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Original Article

Comparison of high sensitive C-reactive protein levels with other biomarkers in cardiovascular disease risk assessment

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Abstract: This study aimed to investigate the correlation of high sensitive C-reactive protein (hs-CRP) levels with other biomarkers which were used for cardiovascular disease (CVD) risk determination. The hs-CRP levels measured by immunonephelometry (Behring Nephelometer II, U.S.A.). Complete blood count parameters and biochemical parameters were determined by a fully automated hematology analyzer and automatic biochemical analyzer (Becman Coulter, U.S.A.). The hs-CRP levels were mostly correlated with erythrocyte sedimentation rate (ESR) and albumin levels. Significantly low hemoglobin (HGB) and hematocrit (HCT) levels were determined in patients with high CVD risk according to hs-CRP levels. High-neutrophil and low-lymphocyte levels were found to be more effective than total white blood cell (WBC) levels for CVD risk. Red cell distribution width (RDW) levels were found significantly higher in the high hs-CRP CVD risk group than in the low hs-CRP CVD risk group in only male patients. There was no significant association between low-density lipoprotein (LDL), high-density lipoprotein (HDL) and hs-CRP CVD risk values. In conclusion, according to our study, the hs-CRP was an effective biomarker that could be used to assess CVD risk with other conventional biomarkers. Hematologic and inflammatory parameters as ESR, albumin, HGB, HCT, neutrophil, lymphocyte and RDW should be accepted as indicative for CVD risk assessment in patients identified as high CVD risk group according to the hs-CRP test. Although LDL and HDL were accepted as classical biomarkers to evaluate CVD risk, new laboratory test parameters independent of LDL and HDL have to be taken into consideration for CVD risk determination.

Keywords: High sensitive C-reactive protein, biomarkers, cardiovascular diseases

Introduction

CVD is the important reason of mortality and morbidity in the world. Inflammatory processis-set up the pathophysiology in CVD. Detection of biomarkers which are associated with inflammation is at the forefront in CVD risk assessment [1]. Hs-CRP, an acute phase protein and a sensitive marker of systemic inflammation, is also an indicator to detect the risk of atherosclerosis and cardiovascular events in patients with CVD [2]. According to epidemiological data, the cut points for risk determination were demonstrated in the guidelines as low risk ≤ 1.0 mg/L, intermediate risk = 1.0-3.0 mg/L, and high risk ≥ 3.0 mg/L; the high-risk category is represented by an approximate twofold greater relative risk than the low-risk category [3]. Utilizing CRP in addition to inflammatory and biochemical biomarkers (like blood lipid and hematologic parameters) and standard risk factors (such as age, sex) have provided meaningful predictive value to future cardiovascular risk prediction in the patients without a family-history of CVD [4-6]. Although hs-CRP and conventional biomarkers have been used for CVD risk determination, few studies investigated the relationship between these laboratory parameters.

This study aimed to investigate the correlation and compatibility of hs-CRP levels with related biomarkers which were used for CVD risk determination in patients.

Material and methods

A retrospective observational cohort study was conducted at Bursa Yuksek Ihtisas Training and Research Hospital, Turkey, which is a tertiary

Table 1. Distribution of the parameters by sex

Variables	Female Mean ± Std Deviation	Male Mean ± Std Deviation	P
Age	61 ± 16	60 ± 13	0.405[a]
hs-CRP	7.0 ± 4.1	6.3 ± 4.1	0.175[b]
WBC	8.9 ± 3.7	9.4 ± 3.1	0.051[a]
RDW	15.4 ± 2.9	15.0 ± 2.3	0.033[a,*]
PLT	270 ± 113	272 ± 129	0.673[a]
TGC	166 ± 127	160 ± 103	0.770[a]
ESR	42 ± 28	34 ± 34	0.003[a,**]
Neutrophil (%)	65.8 ± 11.2	65.2 ± 11.0	0.719[b]
Lymphocyte (%)	24.1 ± 10.3	23.2 ± 10.0	0.554[b]
HGB	11.2 ± 1.8	12.4 ± 2.2	0.000[b,**]
HCT	34.6 ± 5.4	38.1 ± 6.6	0.000[b,**]
MPV	8.7 ± 1.1	8.5 ± 1.1	0.276[b]
Cholesterol	187 ± 57	174 ± 49	0.122[b]
LDL	115.5 ± 51.0	101.8 ± 34.3	0.089[b]
HDL	44 ± 9	38 ± 8	0.000[b,**]
Albumin	3.3 ± 0.5	3.3 ± 0.6	0.971[b]

[a]Mann Whitney U test *P* value, [b]Independent sample t test *P* value. *P < 0.05, **P < 0.01.

care hospital located in the South Marmara Region. We collected hematological and inflammatory parameters test results in blood samples of 200 patients who were diagnosed with atherosclerotic cardiac disease in June 2016, retrospectively. We included the patients with CVD diagnose and excluded the patients with otoimmun inflammatory disease like romatoid artrit to the study. The patients who were followed at the cardiology and cardiovascular surgery clinical departments, intensive care units and outpatient clinics were included in the study. The hs-CRP levels of patients were categorised according to CVD risk as high CVD risk, intermediate CVD risk and low CVD risk. We investigated the correlation of the hs-CRP levels with serum ESR and albumin as inflammatory biomarkers; WBC, neutrophil (%), lymphocyte (%), HGB, HCT, RDW, platelet (PLT) and mean platelet volume (MPV) as hematological parameters; LDL, HDL, total cholesterol and triglyceride (TGC) as serum lipid biomarkers. The hs-CRP levels measured by immunonephelometry (Behring Nephelometer II, Dade Behring, Inc., Newark, DE, U.S.A.). Complete blood count parameters were determined by a fully automated hematology analyzer (Becman Coulter LH780, USA). Biochemical parameters such as albumin, LDL, HDL, TGC, total cholesterol were measured by automatic biochemical analyzer (Beckman Coulter DXI 800, USA). ESR were measured by device ALS-100, Turkey. This study was approved by Yuksek ihtisas Training and Reseach Hospital reseach ethic comittee (ref: 2011-KAEK-25 2017/08-03).

Statistical analysis

Data were expressed by frequency or related percent values. Normality analyzes were done for data (N > 50) with Kolmogorov-Smirnov test. Comparison of the two groups were done with-independent sample T test for normally distributed parameters and Mann Whitney U test for non-normaly distributed parameters. Comparison of the more than two groups were done with One way anova and Welch tests for normally distributed parameters. Bonferroni and Dunnet'c tests were used for the analysis of the difference. Comparison of more than two groups were done with Kruskal-Wallis tests for non-normally distributed parameters. Correlation and regression analysis between the hs-CRP test and other laboratory tests with normally distribution was determined by Pearson test. Correlation and regression analysis between the hs-CRP tests and other laboratory tests with non-normally distribution was done by Spearman test. Analysis were done in SPSS programme. P < 0.05 and P < 0.01 were accepted as statistically significant.

Results

The comparison of the parameters by sex

The distribution of the parameters by sex was demonstrated in **Table 1**. The average levels of RDW, HDL and ESRwere found significantly higher in female patients than the male patients (P < 0.05). The average levels of HGB and HCT were found significantly lower in female patients than the male patients (P < 0.05). There were no significant differences in age, hs-CRP, WBC, PLT, TGC, neutrophil (%), lymphocyte (%), MPV, cholesterol, LDL, albumin levels according to sex.

Significantly different parameters by sex were evaluated according to hs-CRP CVD risk groups (**Table 2**). HGB and HCT levels were found significantly lower in the high hs-CRP CVD risk group than in the intermediate hs-CRP CVD risk group in female patients (P < 0.05). HGB and

Table 2. Comparison of the parameters according to hs-CRP CVD risk groups

Tests	hs-CRP levels	Female Mean ± Std deviation	P	Male Mean ± Std deviation	P
HGB	≤ 1 mg/L	11.9 ± 1.7	0.003[b,*]	13.8 ± 0.8	0.000[b,**]
	1-3 mg/L	12.5 ± 0.8		13.9 ± 1.5	
	> 3 mg/L	10.8 ± 1.8		11.7 ± 2.2	
HCT	≤ 1 mg/L	34.8 ± 7.1	0.002[b,*]	41.8 ± 2.4	0.000[b,**]
	1-3 mg/L	38.6 ± 2.3		42.9 ± 4.3	
	> 3 mg/L	33.4 ± 5.5		36.1 ± 6.7	
RDW	≤ 1 mg/L	15.2 ± 1.8	0.398[c]	13.8 ± 1.1	0.004[c,*]
	1-3 mg/L	14.3 ± 4.3		14.6±2.2	
	> 3 mg/L	15.8 ± 2.3		15.4 ± 2.4	
HDL	≤ 1 mg/L	55 ± 1	0.088[a]	41 ± 9	0.282[a]
	1-3 mg/L	46 ± 9		37 ± 5	
	> 3 mg/L	43 ± 8		38 ± 8	
ESR	≤ 1 mg/L	19 ± 15	0.000[c,**]	13 ± 9	0.000[c,**]
	1-3 mg/L	23 ± 19		12 ± 7	
	> 3 mg/L	51 ± 28		45 ± 36	

[a]One way anova test *P* value, [b]Welch test *P* value, [c]Kruskal Wallis test *P* value. [**]P < 0.01, [*]P < 0.05.

HCT levels were found significantly lower in the high hs-CRP CVD risk group than in the intermediate and low hs-CRP CVD risk groups in male patients (P < 0.01). ESR levels were significantly higher in the high hs-CRP CVD risk group than in the intermediate and low hs-CRP CVD risk groups in both female and male patients (P < 0.01). RDW levels were found significantly higher in the high hs-CRP CVD risk group than in the low hs-CRP CVD risk group in only male patients (P < 0.05). HDL levels did not differ between the hs-CRP CVD risk groups by sex.

The comparison of the parameters by hs-CRP CVD risk groups

Normally distributed parameters in statistical analysiswere compared according to the hs-CRP CVD risk groups (**Table 3A**). Neutrophil (%) levels were significantly higher in the high hs-CRP CVD risk group than in the intermediate hs-CRP CVD risk group (P < 0.01). Lymphocyte (%) levels were significantly lower in the high hs-CRP CVD risk group than in the intermediate hs-CRP CVD risk group (P < 0.01). HGB levelswere significantly lower in the high hs-CRP CVD risk group than in the intermediate and low hs-CRP CVD risk groups (P < 0.01). HCT levels were significantly lower in the high hs-CRP CVD risk group than in the intermediate and low hs-CRP CVD risk groups (P < 0.01). Albumin levels were significantly lower in the high hs-CRP risk group than in the intermediate and low hs-CRP CVD groups (P < 0.01). There were no significant differences in cholesterol, HDL, LDL and MPV levels according to the hs-CRP CVD risk groups.

Non-normally distributed parameters in statistical analysis were compared according to the hs-CRP CVD risk groups (**Table 3B**). WBC levels were significantly higher in the high hs-CRP CVD risk group than in the intermediate hs-CRP CVD risk group (P < 0.05). RDW levels were significantly higher in the high hs-CRP CVD risk group than in the intermediate and low hs-CRP CVD risk groups (P < 0.05). PLT levels were significantly higher in the high hs-CRP risk group than in the intermediate and low hs-CRP CVD risk groups (P < 0.05). TGC levels were significantly lower in the high hs-CRP CVD risk group than in the intermediate hs-CRP CVD risk group (P < 0.05). ESR levels were significantly higher in the high hs-CRP CVD risk group than in the intermediate and low hs-CRP CVD risk groups (P < 0.01).

The correlation of the hs-CRP and other biomarkers

Correlation and regression analysis between the hs-CRP and other laboratory tests was demostrated in **Table 4**. The hs-CRP levels were correlated positively with neutrophil (%), WBC, RDW, PLT and ESR levels (P < 0.01). The hs-CRP levels were correlated negatively with lymphocyte (%), HGB, HCT, albumin, triglyceride (P < 0.01) and cholesterol levels (P < 0.05). There were no significant correlation between HDL, LDL, MPV levels and the hs-CRP levels.

The influence of independent variables on the hs-CRP variable was examined by simple linear-regression analyzes (**Table 5**). Neutrophil (%) was individually correlated with the hs-CRP by 17.1% positively (P < 0.05). Lymphocyte (%) was individually correlated with the hs-CRP by 19.0% negatively (P < 0.05). HGB was individually correlated with the hs-CRP by 33.0% negatively (P < 0.05). HCT was individually correlat-

Table 3A. Comparison of normally distributed laboratory tests in statistical analyses according to hs-CRP CVD risk groups

Tests	hs-CRP levels	N	Mean ± Std. Deviation	P
Cholesterol	< 1 mg/L	18	191.2 ± 49.2	0.210[a]
	1-3 mg/L	35	187.0 ± 56.4	
	> 3 mg/L	97	172.9 ± 50.7	
	Total	150	178.4 ± 52.1	
LDL	< 1 mg/L	17	111.1 ± 40.8	0.342[a]
	1-3 mg/L	35	114.2 ± 53.0	
	> 3 mg/L	95	102.9 ± 36.0	
	Total	147	106.5 ± 41.2	
HDL	< 1 mg/L	18	42.1 ± 9.8	0.402[a]
	1-3 mg/L	35	40.8 ± 8.5	
	> 3 mg/L	97	39.4 ± 8.2	
	Total	150	40.1 ± 8.5	
MPV	< 1 mg/L	20	9.0 ± 0.8	0.112[a]
	1-3 mg/L	40	8.6 ± 1.1	
	> 3 mg/L	138	8.4 ± 1.1	
	Total	198	8.5 ± 1.1	
Neutrophil (%)	< 1 mg/L	20	60.9 ± 15.6	0.000[b,*]
	1-3 mg/L	40	58.9 ± 8.0	
	> 3 mg/L	138	67.9 ± 10.0	
	Total	198	65.4 ± 11.0	
Lymphocyte (%)	< 1 mg/L	20	27.6 ± 14.5	0.000[b,*]
	1-3 mg/L	40	30.1 ± 7.5	
	> 3 mg/L	138	21.0 ± 8.8	
	Total	198	23.5 ± 10.0	
HGB	< 1 mg/L	20	13.4 ± 1.2	0.000[b,*]
	1-3 mg/L	40	13.3 ± 1.4	
	> 3 mg/L	138	11.3 ± 2.0	
	Total	198	11.9 ± 2.1	
HCT	< 1 mg/L	20	40.4 ± 4.5	0.000[b,*]
	1-3 mg/L	40	41.0 ± 4.1	
	> 3 mg/L	138	35.0 ± 6.3	
	Total	198	36.7 ± 6.3	
Albumin	< 1 mg/L	12	3.7 ± 0.2	0.000[b,*]
	1-3 mg/L	23	3.7 ± 0.5	
	> 3 mg/L	90	3.1 ± 0.4	
	Total	125	3.326 ± 0.5474	

[a]One way anova test *P* value, [b]Welch test *P* value. *P < 0.01.

ed with the hs-CRP by 31.3% negatively (P < 0.05). Cholesterol was individually correlated with the hs-CRP by 4.0% negatively (P < 0.05). Albumin was individually correlated with the hs-CRP by 37.0% negatively (P < 0.05). WBC was individually correlated with the hs-CRP by 4.6% positively (P < 0.05). RDW was individually correlated with the hs-CRP by 5.1% positively (P < 0.05). PLT was individually correlated with the hs-CRP by 8.6% positively (P < 0.05). Triglyceride was individually correlated with the hs-CRP by 3.0% negatively (P < 0.05). ESR was individually correlated with the hs-CRP by 38.5% positively (P < 0.05).

Discussion

Several studies explained that inflammatory biomarkers, especially ESR, play a role in the process of atherosclerosis and adverse cardiovascular events [7, 8]. In addition, low serum albumin levels were demonstrated as the risk factor of myocardial infarction and cardiovascular disease [9-11]. The ESR, one of the inflammatory marker, was found to be higher in the high hs-CRP CVD risk group than in the intermediate and low hs-CRP CVD risk groups in our study. Also albumin, an acute phase reactant, was found lower in the high hs-CRP CVD risk group than in the intermediate and low hs-CRP CVD risk groups in our study. While ESR levels were alone correlated with the hs-CRP levels by 38.5% in the same direction, albumin levels were correlated with the hs-CRP levels by 37% in the opposite direction. The hs-CRP levels were correlated with ESR and albumin levels the most according to our study. While using the hs-CRP test as a CVD risk indicator, it would be more useful to evaluate hs-CRP levels with ESR and albumin levels. However, ESR and albumin were the nonspecific markers of inflammation and could be associated with other factors. As a result, ESR and albumin have to be evaluated with concomitant clinical findings [8].

We investigated the association between the components of the complete blood count and hs-CRP levels to evaluate the risk of cardiovascular disease. According to the review, high white blood cell counts with high-neutrophil and low-lymphocyte counts, were comparable toinflammatory biomarkers including CRP, ESR and other components of the complete blood count such as HGB, HCT and RDW which were associated with CVD risk [12]. Several studies demonstrated that anemia, in additionto low hemoglobin and hemato-

Table 3B. Comparison of non-normally distributed laboratory tests in statistical analyses according to hs-CRP CVD risk groups

Tests	hs-CRP levels	N	Mean ± Std. Deviation	P
WBC	< 1 mg/L	20	8.8 ± 3.7	0.021[a,*]
	1-3 mg/L	40	8.1 ± 2.1	
	> 3 mg/L	138	9.5 ± 3.5	
	Total	198	9.2 ± 3.3	
RDW	< 1 mg/L	20	14.1 ± 1.3	0.002[a,*]
	1-3 mg/L	40	14.5 ± 3.2	
	> 3 mg/L	138	15.5 ± 2.3	
	Total	198	15.2 ± 2.5	
PLT	< 1 mg/L	20	211 ± 53	0.003[a,*]
	1-3 mg/L	40	228 ± 58	
	> 3 mg/L	138	293 ± 137	
	Total	198	271 ± 122	
TGC	< 1 mg/L	20	199 ± 143	0.032[a,*]
	1-3 mg/L	40	170 ± 77	
	> 3 mg/L	138	153 ± 115	
	Total	198	162 ± 112	
ESR	< 1 mg/L	20	15 ± 10	0.000[a,*]
	1-3 mg/L	40	17 ± 14	
	> 3 mg/L	138	47 ± 33	
	Total	198	37 ± 32	

[a]Kruskall Wallis test *P* value. *P < 0.01.

crit levels, was the significant risk factor for heart diseases and associated with worsened symptoms and increased morbidity and mortality in patients with chronic cardiac diseases [13-17]. HGB and HCT levels were found to be lower in the high hs-CRP CVD risk group than in the intermediate and low hs-CRP CVD risk groups in our study. Also the HGB levels were alone correlated with the hs-CRP levels by 33.0% and HCT levels were correlated with the hs-CRP levels by 31.3% in the opposite direction. According to our study, significantly low HGB and HCT levels in the high hs-CRP CVD risk group, were promoted the importance of regulating hemoglobin and hematocrit levels in order to reduce cardiac disease risk in male and female patients.

WBC and neutrophil (%) levels were found significantly higher in the high hs-CRP CVD risk group than the intermediate hs-CRP CVD risk group; but lymphocyte (%) levels were found significantly lower in high hs-CRP CVD risk group than the intermediate hs-CRP CVD risk group in our study. Individually, neutrophil (%) levels were correlated with the hs-CRP by 17.1% in the positive direction; lymphocyte (%) levels were correlated withthe hs-CRP by 19% in negative direction and WBC levels were correlated withthe hs-CRP by 4.6% in the positive direction. Most prospective cohort studies showed that elevated WBC total levels, especially high neutrophils levels and low lymphocytes levels, have been indicated an increased risk for major cardiovascular adverse events [18-20]. According to our study, high-neutrophil and low-lymphocyte levels were found to be more effective than total WBC levels to determine CVD risk in patients.

Increased RDW levels that reflect size heterogeneity of the erythrocytes in the circulation were shown as associated with heart failure, coronary artery disease and death [21, 22]. Despite this, the association of platelet count with CVD was not clear, especially platelet's role in CVD was about their functional [12, 23, 24]. RDW and PLT levels were found higher in the high hs-CRPCVD risk group than the intermediate and low hs-CRP CVD risk groups in our study. Also RDW levels were correlated with hs-CRP levels by 5.1% and PLT levels were correlated with hs-CRP levels by 8.6% in the positive direction, individually. In addition, RDWlevels were found significantly higher in the high hs-CRP CVD risk group than the low hs-CRP CVD risk group in only male patients. In conclusion; RDW, especially in male patients, was an important parameter that could be used for CVD risk evaluation with hs-CRP.

Although high levels of LDL and hs-CRP were associated with an increased risk of cardivascular diseases, several large scale studies demonstrated that elevated hs-CRP levels with low LDL levels can be accepted a risk factor for future atherosclerosis [25]. There was not found any significant association between LDL, HDL and hs-CRP CVD risk valuesin our study, but the hs-CRP, were correlated with cholesterol levels (4%) and triglyceride levels (3%) in the opposite direction. According to recent studies, triglyceride were the independent determinant of CVD risk, moreover the effect of standard CVD risk factors, including other lipid and lipoprotein parameters are controversial [26, 27]. Our study substantiated that, elevated hs-CRP levels could help to diagnosethe CVD risk also in the patients whose blood lipid levels are not predictive of CVD risk [28]. Besides, hs-CRP lev-

Table 4. Correlation analysis between the hs-CRP test and other laboratory tests

Tests	1	2	3	4	5	6	7	8	9	10
hs-CRP	1[a,b]									
Neutrophil (%)	,413[a,**]	1[a]								
Lymphocyte (%)	-,436[a,**]	-,920[a,**]	1[a]							
HGB	-,575[a,**]	-,394[a,**]	,442[a,**]	1[a]						
HCT	-,560[a,**]	-,382[a,**]	,436[a,**]	,982[a,**]	1[a]					
Cholesterol	-,201[a,*]	-,249[a,**]	,294[a,**]	,227[a,**]	,206[a,*]	1[a]				
LDL	-,147[a]	-,210[a,*]	,250[a,**]	,195[a,*]	,177[a,*]	,852[a,**]	1[a]			
HDL	-,119[a]	-,088[a]	,140[a]	-,070[a]	-,078[a]	,255[a,**]	,198[a,*]	1[a]		
Albumin	-,609[a,**]	-,295[a,**]	,360[a,**]	,625[a,**]	,642[a,**]	,342[a,**]	,345[a,**]	,218[a*]	1[a]	
MPV	-,082[a]	,088[a]	-,064[a]	,043[a]	,048[a]	,180[a,*]	,231[a,**]	,072[a]	,069[a]	1[a]
WBC	,250[b,**]	1[b]								
RDW	,283[b,**]	-,046[b]	1[b]							
PLT	,236[b,**]	,225[b,**]	,001[b]	1[b]						
TGC	-,243[b,**]	,007[b]	-,262[b,**]	,039[b]	1[b]					
ESR	,642[b,**]	,136[b]	,141[b]	,252[b,**]	-,128[b]	1[b]				

[a]Pearson test value, [b]Spearman test value. **P < 0.01 *P < 0.05.

Table 5. Simple regression model explaining the effect of independent variables on hs-CRP variable

İndependent variable	Unstandardized Coefficients		Standardized Coefficients	t	P	R^2
	B	Std. Error	Beta			
Neutrophil (%)	,154	,024	,413	6,356	,000	%17,1
Lymphocyte (%)	-,179	,026	-,436	-6,791	,000	%19,0
HGB	-1,122	,114	-,575	-9,834	,000	%33,0
HCT	-,362	,038	-,560	-9,458	,000	%31,3
Cholesterol	-,016	,006	-,201	-2,496	,014	%4,0
Albumin	-4,548	,535	-,609	-8,506	,000	%37,0
WBC	,268	,087	,215	3,082	,002	%4,6
RDW	,372	,114	,227	3,258	,001	%5,1
PLT	,010	,002	,294	4,302	,000	%8,6
TGC	-,006	,003	-,174	2,146	,033	%3,0
ESR	,080	,008	,621	10,533	,000	%38,5

els were not associated withblood lipidparameter changes in CVD risk assessment of the patients. In conclusion, it was necessary to develop new parameters leading to detect CVD risk by the studies including genetic and proteomic methods [29, 30].

The limitations in our study; the parameters were non specific in CVD determination and could be effected by many concomitant diagnosis like infection; also there were not any available data about the number of drugs taken by each patient, especially statins for hiperlipidemia treatment.

In conclusion, according to our study, the hs-CRP was an effective biomarker that could be used to assess CVD risk with other conventional biomarkers. Hematologic and inflammatory parameters as ESR, albumin, HGB, HCT, neutrophil, lymphocyte, RDW should be accepted as indicative for CVD risk assessment in patients identified as high CVD risk group according to the hs-CRP test. Although LDL and HDL were accepted as classical biomarkers to evaluate CVD risk, new laboratory test parameters independent of LDL and HDL have to be taken into consideration for CVD risk determination.

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Disclosure of conflict of interest

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