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Research article

ASSOCIATION OF PREPROCEDURAL LEVELS OF MATRIX METALLOPROINASE-9, HIGH SENSITIVE C-REACTIVE PROTEIN, SERUM AMYLOID A, AND NEOPTERIN WITH ANGIOGRAPHIC IN STENT RESTENOSIS

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ABSTRACT

Objective: Vascular inflammation induced by percutaneous coronary intervention (PCI) has an important role in the pathogenesis of in-stent restenosis (ISR). Previous studies have addressed that serum amyloid A (SAA), high sensitive C-reactive protein (hs-CRP), neopterin, and matrix metalloproteinase-9 (MMP-9) play an important role in inflammatory process of development of ISR. **Aim:** We aimed to investigate the relationship of preprocedural levels of these inflammatory markers and the development of ISR. **Methods and Materials:** This was a prospective-case controlled study. 76 of 123 screened consecutive patients with stable angina who underwent coronary angiography, were scheduled for bare metal stent (BMS) placement. Control angiography was performed 6-12 months after the index intervention. **Results:** ISR was documented in the of 23 patients (30%), it was not documented in the remaining 53 patients (70%). The basal serum neopterin level was 2.32 ± 1.27 ng/ml and 1.67 ± 0.89 ng/ml, hs-CRP level was 9.16 ± 8.73 mg/L and 5.85±5.59 mg/L, the serum basal SAA level was 18.28 ±39.84 ng/ml and 12.77±23.67 ng/ml, the serum basal MMP-9 level was 75.06 ±35.05 ng/ml and 66.78±38.32 ng/ml, in patients with and without restenosis, respectively. Neopterine and hs-CRP levels exhibited a significant association with the ISR (p:0.01, p:0.04, respectively), SAA and MMP-9 levels did not (p:0.46, p:0.36, respectively). **Conclusions:** In present study, serum baseline neopterin and hs-CRP concentrations were predictive for the development of ISR. We also observed a significant correlation between the neopterin and hs-CRP in restenosis group.

Keywords: In-stent restenosis, Matrix metalloproteinase-9, High sensitive C-reactive protein, Serum amyloid A, Neopterin

INTRODUCTION

Percutaneous coronary intervention is the most widely used revascularization technique to treat the coronary heart disease. But postinterventional restenosis is a major long-term complication and the main limiting factor to the long-term efficacy of the procedure.[1-2]

Localized injury of the coronary artey wall induced by coronary intervention is followed by a cascade of complex molecular and cellular events.[3,4] The role of inflammation in the pathogenesis of ISR has been displayed by previous studies.[4,5] Measurement of several markers in blood samples can provide

significant information about inflammatory process triggered by PCI and its severity in developing ISR. In previous studies that elevated baseline levels of acute-phase proteins such as C-reactive protein (CRP), SAA were associated with ISR.[6,-8] SAA is an acute-phase reactant and synthesized in the hepatic and extrahepatic cells in response to infection, inflammation, trauma, and neoplasia.[9,10] It has been reported that SAA inhibits platelet aggregation, induces adhesion and migration of mononuclear and polymorphonuclear leukocytes, binds to extracellular matrix proteins, and induces matrix metalloproteinases (MMPs).[9]

Neopterin is a pteridine derivative and produced by activated monocytes/macrophages and has an important role in athetrogenesis via impairing reverse cholesterol transport, enhancing production of MMPs and other proinflammatory cytokines.[11-12] Matrix metalloproteinases zinc-dependent endopeptidases with proteolytic activity against extracellular matrix proteins, have an important role in pathophysiology of atherosclerosis, its complications and restenosis via breakdown and reorganization of extracellular matrix and so leading to inappropriate pathological vascular remodelling.[13-14]

Although previous studies[15,-19] indicated that SAA, hs-CRP, MMP-9, and neopterin play an important role in the development of ISR, little is known about clinical significance of preprocedural levels of these markers in patients underwent stent placement. Because of that, we aimed to evaluate whether basal serum levels of these inflammatory markers can predict of the development ISR in stable patients underwent elective BMS placement.

METHODS AND MATERIALS

This was a prospective-case controlled study. From October 2006 to December 2007, 123 consecutive patients with stable angina, who underwent coronary angiography and BMS placement were screened. A detailed record of individual's current medications, previous cardiac and noncardiac medical history and, risk factor history was obtained. Physical examination, surface electrocardiogram and transthoracic echocardiography performed in all patients. And if required excercise or pharmacologic stres test was performed. All participitants gave written informed consents before being recruited into this the study. The study approved by the local ethics comittee.

Patients with acute coronary syndrome, those with restenosis, those who underwent drug-eluting stent (DES) placement, those who only underwent balloon angioplasty, those with vascular aneurysm, those who were directed to surgery as well as those with apparent severe illnesses (cancer, hepatic or renal disease with GFR < 30 mL/1.73 m²/min, chronic infections or inflammatory disease) , those who withdrew their consent and refused to take control angiography in the follow up period were excluded. The present study included all patients with stable angina, who underwent coronary angiography and intended BMS implantation.

Blood samples to evalute lipid panels, fasting blood glucose, blood urea nitrogen, serum creatinine, and complete blood cell counts, hs-CRP, MMP-9, SAA and neopterin were taken after 12 hours of fasting from the antecubital vein directly before the intervention. Blood samples were allowed to clot for 30 minutes before centrifugation and after centrifugation (3500 rpm for 15 min). They were stored as frozen at -20 °C to-30 °C. Prior to assay, the frozen samples were brought to room temparature and mixed gently. Serum hs-CRP level was measured using the BN ProSpec® nephelometric system analyser (Dade Behring) and hs-CRP < 3.36 mg/L were accepted as normal. Serum MMP-9 level was measured by using competetive enzyme-linked immunosorbent assay (ELISA) (MMP-9 ELISA A-1030 kits, Bender MedSystems Campus Vienna Biocenter 2, Vienna, Austria, Europe) with ranges of 9.6-87.3 ng/ml accepted as normal. Serum SAA level was measured by using nephelometric metod (SAA-38989 kits Siemens Healthcare Diagnostics Products GmbH) with ranges of 0.0-5.0 ng/ml accepted as normal. Serum neopterin level was measured by using competetive ELISA (Neopterin ELISA EIA-1476 kits, DRG İnstruments GmbH) with ranges of 0.3-3.0 ng/ml for neopterin levels accepted as normal. Glomerular filtration rate (GFR) calculated by using modification of diet in renal disease (MDRD) formulas.

PCIs were performed by a team of experienced operators and size, length and type of the stent used were left to the discretion of the operator. All subjects enrolled in the study were prescribed with asetil salisilic asid (ASA) indefinetely and with clopidogrel

for 12 months. In addition to this, dual antiplatelet therapy beta-blockers, angiotensine convetring enzyme inhibitors or angiotensine receptor blockers, statins and nitrats were prescribed by attending to physician's discretion. Control angiography was performed 6-12 months after the index intervention. Coronary angiograms were analyzed by two experienced interventionalist blinded to clinical data. Angiographically ISR was defined as the presence of ≥ 50% diameter narrowing either within the stent or within 5 mm proximally or distally to the stent margin.

Statistical Analysis: Continuous variables were expressed as mean ± SD and percentage for categorical variables. Nonnormally distributed variables are given as medians. Arithmetic mean of the demographic data were obtained and standard deviation of the data were calculated (mean ± SD). Comparison of two groups independently was performed by independent samples t test for normally distributed data and Mann-Whitney U test for nonnormally distributed data. Group comparisons of categorical variables were performed using the Chi-square or Fisher's Exact test, as appropriate. Two quantitative property relationships were analyzed by the Spearman correlation coefficient. We performed receiver-operating characteristic (ROC) curves to identify spesific threshold concentrations of hs-CRP, MMP-9, SAA, and neopterin for maximized predictive value for the occurrence of ISR. Multiple logistic regression analysis could not be performed to identify factors related to in-stent restenosis because of small volume of study. Values of $p < 0.05$ were considered significant in all analyses. Statistical analysis were performed using IBM SPSS (Statistical Package for Social Sciences) for Windows version 19.0 (Chicago, Illinois, USA). The authors had full access to the data and take responsibility for its integrity. All authors have read and agreed to the manuscript as written.

RESULTS

The median follow-up time was 7.17 months (±2.01). Study population was scheduled for routinely control coronary angiography to determine the ISR. Figure 1 shows study flow chart. End of the follow up period, seventy and six patients who were scheduled for elective PCI and constituted the actual study population.

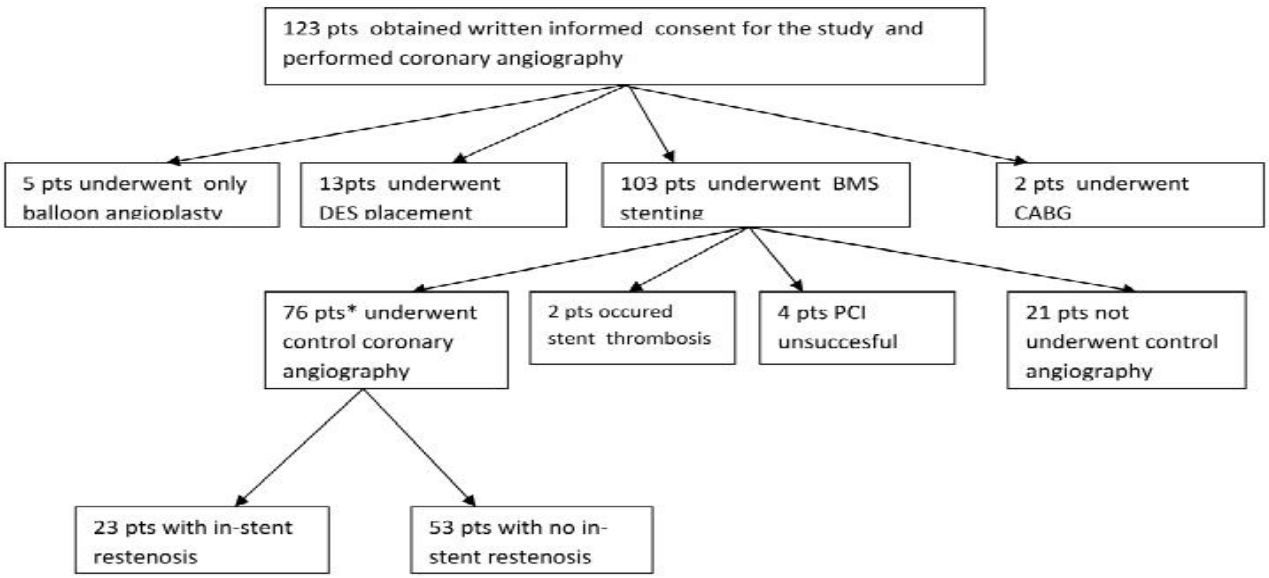

Fig 1. Study Flow Chart

In the of 23 patients (30%), restenosis was documented by coronary angiography, and restenosis was not documented in the remained 53 patients (70%). Table 1 compares the baseline clinical characteristics of the patients who subsequently developed restenosis and who did not. The demographic characteristics were not different in patients with and without restenosis. Table 2 compares the biochemical parameters of the patients who subsequently developed restenosis and who did not. The hs-CRP level was 9.16 ±8.73 mg/L and 5.85±5.59 mg/L, in patients with and without restenosis, respectively. We observed an association

between hs-CRP levels and ISR (p:0.04). The SAA level was 18.28 ±39.84 ng/ml and 12.77±23.67 ng/ml respectively (p:0.46). The MMP-9 levels was 75.06 ±35.05 ng/ml and 66.78±38.32 ng/ml, respectively (p:0.37). Neopterin level was 2.32 ± 1.27 ng/ml on ISR group and 1.67 ± 0.89 ng/ml on the other group (p:0,01). It was also found a significant association between the neopterin concentrations and ISR (0.01). Additionally, we performed receiver-operating characteristic (ROC) curves to identify spesific threshold concentrations of hs-CRP, MMP-9, SAA, and neopterin for maximized predictive value for the occurrence of ISR (Figure 2). While we found a spesific threshold level for neopterin which was 2.29 ng/ml (AUC: 0.65; figure 3) and hs-CRP which was 5.79 mg/L (AUC: 0.63; figure 4), there weren't any threshold level for SAA and MMP-9. When we also made the spearman's rank correlation coefficient analyze, we found a significant correlation between the neopterin and hs-CRP in restenosis group (rs: 0.574, p:0.004) but this relationship was not detected in norestenosis group.

Table 1. Baseline Clinical Characteristics and Association With ISR

	Restenosis (n=23)	No restenosis (n=53)	P value
Age	58.5± 9.6	57.6± 9.9	0.69
Male, n (%)	18 (78)	47 (89)	0.29**
Medical history, n (%)			
Current smoker	12 (52)	35 (66)	0.25*
Hypertension	16 (70)	36 (68)	0.88*
Diabetesmellitus	4 (17)	12 (23)	0.76**
Dyslipidemia	11 (48)	36 (68)	0.98*
Family history	11(48)	33 (62)	0.24*
CAD or equivilant history	6 (26)	22 (42)	0.20*
Cardiovascular medications, n (%)			
Asetil salisilicasit	23 (100)	52 (98)	1.00**
Beta-blockers	21 (91)	48 (91)	1.00**
ACE inhibitors or ARBs	20 (87)	46 (87)	1.00**
Nitrates	20 (87)	31(59)	< **0.02***
Statins	14 (61)	47 (89)	**0.01****
Clopidogrel	22 (96)	48 (91)	0.66**

ISR indicates in-stent restenosis; CAD, coronary artery disease

p<0.05 is significant, *Pearson Chi-Square Test, * * Fisher's Exact Test

Table 2. Biochemical Assays and Association With ISR

	Restenosis (n=23)	No restenosis (n=53)	P value
Fasting blood glucose (mg/dl)	105.4±23.7	105.5±27.3	0.98
HDL(mg/dl)	47.43±9.6	43.5±7.2	0.06
LDL(mg/dl)	114.4±36.2	113± 38.1	0.87
Triglyceride (mg/dl)	163 ±79.5	172.2± 75.2	0.63
hs-CRP, (mg/L)	9.1 ±8.7	5.8± 5.5	**0.04***
MMP-9(ng/dl)	75 ±35	66.7± 38.3	0.37*
Neopterin(ng/dl)	2.3±1.2	1.67± 0.9	**0.01***
SAA(ng/dl)	18.2±39.8	12.7 ± 23.6	0.46*
GFR,mL/1.73m²/min	88.1±19.7	89.29±19.8	0.82

ISR indicates in-stent restenosis; HDL, High-density lipoprotein ; LDL, low-density lipoproptein; GFR, glomerular fitration rate, p<0.05 is significant,*Mann Whitney U Test

Table 3 summurize the interventional and angiographic factors of the patients who subsequently developed restenosis and who did not. The final vessel diameter exhibited insignificant relation with the ISR (p:0.06). while the others did not exhibit.

Table 3. Interventional and Angiographic Factors and Association With ISR

	Restenosis (n:23)	No Restenosis (n:53)	Pvalue
Stented vessel, n (%)	Uncountable*		
LAD & side branches	8 (34)	18 (34)	
LCx &side branches	5 (20)	10 (19)	
RCA & side branches	9 (41)	22 (42)	
By-pass graft	1 (6)	3 (5)	
Reference vessel diameter mm	3.1±0.4	3.00 ± 0.35	0.24
Final vessel diameter, (mm)	3.2± 0.3	3.41 ± 0.43	0.06
Length of lesion (mm)	19.2±4.9	19.66 ± 5.45	0.74

LAD indicates left anterior descending artery; LCx, circumflex artery; RCA, right coronary arter, p<0.05 is significant,*uncountable because of small volume

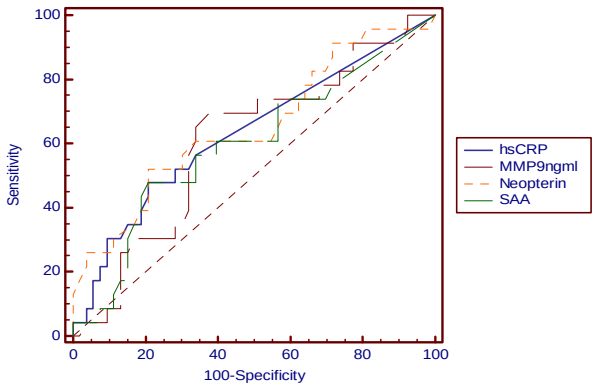

Fig 2. Comparison of ROC curves for hs-CRP, SAA, MMP-9, and Neopterin

hs-CRP ROC Curve: AUC: 0.63; 95% CI: 0.51-0.74; p: 0.05

Neopterin ROC Curve: AUC: 0.65; 95% CI: 0.53-0.76; p: 0.04

MMP-9 ROC Curve: AUC:0.61; 95% CI: 0.49-0.72; p: 0.13

SAA ROC Curve: AUC: 0.60; 95% CI: 0.48-0.71; p: 0.19

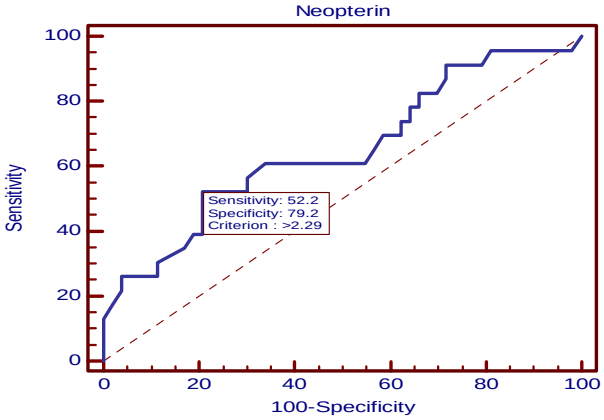

Fig 3: ROC curve of Neopterin exhibites the spesific threshold value as 2.29 ng/ml, for maximized predictive value for the occurrence of ISR (AUC: 0.65; 95% CI: 0.53-0.76; p: 0.04).

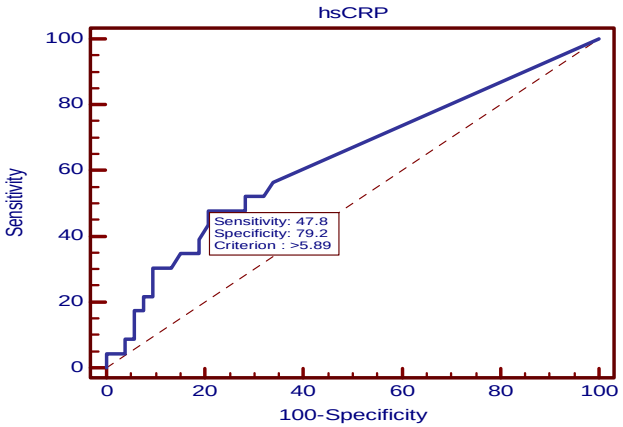

Fig 4: ROC curve of hs CRP exhibites the spesific threshold value as 5.79 mg/L, for maximized predictive value for the occurrence of ISR (AUC: 0.63; 95% CI: 0.51-0.74; p: 0.05)

DISCUSSION

In our study, while the serum basal neopterin and hs-CRP concentrations showed significant association with the development of ISR, SAA and MMP-9 levels did not. In previous studies, increased serum neopterin level was predictor for adverse prognosis for coronary artery disease,[11,12] and was closely associated with restenosis in patients with BMS[15] and with only percutaneous coronary angioplasty.[16] There are only two published studies[15-16] with limited number of patients assessing the association of basal neopterin levels and restenosis after PCI at current literature and their results are similar to our findings. Recently in a study, Mizutani et al. investigated the association of serum neopterin levels measured on admission with ISR. ISR was occured in 123 patients with stable coronary artery disease and 44 patients of whom underwent BMS and the others underwent DES implantation. They showed that neopterin was closely associated with ISR in patients who underwent BMS in contrast to patients underwent DES implantation.[15] We thought that, this result may be related to the anti-inflammatory effects of drugs released from DES. Because of this reason, we primarily evaluated the markers in patients who underwent BMS implantation. Whether neopterin level is a useful marker of ISR in patients with DES, more studies are needed. Although there are some pathophysiological differences in developing restenosis after balloon angioplasty and stent implantation, inflammation has an important role in the restenosis after both therapeutic approaches. In another study Eber et al. found a correlation between neopterin levels and restenosis in the patients undergoing balloon angioplasty.[16] While they did not reported any cut-off level for neopterin for predictive for ISR, we found spesific threshold by using ROC analysis, that appears most predictive at neopterin level > 2.29 ng/ml (AUC: 0.65; 95% CI: 0.53-0.76; p: 0.04).

Systemic and local vascular inflammatory status at the time of PCI plays a pivotal role in the development of ISR. In previous studies, it has been showed that elevated baseline levels of acute-phase proteins such as CRP, SAA were associated with restenosis after coronary intervention.[6,-8] In our study

we determined that any level of hs-CRP > 5.79 mg/L was predictive for ISR (AUC: 0.63; 95% CI: 0.51-0.74; p: 0.05) and preprocedural baseline hs-CRP level was associated with the development of ISR in contrast to SAA. Data focused on the relationship between inflammatory markers including CRP and/or SAA, angiographic and clinical restenosis after PCI have had conflicting results. [1,4,12,20,-22] Similar to our study, Buffon et al. showed that baseline CRP level was independent predictor of restenosis. However, they found significant association between the baseline SAA level and ISR.[20] On the other hand, Gomma et al. did not demonstrate any relationship between the preprocedural CRP level and ISR in stable angina patients undergoing elective coronary stenting. Besides that they found similar finding that preprocedural SAA level didn't show any association with ISR.[8] Additionally, Segev et al. and Rittersma et al. did not find any association between preprocedural plasma levels of CRP and ISR in patients undergoing elective stent implantation for de novo lesions.[4,23] Although it includes stable and unstable patients undergoing balloon angioplasty, Blum et al. demonstrated an association between the increase of SAA by 100% 24 h after PTCA and restenosis rather association between the preprocedural SAA level and restenosis.[18] When these findings included our study and previous studies are evaluated together, the local sustained inflammatory response after stent placement may not be reflected by an increased serum acute phase reactants such as hs-CRP and SAA concentrations. They may be reflector for activation of vascular inflammation as well as progression of atherosclerosis. The extent of the inflammatory process after PCI can be quantified by postintervention measurement of acute-phase reactants. There are few studies with limited number of patients assessing the association of basal MMP-9 levels and ISR and their results are contradictory. Similar to our findings in a small group of 56 patients, Ge et al. investigated the serial changes of serum MMP-9 antigen levels and found similar baseline, but increased 1st, 3rd and 7th day levels in patients with and without restenosis after BMS.[24] In contrast to our study, Zemlianskaia et al. found an independent correlation between pre-PCI MMP-9 antigen levels and development of ISR in a selected patient population with BMS implantation.[25] Gregory et al. evaluated relationship between the ISR and plasma levels of pro-MMP-9, latent MMP-9 and active MMP-9 in patients who received BMS. They reported that active MMP-9 exhibited strong association with the ISR and appeared most predictive at plasma concentrations >2 ng/ml.[26] In present study we evaluated only preprocedural basal MMP-9 antigen level and changes in the serum concentrations and serum activity of MMP-9 during inflammatory period after procedural injury were not measured. Because of that we thought that this finding was insufficient to decide about relationship between serum MMP-9 level and ISR and postprocedural analysis of concentration and serum activity of MMP-9 may be useful to decide about role of MMP-9 in development of ISR as mentioned study. In the present study, we demonstrated that statin therapy reduced the rate of ISR as demonstrated in the previous studies.[19-27] It was thought that, this finding appears to be dependent on their pleitropic effects on vascular wall rather than lipid lowering effects as known.

The clinical variables predicting restenosis were diabetes, lesion complexity, reference vessel diameter, final minimum vessel diameter, lesion length, stent type, and intervention for saphaneous venous bypass grafts and restenosis. [3,28,29] In contrast to previous studies [28,29] diabetes mellitus, interventional and angiographic factors were not associated with ISR in present study. This finding may be explained by small volume of in our cohort. Because of that we overlooked this result.

The main limitation, we assayed only basal levels of biomakers at only preprocedural time. Hence, changes in the serum concentrations of markers during inflammatory period after procedural injury, were not measured. In another one, in this study we evaluated the patients with stable angina pectoris underwent only BMS for de novo lessions. Other, the number of patients in the study was small. Consequently, it should be questioned whether these markers are indicator for activation of vascular inflammation as well as progression of atherosclerosis and/or reflector for vascular inflammation induced by PCI. So that, larger studies will be needed to determine the associaton between the pre- and postprocedural levels of associated biomarkers and in-stent restenosis in patients with stable coronary artery disese or acute coronary

syndrome who undergoing BMS and/or DES implantation.

CONCLUSIONS

In our study, we found that serum baseline neopterin and hs-CRP concentrations were predictive for development of ISR while SAA and MMP-9 levels did not exhibit any association with ISR in patients with stable angina pectoris who underwent elective BMS implantation for de novo lesions. We also determined a significant correlation between the serum preprocedural levels of neopterin and hs-CRP in restenosis group.

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Conflict of interest

No conflict of interest was declared by the authors.

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