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Association Between the Initial Total Bilirubin Level and the Clinical Outcome in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Primary PCI

Seyedeh Samaneh Ahmadi[1], MD; Hamidreza Sanati*[2], MD; Hooman Bakhshandeh[1], MD; Sepideh Jafari Naeini[1], MD; Majid Hajikarimi[1], MD; Alireza Hoghooghi Esfahani[1], MD; Roya Rezaee[1], MD; Alireza Ziaee[1], MD

ABSTRACT

Background: Clarification is needed as regards the relationship between the total bilirubin level and the outcome of primary percutaneous coronary intervention (PCI) in patients with ST-segment elevation myocardial infarction (STEMI).

Methods: Between April 2015 and April 2016, consecutive patients with STEMI who underwent primary PCI were prospectively enrolled in a primary PCI registry. The patients' demographics, initial total bilirubin levels, procedural characteristics, and in-hospital and 6 months' major adverse cardiac events were assessed.

Results: A total of 95 patients who underwent primary PCI were enrolled in the study. The mean bilirubin level was 1.04 mg/dL with a standard deviation of 1.154. We evaluated the relationships between the median of the initial total bilirubin level, the thrombolysis in myocardial infarction (TIMI) flow grade after PCI and following PCI, 6 months' follow-up complications, the amount of the peak troponin and CK-MB levels, the amount of mitral regurgitation, the ejection fraction, and electrocardiographic changes including ST resolution and the Q-wave formation after primary PCI. Except for the levels of troponin and CK-MB, there were no relationships between the initial total bilirubin level and the other end points.

Conclusions: Recent studies have shown that the serum total bilirubin level is independently associated with short-term outcomes in patients with STEMI. We found a direct relationship between the total bilirubin level and the peak levels of troponin and CK-MB after primary PCI. This outcome is consistent with other studies; nonetheless, we found no such relationships vis-à-vis the other end points. This result may be due to our small patient population. ***(Iranian Heart Journal 2019; 20(1):53-59)***

KEYWORDS: Total bilirubin level, ST-segment elevation myocardial infarction, Primary percutaneous coronary intervention, Thrombolysis, Major adverse cardiovascular events

[1] Rajaie Cardiovascular, Medical, and Research Center, Iran University of Medical Sciences, Tehran, IR Iran.
[2] Cardiovascular Intervention Research Center, Rajaie Cardiovascular, Medical, and Research Center, Iran University of Medical Sciences, Tehran, IR Iran.

***Corresponding Authors:** Hamidreza Sanati, MD
Email: sanati56@yahoo.com **Tel:** 09123765828

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The oxidation of lipids and the formation of oxygen radicals are important elements in relation to arterial plaque formation and atherosclerosis and are involved in the pathophysiology of coronary artery disease (CAD). [1]

Oxidative stress plays an important role in atherosclerosis, and several studies have noted an inverse relationship between CAD and circulatory total bilirubin. [2] Bilirubin may reduce the activation of the homeostatic system to inhibit oxidative stress, which could explain its cardioprotective properties shown in many epidemiologic studies. [3] Bilirubin has also been proven to act against plaque formation and heme oxygenase-1 overexpression attenuated post-infarction ventricular remodeling in experimental animals. [2,4] In addition, the Gilbert syndrome is caused by mutation, which increases the level of bilirubin, and it shows a strong association with a lower risk of cardiovascular diseases.[5]

Previous studies have shown that the serum total bilirubin concentration is inversely related with stable CAD, diabetes mellitus, hypertension, and the metabolic syndrome; nonetheless, there are only a few studies on the initial total bilirubin concentration in patients with ST-segment elevation myocardial infarction (STEMI). [6,7]

Although a high serum total bilirubin concentration after primary percutaneous coronary intervention (PCI) has been reported to be inversely associated with in-hospital adverse outcomes, the relation between them is not well known yet. [7,8]

METHODS

This is a single-center trial with a prospective cross-sectional design of patients with acute STEMI undergoing primary PCI. Ninety-five patients were initially evaluated between April 2015 and April 2016. Patients were considered eligible if they were older than 18 years of age and had acute STEMI and indications for primary PCI based on clinical and electrocardiographic characteristics. The institutional Ethics Committee of Rajaie Cardiovascular, Medical, and Research Center approved the trial design.

Procedural protocol and follow-up

The clinical, laboratory, and procedural characteristics of the studied patients were collected and entered in a questionnaire. The coronary angiography and primary PCI procedures were performed according to the standard routines. The intention to treat was for the culprit artery. The total bilirubin level was measured at the time of hospitalization, before the procedure.

The peak cardiac troponin I (cTnI) and creatine-kinase MB (CK MB) levels were defined as the highest amount obtained through serial (3 times) enzyme checks during the first 24 hours of admission. A complete echocardiographic study was performed on the patients the day after the primary PCI. The left ventricular ejection fraction was estimated using the Simpson equation in the 4-chamber view. The patients were observed during the hospitalization and a 6-month follow-up period.

Primary and secondary end points

The primary end point of this study was to determine whether there was a relationship between the initial total bilirubin level and the clinical outcome of primary PCI in patients with STEMI. The objective primarily was to demonstrate the relationship between the initial total bilirubin level and the TIMI flow. The secondary end points were in-hospital adverse cardiac outcomes (defined as post-PCI complications) and 6 months' major adverse cardiac events (MACEs) (defined as death, the acute coronary syndrome, recurrent chest pain, decompensated heart failure, and elective PCI).

RESULTS

A total of 95 patients with STEMI were enrolled in the study and underwent primary PCI.

The mean bilirubin level was 1.04 mg/dL with a standard deviation of 1.154.

Table 1. Relationship between the median bilirubin level and the TIMI flow grade

TIMI Flow	Median Bilirubin (IQR)	*P*
TIMI<3 (N:38)	0.85 (0.6-1.2)	0.97
TIMI=3 (N:57)	0.8 (0.6-1.2)	

TIMI, Thrombolysis in myocardial infarction

From the 95 patients, 38 patients had a TIMI flow grade of less than 3 and 57 patients had a TIMI flow grade of 3 after PCI. The median total bilirubin level in the TIMI flow grade of less than 3 was 0.85 mg/dL and in the TIMI flow grade of 3 was 0.8 mg/dL, which was not statistically significantly different (*P*=0.97).

Table 2. Relationship between the median bilirubin level and the frequency of the patients with the no-reflow phenomenon

No-reflow	Median Bilirubin (IQR)	*P*
Yes (N:7)	0.7 (0.5-1)	0.41
No (N:88)	0.8 (0.6-1.2)	

Seven patients with the no-reflow phenomenon had a median level of bilirubin of 0.7 mg/dL, and the rest of the patients who did not have this complication had a median bilirubin level of 0.8 mg/dL. This difference was not statistically significant (*P*=0.4).

Table 3 depicts the complications which occurred at the time of PCI, after PCI, and during hospitalization among the study population.

Table 3. Relationship between the median bilirubin level and the frequency of post-PCI complications

Post-PCI Complication		N	Median Bilirubin (IQR)	*P*
Cardiogenic shock	Yes	5	1.2 (0.7-1.3)	0.69
	No	90	0.8 (0.6-1.2)	
Intubation	Yes	2	1.05 (0.9-1.2)	0.44
	No	93	0.8 (0.6-1.2)	
IABP	Yes	4	0.951 (0.6-1.71)	0.96
	No	91	0.8 (0.6-1.2)	
VT/VF	Yes	5	1.3 (0.7-1.5)	0.37
	No	90	0.8 (0.6-1.2)	
CHB	Yes	5	1.3 (0.9-1.3)	0.11
	No	90	0.8 (0.6-1.2)	
Perforation	---	---	----	---
Total dissection	---	---	---	---
Subtotal dissection	Yes	4	0.75 (0.65-0.95)	0.79
	No	91	0.8 (0.6-1.2)	
Side-branch occlusion	Yes	3	0.6 (0.5-0.7)	0.18
	No	92	0.8 (0.6-1.2)	
Stent thrombosis	Yes	2	1.05 (0.8-1.3)	0.5
	No	93	0.8 (0.6-1.2)	
Reinfarction	---	---	---	---
Recurrent CP after PCI	Yes	10	0.8 (0.6-1.2)	0.89
	No	85	0.8 (0.6-1.2)	
CIN	Yes	8	1.15 (0.8-1.3)	0.22
	No	87	0.8 (0.6-1.2)	
CVA/TIA	---	---	---	---
Access complication	Yes	6	0.65 (0.5-0.8)	1.1
	No	89	0.8 (0.6-1.2)	
Death	Yes	5	1.2 (0.6-1.3)	0.77
	No	90	0.8 (0.6-1.2)	

IABP, Intra-aortic balloon pump; VT/VF, Ventricular tachycardia/ventricular fibrillation; CHB, Complete heart block; CP, Constrictive pericarditis; PCI, Percutaneous coronary intervention; CIN, Contrast-induced nephropathy; CVA/TIA, Cerebrovascular accident /transient ischemic attack

Cardiogenic shock occurred in 5 patients. These patients had a median bilirubin level of 1.2 mg/dL and the other 90 patients had a median bilirubin level of 0.8 mg/dL; this difference failed to constitute statistical significance (*P*=0.69)

Two patients needed tracheal intubation. The intra-aortic balloon pump was used in 4 patients, and ventricular tachycardia/ventricular fibrillation occurred in 5 patients during PCI. Five patients developed complete heart block after PCI.

The median bilirubin level among these patients exhibited no statistically significant differences.

Perforation and total dissection did not occur among the patients during PCI, but total dissection happened in 4 patients and side-branch occlusion occurred in 2 patients. There was no statistically significant difference between these patients vis-à-vis the median bilirubin level.

Stent thrombosis developed in 2 patients. These patients had a median bilirubin level of 1.05 mg/dL, and the remaining 93 patients had a median level of bilirubin of 0.8 mg/dL; this difference was not significant (*P*=0.5).

After PCI and during hospitalization, 10 patients suffered from recurrent chest pain. The median bilirubin level among these patients was of 0.8 mg/dL, and the other patients had a median bilirubin level of 0.8 mg/dL, with no significant difference (*P*=0.89).

Cerebrovascular accident/transient ischemic attack and reinfarction did not happen during hospitalization. Eight patients developed contrast-induced nephropathy (CIN). The median bilirubin level in these patients was 1.15 mg/dL, and the other patients who did not develop CIN had a median bilirubin level of 0.8 mg/dL (*P*=0.2). Five patients died during hospitalization; the median bilirubin level had no significant difference between them and the survivors (*P*=0.77).

Table 4. Relationship between the median bilirubin level and the ejection fraction

Ejection Fraction	Number	Median Bilirubin (IQR)	*P*
<30 %	16	0.65 (0.5-1.15)	0.28
30-44 %	56	0.85 (0.6-1.25)	
45-55 %	23	0.8 (055-1)	

Sixteen patients had an ejection fraction of less than 30% after PCI, 56 patients had an ejection fraction of between 30% and 44%, and 23 patients had an ejection fraction of between 45% and 55%. The median bilirubin level was 0.65 mg/dL in group 1, 0.85 mg/dL in group 2, and 0.8 mg/dL in group 3; there were no significant differences (*P*=0.28).

Table 5. Relationship between the median bilirubin level and the amount of MR

MR	Number	Median Bilirubin (IQR)	*P*
None	18	0.85 (0.6-1.3)	0.47
Mild (+1)	53	0.9 (0.6-1.2)	
Moderate(≥ +2)	24	0.8 (0.55-0.95)	

MR, Mitral regurgitation

The median bilirubin level had no significant differences between the patients with different amounts of mitral regurgitation (*P*=0.47).

Table 6. Relationship between the median bilirubin level and the amount of ST resolution

ST Resolution	Median Bilirubin (IQR)	*P*
Yes (N:67)	0.8 (0.6-1.15)	0.9
No (N:28)	0.8 (0.5-1.35)	

Table 7. Relationship between the median bilirubin level and the frequency of the Q-wave formation

Q-Wave Formation	Median Bilirubin (IQR)	*P*
Yes (N:57)	0.8 (0.6-1.2)	0.15
No (N:38)	0.8 (0.5-1.1)	

There was no significant relationship between the patients who achieved an ST resolution of greater than 50% and the Q-wave formation and the rest of the patients with respect to the median level of bilirubin.

Table 8. Relationship between the median bilirubin level and the frequency of complications during the 6-month follow-up period

6 Months' Follow-up	Number		Median Bilirubin (IQR)	*P*
ACS	Yes	11	0.9 (0.75-1.6)	0.16
	No	84	0.8 (0.6-1.2)	
Recurrent CP	Yes	8	0.75 (0.5-1.1)	0.46
	No	87	0.8 (0.6-1.25)	
Elective PCI	Yes	9	0.8 (0.6-1)	0.74
	No	86	0.8 (0.6-1.3)	
DHF	Yes	1	0.6 (0.8-1.2)	0.97
	No	94		
Death	Yes	5	1.2 (0.6-1.3)	0.77
	No	90	0.8 (0.6-1.2)	

ACS, Acute coronary syndrome, CP, Constrictive pericarditis; PCI, Percutaneous coronary intervention; DHF, Decompensated heart failure

A 6 months' follow-up, 11 patients were re-admitted with the acute coronary syndrome. Eight patients developed recurrent chest pain, 9 patients underwent elective PCI, 1 patient suffered decompensated heart failure, and 5 patients expired. The median of the bilirubin level did not have any significant differences between them.

In terms of nonparametric correlations according to the Spearman method, the correlation coefficient between the total bilirubin level and the length of hospital stay was 0.18, which was not significant (*P*=0.08). Nonetheless, the correlation coefficient between the total bilirubin level and the peak CK-MB level after PCI was 0.38 and the correlation coefficient between the total bilirubin level and the peak troponin level after PCI was 0.35. These relationships, albeit poor, were significant.

DISCUSSION

A total of 95 patients with STEMI were enrolled in the current study and underwent primary PCI. The mean bilirubin level was 1.04 mg/dL with a standard deviation of 1.154. We sought to determine whether there was a relationship between the initial total bilirubin level and the clinical outcome of primary PCI in patients with STEMI. To achieve this goal, we compared some variables with the median bilirubin levels among the patients.

First, the patients were divided into 2 groups: patients with a TIMI flow grade of less than 3 and patients with a TIMI flow grade of 3 after primary PCI. The no-reflow phenomenon developed in 7 patients. In our study, there was no significant relationship between the median bilirubin level and the grade of TIMI flow. In contrast, Celik et al [9] showed that the total bilirubin level was an independent predictor of the no-reflow phenomenon in patients with STEMI undergoing primary PCI. Liu et al [8] designed a study for the evaluation of the effects of high total bilirubin levels on the prognosis of patients with the no-reflow phenomenon. In that study, a total bilirubin concentration of greater than 0.9 mg/dL was a significant indicator of patients with the no-reflow phenomenon for in-hospital cardiovascular mortality.

We found no significant relationships between peri-PCI and in-hospital MACEs and the median bilirubin level. Chung et al [6] showed that the high total bilirubin concentration group (total bilirubin>0.79 mg/dL) had a high rate of MACEs (a composite of cardiac death, nonfatal MI, definite/probable stent thrombosis, and cardiac death) compared with the low total bilirubin concentration groups and concluded that adding the initial total bilirubin concentration to the TIMI risk score

significantly improved prediction for in-hospital MACEs. Gul et al [7] showed that the in-hospital mortality rate was significantly greater in the high total bilirubin concentration group (total bilirubin>0.9 mg/dL) than in the low total bilirubin concentration group, but no differences were seen in the long-term mortality rates between the 2 groups. In our study, we observed no differences in the long-term outcomes and mortality rates.

Recent studies have shown that the serum total bilirubin level is independently associated with the short-term outcome in patients with STEMI; however, many studies have reported that bilirubin may protect against atherosclerosis. [5] Yao et al [5] showed that a low bilirubin level before PCI was an independent predictor of long-term adverse clinical outcomes in patients with angina pectoris. Mayer et al [1] demonstrated that a serum bilirubin concentration in the upper portion of the reference interval reduced atherogenic risk and provided protection against CAD.

Consequently, different studies have shown that higher serum bilirubin levels are associated with lower cardiovascular risks in patients with stable angina; however, there is an inverse relationship in patients with STEMI.

In our study, CIN occurred in 8 (8.4%) patients and there were no significant associations between the median bilirubin level and the incidence of CIN. Huang at al [10] evaluated the association between the bilirubin level and the development of CIN in patients undergoing PCI and showed that a higher serum bilirubin concentration was associated with a lower risk of CIN and fewer cardiovascular events. Elsewhere, Vuruskan et al [11] showed that a decreased total bilirubin concentration was associated with CIN development after the administration of radiocontrast agents and peripheral artery disease.

We did not find any relationship between the severity of mitral regurgitation and the final ejection fraction after PCI and the median bilirubin level. Miranda et al [4] showed that bilirubin levels on admission were not predictive of the changes in the left ventricular volume or ejection fraction at 6 months measured with serial cardiac magnetic resonance imaging.

We found a direct relationship between the total bilirubin level and the peak of troponin and CK-MB levels after primary PCI; this outcome is consistent with that reported by other studies which showed that the serum total bilirubin level was independently associated with short-term outcomes in patients with STEMI.

In our study, the reduced rate of mortality and MACEs in the setting of primary PCI renders a statistical comparison harder. Indeed, larger populations may be needed to detect potential effects among study groups.

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