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Original Research

Relationship between Serum Total Bilirubin Level and Cardiac Outcomes in Patients with Isolated Coronary Artery Ectasia

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ABSTRACT

Objective: This study aimed to investigate the association of admission serum bilirubin concentrations with major adverse cardiac event (MACE) in isolated coronary artery ectasia (ICAE).

Methods: This study enrolled 75 consecutive patients (42.7% women with the mean age of 52.3±11.4 years) with ICAE. MACE, basal demographic, laboratory, angiographic parameters, and admission serum bilirubin concentrations were recorded on follow-up forms. MACE was defined as heart failure, nonfatal myocardial infarction, and cardiovascular death.

Results: During follow-up (median 61±11 months), 19 (25.3%) patients experienced MACE. The patients were assigned into two groups: with MACE and without MACE. Compared with the non-MACE group, the MACE group had significantly lower serum total bilirubin levels. In addition, when the patients were subcategorized into tertiles of serum bilirubin concentrations, MACE were identified in 11 patients in the first tertile, 7 patients in the second tertile, and 1 patient in the third tertile. In the Cox regression analyses, serum total bilirubin and C-reactive protein (CRP) were found as independent risk factors for MACE ($p<0.05$).

Conclusion: We identified that MACE rates were inversely associated with serum bilirubin concentrations and directly associated with CRP in isolated ICAE patients. To the best of our knowledge, this is the first study to report a relation between total bilirubin level and MACE in patients with ICAE.

Keywords: Atherosclerosis, bilirubin, coronary ectasia

INTRODUCTION

Isolated coronary artery ectasia (ICAE) is described as localized or diffuse dilation of a coronary artery diameter to 1.5 times or more that of the adjacent nonectatic segment without concomitant coronary artery obstruction (1-3). ICAE has a low prevalence and occurs at a rate of 0.08%–1% in patients undergoing coronary angiography (4-6). Typical coronary angiographic characteristics of coronary artery ectasia (CAE) include segmental back flow phenomenon, delayed antegrade coronary opaque filling, stasis, and deposition of opaque in dilated segments (7). Ectatic coronary arteries may cause significant acute cardiac events owing to distal embolization caused by stasis in dilated luminal segments, dissection, slow blood flow, thrombus formation, and impaired coronary flow (8).

Serum bilirubin, the product of heme catabolism, is an important marker of hepatic function with biliary excretion. Bilirubin has been described as a natural antioxidant that inhibits lipid peroxidation (9). Studies indicated that serum bilirubin levels are inversely correlated with the risk of premature coronary artery disease (PCAD), metabolic syndrome, hypertension (HT), and diabetes mellitus. In addition, a lower risk of the cardiovascular events was shown at elevated serum bilirubin levels (10, 11).

The significant relation between serum bilirubin concentrations and ICAE was previously demonstrated (12). However, although bilirubin is associated with a number of cardiovascular endpoints, no data exist in current literature regarding its effect on major adverse cardiac events (MACE) in ICAE over long-term follow-up. Therefore, in this study, we aimed to explore the association between serum total bilirubin concentration and MACE in the ICAE patients.

METHODS

A total of 75 consecutive patients (32 females [42.7%], with the mean age of 52.3±11.4 years) with ICAE between 2010 and 2014 were included in this study. Coronary angiography was considered based on positive noninvasive stress tests or high clinical suspicion for coronary artery disease (CAD). Health Sciences University, Adana Research and Training Hospital ethics committee

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approved the study protocol (486/2019). Medical therapy was standardized according to the clinical indications irrespective of the presence of ICAE. The demographic characteristics of the patients were recorded in accordance with current guidelines. A detailed medical history of the patients was retrieved from the medical files and recorded on forms. Serum total bilirubin levels were obtained with colorimetric method on an Aeroset System (Abbott Laboratories, Chicago, IL, USA). Basal laboratory parameters were analyzed for all patients.

The study exclusion criteria were history of coronary bypass grafting, coronary syndromes, presence of ≥20% stenotic coronary lesions, heart failure, severe or moderate valvular heart disease, congenital heart disease, pre-existing inflammatory/autoimmune/infectious diseases, chronic renal failure, acute or chronic hepatic disease, cholestatic jaundice, gallbladder and bile duct diseases, chronic obstructive pulmonary disease, hematologic disorders, known malignancy, and thyroid dysfunction.

Coronary Angiography

Coronary angiography was performed on a basis using the Judkins technique with 6/7 French catheters. Angiograms were recorded in DICOM format at 15 frames/s and were evaluated by 2 experienced cardiologists. In this study, ICAE was described as dilation of a coronary artery luminal diameter to 1.5 times or more than that of the adjacent nonectatic segment without concomitant coronary artery stenosis (≥ 20%) (2). ICAE was categorized into 4 types based on the Markis classification (4).

Outcomes and Follow-up

The primary endpoint was MACE defined as heart failure, nonfatal myocardial infarction (MI), and cardiovascular death. To evaluate clinical status and adverse events, patients returned to the outpatient clinic at the 6th month and first year after the coronary angiography. Clinical follow-up was carried out by telephone in the 2nd, 3rd, 4th, 5th, and 6th years.

Statistical Analysis

Continuous variables were analyzed for data normality using the Kolmogorov–Smirnov test. The variables following a normal distribution were presented as mean (±standard deviation), and those without a normal distribution were presented as median (interquartile range). The variables that follow normal distribution among groups were compared using the Student's t-test, and the Mann–Whitney U-test was used to compare the variables without normal distribution. Categorical variables were summarized as numbers and percentages and compared between the groups using the Chi-square test or the Fisher's exact test. The receiver operating characteristic (ROC) curve was used to demonstrate the sensitivity and specificity of bilirubin cutoff values for MACE development. Univariate and backward stepwise multivariable Cox regression analyses were performed to determine independent predictors of MACE. Variables with an unadjusted p-value <0.05 in univariate analysis were included in the multivariate analysis. A survival analysis of MACE between tertiles of bilirubin (T1, T2, and T3) was conducted using the Kaplan–Meier method with a log-rank analysis. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS 20.0) for Windows (IBM SPSS Corp.; Armonk, NY, USA). The p-value <0.05 was considered statistically significant.

Main Points:

- We identified that serum total bilirubin value was inversely associated with MACE rates.
- CRP was directly associated with MACE rates in ICAE patients over a long-term follow-up period.
- This is the first study in the literature to report a relation between serum total bilirubin value and MACE in patients with ICAE.
- We identified that serum bilirubin values might be used to predict MACE in ICAE patients.

RESULTS

A total of 75 ICAE patients were included in this study. In the follow-up period (median 61±11 months), MACE was observed in 19 (25.3%) patients, of whom 7 died owing to cardiovascular causes. All of these deaths occurred in hospitalized patients.

The study patients were assigned into 2 groups: with MACE and without MACE. Baseline demographic, laboratory, and angiographic data are presented in Table 1. The groups were similar in terms of demographic and laboratory parameters (p>0.05). Only serum total bilirubin level was statistically significantly lower in the MACE group than in the non-MACE group (p=0.001). In MACE subgroup analysis, serum total bilirubin level was statistically significantly lower in the nonfatal MI and cardiovascular death group than in the non-MACE group (p=0.005 and p=0.021, respectively). However, there was no statistically significant difference between the heart failure group and serum bilirubin levels (p=0.727).

On angiographic assessment, the right coronary artery (n=47, 62.7%) was the most commonly affected vessel. Using the Markis classification, type IV CAE (30.6%) was most common, whereas type III (18.7%) was the least common. There was no significant difference between groups with respect to involved vessels and Markis classification (p>0.05).

The patients were also subcategorized into three groups according to the tertiles of the total bilirubin values at baseline. Table 2 shows a comparison of demographic and laboratory parameters based on total bilirubin tertiles. MACE was found in 11 (57.9%) patients in T1, 7 (18.9%) patients in T2, and 1 (5.3%) patient in T3 (p<0.001). Moreover, we have evaluated the effect of major cardiovascular risk factors on serum bilirubin values, and a statistical relationship was found only between HT and bilirubin values (p=0.034).

To determine the independent risk factors for MACE, univariate and multivariate cox regression analysis was performed (Table 3). In univariate analysis, hyperlipidemia, CRP, and serum total bilirubin were independent predictors of development of MACE. In multivariate Cox regression analysis, CRP (p=0.002) and total bilirubin (p=0.025) were independent predictors of MACE.

Table 1. Demographic, laboratory, angiographic parameters and medications of study population and patients with or without MACE

	All Patients (n=75)	MACE (n=19)	Non-MACE (n=56)	p
Demographic parameters				
Age (years, mean)	52.3±11.4	48.8±12.6	53.5±10.8	0.116
Female, n, (%)	32 (42.7%)	6 (31.6%)	26 (46.4%)	0.258
Body mass index (kg/m^2)	28.8±4.09	27.9±4.00	29.1±4.11	0.283
Left ventricular ejection fraction (%)	60.0±5.66	59.5±5.98	60.2±5.59	0.659
Diabetes mellitus, n, (%)	20 (26.7%)	4 (21.1%)	16 (28.6%)	0.522
Hypertension, n, (%)	34 (45.3%)	10 (52.6%)	24 (42.9%)	0.460
Hyperlipidemia, n, (%)	41 (54.7%)	8 (42.1%)	33 (58.9%)	0.203
Family history of CAD, n, (%)	29 (38.7%)	8 (42.1%)	21 (37.5%)	0.722
Current smoker, n, (%)	37 (49.3%)	12 (63.2%)	25 (44.6%)	0.163
Medications				
Aspirin, n (%)	54 (72.0%)	13(68.4%)	41 (73.2%)	0.688
ACE-I/ARB, n (%)	29 (38.7%)	8 (42.1%)	21 (37.5%)	0.722
β-Blocker, n (%)	18 (24.0%)	4 (20.1%)	14 (25.0%)	0.728
Calcium channel blockers	26 (34.5%)	6 (31.6%)	20 (35.7%)	0.743
Statin/fenofibrat, n (%)	22 (29.3%)	5 (26.3%)	17 (30.3%)	0.738
P2Y12 inhibitors, n (%)	17 (22.7%)	6 (31.5%)	11 (19.7%)	0.283
Laboratory parameters				
Hemoglobin (g/dL)	12.9±1.64	13.3±1.71	12.7±1.61	0.218
Leukocyte ($\times10^3$ /μL)	7.3±1.55	7.7±1.33	7.2±1.61	0.204
Monocyte ($\times10^3$ /μL)	0.77±0.19	0.62±0.20	0.82±0.16	0.410
Platelet ($\times10^3$ /μL)	285±86.4	296±79.0	281±89.0	0.537
Plasma fasting glucose(mg/dL)	117.3±50.2	109.4±47.5	120.0±51.1	0.433
Creatinine (mg/dL)	0.71±0.21	0.71±0.25	0.71±0.20	0.985
Serum uric acid (mg/dL)	5.7±1.50	6.0±1.32	5.6±1.55	0.299
C-reactive protein (mg/ dL)	1.3±0.69	1.6±1.28	1.2±0.24	0.189
LDL-Cholesterol (mg/ dL)	139.6±33.6	141.0±34.5	139.2±33.5	0.849
HDL-Cholesterol (mg/dL)	40.4±11.7	41.0±12.3	40.2±11.6	0.812
Total cholesterol (mg/ dL)	224.1±43.3	222.2±43.6	224.7±43.6	0.832
Triglyceride (mg/ dL)	220.1±105.9	201.7±87.5	226.3±111.5	0.384
Alanine aminotransferase (U/L)	20.2±13.63	18.3±7.36	21.1±15.0	0.289
Aspartate aminotransferase (U/ L)	21.2±16.91	17.3±5.93	22.4±19.1	0.261
Total bilirubin (mg/dL)	0.59±0.23	0.45±0.16	0.64±0.22	0.001*
Angiographic parameters				
Left anterior descending,(n,%)	35 (%46.7)	9 (%25.7)	26 (%74.3)	0.943
Circumflex artery, (n,%)	33 (%44)	5 (%15.2)	28 (%84.8)	0.072
Right coronary artery, (n,%)	47 (%62.7)	15 (%31.9)	32 (%68.1)	0.090
Markis Type I (n,%)	21 (%28)	5 (%23.8)	16 (%76.2)	0.961
Markis Type II (n,%)	17 (%22.7)	5 (%29.4)	12 (%70.6)	
Markis Type III (n,%)	14 (%18.7)	3 (%21.4)	11 (%78.6)	
Markis Type IV (n,%)	23 (%30.6)	6 (%26.1)	17 (%73.9)	
Tertile 1	19 (%25.3)	11 (%57.9)	8 (%42.1)	<0.001*
Tertile 2	37 (%49.4)	7 (%18.9)	30 (%81.1)	
Tertile 3	19 (%25.3)	1 (%5.3)	18 (%94.7)	

CAD: Coronary artery disease, LDL: Low-density lipoprotein, HDL: High-density lipoprotein. ACE-I: angiotensin-converting enzyme inhibitör, ARB: angiotensin receptor blocker *p<0.05 is significant.

Table 2. Comparison of demographic and laboratory parameters among tertiles of total bilirubin levels.

	T1 (n=19)	T2 (n=37)	T3 (n=19)	p1	p2	p3
Demographic parameters						
Age (years, mean)	48.4±11.9	53.5±11.2	54.0±10.8	0.115	0.136	0.884
Female, n, (%)	7 (36.8%)	15 (40.5%)	10 (52.6%)	0.788	0.328	0.389
Body mass index, kg/m^2	28.4±4.24	28.7±3.54	29.4±5.00	0.790	0.513	0.542
Diabetes mellitus, n, (%)	3 (15.8%)	11 (29.7%)	6(%31.6)	0.254	0.252	0.887
Hypertension, n, (%)	8 (42.1%)	13 (35.1%)	13(%68.4)	0.610	0.103	0.018*
Hyperlipidemia, n, (%)	7 (36.8%)	24 (64.9%)	10(%52.6)	0.046*	0.328	0.375
Family history of CAD, n, (%	7 (36.8%)	15 (40.5%)	7(%36.8)	0.788	1.00	0.788
Current smoker, n, (%)	10 (52.6%)	15 (40.5%)	12(63.2)	0.389	0.511	0.109
Left ventricular ejection fraction (%)	60.0±5.4	60.3±5.2	59.4±6.8	0.816	0.774	0.573
Laboratory parameters						
Hemoglobin (g/dL)	13.6±1.58	12.8±1.59	12.3±1.60	0.080	0.014*	0.236
Leukocyte count (×10^3/μL)	7.5±1.48	7.6±1.54	6.8±1.59	0.777	0.172	0.068
Monocyte count (×10^3/μL)	0.64±0.25	0.98±1.27	0.48±0.18	0.246	0.037*	0.094
Platelet count (×10^3/μL)	272.9±64.8	288.6±85.8	291±107.2	0.487	0.514	0.903
Plasma fasting glucose(mg/dL)	104.2±42.9	119.4±46.1	126.2±63.1	0.235	0.216	0.649
Creatinine (mg/dL)	0.77±0.26	0.70±0.21	0.67±0.17	0.317	0.184	0.567
Serum uric acid (mg/dL)	5.45±1.64	5.61±1.44	6.17±1.45	0.707	0.161	0.175
C-reactive protein (mg/dL)	1.61±1.21	1.17±0.35	1.08±0.23	0.137	0.081	0.379
LDL-Cholesterol (mg/dL)	136.3±33.0	140.7±37.4	140.8±27.0	0.662	0.647	0.995
HDL-Cholesterol (mg/dL)	36.0±8.7	41.1±12.8	43.5±11.2	0.125	0.028*	0.497
Total cholesterol (mg/dL)	214.6±40.8	227.4±48.7	227.2±34.7	0.329	0.311	0.988
Triglyceride (mg/ dL)	211.4±78.9	227.5±126	214.3±89.2	0.613	0.915	0.685
Alanine aminotransferase (U/L)	17.3±7.08	24.1±17.9	18.3±5.6	0.119	0.616	0.180
Aspartate aminotransferase (U/ L)	17.8±5.9	23.6±23.3	19.6±5.2	0.299	0.344	0.466

T: Tertile, CAD: Coronary artery disease, LDL-C: Low-density lipoprotein cholesterol, HDL: High-density lipoprotein cholesterol. Total bilirubin level T1: < 0.44 mg/dL, T2: 0.44–0.76 mg/dL, T3: > 0.76 mg/dL p1: T1 vs. T2, p2: T1 vs. T3, p3: T2 vs. T3. *p<0.05 is significant,

In the ROC analyses (Figure 1), a cutoff value of ≤0.465 serum total bilirubin had a 78.6% sensitivity and 68.4% specificity for predicting MACE (p=0.001).

The Kaplan–Meier survival analysis showed that patients at the lowest tertile (T1) of total bilirubin levels were more likely to develop MACE compared with patients at the highest tertile (T3) (p=0.002) (Figure 2).

DISCUSSION

We found that, irrespective of conventional cardiovascular risk factors, serum total bilirubin and CRP values were predictors of development of MACE in ICAE patients on long-term follow-up. To the best of our knowledge, this is the first study to establish a link between serum total bilirubin value and MACE in this specific population.

The exact pathophysiological mechanisms of CAE are yet to be defined. A variety of etiologies, including congenital defects, inflammation, endothelial dysfunction, vasculitis, and atherosclerosis, are associated with the development of CAE, but atherosclerosis is the main cause in nearly half of all CAE cases (13). Patients with CAE are at risk of MI and sudden cardiac death because of coronary vasospasm, dissection, intracoronary thrombosis, and slow flow secondary to dilation of coronary arteries (14).

Table 3. Univariate and multivariate Cox regression analyses

	Univariate analysis		Multivarite analysis	
Parameter	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Total bilirubin	0.021 (0.001–0.89)	0.010	0.035 (0.02–.0.652)	0.025*
Hyperlipidemia	0.353 (0.135–0.922)	0.033		
Current smoker	1.845 (0.726–4.694)	0.198		
Hemoglobin	1.166 (0.868–1.567)	0.308		
Leukocyte	1.079 (0.794–1.467)	0.628		
C–reactive protein	2.437 (1.551–3.829)	<0.001	2.041 (1.288–3.233)	0.002*
Circumflex artery	0.546 (0.194–1.533)	0.251		
Right coronary artery	1.623 (0.522–5.048)	0.402		

HR: hazard ratio; CI: confidence interval. *p<0.05 is significant.

Figure 1. Receiver operating characteristic (ROC) curves for MACE

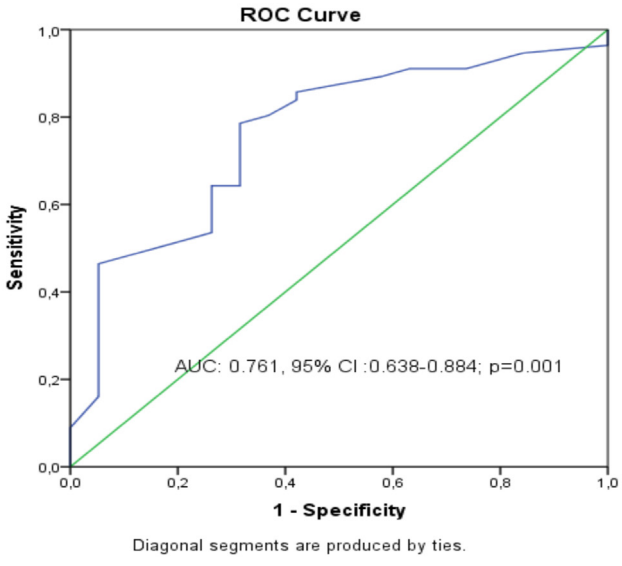
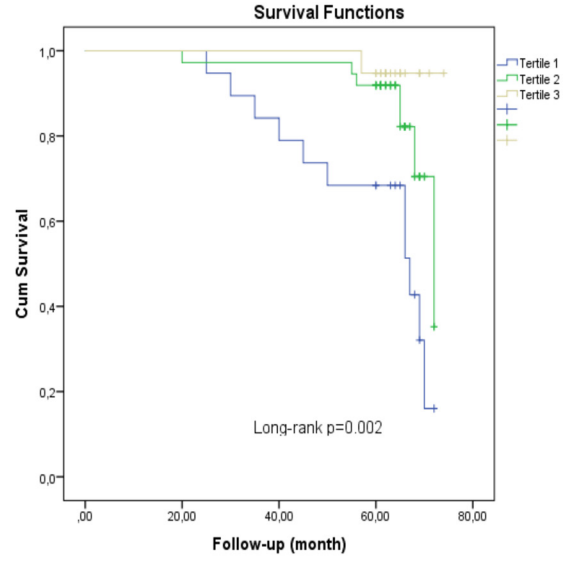


Figure 2. Kaplan-Meier survival plot of patients according to tertiles of total bilirubin levels



Cases of ventricular arrhythmias, nonfatal MI, and sudden cardiac death have been reported with CAE (15, 16). In a study, Boles et al. (17) presented data from a relatively long-term follow-up of patients with CAE (11.4 years). In this study, overall and cardiac death rates were significantly higher in CAE patients compared with non-CAE. The period of follow-up was 61±11 months in our study, during which 19 (25.3%) patients experienced MACE.

Studies have shown that CRP, an inflammation marker, predicts chronic systemic inflammation that occurs in atherosclerotic progression. Furthermore, CRP has been shown to be elevated markedly in many cardiovascular disorders and is related to poor prognosis (18-20). Similarly, in our study, we also found a positive association between CRP level and MACE in ICAE during follow-up.

Bilirubin scavenges reactive oxygen species and reduces the uptake of oxidized low-density lipoprotein, which is an essential feature of the atherosclerotic process (21). Several studies have been published demonstrating the association between serum bilirubin concentrations and oxidative stress mediated disorders, especially atherosclerotic disease (22). Recent studies have found that higher serum bilirubin values confer significant protection against atherosclerotic cardiovascular disorders, and subnormal serum bilirubin values are associated with cardiovascular morbidity and PCAD (23).

Chang et al. (24) reported that bilirubin was associated with the complexity and severity of CAD evaluated by the SYNTAX score and 1st MACE in patients with stable angina pectoris undergoing coronary revascularization. In a study by Demir et al. (12),

serum bilirubin values were negatively correlated with ICAE. In the study by Şahin et al. (25), a strong association between serum bilirubin values and the SYNTAX score in patients with STEMI was found. Consistently, we found a negative association between serum total bilirubin concentrations and MACE in this study.

Study Limitations

The main limitations of our study include small sample size and inclusion of patients from a single center. In addition, bilirubin values were only obtained at the time of diagnosis. Changes in bilirubin levels of the patients during follow-up were not investigated, and this is another limitation of our study.

CONCLUSION

We identified that serum total bilirubin values were inversely associated with MACE rates and directly associated with CRP in ICAE patients over a long-term follow-up period. To the best of our knowledge, this is the first study in the literature to report a relation between serum total bilirubin level and MACE in patients with ICAE. We believe that serum bilirubin values might be used to predict MACE in ICAE patients. Larger, multicenter studies are needed to further evaluate long-term prognosis in patients with ICAE.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Adana Research and Training Hospital (486/2019).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - F.Y.; Design - F.Y.; Supervision - M.K.; Resources - F.Y., M.K.; Materials - F.Y., M.K.; Data Collection and/or Processing - F.Y., M.K.; Analysis and/or Interpretation - F.Y., M.K.; Literature Search - F.Y., M.K.; Writing Manuscript - F.Y.; Critical Review - F.Y.

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