

## Analysis of C reactive protein and other inflammatory markers in the cardiovascular risk prediction in women

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### ABSTRACT

**Objective:** To evaluate the role of C Reactive Protein and other inflammatory markers in cardiovascular risk prediction.

**Study Design:** A prospective case-control study.

**Place and Duration:** At Cardiology Department of Nishtar Medical University & Hospital Multan from 5<sup>th</sup> Oct 2020 to 5<sup>th</sup> Oct 2021.

**Methodology:** A total of 150 postmenopausal women were studied and divided into CVD patients (n=50) and control patients (n=100). The analyzed markers of inflammation included Interleukin-6, high-sensitivity C-reactive Protein, Soluble ICAM-1 (sICAM-1), and Amyloid-A. The Homocysteine, Lipid Profile, and Low and High-density lipoprotein levels were also evaluated. Cardiovascular events considered in our study were death after coronary artery disease, non-fatal heart attack or stroke, or requiring coronary-revascularization methods.

**Results:** In univariate analysis, it was observed that high-sensitivity C-reactive protein levels were the strongest risk predictor of cardiovascular diseases. Amyloid-A, High-density lipoprotein, Cholesterol, Low-density lipoprotein cholesterol, Soluble ICAM-1, Interleukin-6, Apolipoprotein B-100, Homocysteine, total cholesterol, and the ratio of total cholesterol to high-density lipoprotein cholesterol also contributed to predicting cardiovascular diseases. High-sensitivity C-reactive protein (95% CI: 1.4(1.0-2.0)) and Amyloid-A (95% CI: 0.9(0.7-1.5)) were also strong risk predictors in women. On the other hand, in multivariate analyses, only High-sensitivity C-reactive protein and the ratio of total cholesterol to high-density lipoprotein cholesterol were independent risk predictors.

**Conclusion:** As high-sensitivity CRP is an independent cardiovascular risk predictor, adding it to lipid screening may be a good procedure for identifying women at risk of cardiovascular diseases.

**Keywords:** High sensitivity C-reactive protein, Cardiovascular events, Amyloid-A, Lipids, Inflammatory markers

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### INTRODUCTION

People suffering from most myocardial infarctions generally have normal plasma lipid levels<sup>1</sup>. To predict the risk of

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cardiovascular diseases, various screening markers are used such as fibrinolytic capacity, levels of Lipoprotein(a), homocysteine, fibrinogen levels, and apolipoprotein A-I, B-100. But these markers have not been used much clinically due to failure of standardization of assay procedures, variability of probable data, or limited supporting data of significance of these markers against standard lipid screening<sup>2</sup>.

As atherosclerosis has been recognized as an inflammatory process<sup>3</sup>, it has been evaluated that various plasma markers of inflammation can be used to predict the risk of coronary diseases. These markers include systemic inflammatory markers, like high-sensitivity C-reactive protein (hs-CRP) and cytokines including interleukin-6; amyloid A; and cell adhesion molecules like Soluble ICAM-1 (sICAM-1)<sup>4</sup>. As compared to other risk determinants of cardiovascular (CVS) diseases, the status of these inflammatory markers as prognostic factors is unknown. Constant variations have been noted in the levels of inflammation markers so the risk cannot be predicted accurately. Most of the studies conducted to measure the effect of inflammation markers were conducted on patients with similar characteristics, so relative risk prediction by each marker was not easy<sup>5,6</sup>.

Moreover, very little supporting data is available to prove that inflammatory markers improve the standard lipid screening

procedure. In addition, the clinical application of these hypotheses is limited as the standardization of assays for these inflammatory markers is still underdeveloped. The evaluation of markers has mostly been done in middle-aged men which revealed that CRP is a reliable predictor of CVS diseases in smokers, incident cardiovascular events in older people, and also predicts recurrence of cardiovascular events in people who have suffered incident cardiovascular diseases<sup>7-9</sup>. In this study, we assessed the comparative values of inflammatory markers as risk predictors of cardiovascular diseases in women. This study was planned to test the hypothesis that inflammatory markers including CRP improved the standard lipid screening process and acted as risk predictors of cardiovascular diseases. So this study was conducted with an objective to evaluate the role of C Reactive Protein and other inflammatory markers in predicting risk of CVS events.

### METHODOLOGY

This prospective case-control study was conducted in the Department of Cardiology of Nishtar Medical University & Hospital, Multan from 5<sup>th</sup> Oct 2020 to 5<sup>th</sup> Oct 2021. A total of 150 healthy, postmenopausal women were included in the study. The study included women who had a history of cardiovascular diseases in the past 3 years whereas the women who suffered cardiovascular disorders more than 3 years ago were excluded from the study. Baseline characteristics were inquired from each patient.

Myocardial infarction was reaffirmed by testing against the standards of the World Health Organization (WHO)<sup>10</sup> and if abnormal cardiac enzyme levels were observed or their diagnostic ECGs were noted. If a new neurologic deficit was observed in patients that lasted more than 24 hrs, stroke was confirmed. CT scans or MRI images were present of women with confirmed stroke. Hospital records were scanned for confirmation of coronary revascularization. Baseline blood was drawn in EDTA tubes of all study patients and was kept aside with liquid nitrogen until further use. For every woman with confirmed cardiovascular disease, two control patients of the same age and lifestyle were selected from patients who were not diagnosed with any cardiovascular event. In this way, there were 50 CVD patients (women diagnosed with cardiovascular diseases) and 100 control patients (healthy women) included in the study.

Base-line plasma samples of all the patients (both study and control patients) were assayed for high-sensitivity C-reactive protein, Lipoprotein(a), and Amyloid A. An immunoassay was done to simultaneously measure apolipoprotein A-I, B-100. Total cholesterol, high-density lipoprotein cholesterol, and directly obtained Low-density lipoprotein cholesterol levels were also measured by adding reagents. Enzyme-linked immunosorbent assay and IMx homocysteine assay were used to calculate sICAM-1 and interleukin-6 levels and the total plasma homocysteine level, respectively<sup>11</sup>.

**Data Analysis:** All data were analyzed by using SPSS version 21. All variables had a two-tail p-value and a probability value of 0.05 denoted statistical significance. T-test and Pearson's Chi-

squared test were performed to evaluate the significance of differences in means between the two groups and the significance of differences in proportions, respectively. Trends analysis was opted to evaluate the relationship between increasing levels of variables and subsequent cardiovascular risk. Logistic models were used to obtain adjusted risk estimates.

### RESULTS

A total of 150 postmenopausal women were included in the study. The baseline characteristics of study patients and control patients are presented in Table I. It was observed that CVD patients (women diagnosed with cardiovascular diseases) had a high rate of hypertension, history of myocardial infarction, and diabetes. However, the exercise frequency, consumption of alcohol, and use of hormone replacement therapy did not vary significantly in both groups. Due to matching the age of both groups were also similar.

**Table I: Baseline data of participants (N=150)**

Characteristics	CVD patients (50)	Control patients (100)	P-value
Mean age (years)	57.2	57.2	-
Mean weight (kg/m <sup>2</sup> )	26.5	25.0	0.02
History of hypertension (%)	25 (50%)	30 (30%)	0.001
Diabetic history (%)	4 (8%)	2 (2%)	0.001
Family history of myocardial infarction (%)	9 (18%)	10 (10%)	0.02
Frequency of exercise (%)			0.7
> times per week	3 (6%)	8 (8%)	
1-3 times per week	13 (26%)	26 (26%)	
<1 per week	10 (20%)	21 (21%)	
Never	22 (44%)	46 (46%)	
Alcohol consumption (%)			0.4
Daily	-	-	
Once a week	-	-	
Once a month	2 (4%)	-	
Never	48 (96%)	100	
Ongoing hormone replacement therapy (%)	22 (44%)	39 (39%)	0.1

Table II shows that the baseline plasma levels of marks of inflammation high-sensitivity C-reactive protein, amyloid A, Soluble ICAM-1, and interleukin-6 were increased in study patients than in control patients. The same results were observed when plasma levels of total cholesterol, Low-density lipoprotein cholesterol, apolipoprotein B-100, and homocysteine and the ratio of total cholesterol to high-density lipoprotein cholesterol were evaluated. High-density lipoprotein cholesterol was however lower in women in the study group than women in the control group. Lipoprotein (a) plasma levels were higher in the study group and apolipoprotein A-I levels were lower in study patients, but these levels did not differ significantly in both groups.

Table III shows logistic regression analysis to independently determine the predictive capacity of inflammatory markers. It was observed that high-sensitivity CRP level and the ratio of total cholesterol to high-density lipoprotein cholesterol were

independent risk predictors of risk where matching between groups was done or in models that included variation for body weight, and hypertension, diabetes, and history of myocardial infarction. High-sensitivity C-reactive protein remained a significant cardiovascular risk predictor in models only evaluating inflammatory markers. In addition, amyloid A, Soluble ICAM-1, and interleukin-6 were also risk predictors of cardiovascular diseases.

**Table II: Base-Line Values of Lipids and Inflammatory Markers**

Variable	CVD patients	Control patients	P-value
Median hs-CRP (mg/dl)	0.39	0.25	<0.001
Median amyloid A (mg/dl)	.59	.49	.002
Soluble ICAM-1 (ng/ml)	338.8±119.1	318.0±105.2	0.02
Median interleukin-6 (pg/ml)	1.59	1.28	0.002
Total cholesterol (mg/dl)	228.5±39.1	218.1±35.3	0.01
Low-density lipoprotein cholesterol (mg/dl)	129.1±32.4	119.3±28.1	0.002
high-density lipoprotein cholesterol (mg/dl)	42.2±12.4	49.0±13.2	<0.001
Apolipoprotein A-I (mg/dl)	159.6±39.1	166.2±32.1	0.2
Apolipoprotein B-100 (mg/dl)	125.3±29.3	113.2±24.5	<0.001
Median Lipoprotein(a) (mg/liter)	77	72	0.2
The ratio of total cholesterol to high-density lipoprotein cholesterol	4.9±1.5	3.7±1.2	<0.001
Homocysteine (µmol/liter)	13.7±7.7	11.8±5.5	0.01

**Table III: Relative Cardiovascular Risk with Increase in Marker Concentration**

Variable	Adjusted For Other Plasma Markers		Adjusted For Other Plasma Markers and Risk Factor	
	Relative risk (95% CI)	P-value	Relative risk (95% CI)	P-value
Hs-CRP	1.2 (1.1-1.8)	0.01	1.4(1.0-2.0)	0.01
Amyloid A	0.9(0.7-0.3)	0.4	0.9(0.7-1.5)	0.3
Soluble ICAM-1	0.9(0.8-1.3)	0.3	1.0(0.7-1.3)	0.5
Interleukin-6	0.8(0.6-1.1)	0.5	0.7(0.5-1.0)	0.1
Homocysteine	0.9(0.8-1.3)	0.1	0.9(0.7-1.3)	0.5
Lipoprotein(a)	0.9(0.8-1.2)	0.5	0.9(0.7-1.1)	0.7
The ratio of total cholesterol to high-density lipoprotein cholesterol	1.3(1.0-1.6)	0.01	1.3(1.0-1.8)	0.01

**DISCUSSION**

This study aimed to test the applications of inflammatory markers in cardiovascular risk prediction. Results showed that high sensitivity C-reactive protein, amyloid A, Soluble ICAM-1, and interleukin-6 were risk predictors of cardiovascular diseases in the study participants. When the logistic-regression model was only limited to these markers, hs-CRP showed positive results as a

predicting factor. This marker also helped in categorizing women at low risk and high risk of cardiovascular diseases.

Our study drew the following conclusions. As previous data collected on middle-aged men<sup>6,12-16</sup>, our study indicated that inflammatory markers are significant risk predictors of cardiovascular diseases in women, too. Our results also confirm the hypothesis that atherosclerosis is to some degree, an inflammatory condition. We assayed the hs-CRP plasma levels using an inexpensive commercial assay<sup>17</sup>, which shows that screening of these markers is not only practical but can also be used in standard laboratories and hospitals. The results of our study are not only helpful in the prediction of cardiovascular diseases but also in the use of (HMG-CoA) reductase for initial precautions. Some randomized studies have supported the efficacy of HMG-CoA reductase inhibition in patients with low-to-moderate cardiovascular risk<sup>18, 19</sup>, but this approach is costly which limits its clinical applicability. Therefore, our conclusion that high-sensitivity CRP is a cardiovascular risk predictor may also assist in identifying patients who can take advantage of primary prevention. A trial of Cholesterol and Recurrent Events concluded that hs-CRP plasma levels are lowered by long-term pravastatin therapy<sup>20</sup> and this therapy is effective in lowering the cardiovascular risk in patients with high hs-CRP levels. According to our study, the predictive ability of hs-CRP does not depend upon Low-density lipoprotein cholesterol level. Cholesterol and Recurrent Events trial also concluded that pravastatin therapy leads to high-sensitivity C-reactive protein levels and it is regardless of Low-density lipoprotein cholesterol<sup>21, 22</sup>.

The women included in our study were heavier and had a family history of myocardial infarction and diabetes, all these conditions were associated with high levels of CRP and therefore suggest that CRP is a strong predictor of the risk of these conditions. Our results correspond to the results of other studies<sup>6, 7, 23-25</sup>.

In our study, no significant relationship was observed between hs-CRP levels and BMI of the patients. However, in other studies, a positive association was observed between these variables<sup>26-28</sup>. We found that the reason for this observation could be malnutrition-inflammation syndrome. Due to this syndrome, inflammation in the body leads to low BMI levels and decreased risk of cardiovascular diseases. This inflammation causes an increase in inflammatory markers especially hs-CRP mostly found in heavier patients<sup>29</sup>. Further research is needed to investigate the association between the markers and the BMI levels to accurately predict cardiovascular risks. Our study had some limitations. We only included postmenopausal women, so our study may not be very helpful to young women. Secondly, we only analyzed inflammatory markers when participants were admitted so we did not assess the effects of markers by time.

**CONCLUSION**

As high-sensitivity C-reactive protein is an independent cardiovascular risk predictor, adding it to lipid screening may be a good procedure for identifying women at risk of cardiovascular diseases.

## AUTHOR'S CONTRIBUTION

**Shahid M:** Conceived idea, Designed methodology, Data analysis, Manuscript writing, Final critical review of the manuscript

**Ali L:** Manuscript writing, Data analysis, Data collection, Literature review

**Kabir HA:** Manuscript writing, Data compilation and analysis, Literature review

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**Conflict of Interest:** None.

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