

# Relation of Direct, Indirect, and Total bilirubin to Adverse Long-term Outcomes Among Patients With Acute Coronary Syndrome



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**Bilirubin is known as an antioxidant. However, there have been controversies over whether bilirubin is protective against cardiovascular disease or not. In addition, no study has examined the association between subtypes of total bilirubin (direct bilirubin [DB] and indirect bilirubin [IDB]) and long-term outcomes of acute coronary syndrome (ACS) patients. We included 533 consecutive patients with ACS. All the patients were followed up for the composite end point of cardiac death, revascularization, and acute heart failure. At a median follow-up of 2.4 years, Kaplan-Meier curve demonstrated that higher serum DB levels were significantly associated with major adverse cardiac events (MACE) ( $p < 0.05$ ). However, total bilirubin (TB) and IDB were not associated with MACE by Kaplan-Meier analysis. Cox analysis showed that high TB and DB were associated with increased risk of MACE in ACS even after adjustment of cardiovascular risk factors. The receiver operating characteristic curve illustrated that DB had a predictive value of MACE in ACS. In conclusion, we firstly reported that high TB and DB but not IDB were associated with increased risk of MACE in Chinese ACS, and the prognostic value of DB was superior to that of TB or IDB. © 2019 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license. (<http://creativecommons.org/licenses/by-nc-nd/4.0/>) (Am J Cardiol 2019;123:1244–1248)**

Bilirubin is the end product of heme catabolism, which has 2 forms: indirect bilirubin (IDB) and direct bilirubin (DB). IDB is converted to DB in hepatic cells and excreted into bile acid.<sup>1</sup> Considered to be a waste product at first, bilirubin now has been known to have antioxidative,<sup>2</sup> anti-inflammatory,<sup>3</sup> and antithrombotic effects.<sup>4</sup> However, epidemiologic studies lack consistency. A large prospective study indicated an inverse association between total bilirubin (TB) and the risk of cardiovascular disease in general population.<sup>5</sup> And several studies found that low TB was associated with coronary flow reserve impairment in healthy subjects,<sup>6</sup> carotid burden in familial dyslipidemia,<sup>7</sup> and adverse events in patients undergoing percutaneous coronary intervention (PCI).<sup>8</sup> However, others demonstrated that high bilirubin was a risk factor for in-hospital mortality in patients with acute coronary syndrome (ACS),<sup>9–11</sup> and was associated with SYNTAX score.<sup>12,13</sup> In addition, no study has examined the effect of DB and IDB on ACS. Therefore, we conducted this study to investigate the relation between bilirubin (TB, DB, and IDB) and long-term outcomes in ACS patients.

## Methods

The present study was a retrospective analysis of a total of 533 consecutive patients who were admitted to the cardiology department of the First Affiliated Hospital of Xi'an Jiaotong University for ACS from January 2013 to January 2014. ACS was defined as unstable angina pectoris, non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI).<sup>14</sup> Exclusion criteria were liver or renal dysfunctions, New York Heart Association class >II, pregnancy, malignant tumors. Patients who did not have bilirubin measurement at admission were also excluded. The protocol was approved by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University, and written informed consent was obtained from all study participants.

Main demographic data and cardiovascular drugs received were obtained from medical records. The blood pressure, weight and height of patients were measured on admission and body mass index (BMI) was calculated. Fasting blood samples were obtained from the peripheral vein of each patient at the time of hospital admission or on the morning following the admission day. Bilirubin, total cholesterol, triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol, NT-proBNP, high-sensitivity C-reactive protein (hsCRP), creatinine, alanine aminotransferase (ALT), and aspartate aminotransferase (AST) were measured using standard methods. Left ventricular ejection fraction (LVEF) was also measured during admission.

Major adverse cardiac events (MACE) were defined as cardiac death, revascularization, and acute heart failure during the follow-up. Patients were followed up by telephone

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or face-to-face interviews by well-trained cardiologists. Cardiovascular death was defined as death caused by acute myocardial infarction (AMI) or heart failure. Revascularization was defined as undergoing PCI or coronary artery bypass grafting during the follow-up. Acute heart failure was diagnosed by physicians according to guideline.<sup>15</sup>

Categorical variables were presented as numerals and percentages. Continuous variables were presented as means  $\pm$  standard deviations for normally distributed data, or medians (25th, 75th percentiles) for non-normally distributed data. Categorical variables were presented as numerals and percentages. The Kolmogorov-Smirnov test was used to assess the normal distribution of quantitative variables. One-way analysis of variance or Kruskal-Wallis analysis was performed to compare the parametric values in multiple groups as appropriate. For categorical variables, chi-square test was applied. The correlation between bilirubin and CVD risk factors was analyzed using Spearman correlation and partial correlation analysis. Kaplan-Meier curves were plotted according to bilirubin levels. The log-rank test and Wilcoxon test were applied to compare event-free survival between groups. The Cox proportional hazards regression was performed to determine independent predictors for cardiovascular events. The predictive values of bilirubin for events were evaluated using the receiver operating characteristic (ROC) curve. All statistical analyses were performed with SPSS, Version 23 (SPSS Inc., Chicago, Illinois), and a *p* value <0.05 was considered to be statistically significant.

## Results

Baseline characteristics of the 533 patients according to the tertiles of bilirubin are shown in Table 1 for DB, Supplemental Table 1 for TB and Supplemental Table 2 for IDB, respectively. Patients with DB  $\geq 4.6$   $\mu\text{mol/L}$  (highest tertile) were defined as the high direct bilirubin group, those with DB  $\geq 3.2$   $\mu\text{mol/L}$  and  $< 4.6$   $\mu\text{mol/L}$  as the medium group, and those with DB  $< 3.2$   $\mu\text{mol/L}$  (lowest tertile) as the low-bilirubin group. The patients with highest TB, DB, and IDB levels had higher ALT, AST, and creatinine. And bilirubin levels (TB, DB, and IDB) were elevated in men. Interestingly, as shown in Table 1, total cholesterol, triglycerides, and low-density lipoprotein cholesterol levels were significantly lower in patients with higher DB. Medium group of DB had the lowest high-density lipoprotein cholesterol level among 3 tertiles. In addition, participants with higher DB had lower LVEF.

The bivariate correlation analysis between plasma DB levels and cardiovascular disease risk factors is shown in Table 2. The plasma DB level was inversely correlated with LVEF after adjustment for sex, age, and BMI, whereas was not associated with hsCRP, systolic blood pressure, and diastolic blood pressure. As shown in Supplemental Table 3, hsCRP was positively correlated with TB. Similarly, the *p* value was close to significance in the correlation between IDB levels and hsCRP (Supplemental Table 4).

At a median follow-up of 2.4 years, 9 patients died of cardiac cause, 17 patients had revascularization and 23

Table 1  
Baseline characteristics according to the level of serum direct bilirubin

Variable	Direct bilirubin ( $\mu\text{mol/L}$ )			p Value
	<3.2 (n = 172)	3.2–4.6 (n = 186)	>4.6 (n = 175)	
Age (years)	59 $\pm$ 10	61 $\pm$ 10	60 $\pm$ 10	0.240
Men	119 (69%)	145 (78%)	152 (87%)	<0.001
Type of acute coronary syndrome				0.365
ST-segment elevation myocardial infarction	24 (14%)	32 (17%)	39 (22%)	
Non-ST-segment elevation myocardial infarction	15 (9%)	15 (8%)	15 (9%)	
Unstable angina	133 (77%)	139 (75%)	121 (69%)	
Hypertension	92 (53%)	103 (55%)	103 (59%)	0.592
Diabetes mellitus	42 (24%)	42 (23%)	42 (24%)	0.911
Smoker	94 (55%)	102 (55%)	104 (59%)	0.592
Body mass index ( $\text{kg/m}^2$ )	25 $\pm$ 4	25 $\pm$ 3	25 $\pm$ 3	0.524
Total cholesterol (mg/dl)	4.0 (3.4,4.7)	3.7 (3.2,4.2)	3.5 (2.9,4.2)	<0.001
Triglycerides (mg/dl)	1.7 (1.2,2.3)	1.4 (1.1,2.0)	1.3 (0.9,1.8)	<0.001
High-density lipoprotein (mg/dl)	0.9 (0.8,1.1)	0.8 (0.7,1.00)	0.9 (0.8,1.1)	0.035
Low-density lipoprotein (mg/dl)	2.3 (1.9,2.9)	2.1 (1.7,2.7)	2.0 (1.4,2.6)	<0.001
Left ventricular ejection fraction (%)	63 (55,69)	63 (52,69)	60 (45,67)	0.004
Amino terminal pro-brain natriuretic peptide (pg/ml)	300 (121,846)	252 (89,751)	355 (113,1303)	0.163
Creatinine ( $\mu\text{mol/L}$ )	62 (54,71)	68 (60,76)	68 (61,79)	<0.001
Aspartate aminotransferase (U/L)	24 (18,38)	27 (19,50)	31 (21,77)	0.001
Alanine aminotransferase (U/L)	24 (15,39)	25 (18,46)	32 (21,50)	<0.001
Percutaneous coronary intervention	153 (89%)	166 (89%)	154 (88%)	0.927
Dual antiplatelet therapy	164 (95%)	176 (95%)	161 (92%)	0.382
Statin	169 (98%)	181 (97%)	173 (99%)	0.551
Renin-angiotensin aldosterone system inhibitors	154 (90%)	168 (90%)	156 (89%)	0.932
Calcium channel blockers	35 (20%)	46 (25%)	35 (20%)	0.476
$\beta$ -blockers	151 (88%)	160 (86%)	150 (86%)	0.829

Table 2  
Correlation of direct bilirubin with cardiovascular risk factors

Variable	No adjustment		Adjusted for sex, age, and body mass index	
	r	p Value	R	p Value
Age (years)	0.077	0.074		
Body mass index (kg/m <sup>2</sup> )	0.034	0.540		
High-sensitivity C-reactive protein (mg/L)	0.032	0.505	0.113	0.071
Systolic blood pressure (mm Hg)	0.002	0.964	-0.021	0.712
Diastolic blood pressure (mm Hg)	0.044	0.312	0.038	0.498
Left ventricular ejection fraction (%)	-0.148	0.001	-0.114	0.049

patients had acute heart failure. Kaplan-Meier curve in Figure 1 demonstrated that higher plasma DB levels were significantly associated with MACE ( $p = 0.023$ , log-rank test;  $p = 0.039$ , Wilcoxon test). However, TB and IDB were not associated with MACE by Kaplan-Meier analysis (Supplemental Figure 1, and Figure 2).

We then use Cox proportional model for further analysis as shown in Table 3. In univariate Cox regression analysis, we found plasma TB and DB were significantly associated with an increased risk of MACE. This association remained significant after adjustment for age, sex, LVEF, BMI, DM, and hypertension, and additional adjustment for ALT and AST. However, IDB level was not associated with the risk of MACE.

To evaluate the predictive value of plasma bilirubin, we utilized the ROC curve. As shown in Figure 2, the areas under curve were 0.593 ( $p = 0.019$ ) for DB, whereas there was no association between TB, IDB, and long-term adverse events (Supplemental Figure 3).

## Discussion

The major finding of the present study was high levels of TB and DB but not IDB were associated with increased risk of MACE in ACS even after adjustment of cardiovascular risk factors. To the best of our knowledge, this is the first

study to demonstrate the association between DB and IDB with adverse events in ACS patients.

Bilirubin is the end product of heme catabolism. Heme oxygenase (HO) breaks down the heme into biliverdin, ferrous iron, and carbon monoxide. Biliverdin is then degraded into IDB (unconjugated bilirubin) through the actions of biliverdin reductase.<sup>16</sup> IDB is solubilized in the circulation by binding with albumin. After reaching the liver, it is converted to DB (conjugated bilirubin) in hepatocytes by UDP glucuronosyltransferase and then secreted into bile. For many years, bilirubin was regarded as a waste product. Nevertheless, experimental studies have demonstrated the protective role of bilirubin in recent years.<sup>17-19</sup>

However, there have been controversies over whether bilirubin is protective against cardiovascular disease or not in population and epidemiological studies. Evidence suggested that SYNTAX score, which has been shown to predict major adverse events in patients with coronary heart disease,<sup>20</sup> was positively associated with TB in both STEMI and NSTEMI patients.<sup>12,13</sup> Celik et al<sup>11</sup> and Gul et al<sup>9</sup> demonstrated that high TB level was associated with PCI no-reflow as well as increased in-hospital MACE in patients with STEMI. On the contrary, Kim et al<sup>8</sup> found a negative correlation of TB levels and long-term outcomes in patients who underwent PCI. Kuwano et al<sup>21</sup> also reported that patients with higher TB level had lower in-stent restenosis risk after PCI. In addition, Gul et al<sup>9</sup> and Kaya et al<sup>12</sup> found no association between TB levels and long-term mortality in patients with STEMI or NSTEMI. In the present study, we reported that high levels of TB and DB were risk factors for adverse events in Chinese ACS patients. The discrepancy in these studies may be attributed to the different end points, study design, or ethnicity.

Different from the previous studies, we aimed to find out which subtype of TB played a more important role in the prognosis of ACS. Surprisingly, we demonstrated the risk stratification value of DB by Kaplan-Meier curve and the prognostic value of DB by ROC curve in ACS rather than TB or IDB. In the present study, we also found DB was inversely correlated with LVEF. In another study,<sup>22</sup> DB was reported to be associated with increased incidence of coronary heart disease in a dose-response manner in Chinese patients. Likewise, other 2 studies also demonstrated that elevated DB could predict adverse events of acute compensated heart failure<sup>23</sup> and idiopathic pulmonary arterial hypertension.<sup>24</sup> These findings together with ours suggest that it is important to distinguish DB from IDB,<sup>25</sup> as DB is

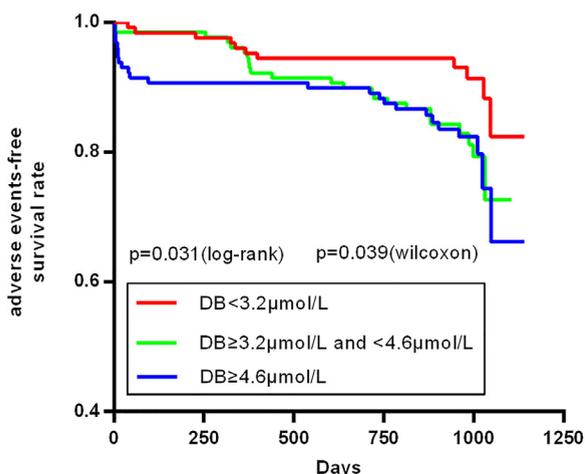


Figure 1. Kaplan-Meier curve analysis on the correlations of serum DB with major adverse cardiac events in ACS patients.

DB = direct bilirubin.

Table 3  
Cox proportional hazards model for composite end point

	Hazards ratio (95[%]CI)					
	Unadjusted	p Value	Model 1	p Value	Model 2	p Value
<b>Total bilirubin</b>						
Tertile 1	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Tertile 2	1.521 (0.756,3.061)	0.240	1.233 (0.513,4.910)	0.639	1.200 (0.492,2.931)	0.689
Tertile 3	2.000 (1.044,3.833)	0.037	2.272 (1.051,4.910)	0.037	2.339 (1.073,5.097)	0.033
P for trend		0.038		0.026		0.021
<b>Direct bilirubin</b>						
Tertile 1	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Tertile 2	2.341 (1.136,4.821)	0.021	1.878 (0.800,4.411)	0.148	1.899 (0.809,4.458)	0.141
Tertile 3	2.382 (1.164,4.876)	0.018	2.420 (1.048,5.590)	0.039	2.508 (1.083,5.805)	0.032
P for trend		0.036		0.047		0.038
<b>Indirect bilirubin</b>						
Tertile 1	1.0 (ref)		1.0 (ref)		1.0 (ref)	
Tertile 2	1.533 (0.772,3.043)	0.222	1.592 (0.676,3.752)	0.288	1.507 (0.633,3.587)	0.354
Tertile 3	1.694 (0.858,3.345)	0.129	2.164 (0.947,4.943)	0.067	2.237 (0.978,5.115)	0.056
P for trend		0.164		0.069		0.052

Model 1: Adjusted for age, sex, left ventricular ejection fraction, body mass index, diabetes mellitus, and hypertension.

Model 2: Further adjusted for aspartate aminotransferase, alanine aminotransferase.

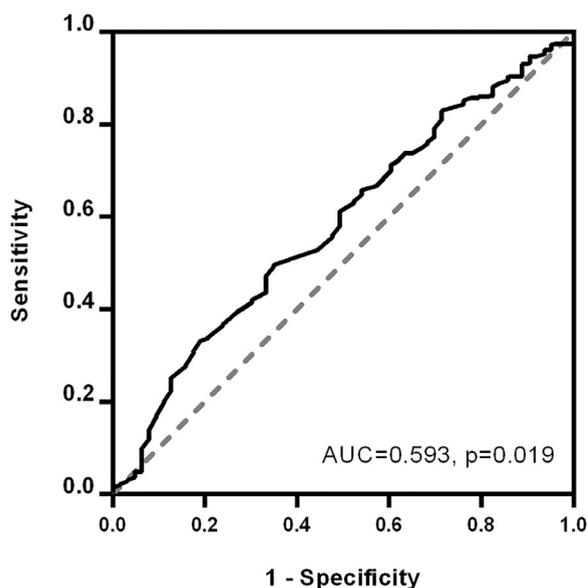


Figure 2. Receiver operating characteristic curve analysis on predictive value of DB.

AUC = area under curve; DB = direct bilirubin.

probably a risk factor in cardiac-pulmonary disease. Further studies need to investigate the role of DB and IDB separately. The mechanism underlying the relation between DB and increased risk of adverse events remains to be elucidated.

In many experimental studies, bilirubin has been shown to be protective in cardiovascular disease.<sup>25</sup> The reason why epidemiological evidence differs from basic research is probably related to the production of bilirubin. HO is a rate-limiting enzyme in bilirubin production, which has

2 isoforms (HO-1 and HO-2). HO-1 is induced by various environmental stresses such as lipopolysaccharides, cytokines, growth factors, and hypoxia.<sup>26</sup> It has been demonstrated that serum HO-1 was activated after acute myocardial infarction (AMI), which subsequently led to the elevation of bilirubin in AMI patients.<sup>27</sup> In the present study, TB and IDB were found to be positively correlated with hsCRP which could also reflect the activation of inflammatory cascade both in the coronary lesion and systemically.<sup>28</sup> Though such elevated response of HO-1 and bilirubin was considered to be the defensive mechanisms toward oxidative stress and inflammation,<sup>29</sup> it could not compensate the detrimental effects caused by coronary heart disease. Furthermore, it's unclear how long the elevation will continue. As a result, it would be inappropriate to simply regard bilirubin as a protective biomarker in human body.

The present study had several limitations. First, our study was a single-center observational study which could not establish causal relation and the subjects were restricted to Chinese Han. Second, the relatively small sample size may have affected the results. In addition, bilirubin levels were not accessible during follow-up, further study in this field needs to examine bilirubin levels at follow-up.

In conclusion, our study is the first to reveal that high TB and DB but not IDB were associated with increased risk of MACE in ACS patients.

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## Disclosures

The authors declare that there are no conflicts of interest to disclose.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at <https://doi.org/10.1016/j.amjcard.2019.01.019>.

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