



Association of high level of hs-CRP with in-stent restenosis: A case-control study



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ABSTRACT

Background: In-stent restenosis (ISR) is one adverse outcome of coronary stent implantation. Although using drug-eluting stents has reduced the rate of ISR, it remains a major problem. Here, we have investigated the relationship between several patient characteristics including serum high sensitive C-reactive protein (hs-CRP) and ISR.

Methods: This was a case-control study comprising 104 individuals with ISR and 202 patients without. Baseline characteristics were collected using a questionnaire. Fasting blood glucose (FBG), serum triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C) and serum high sensitivity C-reactive protein (hs-CRP) were measured using commercial kits on an auto-analyzer. Data were analyzed using SPSS software and a p value ≤ 0.05 was considered significant.

Results: Diabetes mellitus ($p < 0.001$), stent type ($p = 0.005$), serum hs-CRP ($p = 0.006$), FBG ($p = 0.038$) and serum TG ($p = 0.039$) were significantly associated with ISR. The association between hs-CRP and ISR remained significant after adjustment for stent type and DM. For patients with a serum hs-CRP < 2.64 mg/dL, ISR was only associated with diabetes mellitus ($p = 0.016$); while for individuals with a serum hs-CRP ≥ 2.64 mg/dL, ISR was also associated with the presence of diabetes mellitus, serum triglycerides and stent type.

Conclusion: Higher levels of serum hs-CRP were significantly associated with the occurrence of ISR.

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Abbreviations: CHD, coronary artery disease; ISR, in-stent restenosis; PCI, percutaneous coronary intervention; ROS, reactive oxygen species; DES, drug-eluting stents; CRP, C-reactive protein; Hs-CRP, High sensitive C-reactive protein; NISR, non-in-stent restenosis; DM, Diabetes mellitus; HTN, hypertension; FBG, fasting blood glucose; TG, triglycerides; TC, total cholesterol; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure.

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1. Background

Coronary heart disease (CHD) is the major cause of deaths worldwide, and the most common cause of disability [1]. Coronary angioplasty is a minimally invasive interventional for revascularization in all phase of coronary atherosclerosis. In-stent restenosis (ISR) is an adverse outcome of stent placement and remains an important limitation of percutaneous coronary intervention (PCI). Whilst stents reduce acute recoil and facilitate arterial remodeling, they are associated with an increase in neointimal hyperplasia [2]. In the development of neointimal hyperplasia, stent implantation may enhance the inflammatory response, and the release of reactive oxygen species (ROS), which leads to proliferation and migration of smooth muscle cells, leading to in-stent restenosis [3,4]. Whilst, drug-eluting stents (DES) can reduced the ISR rate to 5%, ISR remains an important problem after PCI. Hence, it is may be useful to identify predictive biomarkers related to this condition.

Serum C-reactive protein (CRP), is an acute phase response protein, synthesized and secreted by hepatocytes [5]. Hs-CRP is also used as a biomarker of cardiovascular disease [6,7], with several studies showing that serum hs-CRP is an independent risk factor of CHD [8]. Serum hs-CRP has now been added to the ACCF/AHA Guidelines for identifying individuals for primary prevention of CHD [9]. Although most of the studies have reported higher levels of serum hs-CRP in patients with ISR [10–15], a few studies did not show this [16,17].

We aimed to investigate the relationship between ISR and factors at baseline that may contribute to it, including serum hs-CRP, the first tie in Iran.

2. Material and methods

This case-control study was conducted between December 2014 and April 2017. We included 306 unrelated Iranian patients who previously underwent coronary stent implanting at least one month ago and were subsequently referred for angiography because of chest pain or equivalent symptoms. Based on result of angiography, 104 patients who had >50% stenosis within the stent were placed into the ISR group and 202 patients who had no or <50% stenosis were placed into the non-ISR (NISR) group. The study protocol was given approval by the Ethics Committee of Mashhad University of Medical Sciences and written informed consent was obtained from participants.

Demographic data including sex, age, smoking history, drug history, past history of diabetes mellitus (DM), hypertension (HTN), dyslipidemia, and duration between coronary stenting and subsequent angiography because of chest pain or equivalent symptoms were collected from medical records. Patients with primary PCI, positive troponin, restenosis in the first month after angioplasty due to thrombosis, autoimmune disorder, active cancer, thrombophilia or chronic kidney disease were excluded.

Peripheral blood femoral or brachial catheter was drawn right after entering the catheter before starting angiographic procedure into tube with no anticoagulant. Serum was separated by centrifuging the blood for 15 min at 1000 RCF speed (manufacturer's recommended speed). Serum was stored at -80°C prior to analysis. Hs-CRP levels was measured using a Biosystems assay kit on a BT-3000 auto-analyzer. Fasting blood glucose (FBG), triglycerides (TG), total cholesterol (TC) and high density lipoprotein cholesterol (HDL-C) were measured using Pars Azmoon kits on a BT-3000 auto-analyzer. Low density lipoprotein cholesterol (LDL-C) was calculated using the Friedewald formula.

Continuous variables were reported as mean \pm standard deviation (SD) and categorical variables were expressed as percentage of the group. Logistic regression analyses were conducted to test the relationship between ISR and the variables.

All analyses were performed using SPSS software (Chicago, IL, USA) version 11 and P values <0.05 were considered statistically significant. ROC curve analysis was done by MedCalc free trial software (Fig. 1).

Table 1
Baseline characteristic in relation with ISR and NISRs.

Variables	NISR (N = 202)	ISR (N = 104)	p value	
Age (y)	62.2 \pm 9.2	60.8 \pm 8.4	0.196	
Sex %	Male	138(68.3%)	77(74.8%)	0.101
	Female	64(31.7%)	26(25.2%)	
Smoking %	33(16.7%)	13(13.0%)	0.271	
HTN %	131 (70.4%)	55(52.9%)	0.051	
DM %	70(34.7%)	63(60.6%)	<0.001	
Dyslipidemia %	179(94.2%)	95(96.9%)	0.237	
Statin %	185 (94.4%)	93 (95.9%)	0.235	
Aspirin %	187(95.4%)	94(95.9%)	0.305	
Clopidogrel %	171(87.7%)	88(90.7%)	0.234	
NSAID %	3(1.6%)	3(3.1%)	0.253	
Corticosteroids %	5(2.6%)	0(0.0%)	0.044	
β blocker %	33 (16.3%)	18(17.3%)	0.474	
ARB %	60(29.7%)	25(24.0%)	0.181	
ACE inhibitors %	10(5.0%)	8(7.7%)	0.236	
CCB %	18(8.9%)	4(3.8%)	0.078	
Insulin %	19(9.4%)	11(10.6%)	0.444	
Duration ^a (months)	36.00(12.00–60.00)	6.00(4.00–8.00)	<0.001	
Stent type %	Bare	51(39.5%)	38(60.3%)	0.005
	Drug-eluting	78(60.5%)	25(39.7%)	
Stent number %	1	167(83.5%)	75(72.8%)	0.028
	>1	33(16.5%)	28(27.2%)	
De novo stenosis %	122(63.5%)	16(50.0%)	0.145	
BMI %	Normal	72(39.3%)	29(31.5%)	0.333
	Overweight	85(46.4%)	45(48.9%)	
	Obese	26(14.2%)	18(19.6%)	
%LVEF(Mean \pm SD)	52.11 \pm 10.25	51.94 \pm 7.59	0.897	
SBP (Mean \pm SD)	125.4 \pm 16.6	123.2 \pm 12.5	0.352	
DBP (Mean \pm SD)	77.4 \pm 8.8	78 \pm 7.9	0.377	
FBG (mg/dL)	109.9 \pm 57.0	126.5 \pm 66.9	0.038	
TG (mg/dL)	108 (79–146)	127(78.5–192.5)	0.039	
TC (mg/dL)	148.9 \pm 39.8	153.7 \pm 41.2	0.347	
LDL-C (mg/dL)	89.3 \pm 32.0	88.3 \pm 30.3	0.807	
HDL-C (mg/dL)	35.7 \pm 10.7	35 \pm 8.4	0.581	
Hs-CRP (mg/dL)	2.3(1.3–4.2)	3.46(1.8–7.8)	0.006	

Bold values indicate significance at $p < 0.05$.

^a Duration between coronary stenting and subsequent angiography because of chest pain or equivalent symptoms.

2.1. Definitions

Duration means duration between stent implanting and subsequent angiographic imaging for diagnosis of ISR individuals.

History of diabetes mellitus was defined as being treated with an oral hypoglycemic agent or insulin.

Hypertension was diagnosed in individuals with systolic blood pressure (SBP) at or above 140 mmHg and/or a diastolic blood pressure (DBP) at or above 90 mmHg, or in individuals who were on anti-hypertension medication.

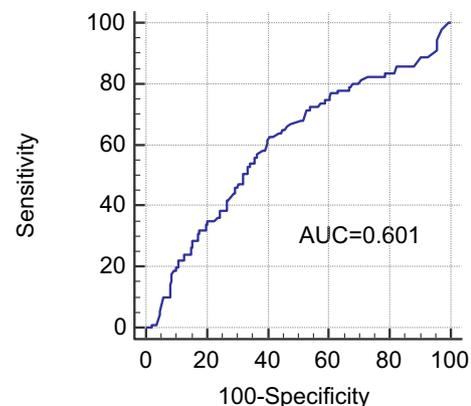


Fig. 1. ROC curve in our study groups testing for hs-CRP.

Table 2
Baseline and biochemical characteristics categorized by hs-CRP level in relation with ISR and NISR.

Variable	Hs-CRP < 2.64 mg/dL		p value	Hs-CRP ≥ 2.64 mg/dL		p value
	NISR	ISR		NISR	ISR	
Age (year)	62.32 ± 9.46	60.91 ± 9.13	0.450	62.48 ± 8.89	60.12 ± 8.35	0.126
Sex %	Male	78(70.3%)	0.353	48 (63.2%)	41 (71.9%)	0.190
	Female	33(29.7%)		28(36.8%)	16(28.1%)	
Smoking %	13 (12.0%)	3(9.4%)	0.171	16(21.3%)	7(12.5%)	0.139
HTN %	69(62.2%)	16(47.1%)	0.087	52(68.4%)	31(54.4%)	0.071
DM %	40(36.0%)	20(58.8%)	0.016	28(36.8%)	35(61.4%)	0.004
Dyslipidemia %	99(93.4%)	32(100.0%)	0.150	72(94.7%)	54(94.7%)	0.645
Statin %	103(96.3%)	27(90.0%)	0.127	69(92.0%)	55(98.2%)	0.119
Aspirin %	104(97.2%)	29(96.7%)	0.110	69(92.0%)	354(96.4%)	0.253
Clopidogrel %	98(91.6%)	26(86.7%)	0.557	62((83.8%)	53(94.6%)	0.047
NSAID %	1(0.9%)	1(3.4%)	0.093	2(2.8%)	2(3.6%)	0.590
Corticosteroids %	3(2.8%)	0(0.0%)	0.105	2(2.7%)	0(0.0%)	0.212
β blocker %	19(17.1%)	5(14.7%)	0.486	13(17.1%)	11(19.3%)	0.458
ARB %	26(23.4%)	7(20.6%)	0.465	28(36.8%)	14(24.6%)	0.093
ACE inhibitor %	7(6.3%)	2(22.2%)	0.645	3(3.9%)	6(10.5%)	0.126
CCB %	9(8.1%)	1(2.9%)	0.271	8(10.5%)	2(3.5%)	0.116
Insulin %	8(7.2%)	4(11.8%)	0.299	10(13.2%)	5(8.8%)	0.307
Duration (months)	36.00(12.00–60.00)	4.00(3.00–7.75)	<0.001	36.00(12.00–60.00)	6.00(4.0–10.00)	<0.001
Stent type %	Bare	28(41.8%)	0.346	20(37.7%)	22(64.7%)	0.012
	Drug-eluting	39(58.2%)	10(50.0%)		33(62.3%)	12(35.3%)
Stent number %	1	92(83.6%)	0.217	60(80.0%)	45(78.9%)	0.525
	>1	18(16.4%)	8(24.2%)	15(20.0%)	12(21.1%)	
De novo stenosis	71(67.0%)	7(70.0%)	0.576	42(58.3%)	7(43.8%)	0.216
BMI	Normal	38(36.9%)	0.934	32(47.1%)	18(35.3%)	0.394
	Over-weight	58(56.3%)	18(60.0%)	21(30.9%)	21(41.2%)	
	Obese	7(6.8%)	2(6.7%)		15(22.1%)	12(42.9%)
SBP (mmHg)	125.03 ± 16.33	123.61 ± 10.40	0.692	124.67 ± 16.91	123.36 ± 13.77	0.665
DBP (mmHg)	76.32 ± 8.40	77.57 ± 7.15	0.515	78.43 ± 9.09	78.00 ± 8.15	0.799
FBG (mg/dL)	106.56 ± 50.43	128.27 ± 63.28	0.078	113.79 ± 67.95	121.91 ± 69.99	0.506
TG (mg/dL)	111.00(82.00–138.00)	107.50(74.25–192.25)	0.439	102.00(71.00–164.50)	145.00(97.75–234.50)	0.026
TC (mg/dL)	144.19 ± 35.46	151.09 ± 34.55	0.333	155.82 ± 43.82	155.84 ± 45.45	0.998
LDL-C (mg/dL)	85.16 ± 29.45	89.23 ± 26.75	0.485	94.94 ± 34.01	87.19 ± 32.69	0.194
HDL-C (mg/dL)	34.72 ± 8.58	34.88 ± 7.38	0.924	37.37 ± 13.21	35.05 ± 8.78	0.257

Bold values indicate significance at $p < 0.05$.

Dyslipidemia was defined as TC ≥ 200 mg/dL (5.18 mmol/L), LDL-C ≥ 130 mg/dL (3.36 mmol/L), or TG ≥ 150 mg/dL (1.69 mmol/L), or HDL-C < 40 mg/dL (1.03 mmol/L) in men and < 50 mg/dL (1.30 mmol/L) in women [18].

3. Result

Of total number of 306 participants, 202 were categorized into NISR group and 104 were categorized into the ISR group. As shown in Table 1 DM ($p < 0.001$), duration ($p < 0.001$), stent type ($p = 0.016$), FBG ($p = 0.039$), serum TG ($p = 0.038$) and hs-CRP were significantly associated with the ISR occurrence. Table 2 shows the association between serum hs-CRP and different characteristics in the study groups. A ROC curve analysis with a cut-off of 2.64 mg/dL for hs-CRP was chosen, which had a specificity of 59.36% and sensitivity of 62.64%. For a serum hs-CRP of <2.64 mg/dL, DM ($p = 0.016$) and duration ($p < 0.001$) was significantly associated with ISR. But in participants with hs-CRP

≥ 2.64 mg/dL, DM ($p = 0.004$), taking clopidogrel ($p = 0.047$), stent type ($p = 0.012$) and TG ($p = 0.014$) were associated with ISR.

In patients with ISR and DM, 15(46.9%) had hs-CRP < 2.64 mg/dL and 33(57.9%) had hs-CRP ≥ 2.64 mg/dL. In individuals with ISR, there was no association between DM and hs-CRP ($p = 0.317$).

Multivariate regression analysis adjusted for duration and stent type and presence of DM has shown in Table 3. Different models of multivariate regression adjusted for different variables have been indicated in Table 4.

4. Discussion

To investigate the association between serum hs-CRP and occurrence of in-stent restenosis we studied 306 patients with a coronary stent who subsequently underwent coronary angiography because of recurrent chest pain or equivalent symptoms This group included 202 patients with NISR and 104 with ISR.

Table 3
DM, FBG, TG and hs-CRP in relation to ISR and NISR after adjustment.

	Variables	OR (CI 95%)	p value
Adjusted for duration and stent type	DM	2.40(1.607–7.192)	0.001
	FBG	1.005(0.999–1.010)	0.097
	TG	1.005(1.000–1.010)	0.046
	Hs-CRP	1.128(1.009–1.261)	0.034
Adjusted for duration and presence of DM	Stent type*	0.211(0.98–0.457)	0.003
	FBG	0.998(0.993–1.003)	0.392
	TG	1.004(1.000–1.008)	0.042
	Hs-CRP	1.104(1.013–1.202)	0.024

Bold values indicate significance at $p < 0.05$.

Table 4
Different models of multivariate regression for hs-CRP and ISR.

		OR (CI 95%)	p value
Hs-CRP	Model 1	1.099 (1.011–1.195)	0.027
	Model 2	1.128 (1.009–1.261)	0.034
	Model 3	1.104 (1.013–1.202)	0.024
	Model 4	1.111 (0.992–1.244)	0.070

Model 1, adjusted for duration; Model 2, adjusted for duration and stent type; Model 3, adjusted for duration and DM; Model 4, adjusted for duration, stent type and DM. Bold values indicate significance at $p < 0.05$.

ISR is an adverse outcome following coronary stent placement, and is thought to occur due to inflammation and oxidative stress, leading to proliferation of smooth muscle cells within the region of the stent. This process is triggered by the vessel wall damage after stenting. Local inflammation stimulates with coronary stenting followed by a systemic inflammatory response which is initially began with inflammatory molecules, such as interleukin-1, interleukin-6, and tumor necrosis factor- α . These molecules cause the liver to produce acute-phase reactants (such as CRP) which could directly amplify the inflammatory stimulus [19,20].

Hs-CRP is a well-established risk factor for CHD. Considering de novo stenosis we have found that ISR occurrence is significantly associated with higher levels of hs-CRP even after the adjustment the effect of duration, stent type. A meta-analysis on 9 prospective studies revealed that elevated pre-procedural CRP is correlated with subsequent ISR after stent implantation due to stable or unstable angina. They did not consider diabetes and stent type for study selection [21]. Another meta-analysis on nine prospective studies only on bare metal stent indicated the same results [22]. But in another prospective study on predictive value of hs-CRP in ISR, they did not find the association between ISR and hs-CRP in patients undergoing elective coronary stenting. Unfortunately, we did not consider the reason of previous stent implantation whether stable angina or unstable angina but our finding was comparable with the two meta-analysis. Moreover, a recent study by Tan et al. did not show any association between ISR and hs-CRP, although higher levels of hs-CRP was associated with readmission and death [17]. Another recent study in China revealed the same result about hs-CRP and ISR Qin et al. studied diabetic patients with drug-eluting stent [16]. Qin et al. findings were to some extent compatible with our 4th regression model adjusted for duration, stent type and DM.

The presence of diabetes mellitus appears to be the most important independent risk factor of restenosis, so implanting drug-eluting stent for coronary revascularization in these patients is strongly recommended [23]. In this study we found that DM and a higher levels of FBG are the most important associated factors in patients with ISR respective of whether bare or drug-eluting stents were used. We also found that even after using drug-eluting stents, DM was the most important risk factor for ISR. Furthermore, we revealed that hs-CRP was not affected with diabetes mellitus in study groups whilst it was related positively related with obesity, similarly has been shown in previous studies [24]. This findings strengthen the relation between ISR and hs-CRP because DM is the most important independent determinant of ISR.

Using ROC analysis, we were able to define a cut-off value of 2.64 mg/dL for serum hs-CRP in this population sample of patients with symptoms following stent placement. Although the sensitivity and specificity of serum hs-CRP using this cut-off was not optimum, it was comparable to previously reports using 3 mg/dL as a cut-off for ISR, although some studies reported 5 mg/dL and even >5 mg/dL [22].

In the group of patients with hs-CRP < 2.64 mg/dL, DM was the only significant related factor to ISR. In individuals with a serum hs-CRP ≥ 2.64 mg/dL in addition to DM, TG and stent type was also associated with ISR. Furthermore, in ISR occurred earlier in individuals with lower levels of hs-CRP in compare with higher levels of hs-CRP. So, it seems that some local factors were responsible for ISR in these patients. For instance, Ge et al. through a cohort study indicated usage of final kissing

balloon post-dilation technique is associated to better long-term outcome [25]. According to 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention some procedural characteristics including stent diameter and stent length are associated with increase of restenosis.

As mentioned before hs-CRP is a novel biomarker of CHD and related disorders. It has been considered in ACCF/AHA Guidelines since 2010 [9]. CRP levels in combination with important risk factor like DM seems promising in predicting ISR after stenting in clinic but larger and more reliable studies with more sensitive and specific cut-off values for hs-CRP could shed light on the implementation of this novel biomarker to guideline for percutaneous coronary intervention.

Unfortunately we did not have the complete data concerning stent size and vessel caliber and this was an important limitation of our study.

5. Conclusion

The presence of DM, serum hs-CRP were positively associated with ISR in individuals with bare or drug-eluting coronary stents. With sensitivity and specificity of 62.64% and 59.36% respectively, we determined the hs-CRP cut-off of 2.64 mg/dL. In patients with a serum hs-CRP less than cut-off, stent related factors appeared to be more important in the development of ISR, whilst in patients with a serum hs-CRP ≥ 2.64 mg/dL, systemic components were prominent.

Ethics approval and consent of participant

This study supported by Mashhad University of Medical Sciences. The study protocol was given approval by the Ethics Committee of Mashhad University of Medical Sciences and written informed consent was obtained from participants.

Consent of publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

There is no competing interest.

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Authors' contributions

Study design: Ghayour-Mobarhan, Pasdar, Hashemi, Salehi; Data gathering: Baktashian, Saffar Soflaei, Kosari, Khosravi, Ahmadinejad, Moohebati, Ebrahimi, Kamene-Bagheri, Ahmadi, Bazhdanzadeh; Data analysis: Baktashian, Saffar Soflaei, Rahmani, Tayefi, Sadabadi; Preparing the manuscript: Saffar Soflaei, Baktashian, Ferns.

Publication ethics

The authors confirm that the content of the manuscript has not been published, or submitted for publication elsewhere.

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References

- [1] Mann DL, Zipes DP, Libby P, Braunwald E, Bonow RO. Braunwald's heart disease: a textbook of cardiovascular medicine; Elsevier/Saunders; 2015.
- [2] Serruys PW, Kutryk MJ, Ong AT. Coronary-artery stents. *N Engl J Med* 2006;354(5):483–95.
- [3] Griendling KK, Fitzgerald GA. Oxidative stress and cardiovascular injury. *Circulation* 2003;108(17):2034–40.
- [4] Lee MS, David EM, Makkar RR, Wilentz JR. Molecular and cellular basis of restenosis after percutaneous coronary intervention: the intertwining roles of platelets, leukocytes, and the coagulation–fibrinolysis system. *J Pathol* 2004;203(4):861–70.
- [5] Moohebati M, Falsoleiman H, Dehghani M, Fazlinezhad A, Daloe MH, Esmaili H, et al. Serum inflammatory and immune marker response after bare-metal or drug-eluting stent implantation following percutaneous coronary intervention. *Angiology* 2011;62(2):184–90.
- [6] Pradhan AD, Manson JE, Rifai N, Buring JE, Ridker PM. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* 2001;286(3):327–34.
- [7] Dehghan A, Kardys I, de Maat MP, Uitterlinden AG, Sijbrands EJ, Bootsma AH, et al. Genetic variation, C-reactive protein levels, and incidence of diabetes. *Diabetes* 2007;56(3):872–8.
- [8] Koenig W. High-sensitivity C-reactive protein and atherosclerotic disease: from improved risk prediction to risk-guided therapy. *Int J Cardiol* 2013;168(6):5126–34.
- [9] Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines developed in collaboration with the American Society of Echocardiography, American Society of Nuclear Cardiology, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Cardiovascular Computed Tomography, and Society for Cardiovascular Magnetic Resonance. *J Am Coll Cardiol* 2010;56(25):e50–103.
- [10] Zheng W-P, Yang M, Su L-X, Ning Y, Wen W-W, Xin M-K, et al. Association between plasma BMP-2 and in-stent restenosis in patients with coronary artery disease. *Clin Chim Acta* 2017;471:150–3.
- [11] Shen Y, Li C, Zhang RY, Zhang Q, Shen WF, Ding FH, et al. Association of increased serum CTRP5 levels with in-stent restenosis after coronary drug-eluting stent implantation: CTRP5 promoting inflammation, migration and proliferation in vascular smooth muscle cells. *Int J Cardiol* 2017;228:129–36.
- [12] Yilmaz S, Akboga MK, Aras D, Topaloglu S. Evaluation of the predictive value of CHA2DS2-VASc score for in-stent restenosis. *Angiology* 2017;0003319717700746.
- [13] Yin J, Shen L, Ji M, Wu Y, Cai S, Chen J, et al. Inverse relationship between serum VEGF levels and late in-stent restenosis of drug-eluting stents. *Biomed Res Int* 2017;2017.
- [14] Kurtul A. Usefulness of the CHA2DS2-VASc score in predicting in-stent restenosis among patients undergoing revascularization with bare-metal stents. *Clin Appl Thromb Hemost* 2017;1076029617716769.
- [15] Murat SN, Yarlioglu M, Celik IE, Kurtul A, Duran M, Kilic A, et al. The relationship between lymphocyte-to-monocyte ratio and bare-metal stent in-stent restenosis in patients with stable coronary artery disease. *Clin Appl Thromb Hemost* 2017;23(3):235–40.
- [16] Qin Z, Zheng F-W, Zeng C, Zhou K, Geng Y, Wang J-L, et al. Elevated levels of very low-density lipoprotein cholesterol independently associated with in-stent restenosis in diabetic patients after drug-eluting stent implantation. *Chin Med J* 2017;130(19):2326.
- [17] Tan Z, Li L, Ma Y, Geng X. Prognostic values of high-sensitivity C-reactive protein for patients receiving percutaneous coronary intervention. *Biomed Res* 2017;28(4).
- [18] Goodman DS, Hulley SB, Clark LT, Davis C, Fuster V, Larosa JC, et al. Report of the National Cholesterol Education Program Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults. *Arch Intern Med* 1988;148(1):36–69.
- [19] Versaci F, Gasparone A. Prevention of restenosis after stenting: the emerging role of inflammation. *Coron Artery Dis* 2004;15(6):307–11.
- [20] J-J Li. Inflammatory response, drug-eluting stent and restenosis. *Chin Med J* 2008;121(6):566–72.
- [21] Li J-J, Ren Y, Chen K-J, Yeung AC, Xu B, Ruan X-M, et al. Impact of C-reactive protein on in-stent restenosis: a meta-analysis. *Tex Heart Inst J* 2010;37(1):49.
- [22] Ferrante G, Niccoli G, Biasucci LM, Liuzzo G, Burzotta F, Galiuto L, et al. Association between C-reactive protein and angiographic restenosis after bare metal stents: an updated and comprehensive meta-analysis of 2747 patients. *Cardiovasc Revasc Med* 2008;9(3):156–65.
- [23] Scheen AJ, Warzée F, Legrand VM. Drug-eluting stents: meta-analysis in diabetic patients. *Eur Heart J* 2004;25(23):2167–8.
- [24] Yudkin JS, Stehouwer C, Emeis J, Coppack S. C-reactive protein in healthy subjects: associations with obesity, insulin resistance, and endothelial dysfunction. *Arterioscler Thromb Vasc Biol* 1999;19(4):972–8.
- [25] Ge L, Airoidi F, Iakovou I, Cosgrave J, Michev I, Sangiorgi GM, et al. Clinical and angiographic outcome after implantation of drug-eluting stents in bifurcation lesions with the crush stent technique: importance of final kissing balloon post-dilation. *J Am Coll Cardiol* 2005;46(4):613–20.