# Serum Bilirubin Level is Positively Correlated with Severity of Coronary Artery Disease in Patients with Non-St Elevation Acute Coronary Syndrome

ST Elevasyonsuz Akut Koroner Sendromlu Hastalarda Bilirubin Düzeyleri ile Koroner Arter Hastalığı Ciddiyeti ve Yaygınlığı Arasındaki Ilişki

Özge Özden[1], Burçak Kılıçkıran Avcı[2], Barış İkitimur [2], Murat Çimci[2], Emre Ertürk[2], Timur Omar[4], İlkin Babayev[5]
Bilgehan Karadağ[2], Zeki Öngen[2], Gülsüm Bingöl[1], Serkan Ünlü[6], İbrahim Keleş[2]

[1]Memorial Bahcelievler Hospital, Istanbul, Turkiye
[2]İstanbul Univercity Cerrahpasa Medical Faculty, Istanbul ,Turkiye
[3]IEU Medical Park Hospital, İzmir, Turkiye
[4]Kafkas University, Kars, Turkiye
[5]Famax Medical Tourism, İstanbul, Turkiye
[6]Gazi University Medical Faculty, Ankara, Turkiye

**ABSTRACT**

**Objective:** We investigated the relationship between serum bilirubin levels and severity and extent of coronary artery disease in patients with non-ST elevation acute coronary syndrome.
**Methods:** The files of the patients who admitted to Cardiology Department of Cerrahpasa Medical Faculty, Istanbul University between the January 2006 and December 2011 with non-ST elevation acute coronary syndrome were researched retrospectively. Patients who have no known coronary heart disease, whom an angigraphy was performed and at least one vessel found to be narrowed > %50 were included in our study. SYNTAX score was calculated. Patients were divided into 2 groups. Group 1 was defined as SX score 22.
**Results:** 180 patients were appropriate for our study design. While 39 patients were not investigated for bilirubin levels, the statistical analyses of bilirubin levels were done with 141 patients. There was significant positive correlation between total bilirubin and narrowed vessel number (p=,019)(r=,200). Direct bilirubin was correlated positively with SYNTAX score (p=,011)(r=,214) and narrowed vessel number (p=,005) (r=,240).
**Conclusion:** There was a significant positive correlation between serum direct bilirubin which is a marker of antioxidant mechanism and SYNTAX score.These results show that bilirubins increase in non-ST elevation acute coronary syndromes as a marker of antioxidant mechanism and could play a very important role in understanding the pathogenesis of oxidative stres related diseases better and may lead to improved treatment strategies in patients with NSTE-ACS.

**Key Words:** Bilirubin , non-ST elevation acute coronary syndrome, SYNTAX score

**ÖZET**

**Amaç:** Çalışmamızda ST elevasyonsuz akut koroner sendromlu (NSTE-AKS) hastalarda, bilirubin düzeyleri ile koroner arter hastalığı ciddiyeti ve yaygınlığı arasındaki ilişkiyi araştırdık.
**Metod:** Cerrahpaşa Tıp Fakültesi Kardiyoloji Kliniği' ne Ocak 2006 ile Aralık 2011 tarihleri arasında yatırılan NSTE-AKS tanılı hastaların verileri geriye dönük olarak incelendi. Daha önce bilinen koroner arter hastalığı olmayan, koroner anjiyografi yapılmış ve en az bir damarda %50 darlık saptanmış olan hastalar çalışmaya alındı. Koroner anjiografi kayıtlarından SYNTAX skoru hesaplandı ve hastalar 2 gruba ayrıldı. Birinci grup SYNTAX skoru< 22 olanlar, ikinci grup ise SYNTAX skoru >22 olanlar olmak tanımlandı.
**Bulgular:** Toplam 180 hasta çalışma kriterlerine uygun bulundu. 39 hastanın bilirubin düzeylerine bakılmamış olduğundan, bilirubinler ile ilgili analizlerde 141 kişilik bir hasta grubu kullanıldı. Yapılan istatistiksel çalışmalarda total bilirubin ile hasta damar sayısı arasında pozitif zayıf korelasyon bulunurken (p=,019) ( r=,200), direkt bilirubin ile SYNTAX skoru (p=,011) (r=,214) ve hasta damar sayısı ( p=,005) (r=,240 )arasında pozitif korelasyon bulunmutur.
**Sonuç:** NSTE-AKS' lerde oksidatif stresle ilişkili bir belirteç olan serum direkt bilirubin düzeyleri ile koroner arter hastalığının ciddiyeti ve yaygınlığını gösteren SYNTAX skoru ve hasta damar sayısı arasında anlamlı pozitif korelasyon saptandı. Bu sonuçlar bilirubinlerin ST elevasyonsuz akut koroner sendromlarda antioksidan mekanizmanın bir belirteci olarak yükseldiğini işaret etmektedir ve oksidatif stresle ilişkili hastalıkların patogenezini daha iyi anlamamızı ve NSTE-AKS' larda gelişmiş tedavi stratejilerinin gelişmesini sağlayabilecektir

**Anahtar Sözcükler:** Bilirubin , ST elevasyonsuz akut koroner sendrom , SYNTAX skoru

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**ORCID IDs:** O.O. 0000-0003-4148-4366, B.K.A. 0000-0001-9285-0608, B.İ.0000-0003-0602-1841, M.Ç.0000-0002-7848-627X, E.E.0000-0002-6191-4493, T.O.0000-0002-2481-0505, İ.B.0000-0003-4703-4331, B.K.0000-00021361-5229, Z.Ö.0000-0003-1835-5929, G.B. 0000-0001-5879-7866, S.Ü. 0000-0001-6179-8579, İ.K.0000-0003-2722-842X

**Address for Correspondence / Yazışma Adresi:** Gülsüm Bingöl,MD Memorial Bahcelievler Hospital, Istanbul, Turkiye E-mail: bulut_gulsum@hotmail.com

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## INTRODUCTION

It has been already shown that oxidative stress has major contribution in the atherosclerotic process. Increased oxidative stress may trigger transformation of low density lipoprotein that is responsible for the progression of the vascular lesions (1,2).

Heme oxygenase is one of the stress-inducible enzymes and shows antioxidant characteristics. Heme is a molecule that is broken down into biliverdin and carbonmonoxyde by the heme oxygenase enzyme. Following that biliverdin is rapidly converted to bilirubin. While heme is very reactive and cytotoxic, carbonmonoxyde and bilirubin is a robust scavenger of reactive oxygen groups and it is known to suppress oxidation of both lipids and lipoproteins (3). It has been shown that heme oxygenase level in myocardial tissue is increased as a response in myocardial infarct (4).

The SYNTAX (SYNergy between PCI with TAXUS and CARdiac Surgery) (SX) is an anatomical score based on coronary angiography. This scoring system assesses the complexity of lesions, morphology, severity and extension of coronary artery disease (CAD).SX score provides prospective risk classification in patients who undergo percutaneous coronary intervention (PCI). The high SX scores predict unintended consequences after PCI in revascularization (5).

Our purpose was to search the relationship between serum bilirubin levels and severity, extension of CAD in non-ST elevation acute coronary syndrome (unstable angina and non-ST elevation myocardial infarction) patient group.

## MATERIALS and METHODS

Individuals who were hospitalized at Cardiology Department of Cerrahpasa Medical Faculty, Istanbul University between the January 2006 and December 2011 with diagnosis of non-ST elevation acute coronary syndrome were enrolled in this retrospective study.

Inclusion criteria were a non-ST elevation myocardial infarct (NSTEMI) clinical diagnosis or unstable angina pectoris (USAP accompanied by a coronary angiography that demonstrates a vessel stenosis greater than 50% at least in one epicardial vessel (≥1.5 mm). Exclusion criteria were ST elevation myocardial infarct, known coronary artery disease, prior percutaneous or surgical revascularization, any hepatic or biliary tract disease, severe renal disease or hemodialysis patients, active infectious disease, inflammatory, autoimmune, or systemic connective tissue disease.

The coronary angiography recordings were reached and re-assessed by two experienced cardiologists. The SYNTAX scoring was calculated via www.syntaxscore.com. Patients were split into two groups according to SX score, as 'lower than 22' and 'greater than 22' point.

Anthropometric parameters and cardiac risk factors such as hypertension, dyslipidemia, diabetes, family history of CAD, smoking, and all medications were collected from patients' file retrospectively. On the other hand, biochemical analysis like serum creatinine, AST, ALT, total and direct bilirubin, HDL, LDL, triglyceride, total cholesterol, CRP and maximum troponin level were obtained from Istanbul University Cerrahpasa Medical Faculty Biochemistry Center Laboratory. The ejection fraction rate was reached from echocardiography reports. The GRACE (Global Registry of Acute Coronary Events), TIMI (Trombolysis in Myocardial Infarction) and eGFR (Estimated Glomerular Filtration Rate) were obtained with data from patients file. TIMI is a simple prognostic data score and may help in classifying the ischemic event risk in CAD.

The endpoints of study were divided into two groups. Primary endpoints were cardiac mortality and death from any reason. Secondary endpoints were stroke, arrhythmias (VT/VF, AF), and rehospitalizations due to decompensated heart failure (CHF) or acute coronary syndrome.

This retrospective study was conducted according to the recommendations of Helsinki Declaration on Biomedical Research that involves human subjects and was approved by the ethics committee of our own institution (İstanbul Univercity Cerrahpasa Medical Faculty, Istanbul, Turkey Date: 02.07.2013). Written, informed consent was obtained from each patient.

*Statistical Analysis*

SPSS statistical software (SPSS 21.0 for Windows, Inc., Chicago, IL, USA) was utilized for the whole statistical analysis. Kolmogorov-Smirnov/ Shapiro Wilk tests were performed as a normal distribution test. Continuous variables were presented as mean ± standard deviation and medians (interquartiles); categorical variables were defined as percentages. Categorical variables were compared by chi-square and continuous variables were compared with Student's t-test. Pearson's correlation coefficient was utilized for the analysis of the correlation between SYNTAX scoring and total bilirubin levels. Statistical significance was set to be $p<0.05$.

## RESULTS

A total of 350 participants' files were screened and 180 of them (51.4%) made our study group. The 55 of them (30%) was female. Patients weresplit into two groups according to the SYNTAX score; as low (<22) and high (>22). 122 (68%) of them were in low score group. The mean age of patients in low score group was 57,57+10,366 years while it was 61,55 + 10,909 years in high score group (Table 1). The 65 patients (35%) had one vessel coronary artery disease, 44 of them (23%) had two vessels coronary artery disease whereas 67 of them (36%) had three vessels coronary artery disease. The angiographic information of nine patients was not eligible. There has been some laboratory lack in serum bilirubin level (39 patients), therefore the correlation analysis was done within 141 patients (78%). There were 22 patients (11%) who reached primary endpoints. The twenty of them had died cause of cardiac disease and others were due to noncardiac disease. There were 14 patients who reached secondary endpoints. The two of them because of decompensated congestive heart failure and 12 of them as a result of acute coronary syndrome were rehospitalized.

The SYNTAX groups were compared according to continuous variables such as age, length, weight, total cholesterol, LDL,HDL, triglyceride, CRP, creatinine clearance, ejection fraction, GRACE score, total bilirubin (TB), direct bilirubin (DB), body mass index (BMI) by T test and only age (p=0,020) and direct bilirubin (p=,011) were significantly elevated in high score group (Table 1).

Categorical variables such as gender, hypertension, diabetes mellitus, hyperlipidemia, smoking status, heart failure, chronic obstructive lung disease, stroke, mortality, rehospitalizations due to ACS and CHF were compared by chi-square between two SYNTAX groups and only diabetes mellitus was found to be significant (p=0,003) in high score group.

The total bilirubin (p=0,139) and direct bilirubin level (p=0,541) of patients with non-ST elevation myocardial infarct (NSTEMI) and unstable angina pectoris (USAP) were assessed and compared by T test that has shown no significant difference.

*Correlations*

There have been some correlations between serum bilirubin levels and other variables. There was negative weak correlation between total bilirubin and ejection fraction (p=0,032/r=-0,226). There was a positive weak correlation between total bilirubin and CHF (p=0,009/r=0,228) and rehospitalizations due to ACS (p=0,038/r=0,175) and number of vessel involved (p=0,019/ r=0,200). There has been shown negative weak correlation between direct bilirubin and total cholesterol (p=0,011/r=-0,244) and LDL cholesterol (p=0,010/r=-0,247). There were positive weak correlation between direct bilirubin and TIMI score (p=0,021/r=0,194) and number of vessel involved (p=0,005/ r=0,240) (Table 2). There was also a positive and weak correlation between direct bilirubin and the SYNTAX score (p=0,011/r=0,214) while there was no significant correlation between total bilirubin and the SYNTAX score (Figure 1).

**Table 1.** Baseline characteristics of study population

| Characteristics | Syntax group | n | Mean ± SD | p |
|---|---|---|---|---|
| Age | 0-21 | 121 | 57.6±10.4 | 0.020 |
| | ≥22 | 56 | 61.6± 10.9 | |
| Length (cm) | 0-21 | 113 | 168.6±9.0 | 0.086 |
| | ≥22 | 52 | 165.3±15.4 | |
| Weight (kg) | 0-21 | 118 | 78.6±13.9 | 0.490 |
| | ≥22 | 54 | 76.9±16.2 | |
| Total Cholesterol (mg/dL) | 0-21 | 89 | 183.2±42.4 | 0.956 |
| | ≥22 | 39 | 183.7±59.4 | |
| LDL (mg/dl) | 0-21 | 88 | 113.2±35.2 | 0.906 |
| | ≥22 | 39 | 114.1±41.1 | |
| HDL (mg/dL) | 0-21 | 89 | 38.2±9.9 | 0.477 |
| | ≥22 | 38 | 39.6±11.2 | |
| Triglyceride (mg/dL) | 0-21 | 89 | 180.7±155.2 | 0.954 |
| | ≥22 | 39 | 182.4±162.4 | |
| CRP (mg/dL) | 0-21 | 89 | 17.7±27.7 | 0.415 |
| | ≥22 | 37 | 13.8±14.7 | |
| Creatinine Clearance (mg/dL) | 0-21 | 107 | 93.1±35.1 | 0.169 |
| | ≥22 | 48 | 84.5±36.2 | |
| Ejection Fraction (%) | 0-21 | 75 | 48.7±9.8 | 0.217 |
| | ≥22 | 40 | 46.4±9.5 | |
| GRACE Score | 0-21 | 122 | 117.5±32.8 | 0.292 |
| | ≥22 | 56 | 123.0±32.7 | |
| Total Bilirubin (mg/dL) | 0-21 | 95 | 0.6±0.3 | 0.091 |
| | ≥22 | 45 | 0.7±0.3 | |
| Direct Bilirubin (mg/dL) | 0-21 | 95 | 0.2±0.1 | 0.011 |
| | ≥22 | 45 | 0.2±0.1 | |
| BMI (kg/m2) | 0-21 | 111 | 27.8±4.3 | 0.483 |
| | ≥22 | 52 | 28.4±7.5 | |

Abbreviations: BMI:Body mass index, CRP:C-reactive protein, GRACE:Global Registry of Acute Coronary Events, HDL: High-density lipoprotein cholesterol, LDL:Low-density lipoprotein cholesterol, SD: Standard deviation

**Table 2.** The correlations between serum bilirubin level and cardiovascular risk factors

| Characteristics | Total Bilirubin | | | Direct Bilirubin | | |
|---|---|---|---|---|---|---|
| | p | r | n | p | r | n |
| Age | 0.62 | -0.042 | 141 | 0.619 | 0.042 | 141 |
| Gender | 0.027 | -0.187 | 141 | 0.577 | -0.047 | 141 |
| Total cholesterol (mg/dL) | 0.054 | -0.186 | 108 | 0.011 | -0.244 | 108 |
| LDL (mg/dL) | 0.080 | -0.169 | 108 | 0.010 | -0.247 | 108 |
| HDL (mg/dL) | 0.242 | -0.114 | 107 | 0.210 | -0.122 | 107 |
| Triglyceride(mg/dL) | 0.245 | -0.113 | 108 | 0.197 | -0.125 | 108 |
| Hypertension | 0.946 | -0.006 | 140 | 0.540 | 0.052 | 140 |
| Diabetes Mellitus | 0.143 | 0.125 | 139 | 0.069 | 0.155 | 139 |
| Hyperlipidemia | 0.422 | -0.070 | 133 | 0.334 | -0.084 | 133 |
| Smoking | 0.776 | 0.025 | 131 | 0.450 | -0.067 | 131 |
| CHF | 0.009 | 0.228 | 132 | 0.059 | 0.165 | 132 |
| Rehospitalization due to ACS | 0.038 | 0.175 | 141 | 0.088 | 0.144 | 141 |
| CRP(mg/dL) | 0.191 | 0.127 | 107 | 0.197 | -0.126 | 107 |
| EF(%) | 0.032 | -0.226 | 90 | 0.167 | -0.147 | 90 |
| GRACE | 0.405 | 0.71 | 141 | 0.184 | 0.112 | 141 |
| TIMI | 0.075 | 0.150 | 141 | 0.021 | 0.194 | 141 |
| Number of Vessels Involved | 0.019 | 0.200 | 137 | 0.005 | 0.240 | 137 |
| BMI(kg/m$^2$) | 0.297 | -0.092 | 132 | 0.171 | -0.120 | 132 |

Abbreviations: ACS:Acute coronary syndrome, BMI:Body mass index, CHF: Congestive heart failure, CRP:C-reactive protein, EF: Ejection Fraction, GRACE: Global Registry of Acute Coronary Events, HDL:High-density lipoprotein cholesterol, LDL: low-density lipoprotein cholesterol, SD: standard deviation, TIMI: Thrombolysis in Myocardial Infarction;

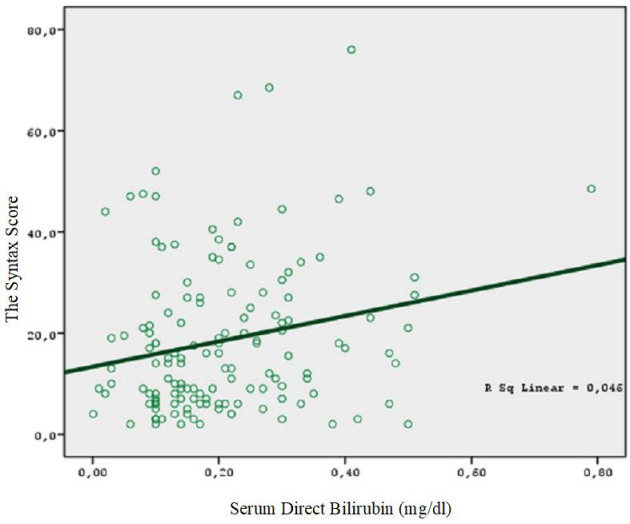


**Figure 1**. The correlation between serum direct bilirubin and Syntax Score

**DISCUSSION**

In our retrospective study, it has been shown that patients with high SYNTAX scores had increased serum direct bilirubin level and demonstrated a positive, weak correlation between direct bilirubin and the SYNTAX score. We report significant positive correlations between serum direct bilirubin levels and TIMI score with number of vessel involved while there were significant negative correlations between direct bilirubin level and total cholesterol with LDL cholesterol.

Bilirubin is known to be a wasted, toxic product of heme pathway for many years (6). However, it has been recently shown that bilirubin is a potent physiologic antioxidant against inflammation, atherosclerosis and coronary artery disease (7,8). Higher levels of bilirubin are believed to be protective against disease processes involve in oxygen and peroxyl radicals (9,10).

It has been shown that heme oxygenase-1 (HO-1) activity increased in myocardial infarction and was associated with high serum bilirubin levels. The HO-1 activity is considered to be an important defense mechanism in terms of cytoprotection. The heme oxygenase-1 (HO-1) and products of heme degradation can alleviate complement-mediated injury and help in removing the remodeling (11).

In a recent study, a positive correlation between bilirubin level and the SYNTAX score in ST elevation myocardial infarct (STEMI) (12) patients was demonstrated. Another studies demonstrated a negative correlation between total bilirubin level and stabile coronary artery disease (13-15). It can be postulated that in actively inflammatory process such as acute coronary syndrome, serum bilirubin level might be increased in order to defense against severity of disease in terms of antioxidant mechanism (positive correlation). However, in stabile conditions such as stabile coronary artery disease, the severity of disease will be diminished when bilirubin level increases and its protective feature augments (negative correlation).

In our study, the direct bilirubin level was elevated in patients with high SX score. In this situation, the direct bilirubin level that is a product of heme oxygenase-1 (HO-1) activated in non-ST elevation myocardial infarct (NSTEMI) was considered to be elevated as a defense mechanism and might show the severity of coronary artery disease (16). The other marker for showing severity of CAD is number of vessels involved. We showed a positive correlation between direct bilirubin level and number of coronary vessels involved as well.

In previous studies, there has been a negative correlation between bilirubin level and CAD risk factors such as obesity, smoking, LDL cholesterol (17,18). We have also demonstrated a negative correlation between direct bilirubin and LDL with total cholesterol.

The positive correlation between direct bilirubin level and TIMI score with serum total bilirubin level and rehospitalization due to ACS might show us prognostic importance of serum bilirubin levels in individuals presenting with NSTE-ACS.

One of the main limitations of our study is the retrospective and cross-sectional design of it. Secondly, this is a single-center study with a limited number of participants. Thirdly, we could not check for the serum HO-1 enzyme activity level, as this was a retrospective study.

**CONCLUSION**

This study showed that the serum level of bilirubin might be utilized for prognosis and risk assessment in patients with NSTE-ACS. Although this study cannot give a certain information on causality, the correlation can aid to understand the oxidative stress related disease pathogenesis and may lead to development in treatment strategies in NSTE-ACS patients. Prospective large-scale studies may show us the certain relationship and clinical benefit in terms of predicting prognosis of the disease.

**Conflict of interest**

No conflict of interest was declared by the authors.

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