Original Research Article

Association of total bilirubin levels with acute coronary syndrome and other risk factors: an observational study

Shubangi Verma*, Omkar Kamble

Department of Medicine, PDMC, Amravati, Maharashtra, India

*Correspondence:
Dr. Shubangi Verma,
E-mail: shubhangi.verma@rediffmail.com

ABSTRACT

Background: Acute coronary syndrome (ACS) refers to clinical symptoms pertaining to acute myocardial infarction. Bilirubin is an antioxidant that helps in removal of excessive heme. The aim of the study was to find the association of ACS and other risk factors for ACS with the total bilirubin levels in our setup.

Methods: A cross sectional observational study was conducted on 100 cases attending the department of medicine in a Dr. Panjabrao Deshmukh Memorial Medical College, Amravati, Maharashtra. Patients fitting the eligibility criteria were subjected to data collection which was done using pre-designed case record form. The case record form had details of demography, detailed clinical history, physical examination and relevant investigations.

Results: The mean age of the cases was 55.64±10.23 years with male preponderance. Majority of the patients presented with chest pain (83%) followed by shortness of breath (65%) and nausea/vomiting (33%). There was moderate significant correlation between total bilirubin levels and LDL levels (r=0.703; p value<0.001) and There was mild significant correlation between total bilirubin levels and TGs (r=0.403, p value<0.001) Based on the median value of 0.48 as cut off, 33% had bilirubin levels more than 0.48. Presence of diabetes and hyperlipidemias had significant association with the total bilirubin levels.

Conclusions: Nearly 1/3rd of the patients in our study had high bilirubin levels. Higher bilirubin levels correlated well with presence of diabetes and presence of hyperlipidemias. There was significant correlation between the serum LDL and TG levels with total bilirubin levels in the present study.

Keywords: Acute myocardial infarction, Total bilirubin levels, Risk factors

INTRODUCTION

Acute coronary syndrome (ACS) refers to clinical symptoms pertaining to acute myocardial infarction.[1] Unstable angina, non ST segment elevation and ST segment elevation are the categories of acute coronary syndrome.[1,2] Several risk factors affect the syndrome like presence of high lipids, hypertension, diabetes and smoking.[1,2] Basic pathophysiology of the syndrome is myocardial ischemia resulting from endothelial dysfunction and damage to endothelium due to these risk factors.[3,4] During this process of inflammation various anti-inflammatory and pro-inflammatory factors come into consideration. Free heme is a pro inflammatory and cytotoxic affects mainly a result of release of free radicals. Bilirubin is an antioxidant that helps in removal of excessive heme.[5]

It was considered that bilirubin was waste product of the heme oxygenase action but now reports suggest that it has strong relation with coronary artery lesion types.[6] This basically is because of its major antioxidant action inhibiting both lipid and protein oxidation.[7]

The aim of the study was to find the association of ACS and other risk factors for ACS with the total bilirubin levels in our setup.

METHODS

A cross sectional observational study was conducted among the patients attending the department of medicine in a Dr. Panjabrao Deshmukh Memorial Medical College, Amravati, Maharashtra. During a period of 1 year (September 2019 to October 2020) the patients with acute coronary syndrome admitted were included in the study.

Necessary permissions from the ethics committee were taken before the start of the study. Written informed consent was taken prior to collecting the data from the patients. Patients with hepatitis of any cause, who were drugs like amiodarone, oral hypoglycemics, anti-pileptics, anti-fungal drugs and anti-tuberculosis drugs were excluded from the study. Patients with diagnosed cirrhosis of liver, bile duct obstruction and haemolytic jaundice were excluded from the study.

A study conducted by Vamadaven AS et al inferred that the prevalence of ACS in India was 8%.[8] With this, 95% confidence interval and 5.5% absolute error, we found minimum sample size to be 93. But, for our convenience, we have included 100 cases of ACS in the present study. Data collection was done using pre-designed case record form. The case record form had details of demography, detailed clinical history and physical examination.

Relevant investigations like complete blood count, electrolytes, electrocardiogram, chest X-ray, serum bilirubin levels, etc were done in all the patients. ACS was diagnosed in the patients using standard guidelines.[9] All the patients were treated according to the standard guidelines of management of ACS.[10]

Statistical analysis

The data was collected, compiled and analysed using EPI info (version 7.2). The qualitative variables were expressed in terms of percentages. The quantative variables were both categorised and expressed in terms of percentages or in terms of mean and standard deviations. Difference between two proportions was analysed using chi square or Fisher exact test. To correlate between the quantative variables we used Pearson's correlation coefficient (r) and scatter diagram with fit line and 95% confidence interval was plotted. All analysis was 2 tailed and the significance level was set at 0.05.

RESULTS

We included 100 cases of acute coronary syndrome in the present study.

The mean age of the cases was 55.64 ± 10.23 years with male preponderance. About 23% had diabetes, 31% had hypertension, 8% had history stroke or transient ischemic attacks, 4% had previous myocardial ischemia, 12% had hyperlipidemias and 25% were current smokers (Table 1).

Table 1: Demographic profile of the sample.

Demographic factors	Frequency	Percentage (%)
Age group (years)		
30 to 40	10	10
40 to 50	34	34
50 to 60	27	27
>60	29	29
Gender		
Male	56	56
Female	44	44
Past history		
Diabetes mellitus	23	23
Hypertension	31	31
Stroke/TIA	8	8
Previous MI	4	4
Hyperlipidemias	12	12
Current smoker	25	25

Majority of the patients presented with chest pain (83%) followed by shortness of breath (65%) and nausea/vomiting (33%) (Table 2).

Table 2: Distribution based on the signs and symptoms (N=100).

Chief complaints	Frequency	Percentage (%)
Chest pain	83	83
Shortness of breath	65	65
Nausea/vomiting	33	33
Dizziness	12	12
Loose stools	14	14
Hypotension	10	10
Tachycardia	14	14

There was moderate significant correlation between total bilirubin levels and LDL levels in the present study (r=0.703, p value<0.001). There was mild significant correlation between total bilirubin levels and TGs in the present study (r=0.403, p value<0.001) (Figure 1-2).
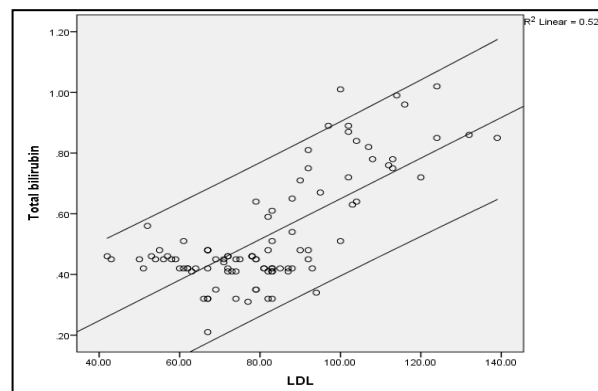

Figure 1: Correlation of total bilirubin levels with LDL in the present sample (r=0.703, p value<0.001).
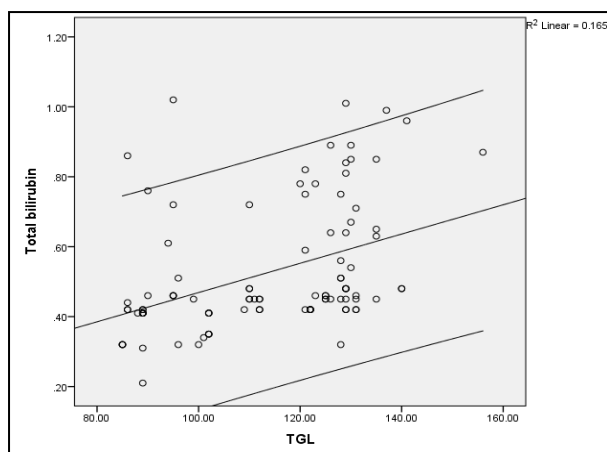
Figure 2: Correlation of total bilirubin levels with TG in the present sample (r=0.403, p value<0.001).

The mean bilirubin levels were 0.48±0.12 in the present study. Based on the median value of 0.48 as cut off, 33% had bilirubin levels more than 0.48 (Table 3).

Table 3: Distribution of study subjects based on total bilirubin levels.

Total bilirubin levels	Frequency	Percentage (%)
<0.48	67	67
>0.48	33	33
Total	100	100
Mean	0.48	
Median	0.47	
SD	0.12	
Range	0.1 to 1.92	

Table 4: Association of different factors with serum total bilirubin levels.

Factors	Low TB (n=67)	High TB (n=33)	P value
	No	No	
Age			
<50	31	13	0.5194
>50	36	20	
Gender			
Male	42	14	0.0549
Female	25	19	
Past history			
Diabetes mellitus	10	13	0.0061
Hypertension	15	8	0.8354
Stroke/TIA	5	3	0.7777
Previous MI	2	2	0.4605
Hyperlipidemias	4	8	0.0081
Current smoker	15	10	0.3900

Patients with diabetes mellitus had significantly higher proportion of total bilirubin levels more than 0.48. Patients with hyperlipidemia had significantly higher proportion of total bilirubin levels more than 0.48. Total bilirubin levels were not significantly associated with past history of hypertension, previous MI, stroke/TIA and current smoking status (p>0.05) (Table 4).

DISCUSSION

ACS is as a result of inflammation induced due to the vessel blockage leading to ischemia and infarction. This process is associated with release of free radicals in the blood. Scavenging these free radicals is of utmost importance and is done by some internal antioxidants. One of such antioxidant is bilirubin levels in the blood.[1,2,5,7,11] With this background, we conducted a study to understand the total bilirubin levels among the patients with ACS and to find association with risk factors for ACS.

Upon analysis of the data, we found that 33% of the patients had more than the median value of total bilirubin levels. Similar inferences were reported by Sahin et al, Hammur et al and Puroshotham et al.[12-14] Presence of diabetes and hyperlipidemias were associated with higher bilirubin levels in the present study. One of unique studies conducted by Okuhara et al reported that change in total bilirubin levels following acute myocardial infarction was related to heme oxygenise activation.[15] Another study conducted by Puroshotham et al inferred that there was moderate significant correlation between the serum LDL and triglyceride levels with total bilirubin levels in their study.[14] Similar inferences were reported by Xu et al and Hopkins et al in their studies.[16,17]

Shen et al conducted a meta-analysis of different studies and inferred that higher bilirubin levels were associated with major cardiac adverse events and mortality among majority of the studies.[18] Hence, total bilirubin is associated with higher morbidity and mortality in patients with ACS. Various studies conducted across have associated total bilirubin levels with the in mortality and major adverse events during follow up of the patients.[19-24] Our study had some limitations. It was a single centre study and an observational study. Follow up studies conducted in this regard would yield better results.

CONCLUSION

Nearly 1/3rd of the patients in our study had high bilirubin levels. Higher bilirubin levels correlated well with presence of diabetes and presence of hyperlipidaemias. There was significant correlation between the serum LDL and TG levels with total bilirubin levels in the present study. Future studies to be conducted to assess the association of total bilirubin levels with all-cause mortality using multivariate models.

REFERENCES

1. Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation. 2001;104(3):365-72.
2. Fuster V, Badimon L, Cohen M, Ambrose JA, Badimon JJ, Chesebro J. Insights into the pathogenesis of acute ischemic syndromes. Circulation. 1988;77(6):1213-20.
3. Corti R, Fuster V, Badimon JJ, Hutter R, Fayad ZA. New understanding of atherosclerosis (clinically and experimentally) with evolving MRI technology in vivo. Ann NY Acad Sci. 2001;947:181-8.
4. Kinlay S, Libby P, Ganz P. Endothelial function and coronary artery disease. Curr Opin Lipidol. 2001;12(4):383-9.
5. Stocker R, Yamamoto Y, Donagh AF, Glazer AN, Ames BN. Bilirubin is an antioxidant of possible physiological importance. Science. 1987;235(4792):1043-6.
6. Jeney V, Balla J, Yachie A, Varga Z, Vercellotti GM, Eaton JW, et al. Pro-oxidant and cytotoxic effects of circulating heme. Blood. 2002;100(3):879-87.
7. Sarady AJK, Liu F, Gallo D, Nakao A, Overhaus M, Ollinger R, et al. Biliverdin administration protects against endotoxin-induced acute lung injury in rats. Am J Physiol Cell Mol Physiol. 2005;289(6):1131-7.
8. Vamadevan A, Prabhakaran D. Coronary heart disease in Indians: Implications of the Interheart study. Indian J Med Res. 2010;132(5):561-6.
9. Sandoval Y, Thygesen K, Jaffe AS. The Universal Definition of Myocardial Infarction: Present and Future. Circulation. 2020;141(18):1434-6.
10. Sidhu NS, Rangaiah SKK, Ramesh D, Veerappa K, Manjunath CN. Clinical Characteristics, Management Strategies, and In-Hospital Outcomes of Acute Coronary Syndrome in a Low Socioeconomic Status Cohort: An Observational Study From Urban India. Clin Med Insights Cardiol. 2020;14:97.
11. Chung SR, Yang TH, Shin HC, Jin HY, Seo JS, Jang JS, 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):1437-44.
12. Sahin O, Akpek M, Elcik D, Karadavut S, Simsek V, Tulmac M, et al. Bilirubin levels and the burden of coronary atherosclerosis in patients with STEMI. Angiology. 2013;64(3):200-4.
13. Hamur H, Duman H, Bakirci EM, Kucuksu Z, Demirelli S, Kalkan K, et al. Bilirubin Levels and Thrombus Burden in Patients with ST-Segment Elevation Myocardial Infarction. Angiology. 2016;67(6):565-70.
14. Purushotham R, Gudage N, Ambali A. Study on relationship of total bilirubin with acute coronary syndrome (ACS) and associated risk factors. Int J Adv Med. 2018;5(1):100.
15. Okuhara K, Kisaka T, Ozono R, Kurisu S, Inoue I, Soga J, et al. Change in bilirubin level following acute myocardial infarction is an index for heme oxygenase activation. South Med J. 2010;103(9):876-81.
16. Xu C, Dong M, Deng Y, Zhang L, Deng F, Zhou J, et al. Relation of Direct, Indirect, and Total bilirubin to Adverse Long-term Outcomes Among Patients With Acute Coronary Syndrome. Am J Cardiol. 2019;123(8):1244-8.
17. Hopkins PN, Wu LL, Hunt SC, James BC, Michael VG, Williams RR. Higher Serum Bilirubin Is Associated With Decreased Risk for Early Familial Coronary Artery Disease. Arterioscler Thromb Vasc Biol. 1996;16(2):250-5.
18. 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. 2019;98(3):13920.
19. Celik T, Kaya MG, Akpek M, Yarlioglues M, Sarli B, Topsakal R, 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.
20. Gul M, Uyarel H, Ergelen M, Akgul O, Karaca G, Turen S, 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):166-71.
21. Huang FY, Peng Y, Huang BT, Yang Y, Pu X, Chen SJ, et al. The correlation between serum total bilirubin and outcomes in patients with different subtypes of coronary artery disease. Clin Chim Acta. 2017;465:101-5.
22. Yao HM, Shen DL, Zhao XY, Wang XF, Sun TW, Zhang JY, et al. Prognostic value of total bilirubin in patients with angina pectoris undergoing percutaneous coronary intervention. Int J Clin Exp Med. 2015;8(9):15930-9.
23. Acet H, Ertş F, Akıl MA, Polat N, Aydın M, Akyuz A, 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. Postepy Kardiol Interwencyjnej. 2014;10(2):91-7.
24. Zhang MM, Gao Y, Zheng YY, Chen Y, Liu F, Ma YT, et al. Association of Fasting Serum Bilirubin Levels with Clinical Outcomes After Percutaneous Coronary Intervention: A Prospective Study. Cardiovasc Toxicol. 2017;17(4):471-7.