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ORIGINAL RESEARCH

Circulating Total Bilirubin and Long-Term Prognosis in Patients With Previous Myocardial Infarction

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ABSTRACT

BACKGROUND Although experimental studies have demonstrated the protective role of total bilirubin (TBil) in cardiovascular diseases, several previous clinical observations are controversial. More importantly, no data are currently available regarding the relation of TBil to major adverse cardiovascular events (MACE) in patients with previous myocardial infarction (MI).

OBJECTIVES This study sought to explore the association between TBil and long-term clinical outcomes in patients with previous MI.

METHODS A total of 3,809 patients who are post-MI were consecutively enrolled in this prospective study. Cox regression models using HRs and CIs were applied to investigate associations between the TBil concentration category (group 1: bottom to median tertiles within the reference range; group 2: top tertile; group 3: above reference range) and main outcome (recurrent MACE) as well as secondary outcomes (hard endpoints and all-cause mortality).

RESULTS During the 4-year follow-up period, 440 patients (11.6%) suffered from recurrent MACE. Kaplan-Meier survival analysis showed the lowest MACE incidence in group 2 ($P < 0.001$). When compared with the reference group (group 1) in multivariable analysis, a J-shaped association was apparent for MACE, with decreased risk in group 2 (HR: 0.76; 95% CI: 0.59-0.96) and elevated risk in group 3 (HR: 1.29; 95% CI: 1.03-1.61). Similar associations were identified regarding hard endpoints and all-cause mortality. Moreover, TBil demonstrated incremental discriminatory strength when added to the predictive model.

CONCLUSIONS In this prospective cohort study with long-term follow-up, higher TBil levels within the physiological range reduced the incidence of long-term cardiovascular events in patients who are post-MI. (JACC: Asia 2023;3:242-251)

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity worldwide and a past history of myocardial infarction (MI) is among the major risk factors for the recurrence of cardiovascular events.[1,2] Over the past decades, despite advances in the management and therapy, patients with previous MI remain at increased risk for long-term mortality following hospital discharge.[3]

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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The relative risk for all-cause death and cardiovascular outcomes was at least 30% higher than that in a general population at 3-5 years after MI.[3,4] Therefore, early identification of patients with previous MI who are at a high risk of adverse events may allow for improving prognosis.

Multiple nontraditional biomarkers have been identified and used for cardiovascular outcome prediction and risk stratification.[5-7] Clinically, circulating total bilirubin (TBil) has been traditionally considered a potentially toxic metabolite and a marker for the diagnosis of some liver diseases.[8-10] However, the latest evidence supports that TBil within the normal physiologic range is a potent endogenous antioxidant with anti-inflammatory, immunomodulatory, antithrombotic, and endocrine properties,[8] which may likely contribute to the protective effect on oxidative stress diseases including diabetes,[11] stroke,[12] peripheral arterial disease,[13] heart failure (HF),[14] and CVD.[15] Many epidemiological studies assessed the clinical significance and prognostic value of TBil, but the results were inconsistent. Some clinical observations reported a negative linear association between circulating TBil levels and incident CVD risk in the general population free of CVD, indicating its antioxidant properties.[16,17] Some studies supported a positive association, suggesting that high TBil levels portend increased risk of pathological injury.[18] Whereas other data found a nonlinear relationship between them, such as L-type and U-type.[19-22] Importantly, it should be noted that most studies on TBil and clinical prognosis have focused on general populations and information on the predictive value of TBil in patients with previous MI remains scarce.

Considering that TBil may have certain potential value in secondary prevention, especially in very-high risk patients with CVD, the potential association between TBil levels and recurrent cardiovascular events warrants further investigation. Hence, in this study, we sought to investigate the association of TBil with long-term major adverse cardiac events (MACEs) in patients who are post-MI without known liver diseases.

METHODS

STUDY DESIGN AND POPULATION. This investigation was a prospective, observational cohort study carried out from March 1, 2009, to January 31, 2019, at Fuwai Hospital, National Center for Cardiovascular Diseases. As shown in Supplemental Figure 1, 11,219 Chinese patients with angiography-proven CVD were consecutively recruited. The inclusion criteria were experienced a history of MI before admission and age ≥18 years. The exclusion criteria included age <18 years; familial hypercholesterolemia, thyroid dysfunction, severe renal insufficiency, infectious or systematic inflammatory disease, or malignant disease; and missing detailed laboratory data. Patients with known hepatic diseases, including any hepatitis, liver cirrhosis, or known liver tumor, as well as those with a history of diseases that can affect bilirubin levels, including cholangitis and hemolytic anemia, were also excluded. Finally, 3,809 patients with a previous MI were successfully enrolled.

The research protocol complied with the Declaration of Helsinki and was approved by the hospital's ethical review board (Fu Wai Hospital and National Center for Cardiovascular Diseases). Each subject provided written, informed consent before enrollment.

ABBREVIATIONS AND ACRONYMS

CVD = cardiovascular disease

FPG = fasting plasma glucose

HbA_{1c} = glycosylated hemoglobin

HF = heart failure

hsCRP = high-sensitivity C-reactive protein

LDL-C = low-density lipoprotein cholesterol

MACE = major adverse cardiac event(s)

MI = myocardial infarction

RI = reference interval

STEMI = ST-segment elevation myocardial infarction

TBil = total bilirubin

BIOCHEMICAL ANALYSIS. Blood samples were taken by direct venipuncture from each patient after at least 12 hours of fasting in the morning and sent to the central laboratory in Fuwai Hospital. Concentrations of TBil, total cholesterol, triglyceride, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, apolipoprotein A-I, apolipoprotein B, and glycosylated hemoglobin (HbA_{1c}) were measured using automatic biochemistry analyzer (Hitachi 7150) in an enzymatic assay, whereas the concentration of high-sensitivity C-reactive protein (hsCRP) was measured by immunoturbidimetry (Beckmann Assay360) as previously described.[23] Other related biochemical and hematological indicators were measured according to standard tests.

CLINICAL ASSESSMENT. On admission, demographic data, medical history, and drug use were collected from each patient by professional cardiologists and nurses. ST-segment elevation myocardial infarction (STEMI) was defined as the presence of persistent chest pain, new or presumed new ST-segment elevation in 2 or more contiguous leads, and elevated cardiac biomarkers. Non-STEMI was diagnosed by ischemic symptoms and positive cardiac biomarkers without new ST-segment elevation. Body mass index was calculated as the ratio between weight and height squared. Hypertension was defined as systolic blood pressure ≥140 mm Hg or diastolic blood pressure ≥90 mm Hg for 3 or more consecutive times or currently taking antihypertensive medications. Diagnostic criteria for diabetes included fasting plasma glucose (FPG) level ≥7.0 mmol/L, 2-hour serum glucose of the oral glucose tolerance test ≥11.1 mmol/L, or currently using hypoglycemic

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drugs or insulin. Current smoking indicated regular smoking within 12 months before admission. The severity of coronary artery stenosis was evaluated by the Gensini score, which was scored according to stenosis position and severity.[24]

STUDY ENDPOINTS. Patients were followed up at 6-month intervals either by direct interview or telephone communication by well-trained nurses or cardiologists who were blinded to the aim of the study; follow-up continued until death occurred or to the last day of the follow-up period. The primary endpoint was a composite of MACE, including nonfatal MI, nonfatal ischemic stroke, ischemia-driven target-vessel revascularization, and cardiovascular death. MI was diagnosed as positive cardiac troponins along with typical chest pain or typical electrocardiogram serial changes. Ischemic stroke, excluding lacunar infarction, was defined by persistent neurological dysfunction with documentation of acute cerebral infarction on computed tomography and/or cardiac magnetic resonance. Revascularization was defined as percutaneous coronary intervention or coronary artery bypass graft when myocardial ischemia was confirmed beyond 90 days after discharge. Cardiovascular death was diagnosed as death mainly caused by acute MI, malignant arrhythmia, HF, or other structural or functional cardiac diseases. Diagnosis of cardiovascular death was confirmed with additional information from hospital records, death certificates, and family contact. The secondary efficacy endpoints included: 1) the hard endpoint was the combined endpoint of nonfatal MI, nonfatal ischemic stroke, or cardiovascular death; and 2) all-cause mortality. All events were carefully checked and verified by 2 experienced clinical physicians.

STATISTICAL ANALYSIS. The reference intervals (RIs) for TBil were defined as 5.1-17.1 μmol/L. Given the potential J-curve or U-curve association and previous data indicating that TBil was toxic at high concentrations, but might serve as a powerful antioxidant in the serum within the normal physiologic range, we substratified participants within the normal RI into tertiles as follows: low-normal, 5.1-10.9 μmol/L; middle-normal, 11.0-14.3 μmol/L; and high-normal, 14.4-17.1 μmol/L. Then, 3 groups were applied in our analyses: group 1 was composed of patients who had a TBil value in the lower 2 tertiles; group 2 was composed of patients who had a TBil value in the third tertile; and group 3 was composed of patients who had a TBil value above normal range (>17.1 μmol/L).

We use mean ± SD to describe continuous variables with a normal distribution and median (IQR) to describe other measurement data with a non-normal distribution. Categorical variables are expressed by quantities and percentages. The differences of clinical characteristics and biochemical parameters among groups were assessed using Student's *t*-test, Mann-Whitney *U* test, or analysis of variance, appropriately for continuous variables, and chi-square test for categorical ones. The correlation between TBil and other biomarkers was evaluated by Spearman correlation test. The log-rank test and Kaplan-Meier survival analyses were performed to explore differences in event-free survival among the different groups. The predictive value for adverse events during the follow-up period was assessed by Cox proportional hazards analysis with HRs and 95% CIs. The multivariate Cox proportional hazards analysis was performed using confounders that were significant in the univariate model. No adjustment for multiplicity. In addition, restricted cubic spline analyses with 5 knots (at the 5th, 27.5th, 50th, 72.5th, and 95th centiles) were performed to explore the associations between levels of TBil and the endpoints.

To assess whether adding plasma TBil levels to the risk prediction model with established cardiovascular risk factors could improve the ability for predicting future events, we calculated the Harrell C-statistic and area under curve (AUC). Finally, we performed sensitivity analyses to test the robustness of our findings. A P value <0.05 was considered statistically significant. SPSS Statistics (version 26, IBM Corp), R (version 4.1.2, R Foundation), and Stata/MP (version 14, StataCorp) were used to perform the statistical analyses.

RESULTS

BASELINE CHARACTERISTICS. The general characteristics of the study population with or without recurrent MACE are shown in **Table 1**. A total of 3,809 patients with a history of MI were enrolled in our study. Mean age was 61.7 ± 16.1 years, 3,303 patients (86.7%) were men, 2,295 patients (60.3%) suffered from hypertension, 1,153 participants (30.3%) were diagnosed with diabetes, and >60% of patients were current smokers. Patients with MACE were older, predominantly of female sex, with a higher prevalence of hypertension, diabetes, and low utilization rate of statin. Total cholesterol, apolipoprotein B, hsCRP, FPG, HbA_{1c}, and TBil levels were higher in patients with MACE than in those without, but no

TABLE 1 Baseline Characteristics of Study Patients

	Total (N = 3,809)	Non-MACE (n = 3,369)	MACE (n = 440)	*P* Value
Age, y	61.7 ± 16.1	60.7 ± 16.0	69.6 ± 14.8	<0.001
Male	3,303 (86.7)	2,701 (80.2)	332 (75.5)	0.021
Body mass index, kg/m^2	24.26 ± 3.04	24.25 ± 3.05	24.33 ± 2.96	0.609
Family history of CVD	471 (12.4)	414 (12.3)	57 (13.0)	0.747
Current smoker	2,291 (60.1)	2,025 (60.1)	266 (60.5)	0.889
Hypertension	2,295 (60.3)	1,998 (59.3)	297 (67.5)	0.001
Diabetes	1,153 (30.3)	979 (29.1)	174 (39.5)	0.001
Prior revascularization	1,398 (36.7)	1,252 (37.2)	146 (33.2)	0.103
STEMI	2,232 (58.6)	1,969 (58.4)	263 (59.8)	0.595
LVEF, %	53.19 ± 9.68	53.24 ± 9.62	52.82 ± 10.14	0.417
Systolic blood pressure, mm Hg	124.86 ± 17.80	124.50 ± 17.67	127.59 ± 18.57	0.001
Diastolic blood pressure, mm Hg	75.46 ± 11.16	75.56 ± 11.15	74.68 ± 11.18	0.116
Gensini score	40 (12, 74)	40 (14, 72)	42 (6, 88)	0.142
Total cholesterol, mmol/L	3.93 ± 0.99	3.92 ± 1.00	4.02 ± 0.91	0.041
HDL cholesterol, mmol/L	1.01 ± 0.28	1.01 ± 0.28	0.99 ± 0.27	0.158
LDL cholesterol, mmol/L	2.37 ± 0.84	2.36 ± 0.84	2.45 ± 0.77	0.026
Triglyceride, mmol/L	1.40 (1.08-1.89)	1.40 (1.07-1.89)	1.45 (1.10-1.87)	0.902
Apolipoprotein A-I, mg/dL	1.25 ± 0.27	1.25 ± 0.27	1.23 ± 0.28	0.111
Apolipoprotein B, mg/dL	0.86 ± 0.29	0.85 ± 0.29	0.89 ± 0.28	0.028
hsCRP, mg/L	2.09 (0.98-5.59)	1.99 (0.96-5.25)	2.96 (1.31-10.18)	0.001
Fasting plasma glucose, mmol/L	6.11 ± 2.01	6.07 ± 1.95	6.39 ± 2.44	0.002
Hemoglobin A_{1c}, %	6.45 ± 1.22	6.43 ± 1.21	6.65 ± 1.25	0.001
Total bilirubin, μmol/L	14.47 ± 5.18	14.35 ± 5.00	15.41 ± 6.44	<0.001
Medication				
ACE inhibitor/ARB	1,365 (35.8)	1,203 (35.7)	162 (36.8)	0.648
Beta-blockers	2,013 (52.8)	1,775 (52.7)	238 (54.1)	0.579
Aspirin	2,874 (75.5)	2,582 (76.6)	292 (66.4)	0.001
Statins	2,665 (70.0)	2,401 (71.3)	264 (60.0)	0.001
CCB	610 (16.0)	539 (16.0)	71 (16.1)	0.941

Values are mean ± SD, n (%), or median (IQR) unless otherwise indicated.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CCB = calcium channel blocker; CVD = cardiovascular disease; HDL = high-density lipoprotein; ; hsCRP = high-sensitivity C-reactive protein; LDL = low-density lipoprotein; LVEF = left ventricular ejection fraction; MACE = major adverse cardiovascular event(s); STEMI = ST-segment elevation myocardial infarction.

differences were found in Gensini score, LDL-C, and triglycerides.

All participants were separated into 3 groups based on TBil concentrations (group 1: RI tertiles 1+2, 5.1-14.3 μmol/L, n = 1,973; group 2: RI tertile 3, 14.4-17.1 μmol/L, n = 987; group 3: above RI, >17.1 μmol/L, n = 849). Detailed baseline data are shown in **Table 2**. We found statistically significant differences among the 3 groups in age, sex, body mass index, history of previous STEMI, and HbA_{1c} levels. There was no significant differences among these 3 groups regarding hypertension, diabetes, total cholesterol, LDL-C, apolipoprotein B, hsCRP, and FPG. The correlation analyses further showed that TBil levels were moderately and inversely associated with left ventricular ejection fraction, but no significant correlations were found with TBil and age, Gensini score, hsCRP, FPG, or HbA_{1c} (Supplemental Table 1).

ASSOCIATION OF TBil WITH CLINICAL OUTCOMES. The median duration of follow-up was 4.0 (IQR: 2.4-5.8) years, during which 440 MACEs (39 nonfatal MIs, 51 ischemic strokes, 118 ischemia-driven target-vessel revascularizations, and 232 cardiovascular deaths) were identified. Obviously, patients in group 1 (11.3%) and group 3 (15.0%) had a significantly higher incidence of MACE than did those in group 2 (9.1%; $P < 0.001$) (**Figure 1**). Kaplan-Meier survival analyses showed a significant difference in the incidence of MACE among the 3 groups at the 4-year follow-up, with the highest cumulative event-free survival rates in group 2 (log-rank $P = 0.004$). When hard endpoints and all-cause mortality were considered respectively, group 2 also had significantly higher event-free survival rates than groups 1 and 3 did.

Restricted cubic spline analyses showed J-curved associations between TBil levels and the risk of

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TABLE 2 Baseline Characteristics of Study Patients According to TBil Levels

	TBil, μmol/L			
	Group 1: RI Tertile 1+2 (n = 1,973)	Group 2: RI Tertile 3 (n = 987)	Group 3: 17.1 (n = 849)	*P* Value
Age, y	62.38 ± 16.36	60.30 ± 14.85	61.74 ± 16.75	0.004
Male	1,470 (74.5)	830 (84.1)	733 (86.3)	0.001
Body mass index, kg/m^2	24.13 ± 3.04	24.48 ± 2.93	24.31 ± 3.15	0.012
Family history of CVD	259 (13.1)	118 (12.0)	94 (11.1)	0.284
Current smoker	1,164 (59.0)	616 (62.4)	511 (60.2)	0.202
Hypertension	1,165 (59.0)	618 (62.6)	512 (60.3)	0.174
Diabetes	626 (31.7)	287 (29.1)	240 (28.3)	0.119
Prior revascularization	706 (35.8)	359 (36.4)	333 (39.2)	0.214
STEMI	1,085 (55.0)	615 (62.3)	532 (62.7)	0.001
LVEF	53.57 ± 9.20	52.83 ± 10.23	52.73 ± 10.06	0.042
Systolic blood pressure, mm Hg	124.40 ± 17.86	125.53 ± 17.54	125.15 ± 17.97	0.381
Diastolic blood pressure, mm Hg	74.55 ± 10.78	76.50 ± 11.80	76.36 ± 11.08	0.001
Gensini score	40 (14, 72)	42 (14, 76)	40 (8, 74)	0.371
Total cholesterol, mmol/L	3.97 ± 1.01	3.91 ± 0.96	3.87 ± 0.97	0.053
HDL cholesterol, mmol/L	1.01 ± 0.29	1.01 ± 0.28	1.01 ± 0.28	0.917
LDL cholesterol, mmol/L	2.39 ± 0.84	2.36 ± 0.83	2.33 ± 0.83	0.191
Triglyceride, mmol/L	1.43 (1.08-1.94)	1.40 (1.09-1.88)	1.36 (1.05-1.82)	0.122
Apolipoprotein A-I, mg/dL	1.25 ± 0.27	1.25 ± 0.29	1.25 ± 0.26	0.693
Apolipoprotein B, mg/dL	0.86 ± 0.28	0.87 ± 0.28	0.85 ± 0.31	0.524
hsCRP, mg/L	2.28 (1.08-5.97)	1.99 (0.94-5.21)	1.84 (0.86-5.33)	0.721
Fasting plasma glucose, mmol/L	6.15 ± 2.08	6.00 ± 1.87	6.14 ± 2.00	0.116
Hemoglobin A_{1c}, %	6.52 ± 1.26	6.37 ± 1.14	6.40 ± 1.21	0.007
TBil, μmol/L	10.77 ± 2.20	15.48 ± 0.77	21.90 ± 4.48	<0.001

Values are mean ± SD, n (%), or median (IQR) unless otherwise indicated.
TBil = total bilirubin; other abbreviations as in Table 1.

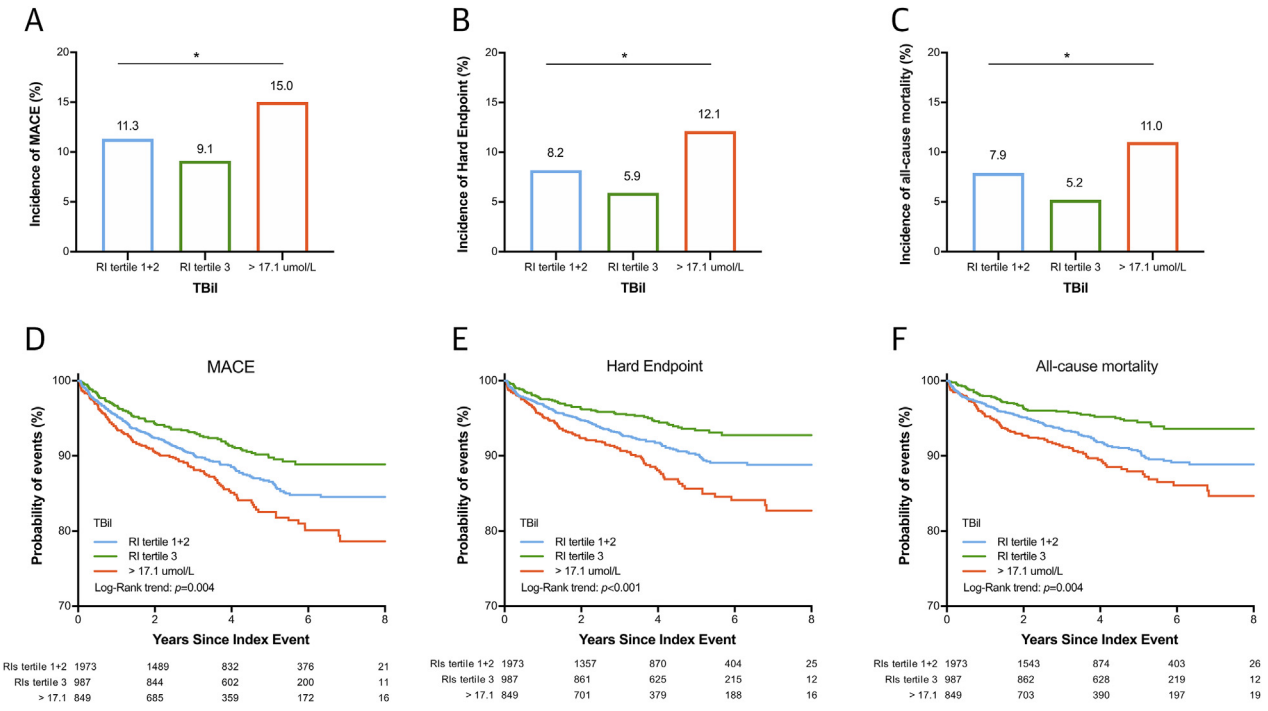
MACE, hard endpoints, and all-cause mortality (all *P* values for nonlinearity <0.05) (Supplemental Figure 2). As presented in **Figure 2** and Supplemental Table 2, the results of univariable analysis showed that in comparisons with patients in group 1, the HRs for MACE were 0.72 (95% CI: 0.56-0.91) for patients in group 2 and 1.30 (95% CI: 1.05-1.62) for those in group 3 (both $P < 0.05$). In Cox regression analyses with adjustment for sex and age, those in group 2 had the lowest risk for MACE incidence (HR: 0.76; 95% CI: 0.60-0.97), whereas those in group 3 had a higher risk for MACE incidence (HR: 1.28; 95% CI: 1.03-1.60) in comparison to patients in group 1. In the fully adjusted model, adjusting for the various cardiovascular risk factors, TBil was associated with lower likelihood of having MACE among participants with higher TBil levels within the RI (HR: 0.76; 95% CI: 0.59-0.96) and higher likelihood of having MACE among participants with elevated TBil levels (>17.1 μmol/L) (HR: 1.29; 95% CI: 1.03-1.61).

To further test the robustness of the association between TBil levels and long-term prognosis, we carried out sensitivity analysis (Supplemental Table 3). The significant associations between TBil levels and each endpoint remained unchanged in sensitivity analysis in which each of the other significant variables in univariate analysis was forced into the model. We also evaluated whether TBil would further increase the predictive value of conventional risk factors (Supplemental Table 4). Applying C-statistic, the AUC improved by adding TBil to the conventional model: for MACE increased from 0.687 to 0.714 ($P = 0.024$), for hard endpoints increased from 0.770 to 0.798 ($P = 0.036$) and for all-cause mortality increased from 0.811 to 0.837 ($P = 0.039$).

DISCUSSION

In the current study, the long-term association between circulating TBil levels and adverse cardiovascular events in patients with previous MI was evaluated. The results showed a J-shaped association between TBil levels and risk of MACE incidence,

FIGURE 1 **TBil and Different Clinical Outcomes During Follow-Up**

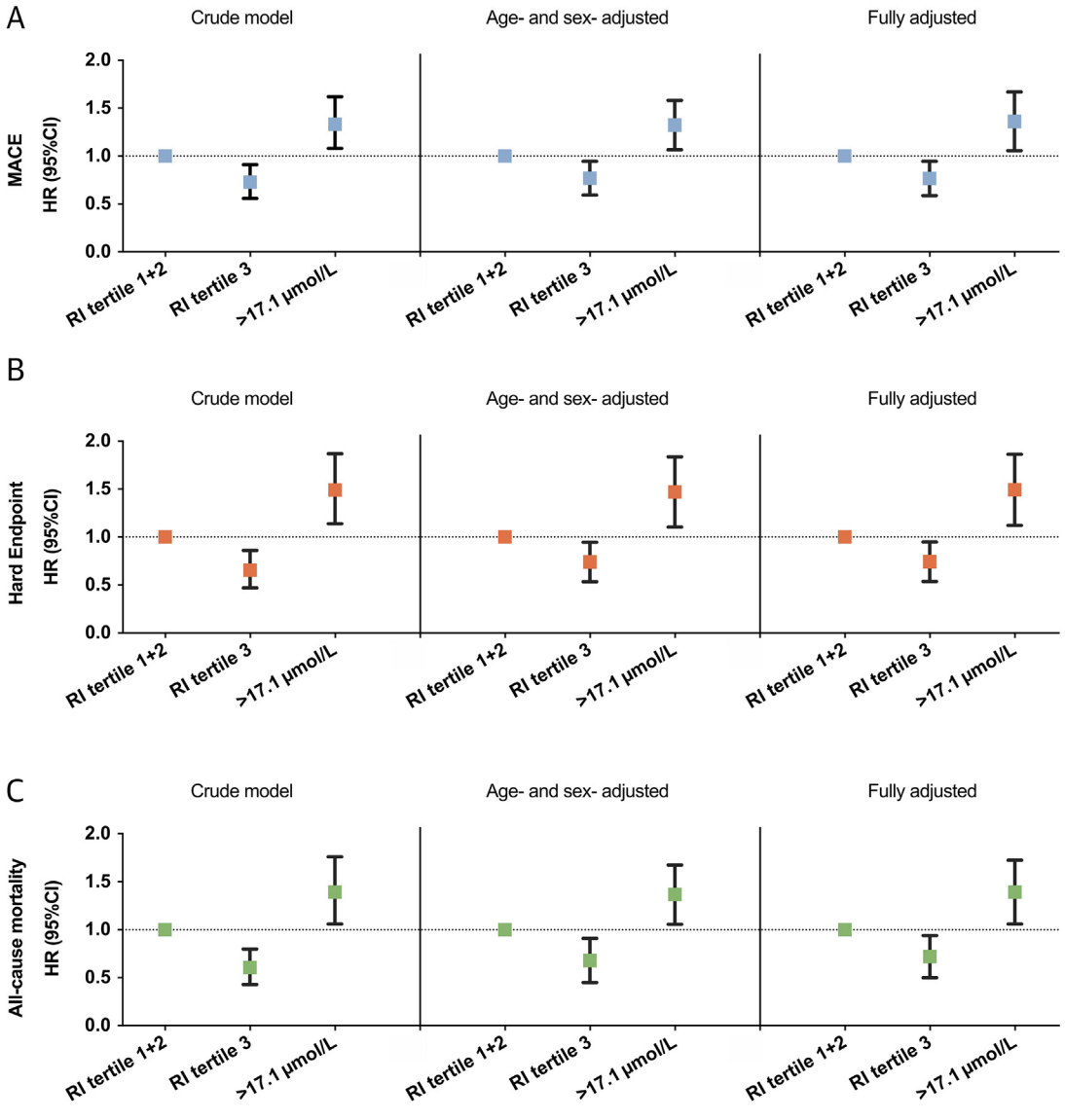


The incidence of **(A)** major adverse cardiovascular event (MACE), **(B)** hard endpoint, and **(C)** all-cause mortality during follow-up. Kaplan-Meier curves for **(D)** MACE, **(E)** hard endpoint, and **(F)** all-cause mortality during follow-up. RI = reference interval; TBil = total bilirubin. *$P < 0.05$.

which might indicate that only moderately elevated TBil levels within physiological concentration range contributed to decreased risk for MACE incidence and when the TBil level exceeded 17.1 μmol/L, the harmful effects gradually appeared with increasing bilirubin levels (**Central Illustration**). As a novel finding, we observed that clinical outcome is related to tertiles of normal TBil levels and elevated levels, clearly demonstrating that the association between TBil and cardiovascular events is not a simple linear relationship in patients who are post-MI. Thus, the present study provided novel information and evidence for the clinical application of this biomarker.

Traditionally, TBil is considered as a potentially toxic metabolite and could cause damage to the central nervous system.[9,10] It was not until the 1980s that researchers discovered that TBil plays a complex role in vivo: TBil is toxic at high doses, but within the physiologic range it could serve as a powerful endogenous antioxidant.[8] Subsequent evidence has also showed that TBil may be a protective factor for atherosclerosis by inhibiting oxidative modification of LDL-C and activity of human protein kinase C, reducing the levels of proinflammatory cytokines, and increasing the solubility of serum cholesterol.[9,25,26] With the experimental investigation, researchers further assessed the associations between TBil and clinical outcomes in various clinical settings but did not reach a consistent conclusion. Some studies showed that TBil was a protective factor of MACE, whereas other reports supported a positive linear association between higher TBil levels and poor functional outcomes.[16-18] Previous studies also have reported a nonlinear relationship between TBil and CVD, which is consistent with our findings.[19,20,22] Breimer et al[19] first reported a U-shaped relationship between TBil levels and risk of ischemic heart disease in middle-aged British men without CVD. Another prospective study including Chinese elderly individuals free of CVD also confirmed the U-shaped association.[20] Additionally, Horsfall et al[21] identified

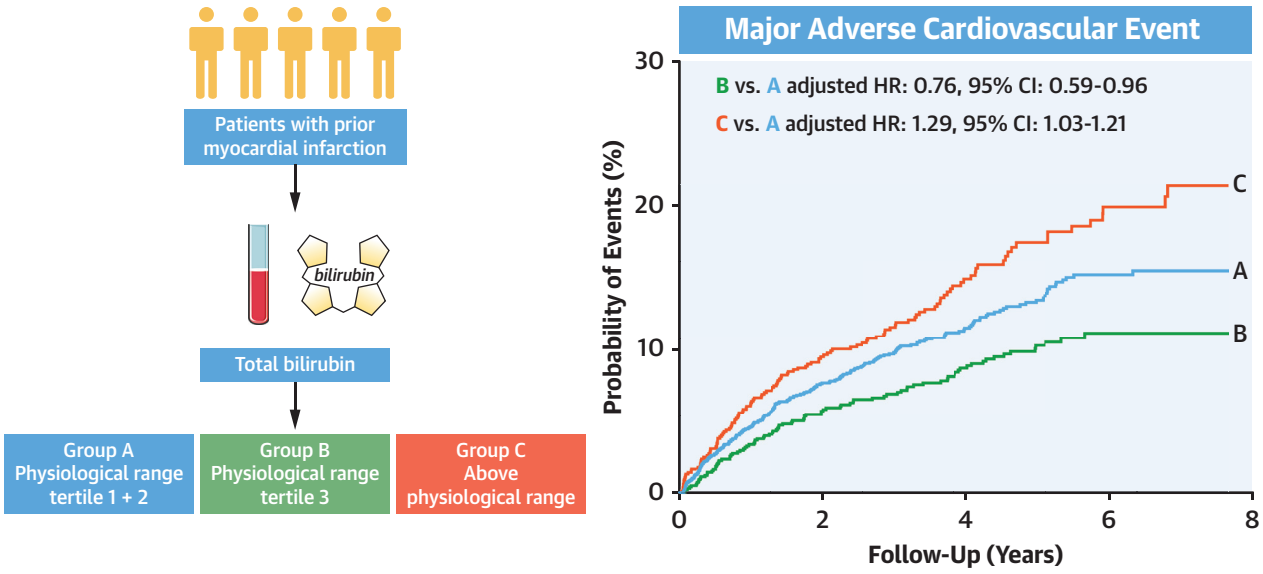
FIGURE 2 **Forest Plots for the HRs of Different Clinical Outcomes**



Forest plots for **(A)** MACE, **(B)** hard endpoint, and **(C)** all-cause mortality. Abbreviations as in **Figure 1**.

patients from a primary care database and reported an L-shaped association between TBil and CVD incidence. More recently, a meta-analysis of 12 prospective studies enrolling general populations also revealed a U-shaped dose-response relationship.[22] Regardless of whether the relationship is U-patterned or L-shaped, these studies indicate that the association is not linear in the general population. These studies also showed that the protective effect of TBil level on CVD might be strongest in the range of 15-20 μmol/L,[22,27] which is in line with our findings that the lowest risk of MACE was observed in participants with a TBil of 14.4-17.1 μmol/L. Hence, the current report extends a nonlinear relationship to a setting of secondary prevention in patients at very-high CVD risk.

CENTRAL ILLUSTRATION **Total Bilirubin and Clinical Outcomes in Patients With Prior Myocardial Infarction**



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Patients with prior myocardial infarction within the physiological range of total bilirubin (TBil) were substratified into tertiles. Group A (blue) was defined as TBil values in the lower 2 tertiles, group B (green) as TBil values in the top tertile, and group C (red) as TBil values above physiological range (>17.1 μmol/L). The results showed a J-shaped association between TBil levels and risk of major adverse cardiovascular event incidence, which implied that moderately elevated TBil levels within the physiological range has a protective effect, whereas TBil levels that exceeded 17.1 μmol/L increased the cardiovascular risk. Major adverse cardiovascular event was defined as nonfatal myocardial infarction, nonfatal ischemic stroke, coronary revascularization, and cardiovascular death.

Although a number of studies have evaluated the predictive value of TBil, most of them focused on the general population.[16-18] With respect to MI, most studies evaluated patients in the acute phase of disease, whereas data are lacking concerning the impact of TBil in patients with prior MI. Chung et al[28] included 1,111 patients with STEMI undergoing percutaneous coronary intervention and found that initial high TBil was a significant predictor of in-hospital MACE. Similar observations were also made in a prospective study recruiting patients with HF following MI, by demonstrating that patients with a TBil concentration of >17.1 μmol/L had a significantly higher risk of cardiovascular mortality and all-cause mortality at 90 days.[14] However, another retrospective analysis suggested there was no significant relation between TBil and 2-year mortality in 670 patients with acute MI.[29] More recently, a retrospective study enrolling 3,708 patients with STEMI showed that the cumulative survival rate was significantly lower in patients who had a TBil level of ≥22 μmol/L.[30] The discrepancy in these studies may be attributed to different endpoints, study designs, or ethnicities. In the present study with a larger sample size and long-term follow-up period, we found that the association between TBil and cardiovascular events did not follow a simple linear trend but is more consistent with the J-shaped model in patients with previous MI. Undoubtedly, this study adds relevant information to the published reports regarding the prognostic implications of TBil in secondary prevention.

Although the exact underlying mechanisms are still unclear, there are several potential mechanisms that may explain the associations of TBil and clinical outcomes. On one hand, as alluded to in the introduction section, TBil has antioxidant and anti-inflammatory activities within the physiological concentration that are reported to play a protective role in the occurrence and development of CVD.[8,9] For example, monocyte migration plays an important role in atherosclerotic lesion progression. Previous studies showed that TBil blocked tumor necrosis factor-α-stimulated monocyte migration, with maximal inhibition within the upper-normal physiological range.[26] On the other hand, elevated TBil levels could represent an increased chronic inflammation response and oxidative stress response

predicting a dismal prognosis.[31] Moreover, high TBil concentrations accumulated within biological tissues might cause cell toxicity and tissue injury.[8] It also should be noted that elevated TBil levels beyond the normal range might indicate potential hepatocellular injury such as hepatic or obstructive jaundice, while being associated with increased risk of CVD incidence.[10] Furthermore, a high level of TBil may result from reduced arterial perfusion of the liver caused by cardiac dysfunction, because TBil was reported to be independently associated with the development of post percutaneous coronary intervention coronary no-reflow phenomenon and high thrombus burden in patients with MI.[30,32] Furthermore, TBil has been found to be inversely correlated with left ventricular ejection fraction.[14] Consequently, the J-shaped association might be the result of a combined effect of potential antioxidant effect and hepatocellular toxicity. Nevertheless, these speculations require further investigation.

The important clinical implications of our study provided detailed evidence regarding the prognostic value of TBil for secondary adverse cardiovascular events. Another important practical implication is that TBil is a low-cost, noninvasive, and easily measured biomarker. Also, TBil provides prognostic information and might help the clinician to further risk stratify patients who are post-MI.

STUDY LIMITATIONS. This is the first study to focus on the prognostic role of TBil in patients with a history of MI. Moreover, we evaluated the nonlinear correlation between TBil and long-term adverse cardiovascular events and, for the first time, propose a J-shaped association between circulating TBil levels and poor prognosis. We only recorded the baseline levels of TBil, which might have a dynamic change during the follow-up period. Moreover, we did not record the SYNTAX (Synergy Between Percutaneous Coronary Interventions With Taxus and Cardiac Surgery) score, which was independently associated with serum TBil level in patients with acute MI in previous studies.[33] Furthermore, although the results showed an inverse relationship between TBil and left ventricular ejection fraction in line with previous studies,[14] any other measures of HF including peripheral edema, jugular venous pressure, and echocardiography were not recorded. Furthermore, TBil concentrations might be affected by exercise and higher intake of fruits and vegetables, which could not be adjusted for in our analysis.[34] Finally, we could not deal with the question of causality because the design of the study was observational. Future investigations with larger sample sizes and longitudinal measures of TBil levels and MACE are warranted to overcome these limitations and to verify and validate our findings.

CONCLUSIONS

A J-shaped association existed between TBil and risk of adverse events incidence, which implied that moderately elevated TBil levels within the physiological range have a protective effect, whereas TBil level exceeding 17.1 μmol/L increased the cardiovascular risk. Further studies are needed to confirm our findings and identify the potential mechanisms of the J-shaped association.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Our analysis firstly showed a J-shaped association among TBil levels and risk of major adverse cardiac events, hard endpoints, and all-cause mortality, which implied that only moderately elevated TBil levels within physiological concentration range contribute to decreased risk for adverse events incidence.

TRANSLATIONAL OUTLOOK: Circulating TBil levels may be useful for long-term risk prediction and stratification of recurrent cardiovascular events in patients with previous MI.

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KEY WORDS myocardial infarction, prognosis, total bilirubin

APPENDIX For supplemental figures and tables, please see the online version of this paper.