ISSN:0975-1459
Journal of Pharmaceutical Sciences and Research
www.jpsr.pharmainfo.in

Association of serum total bilirubin with troponins in patients with myocardial infarction

Sneha Chandrasekaran, E.Keerthika
Department of Biochemistry, Saveetha Medical college and Hospital, Chennai – 602105

Abstract:

Objective: Myocardial infarction (MI) is the most common cause of death in the world. Comprehensive risk assessment of patients presenting with chest pain and eliminating undesirable results should decrease morbidity and mortality rates, increase the quality of life of patients. Previous studies have reported a relationship between serum total bilirubin (STB) and coronary artery disease (CAD). Objective of this study is To assess the cardiac troponin levels in patients with MI and To evaluate serum total bilirubin as a biomarker for MI.

Methods: This prospective cohort study will be carried out in the clinical biochemistry laboratory in saveetha medical college and hospital with 50 MI patients and 50 age and sex matched controls. the sample will be processed in vitros 5600 automated dry chemistry.

The patients were divided into two groups: Test and Control groups based on the optimal cutoff value achieved in the receiver operating characteristic curve analysis. The relationships between serum TB at admission and clinical were analyzed in multivariable logistic regression models.

Results: The bilirubin and troponin levels will increase in patients with myocardial infarction. hence the bilirubin can serve as a useful biomarker for detecting myocardial infarction.

In all patients, TB>1.4 mg/dL was associated with Myocardial infaractions. The odds ratio (95% confidence interval) was 1.60 (1.22–2.10) and 1.81 (1.22–2.70) for Total billirubin and Troponins, respectively. The association between TB and TnI was not altered by clinical presentation (p for interaction=0.949).

Conclusion: In patients with MI undergoing Treatment, elevated serum TB and Troponin was associated with increased risk of cardiovascular death.

Key words: Myocardial infaraction, Troponin, Total billirubin, Coronary artery disease and Bio markers.

INTRODUCTION

Serum bilirubin is a metabolic end product of heme, which partially reflects the activity of heme oxygenase (HO).1 In addition, bilirubin is a powerful antioxidant, which has been demonstrated to have a potential antioxidant capacity.2,3 The potential mechanism may be attributed to scavenging of reactive oxygen species. Bilirubin also has an anti-inflammatory property based on the inhibition of endothelial adhesion molecules, such as intercellular adhesion molecule-1, vascular cell-adhesion molecule-1, and E-selectin, by tumor necrosis factor-alpha.4

The protective effects of serum total bilirubin (TB) against cardiovascular-related disease and adverse cardiovascular events have been reported in the last decade. Serum TB has been reported to exert a protective effect on hypertension, diabetes mellitus (DM), atherosclerosis, and coronary artery disease (CAD).5–8

In patients with hypertensive and acute syndrome X, this inverse relationship between serum TB and adverse cardiovascular events remained.[13–15] Conversely, recent studies found that serum TB concentration was elevated in patients with myocardial infarction (MI), and several cohort studies suggested that higher serum TB was associated with adverse outcomes in patients with MI. [2,16–21] Based on bilirubin's anti-inflammatory and anti-oxidative properties, and different effects of serum TB on cardiovascular events in different populations, serum TB has become a heated research issue recently.

Although previous studies have evaluated the impact of the baseline serum TB on in-hospital cardiovascular outcomes after PCI, few studies have examined its influence on long-term follow-up outcomes. Furthermore, most previous studies focused on the relationship between serum TB and outcomes after PCI in patients with acute coronary syndrome (ACS), and limited evidence was available on patients with stable angina (SA).

Nowadays, the most important cardiac proteins involved in the diagnosis of MI are TnC, TnI and TnI. [17] TnI and TnI are known as cardiac troponins because they are present in heart and skeletal muscle. Cardiac proteins are synthesized and released from cardiac muscle. These proteins interact with tropomyosin to form the main structure of the striated

heart muscle. Cardiac troponin (cTn) acts on myocardial contraction by regulating the calcium-dependent interaction of actin and myosin.

Our objective was to clarify the association between serum TB at admission and Cardiac protein – Troponin i, particularly short-term clinical outcomes in patients with Myocardial Infaraction.

METHODS

Present study is cross sectional study with follow up. The sample size of patients is 100, 50 MI and 50 normal patients. Patients in this study were excluded based on the following criteria: (1) age <18 years; (2) patients with serum TB at admission >2.0 mg/dL The study was approved by the Ethics Committee of the Saveetha medical college and Hospital, Chennai with a waiver of informed consent. Data were analyzed anonymously in this study.

Baseline data collection

All basic clinical characteristics information was collected at admission, including demographic information. Smoking was defined as patients who smoked within the

previous 10 years. Diabetes mellitus (DM) was defined as a fasting plasma glucose concentration ≥126 mg/dL or current treatment with hypoglycemic agents. Hypertension was defined as a systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or use of antihypertensive drugs. Other disease histories were self-reported. [22]

Statistical analysis

All patients were divided into two groups: troponin and TB groups. The optimal cutoff point (0.60 mg/dL) was determined by receiver operating characteristic curve analysis. Normally distributed, continuous variables were presented as means (standard deviation), and non-normally distributed data were shown as medians [inter-quartile ranges]. Categorical variables were shown as percentages. Student t-test or Mann–Whitney U test were used to compare continuous variables in two groups. Multiple linear regression analysis was used to determine the relationship of serum TB with Tni, including age, sex, history of MI. The regression coefficient and 95% CI were depicted. The associations of serum TB and TnI with cardiovascular events were assessed using multivariable logistic regression analysis. To assess the shape of the association between TB and Troponin, we introduced terms with common transformations of TB inclusive of linear, quadratic, logarithmic, categorical (tertiles), and binary (groups as specified above) in multivariable models and used nonparametric restricted cubic splines with four knots defined as the 5th, 35th, 65th, and 95th percentiles of the distribution of TB. The reference value for TB was 0.52 mg/dL (the median value of TB).

A two-tailed p≤0.05 was considered statistically significant. Statistical analysis was conducted using SPSS.

RESULTS

Baseline characteristics

50 patients sample were received from november 2019 to March 2020, The mean age was 59.9 ±11.1 years, and approximately 68.0% of the patients were men. The mean serum TB level at admission in the high (>0.60 mg/dL) and low TB groups (≤0.60 mg/dL) was 0.70 mg/dL [0.60–0.90] and Furthermore, 50 patients had Cardiac TnI >0.4 mg/dL [0.30–0.50], respectively.

In addition, the high TB group tended to have more male patients, a higher percentage of more comorbidities, including previous coronary artery bypass graft (CABG), heart failure, and more complex lesions, including bifurcation lesions and ostial lesions compared with the low TB group.

Association between TB and TnI

Associations between serum TB at admission and Cardiac Troponin t in the total population are listed in Table 1. In follow-up outcomes, serum TB was associated with TnI and cardiovascular death in logistic regression analysis (TnI: OR and 95% CI, 1.60 [1.23–2.09], p<0.001; cardiovascular death: OR and 95% CI, 1.94 [1.32–2.86], p=0.014).

Table 1 Clinical information

Variable	TB	TnI	*p*-value
	n=50	n=50	
Age (years)	59.7±11.2	60.1±11.0	0.258
Male, *n* (%)	(32)	(34)	<0.001

Besides, after transformation of TB, relationships of linear, quadratic, logarithmic, and categorical (tertiles) TB with TnI in fully adjusted models are shown in Figure 1. When TB was a categorical variable, a positive association was observed (OR=0.94, 95% CI: 0.56–1.59 for tertile 2 vs tertile 1; OR=1.44, 95% CI: 0.89–2.34 for tertile 3 vs tertile 1). When TnI was a continuous, logarithmic, or quadratic variable, a positive association was also observed (Figure 1).

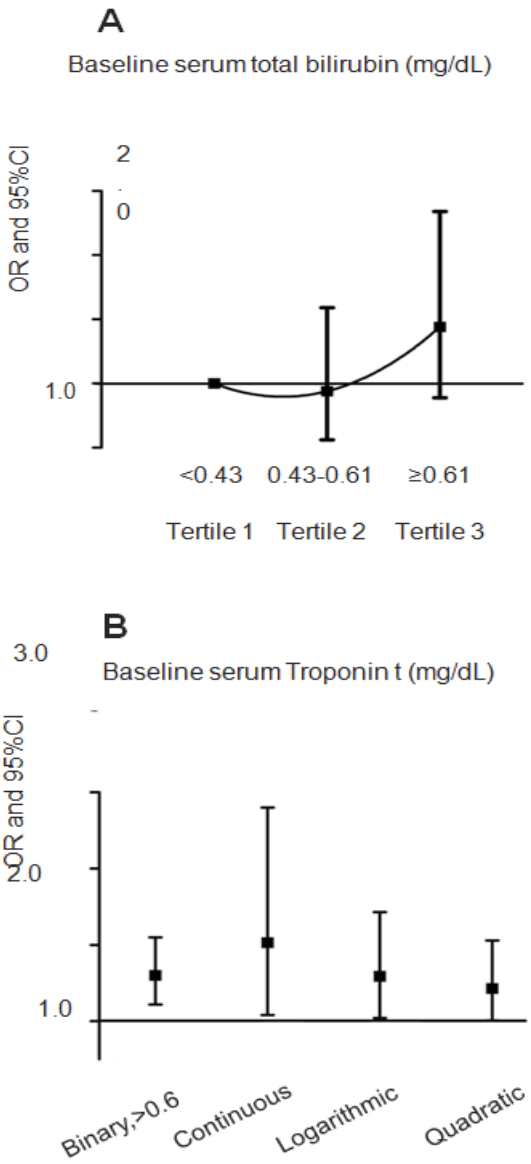

Figure 1 : Correlation of total bilirubin (TB) with Cardiac Troponin [TnI] and cerebrovascular events. (A) Categorical TB with tertiles; (B) binary, continuous, logarithmic and quadratic TnI.

In group analysis, higher TB was associated with a greater risk of MI (OR and 95% CI, 1.61 [1.20–2.17], p<0.001) and cardiovascular death (OR and 95% CI, 1.89 [1.22–2.93]).

The dose–response relationship between serum TB and MI is given in Table 2.

Table 2 Dose–response relationship between total serum bilirubin and MI

Serum total bilirubin (mg/dL)	MI	
	OR	95% CI
0.21	0.81	0.50–1.33
0.44	0.88	0.79–0.97
0.52	1.0 (Reference)	
0.6	1.16	1.01–1.32
1.06	1.41	1.01–1.97
p overall	0.025	
p nonlinear	0.208	

DISCUSSION

The main finding of the present study was that serum TB level at admission was related with Troponin t and cardiovascular death during a 6 months follow-up with adjustment for age, sex, DM, hypertension, heart rate, smoking, atrial fibrillation, heart failure, history of MI, multiple diseased vessels, lesion of left main stem, restenosis lesions, and acute coronary syndrome.

Our study result clearly showed that a high baseline serum TB and TnI level was a simple and powerful predictor of Myocardial infaraction in patients undergoing clinical presentation of CAD.

Previous literature demonstrated that increased serum TB may be protective against adverse vascular events under normal condition.1–3,9–11,13,14,24–26 Conversely, recent reports found that initial serum TB and TnI were a prognostic marker of no-reflow and in-hospital adverse outcomes in patients with ST elevation myocardial infarction (STEMI) and MI undergoing PCI.2,17–19,21,27 Sahin et al found that patients with STEMI with higher TB level accumulated in the high SYNTAX score group than the low SYNTAX score group.28 The results involving TB and cardiovascular outcomes may be different between emergent and non-emergent patients, and most studies observed in-hospital outcomes in patients with ACS rather than patients with SA. Therefore, the present study might provide evidence to fully evaluate the association between serum TB and TnI over a 6 months follow-up in patients with Heart disease.

One conceivable reason to explain the positive relationship between TB and TnI after PCI is that higher serum TB level at baseline may be a reflection of more severe disease status. It can be postulated that the elevation of bilirubin may result from inadequate arterial perfusion of liver and hepatic congestion owing to cardiac dysfunction.21,27 Our finding supported this hypothesis because we observed that patients with higher bilirubin concentration tended to be older and had worse co-morbidities, including atrial fibrillation and heart failure, which may cause higher possibility of increased troponins after PCI. In addition, recent finding from Htun et al suggested that elevated bilirubin and cardiac proteins may be a surrogate marker of unstable plaques, which may cause MI, stroke, and death.29

Another hypothesis that may explain the relationship between serum TB and TnI in patients with ACS is acute stress reaction. An inducible isoform in response to diverse cellular stress, such as oxidative stress, hypoxia, heavy metals, cytokines, and heme oxygenase 1 (HO-1), reflects the extent of inflammatory reaction to myocardial damage. In previous reports, HO-1 was found to be notably upregulated in the myocardium under infarction and pressure overload condition in animal models.30 The study by Okuhara et al demonstrated a positive correlation between HO-1 protein and its end product bilirubin.31

Amanvermez et al also found that oxidative end products in the first hour of patients with ACS were higher than those in the healthy population.32 Therefore, higher serum TB concentration may also represent more serious myocardial damage in the acute period and following poor outcomes. Acute stress reaction may cause an evident correlation between TB and Troponins in patients with ACS.

Some limitations still need to be considered. First, only serum TB and TnI value at admission was assessed in the study. There was no information regarding the dynamic alteration of serum TB level and time points of adverse event occurrence. Confirmation of the time-dependent association between serum TB level and TnI by their prognosis is impossible. Second, HO-1 and other markers related to oxidative stress were not measured.18 Third, follow-up information obtained through a telephone interview may be an important bias in the data collection. Finally, although multivariable logistic regression analyses were performed in our analyses because of the limited sample size.

CONCLUSION

We conclude that in patients with MI who underwent treatment, elevated serum TB and TnI levels were associated with a greater risk of MI and cardiovascular death. Baseline serum TB may be treated as an indicator of poor outcome after treatment regardless of whether they are patients with ACS or SA.

Acknowledgments

This work was supported by the Clinical Biochemistry Research department of the Saveetha medical college and Hospital, Chennai.

REFERENCES

1. Mahabadi AA, Lehmann N, Mohlenkamp S, et al. Association of bilirubin with coronary artery calcification and cardiovascular events in the general population without known liver disease: the Heinz Nixdorf Recall study. *Clin Res Cardiol*. 2014;103(8):647–653. doi:10.1007/s00392-014-0697-z
2. Chung SR, Yang TH, Shin HC, et al. Initial total bilirubin and clinical outcome in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention with drug-eluting stents. *Circ J*. 2016;80(6):1437–1444. doi:10.1253/circj. CJ-15-1397
3. Ajja R, Lee DC, Sui X, Church TS, Steven NB. Usefulness of serum bilirubin and cardiorespiratory fitness as predictors of mortality in men. *Am J Cardiol*. 2011;108(10):1438–1442.

doi:10.1016/j. amjcard.2011.06.067
4. Nishimura T, Tanaka M, Saisho Y, Miyakoshi K, Tanaka M, Itoh H. Lower serum total bilirubin concentration is associated with higher prevalence of gestational diabetes mellitus in Japanese pregnant women. *Endocr J*. 2018;65(12):1199–1208. doi:10.1507/endocrj.EJ17-0533
5. Chin HJ, Song YR, Kim HS, et al. The bilirubin level is negatively correlated with the incidence of hypertension in normotensive Korean population. *J Korean Med Sci*. 2009;24:S50–S56. doi:10.3346/ jkms.2009.24.S1.S50
6. Han SS, Na KY, Chae DW, Kim YS, Kim S, Chin HJ. High serum bilirubin is associated with the reduced risk of diabetes mellitus and diabetic nephropathy. *Tohoku J Exp Med*. 2010;221(2):133–140.
7. Hopkins PN, Wu LL, Hunt SC, James BC, Vincent GM, Williams RR. Higher serum bilirubin is associated with decreased risk for early familial coronary artery disease. *Arter Thromb Vasc Biol*. 1996;16(2):250–255. doi:10.1161/01.ATV.16.2.250
8. Schwertner HA, Jackson WG, Tolan G. Association of low serum concentration of bilirubin with increased risk of coronary-artery disease. *Clin Chem*. 1994;40(1):18–23.
9. Kunutsor SK, Bakker SJ, Gansevoort RT, Chowdhury R, Dullaart RP. Circulating total bilirubin and risk of incident cardiovascular disease in the general population. *Arterioscler Thromb Vasc Biol*. 2015;35 (3):716–724. doi:10.1161/ATVBAHA.114.304929
10. Kim HW, Choi DH, Lim L, et al. Usefulness of serum bilirubin levels as a biomarker for long-term clinical outcomes after percutaneous coronary intervention. *Heart Vessels*. 2015;30(6):728–733. doi:10.1007/s00380-014-0546-z
11. Zhang MM, Gao Y, Zheng YY, et al. Association of fasting serum bilirubin levels with clinical outcomes after percutaneous coronary intervention: a prospective study. *Cardiovasc Toxicol*. 2017;17 (4):471–477. doi:10.1007/s12012-017-9405-3
12. Wei S, Mao L, Liu B, Zhong L. Serum biomarkers and the prognosis of AMI patients. *Herz*. 2014;39(3):384–389. doi:10.1007/s00059- 013-3828-9
13. Huang SS, Huang PH, Leu HB, Wu T-C, Lin S-J, Chen J-W. Serum bilirubin predicts long-term clinical outcomes in patients with cardiac syndrome X. *Heart*. 2010;96(15):1227–1232. doi:10.1136/ hrt.2009.192393
14. McCallum L, Panniyammakal J, Hastie CE, et al. Longitudinal blood pressure control, long-term mortality, and predictive utility of serum liver enzymes and bilirubin in hypertensive patients. *Hypertension*. 2015;66(1):37–43. doi:10.1161/HYPERTENSIONAHA.114.04915
15. Yao HM, Shen DL, Zhao XY, et al. Prognostic value of total bilirubin in patients with angina pectoris undergoing percutaneous coronary intervention. *Int J Clin Exp Med*. 2015;8(9):15930–15939.
16. Acet H, Erts F, Akil MA, et al. 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. *Postep Kardiol Inter*. 2014;10(2):91–97. doi:10.5114/pwki.2014.43513
17. Celik T, Kaya MG, Akpek M, et al. Does Serum Bilirubin level on admission predict TIMI flow grade and in-hospital MACE in patients with STEMI undergoing primary PCI. *Angiology*. 2014;65 (3):198–204. doi:10.1177/0003319712474948
18. Gul M, Uyarel H, Ergelen M, et al. Prognostic value of total bilirubin in patients with ST-segment elevation acute myocardial infarction undergoing primary coronary intervention. *Am J Cardiol*. 2013;111 (2):166–171. doi:10.1016/j.amjcard.2012.09.011
19. Huseynov A, Baumann S, Becher T, et al. Liver and cholestatic parameters as prognostic biomarkers of in-hospital MACE in patients with STEMI. *Eur J Clin Invest*. 2016;46(8):721–729. doi:10.1111/eci.12655
20. Wu AH, Levy WC, Welch KB, et al. Association between bilirubin and mode of death in severe systolic heart failure. *Am J Cardiol*. 2013;111(8):1192–1197. doi:10.1016/j.amjcard.2012.12.048
21. Frikha Z, Ferreira JP, Bozec E, et al. Relation of high serum bilirubin to short-term mortality following a myocardial infarction complicated by left ventricular systolic dysfunction (from the high-risk myocar- dial infarction database initiative). *Am J Cardiol*. 2018;121 (9):1015–1020. doi:10.1016/j.amjcard.2018.01.012
22. Yao HM, Wan YD, Zhang XJ, et al. Long-term follow-up results in patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stents: results from a single high-volume PCI centre. *BMJ Open*. 2014;4(8):e004892. doi:10.1136/bmjopen-2014-004892
23. Yao H, Wan Y, Zhang X, et al. Data from: long-term follow-up results in patients undergoing percutaneous coronary intervention (PCI) with drug-eluting stents: results from a single high-volume PCI center. *Dryad Digital Repository*. 2014. doi:10.5061/dryad.13d31
24. Breimer LH, Mikhailidis DP. Is bilirubin a marker of vascular disease and/or cancer and is it a potential therapeutic target? *Curr Pharm Des*. 2011;17(33):3644–3655.
25. Kimm H, Yun JE, Jo J, Jee SH. Low serum bilirubin level as an independent predictor of stroke incidence: a prospective study in Korean men and women. *Stroke*. 2009;40(11):3422–3427. doi:10.1161/STROKEAHA.109.560649
26. Amor AJ, Ortega E, Perea V, et al. Relationship between total serum bilirubin levels and carotid and femoral atherosclerosis in familial dyslipidemia. *Arter Thromb Vasc Biol*. 2017;37(12):2356–2363. doi:10.1161/ATVBAHA.117.310071
27. Shen H, Zeng C, Wu X, Liu S, Chen X. Prognostic value of total bilirubin in patients with acute myocardial infarction: A meta-analysis. *Medicine (Baltimore)*. 2019;98(3):e13920. doi:10.1097/MD.0000000000013920
28. Sahin O, Akpek M, Elcik D, et al. Bilirubin levels and the burden of coronary atherosclerosis in patients with STEMI. *Angiology*. 2013;64 (3):200–204. doi:10.1177/0003319712440619
29. Htun NM, Chen YC, Lim B, et al. Near-infrared autofluorescence induced by intraplaque hemorrhage and heme degradation as marker for high-risk atherosclerotic plaques. *Nat Commun*. 2017;8(1):75. doi:10.1038/s41467-017-00138-x
30. Mito S, Ozono R, Oshima T, et al. Myocardial protection against pressure overload in mice lacking Bach1, a transcriptional repressor of heme oxygenase-1. *Hypertension*. 2008;51(6):1570–1577. doi:10.1161/HYPERTENSIONAHA.107.102566
31. Okuhara K, Kisaka T, Ozono R, et al. Change in bilirubin level following acute myocardial infarction is an index for heme oxygenase activation. *South Med J*. 2010;103(9):876–881. doi:10.1097/ SMJ.0b013e3181eac06a
32. Amanvermez R, Acar E, Gunay M, Baydın A, Yardan T, Bek Y. Hsp 70, hsCRP and oxidative stress in patients with acute coronary syndromes. *Bosn J of Basic Med Sci*. 2012;12(2):102–107. doi:10.17305/bjbms.2012.2508