

## Relationship between C-Reactive Protein and Cardiovascular Diseases in Patient with ESRD

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### Abstract

**Background-** Cardiovascular mortality is significantly higher in ESRD patient. There are various risk factors for development of cardiovascular diseases including traditional risk factors, factors unique to ESRD patients and emerging risk factors. It is believed that their combined actions are integrated in the progression of atherosclerosis and inflammation plays a central role. C-reactive protein is a valuable marker of inflammation. Determination of serum c-reactive protein levels may be a useful predictor of cardiovascular diseases in ESRD patients

**Objective-** To find out relationship between c-reactive protein and cardiovascular diseases.

**Methods-** This cross sectional study was carried out into department of Nephrology, Dhaka Medical College Hospital, Bangladesh following fulfillment of inclusion and exclusion criteria. For analytical purpose total study population were divided into two groups on the basis of c-reactive protein level. Patients having c-reactive protein  $\leq 6$  mg/L were considered as group A and  $>6$  mg/L were considered as Group B. The differences between groups were analyzed by unpaired t-test, fisher's exact test or chi-square ( $X^2$ ) test. Multivariable regression analysis was done to see the association between c-reactive protein and cardiovascular diseases.

**Results-** Patients with raise c-reactive protein have significantly higher cardiovascular disease than that of normal c-reactive protein. Multivariable linear regression analysis after adjusting for age, sex, smoking and diabetes shows that subject with CRP  $\leq 6$  mg/L vs  $>6$  mg/L had 1.51 (95% CI 1.02 to 2.19) times increase risk of having cardiovascular disease.

**Conclusion-** Inflammatory process has a role in development of cardiovascular diseases in ESRD patient.

### Key Words:

ESRD, C-reactive protein, Cardiovascular diseases.

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### Introduction

The mortality of patients with end stage renal disease (ESRD) remains high, with most deaths resulting from cardiovascular disease<sup>1</sup>. Several authors<sup>2,3</sup> have found that overall mortality and cardiovascular mortality were

significantly higher in hemodialysis patients with elevated c-reactive protein. There are several risk factors for development of cardiovascular diseases in ESRD patients. These are traditional risk factors including age, sex, hypertension, diabetes, smoking, hypercholesterolaemia. Factors unique to ESRD patients are anemia, elevated calcium-phosphorus product. And emerging risk factors include inflammation, hyperhomocystenaemia and accumulation of endogenous inhibitors of nitric oxide synthase. It is believed that their combined actions are integrated in the progression of atherosclerosis<sup>4</sup> and inflammation plays a central role. C-reactive protein is a valuable marker of inflammation. There are many clinical and experimental studies have shown that c-reactive protein may contribute directly to the pathogenesis of atherosclerosis and its complications<sup>5</sup>. Increase c-reactive protein is a strong risk factor for death within one year in patient with chronic kidney disease<sup>6</sup>. Furthermore,

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elevated c-reactive protein levels have been identified as a risk factor for cardiovascular disease in healthy men<sup>7</sup>. Statistical modeling, calculation of relative risk and cost considerations indicate that determination of serum c-reactive protein levels may be a useful predictor of cardiovascular diseases in ESRD patients<sup>4</sup>.

### Methods

This cross sectional study was carried out into the Department of Nephrology, Dhaka Medical College Hospital, Dhaka in the period December 2012 to November 2013 following fulfillment of inclusion and exclusion criteria. An informed written consent from patient was taken. Every patient had gone through detailed history taking- particulars of the patients and medical history includes patient had acute and chronic infection, malignancy, on any anti-inflammatory drugs, renal transplant recipient, had coronary artery diseases or other cardiovascular diseases. Meticulous physical examination was done.

Newly diagnosed ESRD patients were examined after admission into hospital and before undergo dialysis whereas on maintenance hemodialysis patients were examined just after dialysis. Laboratory investigations like hemoglobin concentration, serum creatinine, c-reactive protein, ECG, ECHO were done.

Statistical analyses were performed by using SPSS 16.0 (Statistical Package for Social Science, Inc., Chicago, IL, USA). Continuous variables were expressed as means  $\pm$  standard deviation and categorical variables as frequencies and proportions. For analytical purpose total study population were divided into two groups on the basis of c-reactive protein level. Patients having c-reactive protein  $\leq 6$  mg/L were considered as group A and  $>6$  mg/L were considered as Group B.

The differences between groups were analyzed by unpaired t-test, fisher' exact test or chi-square ( $X^2$ ) test. Multivariable regression analysis was done to see the association between c-reactive protein and cardiovascular diseases.

### Results

The study included 98 ESRD patients. Study population was divided into two groups. Group A comprises those who had c-reactive protein  $<6$  mg/L and Group B comprises those had c-reactive protein  $>6$  mg/L. Group A belonged 23 patients and group B belonged 75 patients. Majority of the patients (39.1%) were age belonged to 31-40 years in group A and in group B majority (30.7%) belong to 51-60

years. About three fourth (73.9%) patients were male in group A and 68% in group B. Out of 98 patients 64.29% patients were unemployed and 61.2% patients reside in rural area. Smoker were found to be 21.7% in group A and 42.7% in group B. Glomerulonephritis was the leading cause of ESRD followed by diabetes mellitus with or without hypertension and others.

Hypertensive were found to be 78.3% in group A and 98.7% in group B, diabetic were 8.7% in group A and 33.3% in group B whereas cardiovascular disease was present 13% patient in group A and 100% patient in group B. Differences between two groups were statistically significant ( $p= 0.002, 0.020, 0.001$  respectively). Regarding type of cardiovascular diseases, most of the patient had left ventricular hypertrophy and it was found to be 13% in group A and 37.3% in group B followed by ischemic heart disease, left ventricular failure and others. Multivariable linear regression analysis after adjusting for age, sex, smoking and diabetes shows that subject with CRP  $\geq 6$  mg/L vs  $>6$  mg/L had 1.51 (95% CI 1.02 to 2.19) times increase risk of having cardiovascular disease.

**Table I**

*Age distribution of the study patients and relation with CRP (n=98).*

Age (in year)	Group A(n=23)		Group B(n=75)		P value
	n	%	n	%	
$\leq 20$	0	0.0	1	1.3	
21-30	6	26.1	12	16.0	
31-40	9	39.1	11	14.65	
41-50	5	21.7	20	26.7	
51-60	1	4.3	23	30.7	
$>60$	2	8.7	8	10.65	
Mean $\pm$ SD	38.61 $\pm$ 11.5		46.55 $\pm$ 13.1		0.010 <sup>s</sup>
Range (min-max)	24-65.0		19-75.0		

s=significant

P value reached from unpaired t-test

Table I shows that majority (39.1%) patients were age belonged to 31-40 years in group A and 23(30.7%) in group B belong to 51-60 years. The mean age was found 38.61 $\pm$ 11.5 years in group A and 46.55 $\pm$ 13.1 years in group B. The mean age difference was statistically significant ( $p<0.05$ ) between two groups.

**Table II**

*Distribution of the study patients by smoking status and relation with CRP (n=98).*

Smoker	Group A(n=23)		Group B(n=75)		P value
	n	%	n	%	
Yes	5	21.7	32	42.7	0.070 <sup>ns</sup>
None	18	78.3	43	57.3	

ns= not significant

P value reached from chi square test

Table II shows that 5(21.7%) were smoker in group A and 32(42.7%) in group B. The difference was not statistically significant ( $p>0.05$ ) between two groups.

**Table III**

*Distribution of the study patients by etiology of ESRD and relation with CRP (n=98).*

Etiology of ESRD	Group A(n=23)		Group B(n=75)		P value
	n	%	n	%	
GN	18	78.3	32	42.7	0.002 <sup>s</sup>
HTN	2	8.7	16	21.3	0.142 <sup>ns</sup>
DM	1	4.3	6	8.0	0.478 <sup>ns</sup>
DM & HTN	1	4.3	18	24.0	0.028 <sup>s</sup>
ADPKD	1	4.3	3	4.0	0.663 <sup>ns</sup>

s= significant, ns= not significant

P value reached from chi square test.

Table III shows that GN were found 18(78.3%) in group A and 32(42.7%) in group B. HTN were found 2(8.7%) in group A and 16(21.3%) in group B. DM were found 1(4.3%) in group A and 6(8.0%) in group B. DM & HTN were found 1(4.3%) in group A and 18(24.0%) in group B. ADPKD were found 1(4.3%) in group A and 3(4.0%) in group B. The GN difference was statistically significant ( $p<0.05$ ) between two groups.

**Table IV**

*Distribution of the study patients by blood pressure status and relation with CRP (n=98).*

HTN	Group A(n=23)		Group B(n=75)		P value
	n	%	n	%	
Present	18	78.3	74	98.7	0.002 <sup>s</sup>
Absent	5	21.7	1	1.3	

s= significant

P value reached from fisher exact test

Table IV shows that HTN was present 18(78.3%) in group A and 74(98.7%) in group B. The difference was statistically significant ( $p<0.05$ ) between two groups.

**Table V**

*Distribution of the study patients by diabetes mellitus and relation with CRP (n=98).*

Diabetes Mellitus	Group A(n=23)		Group B(n=75)		P value
	n	%	n	%	
Present	2	8.7	25	33.3	0.020 <sup>s</sup>
Absent	21	91.3	50	66.7	

s= significant

P value reached from fisher exact test

Table V shows that diabetes mellitus was present 2(8.7%) in group A and 25(33.3%) in group B. The difference was statistically significant ( $p<0.05$ ) between two groups.

**Table VI**

*Status of cardiovascular diseases among study patients and relation with CRP (n=98).*

CVD	Group A(n=23)		Group B(n=75)		P value
	n	%	n	%	
Present	3	13.0	75	100.0	0.001 <sup>s</sup>
Absent	20	87.0	0	0.0	

s= significant

P value reached from fisher exact test

Table VI shows that CVD was present 3(13.0%) patients in group A and 75(100.0%) in group B. The difference was statistically significant ( $p<0.05$ ) between two groups.

**Table VII**

*Distribution of the study patients according to type of cardiovascular diseases and relation with CRP (n=98).*

Cardiovascular disease	Group A(n=23)		Group B(n=75)		P value
	n	%	n	%	
Absent	20	87.0	0	0.0	
Present					
Ischemia	0	0.0	13	17.34	
Ischemia with LVH	0	0.0	6	8.0	
LVH	3	13.0	28	37.3	
Old MI	0	0.0	11	14.7	0.001 <sup>s</sup>
Old MI with LVH	0	0.0	12	16.0	
Old MI with LVF	0	0.0	4	5.33	
Ischemia with Arrhythmia	0	0.0	1	1.33	

s= significant

P value reached from chi square test

Table VII shows that 3(13.0%) patients had LVH in group A and 28(37.3%) in group B. Others result are depicted in the table. The difference was statistically significant ( $p<0.05$ ) between two groups.

**Table VIII**

*Multivariable regression analysis for association between CVD and CRP levels (n=98).*

	OR	95% Confidence Interval (Lower, Upper)	P value
Age (years)	0.24	(1.01, 1.37)	0.074 <sup>ns</sup>
Sex (male vs female)	0.06	(0.12, 0.93)	0.464 <sup>ns</sup>
CRP ( $\leq 6$ mg/L vs $> 6$ mg/L)	1.51	(1.02, 2.19)	0.001 <sup>s</sup>
Smoker	1.32	(0.32, 2.87)	0.048 <sup>s</sup>
Diabetes	1.45	(0.22, 3.03)	0.087 <sup>ns</sup>

S= significant, ns= not significant.

Table VIII shows that a subject with CRP  $\leq 6$  mg/L vs  $> 6$  mg/L had 1.51 (95% CI 1.02 to 2.19) times increase in odds having cardiovascular disease. A subject with smoker had 1.32 (95% CI 0.32 to 2.87) times increase in odds having cardiovascular disease. Age, sex and diabetes were not significantly associated with cardiovascular disease.

## Discussion

This cross sectional study was carried out with an aim to find out relationship between c- reactive protein and cardiovascular diseases in patients with ESRD. Total 98 diagnosed case of ESRD (both maintenance hemodialysis and pre dialysis) were included in this study as per inclusion criteria. The study patients were divided into 2 groups based on CRP level. Normal CRP ( $\leq 6$  mg/L) and high CRP ( $> 6$  mg/L) were considered as group A and group B respectively.

In this study mean age was found  $38.61 \pm 11.5$  years in group A and  $46.55 \pm 13.1$  years in group B. The mean age was significantly ( $p<0.05$ ) higher in group B. Similarly, Menon et al. (2003) found that mean age was  $50 \pm 12.6$  (SD) years and  $56.1 \pm 10.4$  years in group A group and group B respectively, which was significantly ( $p<0.05$ ) higher in group B. The reason of elevated c-reactive protein associated with older age is not clear. But it may be due to ESRD patient with older age has various co-morbidity resulting in raise c-reactive protein. In this current study it was observed that 21.7% were smoker in group A and 42.7% in group B. The difference was not statistically significant ( $p>0.05$ ) between two groups. Menon et al.

(2003) showed current smoker were found 9.0% in group A and 11.0% in group B. Elsaid, (2009) showed smoker were 16.5% of their study patients, which are lesser with the current study.<sup>8</sup>

Regarding the etiology it was observed that glomerulonephritis (GN) were found 78.3% in group A and 42.7% in group B. Hypertension (HTN) were found 8.7% in group A and 21.3% in group B. Diabetes (DM) were found 4.3% in group A and 8.0% in group B. Diabetes & Hypertension were found 4.3% in group A and 24.0% in group B. Elsaid, (2009) obtained that the cause of chronic renal failure in 41.0% patients were due to diabetic nephropathy, in 20.0% patients due to hypertension, 6.0% patients chronic glomerulonephritis, 4.0% hypoplastic kidney, 3.0% lupus nephritis, 22.0% were unknown etiology, other causes included were obstructive uropathy 2.0%, tubulo-interstitial nephritis 1.0% and contrast nephropathy in 1.0%. This dissimilarity was due to glomerulonephritis still the major cause of CKD in our country.

In this study it was observed that HTN was present 78.3% in group A and 98.7% in group B. HTN was significantly ( $p<0.05$ ) higher in group B. Elsaid (2009) and Alharbi and Enrione (2012) showed 81.0% and 54.5% respectively of their study patients were hypertensive,<sup>9</sup> which are comparable with the current study. It was observed that diabetes was present 8.7% in group A and 33.3% in group B. Diabetes was significantly ( $p<0.05$ ) higher in group B. Similarly, Menon et al. (2003) showed that diabetes was 3.0% and 11.0% in group A and group B respectively, that indicates that diabetes was higher in group B, which is comparable with the current study. Elsaid, (2009) also showed diabetes mellitus were 44.0% in their study patients. In this present study 39.1% patient was on dialysis in group A and 57.3% in group B, which is higher in group B but not statistically significant ( $p>0.05$ ).

In this present study it was observed that cardiovascular diseases (CVD) was present 13.0% patients in group A and all patients in group B. That indicate patient having cardiovascular diseases have significantly higher c-reactive protein than that of patients without cardiovascular diseases. Atherosclerotic processes play a major role to develop cardiovascular diseases. Inflammation is closely associated with atherosclerosis and c-reactive protein is an important marker of inflammation. Similarly, Menon et al. (2003) showed history of CVD was found 11.0% in group A and 19.0% in group B. Manjunath et al. (2003) showed cardiovascular disease in 5.8% of their study patients. In another study Shlipak et al. (2003) found renal insufficiency present in 11.0% patients of their cardiovascular health study participants.<sup>10</sup>

As regards the type of cardiovascular diseases it was observed in this current study that 13.0% patients had LVH in group A and 37.3% in group B. Whereas ischemia found 17.34%, ischemia with LVH 8.0%, LVH 37.3%, Old MI 14.7%, Old MI with LVH 16.0%, Old MI with LVF 5.33% and Ischemia with Arrhythmia (Supraventricular tachycardia) 1.33% in group B. Foley et al. (1995) studied on ESRD patient where 74% patients had LVH and 19% had ischemia<sup>11</sup>. Both of the study results are comparable.

In multivariable linear regression analysis, after adjusting for age, sex, smoking, diabetes a subject with CRP  $\leq 6$  mg/L vs  $>6$  mg/L had 1.51 (95% CI 1.02 to 2.19) times increase in odds having cardiovascular disease. A subject with smoker had 1.32 (95% CI 0.32 to 2.87) times increase in odds having cardiovascular disease. Age, sex and diabetes were not significantly associated with cardiovascular disease.

Similarly, Menon et al. (2003) obtained that median CRP level was higher ( $P < 0.001$ ) in subjects with a history of CVD (CRP, 0.46 mg/dl) compared with those without CVD (CRP, 0.22 mg/dl). In multivariable logistic regression analysis, the odds of CVD were 1.73 times greater in patients with high CRP levels ( $>0.6$  mg/dl) than those with low CRP levels ( $\leq 0.6$  mg/dl).

Here it could be said that c-reactive protein is an independent risk factors like others for development of cardiovascular diseases in ESRD patient. Diabetes, age and sex were not signified in this study probably due to small sample size.

### Conclusion

From this study it has been shown that high c-reactive protein ( $>6$  mg/L) is associated with 1.5 times increase risk for cardiovascular diseases in ESRD patient. So it could be concluded that inflammatory processes have a role in

the development of cardiovascular diseases in ESRD patient.

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