

## Chronic Kidney Disease specific cardiovascular risk factors among non dialytic patients with Chronic Kidney Disease stage-V—An experience of a specialized hospital

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### Abstract

The study was carried out to see prevalence of Chronic Kidney Disease (CKD) specific cardiovascular risk factors and cardiovascular events among patients with Chronic Kidney Disease stage-V (CKD-V) before starting dialysis therapy in the department of Nephrology of National Institute of Kidney Diseases & Urology (NIKDU), Dhaka, Bangladesh. Among CKD specific cardiovascular risk factors, anemia showed the highest prevalence (96.7%) in study population. More than fifty percent of CKD-V patients had both hypocalcaemia and hyperphosphataemia. Calcium-Phosphate Product (CaXP) was elevated among 23 percent of the population. C-reactive protein, an acute phase protein was positive in 78% of CKD-V patients. Besides, among traditional risk factors, Hypertension and Diabetes Mellitus were present in 83.3% and 23% of the study population respectively. The prevalence of cardiovascular events among CKD-V patients showed that 18.3% had ischemic heart disease, 38% heart failure, 4.7% arrhythmia and 9% left ventricular hypertrophy. Females were significantly prone to develop cardiovascular events than their male counterpart (p=0.028). Diabetes was significantly higher in patients with cardiovascular complications than in patients without cardiovascular complications (p=0.021).

### Introduction

Chronic Kidney Disease (CKD) is a global problem equally affecting the people of developed countries as well as developing countries. Cardiovascular disease is by far the leading cause of morbidity and mortality in CKD patients, accounting for almost 40% of hospitalizations<sup>1</sup> and almost 50% of deaths<sup>1,2</sup>. After stratification for age, race and gender, the cardiovascular mortality rate in End Stage Renal Disease (ESRD) patients is 10–20 times that in the general population<sup>3</sup>. At the time of starting renal replacement therapy, prevalence of cardiovascular disease among Chronic Kidney Disease (CKD) patients is high<sup>1,4,5</sup>. The prospective Canadian study had reported an incidence of approximately 10% per year for both ischemic heart disease and cardiac failure in incident patients, significantly greater than values seen in general population<sup>6</sup>. In Hemo study, the most common cause of death in dialyzed patient was ischemic heart diseases (20.4%) followed by cardiac rhythm disorder (10.4%)<sup>7</sup>. The results of a number of studies suggest that factors leading to the development of cardiovascular abnormalities begin to operate very early in the progression of CKD, well before the patients reach ESRD<sup>8</sup>.

In a community-based cohort, it was found that the prevalence of all the major traditional cardiovascular risk factors other than smoking (including hypertension, diabetes, hypercholesterolaemia and overweight) was significantly higher in patients with even mild renal failure (serum creatinine >1.5 mg/dl) than in those with normal renal function, suggesting that they are associated even with the earliest stages of CKD<sup>9</sup>. A series of CKD specific risk factors can further increase a patient's cardiovascular risk from the earliest stages of the disease<sup>2</sup>.

In Bangladesh approximately 100-120 Patients per Million Population (PMP) reach End Stage Renal Disease (ESRD) every year<sup>10</sup>. The incidence of CKD is increasing rapidly. At the same time cardiovascular risk factors and events increase the fatal outcome of CKD patients. Many of the CKD-V patients can not start or continue dialysis because of cardiovascular diseases. Besides, cardiovascular events are the leading causes of mortality among dialysis patients. This is extremely important as it has been widely shown that the cardiovascular status at the beginning of dialysis greatly affects patient outcomes<sup>5</sup>. There is no study done before in Bangladesh to see the prevalence of CKD specific

cardiovascular risk factors among Non-dialytic patients with CKD-V. But such base line information about cardiovascular factors before starting dialysis among CKD-V patients is essential to develop effective preventive and control strategy for the prevention of cardiovascular events in CKD patients. This study was done to observe CKD specific cardiovascular risk factors and cardiovascular events among patients with CKD-V before initiation of dialysis in a tertiary level hospital of Bangladesh.

## Materials and Methods

This study was carried out on CKD-V patients before initiation of dialysis therapy in nephrology department of National Institute Kidney Diseases & Urology for one year period from July, 2008 to June, 2009. At first, CKD-V patients were selected randomly according to inclusion criteria, then relevant history was taken and physical examination was carried out after taking permission of subjects. Relevant investigations were done. Initially there were 316 patients, later on 16 patients were dropped out due to lack of availability of all investigations. Data were analyzed to find out etiology of CKD and prevalence of cardiovascular risk factors with events with the help of computer software SPSS (Statistical Package for Social Sciences), version 11.5.

### Inclusion Criteria:

1. Age above 18 years
2. Patients with CKD-V [Estimated Glomerular Filtration Rate (eGFR)  $<15 \text{ ml/min/1.73m}^2 \geq 3$  months] before starting dialysis therapy

### Exclusion Criteria:

1. Age below 18 years
2. Patients with CKD-V who had already started haemodialysis

### Operational definitions:

*CKD specific Cardiovascular risk factors:* Anemia, C-reactive protein,  $\text{S Ca}^{++}$ ,  $\text{S PO}_4^{-}$  and  $\text{Ca X P}$  product

*Traditional Cardiovascular risk factors:* Hypertension, Diabetes Mellitus, Age, Sex, Obesity or Overweight, Smoking, Dyslipidaemia,

*Cardiovascular Events:* We have seen the following cardiovascular events Ischemic Heart Disease (IHD), Arrhythmia, Left ventricular hypertrophy (LVH), Congestive Heart Failure (CCF). As Echocardiogram is not available in this institute, we included clinical, ECG and Radiological criteria to define cardiac events.

### CKD-V:

According to Kidney Disease Outcome Quality Initiative (KDOQI) guidelines Patients with eGFR  $<15 \text{ ml/min/1.73m}^2 \geq 3$  months was considered as CKD-V<sup>11</sup>. Estimated Glomerular filtration rate (eGFR) was estimated from serum creatinine level by using Modification of Diet in Renal Disease (MDRD) prediction equation.

The MDRD equation:

$$\text{GFR (ml/min/1.73m}^2) = 186 \times (\text{Scr})^{-1.154} \times (\text{Age})^{-0.203} \times (0.742 \text{ if female})$$

*Anaemia:* When Hb%  $<11 \text{ gm/dl}$  in premenopausal women and when Hb%  $<12 \text{ gm/dl}$  in men and post menopausal women<sup>11</sup>.

*Ischemic Heart Disease (IHD):* To define Ischemic Heart Disease we had included known cases of Ischemic Heart Disease or new cases of Ischemic Heart Disease<sup>3</sup>.

*Arrhythmia:* Atrial or ventricular rhythm disorder requiring therapy<sup>3</sup>.

*Cardiac Failure:* Persistent or recurrent dyspnea plus two of the followings: Raised jugular venous pressure, bibasilar crackles, pulmonary venous hypertension or interstitial edema on chest X-ray<sup>12</sup>.

*Left Ventricular Hypertrophy (LVH):* individuals needed to meet voltage criteria and had either the S-T segment characteristics or T wave characteristics.

R-wave amplitude  $\geq 25 \text{ mm}$  in any deflection in precordial leads

R-wave amplitude  $\geq 20 \text{ mm}$  in standard Leads

R-wave amplitude  $\geq 11 \text{ mm}$  in augmented unipolar leads

R-wave amplitude in V5 or V6 plus S amplitude in V1 or V2  $\geq 35 \text{ mm}$

S-T segment characteristics "Depressed S-T segments"

T wave characteristics "Flattened to inverted T waves"<sup>13,14</sup>

## Results

Among study population, 22.7% was below 30 years of age, 19.3% between 30-40 years, 17% between 40- 50 years, 19.3% between 50-60 years and 21.7% 60 years or above. The mean age of the patients was  $43.5 \pm 15.3$  years; the lowest and highest ages were 14 and 80 years respectively. Fifty eight percent of the patients were male and the rest (42%) was female, giving a male to female ratio of roughly 3:2 respectively. About 41% of patients were urban resident and the rest 59.7% rural residents. Majority (93.3%) of the patients was Muslim, 6.4% was Hindu and 0.3% was belonged to other religion. Over two-third (68%) patients had Glomerulonephritis, 21.3% Diabetes, 2% Hypertension and 8.7% other causes.

Anemia showed the highest prevalence (96.7%) among CKD specific factors. More than fifty Percent of study population had hypocalcaemia and hyperphosphataemia. CaXP Product was elevated among 23 percent of the population. Seventy eight percent of ESRD patients were positive for C-reactive protein, an acute Phase protein (Table-I).

Among traditional risk factors, 83.3% had Hypertension and 23% had Diabetes mellitus. Regarding Dyslipidaemia, 46.6% had raised LDL cholesterol and 57.3% had raised Triglyceride level. Of them, 27% had habit of smoking where as 20% was suffering from overweight and obesity.

Data on prevalence of cardiovascular events among CKD-V patients showed that 18.3% had ischemic heart disease, 38% heart failure, 4.7% arrhythmia and 9% left ventricular hypertrophy. Half of the patients did not have any cardiovascular events, about one-third (32.3%) had single event, 15% two events and 2.7% had three events.

Females with CKD were significantly prone to develop cardiovascular events like IHD, heart failure, arrhythmia or LVH than their male counterpart (p=0.048). But age was not found to have significant association with cardiovascular events (p=0.080).

Smoking habit and body mass index were almost identically distributed between groups (p=0.897 and p=0.564 respectively).The prevalence of Anaemia and Hypertension had no significant difference (p=0.185 and p=0.535 respectively) between groups. Diabetes was significantly higher in patients with cardiovascular complications than those patients without cardiovascular complications (p=0.021) (Table-II).

None of the CKD Specific factors had any significant difference between subjects who developed cardiovascular events and subjects who did not develop cardiovascular events (p>0.05 in each case) (Table-III).

**Table I.** Distribution of patients by CKD Specific risk factors (n=300)

Specific factors related to CKD	Frequency	Percentage
Anaemia	290	96.7
Hypocalcaemia (< 8.1 mg/dl)	172	57.3
Hyperphosphatemia (> 5.5 mg/dl)	165	55
Product of calcium and phosphate (> 55 mg <sup>2</sup> /dl <sup>2</sup> )	69	23
C-reactive protein	234	78

**Table II:** Association between Traditional Risk factors and CV events (n=300).

Traditional Risk factors	Cardiovascular events		p-value
	Developed (n=150)	Not developed (n=150)	
Smoking habit			
Smoker	40(26.7)	41(27.3)	0.897
Non-smoker	110(73.3)	109(72.7)	
BMI (Nutritional status)			
Under weight & normal	118(78.7)	122(81.3)	0.564
Overweight & obese	32(21.3)	28(18.7)	
Anaemia (< 12 g/dl)			
Present	146(97.3)	144(96.0)	0.185
Absent	4(2.7)	6(4.0)	
Hypertension			
Present	127(84.7)	123(82.0)	0.535
Absent	23(15.3)	27(18.0)	
Diabetes mellitus			
Present	44(29.3)	27(18.0)	0.021
absent	106(70.7)	123(82.0)	

# Chi square ( $\chi^2$ ) Test was employed to analyze the data; Figures in the parenthesis denote corresponding percentage.

**Table III:** Association between CKD Specific factors and CV events (n=300)

Specific factors related to CKD	CV events		p-value
	Developed (n = 150)	Not developed (n = 150)	
Raised LDL (> 100 mg/dl)	65(43.3)	72(48.0)	0.417
TG (> 150 mg/dl)	89(59.3)	83(55.3)	0.484
Low HDL (< 40 mg/dl)	117(78.0)	128(85.3)	0.101
Hypocalcaemia (< 8.1 mg/dl)	81(54.0)	91(60.7)	0.243
Hyperphosphatemia (>5.5 mg/dl)	78(52.0)	87(58.0)	0.296
Product of calcium and phosphate (> 55 mg <sup>2</sup> /dl <sup>2</sup> )	34(22.7)	35(23.3)	0.891
C-reactive protein (Positive)	120(80.0)	114(76.0)	0.347

Data were analyzed using Chi-square ( $\chi^2$ ) Test. Figures in the parentheses denote corresponding percentage.

## Discussion

This was the hospital based study on CKD-V patients to see the prevalence of CKD Specific cardiovascular risk factors and events before starting of dialysis therapy.

There are several cardiovascular risk factors which are specific for CKD. Anaemia, Hypocalcaemia, Hyperphosphataemia, Calcium-Phosphate product, inflammatory proteins like C - reactive protein and Homocystinaemia are those specific factors responsible for cardiovascular disease in Chronic Kidney Disease patients. Anaemia, which is thought to make a substantial contribution to the development of cardiac abnormalities in CKD patients, is a very frequent complication. Anaemia is itself responsible for Left Ventricular Hypertrophy which is the hallmark of cardiovascular events. A number of observational studies have shown that it inversely correlates with residual renal function, yet its prevalence is already high during the earlier stages of CKD<sup>15-17</sup>.

Astor BC et al found in a large-scale study of haemodialysis patients, higher hyperphosphataemia levels were significantly associated with an increased risk of death, even after adjusting for pre-existing medical conditions, the delivered dialysis dose, estimates of nutritional status and estimates of non-compliance<sup>18</sup>. These results, which have been confirmed and even extended by another study<sup>19</sup>, clearly demonstrate that hyperphosphataemia directly contributes to the excessive mortality of CKD patients, in whom it recently has been defined as a 'silent killer'<sup>20</sup>. The exact mechanisms by which hyperphosphataemia leads to increased mortality have not yet been completely clarified, but they probably involve the calcification (due to increased calcium-phosphate product and/or secondary hyperparathyroidism) of coronary plaques, cardiac valves and myocardial tissue<sup>21</sup>. According to our study, anaemia was found to be most prevalent (96.7%) among CKD specific risk factors. Hypocalcaemia (57.3%) and hyperphosphataemia (55%) also showed higher distribution in study population. CaXP Product was elevated among 23 percent of the population.

Now a day it is established that high serum concentrations of markers of systemic inflammation (including C-reactive protein and interleukin-6) have been associated with atherosclerosis<sup>22,23</sup> and increased cardiovascular mortality in ESRD patients<sup>24-26</sup>. In our study 80% of CKD-V patients were positive for C-reactive protein. This high inflammatory protein clearly indicates that most of CKD-V patients are in great risk of developing atherosclerosis and cardiovascular diseases.

Hypertension, Diabetes mellitus, Smoking, Dyslipidaemia and old age are the established risk factors for developing cardiovascular disease in CKD patients. Locatelli et al found that age, gender, smoking, previous cardiovascular disease, hypertension, diabetes and total serum cholesterol were all significantly increased ( $P < 0.001$ ) in patients with an estimated creatinine clearance of  $\leq 60$  ml/min<sup>27</sup>. In our study, among traditional risk factors, more than 50 percent patients had Hypertension, high LDL cholesterol and high Triglyceride where as prevalence of Diabetes, habit of Smoking and Obesity was less than 30 percent. As a whole all the major risk factors that we had seen in our study, were present in significant number among study population.

A large scale study from western countries conducted by Foley RN and his colleagues revealed that clinical manifestations of cardiovascular disease were highly prevalent at the start of ESRD therapy: 14% had coronary artery disease, 19%

angina pectoris, 31% cardiac failure, 7% dysarrhythmia and 8% peripheral vascular disease. On echocardiography 15% had systolic dysfunction, 32% left ventricular dilatation and 74% left ventricular hypertrophy. The overall median survival time was 50 months<sup>4</sup>.

In our study, we found that 18.3% had ischemic heart disease, 38% heart failure, 4.7% arrhythmia and 9% left ventricular hypertrophy. Although, LVH is very frequent among CKD patients, in our study, prevalence of left ventricular hypertrophy was underestimated because only ECG criteria was used for detection of LVH. The Canadian Multi-Center Study of Renal Anemia in patients with various stages of CKD found that the prevalence of LVH progressively increased with declining renal function from the 30% prevalence at an early CKD stage (creatinine clearance 50–75 ml/min)<sup>28</sup>.

When we tried to elicit association between cardiovascular risk factors and cardiovascular events, we found that age had no significant association with cardiovascular events ( $p = 0.080$ ). Females were significantly prone to develop cardiovascular events than their male counterpart ( $p = 0.048$ ). Diabetes was significantly higher in patients with cardiovascular complications than that in patients without cardiovascular complications ( $p = 0.021$ ). But it was seen that Anemia, Hypertension, Smoking and Obesity had no significant relationship to develop cardiovascular events. In addition, none of the CKD specific risk factors were significantly associated with cardiovascular complications.

The prevalence of both cardiovascular risk factors and events was high in our study but it was failed to find out significant association between most of the cardiovascular risk factors and cardiovascular events among CKD-V patients before starting dialysis therapy because most of our study population was below fifty years and major cause of CKD of our study population was glomerulonephritis.

*Conclusion:* Cardiovascular diseases are the leading cause of morbidity and mortality among CKD patients. The result of this study suggests that both cardiovascular risk factors and events are prevalent among patients with CKD-V. Female sex and Diabetes Mellitus are significantly associated with cardiovascular events in same group of patients. A large scale study is essential for detection and management of CKD specific cardiovascular risk factors in the early stages of Chronic Kidney Disease to prevent and halt the morbidity and mortality of CKD patients.

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