

A novel predictor of infarct-related artery patency before percutaneous intervention and in-hospital outcomes for ST-segment elevation myocardial infarction patients: serum bilirubin level

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Abstract

Introduction: Previous studies have reported a relationship between serum bilirubin levels and coronary artery disease (CAD). However, data are rare up to now regarding the relation of bilirubin levels with infarct-related artery (IRA) patency in the setting of ST-segment elevation myocardial infarction (STEMI). Moreover, previous studies reported that increased bilirubin was related to impaired post-intervention coronary flow. To our knowledge, the association between serum total bilirubin (TB) levels and pre-primary percutaneous coronary intervention (PCI) with patency of IRA flow in STEMI patients has not been investigated.

Aim: To evaluate the association of TB with pre-primary PCI, coronary flow and in-hospital major adverse cardiac events (MACE) in patients with STEMI.

Material and methods: A total of 360 consecutive patients with STEMI (mean age = 61.4 ±13.7 years) admitted within 12 h from the time of symptom onset were enrolled. Patients were divided into 2 groups based on the serum TB levels. We defined normal flow as pre-PCI TIMI 3 flow, while impaired flow was defined as pre-PCI TIMI ≤ 2 flow.

Results: Pre-PCI impaired flow was higher in the TB group than pre-PCI normal flow ($p < 0.001$). In-hospital mortality and MACE were significantly higher in the high TB group ($p = 0.002$, $p < 0.001$ respectively). In the receiver operating characteristic curve analysis, TB > 0.825 mg/dl predicted impaired IRA flow before p-PCI with a sensitivity of 79% and specificity of 71%.

Conclusions: The TB is an inexpensive and readily available marker for STEMI patients undergoing PCI. It can be used for risk stratification in this patient population.

Key words: bilirubin, percutaneous coronary intervention, novel predictor.

Introduction

The basal thrombolysis in myocardial infarction (TIMI) flow in an infarct-related artery (IRA) is crucial for patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI). However, pre-PCI patency of IRA in patients with STEMI is a major determinant of post-PCI TIMI flow; this is related to improved clinical outcome [1]. Early and rapid restoration of coronary flow in an IRA improves ventricular performance, lowers the incidence of congestive heart failure, and decreases mortality compared with patients without initial TIMI flow 3 in patients with STEMI [2].

Bilirubin is a bile pigment formed as the end product of the breakdown of heme [3]. The heme oxygenase (HO) enzyme that is responsible for the degradation of heme groups in the metabolism of bilirubin is a stress-inducible enzyme and has antioxidative features [4]. There are 2 isozymes of this enzyme, HO-1 and HO-2 [5]. The HO-1 is induced by various cellular stresses but is not expressed under normal conditions. A large number of outcomes are possible [1]. Previous studies demonstrated that HO-1 can be induced by stress, including as part of the acute phase response [5]. It has been demonstrated that HO-1 enzyme activity is markedly upregulated in the myocardium in response to infarction [6].

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Previous studies have reported a relationship between serum bilirubin levels and the risk of coronary artery disease (CAD) [7]. However, data are rare up to now regarding the relation of bilirubin levels with IRA patency in the setting of STEMI. Moreover, previous studies reported that increased bilirubin was related to impaired post-intervention coronary blood flow in patients with STEMI [8]. To our knowledge, the relationship between serum total bilirubin (TB) levels and pre-PCI with patency of IRA flow in STEMI patients has not been investigated.

Aim

Therefore, in this study, we evaluated the relationship between TB IRA flow as confirmed by angiography before receiving PCI and in-hospital major adverse cardiac events (MACE) in patients with STEMI.

Material and methods

Study population

A total 760 consecutive patients with STEMI undergoing PCI within 12 h from the time of symptom onset between January 2012 and December 2013 were included in this study. The STEMI was defined based on the criteria formulated by the American College of Cardiology and the European Society of Cardiology [9] as an increase in troponin I > 1 ng/ml with a new ST elevation measured from the J point in ≥ 2 contiguous leads with at least 0.2 mV in leads V1, V2 and V3 or at least 0.1 mV in the remaining leads during the first 12 h after the onset of symptoms.

Patients with severe liver disease, autoimmune disease, known malignancy, hematological disorders, severe valvular disease, known cases of hypothyroidism, inflammatory or infectious diseases, a history of bleeding diathesis, patients not given a PCI, a bilirubin value was missing or unavailable and follow-up was not documented before PCI, patients who were treated with thrombolytic therapy or the use of glycoprotein IIb/IIIa inhibitors, patients with poor echocardiographic windows, and patients who presented > 12 h from the onset of symptoms were excluded from the study. After these exclusions were accounted for, the final study population consisted of 360 patients. All patients underwent a complete physical examination; coronary risk factors, and their medical histories and clinical features were recorded.

In-hospital follow-up and MACE were defined as acute stent thrombosis, cardiogenic shock, new advanced heart failure, pulmonary edema, complete atrioventricular block (AVB) requiring a transient pacemaker, serious ventricular arrhythmia, major bleeding requiring blood transfusion and in-hospital mortality during the in-hospital follow-up period. In-hospital mortality had to

be verified as death due to myocardial infarction, cardiac arrest or other cardiac causes. Acute in-stent thrombosis was defined as an abrupt onset of cardiac symptoms after stent deployment in the first 24 h and angiographic evidence of a flow-limiting thrombus near a previously placed stent. Cardiogenic shock was defined as marked and persistent (> 30 min) hypotension with systolic arterial pressure < 80 mm Hg and signs of hypoperfusion due to left ventricular dysfunction, right ventricular infarction, or mechanical complications. New advanced heart failure was defined as New York Heart Association functional classification \geq III. Serious ventricular arrhythmia was defined on admission as advanced ventricular fibrillation-tachycardia or asystole 48 h later. Patients were also evaluated according to the Killip clinical examination classification [10].

Blood samples and echocardiography

Venous blood samples were drawn when the patient initially presented to the emergency room or the intensive coronary care unit (ICCU) before PCI. Hematologic indexes counts were measured by an automated hematology analyzer (Abbott Cell-Dyn 3700; Abbott Laboratory, Abbott Park, Illinois). Bilirubin and other biochemical parameters were measured using the Abbott Architect C16000 auto analyzer (Abbott Laboratory). Normal total bilirubin and direct bilirubin levels were defined according to our laboratory (0.2–1 mg/dl and 0.0–0.5 mg/dl respectively). Transthoracic two-dimensional echocardiography was performed on ICCU admission in order to measure left ventricular ejection fraction (LVEF) (Vivid S6, GE Medical Systems, USA).

Coronary angiography (TIMI flow)

All patients underwent selective coronary angiography using the Judkins technique. The PCI procedures were performed with a standard femoral approach using a 7 Fr guiding catheter. Digital angiograms were analyzed by three independent and experienced interventional cardiologists, blinded to all data. Coronary blood flow patterns before PCI were subjected to a thorough evaluation on the basis of TIMI flow grade, using grades 0, 1, 2, and 3 [11]. We defined normal flow or spontaneous coronary reperfusion (SR) as pre-PCI TIMI 3 flow (SR group), while impaired or non-SR flow was defined as pre-PCI TIMI \leq 2 flow (non-SR group). For all study participants, only one artery was identified as the IRA. Coronary vessel disease was defined as a greater than 50% stenosis in one of the major coronary arteries. The Gensini scoring system was used to determine the severity of CAD [12, 13]. TIMI flow grade was determined by three independent interventional cardiologists. Intra- and inter-observer reliability was determined from a random sample of 100 patients from the study sample.

Statistical analysis

All analyses were performed using SPSS for Windows version 18.0 (SPSS Inc. Chicago, Illinois, USA). Continuous variables were expressed as mean \pm standard deviation (SD) and categorical variables were expressed as percentages. Distribution of continuous variables was assessed with a two-sample Kolmogorov-Smirnov test. Comparisons of categorical and continuous variables between the two groups (high and low TB level) were performed using the χ^2 or Fisher's exact test and independent samples *t* or Mann-Whitney *U* test, respectively. Relationships between the variables were examined with Spearman's correlation coefficients. The inter-rater agreement between the three cardiologists in determining intra- and inter-observer agreement for the coronary blood flow patterns before PCI were subjected to a thorough evaluation on the basis of TIMI flow, investigated using the Kappa (κ) test. Statistical significance was defined as $p < 0.05$. The cut-off values for TB for predicting non-SR, in-hospital MACE and in-hospital death with corresponding sensitivity and specificity were estimated by receiver operator characteristic (ROC) curve analysis.

The study protocol was in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee.

Results

A total of 360 patients were included in the data analysis. 101 (28%) were in the SR group and 259 (72%) were in the non-SR group. Out of all the study participants, 130 (36%) were in the low TB group and the remaining 230 (64%) were stratified into the high TB group. The baseline characteristics of the 2 groups are summarized in Table I. Killip classes III-IV were more common in high TB group patients ($p = 0.017$).

Initial laboratory findings were compared according to the high TB group and the low TB group (Table II). In the high TB group, TB ($p < 0.001$), direct bilirubin ($p < 0.001$), aspartate amino transferase ($p = 0.015$), alanine amino transferase ($p = 0.002$), lactate dehydrogenase ($p = 0.002$), C-reactive protein (CRP) ($p = 0.002$), serum uric acid (UA) ($p < 0.001$), creatine ($p = 0.017$), peak troponin ($p < 0.001$), peak CK-MB ($p < 0.001$) and neutrophil to lymphocyte ratio (NLR) ($p = 0.035$) values were significantly greater than those of the low TB group. Moreover, mean platelet volume, hemoglobin, and serum glucose on admission were higher in the high TB group patients.

Angiographic characteristics are listed in Table III. Pre-PCI TIMI flow 3 was higher in the low TB group than the high TB group ($p < 0.001$). Similarly, the non-SR group TB ($p < 0.001$) value was significantly greater than that of the

Table I. Baseline characteristics of study patients

Variables	Low serum TB group (n = 130)	High serum TB group (n = 230)	Value of <i>p</i>
Age, mean \pm SD [years]	60.3 \pm 13.5	62.0 \pm 13.8	0.242
Sex, male, <i>n</i> (%)	97 (75)	165 (72)	0.556
Hypertension, <i>n</i> (%)	46 (35)	83 (36)	0.894
Diabetes mellitus, <i>n</i> (%)	30 (23)	57 (25)	0.717
Smoking, <i>n</i> (%)	74 (57)	127 (55)	0.754
Hyperlipidemia, <i>n</i> (%)	8 (6)	9 (4)	0.336
Family history of CAD, <i>n</i> (%)	32 (25)	39 (17)	0.079
Previous MI or CAD, <i>n</i> (%)	8 (6)	10 (4)	0.450
Previous PCI, <i>n</i> (%)	5 (4)	14 (6)	0.361
Killip class on admission, <i>n</i> (%):			
I-II	126 (97)	207 (90)	0.017
III-IV	4 (3)	23 (10)	
Admission SBP, mean \pm SD [mm Hg]	128.5 \pm 20.9	127.4 \pm 25.2	0.650*
Admission heart rate, mean \pm SD [bpm]	82.6 \pm 15.6	84.1 \pm 17.4	0.416*
STEMI location, <i>n</i> (%):			
Anterior	61 (47)	105 (46)	0.816
Nonanterior	69 (53)	125 (55)	
Duration of chest pain, mean \pm SD [h]	5.5 \pm 3.2	5.9 \pm 3.5	0.194*
Admission LVEF, mean \pm SD (%)	44.1 \pm 9.7	42.8 \pm 10.9	0.259*

*Student's *t*-test, χ^2 test, MI – myocardial infarction, CAD – coronary artery disease, PCI – percutaneous coronary intervention, SBP – systolic blood pressure, LVEF – left ventricular ejection fraction

Table II. Initial laboratory findings of study patients

Variables	Low serum TB (n = 130)	High serum TB (n = 230)	Value of p
Total bilirubin [mg/dl]	0.56 ±0.18	1.38 ±0.32	< 0.001*
Direct bilirubin [mg/dl]	0.21 ±0.09	0.33 ±0.32	< 0.001*
Aspartate amino transferase	89.53 ±87.2	123.89 ±141.99	0.015*
Alanine amino transferase	32.54 ±30.80	54.65 ±90.34	0.002*
Lactate dehydrogenase	334.96 ±171.59	443.82 ±306.83	0.002*
C-reactive protein	0.71 ±0.72	2.33 ±4.95	0.002
Uric acid [mg/dl]	6.34 ±2.54	7.31 ±2.60	< 0.001*
Peak troponin I [ng/ml]	38.1 ±36.9	64.7 ±34.7	< 0.001*
Peak CK-MB mass [ng/ml]	140.9 ±115.9	207.8 ±106.4	< 0.001*
Glucose on admission [mg/dl]	173.02 ±98.40	175.27 ±84.64	0.819
Creatinine on admission [mg/dl]	0.91 ±0.58	0.93 ±0.37	0.017*
Total cholesterol [mg/dl]	178.90 ±43.25	178.85 ±37.35	0.992
Low-density lipoprotein [mg/dl]	116.22 ±34.72	114.54 ±30.55	0.633
High-density lipoprotein [mg/dl]	36.04 ±9.45	34.67 ±9.88	0.199
Triglycerides [mg/dl]	147.23 ±88.50	153.73 ±94.74	0.523
White blood cell count [K/μl]	13.07 ±4.06	13.99 ±6.09	0.123
Neutrophil count, NULL	10.13 ±3.84	11.31 ±5.59	0.019
Lymphocyte count, NULL	2.05 ±1.27	1.93 ±1.22	0.382
Neutrophil to lymphocyte ratio	6.45 ±4.07	7.71 ±5.39	0.035*
Hemoglobin [g/dl]	13.82 ±1.81	13.94 ±1.54	0.532
Mean platelet volume	8.04 ±1.21	8.35 ±1.62	0.057

Values are mean ± SD,*Mann-Whitney U test, Student's t-test

Table III. Angiographic characteristics of patients

Variables	Low serum TB group (n = 130)	High serum TB group (n = 230)	Value of p
IRA:			
Left anterior descending	64 (49)	108 (47)	0.889
Right	41 (32)	94 (41)	
Circumflex	25 (19)	28 (12)	
Narrowed coronary vessels:			
1 vessel	63 (49)	91 (40)	0.101
> 1 vessel	67 (52)	139 (60)	
Initial TIMI flow (pre-PCI):			
0–1	50 (39)	184 (80)	< 0.001
2	9 (7)	16 (7)	
3	71 (55)	30 (13)	
Gensini score	52.76 ±29.76	65.24 ±31.05	< 0.001

Values are mean ± SD or n (%), χ^2 test; Student's t-test, IRA – infarct-related artery, TIMI – Thrombolysis In Myocardial Infarction grade, PCI – percutaneous coronary intervention

SR group (Figure 1 A). The Gensini score was higher in the high TB group as compared to the low TB group ($p < 0.001$).

The in-hospital adverse outcomes are listed in Table IV. The in-hospital death rate was greater in the high TB

group than in the low TB group (14% vs. 4%, $p = 0.002$). MACE were more frequent in the high TB group than in the low TB group (30% vs. 12%, $p < 0.001$). Similarly, in-hospital cardiogenic shock ($p = 0.005$), complete

Table IV. In-hospital cardiac events according to serum bilirubin level

Variables	Low serum TB group	High serum TB group	Value of p
In-hospital MACE	15 (12)	68 (30)	< 0.001
Advanced heart failure	6 (5)	18 (8)	0.241
Advanced pulmonary edema	4 (3)	14 (6)	0.208
Cardiogenic shock	3 (2)	24 (10)	0.005
Acute stent thrombosis	2 (2)	7 (3)	0.380
Complete AVB requiring transient pacemaker	2 (2)	16 (7)	0.023
Serious ventricular arrhythmia	4 (3)	22 (10)	0.022
Major bleeding requiring blood transfusion	1 (0.8)	0 (0)	0.183
In-hospital death	5 (4)	33 (14)	0.002
Cardiopulmonary resuscitations	5 (4)	37 (16)	0.001
Cardiac arrest on admission	3 (2)	24 (10)	0.005
Hospitalization [days]	4.8 ±2.9	5.5 ±5.3	0.107*

Values are mean ± SD or n (%), χ^2 test, Student's t-test, *Mann-Whitney U test, MACE – major adverse cardiovascular event, AVB – atrioventricular block

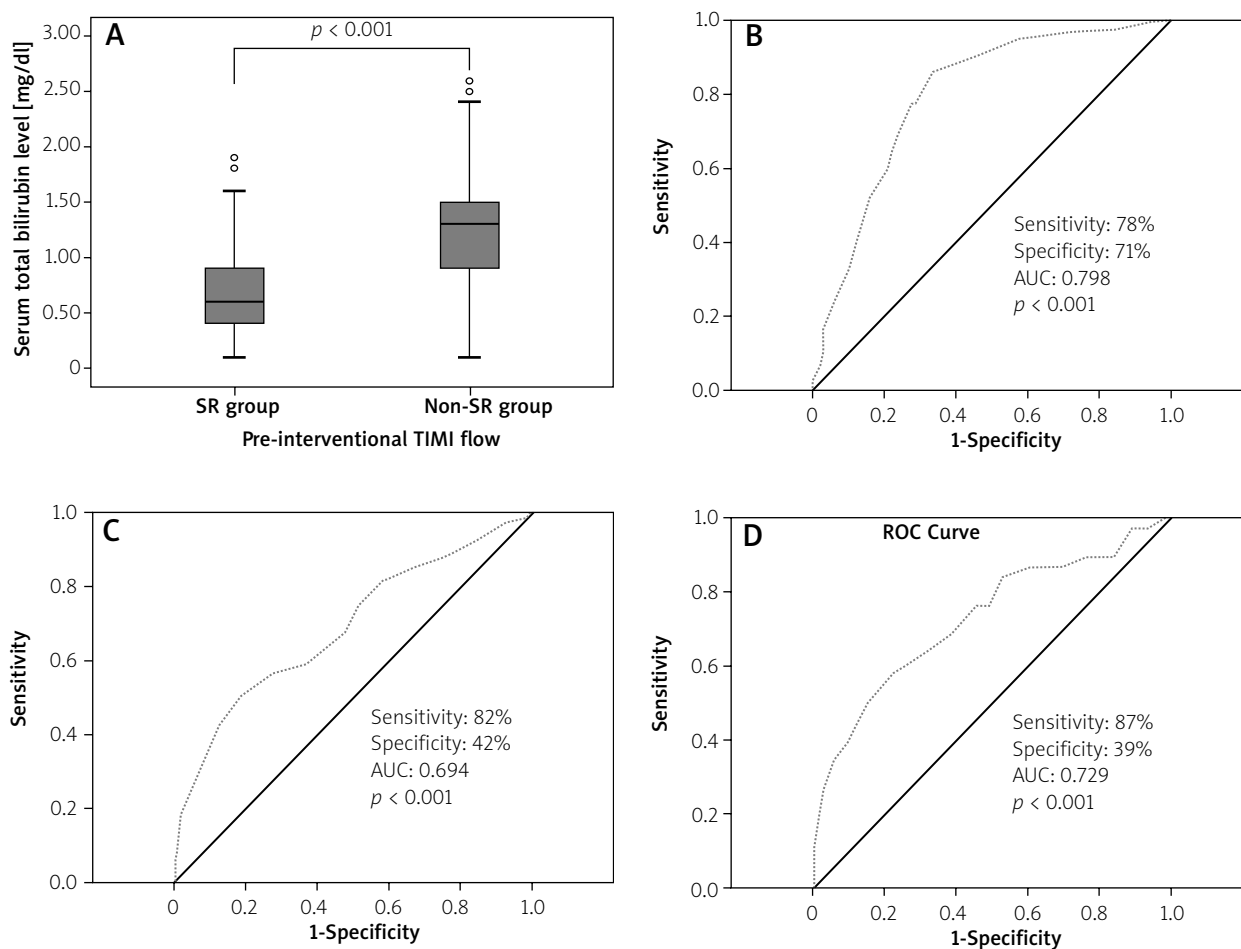


Figure 1. A – Box plot comparison of serum total bilirubin levels among SR and non-SR patient groups before primary PCI, B – receiver operator characteristic curve analysis of serum total bilirubin in predicting pre-PCI IRA patency, C – receiver operator characteristic curve analysis of serum total bilirubin in predicting in-hospital major adverse outcomes, D – receiver operator characteristic curve analysis of serum total bilirubin in predicting in-hospital mortality

AVB requiring a transient pacemaker ($p = 0.023$), severe ventricular arrhythmia ($p = 0.022$), cardiac arrest on admission ($p = 0.005$) and cardiopulmonary resuscitations ($p = 0.001$) were higher in the high TB group patients.

Spearman's correlation analysis revealed significant associations between a high TB value and UA ($r = 0.199$, $p < 0.001$), NLR ($r = 0.155$, $p = 0.004$), peak troponin ($r = 0.128$, $p = 0.015$), peak CK-MB ($r = 0.126$, $p = 0.017$) and Gensini score ($r = 0.245$, $p < 0.001$).

A cut-off level of 0.825 mg/dl for TB predicted impaired IRA flow before PCI with a sensitivity of 77.6% and a specificity of 71.3% (ROC area under the curve (AUC) 0.798, 95% CI: 0.745–0.853, $p < 0.001$) (Figure 1 B). A cut-off level of 0.825 mg/dl for TB was identified as in STEMI for in-hospital MACE with a sensitivity of 81.9% and a specificity of 41.5% (ROC AUC 0.694, 95% CI: 0.626–0.763, $p < 0.001$) (Figure 1 C), and a TB value > 0.825 mg/dl was identified as an effective cut-off point in STEMI for in-hospital mortality with a sensitivity of 86.8% and a specificity of 38.8% (ROC AUC 0.729, 95% CI: 0.635–0.823, $p < 0.001$) (Figure 1 D).

The κ value for intra-observer reliability was 0.907 ($p < 0.001$). The inter-observer reliability was a κ of 0.889 ($p < 0.001$) before PCI TIMI flow grade assignments 0 to 3. Inter-rater reliability and the intraclass correlation coefficient had an r -value of 0.961 with a $p < 0.001$.

Discussion

Our data demonstrated that high serum TB was associated with impaired pre-PCI IRA flow and increased in-hospital MACE and death occurred in patients with STEMI. Also this study demonstrated increased TB levels that correlated with serum UA and NLR, which are markers of inflammation [14, 15]. In addition, we found that high levels of TB were significantly associated with increased CAD severity according to Gensini scoring results. Moreover, we found that TB values greater than 0.825 mg/dl predict initial IRA TIMI flow grades of less than 3, in-hospital MACEs and in-hospital death. The sensitivity and specificity for the association between TB and low IRA patency pre-PCI TIMI flow grades were 78% and 71%, in hospital-MACE were 82% and 42%, and in-hospital mortality was 87% and 39% respectively.

Bilirubin levels prolonged the survival of human ventricular myocytes against in situ generated oxyradicals [16]. It was also found that HO-1 protein and HO activity are markedly upregulated in the myocardium in response to MI. The activation of HO-1 is an important defensive mechanism that may improve cytoprotection via its antioxidant activity, which may limit tissue damage and ameliorate the post-MI remodeling [17, 18]. A previous study tested the hypothesis that HO-1 is activated in the myocardium after acute MI in humans [6]. In assessing the serum concentration of bilirubin levels and HO-1 enzyme activity during the hospitalization period in pa-

tients with acute MI, it was found that HO-1 enzyme activity is a stress-inducible enzyme and closely correlated with serum bilirubin levels.

Gullu *et al.* [19] reported that greater serum bilirubin concentrations had a protective effect against impaired coronary flow reserve and coronary microvascular dysfunction. Erdogan *et al.* [20] evaluated undergoing coronary angiography for CAD and found that greater bilirubin levels were related to favorable coronary collateral flow in patients with chronic total occlusion. Okuhara *et al.* [6] reported that serum bilirubin levels were elevated in those with acute MI but not in nonacute MI. Celik *et al.* [8] found that serum bilirubin levels were independently associated with the development of post-PCI coronary no-reflow with TIMI flow grade as well as increased in-hospital MACE in patients with STEMI. Gul *et al.* [21] demonstrated that high TB was one of the independent predictors of in-hospital cardiovascular mortality and morbidity in patients with acute STEMI.

Wei *et al.* [22] found that serum TB levels correlated with the angiographic complexity of CAD. Erkan *et al.* [23] found a moderate and significant positive correlation between direct bilirubin levels and the Gensini score. There was no significant correlation between TB levels and the Gensini score. In contrast, we demonstrated that a high TB level is significantly associated with the Gensini score in patients with STEMI. In addition, Gensini score correlated with TB and direct bilirubin levels.

We demonstrated that serum TB levels, a sign of HO-1 enzyme activity, are significantly associated with PCI coronary flow and adverse outcomes during the in-hospital period. This suggests that the activity of the stress-inducible enzyme HO-1 is independently related to impaired pre-PCI coronary blood flow, in hospital-MACEs and death in patients with STEMI. These results could play an important role in better understanding the pathogenesis of oxidative stress associated diseases and may lead to the development of new treatment strategies in the management of patients with STEMI.

The present study has the well-known limitation of retrospective design and a small number of patients. In addition, it was a single-center study. However, our population contains homogeneous unselected patients with STEMI submitted to PCI within 12 h from the time of symptom onset, thus mirroring the real-world scenario. The other limitation is that we did not measure HO-1 activity, but we did examine NLR and UA markers of inflammation. Also there was a significant correlation between serum markers and serum TB level.

Conclusions

From the findings of the present study, we suggest that TB is an inexpensive and readily available biochemical marker for clinicians to use as a parameter and a powerful prognostic factor for patients undergoing PCI

for STEMI. It can be used for risk stratification in this patient population.

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