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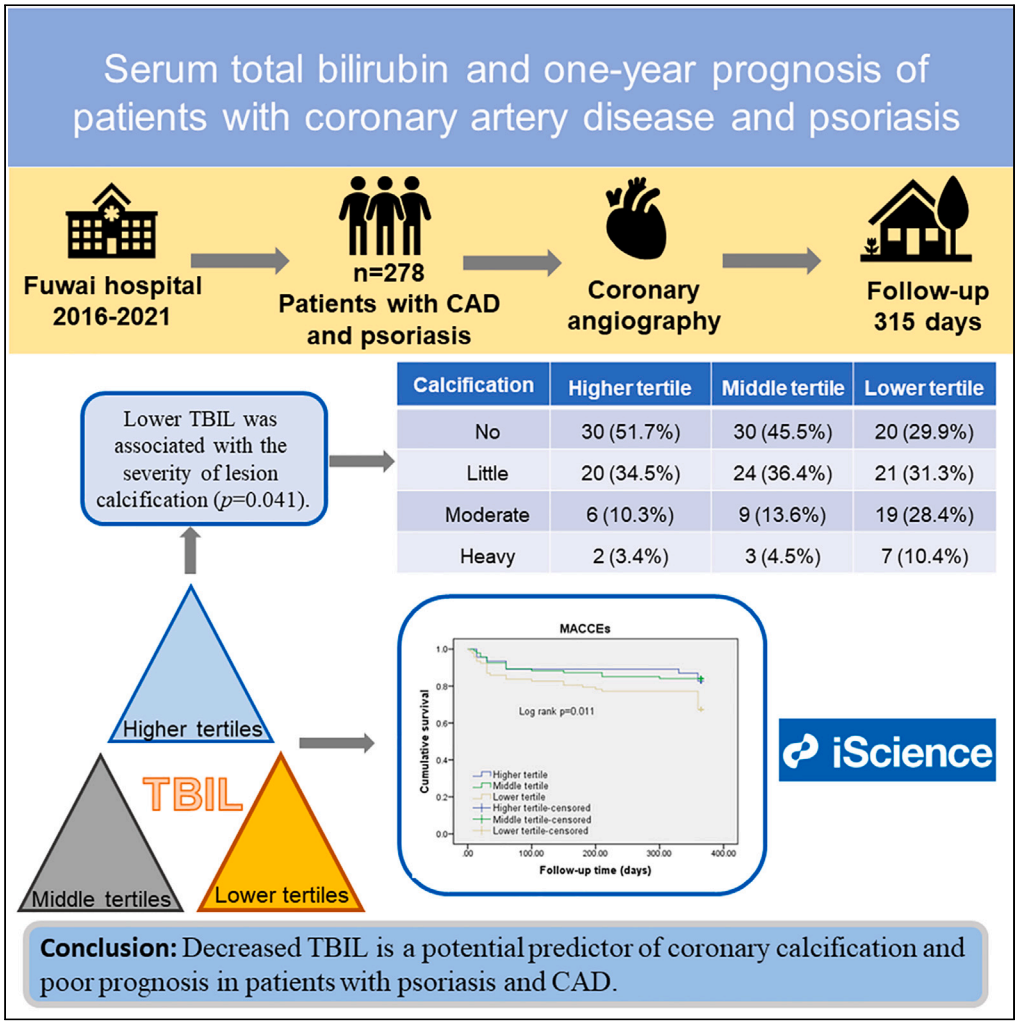

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Highlights

Lower TBIL is a potential predictor of severe coronary artery calcification

Decreased TBIL is associated with poor prognosis in psoriasis patients

The characteristics of coronary angiography in psoriasis patients were detailed

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Serum total bilirubin and one-year prognosis of patients with coronary artery disease and psoriasis

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SUMMARY

To evaluate the potential predictive value of total bilirubin (TBIL) for one-year prognosis in patients with coronary artery disease (CAD) and psoriasis. 278 psoriasis patients who underwent coronary angiography and were diagnosed as CAD were recruited. Baseline TBIL was measured at admission. Patients were divided into three groups according to the third tertiles of TBIL. The coronary angiography showed that lower TBIL was associated with the severity of lesion calcification. After a mean follow-up of 315 days, major adverse cardiac and cerebrovascular events (MACCEs) were reported in 61 patients. Compared with patients with higher TBIL tertiles, the incidence of MACCEs increased significantly in patients with middle and lower TBIL tertiles. The incidence of MACCEs in one-year follow-up was significantly different between higher and lower tertiles. The findings indicate that decreased TBIL is a potential predictor of poor prognosis in patients with psoriasis and CAD.

INTRODUCTION

Psoriasis is a chronic inflammatory, systemic disease that affects skin, nail, and arthritis.[1] It affects 1–4% population in the world and has a significant impact on patients' quality of life.[2] It has been reported that psoriasis is associated with an increased prevalence of cardiovascular disease, which is underestimated in traditional cardiovascular risk evaluation.[3] Previous studies have shown that enhanced inflammation and oxidative stress is involved in pathogenesis of psoriasis.[4] Serum total bilirubin (TBIL) is a product of heme metabolism, including indirect and direct bilirubin, has been suggested to exert potential endogenous anti-oxidative and anti-inflammatory effects at the physiological level.[5] A number of researchers have reported that patients with lower serum TBIL levels showed endothelial dysfunction and proliferation of smooth muscle cells (SMC).[5,6] Sevket Balta showed that lower TBIL is associated with an increased risk of atherosclerosis and carotid intima media thickness (CIMT) in patients with psoriasis, which predict coronary artery disease (CAD).[7] Circulating TBIL is inversely and independently associated with CAD risk in general population.[8] However, the association between TBIL and an increased risk of cardiovascular events in patients with psoriasis and CAD has not been elaborated. The effect of TBIL on cardiovascular lesions has not been reported, and few previous studies have investigated whether TBIL is an independent risk factor for major adverse cardiac and cerebrovascular events (MACCEs) in patients with CAD and psoriasis. Thus, the aim of this study is to systematically evaluate the potential associations between serum TBIL with severity of coronary artery lesion and one-year prognosis in patients with psoriasis and CAD.

RESULTS

Baseline characteristics

The baseline characteristics of a total of 278 patients were presented in Table 1. The results showed that patients with higher TBIL levels were probable to be males ($p = 0.001$), smokers ($p = 0.038$) and with higher erythrocyte sedimentation rate (ESR) ($p < 0.001$). No significant difference was observed in age ($p = 0.679$), BMI ($p = 0.135$), history of hypertension ($p = 0.318$), diabetes ($p = 0.384$), hyperlipemia ($p = 0.334$), and family history of CAD ($p = 0.930$) among three tertiles. The duration of psoriasis ($p = 0.758$), PASI score ($p = 0.878$), biologic therapy ($p = 0.971$), and nonbiologic systemic therapy ($p = 0.076$) showed no difference among three groups.

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Table 1. The baseline characteristics of a total of 278 patients with psoriasis and CAD

Variables	Higher tertile (TBIL ≥ 14.203) n = 92	Middle tertile (9.528 < TBIL < 14.203) n = 94	Lower tertile (TBIL ≤ 9.528) n = 92	*t/K/χ2*	*p*
Age (years)	59 (59, 64)	58 (53, 64)	61 (52, 65)	0.744	0.679
Sex				13.463	**0.001**
Male (n = 241)	84 (34.9%)	87 (36.1%)	70 (29.0%)		
Female (n = 37)	8 (21.6%)	7 (18.9%)	22 (59.5%)		
BMI (kg/m2)	26.6 (24.3, 28.6)	26.0 (24.0, 28.2)	25.15 (23.3, 27.7)	3.998	0.135
Hypertension, n (%)	59 (64.1%)	50 (53.2%)	54 (58.7%)	2.294	0.318
Diabetes, n (%)	29 (31.5%)	35 (37.2%)	38 (41.3%)	1.913	0.384
Hyperlipemia, n (%)	88 (95.7%)	90 (95.7%)	84 (91.3%)	2.192	0.334
CAD family history	12 (13.0)	13 (13.8%)	11 (12.0%)	0.146	0.930
Smoking history, n (%)	65 (70.7%)	65 (69.1%)	50 (54.3%)	6.562	**0.038**
Diagnosis				2.677	0.262
CCS, n (%)	41 (44.6%)	31 (33.0%)	37 (40.2%)		
ACS, n (%)	51 (55.4%)	63 (67.0%)	55 (59.8%)		
LVEF (%)	62 (58, 65)	62 (58, 65)	62 (57, 65)	0.130	0.937
Creatinine (μmol/L)	85.7 (75.1, 95.1)	86.0 (76.3, 94.2)	79.8 (71.5, 90.7)	4.008	0.135
FBG (mmol/L)	5.76 (5.19, 7.62)	6.01 (5.13, 7.86)	6.40 (5.32, 9.44)	3.088	0.213
HbA1c (%)	6.2 (5.7, 6.9)	6.2 (5.7, 7.9)	6.3 (5.3, 9.4)	3.214	0.201
TG (mmol/L)	1.47 (1.11, 2.20)	1.52 (1.07, 1.97)	1.49 (1.04, 2.02)	1.022	0.600
TC (mmol/L)	3.67 (3.15, 4.42)	3.85 (3.24, 4.58)	3.70 (3.13, 4.32)	1.231	0.540
LDL-C (mmol/L)	2.14 (1.78, 2.79)	2.29 (1.76, 2.89)	2.06 (1.62, 2.64)	2.537	0.281
HDL-C (mmol/L)	1.09 (0.89, 1.22)	1.04 (0.91, 1.29)	1.04 (0.89, 1.26)	0.120	0.942
hs-crp (mg/L)	1.47 (0.64, 2.99)	1.52 (0.62, 3.93)	1.78 (0.65, 5.49)	2.652	0.265
ESR (mm/h)	5 (2, 8)	8 (3, 7)	10 (5, 22)	21.58	**<0.001**
Time of psoriasis (years)	23.66 ± 10.93	23.02 ± 11.71	24.35 ± 13.39	0.277	0.758
PASI score	7.49 ± 8.05	7.29 ± 8.31	7.90 ± 8.52	0.130	0.878
Biologic treatment, n (%)	8 (8.7%)	9 (9.6%)	8 (8.7%)	0.059	0.971
Nonbiologic systemic treatment, n (%)	24 (26.1%)	26 (27.7%)	37 (40.2%)	5.145	0.076
Severity of lesions					
LM ≥ 50%, n (%)	13 (14.1%)	11 (11.7%)	5 (5.4%)	3.968	0.138
Multi-vessel disease, n (%)	36 (39.1%)	39 (41.5%)	43 (46.7%)	1.143	0.565
Proximal/ostial lesion, n (%)	43 (46.7%)	45 (47.9%)	42 (45.7%)	0.092	0.955
Medications after discharge					
Antiplatelet drugs, n (%)	76 (82.6%)	84 (89.4%)	84 (91.3%)	3.576	0.167
β-receptor blockers, n (%)	69 (75.0%)	62 (66.0%)	67 (72.8%)	2.027	0.363
ACEI/ARB/ARNI, n (%)	41 (44.6%)	50 (53.2%)	49 (53.3%)	1.847	0.397
CCB, n (%)	21 (22.8%)	15 (16.0%)	21 (22.8%)	1.801	0.406
SGLT2 inhibitors	7 (7.6%)	7 (7.4%)	12 (13.0%)	2.211	0.331
Statins, n (%)	89 (96.7%)	91 (96.8%)	91 (98.9%)	1.148	0.563
PCSK9 inhibitors, n (%)	2 (2.2%)	1 (1.1%)	1 (1.1%)	0.524	0.769
Ezetimibe, n (%)	23 (25.0%)	22 (23.4%)	33 (35.9%)	4.216	0.121

CAD, Coronary artery disease; TBIL, Total bilirubin; BMI, Body mass index; CCS, Chronic coronary syndrome; ACS, Acute coronary syndrome; LVEF, Left ventricular ejection fraction; FBG, Fasting blood glucose; HbA1c, Glycated hemoglobin; TG, Triglyceride; TC, Total cholesterol; LDL-C, Low density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; ESR, Erythrocyte sedimentation rate; PASI, Psoriasis Area and Severity Index; LM, Left main branch; ACEI, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin receptor blockers; ARNI, Angiotensin receptor neprilysin inhibitors; CCB, Calcium-channel-blocker; SGLT2, inhibitors Sodium-glucose cotransporter 2 inhibitors; PCSK9, inhibitors Proprotein convertase subtilisin/kexin-type 9 inhibitors.
Values of $p < 0.05$ are indicated in bold.

Table 2. Characteristics of target lesions in coronary angioplasty

Variables	Higher tertile (TBIL ≥ 14.203) n = 58	Middle tertile (9.528 < TBIL < 14.203) n = 66<	Lower tertile (TBIL ≤ 9.528) n = 67	$K/\chi 2$	p
Lesion types				6.189	0.402
Type A	5 (8.6%)	7 (10.6%)	3 (4.5%)		
Type B1	6 (10.4%)	9 (13.6%)	8 (11.9%)		
Type B2	17 (29.3%)	9 (13.6%)	15 (22.4%)		
Type C	30 (51.7%)	41 (62.1%)	41 (61.2%)		
Targeted lesion length (mm)	20.50 (15.00, 32.25)	25.00 (16.00, 35.75)	27.00 (18.00, 38.00)	2.949	0.229
Lesion length[a]				5.565	0.234
Discrete	10 (17.2%)	5 (7.6%)	4 (6.0%)		
Tubular	12 (20.7%)	19 (28.8%)	19 (28.4%)		
Diffuse	36 (62.1%)	42 (63.6%)	44 (65.7%)		
Eccentric lesion	50 (86.2%)	56 (84.8%)	59 (88.1%)	0.294	0.863
Irregular contour	46 (79.3%)	54 (81.8%)	60 (89.6%)	2.681	0.262
Angulation				10.769	0.052
Non-angulated	30 (51.7%)	33 (50.0%)	29 (43.3%)		
Moderate angulated	23 (39.7%)	33 (50.0%)	37 (55.2%)		
Extremely angulated	5 (8.6%)	0 (0.0%)	1 (1.5%)		
Calcification				12.856	**0.041**[b]
No calcification	30 (51.7%)	30 (45.5%)	20 (29.9%)		
Little calcification	20 (34.5%)	24 (36.4%)	21 (31.3%)		
Moderate calcification	6 (10.3%)	9 (13.6%)	19 (28.4%)		
Heavy calcification	2 (3.4%)	3 (4.5%)	7 (10.4%)		
Ostial segment involvement	12 (20.7%)	9 (13.6%)	6 (9.0%)	3.548	0.170
Major branch involvement	18 (31.0%)	18 (27.3%)	22 (32.8%)	0.504	0.777
Some thrombus present	4 (6.9%)	3 (4.5%)	6 (9.0%)	1.041	0.592
In-Stent Restenosis	6 (10.3%)	4 (6.1%)	9 (13.4%)	2.032	0.362
Stenoses before angioplasty (%)	90 (90, 100)	90 (80, 99)	90 (80, 100)	1.010	0.604
Stenoses after angioplasty (%)	0 (0, 0)	0 (0, 0)	0 (0, 0)	2.370	0.306
Total occlusion	12 (20.7%)	15 (22.7%)	21 (31.3%)	2.185	0.335
Total time of angioplasty	34.50 (20.00, 57.75)	30.00 (21.75, 49.25)	35.00 (24.00, 55.00)	2.333	0.311

TBIL, Total bilirubin.

Values of $p < 0.05$ are indicated in bold.

[a]Lesion length: discrete (< 10mm), tubular (10-20mm) and diffuse (> 20mm). Angulation: Non-angulated (< 45°), moderate angulated (> 45°, < 90°), and extremely angulated (> 90°).

[b]Higher TBIL was associated with the severity of lesion calcification ($p = 0.041$). Column proportions compare (Bonferroni method) was performed to clarify the difference of calcification, which indicated that compared with patients in higher tertile group, patients in lower TBIL tertile were more likely to have moderate coronary artery calcification and less likely to be without calcification.

Potential association between TBIL and severity of target lesions

Among the 278 patients, 191 (68.7%) patients were prepared to get angioplasty. Finally, 158 patients underwent successful coronary stent implantation, 23 patients underwent successful balloon angioplasty, and 10 patients failed with angioplasty. Table 2 shows the characteristics of target lesions. The results showed that the severity of lesion calcification is significantly different among three tertiles ($p = 0.041$). Column proportions comparison indicated that compared with patients in higher tertile group, patients in lower TBIL tertile were more likely to have moderate coronary artery calcification and less likely to be without calcification. All 191 patients who were prepared to get angioplasty were grouped based on calcification: no and mild calcification (n = 145), moderate and severe calcification (n = 46). In order to investigate the association between cardiovascular risk factors and calcification, multivariate regression analysis

Table 3. The 1-year prognosis of a total of 278 patients with psoriasis and CAD

Variables	Higher tertile (TBIL ≥ 14.203) n = 92	Middle tertile (9.528 < TBIL < 14.203) n = 94	Lower tertile (TBIL ≤ 9.528) n = 92	$t/K/\chi 2$	p
MACCE	16 (17.4%)	15 (16.0%)	30 (32.6%)	9.189	**0.010**
All-cause death, n (%)	2 (2.2%)	1 (1.1%)	6 (6.5%)	4.918	0.106
Cardiac death, n (%)	1 (1.1%)	1 (1.1%)	5 (5.4%)	4.766	0.204
Non-fatal MI, n (%)	6 (6.5%)	6 (6.4%)	13 (14.1%)	4.436	0.109
Non-fatal stroke, n (%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	2.029	0.363
Unplanned revasculation, n (%)	1 (1.1%)	4 (4.3%)	7 (7.6%)	4.738	0.090
Rehospitalization, n (%)[a]	6 (6.5%)	4 (4.3%)	4 (4.3%)	0.636	0.787

CAD, Coronary artery disease; TBIL, Total bilirubin; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction.
Values of $p < 0.05$ are indicated in bold.
[a]Rehospitalization was defined as readmission to hospital because of heart failure or angina.

was performed and the results were presented in Table S1. After adjusted for age, sex, BMI, hypertension, hyperlipemia, diabetes, smoking history, biologic therapy and the use of statins, multivariate regression analysis showed that lower TBIL was independently associated with coronary artery calcification, with an adjusted OR and 95% CI of 0.919 (0.850–0.993) for TBIL ($p = 0.032$).

Incidence of MACCEs according to the TBIL

Table 3 shows the incidence of clinical outcomes during a mean follow-up of 315 days. The incidence of MACCEs increased significantly in patients with lower serum TBIL ($p = 0.010$). However, the incidence of all-cause death ($p = 0.106$), cardiac death ($p = 0.204$), non-fatal myocardial infarction (MI) ($p = 0.109$), non-fatal stroke ($p = 0.363$), unplanned revasculation ($p = 0.090$), and rehospitalization because of heart failure and angina ($p = 0.787$) was not, respectively, statistically different.

As shown in Figure 1 A, Kaplan-Meier analysis demonstrated that the incidence of MACCEs in one-year follow-up was significantly different between higher and lower tertiles ($p = 0.018$), but not significant between higher and middle tertiles ($p = 0.839$). The incidence of all-cause death ($p = 0.069$), cardiac death ($p = 0.076$), non-fatal MI ($p = 0.088$), non-fatal stroke ($p = 0.392$), unplanned revasculation ($p = 0.080$), and rehospitalization because of heart failure and angina ($p = 0.781$) was not significantly different among three tertiles of TBIL as shown in Figure 1B–G.

Stratified analysis

Figure 2 showed the results of stratified analyses by sex, age, BMI, hypertension, diabetes, smoking history, and diagnosis. Only males ($p = 0.043$), age < 60 ($p = 0.028$), BMI < 26 ($p = 0.036$), diabetes ($p = 0.037$), and acute coronary syndrome (ACS) patients ($p = 0.031$) showed a significant association with increased risk of MACCEs. Subgroups of patients without hypertension ($p = 0.024$) or smoking history ($p = 0.025$) present increased risk of MACCEs. All p for interaction > 0.05.

Predictors of clinical outcomes

The results of univariate cox regression analysis in Table 4 indicated that hyperlipemia ($p = 0.036$), decreased LVEF (left ventricular ejection fraction) ($p = 0.038$), proximal/ostial coronary lesion ($p = 0.019$), middle TBIL tertile ($p = 0.023$) and lower TBIL tertile ($p = 0.014$) were potential predictors of MACCEs. Subsequent multivariate cox regression analysis showed that middle and lower TBIL tertiles was independently associated with an increased risk of MACCEs ($p = 0.008$ and $p = 0.018$, respectively), after adjustment for age, BMI, and the uses of statins.

DISCUSSION

The predictive value of TBIL for severity of coronary artery calcification and poor prognosis in patients with CAD and psoriasis is being assessed for the first time in this study. Lower TBIL was associated with the severity of lesion calcification. With a mean follow-up of 315 days, lower TBIL at baseline was an independent predictor for an increased incidence of MACCEs in patients with CAD and psoriasis. These results

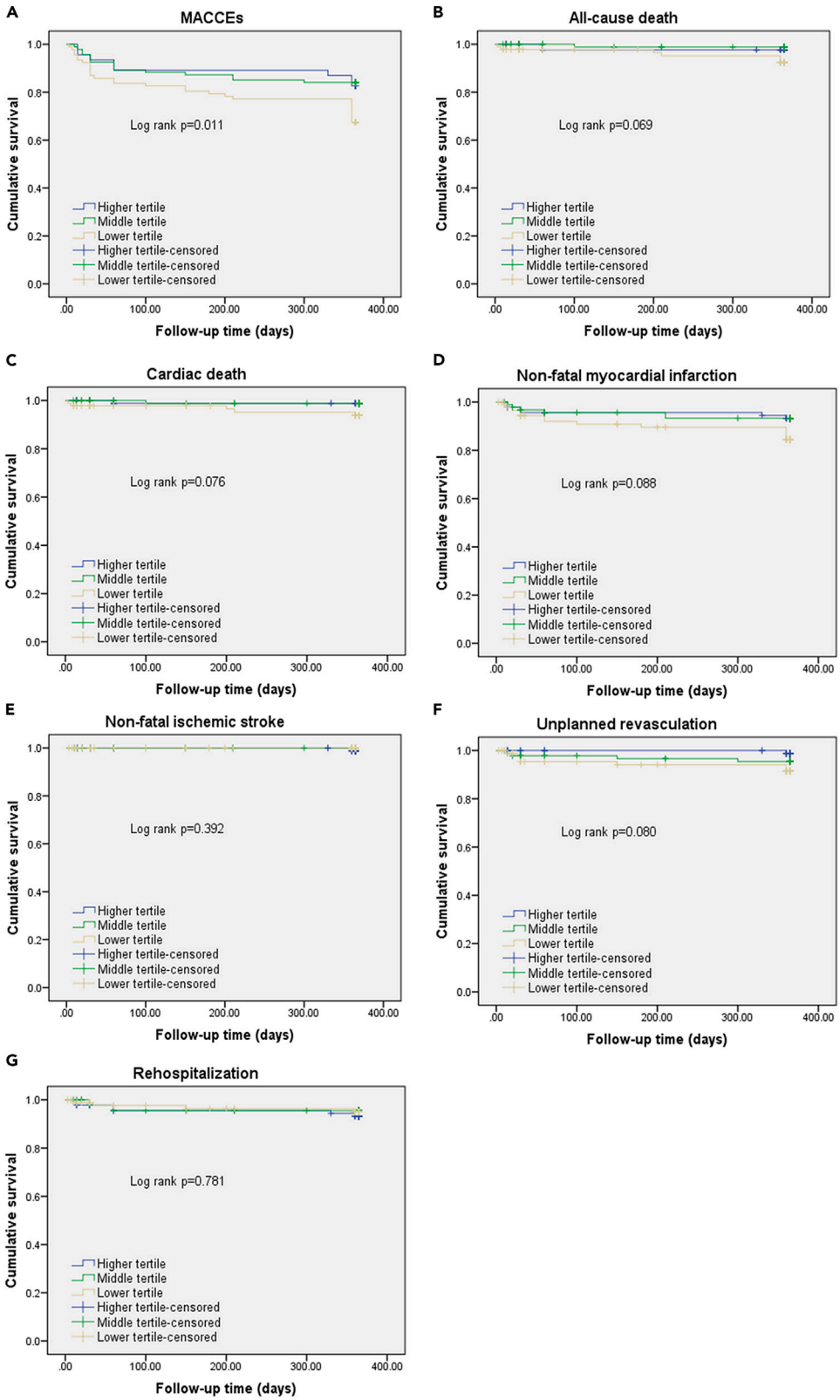
A
MACCEs
Log rank p=0.011
B
All-cause death
Log rank p=0.069
C
Cardiac death
Log rank p=0.076
D
Non-fatal myocardial infarction
Log rank p=0.088
E
Non-fatal ischemic stroke
Log rank p=0.392
F
Unplanned revasculation
Log rank p=0.080
G
Rehospitalization
Log rank p=0.781
Cumulative survival
Follow-up time (days)
Higher tertile
Middle tertile
Lower tertile
Higher tertile-censored
Middle tertile-censored
Lower tertile-censored

Figure 1. Cumulative incidence of events in patients with psoriasis and CAD according to TBIL tertiles

(A) Cumulative incidence of MACCEs in patients with psoriasis and CAD according to TBIL tertiles (p = 0.011). Higher vs. lower tertiles (p = 0.018). Higher vs. middle tertiles (p = 0.839).

(B) Cumulative incidence of all-cause death in patients with psoriasis and CAD according to TBIL tertiles (p = 0.069).

(C) Cumulative incidence of cardiac death in patients with psoriasis and CAD according to TBIL tertiles (p = 0.076).

(D) Cumulative incidence of non-fatal myocardial infarction in patients with psoriasis and CAD according to TBIL tertiles (p = 0.088).

(E). Cumulative incidence of non-fatal ischemic stroke in patients with psoriasis and CAD according to TBIL tertiles (p = 0.392).

(F) Cumulative incidence of unplanned revasculation in patients with psoriasis and CAD according to TBIL tertiles (p = 0.080).

(G) Cumulative incidence of rehospitalization because of heart failure or angina in patients with psoriasis and CAD according to TBIL tertiles (p = 0.781). Abbreviation: MACCE, major adverse cardiovascular and cerebrovascular event; CAD, coronary artery disease; TBIL, Total bilirubin.

suggested the ability of serum TBIL to forecast the possibility of severe coronary artery calcification and unfortunate prognosis in patients with CAD and psoriasis.

Many studies show a positive association between psoriasis and CAD. Gregor. J et al. showed that psoriasis was associated with ischemic heart disease and many cardiovascular risk factors, including hypertension, diabetes, hyperlipemia, obesity, and smoking, along with metabolic syndrome.[18] Inflammation is involved in the potential mechanisms between psoriasis and cardiovascular risks.[19] Activated T cell subsets, myeloid cells, and proinflammatory cytokines synergistically contribute to vascular endothelial dysfunction and atherosclerosis.[9] A previous analysis among psoriasis patients showed that the rate of MI in patients treated with anti-inflammatory therapy was reduced by 50% compared to topical therapy.[20] In addition, biologic therapies decreased inflammatory biomarkers such as ESR, consistently may also prevent cardiovascular disease.[21] TBIL is also inversely associated with several cardiovascular risk factors, such as smoking, diabetes, and hyperlipemia.[22] It has been suggested that TBIL has potential anti-inflammatory effects on the vasculature.[23] Furthermore, decreased TBIL can exert anti-inflammatory effects and might independently predict unfortune prognosis in non-ST elevated MI.[24,25] However, there are few studies about TBIL in prognosis of patients with CAD and psoriasis. Our findings show that among those patients, decreased serum bilirubin levels had increased ESR and increased prevalence of MACCEs.

Psoriasis patients harbor heavier coronary artery calcification. Compared to non-psoriasis patients, psoriasis patients have double odds of coronary artery calcium.[26] In previous analysis, coronary computed tomography angiography (CCTA) was used to estimate the severity of coronary artery calcification in psoriasis patients. Those patients showed severe coronary artery calcification and an increased risk for cardiovascular events.[27,28] Bilirubin can exert potent antioxidative and anti-inflammatory function as the end product of heme catabolism.[29] Under physiological conditions, TBIL inhibits inflammation in the vasculature and subsequently multiple steps in atherosclerosis.[30] Besides, TBIL might directly mediate CAD via alleviating oxidative stress and further oxidation of lipids and lipoproteins. It has been reported that TBIL level was negatively correlated with coronary artery calcium score and coronary artery stenosis.[31] Our findings are consistent with previous evidence that subjects with lower TBIL have increased prevalence of severe coronary artery calcification. Besides, it is applicable among patients with psoriasis and CAD at the same time. Thus, lower TBIL is a potential predictor of coronary artery calcium subsequent MACCEs. In addition, our study indicates that decreased TBIL may slightly increase the prevalence of in-stent restenosis in psoriasis and CAD patients. But we failed to prove the statistically significant correlation between TBIL and in-stent restenosis (ISR). Further prospective large-scale clinical studies are needed to identify the lesion characteristics and clarify the pathologic and prognostic role of bilirubin in CAD and psoriasis patients.

In addition to the traditional cardiovascular risk factors, there are the added potential factors of external influences, such as TBIL in psoriasis and CAD patients.[19] In order to identify the prognostic functions of TBIL for these patients, stratified analysis was performed to eliminate the effect of these factors. There are some previous studies showed that the relation between TBIL and CAD varies by gender.[30,32] Consistently, in this study, the negative correlation of TBIL level with MACCEs is tenable only in males. It probably resulted from the small population of female patients, we failed to identify the same tendency in females. Thus, further larger-scale study in female patients remains necessary.

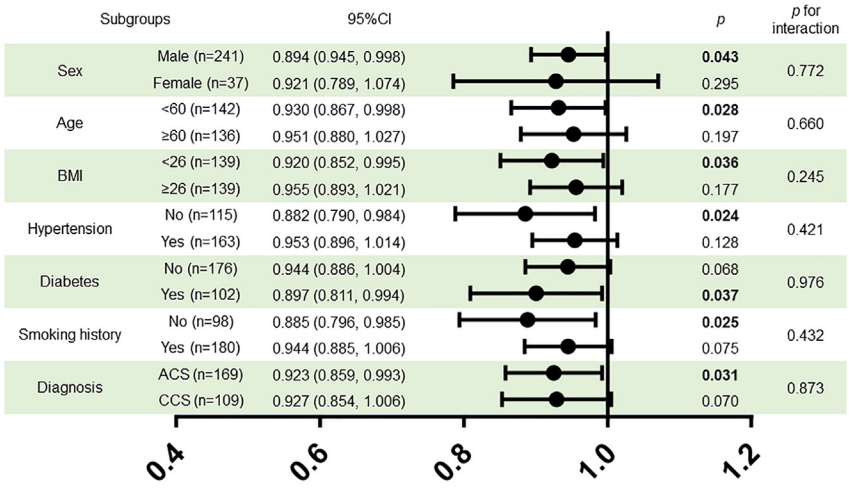

Figure 2. Subgroup analysis evaluating the robustness of TBIL in predicting the risk of the MACCE

Abbreviation: TBIL, Total bilirubin; MACCE, major adverse cardiovascular and cerebrovascular event; CI, confidence interval; BMI, Body mass index; ACS, Acute coronary syndrome; CCS, Chronic coronary syndrome.

Psoriasis is associated with a high prevalence of cardiovascular risk factors, such as obesity, diabetes, hyperlipidemia, and hypertension, which constitute the metabolic syndrome.[33] Those patients with psoriasis and metabolic syndrome have more active inflammation, leading to increased incidence of coronary heart disease, MI, and cardiac death, and stroke.[34] Furthermore, previous related studies showed that serum TBIL level within the physiological range were negatively associated with metabolic syndrome in middle-aged and elderly Chinese.[35] It has been demonstrated that after adjusting other confounders, TBIL levels were independent inversely associated with metabolic syndrome.[36] The underlying mechanisms of decreased TBIL for heightened risk of metabolic syndrome are not completely understood. Systemic inflammation and oxidative stress, which have been implicated to promote insulin resistance, diabetes, hyperlipidemia, hypertension, and obesity, is probably involved in the pathogenesis of metabolic syndrome.[37] However, the interactions among TBIL, metabolic syndrome, psoriasis, and CAD are complicated and interdependent. In this study, we found that in stratified analysis, TBIL in subjects with hypertension, diabetes, or BMI $\geq$26 tended to have different effects on MACCEs. Atherosclerotic development in patients with psoriasis and metabolic cardiovascular syndrome is a combination of active inflammation and oxidative stress. Therefore, for the most part of those populations, serum TBIL is very likely to be lower concentration. After stratification, each group has limited sample size. In population with lower TBIL, bilirubin is not a strong and stable predictor of poor prognosis. Although we found the predictable effect on MACCEs varies from different stratified population, it was probably caused by the small population of included subjects.

Although it is suggested in previous study that lower TBIL probably exerts function as a prognostic factor in CAD, the results vary from subtypes of CAD. A retrospective, observational cohort study that included 3708 subjects with STEMI undergoing primary coronary intervention demonstrated that TBIL can be used to predict MACCEs.[38] In addition, in previous related study, a significant association was found between TBIL and the severity of coronary artery lesions in NSTEMI patients.[25] However, with a follow-up of 1 year, other retrospective cohort study suggested that TBIL is positively related with short-term mortality of acute MI patients and independent negatively associated with one-year mortality in stable CAD or UA pectoris patients.[8] Because the stratified method in this investigation is inconsistent with previous studies, and subjects included in our study are both psoriasis and CAD patients, we draw a conclusion that TBIL was inversely correlated with poor prognosis in ACS patients. And we failed to suggest the same results in subjects with psoriasis and stable coronary syndrome.

Limitations of the study

First, the present investigation was a retrospective observational study and included with small population enrolled. Therefore, a larger-scale prospective cohort study is needed to further validate the findings. Second, the TBIL categories are based on a single assessment of laboratory blood test, which may result

Table 4. Cox regression analysis of risk factors for MACCEs in patients with psoriasis and CAD

	Univariate analysis			Multivariate analysis		
Variables	HR	95% CI	p value	HR	95% CI	p value
Age (years)	1.004	0.979–1.030	0.751	0.998	0.973–1.025	0.900
Male, n (%)	0.661	0.344–1.270	0.214			
BMI (kg/m2)	0.991	0.916–1.072	0.819	1.011	0.929–1.101	0.798
Hypertension, n (%)	1.221	0.728–2.049	0.450			
Diabetes, n (%)	0.814	0.477–1.390	0.451			
Hyperlipemia, n (%)	0.431	0.196–0.947	**0.036**	0.542	0.231–1.273	0.160
CAD family history	1.148	0.566–2.330	0.702			
Smoking history, n (%)	0.896	0.534–1.503	0.677			
ACS, n (%)	0.870	0.524–1.445	0.591			
LVEF (%)	0.973	0.949–0.998	**0.038**	0.973	0.947–1.000	0.050
Creatinine (μmol/L)	1.000	1.000–1.000	0.893			
FBG (mmol/L)	1.037	0.959–1.120	0.364			
HbA1c (%)	1.068	0.877–1.302	0.512			
TG (mmol/L)	0.884	0.650–1.202	0.432			
TC (mmol/L)	1.011	0.779–1.314	0.932			
LDL-C (mmol/L)	1.073	0.802–1.437	0.635			
HDL-C (mmol/L)	1.191	0.643–2.207	0.579			
hs-crp (mg/L)	1.034	0.968–1.106	0.318			
ESR (mm/h)	1.007	0.992–1.022	0.353			
Time of psoriasis (years)	0.982	0.960–1.006	0.136			
PASI score	0.982	0.950–1.015	0.269			
Biologic treatment, n (%)	0.663	0.241–1.828	0.428			
Nonbiologic systemic treatment, n (%)	1.381	0.823–2.318	0.222			
Severity of lesions						
LM ≥ 50%, n (%)	1.047	0.476–2.301	0.909			
Multi-vessel disease, n (%)	1.567	0.948–2.590	0.080			
Proximal/ostial lesion, n (%)	1.853	1.108–3.097	**0.019**	1.869	1.094–3.190	**0.022**
Medications after discharge						
Antiplatelet drugs, n (%)	0.754	0.274–2.079	0.586			
β-receptor blockers, n (%)	1.574	0.853–2.905	0.147			
ACEI/ARB/ARNI, n (%)	0.908	0.549–1.500	0.705			
CCB, n (%)	1.069	0.579–1.973	0.831			
SGLT2 inhibitors, n (%)	0.300	0.073–1.228	0.094			
Statins, n (%)	0.615	0.150–2.516	0.498	0.523	0.121–2.264	0.386
PCSK9 inhibitors, n (%)	0.049	0.000–369.36	0.507			
Ezetimibe, n (%)	1.089	0.628–1.889	0.760			
TBIL tertiles						
Middle vs. higher	0.495	0.270–0.907	**0.023**	0.408	0.210–0.791	**0.008**
Lower vs. higher	0.460	0.248–0.855	**0.014**	0.466	0.247–0.878	**0.018**

MACCE, major adverse cardiac and cerebrovascular events; CAD, Coronary artery disease; HR, hazard ratio; CI, confidence interval; BMI, Body mass index; ACS, Acute coronary syndrome; LVEF, Left ventricular ejection fraction; FBG, Fasting blood glucose; HbA1c, Glycated hemoglobin; TG, Triglyceride; TC, Total cholesterol; LDL-C, Low density lipoprotein cholesterol; HDL-C, High-density lipoprotein cholesterol; ESR, Erythrocyte sedimentation rate; PASI, Psoriasis Area and Severity Index; LM, Left main branch; ACEI, Angiotensin-converting enzyme inhibitors; ARB, Angiotensin receptor blockers; ARNI, Angiotensin receptor neprilysin inhibitors; CCB, Calcium-channel-blocker; SGLT2 inhibitors, Sodium-glucose cotransporter 2 inhibitors; PCSK9 inhibitors, Proprotein convertase subtilisin/kexin-type 9 inhibitors; TBIL, Total bilirubin.
Values of $p < 0.05$ are indicated in bold.

in a misclassification bias. In addition, coronary artery lesion characteristics in patients without percutaneous angioplasty were not recorded. Selection bias is involved in the evaluation of lesion types, including coronary artery calcification. Furthermore, only hospital-based patients were included in our study, which might not reflect the general population of patients with CAD and psoriasis. Finally, subjects enrolled in this study were Chinese, therefore the results may not be applicable to subjects in other areas.

Conclusion

The results of this study suggest that lower TBIL is a potential predictor of severe coronary calcification and poor prognosis in patients with psoriasis and CAD. Because the measurement of serum TBIL is convenient and cost-effective, the risk stratification for patients with psoriasis and CAD can be improved by incorporation of TBIL level.

STAR★METHODS

Detailed methods are provided in the online version of this paper and include the following:

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SUPPLEMENTAL INFORMATION

Supplemental information can be found online at https://doi.org/10.1016/j.isci.2023.107106.

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AUTHOR CONTRIBUTIONS

Conceived and designed the study: L.S., L.Z., Z.Z., X.L.Z., and W.X.Y. Data collection and analyzed the data: L.S., L.Z., K.Q.Y., Z.Z.L., Y.W., T.J.W., and M.W. Quality control the study and revision: Z.Z., X.L.Z., and W.X.Y. Wrote the paper: L.S., L.Z. All authors read and approved the final manuscript.

DECLARATION OF INTERESTS

The authors declare that they have no conflict of interest.

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STAR★METHODS

KEY RESOURCES TABLE

REAGENT or RESOURCE	SOURCE	IDENTIFIER
Software and algorithms		
SPSS (version 23.0)	IBM SPSS Statistics	N/A
Graphpad Prism (version 7.0)	GraphPad Software	N/A

RESOURCE AVAILABILITY

Lead contact

Further information and requests for resources should be directed to and will be fulfilled by the lead contact, Yan Zeng (zyminny@163.com).

Materials availability

This study did not generate new unique reagents.

Data and code availability

Data reported in this paper will be shared by the lead contact upon request.

This paper does not report original code.

Any additional information required to reanalyze the data reported in this paper is available from the lead contact upon request.

METHOD DETAILS

Experimental model and participant details

We collected 313 clinical records of psoriasis patients. Finally, our study recruited psoriasis patients (n = 278) from January 2016 to November 2021 in Fuwai Hospital who underwent coronary angiography and were diagnosed as CAD, including ST-segment elevation MI (STEMI), non-ST-segment elevation MI (NSTEMI), unstable angina pectoris, and angina pectoris. CAD was defined as $\geq$ 50% stenosis in at least one major coronary artery (left main coronary artery, anterior descending branch, circumflex branch, and right coronary artery). The diagnosis of all types of CAD and psoriasis, and the standard for PASI (Psoriasis Area and Severity Index) score were based on the criteria in previous guidelines.[9,10] The age, sex distribution of the cohorts is described in Table 1. The exclusion criteria are as follows: (1) patients with potential Gilbert syndrome (TBIL>34.2 μmol/L, alanine transaminase<80IU/L, aspartate aminotransferase<80IU/L, gamma glutamyl transpeptidase<80 IU/L, and without history of hepatobiliary disease; n = 3) and patients with potential hepatobiliary disease (total bilirubin>34.2 μmol/L or alanine transaminase>80IU/L or aspartate aminotransferase >80 IU/L or gamma glutamyl transpeptidase>80 IU/L, or with history of hepatobiliary disease; n = 15).[11,12] (2) patients with renal dysfunction, estimated glomerular filtration rate lower than 30 mL/min/1.73m. (3) patients with malignant tumors, or severe infection. This study was approved by the Ethics Committee of Fuwai Hospital (No.2021-1544).

History collection and physical examination

The measurement of height, weight after hospitalization was recorded and body mass index (BMI) was calculated. The diagnosis of hyperlipemia, hypertension, and diabetes were based on previous medical records and current guideline.[13–15] Smoking history was defined as current or former smoking if they had quit smoking <3 years before.[16] All patients were evaluated by transthoracic echocardiography before cardiovascular angiography. Biologic treatments for psoriasis included interleukin 17A, interleukin 12/23, and tumor necrosis factor alpha inhibitors. Nonbiologic systemic treatments included steroids and methotrexate. Medications after discharge were recorded, including antiplatelet drugs, statins, ezetimibe, proprotein convertase subtilisin/kexin-type 9 (PCSK9) inhibitors, β-receptor blockers, angiotensin-converting enzyme inhibitors (ACEI), angiotensin receptor blockers (ARB), angiotensin receptor neprilysin inhibitors (ARNI), calcium-channel-blocker (CCB), and sodium-glucose cotransporter 2 (SGLT2) inhibitors.

Biochemical measurements

Peripheral venous blood samples were drawn after admission for biochemical measurements. Hepatic and renal function test, lipid metabolism, fasting blood glucose (FBG), glycated hemoglobin (HbA1c), high sensitivity C-reactive protein (hs-CRP), and erythrocyte sedimentation rate (ESR) were measured.

Coronary angiography and lesion assessments

After admission, all patients underwent coronary angiography. Among patients being prepared for percutaneous transluminal coronary angioplasty (PTCA), lesion details were recorded according to previous criteria.[17] The severity of CAD was determined by the number of affected vessels (left anterior descending branch, circumflex branch, or right coronary artery with stenosis greater than 70%), stenosis of left main coronary artery (greater than 50%), location of the lesions and recorded lesion characteristics.

Follow-up

Patients were followed-up by telephone or clinic visits and all events were obtained through outpatient records and telephone calls. The observational endpoint was MACCEs, which was the composite of all-cause death, cardiac death, non-fatal MI, non-fatal ischemic stroke, unplanned revascularization, and re-hospitalization because of heart failure or angina.

QUANTIFICATION AND STATISTICAL ANALYSIS

Patients were grouped according to the tri-sectional quantiles of serum TBIL: higher tertile $\geq$ 14.203 μmol/L (n = 92), middle tertile 9.528–14.203 μmol/L (n = 94), and lower tertile $\leq$ 9.528 μmol/L (n = 92). Quantitative variables were tested for normal distribution by Kolmogorov-Smirnov test, and were expressed as mean and standard deviation if normally distributed. Otherwise, data were summarized as medians and interquartile ranges. Categorical variables were expressed as percentages. Normal distributed continuous variables of three groups were compared by using ANOVA. If not normally distributed, Mann–Whitney U test or Kruakal-Walli's test was used. Categorical variables were compared by Chi-squared ($\chi 2$) test or Fisher exact test (Bonferroni method was used for comparison of column proportions). All 191 patients who were prepared to get angioplasty were grouped based on calcification: no and mild calcification (n = 145), moderate and severe calcification (n = 46). Multiple logistic regression analysis was performed to identify the relationship between TBIL and coronary artery calcification, in which we adjusted for sex, age, BMI, hypertension, hyperlipemia, diabetes, smoking history, biologic therapy and the use of statins. We computed adjusted odds ratios (ORs) and 95% confidence intervals (CIs). The potential independent factors were identified by univariate logistic Cox regression analysis and were included in the multivariate Cox regression test in which potential confounders including age, BMI, and the uses of statins were adjusted for. And hazard ratios (HRs) and 95% CIs were computed. The predictive efficacy of TBIL for prognosis was analyzed by using Kaplan-Meier survival and Log Rank test. A series of stratified analyses were performed to identify the potential modification effects of sex, age (<60 vs. $\geq$ 60 years), BMI (<26 vs. $\geq$ 26 kg/m^2), hypertension, diabetes, smoking history, diagnosis of acute coronary syndrome (ACS) or chronic coronary syndrome (CCS). *P* for interaction was used for testing the interaction between subgroups. SPSS software version 23.0 and Graphpad Prism 7.0 were used for the statistical analysis. p value < 0.05 was considered as statistically significant.