Serum Total Bilirubin and Long-Term Prognosis of Patients With New-Onset Non-ST Elevation Myocardial Infarction: A Cohort Study

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Serum total bilirubin and long-term prognosis of patients with new-onset non-ST elevation myocardial infarction: a cohort study

Running title: total bilirubin and NSTEMI

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Abstract

Background: The potential prognostic role of total bilirubin (TBIL) in patients with new-onset non-ST elevation myocardial infarction (NSTEMI) is not fully understood. This study aims to evaluate the potential predictive value of TBIL for long-term prognosis in patients with new-onset NSTEMI.

Methods: Patients with new-onset NSTEMI that underwent emergency coronary angiography in our department from June 2015 to March 2020 were included. Baseline TBIL was measured at admission. SYNTAX scores were used to indicate the severity of coronary lesions. The association between TBIL and SYNTAX scores was analyzed using multivariate logistic regression. The patients were followed for the incidence of major adverse cardiac and cerebrovascular events (MACCEs). The association between TBIL and MACCEs was analyzed using Kaplan–Meier survival methods.

Results: In total 327 patients were included in this study. Patients were divided according to tertiles of TBIL (first tertile <10.23 μmol/L, n = 109; second tertile 10.23 – 14.30 μmol/L, n = 109; and third tertile ≥14.30 μmol/L, n = 109). TBIL was independently associated with the severity of coronary lesions in patients with NSTEMI, with an adjusted odds ratio (OR) and 95% confidence interval (CI) for the third tertile and the second tertile compared with the first tertile of TBIL of 2.259 (1.197-4.263) and 2.167 (1.157-4.059), respectively (both p<0.05). After a mean follow-up of 30.33 months, MACCE had occurred in 57 patients. TBIL was

independently associated with the increased risk of MACCEs, with an adjusted hazard ratio (HR) and 95% CI for the third tertile and the second tertile compared with the first tertile of TBIL of 2.737 (1.161 -6.450) and 3.272 (1.408-7.607), respectively (both $p<0.05$).

Conclusions*:* Higher myocardial infarction admission TBIL might independently predict poor prognosis in patients with NSTEMI.

Keywords: cohort study; major adverse cardiac and cerebrovascular events; non-ST elevation myocardial infarction; SYNTAX scores; total bilirubin.

Introduction

The pathological features of acute coronary syndrome (ACS) involve inflammation and oxidative stress that have been associated with conventional risk factors for coronary artery disease (CAD), such as diabetes mellitus, smoking, and hypertension [1-3]. However, the evidence suggests that some individuals without the previous risk factors could develop ACS, which suggests that there are potential unknown risk factors for CAD in these patients [4-6]. Clinically, non-ST elevation myocardial infarction (NSTEMI) is a subtype of non-ST elevation ACS (NSTE-ACS), which usually is associated with a more severe clinical status and worse outcomes than patients with unstable angina (UA), the other subtype of NSTEACS [7]. Therefore, identification of the novel risk factors that might predict the prognosis in patients with NSTEMI is of important clinical significance in current cardiovascular practice.

Previous studies have confirmed that bilirubin, which is a product of heme metabolism, could potentially exert endogenous anti-oxidative and anti-inflammatory efficacies at the physiological level [8]. Under pathological conditions, bilirubin could modulate the progression of atherosclerosis by the inhibition of the oxidative modification of low-density lipoprotein and proliferation of smooth muscle cells (SMC) [8]. However, elevated bilirubin post-myocardial infarction might reflect increased heme breakdown that includes increased red cell mass, heme oxygenase 1 enzyme (HO-1) expression, myoglobin breakdown, and decreased hepatic bilirubin glucuronidation, or both

caused by reduced hepatic blood flow following myocardial infarction [9]. Therefore, previous clinical studies have suggested that higher serum levels of total, direct, and indirect bilirubin might be associated with an increased risk of the combined outcomes of major adverse cardiac and cerebrovascular events (MACCEs) in patients with ACS, which include all-cause death, myocardial infarction, and stroke [10-11]. However, some of the previous studies have indicated that total bilirubin (TBIL) might confer better prognostic efficacy than direct or indirect bilirubin in ACS patients [12-13], other studies that evaluated the predictive role of serum TBIL in ACS patients based on the subtype of ACS showed inconsistent results [11,13-15]. Some of the studies did not support that serum TBIL was associated with an increased risk of MACCEs in ACS patients [14-15]. In addition, the sample sizes of previous studies were limited, and patients with previously diagnosed CAD were included, which might affect the results of the studies. Because of the important role of inflammation in the pathogenesis of NSTEMI, as well as the potential role of bilirubin as an endogenous anti-inflammatory factor, this study aims to systematically evaluate the potential associations between serum TBIL with severity and prognosis in patients with new-onset NSTEMI.

Methods

Patients and study design

Patients with new-onset NSTEMI and without previously known CAD that underwent urgent coronary angiography in the Xinjiang Medical University Affiliated Hospital of

Traditional Chinese Medicine from June 2015 to March 2020 were included in this study. The diagnosis of NSTEMI was based on the criteria in previous guidelines [17]. Patients with any of the following clinical conditions were excluded: (1) hepatic or renal dysfunction that might affect serum TBIL; (2) diagnosis of ST-segment elevation myocardial infarction (STEMI), unstable angina pectoris, or with previous revascularization therapy, which included percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG); (3) new-onset NSTEMI with a previous diagnosis of CAD; (4) patients that had pacemaker-implantation, malignant tumors, or severe infection; (5) patients with previously diagnosed systemic inflammatory disease, a history of alcohol consumption, hemolysis, blood transfusion, viral infections of the liver, or with poor compliance to treatment; and (6) patients who were at risk of hepatotoxicity induced by medications, such as the use of statins or amidarone. The flow chart of participant enrollment is shown in **Fig. 1.**

Blood sampling

Peripheral venous blood samples were drawn immediately before urgent coronary angiography for each of the patients and sent to the Department of Clinical Laboratory of the Xinjiang Medical University Affiliated Hospital of Traditional Chinese Medicine for further analysis. Parameters of blood cell count, biochemical parameters for lipids and glucose metabolism, hepatic and renal function, serum uric acid, serum creatine phosphokinase-MB (CK-MB), and troponin T were measured.

Coronary angiography and SYNTAX score

After admission, all patients underwent emergency coronary angiography using a standard protocol that was carried out by experienced cardiologists. The SYNTAX score was used as the indicator for the severity of the coronary lesions, which was calculated by two experienced cardiologists independently according to the online tool of the score . If disagreement occurred, they were resolved by consensus with the third investigator. If indications for PCI were detected, the modality of PCI was determined by a group of experienced attending physicians based on coronary anatomy and the clinical status of the individual patients. After PCI, patients continued with optimized medical treatments and were followed-up at clinics regularly after discharge.

Follow-up

Patients were discharged and followed-up by telephone interview or clinic visits. All events were carefully monitored by an independent panel of clinical physicians. The primary outcome of this study was the incidence of a combined outcome for MACCEs, which included cardiac mortality, myocardial infarction, stent thrombosis, stroke and revascularization. The secondary outcome of this study was all-cause mortality.

Statistical analysis

Patients were grouped based on the tertiles of the serum TBIL (first tertile <10.23 μmol/L, second tertile 10.23–14.30 μmol/L, and third tertile ≥14.30 μmol/L, with 109 patients in each tertile) or tertiles of the SYNTAX score at baseline. Continuous

variables were summarized as mean and standard deviation if normally distributed; otherwise, medians and interquartile ranges (IQRs) were used. Categorical variables were expressed as percentages. Comparisons with means between multiple groups were performed using ANOVA, and for the nonnormally distributed variables, Mann–Whitney U test or Kruskal–Wallis variance analysis was applied. For the categorical variables, a Chi-squared ($\chi 2$) test was employed. Multiple logistic regression analysis was performed to identify the independent factors that were associated with the severity of coronary lesions, as evidenced by the SYNTAX score. The potential predictive efficacy of serum TBIL at baseline for prognosis in NSTEMI patients was analyzed using the Kaplan–Meier survival method. Univariate analysis was performed first, and then the significant variables were included in the multivariate Cox regression analysis. A p-value<0.05 indicated a statistically significant difference. SPSS 23 was used for the statistical analysis.

Results

Characteristics of the included patients

In total, 327 patients with new-onset NSTEMI were retrospectively included in this study. The baseline characteristics for all the patients included in this study based on the tertiles of TBIL (first tertile <10.23 μmol/L, n = 109; second tertile 10.23–14.30 μmol/L, n = 109; and third tertile ≥14.30 μmol/L, n = 109) are presented in **Table 1**. The results showed that patients with higher TBIL levels were probable to be male and

smokers, with higher apolipoprotein A1, (Apo-AI), increased high-density lipoprotein cholesterol, and a higher SYNTAX score (all $p<0.05$). The baseline characteristics for all the patients in this study were based on tertiles of the SYNTAX score as given in **Table 2**. Age, the prevalence of diabetes mellitus, smoking status, left ventricle ejection fraction (LVEF), TBIL, and TBIL tertiles group were significantly different between the patients based on the tertiles of SYNTAX score (all $p<0.05$).

Potential association between TBIL and severity of coronary lesions

The results of multivariate logistic analyses showed that a higher TBIL was independently associated with the severity of coronary lesions based on the SYNTAX score, with an adjusted odds ratio (OR) and 95% confidence interval (CI) for the third tertile and the second tertile compared with the first tertile of TBIL of 2.259 (1.197–4.263) and 2.167 (1.157–4.059), respectively as given in Table 3 (both $p<0.05$) In addition, other factors that include diabetes (OR: 1.954, $p = 0.016$), smoker (OR: 1.829, $p = 0.023$), and LVEF (OR: 0.954, p = 0.032; **Table 3**) were associated with the severity of coronary lesions in patients with new-onset NSTEMI.

Incidence of MACCEs and all-cause mortality according to the TBIL

The incidences of primary and secondary clinical outcomes during a mean follow-up of 30.33 months for the patients in this study with new-onset NSTEMI, based on the tertiles of TBIL at baseline are given in **Table 4**. During follow-up, 57 patients

experienced MACCEs. The results showed that the incidence of MACCEs increased in patients based on the tertiles of serum levels of TBIL (p = 0.001). However, the incidence of all-cause mortality was not statistically different between patients with new-onset NSTEMI, based on the tertiles of TBIL at baseline (p = 0.177).

Predictors of clinical outcomes

Kaplan–Meier analysis demonstrated that the incidence of MACCEs was significantly different among patients with new-onset NSTEMI based on the tertiles of TBIL ($\chi2$=15.243, p<0.001) as shown in **Fig. 2** and the incidence of all-cause mortality was not significantly different among patients based on the tertiles of TBIL ($\chi2$=4.430， p=0.109) as shown in **Fig. 3**. The Results of univariate Cox regression analysis indicated that gender (female), hypertension, diabetes, increased troponin T, unprotected left main trunk coronary artery lesions, higher TBIL tertile, and higher SYNTAX score tertile were potential predictors of MACCEs, as given in Table 5 (p-values all <0.05). Subsequent multivariate analysis showed that TBIL was independently associated with an increased risk of MACCEs, with adjusted hazard ratio (HR) and 95% CI for the third tertile and the second tertile compared with the first tertile of TBIL of 2.737 (1.161 -6.450) and 3.272 (1.408-7.607), respectively (both p<0.05). Other independent risk factors for the increased incidence of MACCEs in patients with new-onset NSTEMI included diabetes (HR: 1.800, 95% CI: 1.041-3.113, p = 0.035), UPLMCA (HR: 2.042, 95% CI: 1.063-3.923, p = 0.032),

increased troponin T (HR: 1.172, 95% CI: 1.007-1.365, p = 0.040), and increased SYNTAX scores (third tertile versus first tertile, HR: 3.165, 95% CI: 1.280-7.827, p=0.013); and second tertile versus first tertile (HR: 2.767, 95% CI: 1.097-6.980, p = 0.031) as given in **Table 5**.

Discussion

In this retrospective cohort study that included patients with new-onset NSTEMI, a higher TBIL at baseline was independently associated with the severity of coronary lesions as shown by the higher SYNTAX score. In addition, with a mean follow-up of 30.33 months, higher serum TBIL at baseline was an independent predictor for an increased incidence of MACCEs in patients with new-onset NSTEMI. Because of the convenience and cost-effectiveness of measuring myocardial infarction admission TBIL in clinical practice, these results suggested that serum TBIL might be an inexpensive predictor for poor prognosis in patients with new-onset NSTEMI.

The risk stratification for patients with new-onset NSTEMI needs to be improved, in particular, for the identification of potential prognostic factors for these patients [7]. Although previous studies have suggested a potential role of TBIL as a prognostic factor in CAD, the results of these studies might be different based on the subtype of CAD. A previous study that included 7,685 healthy individuals with a mean follow-up of 11.5 years showed that higher TBIL might be a risk factor for the increased incidence of ischemic heart disease [18]. A retrospective study that included 3,013

patients with angiographically obstructive CAD suggested a positive and independent correlation between baseline levels of TBIL and short-term mortality of acute myocardial infarction patients, and the negative correlation between baseline levels of TBIL and long-term mortality in stable CAD or UA pectoris patients was confirmed in a cohort study with a follow-up of 1 year [19]. In addition, high serum TBIL levels have been independently and significantly correlated with the burden of coronary atherosclerosis in patients with STEMI, and no significant association between high serum TBIL levels and poor long-term prognosis was found in these studies [15, 20].

In this retrospective cohort study, a significant association was found between myocardial infarction admission TBIL and the severity of coronary lesions. In addition, higher myocardial infarction admission TBIL was independently associated with a higher risk of MACCEs in new-onset NSTEMI patients with a mean follow-up of 30.33 months. However, TBIL might be a potential protective factor for coronary lesions based on the potential endogenous anti-oxidative and anti-inflammatory characteristics of bilirubin. These findings agreed with a previous hypothesis that myocardial infarction admission TBIL was elevated shortly after myocardial infarction because of the acute response to impaired liver function [21]. In addition, previous studies demonstrated that the TBIL changed dramatically as regulated by HO-1 and the maximal levels of bilirubin were usually observed during an acute myocardial infarction event [22-23]. Moreover, STEMI patients with high bilirubin levels were shown to have a higher incidence of adverse outcomes and mortality during

hospitalization [24], which suggested a role for increased TBIL as a predictor for poor prognosis in STEMI patients. This study, by strictly excluding patients with a previous diagnosis of CAD and other concurrent comorbidities that might affect the TBIL level, showed that higher TBIL at baseline was independently associated with a higher risk of MACCEs in new-onset NSTEMI patients. These findings support the incorporation of baseline TBIL levels for risk stratification of patients with new-onset NSTEMI.

The pathophysiological mechanisms that underly the association between bilirubin and poor prognosis in patients with new-onset NSTEMI need to be determined. Based on this study, it could be hypothesized that acute myocardial ischemia might induce an immediate increase in the levels of various inflammatory cytokines and reduced hepatic blood flow, which might exceed the protective antioxidant effect of bilirubin in vivo. In addition, it could be inferred that there was a compensatory increase of TBIL by dramatically up-regulated HO-1 activity under stress to exert anti-inflammatory and anti-oxidative effects in new-onset NSTEMI patients. This is consistent with previous findings that patients with increased serum bilirubin levels had increased cardiac troponin I release that was correlated with myocardial infarction size and the severity of coronary atherosclerotic burden [25]. Therefore, high TBIL levels might have a protective anti-oxidative effect on the cardiovascular system in stable CAD and healthy population. In addition, it has been suggested that long-term therapy with statins or aspirin might be associated with increased TBIL levels [26-27]. However, this appears not to be the main influencing factors in this study, because only new-onset

NSTEMI patients without a previous diagnosis of CAD were included.

Study limitations

Several limitations of this study are noted. First, this was a retrospective observational study with limited sample size, and the findings should be validated in large-scale prospective cohort studies. In addition, the serum TBIL was only measured once at admission, and whether dynamic changes in serum TBIL during hospitalization had a more significant impact on the prognosis of these patients is unknown. In addition, this was an observational study, and a causative association between increased serum TBIL and poor prognosis in these patients could not be derived based on the findings. Finally, the optimal cut-off value for the prognostic efficacy of TBIL is unknown, which deserves further investigation.

Conclusions

The results of this study suggest that myocardial infarction admission TBIL might be an inexpensive predictor of poor prognosis in patients with new-onset NSTEMI. Because of the convenience and cost-effectiveness of measuring serum TBIL, the findings support the incorporation of the measurement of serum TBIL when risk stratification for patients with new-onset NSTEMI is performed.

Abbreviations

ACEI = angiotensin-converting enzyme inhibitor; Apo-AI = apolipoprotein A1; Apo-B = apolipoprotein B; ARB = angiotensin II receptor blocker; BMI = body mass index; BUN = blood urea nitrogen; CCB = calcium channel blocker; Cr = creatinine; CK-MB = creatine kinase-MB; DBP = diastolic blood pressure; HDL-C = high-density lipoprotein cholesterol; LAD = left anterior descending artery; LCX = left circumflex artery; LDL-C = low-density lipoprotein cholesterol; LVEDD = left ventricular end-diastolic dimension; LVEF = left ventricle ejection fraction; PCI = percutaneous coronary intervention; RCA = right coronary artery; SBP = systolic blood pressure; TC = total cholesterol; TG = triglyceride; and UPLMT = unprotected left main trunk.

Declarations

The authors declare that they have no conflict of interests.

Ethical approval

Because this was a retrospective observational study, the ethics committee of the Xinjiang Medical University Affiliated Hospital of Traditional Chinese Medicine granted an exemption from ethics approval.

Informed consent

Because this was a retrospective observational study, the ethics committee of the Xinjiang Medical University Affiliated Hospital of Traditional Chinese Medicine waived the requirement for informed consent from eligible patients.

Consent for publication:

Not applicable.

Availability of data and material

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request. Requests to access these datasets should be directed to Tongjian Zhu, whuzhutongjian@126.com.

Competing Interest:

The authors declare that they have no conflict of interest.

Funding:

None of.

Authors' contributions:

Conceived and designed the study: TZ and KM. Data collection and analyzed the data:YY.Quality control the study and revision: JW and YX. Wrote the paper: YY and AD. YY, JW and AD contributed to the work equally and should be regarded as co-first authors. The manuscript was approved by all above authors.

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Figure 1. Flowchart of patient enrollment.

Figure 2. Cumulative incidence of MACCE in patients with NSTEMI according to TBIL tertiles.

Figure 3. Cumulative incidence of all-cause mortality in patients with NSTEMI according to TBIL tertiles.

Figures

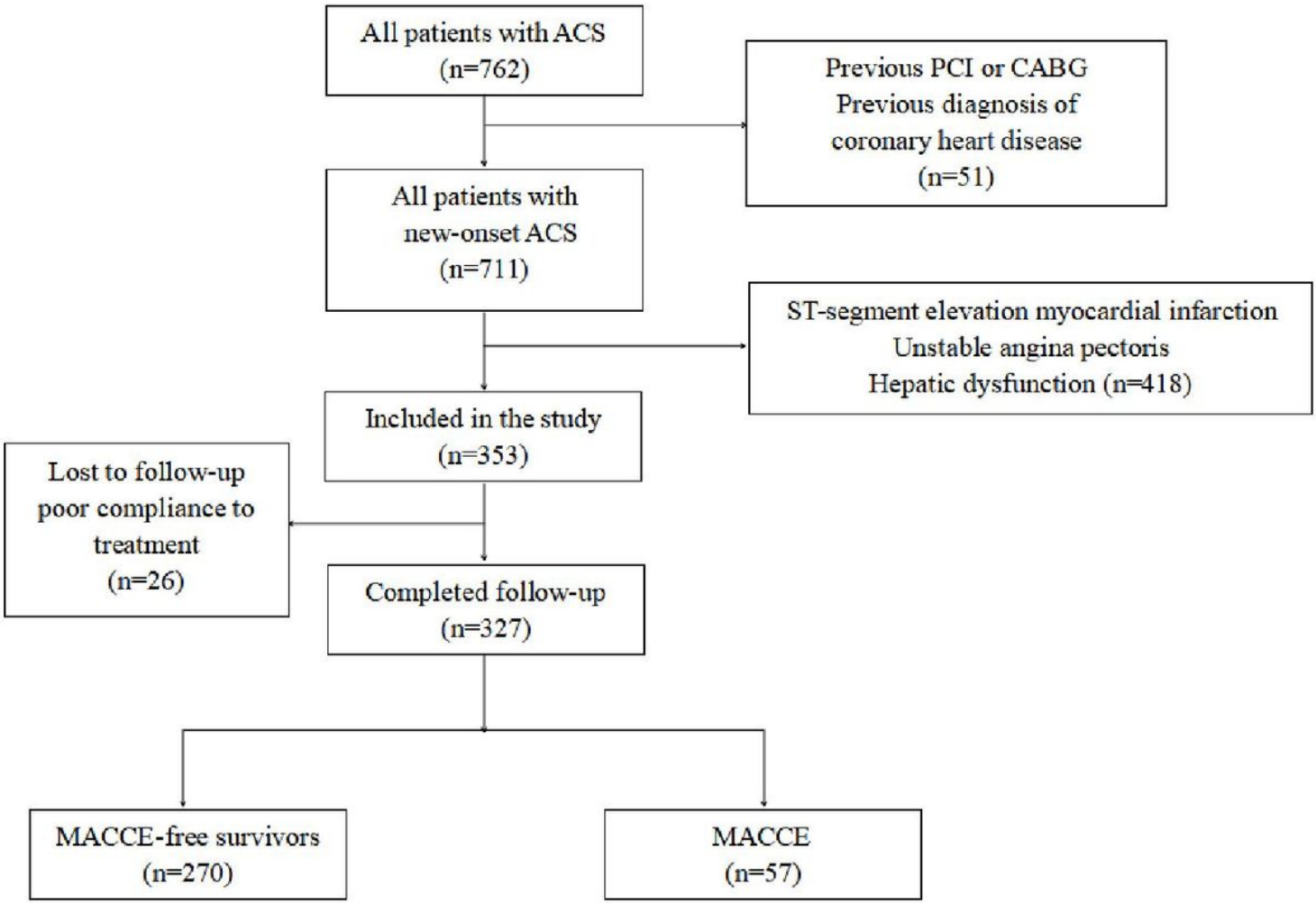

Figure 1

Flowchart of patient enrollment.

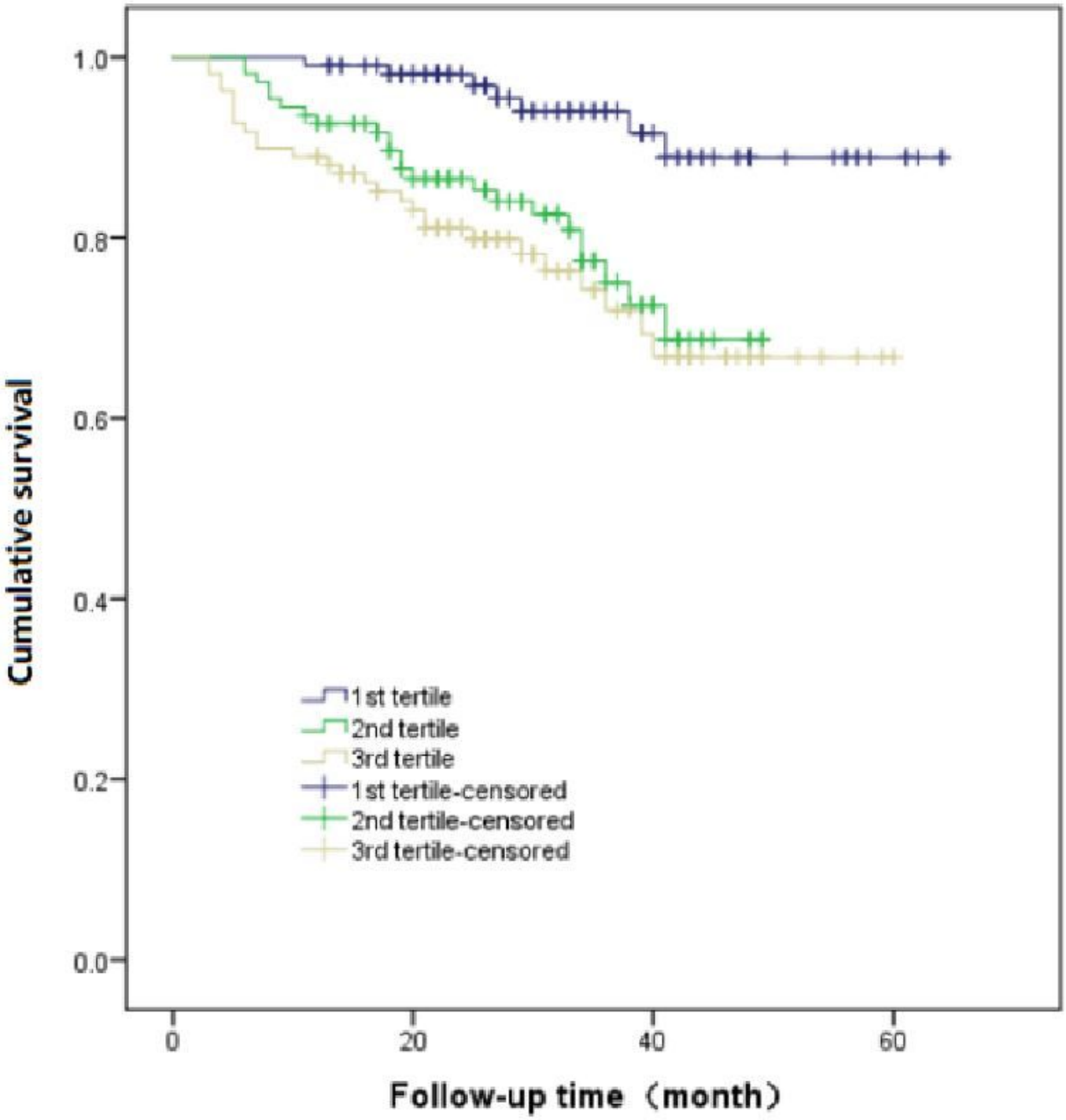

Figure 2

Cumulative incidence of MACCE in patients with NSTEMI according to TBIL tertiles.

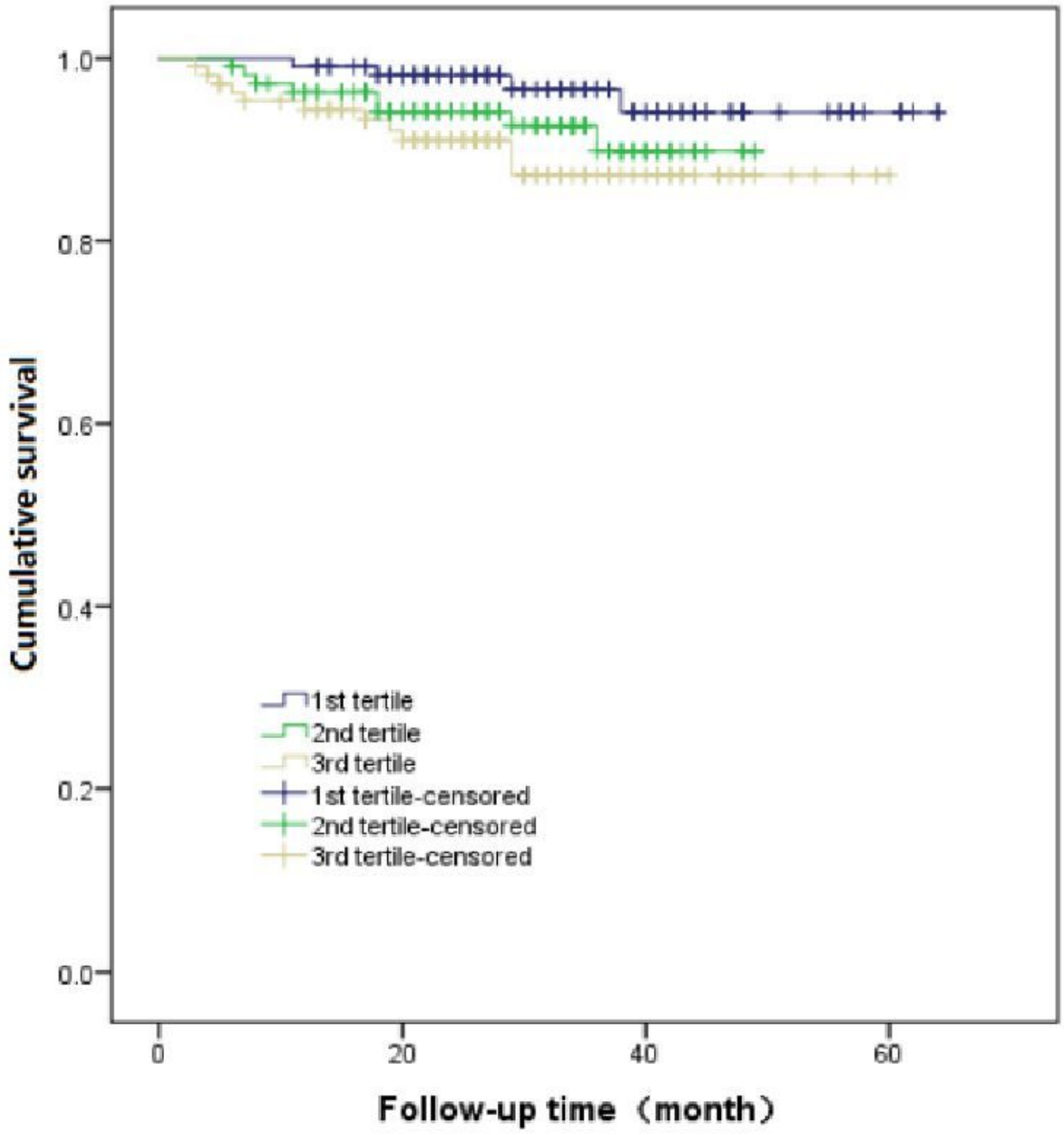

Figure 3

Cumulative incidence of all-cause mortality in patients with NSTEMI according to TBIL tertiles.