Acta Medica Alanya

RESEARCH ARTICLE

ARAŞTIRMA

Acta Medica Alanya

2021;5(3): 244-249

DOI:10.30565/medalanya.887847

The relationship between contrast associated acute kidney injury and direct bilirubin levels

Kontrast ilişkili akut böbrek hasarı ve Direkt Bilirubin Düzeyleri Arasındaki İlişki

Yasemin Kaya[1*], Ahmet Kaya[2], Ahmet Karataş[3], Osman Bektaş[2], Mustafa Yenerçağ[2], Fatih Akkaya[2]

1. Ordu University Faculty of Medicine, Department of Internal Medicine, Ordu, Turkey
2. Ordu University Faculty of Medicine, Department of Cardiology, Ordu, Turkey
3. Ordu University Faculty of Medicine, Department of Nephrology, Ordu, Turkey

ABSTRACT

Aim: In this study we aimed to association between bilirubin levels, which is known to have anti-oxidative, anti-inflammatory and anti-thrombotic effects, and contrast associated acute kidney injury (CA-AKI) in patients with acute coronary syndrome (ACS).
Methods: Between 2017-2020, consecutive patients over 18 years of age who applied percutaneous angioplasty with the ACS diagnosis and met the exclusion and inclusion criteria (n:514) were retrospectively screened. Age, gender, chronic diseases and complete blood count parameters of the cases were recorded. Biochemical parameters, before applying contrast and 48 hours after applying contrast, were recorded. A 25% increase in creatinine level measured 48 hours after contrast application compared to basal creatinine was defined as CA-AKI.
Results: CA-AKI rate was higher in females(p=0.011). In the CA-AKI positive patient group, the mean age was found significantly higher (p=0.04), hemoglobin (p=0.007), direct bilirubin (p=0.008) levels were found significantly lower. Direct bilirubin was found to be a predictor as a result of our statistical analysis to identify independent predictors of CA-AKI (Beta:0.051 OR 95% CI:0.007-0.392, p=0.004). It was found that the direct bilirubin value of 0.065 predicted CA-AKI with 90% sensitivity and 91% specificity.
Conclusions: It was observed that the direct bilirubin values were significantly lower in the CA-AKI positive patient group, and the direct bilirubin value of 0.065 predicted CA-AKI with 90% sensitivity and 91% specificity.

Keywords: contrast associated acute kidney injury; direct bilirubin; bilirubins

ÖZ

Amaç: Bu çalışmada akut koroner sendromlu (AKS) hastalarda antioksidatif, anti-inflamatuar ve antitrombotik etkileri olduğu bilinen bilirubin düzeyleri ile kontrast ile ilişkili akut böbrek hasarı (KI-ABH) arasındaki ilişkiyi araştırmayı amaçladık.
Yöntemler: 2017-2020 tarihleri arasında AKS tanısı ile perkütan anjioplasti yapılan, dışlama ve dahil edilme kriterlerine uyan ardışık 18 yaş üstü hastalar (n:514) retrospektif olarak tarandı. Hastaların yaş, cinsiyet, kronik hastalıkları, tam kan sayımı parametreleri, kontrast öncesi ve kontrast verildikten 48 saat sonraki biyokimyasal parametreleri kaydedildi. Kontrast ile ilişkili akut böbrek hasarı tanısı kontrast uygulandıktan 48 saat sonraki serum kreatininde bazal kreatinine göre %25 artış olarak tanımlandı.
Bulgular: Kadınlarda KI-ABH oranı daha yüksek bulundu (p=0.011). Hastalar KI-ABH pozitif ve negatif olmak üzere iki gruba ayrıldı. KI-ABH pozitif hasta grubunun yaş ortalaması anlamlı olarak daha yüksek (p= 0.04), Hemoglobin (p=0.007) ve direkt bilirubin (p=0.008) düzeyleri anlamlı olarak daha düşük bulundu. KI-ABH'nın bağımsız öngördürücüleri tespit etmek amacıyla yaptığımız istatistiksel analizi sonucunda direkt bilirubin (Beta: 0,051 OR (95% CI 0,007/0,392 p=0,004) bir öngördürücü olarak bulundu. Direkt Bilirubin 0.065 değerinin %90 sensivite ve %91 spesivite ile KI-ABH 'nı öngördürdüğü tespit edildi.
Sonuçlar: KI-ABH pozitif hasta grubunda direkt bilirubin düzeylerinin anlamlı olarak daha düşük olduğu ve Direkt Bilirubin 0.065 değerinin %90 sensivite ve %91 spesivite ile KI-ABH 'nı öngördürdüğü bulunmuştur.

Anahtar Kelimeler: Kontrast ile ilişkili akut böbrek hasarı (KI-ABH); direkt bilirubin; bilirubinler;

Received: 27.02.2021 Accepted: 24.07.2021 Published (Online):31.12.2021

*Corresponding Author: Yasemin KAYA, Ordu University Faculty of Medicine Department of Internal Medicine, 52000, Ordu, Turkey. +904522252342, ysmnkcmz@gmail.com

ORCID: 0000-0001-7360-8090

To cited: Kaya Y, Kaya A, Karataş A, Bektaş O, Yenerçağ M, Akkaya F. he relationship between contrast associated acute kidney injury and direct bilirubin levels. Acta Med. Alanya 2021;5(3): 244-249 doi:10.30565/medalanya.887847

INTRODUCTION

The incidence of contrast associated acute kidney injury (CA-AKI) in the normal population is 1-2% and the incidence in the patient group with risk factors is 50% [1]. It has been reported that 13% of all CA-AKI cases occur secondary to the use of contrast agent [2]. CA-AKI increases the length of hospitalization and has negative effects on morbidity and mortality [1]. The contrast agent increases the release of inflammatory markers, induces the production of various mediators that increase vasoconstriction in the renal medulla and reduces vasodilation, ultimately causing hypoxia, acute tubular necrosis and acute kidney injury [3]. It is also known that oxidative stress plays an important role in the development of CA-AKI [1].

Bilirubin mainly occurs as a result of the breakdown of the erythrocytes that have expired and the destruction of the heme proteins in the erythrocytes. Indirect bilirubin is converted to direct bilirubin in hepatic cells and direct bilirubin is excreted with bile. Previously, bilirubin was known as a waste product, but it is now known to be an anti-oxidative, anti-inflammatory and anti-thrombotic [4, 5]. Different results have been found in studies to show the association between bilirubin and diseases. It was shown in a study that an inverse relationship exists between total bilirubin and cardiovascular disease risk. In another study, in patients with acute coronary syndrome (ACS), total bilirubin and direct bilirubin have been shown to predict long-term adverse events [5]. In yet another study, it was stated that in heart failure patients, bilirubin predicts a poor prognosis in decompensated heart failure [6]. Other reports have shown that mild bilirubin elevation may protect against all-cause mortality and cardiovascular disease. There are findings in the literature that bilirubin protects from kidney damage [7]. In this research it was aimed to investigate the relationship between bilirubin levels and CA-AKI in patients who applied coronary angiography.

METHODS

Between 2017 and 2020, the files of 514 patients over the age of 18 who applied primary percutaneous coronary intervention (P-PCI) with ACS were analyzed retrospectively. Age, gender, chronic diseases and complete blood count (CBC) parameters of the cases were recorded. Biochemical parameters, before applying contrast and 48 hours after applying contrast, were documented and it was evaluated whether CA-AKI developed in the patients. Patients with allergies to contrast agents, cardiogenic shock, hematological disease, chronic inflammatory or autoimmune disease, those using oral anticoagulants, those with creatinine clearance <60 mL / min and those with chronic renal failure requiring dialysis were all excluded from the study. It was approved by the Ordu University Clinical Research Ethics Committee (2020/163).

Definitions: Acute coronary syndrome diagnosis was made with typical increase or decrease in cardiac troponins together with evidence of myocardial ischemia, according to the myocardial infarction diagnostic criteria [7][8]. Patients were classified as ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA), in accordance with ischemic electrocardiographic changes and clinical findings.

P-PCI was administered to all these patients within the first 12 hours after the onset of chest pain. Before the procedure, all patients were given 300 mg aspirin and 600 mg clopidogrel or 180 mg ticagrelor loading dose, standard heparin and 10.000 U i.v. After the P-PCI procedure, all patients were given acetylsalicylic acid 100 mg / day and clopidogrel 75 mg / day or ticagrelor 180 mg / day and subcutaneous enoxapine 1 mg / kg twice a day. For patients undergoing P-PCI, iopromide (Ultravist®) was used as the non-ionic iso-osmolar contrast agent. All patients were hydrated (0.9% sodium chloride 1 ml / kg / hour) via intravenous route for 12 hours after the intervention. The term contrast-induced nephropathy is usually defined as a serum creatinine rise of 25% or 0.5 mg/dl occurring approximately 2–5 days after contrast exposure [9].

The mean of two blood pressure measurements of the patients was taken. Mean blood pressure results above 140/90 mmHg or those patients using anti-hypertensive drugs, were defined as hypertension. Diabetes mellitus was defined as at least two fasting blood glucose levels above 126

mg / dl or the use of antidiabetic agents. CA-AKI was diagnosed 48-72 hours after intravascular contrast administration, with an increase in serum creatinine > 25% relative to basal creatinine, or an absolute increase in serum creatinine of at least 44 µmol / L (0.50 mg / dl) [8] [10].

Blood sampling analysis: Blood samples were taken before P-PCI treatment and 48 hours after PCI treatment. Complete blood count and urea creatinine were studied from blood samples. The creatinine clearance was calculated using the MDRD (Modification of Diet in Renal Disease study) GFR= 186 X ([Scr] -1.154) X ([Age] -0.203) X (0.742 if woman). Biochemical parameters were analyzed using the ARCHITECT c8000 clinical analyzer (Abbott, IL, USA). A CELL-DYN Ruby automated hematology analyzer (Abbott, IL, USA) was used for hemogram parameters.

Statistical analysis: The Shapiro Williams-W Normality Test was applied to evaluate the distribution of the data. Homogeneity control of group variances was done by with the Levene Test. Homogeneously distributed data were compared with the Student T test and non-homogeneously distributed data with the Mann-Whitney U test. The Chi-square test was used for categorical variables; if a cell had an expected frequency below 5, the likelihood ratio chi-square value was used instead of Pearson chi-square value. Numerical variables were expressed as median (minimum and maximum) and mean ±SD and categorical variables were given as percentages. The parameters predicting CA-AKI were evaluated via Binary Logistic regression analysis. ROC curve analysis was performed to find the cut off value of direct bilirubin, which predicted CA-AKI. The SPSS 25.0 Statistical Package Program for Windows (SPSS Inc., Chicago, IL, USA) was used for all statistical analysis. A P<0.05 value was considered statistically significant.

RESULTS

In comparison of CA-AKI positive and negative patients groups, with respect to chronic diseases, no significant difference was found between the groups (p> 0.05). When compared in terms of gender and the rate for women, there were more female patients in the CA-AKI positive group (29.9%) (p = 0.011) (Table 1).The median age of the CA-AKI positive patient group was found to be significantly higher (p = 0.04). Also, ALP (p = 0.013) was significantly higher and GGT (p = 0.013), albumin (p = 0.020), hemoglobin (p = 0.007) and direct bilirubin (0.008), were significantly lower in CA-AKI positive patient group (Table 2).

Table 1: Comparison of Gender And Chronic Diseases

	CA-AKI (-) n=347	CA-AKI (+) n=167	P Value
Gender			
Male (n,%)	278 (80,1)	117 (70,1)	0,011
Female (n,%)	69 (19,9)	50 (29,9)	
Diabetes Mellitus (n,%)	85 (24,5)	49 (29,3)	0,241
Hypertension (n,%)	138 (39,8)	76 (45,5)	0,216
Coronary Artery Disease (n,%)	85 (45,7)	49 (36,6)	0,102
Heart Failure (n,%)	45 (13)	27 (16,2)	0,328
Cerebrovascular Accident (n,%)	17 (9,1)	11 (8,3)	0,780
Hyperlipidemia (n,%)	10 (5,4)	7 (5,3)	0,959
Chronic Renal Failure (n,%)	6 (3,2)	4 (3)	0,903
Chronic Obstructive Pulmonary Disease(n,%)	14 (7,5)	10(7,5)	0,983

Table 2: Comparison of Blood Parameters

	CA-AKI (-) n=347	CA-AKI (+) n=167	P Value
Age (year)	61,48±12,27	64,90±13,6	0,040
Blood Urea Nitrogen, mg/dl	18,2 (7,50-71)	17,3	0,226
Pre-contrast Creatinine, mg/dl	0,9 (0,42-5,1)	0,8 (0,4-2,9)	0,000
Post-contrast Creatinine, mg/dl	0,9 (0,40-5,1)	1,3 (0,65-7)	0,000
Pre-contrast GFR, ml/dk/1.73m2	87,67(11,47-175,23)	88,71(16,72-162,42)	0,213
Post-contrast GFR, ml/dk/1.73m2	87,29(11,47-197,89)	57,14(6,17-102,19)	0,000
Aspartate Aminotransferase, U/L	35 (10-648)	40 (11-550)	0,119
Alanine Aminotransferase, U/L	25 (5-1225)	27 (5-368)	0,240
Alkaline Phosphatase, U/L	85 (32-1120)	91 (29-296)	0,013
Gamma Glutamyl Transferase,U/L	33 (3-555)	27 (3-487)	0,013
Lactate Dehydrogenase,U/L	326 (167-2156)	341 (176-1468)	0,249
Total bilirubin, mg/dl	0,52 (0,02-4,80)	0,58(0,06-2,37)	0,546
Direct bilirubin, mg/dl	0,12 (0,00-3,30)	0,10 (0,01-0,72)	0,008
Total protein, g/dl	7,13±0,69	7,17±0,62	0,657
Albumin, g/dl	4,07±0,47	3,98±0,43	0,030
glucose, mg/dl	136 (70-795)	132 (11-561)	0,455
Hemoglobin, g/dl	15,47±2,03	14,96±2,02	0,007
White blood cell 10*3/U/L	10,83(3,40-46,9)	11,09 (4,7-28,8)	0,870
Platelet, 10*3/U/L	240 (8,4-934)	239 (6-592)	0,442
C reactive protein, mg/L	4,21(0,97-114)	4,56 (2,97-130)	0,360

As a result of the Binary Logistic regression analysis performed to find independent predictors of CA-AKI, age (Beta: 1.022 OR 95% CI: 1.003-1.041, p = 0.021) and direct bilirubin (Beta: 0.051 OR 95% CI: 0.007-0.392, p = 0.004) were found to be independent predictors (Table 3). The direct bilirubin value of 0.065 predicted CA-AKI with 90% sensitivity and 91% specificity (AUC: 0.576, 95% CI: 0.571-0.630, p=0.09) (Figure 1). When the correlation between Bilirubins and Blood Urea Nitrogen, Post-Contrast Creatinine, Post-Contrast GFR is examined no significant relationship was found.

Table 3 Investigation of CA-AKI 's Independent Predictors with Binary Logistic Regression Analysis

	Beta	OR (%95 Cl)	P
Age	1,022	1,003/1,041	0,021
Hemoglobin	0,937	0,833/1,055	0,283
ALP	1,005	0,999/1,010	0,113
GGT	0,999	0,994/1,003	0,628
Albumine	0,839	0,514/1,370	0,484
Direct bilirubin	0,051	0,007/0,392	0,004

ALP:Alkaline Phosphatase, GGT:Gamma Glutamyl Transferase

DISCUSSION

In this study, CA-AKI rate (29.9%) in women and the mean age of CA-AKI positive patient group were found to be significantly higher (p = 0.011 and p = 0.04, respectively). Also, direct bilirubin was significantly lower in CA-AKI positive patient group (p = 0.008). As a result of analysis to find independent predictors of CA-AKI, age and direct bilirubin were found to be independent predictors. It was shown that direct bilirubin predicted CA-AKI with 90% sensitivity and 91% specificity at 0.065 level.

As has been shown, the contrast agent has a direct toxic effect on the endothelium, reducing renal medullary blood flow and causing renal artery vasoconstriction, causing renal ischemia and kidney damage [7]. Free radicals, which have been shown to be involved in the pathophysiology of many diseases, are becoming more and more important. Antioxidants and free radicals are in balance in healthy individuals, however when this balance is altered in favor of free radicals, oxidative stress is observed, and diseases occur. One of the most important causes of CA-AKI formation is oxidative stress resulting from hypoxia [1]. Reactive oxygen species (ROS) are formed by oxidative stress. These are superoxide (O2-), hydrogen peroxide (H2O2) and hydroxyl radicals (OH-). O2- captures nitric oxide (NO) rapidly and renal microcirculation is disrupted as a result of the decrease in NO level. At the same time, ROS activates vasoconstrictor substances (such as angiotensin 2, thromboxane A2, endothelin 1, adenosine and norepinephrine) by creating extracellular signals [1]. Contrast media inhibits mitochondrial enzyme activities and then increases adenosine through hydrolysis of ATP. Both adenosine catabolism and medullary hypoxia produce ROS that scavenges NO [3].

Bilirubin, albumin, uric acid, transferrin, ceruloplasmin etc. are known as endogenous antioxidants [11,12]. It has been reported in the literature that bilirubin was a cytotoxic metabolite causing brain damage at high concentrations, while it acts as an endogenous antioxidant at low concentrations [13,14]. Experimental studies have shown that bilirubin has antioxidant properties such as scavenging ROS and inhibiting nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity. It has been stated that this causes a decrease in oxidative stress [15].

Ischemia-perfusion damage resulting from restoration of blood flow after tissue ischemia leads to endothelial cell apoptosis, inflammation and organ dysfunction. Increase in bilirubin reduces ischemia-perfusion damage in organs. Bilirubin also increases endothelial function with its antioxidant effect [7].

It has been shown in studies that serum bilirubin could be a biomarker of many other diseases [16]. He et al. found that bilirubin levels were significantly lower in patients with lupus nephritis compared to controls, and the bilirubin level increased after steroid therapy was given to these patients and the amount of protein in 24-hour urine decreased [16]. In another publication, it was mentioned that patients with mild elevations in unconjugated bilirubin serum levels had a much lower prevalence / incidence of coronary heart and peripheral vascular diseases [17]. Li et al. showed that bilirubin (TBil, DBil and IBil) levels were low in patients diagnosed with pemphigus vulgaris and were associated with disease

severity [18]. Demir et al. observed that bilirubin levels were lower in patients with coronary artery ectasia than in the control group [19]. It has been stated that there is an inverse correlation between bilirubin and coronary artery disease, whose pathophysiology involves lipid oxidation and the formation of oxygen radicals. In addition, Erkan et al. reported that bilirubin could be protective against atherosclerosis as a result of their study [20].

The important limitations of our study were that the study was single centered, the number of patients was insufficient and only one antioxidant parameter was examined. The amount of applied contrast substance and duration of process (Primary percutaneous coronary intervention (P-PCI)) were not included in the study because they were not recorded in the files. Also, echocardiography findings of all patients were not recorded as the patients were evaluated in the emergency clinic.

In view of the results of this study, bilirubin levels can be used as an independent risk factor to predict the development of after P-PCI contrast nephropathy. It is known that many different pathological mechanisms coexist in the emergence of contrast nephropathy. It is not known which pathophysiological mechanisms are more dominant in which patient. Taking preventive measures before applying contrast can reduce the development of CA-AKI. As itt is known that there is no specific treatment once CA-AKI develops, it is clear that preventive measures are required, especially in patients with high risk of developing CA-AKI. According to these results, we believe that administration of treatments with antioxidant properties may be worthy of further investigation in the prevention or early intervention of CA-AKI.

CONCLUSIONS

It was found that the direct bilirubin levels were significantly lower in the CA-AKI positive patient group and the direct bilirubin value of 0.065 predicted CA-AKI with 90% sensitivity and 91% specificity.

Conflict of Interest: The authors declare no conflict of interest related to this article.

Funding sources: The authors declare that this study has received no financial support

Ethics Committee Approval: Ordu University Clinical Ethics Boards, 2020 / 163

Peer-review: Externally and internally peer reviewed.

REFERENCES

1. Wong PC, Li Z, Guo J, Zhang A. Pathophysiology of contrast-induced nephropathy. Int J Cardiol. 2012;158(2):186-92. doi: 10.1016/j.ijcard.2011.06.115.
2. Büyüklü M, Bakırcı EM, Değirmenci H, Ceyhun G, Topal E. Contrast-Induced Nephropathy: Management by Antioxidant Therapy. Koşuyolu Heart J. 2017;20(1):59-62. doi: 10.5578/khj.9543.
3. Acar G, Akçay S, Aslan SM, Köroğlu M, Oyar O. Kontrast madde nefropatisi. S.D.Ü. Tıp Fak. Derg. 2005;12(3):62-8.
4. Karabulut H, Gülay MŞ. Antioksidanlar. MAE Vet Fak Derg. 2016;1(1):65-76. doi: 10.24880/maeuvfd.260790.
5. 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):1244-48. doi: 10.1016/j.amjcard.2019.01.019.
6. Chintanaboina J, Haner MS, Sethi A, Patel N, Tanyous W, Lalos A, et al. Serum bilirubin as a prognostic marker in patients with acute decompensated heart failure. Korean J Intern Med. 2013;28(3):300-5. doi: 10.3904/kjim.2013.28.3.300.
7. Boon AC, Bulmer AC, Coombes JS, Fassett RG. Circulating bilirubin and defense against kidney disease and cardiovascular mortality: mechanisms contributing to protection in clinical investigations. Am J Physiol Renal Physiol. 2014;307(2):123-36. doi: 10.1152/ajprenal.00039.2014.
8. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD et al. Third universal definition of myocardial infarction. Circulation. 2012;126(16):2020–35. doi: 10.1161/CIR.0b013e31826e1058.
9. Meraz-Muno˜z A, Ron Wald R. Contrast-Associated Acute Kidney Injury: Will Clarifying Mechanisms Allay Anxiety? Clin J Am Soc Nephrol. 2020;15(9):1225-27, doi: 10.2215/CJN.11960720.
10. Delgado Acosta F, Jiménez Gómez E, Bravo Rey I, Valverde Moyano R, de Asís Bravo-Rodriguez F, Oteros Fernández R. Contrast-induced nephropathy: A dilemma between loss of neurons or nephrons in the setting of endovascular treatment of acute ischemic stroke. Interv Neuroradiol. 2020;26(1):33-7. doi: 10.1177/1591019919883755.
11. Aydemir B, Karadağ Sarı E. Antioksidanlar ve Büyüme Faktörleri ile İlişkisi. Kocatepe Veterinary Journal. 2009;2(2):56-60.
12. Sen S, Chakraborty R. Oxidative Stress: Diagnostics, Prevention and Therapy. Chapter 1: In Saikat Sen and Raja Chakraborty, editors. In:The Role of Antioxidants in Human Health. American Chemical Society, 2011.p.1-37. doi: 10.1021/bk-2011-1083.ch001.
13. Stocker R, Yamamoto Y, McDonagh AF, Glazer AN, Ames BN. Bilirubin is an antioxidant of possible physiological importance. Science. 1987;235(4792):1043-6. doi: 10.1126/science.3029864.
14. Stocker R, Glazer AN, Ames BN. Antioxidant activity of albumin-bound bilirubin. Proc Natl Acad Sci U S A, 1987;84(16):5918-22. doi: 10.1073/pnas.84.16.5918.
15. Kwak JY, Takeshige K, Cheung BS, Minakami S. Bilirubin inhibits the activation of superoxide-producing NADPH oxidase in a neutrophil cell-free system. Biochim Biophys Acta. 1991;1076(3):369-73. doi: 10.1016/0167-4838(91)90478-i.
16. He Q, Jiang K, Xie L. The Relationship between Bilirubin Levels and Patients with Lupus Nephritis. Clin Lab. 2019;65(4). doi: 10.7754/Clin.Lab.2019.181125.
17. Vítek L. Bilirubin and atherosclerotic diseases. Physiol Res. 2017;66(1):11-20. doi: 10.33549/physiolres.933581.
18. Li WC, Mo LJ, Shi X, Lin ZY, Li YY, Yang Z et al. Antioxidant status of serum bilirubin, uric acid and albumin in pemphigus vulgaris. Clin Exp Dermatol. 2018;43(2):158-63. doi: 10.1111/ced.13289.
19. Demir M, Demir C, Keçeoğlu S. The relationship between serum bilirubin concentration and coronary artery ectasia.Postepy Kardiol Interwencyjnej. 2015;11(3):202-5 doi: 10.5114/pwki.2015.54014
20. Erkan A, Ekici B, Uğurlu M, Iş G, Seker R, Demirtaş S. et al. The role of bilirubin and its protective function against coronary heart disease. Herz. 2014;39(6):711-5. doi: 10.1007/s00059-013-3872-5.

Author / ORCID	Authorship Contrubition
Yasemin Kaya 0000-0001-7360-8090	Consept, Design, Materials, Analysis, Interpretation, Manuscript Writing, Final approval
Ahmet Kaya 0000-0001-9845-7938	Consept, Design, Materials, Data collection, Interpretation, Final approval Manuscript Writing, Critical Review, Süpervision
Ahmet Karataş 0000-0001-9095-6054	Materials, Interpretation, Final approval
Osman Bektaş 0000-0002-6616-9891	Materials ,Data collection, Final approval, Critical Review
Mustafa Yenerçağ 000-0002-0933-7852	Materials ,Data collection, Final approval, Critical Review
Fatih Akkaya 0000-0002-9016-4986	Materials ,Data collection, Final approval, Critical Review