints were recorded. This study also collected information on

TABLE 1. Baseline characteristics of participants

Variables	MACE (n=187)	Non-MACE (n=965)	P
Male (%)	118 (63.1)	664 (68.8)	0.13
Age (y)	62.04±11.36	60.59±10.68	0.09
BMI (kg/m ² , %)			0.42
< 24	56 (29.9)	302 (31.3)	
24~28	99 (52.9)	465 (48.2)	
> 28	32 (17.1)	198 (20.5)	
STB (μmol/L)	8.37±4.09	10.42±5.29	< 0.01
Previous infarction (%)	42 (22.5)	165 (17.1)	0.08
Hypertension (%)			< 0.01
No hypertension	85 (45.5)	481 (49.8)	
Controlled Hypertension	72 (38.5)	454 (47.0)	
Uncontrolled Hypertension	30 (16.0)	30 (3.1)	
DM (%)			< 0.01
No DM	131 (70.1)	752 (77.9)	
Controlled DM	26 (13.9)	157 (16.3)	
Uncontrolled DM	30 (16.0)	56 (5.8)	
Smoking (%)			0.11
No smoking	133 (71.1)	625 (64.9)	
Ex-smoker	24 (12.8)	185 (19.0)	
Current smoker	30 (16.0)	155 (16.0)	
SBP (mmHg)	133.18±18.96	129.59±18.31	0.02
DBP (mmHg)	80.57±11.76	80.53±11.20	0.97
Heart rate (beats/min)	73.77±12.74	74.36±11.71	0.53
Nitrate (%)	92 (49.2)	428 (44.4)	0.22
Post-PCI therapy			
Aspirin (%)	139 (74.3)	869 (90.1)	< 0.01
Clopidogrel (%)	149 (79.7)	943 (97.7)	< 0.01
β-blocker (%)	100 (53.5)	656 (68.0)	< 0.01
ACEI/ARB (%)	65 (34.8)	443 (45.8)	< 0.01
Statin (%)	128 (68.4)	751 (77.9)	< 0.01
LMH (%)	132 (70.6)	674 (69.9)	0.84
Coronary lesions (%)			0.02
Single vessel	50 (26.7)	322 (33.3)	
Double vessel	69 (36.9)	383 (39.7)	
Triple vessel	68 (36.4)	259 (26.9)	
ALT (U/L)	25.34±15.07	27.42±15.67	0.19
BIL (umol/L)	8.93±5.17	10.62±6.06	< 0.01
IBIL (umol/L)	5.81±4.48	7.45±6.62	0.20
TC (mmol/L)	4.38±1.19	4.29±1.10	0.31
TG (mmol/L)	1.99±1.22	1.93±1.46	0.63
HDL (mmol/L)	1.08±0.35	1.07±0.34	0.75
LDL (mmol/L)	2.88±1.10	2.74±0.97	0.09 ^a
Cre (umol/L)	77.54±65.76	72.71±29.01	0.33
UA (umol/L)	312.27±108.77	306.72±100.40	0.50
HS-CRP (mg/L)	5.97±10.69	6.65±20.26	0.77
Lp(a) (g/L)	0.30±0.54	0.28±0.61	0.84
WBC (10 ⁹ /L)	7.05±2.35	7.91±20.10	0.56
PLT (10 ⁹ /L)	209.40±65.89	202.21±63.42	0.16
FIB (g/L)	5.57±25.44	3.55±1.47	0.32 [*]
LVEDV (ml)	124.46±51.19	114.66±33.07	0.04 [*]
LVESV (ml)	53.56±35.75	49.05±22.49	0.18 [*]
LVEF (%)	60.01±9.13	60.58±8.49	0.50

^aKruskal-Wallis analysis.

MACE, major adverse cardiovascular events; BMI, body mass index; STB, serum total bilirubin; DM, diabetes mellitus; SBP, systolic blood pressure; DBP, diastolic blood pressure; ACEI, angiotensin-converting enzyme inhibition; ARB, angiotensin receptor blocker; LMH, low molecular heparin; ALT, alanine aminotransferase; DBIL, direct bilirubin; IBIL, indirect bilirubin; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; Cre, creatinine; UA, uric acid; hsCRP, hypersensitive C reactive protein; Lp(a), lipoprotein a; WBC, white blood cell; PLT, platelet; FIB, fibrinogen; LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; LVEF, left ventricular ejection fraction.

drugs including aspirin, clopidogrel, ACEI or ARB, β -blockers and statins. The composite endpoint was defined as major adverse cardiovascular events (MACE), namely death from any cause, myocardial infarction (MI), repeat revascularization (by PCI or coronary artery bypass grafting) or readmission due to angina pectoris, heart failure or stroke. The sub-index of MACE was also analyzed

Statistical Analysis

The SPSS17.0 package was used for statistical analysis. All continuous variables were shown as mean $\pm$ standard deviation if they were normally distributed. Comparisons of continuous variables between groups were performed by t-test or ANOVA. The differences in the categorical variables between the subgroups were compared using the Chi-square test. Cox regression analysis was performed to identify independent predictors of endpoints. Kaplan-Meier curves were used to analyze cumulative survival rates in patients with different levels of STB. $P < 0.05$ was considered statistically significant.

Results

General Findings

A total of 1,273 patients were enrolled in the study. Follow-up studies were completed for 1,152 patients (90.5%) ranging from 27 to 92 years old. Among them, 782 were male and 370 were female with an average age of 60.8 ± 10.8 years. The mean follow-up period was 30.4 ± 5.0 months. Follow-up was not possible for 121 patients due to a change of telephone number

or address. In total, 187 patients experienced MACE (16.2%), including 45 deaths (3.9%) and 142 MI/revascularization/readmission (12.3%).

Participant Characteristics

Patient characteristics are summarized in Table 1. No significant differences in gender, age, BMI, blockage history, cigarette smoking, diastolic blood pressure, heart rate (HR), ALT, HDL, TG, TC, left ventricular end-systolic volume (LVESV) or fibrinogen levels were observed between patients with and without endpoints ($P > 0.05$). Patients experiencing MACE had a higher prevalence of diabetes mellitus, hypertension, elevated left ventricular end-diastolic volume (LVEDV) and systolic blood pressure (SBP) and a greater number of coronary lesions than patients without endpoints ($P < 0.05$). The patients experiencing MACE were also less likely to have been treated with aspirin, clopidogrel, ACEI/ARB, β -blockers or statins than patients without endpoints ($P < 0.01$). As shown in Table 1, the concentration of STB in the group with endpoints was lower ($P < 0.01$).

Predictive Value of STB for Endpoints After PCI

The follow-up results of the four groups are listed in Table 2. The incidence of all adverse cardiovascular events in all four groups gradually decreased ($P < 0.01$). The differences in the mortality in the four groups were not statistically significant ($P = 0.50$). The incidences of MI or target lesion revascularization

TABLE 2. Comparison of endpoint in different levels of STB (case, %)

Follow-up	Group 1 (n=61)	Group 2 (n=624)	Group 3 (n=361)	Group4 (n=106)	P
MACE	19 (28.8)	116 (17.1)*	43 (11.2)*†	9 (8.5)*†	< 0.01
Death	4 (6.6)	27 (4.3)	11 (3.0)	3 (2.8)	0.50
Readmission	15 (24.6)	89 (14.3)*	32 (8.9)*†	6 (5.7)*†	< 0.01
MI/revascularization	6 (9.8)	24 (3.8)	7 (1.9)*†	2 (1.9)	0.011
Angina pectoris	10 (16.4)	59 (9.5)	21 (5.8)*†	2 (1.9)*†	< 0.01
Heart failure	3 (4.9)	8 (1.3)	2 (0.6)*	2 (1.9)	0.12
Stroke	2 (3.3)	14 (2.2)	3 (0.8)	1 (0.9)	0.25

Group 1: STB < 3.4 $\mu\text{mol/L}$, Group 2: 3.4 $\mu\text{mol/L} \leq \text{STB} \leq 10.3 \mu\text{mol/L}$, Group 3: 10.3 $\mu\text{mol/L} < \text{STB} \leq 17.1 \mu\text{mol/L}$, Group4: STB > 17.1 $\mu\text{mol/L}$;

* $P < 0.05$ compared with Group 1;

† $P < 0.05$ compared with Group 2.

MACE, major adverse cardiovascular events; MI, myocardial infarction.

and angina pectoris in G3 and G4 were lower than in G1 and G2 ($P < 0.05$).

Bivariate analysis results

Cox regression analysis was performed to assess MACE predictors. STB levels, history of hypertension and oral clopidogrel after PCI were entered into the Cox proportional hazards regression model (Table 3), after adjusting for age, gender, history of diabetes, smoking history, number of coronary lesions, history of diabetes mellitus, oral aspirin, β -blockers and statins. Elevated serum bilirubin was a protective factor for MACE. The total incidence of MACE in G2, G3 and G4 decreased by 70.7% (risk ratio (RR): 0.293, 95% confidence index (CI): 0.167-0.517; $P < 0.01$), 85.8% (RR=0.142, 95% CI 0.065-0.312, $P < 0.01$) and 86.6% (RR=0.134, 95% CI 0.071-0.252, $P < 0.01$), respectively. Hypertension was a risk factor for endpoints.

Fig. 1 shows Kaplan-Meier survival curves for the four groups with different levels of STB. Log-rank tests showed significant differences between the four groups in terms of cumulative survival rates without MACE ($P < 0.01$).

Discussion

The present study showed that at low serum STB levels were associated with a higher risk of MACE. And it demonstrated that high serum STB levels are a protective factor in the patients with PCI, after correcting for age, gender, history of diabetes or hypertension, smoking history, number of coronary lesions, and oral clopidogrel, β -blockers, aspirin or statins. The incidence of nonfatal MI or target lesion revascularization in patients with low levels of STB was higher than in patients with high-normal or high levels of STB. Cox regression analysis also demonstrated that STB levels were correlated with the

risk of MACE in patients after PCI. The incidence of endpoints in G2, G3 and G4 were reduced by 70.7%, 85.8% and 86.6%, respectively, compared to G1. In addition, Kaplan-Meier analysis showed a lower survival rate in patients with low STB levels. Previous studies have shown that elevated STB levels are associated with a significant decrease in the odds of MACE [5].

Historically, bilirubin has been considered to be a marker of hepatobiliary system disease; however, recent studies have demonstrated that patients with high levels STB have an increased circulating antioxidant status and an improved resistance to serum oxidation [11] and elevated levels may actually decrease the risk of atherosclerosis and coronary artery disease [11,12,13] due to the protective properties of LDL from oxidation, scavenging oxygen-free radicals, and inhibiting complement-mediated inflammatory response [20,21,22]. Current evidence indicates mildly elevated bilirubin is associated with protection from cardiovascular disease and all-cause mortality in adults [20] and that this protective effect is via an

FIGURE 1. Kaplan-Meier estimates of four groups of different levels of STB in patients with Kaplan-Meier analysis of survival curves. G1: STB $< 3.4 \mu\text{mol/L}$, G2: $3.4 \mu\text{mol/L} \leq \text{STB} \leq 10.3 \mu\text{mol/L}$, G3: $10.3 \mu\text{mol/L} < \text{STB} \leq 17.1 \mu\text{mol/L}$, and G4 STB $> 17.1 \mu\text{mol/L}$. Log-rank test results showed that there were significant differences among the four groups with respect to cumulative survival rates without endpoint.

TABLE 3. Bivariate analysis for the MACE

Group	RR	95%CI	P
Group 1			< 0.01
Group 2	0.293	0.167 - 0.517	< 0.01
Group 3	0.142	0.065 - 0.312	< 0.01
Group 4	0.134	0.071 - 0.252	< 0.01
Uncontrolled hypertension	1.327	1.033-1.705	0.027
Oral Clopidogrel	0.148	0.095-0.232	< 0.01

MACE, major adverse cardiovascular events; RR, risk ratio.

anti-inflammatory effect on HDL [21,22]. Patrick et al. demonstrated that STB levels were inversely associated with coronary heart disease, and negatively correlated with BMI, LDL cholesterol and TC [17]. Few studies have demonstrated the relationship between STB levels and the prognosis of ACS patients after PCI.

In our study population, no differences in mortality were seen in patients with different STB concentrations, but these outcomes should be interpreted with caution because of the low mortality of the patients. Huang et al. found that the incidence of cardiovascular death and all-cause mortality in patients with STB levels $> 11.97 \mu\text{mol/L}$ was lower than in patients with STB $\leq 8.55 \mu\text{mol/L}$ [5]. Rahma et al. found that mortality in patients with cardiovascular disease was inversely correlated with the level of STB [23]; however, for patients treated by PCI for STEMI, a higher STB level was associated with a lower incidence of in-hospital mortality, although no differences were found in the long-term mortality between the groups [24].

PCI treatment is an accepted treatment for patients with coronary stenosis $>70\%$. Previous studies reported that in more than 10% of patients, myocardial infarction, revascularization or cardiac death still reoccurred [25]. In the present study, vascular endothelial integrity violation, subendothelial matrix exposure, platelet activation, thrombosis, coronary artery spasm, vascular smooth muscle cells and stromal proliferation were demonstrated to be positively and independently correlated with restenosis in patients after PCI. Several studies have shown that the risk factors of coronary stent restenosis include age, male gender, smoking, hypertension, diabetes, left ventricular ejection fraction, plasma cystatin C, history of PCI, multivessel disease, minimum stent diameter and total stent length [1,5,26]. In the present study, it was demonstrated that the risk factors for endpoints in patients with ACS after PCI include hypertension, diabetes, SBP and multivessel disease, while aspirin, clopidogrel, β -receptor blockers, ACEI/ARB and statins are protective factors in the treatment of STB. Likewise, guidelines for percutaneous coronary intervention have pointed out that patients with ACS after PCI should take oral antiplatelet therapy, aspirin indefinitely, and clopidogrel for at least 12 months as long as they are not at high risk of excessive bleeding [1]. Other pharmacologic treatments, such as β -blockers and ACEI/ARB, are recommended for secondary prevention, while oral statins have an anti-inflammatory effect and improve endothelial function, inhibition of platelet aggregation and control of LDL concentration $<2.6 \text{ mmol/L}$. The inability of the present study to demonstrate an association between age, smoking, previous history of infarction, and end-

points may be due to the single-center nature of this study and sampling error.

In conclusion, this descriptive study indicates that high STB concentration is associated with lower MACE in patients with ACS after PCI.

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