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Relationship between serum high sensitivity C-reactive protein with angiographic severity of coronary artery disease and traditional cardiovascular risk factors

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Abstract

Serum high-sensitivity C-reactive protein (hs-CRP) is predictive of coronary artery disease (CAD). The aim of this study was to examine the possible association of hs-CRP with presence and severity of CAD and traditional CAD risk factors. This case-control study was carried out on 2,346 individuals from September 2011 to May 2013. Of these 1,187 had evidence of coronary disease, and were subject to coronary angiography, and the remainder were healthy controls ($n = 1,159$). Characteristics were determined using standard laboratory techniques and serum Hs-CRP levels were estimated using enzyme-linked immunosorbent assay (ELISA) kits, and severity of CAD was assessed according to the score of obstruction in coronary artery. Serum hs-CRP levels were higher in those with severe coronary disease, who had stenosis ≥ 50% stenosis of at least one coronary artery (all $p < 0.001$ vs. individuals in healthy control), and correlated significantly with the score for coronary artery disease (all $p < 0.01$). After adjustment for conventional risk factors, regression analysis revealed that smoking habits, fasting blood glucose,

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total cholesterol, high-density lipoprotein, hs-CRP, blood pressure, anxiety, dietary intake of vitamin E, and cholesterol remained as independent determinants for angiographic severity of CAD. The area under the receiving operating characteristic (ROC) curve for serum hs-CRP was 0.869 (CI 95% 0.721–0.872, $p < 0.001$). The optimal values for the cut-off point was a serum hs-CRP of 2.78 mg/l (sensitivity 80.20%, specificity 85%) to predict severity of CAD. Increased serum hs-CRP levels are significantly associated with angiographic severity of CAD, suggesting its value as a biomarkers for predicting CAD.

KEYWORDS
angiography, biomarker, coronary artery disease, hs-CRP, traditional risk factor

1 | INTRODUCTION

Coronary artery disease (CAD) account for 31% of cardiovascular disease (CVD) deaths globally in 2016, representing 17.9 million people died annually from CVDs. In Iran, CVD are the first cause of death and 43% people die annually due to CVDs (Goudarzi et al., 2015; Khatib et al., 2016).

Coronary angiography, intensive lipid-lowering treatments, and drug-eluting stents following percutaneous coronary intervention (PCI) are often important for definitive evaluation and treatment of coronary artery disease (CAD; Sukhija et al., 2007; Zheng et al., 2010) However, a large proportion of patients suffer from recurrence of angina and coronary lesions with atherosclerotic progression, which often lead to a complicated clinical courses and exhibit complex morphology at angiography (Pan et al., 2015). Therefore, the use of traditional risk factors and biomarkers as a tool for the diagnosis of CAD events and coronary artery occlusion and degree of obstruction has generated great interest because of their promise to either "rule-out" or "rule-in" advanced CVD (Avan et al., 2018; Saito et al., 2003).

According to recent estimates, the risk of developing CVD is often dependent on the effects of traditional risk factors (Albert, Glynn, Buring, & Ridker, 2006; Penson et al., 2018). However, more than 50% of cases of CAD can be ascribed to nontraditional risk factors, and the mechanisms of coronary lesions with atherosclerotic progression have not been fully understood (Saito et al., 2003). The role of inflammation process in the atherosclerosis process is thought to be important, particularly in relation to plaque stability (Lassale, Batty, & Zaninotto, 2017). Atherosclerosis initially develops following the induction of adhesion molecules on the vascular endothelium leading to the accumulation of inflammatory cells that are subsequently involved in the production of inflammation mediators that include cytokines and C-reactive protein (Martin et al.,2017).

Serum high sensitivity C-reactive protein (hs-CRP) has emerged as an important inflammation-related marker, and is well evaluated as a predictor of adverse outcome in patients with CAD (Elkind, Leon, Moon, Paik, & Sacco, 2009; Ridker & Silvertown, 2008). Epidemiological studies show that hs-CRP is not only a mediator and biomarker of CVD and atherosclerosis but it is also independently predicts CVD events, including sudden cardiac death, myocardial infarction, and ischemic stroke. Here is evidence that the commercial hs-CRP causes make high sensitive monitoring for this biomarker simple, reproducible and reliable, and can be implemented in clinical practice as a guide to prognosis and diagnosis of CVD (Avan et al., 2018; Kazemi-Bajestani et al., 2017; Lassale et al., 2017).

Since, hs-CRP is closely related to a prognostic features in patients with CAD (Avan et al., 2018; Lassale et al., 2017), and also since reflected active systemic inflammation, we hypothesized that measurement of hs-CRP could be useful in estimating severity of CAD risk or atherosclerotic burden in patients who are hospitalized with acute chest pain. Further, we hypothesized that an increase in serum hs-CRP might also be associated with some traditional risk factor of CAD. In this context, our objectives were to examine: (a) Whether traditional risk factors of CAD associate with the angiographic severity of CAD; (b) whether serum hs-CRP remains an independent predictor of severity of CAD as assessed by angiographic findings; (c) whether serum hs-CRP is associated with individual traditional risk factors of CAD after adjustment for angiographic findings; and (d) the best cut-off point for hs-CRP with the greatest specificity and sensitivity to CAD diagnosis.

2 | METHODS AND MATERIALS

The study was conducted using the Helsinki declaration and with approval from the ethics committee of Ghaem Hospital. Informed written consent was obtained from all participants.

2.1 | Patient population

To select eligible participants, a multistep, cluster sampling method was used in the Cardiology Clinic of Ghaem Hospital, Mashhad, Iran. In total, 2,346 subjects were included who were referred to cardiology clinic for routine medical assessment or pre-employment medical examinations from September 2011 and May 2013. Subjects were divided into control and case groups. The control or "healthy" group consisted of subjects

who had no signs or symptoms of CAD (such as cardiac chest pain, unstable angina, exertion angina, and no positive finding in cardiologist examination). This group underwent routine laboratory investigation and physical examination to monitor for somatic and chronic illness. Participants were excluded from the control group if they (a) unable to give informed consent; (b) had a history of hospitalization for any illness during the 5 years ago; (c) had symptoms of infection, angina, and systemic illness (cancer, chronic or acute liver disease, renal disorder, rheumatic disease, etc.); (d) were pregnant or breast-feeding; and (e) used medication, vitamin supplements, anticonvulsants, alcohol, estrogen, and lipid-lowering therapy that might affect serum bilirubin, or hs-CRP levels. Finally, 1,159 participants were included in our control group after these exclusions, and who completed all clinical questionnaires. The case group included patients who were admitted to hospital and underwent coronary angiography for evaluation of symptoms suggestive of CVD. Angina was defined according to the Canadian Cardiovascular Society guidelines (Skanes et al., 2012). To avoid confounding data of serum biomeasurements, we excluded participants with acute myocardial infarction before the study entry because of great changes of hs-CRP levels by acute-phase reaction. Exclusion criteria also included those with ongoing systemic inflammatory diseases, congestive heart failure, malignancy, and hepatic dysfunction. The remaining 1,187 patients who had completed all clinical questionnaires and angiographic documents formed the case group.

2.2 | Physical measurements

All participants completed a general questionnaire, which included participant's demographic information (e.g., age, gender, educational level, marital status, and occupation), family history of CVD, anthropometric parameters (body mass index [BMI] and blood pressure), and smoking habits. Blood pressure (systolic and diastolic) was measured twice at an interval of 15 min, using an automated blood pressure monitor (Snoqualmie, WA, BPTru device). The average of the two systolic blood pressure measurements was considered as systolic blood pressure (SBP), and the average of two diastolic blood pressure measurements was considered as diastolic blood pressure (DBP; Kazemi-Bajestani et al., 2007). Hypertension in the present study is defined as SBP ≥ 140 mmHg, and/or DBP ≥ 90 mmHg (Association, 2015; Zager et al., 1998). BMI was calculated as weight in kilograms divided by height in meters squared (kg/m^2) as proposed by the National Institutes of Health Consensus Statement (Bray, Kim, Wilding, & Federation, 2017). The normal range of BMI was 18.5–24.9 kg/m^2, if BMI followed by 25–29.9 kg/m^2 as overweight and if BMI was equal or more than 30 kg/m^2, it was considered as obese (Bray et al., 2017). Diabetes mellitus was considered to be present in patients with a known history of diabetes and in patients with a fasting glucose ≥ 126 mg/dL (7.0 mmol/L) according to the American Diabetes Association criteria (Handelsman et al., 2015). Family history of CVD in this study includes a female first-degree relative with CVD by the age of 65 years and a male first-degree relative with CVD by the age of 55 years (Renjen, Beg, & Ahmad, 2015). The National Health Interview Survey (NHIS) was used to assess smoking habits (Blackwell, Lucas, & Clarke, 2014).

2.3 | Biochemical investigation

Blood samples (20 ml) were collected in all patients after overnight fasting. All samples were centrifuged (4,000 RPM for 5 min) to collect plasma and their serum was stored at −80°C. Plasma levels of glucose (FBG), creatinine, and lipid profiles including total cholesterol (TC), low-high-density lipoprotein cholesterol (HDL-C), and density lipoprotein cholesterol (LDL-C), triglycerides, and protein were measured with standard laboratory techniques on a Cobas analyzer system (ABX Diagnostics, Montpellier, France; Kazemi-Bajestani et al., 2007). We measured hs-CRP level using a high-sensitivity enzyme-linked immunosorbent assay (ELISA) kit (Biocheck Laboratories, Toledo, OH). The minimum detection limit of the hs-CRP assay was 0.05 mg/dl, within-run and between-run coefficients of variation were 3.7–4.4% and 3–3.9%, respectively. The test for all samples with a CRP was standardized using the International Federation of Clinical Chemistry International Reference Preparation for Plasma Proteins. We chose a priori to define an normal CRP level as ≤ 1.0 mg/dl, a commonly used cut-point to define risk in CAD populations; the levels between 1–3 mg/l were defined as mildly elevated and associated with an increased risk for CAD, and a highly elevated CRP level was set as ≥ 2.0 mg/dl, approximately the top CRP quintile (Inflammation, 2010; Ridker, 2003).

2.4 | Angiographic procedure

Coronary arteriography was conducted using the standard Judkins technique (Moncalvo et al., 2018). To avoid artery spasm, intracoronary injection of nitroglycerin (100 μg) was routinely made. Analysis of all angiograms were performed with Imaging analysis system (Centricity Cardiology CA 1000. v1.0), by two cardiologists who were blind to CRP level and others biochemical outcome. The cumulative coronary obstruction was estimated by summing all percent diameter stenosis in standard index units (50% = 0.50; Zheng et al., 2010) everity of CAD was defined according to the score of obstruction in coronary artery. Lesion was diagnosed if one of the following criteria was met: (a) Those with significant or severe lesion (angiography$^+$, 782 patients) who had stenosis occluding ≥ 50% in diameter in at least one coronary artery, or (b) those with a normal angiogram (angiography$^-$, 405 patients) indicating lower degree of obstruction (< 50%) in coronary arteries.

2.5 | Dietary assessment

Participants' dietary intake was collected using a 24-hr dietary recall (Yuan et al., 2017), using Diet Plan 6 software (Forest field Software Ltd., United Kingdom) to analyze macro and micro nutrient intake. A trained interviewer asked about all foods and beverages that consumed by subjects in a face-to-face interview.

2.6 | Assessment of depression and anxiety

The Persian version of Beck Depression Inventory (BDI; Dadfar & Kalibatseva, 2016) and Beck Anxiety Inventory Questionnaires (BAI; Julian, 2011) were used as a reliable and valid test to assess the severity of an individuals' anxiety and depression. This questionnaire includes two parts with a total of 21 items. The first part assesses somatic factors using 12 items that related to physiological symptoms such as, numbness or tingling and feeling dizzy or lightheaded. The second part included nine items to assess subjective anxiety and panic (e.g., "fear of the worst happening" and "unable to relax"). Responses for the all questions range from 0 (not at all) to 3 (most of the time) and higher scores indicating high severity of anxiety. According to the BDI score, a score of 15 or less from this test signifies no depression, mild depression is between 16 and 30, for moderate depression the score is 31–46, and severe depression is more than 47 (Dadfar & Kalibatseva, 2016; Vasegh & Mohammadi, 2007). According to the BAI, if a person gets 7 or less from this test has minimal anxiety, mild anxiety score is between 8 and 15 and moderate anxiety is between 16 and 25, whereas more than 25 is severe anxiety. According to pervious study in Iran, the reliability coefficient (Cronbach's α) for BDI and BAI were 0.92% and 0.89%, respectively (Beck, Ward, Mendelson, Mock, & Erbaugh, 1961).

2.7 | Statistical analysis

We used SPSS 13.0 for Windows (SPSS, Inc., Chicago, IL) to conduct statistical analysis. All categorical data are reported as percentages, and continuous parameters are expressed as mean ± *SD*. The Kolmogorov–Smirnov test was used to examine normality of the continuous variables. Because hs-CRP was not normally distributed, logarithmic transformation was conducted before analysis. We used unpaired 2-tailed *t*-test and the Mann–Whitney U-test, one-way analysis of variance (ANOVA) test, the chi-square test, and Bonferroni correction to examine differences among continuous variables between two groups. The Pearson's test was used to assess correlation between variables, and multivariate logistic regression analysis (Backward: LR) was also used to assess the independent determinants of lesion progression. We estimated odds ratios (OR) to assess the risk of CVD factor, which associated with presence of or change various risk factors. Optimal cut-off point, sensitivity and specificity of hs-CRP were estimated with receiver operating characteristic (ROC) analysis. Area under the curve (AUC) values in ROC curve were used to measure severity of CAD and diagnostic values.

3 | RESULTS

3.1 | Clinical characteristics in participants

Tables 1 **and** 2 show the comparison of baseline and demographic characteristics, and conventional risk factors for CAD between the control and case groups. There were no significant difference existed with respect to marital status, BMI and depression scores between participants in control and case groups. Patients who were Angio$^+$ were more likely to be male and were older ($p < 0.05$), with higher FBG, triglyceride, cholesterol concentrations, blood pressure, and to have a positive smoking history and family history, and significantly lower level of educational attainment, income, anxiety score, serum HDL, and LDL concentrations than did Angio$^-$ patients and the control groups. As Table 2 and Figure 1 shown, serum hs-CRP levels was significantly higher among patients in the case group compared with those in control ($p < 0.001$), likewise, serum hs-CRP was significantly higher in the Angio$^+$ than in the Angio$^-$.

As Supporting Information Tables S1 and S2 show, there was a significant difference between case and control groups for micro and macro nutritional intake. Patients in the case group reported having a significantly higher dietary intake of energy and all macronutrients (except for carbohydrate, fiber, monounsaturated fatty acid, and trans fatty acid) more often than did control group ($p < 0.05$). Likewise, they had a significant higher reported intake of micronutritional (potassium, phosphorus, calcium, iron, copper, zinc, selenium, iodine, retinol, vitamin E, vitamin D, thiamin (B1), and riboflavin (B2)), and lower reported intake of manganese, magnesium, carotene, vitamin C, and then the control groups.

3.2 | Association analysis

Univariate analysis showed that age, education, family income, smoking habit, family history, anxiety, FBG, lipid profile, hs-CRP, blood pressure, and dietary intake of macro and micronutritional intake were significantly ($p < 0.05$) associated with angiographic severity of CAD. After adjustment for conventional risk factors (gender, age, income, and education), multivariate logistic regression analysis revealed that smoking, FBG, TC, HDL, hs-CRP, blood pressure, anxiety, dietary intake of vitamin E, and cholesterol remained as independent determinants for angiographic severity of CAD (Tables 3 and 4). Unexpectedly, family history, serum triglyceride, HDL, and micronutritional did not appear to be associated with severity of CVD.

The relationship between CVD risk factors and hs-CRP among all subjects (case and control) was evaluated using multiple linear regression models adjusted for covariates by employing stepwise elimination. A multiple linear regression analysis revealed that smoking, anxiety, depression, family history, BMI, age, cholesterol, triglycerides, glucose, and intake of some macro (protein, carbohydrate, high-density lipoprotein, monounsaturated fatty acid, and trans fatty acid) and micronutrients (Iron, Vitamin D, carotene, sodium, retinol, and copper) were statistically ($R^2 = 0.45$; $F = 48.771$; $p < 0.001$) associated with elevated level of serum hs-CRP.

3.3 | Receiving operating characteristic (ROC) analysis

An area under the curve of hs-CRP was 0.869 (CI 95% 0.721–0.872, $p < 0.001$). The optimal values of cut-off point were 2.7 mg/l (sensitivity 80.2%, specificity 85%) for hs-CRP to predict lesion severity (Table 5; Figure 2).

TABLE 1 Comparison of demographic and baseline characteristics in different study groups

Characteristics	Control Healthy $n = 1,159$)	Case (patients)				
		Angiography$^-$ ($n = 405$)	Angiography$^+$ ($n = 782$)	p_0	p_1	p_2
Age (years)	52.97 ± 9.34	53.58 ± 11.40	58.93 ± 10.57	0.545	<0.001	<0.001
Gender, *n* (%)						
Male	584 (50.4)	238 (58.7)	475 (60.7)	0.066	0.058	0.11
Female	575 (49.6)	167 (42.3)	307 (39.3)	0.03	0.041	0.09
BMI (kg/m^2), *n* (%)						
Normal	390 (34)	128(32.7)	255 (33.1)	0.34	0.623	0.781
Overweight	468 (40.8)	164(40.9)	302 (39.2)	0.82	0.79	0.81
Obesity	290 (25.3)	99(26.3)	214 (27.8)	0.83	0.623	0.76
Smoking habit, *n* (%)						
Current	229 (19.8)	62 (15.3)	189 (24.2)	0.03	0.023	<0.001
Former	144 (12.4)	52 (12.8)	125 (16.0)	0.82	0.03	0.035
Never	786 (67.8)	291 (71.9)	468 (59.8)	0.082	0.033	0.041
Marital Status, *n* (%)						
Single	15 (1.3)	7 (1.7)	7 (0.9)	0.89	0.091	0.026
Married	1,063 (91.7)	354 (87.6)	709 (89.7)	0.082	0.12	0.092
Divorced	17 (1.5)	7 (2)	5 (1.4)	0.073	0.62	0.041
Widow	64 (5.5)	35 (8.7)	63 (8.0)	0.031	0.038	0.62
Education, *n* (%)						
Primary school	682 (58.8)	285 (70.4)	519 (66.4)	0.025	0.033	0.071
High school	325 (28.0)	47 (11.6)	120 (15.3)	<0.001	<0.001	0.11
Bachelor	131 (11.3)	63 (15.6)	112 (14.3)	0.018	0.011	0.23
Master /PhD	21 (1.8)	10 (2.4)	31 (4.0)	0.072	0.009	0.062
Family income, *n* (%)						
low	177 (15.3)	204 (50.37)	497 (63.55)	<0.001	<0.001	0.007
Moderate	334 (28.8)	139 (34.32)	208 (26.59)	0.26	0.67	0.072
High	648 (55.9)	62 (15.30)	77 (9.8)	<0.001	<0.001	0.038
Family history, *n* (%)	392 (33.82)	209 (51.99)	570 (72.89)	<0.001	0.001	<0.004
Depression, *n* (%)						
Normal	847 (73.1)	311 (76.7)	550 (70.4)	0.32	0.13	0.085
Mild	274 (23.6)	85 (21.1)	192 (24.5)	0.14	0.11	0.15
Moderate	38 (3.3)	9 (2.2)	40 (5.1)	0.072	0.032	0.006
Anxiety, *n* (%)						
Normal	650 (56.1)	203 (50.2)	359 (45.9)	0.053	0.026	0.007
Mild	300 (25.9)	110 (27.1)	217 (27.8)	0.17	0.15	0.82
Moderate	155 (13.4)	63 (15.5)	218 (15.1)	0.37	0.38	0.63
Sever	54 (4.6)	29 (7.2)	85 (10.8)	0.057	0.025	0.041

Data are *n* (%) and mean ± *SD*; *n*, number of participants. *Note*: BMI, body mass index; p_0 is a significant difference between control and angiography$^-$; p_1 is a significant difference between control and angiography$^+$, p_2 is a significant difference between angiography$^-$ and angiography.

TABLE 2 Comparison of lipid profile and hs-CRP in different study groups

	Control	Case (patients)				
	Healthy (n = 1159)	Angiography$^-$ (n = 405)	Angiography$^+$ (n = 782)	p_0	p_1	p_2
FBG (mg/dl)	83.19 ± 13.38	113.81 ± 38.18	127.73 ± 44.92	<0.001	<0.001	<0.001
TC (mg/dl)	160.77 ± 33.64	167.54 ± 41.77	168.41 ± 40.00	<0.001	<0.001	0.923
LDL-C (mg/dl)	113.02 ± 30.14	97.19 ± 32.55	97.83 ± 30.98	<0.001	<0.001	0.938
HDL-C (mg/dl)	44.42 ± 9.41	42.17 ± 10.71	40.37 ± 10.14	<0.001	<0.001	0.008
TG (mg/dl)	113.31 ± 53.72	135.90 ± 59.43	146.41 ± 58.57	<0.001	<0.001	0.007
SBP (mmHg)	120.61 ± 15.49	132.88 ± 24.66	138.88 ± 16.13	<0.001	<0.001	0.034
DBP (mmHg)	74.88 ± 9.89	79.41 ± 7.11	84.25 ± 11.47	<0.006	<0.002	0.042
hs-CRP (mg/dl)	1.40 ± 0.65	3.91 ± 2.13	5.12 ± 2.73	<0.001	<0.001	<0.001

Note. Data are n (%) and mean ± SD; n, total of participants.
DBP: diastolic blood pressure; FBS: fasting blood sugar; HDL-C: high-density lipoprotein cholesterol; hs-CRP: high sensitivity C-reactive protein; LDL-C: low-density lipoprotein cholesterol; p_0 is a significant difference between control and angiography$^-$; p_1 is a significant difference between control and angiography$^+$: p_2 is a significant difference between angiography$^-$ and angiography; SBP: systolic blood pressure; TC: total cholesterol; TG: triglyceride.

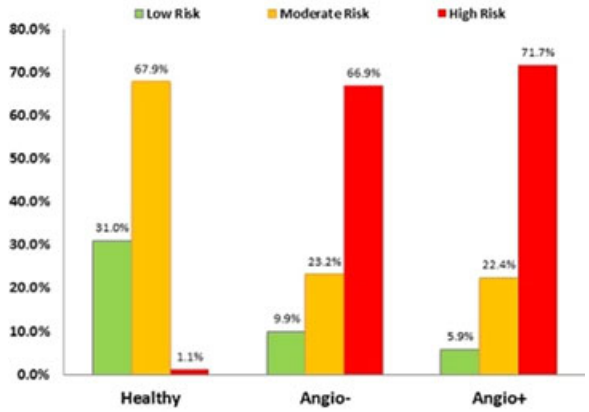

FIGURE 1 Comparison of patients and healthy individuals respondents with categories of hs-CRP. hs-CRP: high sensitivity C-reactive protein [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

4.1 | Traditional risk factor and severity of CAD

Some demographic factors were significantly associated with angiographic severity of CAD. The risk of CAD increased with age. It is intuitive that age is an independent risk factor for developing CAD, which is obviously a nonmodifiable risk factor for CVD events (Hartiala et al., 2012; Saito et al., 2003). Likewise, we observed socioeconomic position (e.g., education and family income) were inversely associated with severity of CAD. This is consistent with research evidence, which shows a positive association between CVD incidence in developed countries and lower/middle social classes (Saito et al., 2003). This may be addressed through the promotion of healthier lifestyles and the support of policy and environmental changes (Collet et al., 2012). In addition, increased education and knowledge about risk factors

TABLE 3 Logistic regression coefficients of risk factors for angiographic severity of CAD

	Beta ± SE	OR	95% CI	p-value
Smoking habits	0.365 ± 0.154	1.441	1.065–1.94	0.018
FBG	0.182 ± 0.002	1.108	1.06–1.18	0.01
TC	0.219 ± 0.080	1.245	1.014–1.417	0.006
HDL	−0.18 ± 0.07	0.749	0.689–0.996	0.01
Hs-CRP	0.184 ± 0.030	1.202	1.065–1.457	<0.001
SBP	0.181 ± 0.085	1.193	1.093–1.21	0.0023
DBP	0.151 ± 0.062	1.161	1.042–1.192	0.013
Dietary intake of cholesterol	0.154 ± 0.061	1.173	1.11–1.27	0.027
Dietary intake of vitamin E	−0.183 ± 0.09	0.777	0.760–0.994	0.008
Anxiety	0.120 ± 0.008	0.880	0.864–0.996	0.014

Note. CAD: coronary artery disease; CI: confidence interval; DBP: diastolic blood pressure; FBG: fasting blood glucose; HDL: high-density lipoprotein; hs-CRP: high sensitivity C-reactive protein; OR: odd ratios; SBP: systolic blood pressure; TC: total cholesterol.

TABLE 4 Relationship between traditional CAD risk factors and hs-CRP

	B	β	*t*	*p* value
Age	0.019 ± 0.004	0.079	4.476	<0.001
Family history	1.473 ± 0.146	0.156	−3.224	0.002
Smoke habits	0.304 ± 0.092	0.057	3.319	<0.001
BMI	0.040 ± 0.014	0.143**	2.922	0.004
Depression score	−0.012 ± 0.006	−0.041	−1.995	0.046
Anxiety score	0.018 ± 0.006	0.067	3.219	<0.001
Cholesterol	−0.002 ± 0.001	−0.109	−4.435	<0.001
Triglycerides	0.003 ± 0.001	0.060	3.326	<0.001
Fasting blood glucose	0.015 ± 0.001	0.218	11.291	<0.001
Protein	0.020 ± 0.003	0.302	7.374	<0.001
Carbohydrate	0.002 ± 0.001	0.069	2.179	0.029
Dietary sugar	−0.004 ± 0.001	−0.073	−2.929	0.003
High-density lipoprotein	0.011 ± 0.004	0.046	2.594	0.009
Monounsaturated fatty acid	−0.022 ± 0.009	−0.063	−2.439	0.015
Trans fatty acid	−0.418 ± 0.101	−0.097	−4.139	<0.001
Iron	0.066 ± 0.011	0.154	5.826	<0.001
Vitamin D	0.049 ± 0.014	0.063	3.441	<0.001
Retinol	0.002 ± 0.001	0.080	3.741	<0.001
Copper	−0.746 ± 0.177	−0.145	−4.222	<0.001
Zinc	0.081 ± 0.022	0.137	3.604	<0.001
Phosphorus	− 0.001 ± 0.001	−0.109	−2.737	0.006
Carotene	−3.95 ± 0.001	−0.058	−3.029	0.003
Sodium	−4.62 ± 0.001	−0.042	−2.272	0.023

Note. $R^2 = 0.45$; $F = 48.771$, $p < 0.001$.
CAD: coronary artery disease; hs-CRP: high sensitivity C-reactive protein.

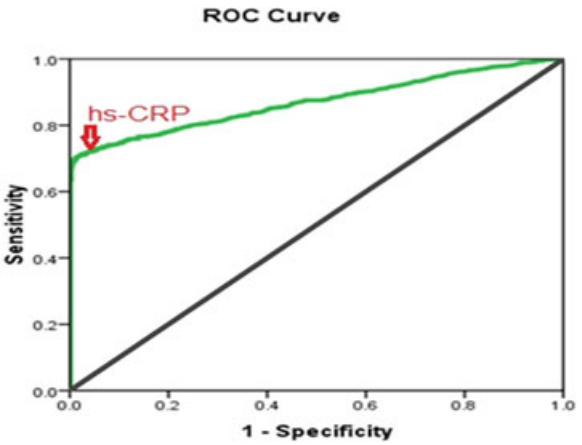

FIGURE 2 ROC analysis showing the power Hs-CRP levels for predicting severity of CAD and an area under the curve was 0.869 (CI 95% 0.721–0.872: $p < 0.001$). CAD: coronary artery disease; hs-CRP: high sensitivity C-reactive protein [Color figure can be viewed at wileyonlinelibrary.com]

in daily life activities may have been partially contributed to the decline in CAD events among the higher social classes (Avan et al., 2018). A positive smoking habit and family history were a significant risk factor for angiographic severity of CAD. Several epidemiological studies have demonstrated a strong association between CVD events and cigarette smoking (King et al., 2017). Although, the mechanism by which smoking is associated with CAD is related to atherogenesis, as well as thrombogenesis, and blood platelet function is thought to be prominent among the mechanisms involved in atherogenesis and thrombogenesis (Inoue, 2004). Family history is the medical information from individuals' first- and second-degree relatives that is most informative because an individual shares 50% and 25%, respectively, of their genes with them (Hopkins et al., 1988; Venkataraman, Huynh, Marwick, & Investigators, 2018). Therefore, family history could be considered as potential screening tools to identify people, who are at increased CVD risk. However, the predictive value of adding family history to established risk scores of CVD is often small, and many people with a positive family history may not be at increased risk of CVD (Hindieh et al., 2016; Zheng et al., 2010).

There was a significant relationship between dietary intake of macro/micro nutrient and risk for CAD, which is consistent with other studies that have shown a strong relationship between diet and the risk for CAD (Anderson, 1987; Mehramiz et al., 2016; Reedy et al., 2014). Dietary modification may slow the progress of CVD, and may facilitate the regression of CAD and also modifies the risk factors (Avan et al., 2018; Nazeminezhad et al., 2014; Reedy et al., 2014). Although, micro/macronutrients are essential in optimal quantities for human health, suboptimal consumption can have several harmful consequences for the health. The results of this study indicate that the mean dietary intake of most macronutrients (except for carbohydrate and monounsaturated fatty acid) and micronutrients (apart from retinol) in case group was significantly higher than in control group. Likewise, our data highlight that dietary cholesterol and vitamin E were significant predictors for CAD. In addition, saturated fatty acids and polyunsaturated fatty acids, and cholesterol in the healthy group were found to be less than the values for the patients. These findings are consistent with previous studies, which showed

TABLE 5 Receiver operating characteristic analysis for hs-CRP

Cut-off point (pg/ml)		Sensitivity (CI 95%)	PPV (CI 95%)	NPV (CI 95%)	*p*-value	Area under curve	Youden index J
> 2.78	80.20 (73.4–84.2)	85.00 (77.3–90.8)	91.0 (86.2–94.6)	68.0 (59.9–75.3)	< 0.001	0.869	0.6897

Note. hs-CRP: high sensitivity C-reactive protein; PPV: positive predictive value; NPV: negative predictive value.

that high-density fatty acids and cholesterol increase the risk of CAD through the raise of serum total cholesterol and LDL (Avan et al., 2018; Bray et al., 2017; Peyman & Oakley, 2011). The mean dietary fiber intake in the control group was significantly higher than the case group. The American Heart Association have reported that the dietary fiber intake reduces the risk for CAD because soluble fiber can lead to reduce serum cholesterol concentration, especially low-density lipoprotein cholesterol concentration, without affecting the concentration of high-density lipoprotein cholesterol (January et al., 2014). Dietary fiber has been shown to delay the absorption of carbohydrates and consequently, and reduce the total and low-density lipoprotein cholesterol levels (Anderson, 1987).

Although a low diastolic (<70 mmHg) and low systolic (<120 mmHg) blood pressures were significantly associated with an increased severity of CAD, that is consistent with several clinical studies (Nissen et al., 2004; Weber et al., 2016; Zheng et al., 2010) diastolic blood pressure was the strongest predictor of CAD in patient with positive angiogram (Nissen et al., 2004). Here is evidence that level of systolic and diastolic pressures are independent risk indicators for the risk and severity CAD. However, this association might be affected by drug therapy. Based on the clinical randomization method, the confounding impacts of drug therapy might be overcome (Nissen et al., 2004; Weber et al., 2016; Zheng et al., 2010).

Depression and anxiety disorders have been found as an independent risk factor to be associated with CAD. Several studies have reported that psychological factors such as depression and anxiety cause more than 80% of increased risk of CVD when adjusted for CAD risk factors (Cohen, Edmondson, & Kronish, 2015; Rutledge et al., 2009). The degree of depression and anxiety are associated with a greater decline in physical functioning of patients with heart failure, and leads to the deterioration of the autonomic dysfunction of nervous system through increased sympathetic or decreased vagal control, which is associated with the increase in cardiac mortality (Rutledge et al., 2009).

4.2 | C-reactive protein and severity of CAD

By use of a case-control approach from observations made in angiographic procedure in this study, we have shown significant association between elevated plasma levels of CRP and angiographic severity of CAD. In line with previous clinical studies, an increased serum hs-CRP level was an independent predictor for severity of CAD (Sukhija et al., 2007; Zheng et al., 2010), we also observed that serum hs-CRP levels were significantly higher in patients with severe coronary lesion with a ≥ 50% reduction in diameter in at least one coronary artery, and correlated positively with the score of obstruction in coronary artery.

In the prospective Atherosclerosis Risk in Communities Study, high hs-CRP level is an acute-phase protein marker that can demonstrate the occurrence and extent of CAD (Sukhija et al., 2007). This association between serum hs-CRP biomarker and severity of CAD was also apparent after adjustment for conventional CAD risk factors (e.g., gender, age, and education). This observation suggests that the association of hs-CRP with angiographic severity of CAD is could due to its association with coronary atherosclerosis directly. However, our study has shown low adjusted relative risk (OR, 1.22; 95% CI, 1.065–1.45) for hs-CRP. Danesh et al. conducted a meta-analysis using 22 prospective studies that examined the level of hs-CRP as a predictor of CAD, and all of these studies were adjusted for at least some CAD risk factors. The combined multivariate adjusted odds relative risk was similar for hs-CRP 1.58 (OR, 1.58; 95% CI, 1.48–1.68; Danesh et al., 2004). In the Framingham Heart Study population, the significant correlation was observed between coronary artery calcium and hs-CRP, but after adjustment for BMI, and age, this correlation was week ($r < 0.19$, $p < 0.05$; Albert, Glynn, & Ridker, 2003). Although more studies have reported elevated levels of hs-CRP in serum in patients with CAD compared with those without CAD, this relationship was strong or modest, or not adjusted for other risk factors (Albert et al., 2003; Lassale et al., 2017).

In addition, we found that serum hs-CRP levels tended to increase in the presence of various traditional risk factors of CAD in the whole study patients. As expected, traditional risk factors were more prevalent among patients with elevated levels of hs-CRP in present study, which was accordant with previous studies (Avan et al., 2018; Sukhija et al., 2007). Although the exact interaction between serum hs-CRP to these risk factors remains not fully understood, a multiple interactive mechanism could be involved as activated macrophages in CAD lesions may release inflammatory factors (Sukhija et al., 2007; Zheng et al, 2010) This suggests that the apparent significant association of serum hs-CRP with CAD severity defined by coronary angiography is predominantly due to their association with traditional risk factors. Several investigators have reported the association between hs-CRP and CVD can be explained by the presence of traditional risk factors that are usually present among patients with CVD (Avan et al., 2018; Danesh et al., 2004; Sukhija et al., 2007).

ROC analysis showed that a serum hs-CRP can predict the extent of angiographically-defined CAD with 80.20% sensitivity, 85.00% specificity and 91.0% PPV, suggesting its value as a biomarker for predicting the severity of coronary artery disease. These data substantiate the concept that serum hs-CRP reflects both atherosclerotic progression and CAD development among patients with CAD (Avan et al., 2018; Zheng et al., 2010) Previous studies displayed an elevated of hs-CRP secretion was acceptable for patients at intermediate risk of CAD compared with other biomarkers, since CRP is strong independent predictor of CAD risk in first cardiovascular events from 10% to nearly 20% (Lubrano & Balzan, 2015; Shi et al., 2010). It is also of interest that the elevation level of hs-CRP predicts clinical outcomes in acute coronary syndromes and used to identify high-risk patients for more aggressive management with antiplatelet agents and statins (Kelly, Scanlan, McNally, Prichard, & Dodd, 2017; Nakou, Liberopoulos, Milionis, & Elisaf, 2008).

This study has several strengths. First, the sample size was relatively large, therefore, all group comparisons have power to detect significant differences for select variables. Second, this study is a case-control study of selected patients with and without cardiac

chest pain. Third, we performed a very extensive and detailed analysis (nutritional and psychological data) of coronary angiograms to detect any possible association with hs-CRP markers and severity of CAD. Finally, since, no such study has been done in Iran till now, the novelty of our study, its controversy concerning the effect of regional factors make the study distinguished.

There are several limitations of this study. First, using a self-report item to report sociodemographic characteristic, (family income, depression, and anxiety) which may have led to over-estimation or underestimation of mean scores. Second, CAD lesion progression involved complex mechanisms including thrombosis on the internal surface of vessel, therefore, characterization of severity of CAD needs more observation during long-term follow-up in this setting is promising for future studies. Finally, as individuals candidate for angiography were evaluated, the results of this study could not be generalized to the whole patients with CVD.

Understanding the association between increased serum hs-CRP and progression of CAD would extend our understanding of mechanisms of lesion progression and degree of obstruction in the coronary artery, and also the relation of hs-CRP to other risk factors of CAD. CAD progression, whether related to acute cardiovascular events or clinically silent, has been shown to be major predictor for cardiovascular mortality, thus, risk reduction and prevention of atherosclerosis progression could crucial to improve health outcomes for patients with CAD. Putting it in perspective, measurement of serum hs-CRP concentration is clinically useful to predict progression of CAD, and medical diagnosis including the severity of angiographically-proven CAD may be of prognostic significance among patients with CAD.

5 | CONCLUSION

Our results implies that the significant association of elevated serum hs-CRP with CAD severity on coronary angiography is could due to their association with coronary atherosclerosis and CAD traditional risk factors. Therefore, measurement of inflammation biomarker provides at best a progressive value in examining severity of CAD.

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CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

ETHICAL APPROVAL

Since this study is supposed to be done in Ghaem hospital, the researcher first obtained a letter from the Ethical Committee of Mashhad University of Medical Sciences (Ethics registration number: MUMS/900671) and then forwarded it to the Ethical Committee of Faculty of Medicine and Health Sciences, University Putra Malaysia ([FPSK/UPM/PADS/T7-[JKKFEB[11]01]). Afterward, this committee permitted the researcher to begin the study in Mashhad University of Medical Sciences.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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