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The correlation between serum total bilirubin and outcomes in patients with different subtypes of coronary artery disease

Fang-Yang Huang [a], Yong Peng [a], Bao-Tao Huang [a], Yong Yang [a], Xiao-bo Pu [a], Shi-Jian Chen [a], Yi-Yue Gui [a], Tian-Li Xia [a], Fei Chen [a], Rui-Shuang Liu [b], Ye Zhu [a,*], Mao Chen [a,*]

[a] Department of Cardiology, West China Hospital, Sichuan University, Chengdu, China
[b] Department of General Practice Medicine, West China Hospital, Sichuan University, Chengdu, China

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ABSTRACT

Backgrounds: The relation between serum total bilirubin (TBi) and mortality in patients with established coronary artery disease (CAD) remains undefined. We try to investigate the role of the subtypes of CAD in the association.

Methods: A total of 3013 patients with angiographically obstructive CAD were enrolled. A retrospective analysis was conducted. Patients were divided into 3 groups as follows: stable CAD (SCAD), unstable angina pectoris (UAP) and acute myocardial infarction (AMI). The predictive values of TBi for 30-day and long-term mortality were assessed using logistic and Cox regression, respectively.

Results: Higher initial serum TBi levels were significantly associated with increased risk of short-term mortality (OR 2.35, 95% CI 1.15–4.77) in AMI group. However, the association was absent among patients with SCAD and UAP. Serum TBi was able to independently predict the long-term mortality in SCAD (HR 0.34, 95% CI 0.16–0.70) and UAP (HR 0.49, 95% CI 0.31–0.78) groups. However, there was no significant relation between TBi and long-term mortality in AMI groups.

Conclusion: The different subtypes of CAD affected the relation between serum TBi and clinical prognosis. Initial serum TBi was positively correlated with short-term mortality of AMI patients, and negatively correlated with long-term mortality in SCAD or UAP patients.

1. Introduction

Bilirubin, a catabolite of heme, was considered a useless waste. Initially believed to be toxic, however, emerging evidence showed that bilirubin is a potent antioxidant and anti-inflammatory mediator that may protect against atherosclerosis [1–3]. An inverse association between serum total bilirubin (TBi) levels and risks of coronary artery disease (CAD), such as hypertension, diabetes and coronary artery calcium, has been documented [4–6]. Several lines of evidence showed that low serum TBi seemed to predispose apparently healthy individuals to future cardiovascular events [7]. However, it remains unknown whether the association between serum TBi and mortality found in the general population still exists in patients with obstructive CAD. After all, subjects with obstructive CAD generally have lower levels of serum TBi than those with normal coronary angiogram [6,8]. So far, the findings of several relevant studies were conflicting. In a cohort of patients with cardiac syndrome X, Huang et al. reported that low serum TBi levels were associated with increased risk of cardiovascular events [9]. Nevertheless, other studies have shown that high serum TBi group had a higher rate of in-hospital adverse events in ST-segment elevation myocardial infarction (STEMI) patients undergoing percutaneous coronary intervention (PCI) [10]. It appears that serum TBi plays distinct roles in different subtypes of CAD. In the present study, we evaluated whether serum TBi is able to predict mortality of patients with established CAD, and we focused on the relation between serum TBi and short-term and long-term mortality in different subtypes of CAD.

2. Methods

2.1. Study population

The study used data from West China Hospital CAD database. This single center database prospectively included the data of consecutive patients suspected to have coronary artery disease and those who underwent coronary angiography between July 2008 and September 2012. In the present study, the patients were eligible for inclusion only if they have angiographic evidence of ≥50% stenosis in ≥1 coronary artery. Subjects with serum TBi >34.2 μmol/l (2 mg/dl) were excluded

* Corresponding authors at: Department of Cardiology, West China Hospital, Sichuan University, 37 Guoxue Street, Chengdu 610041, Sichuan, China.
E-mail addresses: zhuye1974@163.com (Y. Zhu), hmaochen@vip.sina.com (M. Chen).

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due to possible chronic liver disease or Gilbert's syndrome. The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the institutional review board of West China Hospital, Sichuan University. All participants provided informed consent.

2.2. Baseline characteristics and laboratory measurements

Comprehensive information on anthropometric data and medical history, cardiovascular risk factors, echocardiographic data, final diagnoses and medications at discharge were obtained from electronic medical records and reviewed by a trained study coordinator. Hypertension was defined as those with systolic blood pressure (SBP) ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg. A patient was considered to have diabetes if the fasting plasma glucose level, 2-h plasma glucose level after a 75-g oral glucose tolerance test, or hemoglobin A1c level satisfied the ADA criteria at the time of presentation, diabetes was diagnosed by a previous physician, and/or the patient was using insulin or oral hypoglycemic agents. Venous blood samples were collected in tubes containing ethylene diamine tetraacetic acid (EDTA), and plasma biomarkers including liver and kidney function, blood glucose, serum lipid, etc. were analyzed at the Department of Laboratory Medicine, West China Hospital, accredited by College of American Pathologies. The initial serum total bilirubin was measured using standard methods [reference range TBi: 5.0–28.0 μmol/l (0.3–1.6 mg/dl)]. The chronic kidney disease epidemiology (CKD-EPI) equation was used to determine the estimated glomerular filtration rate (eGFR).

2.3. Follow-up and end point

The follow-up period ended on January 2013. Follow-up information was obtained by contacting patients and/or their relatives via letters or the telephone, or through outpatient visits. All data were corroborated with hospital records. Due to the relatively low incidence of adjudicated defined cardiovascular deaths, the endpoint in this study was all-cause mortality.

2.4. Statistical analyses

We conducted the post hoc analysis on a retrospective basis. Baseline demographics and clinical characteristics were compared among patients categorized by the types of CAD as 3 groups: stable CAD (SCAD), unstable angina pectoris (UAP) and AMI. The χ^2 test or Fisher's exact test was used to compare categorical variables across the 3 groups. The Kolmogorov–Smirnov test was used to assess the distribution of the data. If the data followed normal distribution, the data were compared using one-way analysis of variance; otherwise, the data were compared using the Kruskal–Wallis test. Because the serum TBi data followed non-normal distribution, the data were log-transformed for analyses. To evaluate the relationship between serum TBi and outcomes, patients were divided into 3 groups based on TBi tertiles, and the comparisons of mortality between groups were examined using log-rank test. Furthermore, logistic model was used to evaluate the association between serum TBi and short-term (<30 days after admission) mortality. Then, Cox proportional hazard analyses were performed to identify the long-term prognostic value of log TBi levels in the 3 subtypes of CAD. Model 1 adjusted for age, sex, and body mass index (BMI). Model 2 adjusted for age, sex, BMI, medical history (pre-hypertension, diabetes mellitus and prior revascularization), systolic blood pressure, diastolic blood pressure, left ventricular ejection fraction (LVEF), total cholesterol, eGFR, white blood count, CK-MB, severity of CAD (left main artery or 3 vessel disease), and medications at discharge. To minimize analytic biases introduced by missing data, we employed multiple imputation and combined results in STATA 13.0 to create 10 data sets for analysis.

3. Results

3.1. Demographic characteristics of study patients

Of the 3300 participants enrolled in our database, 197 patients had serum TBi >34.2 μmol/l (2 mg/dl). Therefore, a total of 3103 patients with established CAD were included in the present study. The patients were divided into 3 group as follows: the SCAD group, the UAP group and the AMI group. The baseline data of the 3 groups are shown in the Table 1. Briefly, compared with other groups, the AMI group had a larger

Table 1
Baseline characteristics of patients included.

	Total	SCAD	UAP	AMI	P value
No. of patients	3103	893	1513	697	
Age, y	64.4 (10.7)	64.0 (10.9)	64.7 (10.0)	64.2 (11.9)	NS
Male, n (%)	2466 (79.5)	719 (80.5)	1170 (77.3)	577 (82.8)	0.008
BMI, kg/m^2	24.3 (3.3)	24.1 (3.5)	24.3 (3.1)	24.5 (3.5)	NS
Hypertension, n (%)	1710 (55.1)	504 (56.4)	869 (57.5)	337 (48.4)	<0.001
Diabetes mellitus, n (%)	681 (22.0)	197 (22.1)	336 (22.2)	148 (21.2)	0.028
Prior revascularization, n (%)	402 (13.0)	215 (24.1)	155 (10.2)	32 (4.6)	<0.001
Systolic blood pressure, mmHg (SD)	130.5 (21.2)	130.5 (19.1)	132.6 (21.0)	126.2 (23.3)	<0.001
Diastolic blood pressure, mmHg (SD)	76.5 (12.4)	76.6 (11.7)	76.8 (12.0)	75.5 (13.8)	NS
Left ventricular ejection fraction, % (SD)	59.8 (11.7)	60.5 (11.9)	61.7 (10.8)	54.9 (12.0)	0.001
Total bilirubin, μmol/l (IQR)*	11.7 (8.8–15.4)	11.7 (9.1–15.2)	11.4 (8.6–15.0)	12.5 (9.0–16.6)	0.001
Total cholesterol, mmol/l (SD)*	4.0 (1.1)	3.9 (1.2)	4.1 (1.1)	4.1 (1.2)	0.001
eGFR, ml/kg	76.7 (21.0)	77.4 (20.5)	76.6 (20.6)	75.9 (22.3)	NS
White blood counts	7.4 (3.6)	6.5 (2.1)	6.9 (3.0)	9.8 (5.1)	<0.001
CK-MB, ng/ml(IQR)	2.7 (1.9–5.5)	2.4 (1.7–3.2)	2.5 (1.9–3.7)	10.2 (3.1–64.7)	<0.001
Left main disease or three vessel disease, n (%)	988 (31.8)	225 (25.2)	498 (32.9)	265 (38.0)	<0.001
Medications at discharge, n (%)					
Aspirin	2852 (91.9)	799 (89.5)	1415 (93.5)	638 (91.5)	0.002
Clopidogrel	2768 (89.2)	727 (81.4)	1398 (92.4)	643 (92.3)	<0.001
Statin	2797 (90.1)	801 (89.7)	1361 (90.0)	635 (91.1)	NS
ACEI/ARB	1775 (57.2)	521 (58.3)	861 (56.9)	393 (56.4)	NS
Beta-blocker	2043 (65.8)	592 (66.3)	1022 (67.6)	429 (61.6)	0.021
Calcium channel blocker	825 (26.6)	266 (29.8)	479 (31.7)	80 (11.5)	<0.001

ACEI = angiotensin-converting enzyme inhibitor; AMI = acute myocardial infarction; ARB = angiotensin receptor blocker; IQR = interquatile range; CK-MB = creatine kinase-MB; SCAD = stable coronary artery disease; SD = standard deviation; UAP = unstable angina pectoris.

* The unit conversion factor for bilirubin mg/dl to μmol/l is 17.1; that is 38.6 for total cholesterol mmol/l to mg/dl.