Cardiovascular Risk Factors in Pre-dialysis Chronic Kidney Disease patients of Nepal

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Abstract

Background and Aims: Cardiovascular disease (CVD) is the commonest cause of morbidity and mortality in patients with chronic kidney disease (CKD) due to increased prevalence of traditional and nontraditional CVD risk factors. Our study aimed to evaluate these risk factors in pre-dialysis Nepalese CKD patients.

Methods: This was a cross-sectional study conducted in Department of Nephrology, Bir hospital. Total 100 consecutive pre-dialysis CKD patients were enrolled. Ten traditional and six nontraditional CVD risk factors were analyzed and compared between CKD stages. Descriptive statistics was used to illustrate the socio-demographic and clinical characteristics, chi square test for categorical variables and multiple logistic regression analysis was done to determine the risk factors of CVD in CKD patients. p-value<0.05 was considered to be statistically significant.

Results: Mean patient age was 52.03±13.64 years with majority (60%) of the patients being male. Comparison of traditional risk factors in different stages depicted similar trend except for old age in Stage 3 CKD (p=0.002). Anemia (p<0.001), hyperphosphatemia (p=0.01), hyperparathyroidism (p<0.01) and cumulative nontraditional risk factors were significantly higher (p=0.01) in stage 5 CKD. The predicted CVD events by Framingham risk score showed high risk in 37% with no significant difference among the stages. Multiple logistic regression analysis showed increased body mass index, low serum albumin and increased serum phosphate as the three significant predictors for left ventricular hypertrophy.

Conclusion: Our study shows that the CVD risk factors were prevailing along the various stages of CKD. The occurrence of non-traditional risk factors increased with increasing stage of CKD.

Introduction

Cardiovascular disease (CVD) is considered as one of the foremost cause of morbidity and premature mortality in chronic kidney disease (CKD) patients affecting pre-dialysis, dialysis and transplant patients.[1-3] Though the CVD risk is much higher in ESRD patients, high rate of fatal and nonfatal CVD has been reported even in patients at early stages of CKD. Hence, all patients with CKD are considered to be in the highest risk group for CVD.[4-5]

Presence of traditional risk factors (old age, hypertension, dyslipidemia, diabetes mellitus, smoking, low physical activity/ obesity and prior cardiovascular events) [1, 3] and CKD specific, nontraditional (anemia, abnormal calcium and phosphorus, hypoalbuminemia, hyperhomocysteinemia, inflammation, oxidant stress, insulin resistance, altered renin–angiotensin axis and endothelial dysfunction) CVD risk factors and their combination is associated with greater prevalence of ventricular hypertrophy, myocardial fibrosis, valvopathy, arrhythmia, and sudden death risk.[6-8] In addition, increased proteinuria and lower estimated glomerular filtration rate (eGFR) has been reported to be associated with higher CVD prevalence in pre-dialysis CKD population.[8,9]

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Studies reported from Nepal have shown that there is a high risk of traditional CVD risk factors in CKD patients than those without CKD.[10] This is associated with rising prevalence of anemia,[11] hypoalbuminemia and hyperphosphatemia[12] with increasing CKD stages. Thus, the present study aimed to assess the prevalence of individual and cumulative traditional and nontraditional risk factors, their association with status of kidney function and left ventricular hypertrophy in predialysis Nepalese CKD patients.

Methods:

This was a hospital based descriptive cross-sectional study conducted in Department of Nephrology, National Academy of Medical Sciences (NAMS), Bir Hospital, Kathmandu, Nepal from July 2019 to March 2020. The study was conducted after obtaining the ethical approval from the Institutional Review Board (IRB) of NAMS. Informed written consent was obtained from all the study participants before enrollment. A total of 100 pre-dialysis CKD patients were included. Sample size was calculated based on the similar study done by Shlipak et al[13] who had reported the prevalence of LVH in patients with CKD as 7%.[13] A predesigned proforma was used for data collection. Consecutive patients with confirmed diagnosis of CKD not on dialysis were included. Patients with age < 30 years and >75 years, kidney transplant recipient, patients under treament with iron, folic acid, calcium, phosphate binders, erythropoetin stimulating agents, vitamin D, febuxostat/ allopurinol, statins and those who refused to give consent were excluded.

A detailed medical history including diabetes mellitus, hypertension, smoking, previous episode of CVD, family history of CVD and current medications were recorded. Patient's height in meter (m), weight in kilograms (kgs) were recorded. Height and weight were taken following standard measurement protocol. Patient was asked to remove shoes and heavy outer clothing such as sweater, jacket, belt, empty their pockets of heavy objects such as cell phones. Patient was asked to step on scale, with both feet on platform, and remain still. Weight was immediately recorded on the data form before patient got off the scale. Body mass index was calculated as body weight (kg) divided by height (m^2).[14] For blood pressure (BP) measurement, patient was seated on a chair for 5 minutes without talking or moving around. The clothing covering the location of cuff placement was removed. The patient's arm was supported on a table and BP was measured in both arms using aneroid sphygmomanometer.

Blood sample was sent for complete blood count, fasting blood sugar, urea, serum creatinine, sodium, potassium, fasting lipid profile, uric acid, calcium, phosphorus, intact parathyroid hormone (iPTH), albumin and glycated hemoglobin (HbA1c). For urine protein-creatinine ratio, early morning sample was advised. ECG and Echocardiography was done.

Case definition: Patient's eGFR was calculated by using serum creatinine based MDRD equation.[15] CKD diagnosis and staging was done as per KDIGO.[2] Patients were diagnosed diabetes if on antidiabetic drugs or if fasting blood sugar ≥126 mg/dl or HbA1c ≥6.5% and hypertensive if on antihypertensive drug or if BP was ≥130/80 mm of Hg.[16] Other CVD risk factors were smoking (current smoker), old age (>45 years), obesity (BMI ≥25kg/m2), family history of CVD if sudden death before 55 years in father or 1st degree male relatives or in mother before age of 65 years or other 1st degree female relatives[17] and dyslipidemia (total cholesterol >240 mg/dL, low-density lipoprotein (LDL) cholesterol >130 mg/ dL, fasting triglycerides (TG) >150 mg/ dL and HDL cholesterol <40 mg/dl in male and <50 mg/dL in female).[18] Moreover, non traditional risk factors were defined as protenuria (uPCR ≥150mg/ gm),[19] anemia (Hb <13g/dL in males and <12g/dL in females),[20] hyperuricemia (>7 mg/dL),[21] hyperphosphatemia (>5 mg/dL),[22] hyperparathyroidism (>600pg/ml)[23] and hypoalbuminemia (<4 g/ dL).[24]

CVD risk was calculated by using Framingham general cardiovascular risk score and 10 year CVD risk of ≥20% , 10% to 20% and <10% was considered high risk, intermediate risk and low risk of CVD respectively.[25]

Statistical analysis: Data obtained was entered in MS Excel and statistical analysis was done by SPSS version 22. Normality test was performed using Kolmogorov-Smirnov test. The tests of significance used for data analysis were Chi-square test for the categorical variables and ANOVA to compare the mean difference between the three groups. Multiple logistic regression analysis was used to determine the association of LVH with other cardiovascular risk factors. P value <0.05 was considered as statistically significant at 95% confidence interval.

Results:

A total of 100 pre-dialysis CKD patients (stage 3 to 5ND) were included in the study and assessed for ten traditional risk factors and six nontraditional risk factors. The baseline clinical and laboratory characteristics of the study population is shown in Table 1. The number of patients in stage 3 (n=36), 4 (n=30) and 5 (n=34) were almost equal. Mean age of the study population was 52.03±13.64 years and 60% were male. From stage 3 to stage 5 there was significantly decreasing trend of age from stage 3 to stage 5(p=0.01). Similarly, there was lower level of hemoglobin (p<0.001), albumin (p=0.03) and gradual increment of uPCR (p<0.001), phosphate (p<0.001), iPTH (p<0.001) and total cholesterol (p=0.01) from Stage 3 to Stage 5 CKD respectively.

Among the traditional risk factors hypertension was the commonest (67%) followed by old age (67%) and male gender (60%). LVH was present in 53% patients affecting all stages of CKD. There was significantly increased prevalence of old age (> 45 years) in stage 3 compared to stage 4 and 5 (p=0.002) with high prevalence in stage 3 CKD as shown in Table 2. Comparison of prevalence of nontraditional factors showed significant difference of anemia (p<0.001), hyperphosphatemia (p=0.01) and hyperparathyroidism (p=0.01) and no difference in proteinuria, hypoalbuminemia and hyperuricemia in different stage of CKD. On calculation of cumulative risk factors as shown in Table 3, the mean traditional risk factor was 4.13±1.94 with highest being in stage 3 CKD with no significant difference. Mean nontraditional risk factor was 3.85±1.01 with highest in stage 5 with significant difference (p=0.01). CVD risk scoring by Framingham risk score between the stages of CKD was statistically insignificant (p=0.12) as shown in Table 4.

Among the various risk factors studied, multiple logistic regression analysis showed increased BMI (p=0.04), decreased serum albumin (p=0.02) and increased serum phosphate (p=0.001) as the three significant predictors for LVH in CKD patients as shown in Table 5.

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Table 1: Clinical and Biochemical parameters of the study population

Parameters	Total (n=100)	Stage 3 n= 36	Stage 4 n=30	Stage 5 ND n=34	p value
Age	52.03±13.64	56.33±13.88	55.18±12.27	44.73±11.74	0.001[a*]
BMI	22.78±3.09	23.72±3.41	22.55±2.95	21.97±2.63	0.05
Hemoglobin	10.29±2.42	12.24±1.97	10.10±2.06	8.42±1.45	<0.001[a*]
Urea	91.32 ± 56.41	52.91 ± 24.50	80.43 ± 29.78	141.61 ± 61.70	< 0.001
Creatinine	4.62 ± 3.80	2.08 ± 0.60	3.25 ± 0.78	8.51 ± 4.26	<0.001
Serum Albumin	3.31 ± 0.63	3.48 ± 0.57	3.35 ± 0.65	3.09 ± 0.65	0.03[a*]
UPCR	2.83 ± 2.19	2.03 ± 1.72	2.43 ± 2.19	4.01 ± 2.19	<0.001 [a*]
EGFR	24.15 ± 15.05	40.27 ± 10.42	21.96 ± 5.53	9.00 ± 3.65	< 0.001
Uric Acid	8.18±2.06	8.24 ± 1.74	8.64± 2.76	8.22 ± 2.55	0.95 [a]
Phosphate	4.83±1.60	4.32±1.16	4.30±1.31	5.85±1.76	< 0.001[a]
iPTH	226.41 ± 172.62	116.31 ± 65.17	204.29 ± 140.84	393.05 ± 224.68	< 0.001
Total Cholesterol	186.54±25.48	176.86±14.89	191.93±23.50	192.02±32.65	0.01 [a*]
LDL	111.46±20.64	105.75±13.40	115.26±20.04	114.14±26.05	0.11 [a]
HDL	44.35±8.17	42.05±7.87	45.60±7.92	45.67±8.40	0.10 [a]
Triglyceride	153.54±40.87	148.25±34.58	148.93±41.53	163.20±45.62	0.23 [a]

a= ANOVA; *p value <0.05 is considered to be statitically signfiicant

Table 2: Traditional and non-traditional risk factors in study population

Risk Factors	Total (n=100)	Stage 3 (n=36)	Stage 4 (n=30)	Stage 5 (n=34)	P value
Traditional Risk Factors					
Old Age	67%	28 (78%)	24 (80%)	15(44%)	0.002[a*]
Male Gender	60%	27 (75%)	14 (47%)	19 (56%)	0.05[a*]
Family History	1%	0	0	1 (3%)	0.37 [a]
History of CVD	11%	6 (17%)	3 (10%)	2 (6%)	0.34
Smoking	25%	11 (31%)	5 (17%)	9 (26%)	0.41 [a]
Obesity	34%	16 (44%)	9 (30%)	9 (26%)	0.24 [a]
T2DM	33%	14 (39%)	10 (33%)	9 (26%)	0.54 [a]
Hypertension	83%	29 (81%)	26 (87%)	28 (82%)	0.79 [a]
Dyslipidemia	55%	19 (53%)	17 (57%)	19 (56%)	0.94 [a]
LVH	53%	21 (58%)	15 (50%)	17 (50%)	0.72 [a]
Nontraditional risk factors					
Anemia	78%	19 (53%)	26 (87%)	33 (97%)	< 0.001[a*]
Proteinuria	99%	35% (97%)	30 (100%)	34 (100%)	0.40[a]
Hyperuricemia	71%	25 (69%)	22 (73%)	24 (71%)	0.94[a]
Hyperphosphatemia	42%	12 (33%)	9 (30%)	21 (62%)	0.01[a*]
Hyperparathyroidism	4%	0	0	4 (12%)	0.01[a*]
Hypoalbuminemia	93%	92%	97%	94%	0.69[a]

a=Chi Square test; *p value < 0.05 is considered to be statistically significant.

Table 3: Cumulative CVD risk factors in Stages of CKD

Stages	Total	Stage 3	Stage 4	Stage 5	P value
Traditional Risk Factors	4.13±1.94	4.75 ± 2.19	3.38 ± 0.93	3.61 ± 1.74	0.07[a]
Non-Traditional risk factors	3.85±1.01	3.96 ± 1.67	3.83 ± 0.98	4.35 ± 0.91	0.01[a*]
Total Risk	7.98±2.14	8.13 ± 2.35	7.80 ± 2.10	7.97 ± 1.97	0.76[a]

a= ANOVA; *p value < 0.05 is considered to be statistically significant

Table 4: Risk of cardiovascular disease as per Framingham Heart Score in different stages of CKD

Risk	Stage 3 (n=36)	Stage 4 (n= 30)	Stage 5 (n= 34)	p value
High Risk	19 (53%)	8 (27%)	10 (30%)	0.12[a]
Intermediate Risk	9 (25%)	8 (26%)	9 (26%)	
Low Risk	8 (22%)	14 (47%)	15 (44%)	

a=Chi-Square test

Table 5: Multiple logistic regression analysis for association of LVH in CKD patients

Variables	Coefficient	SE	OR(95%CI)	p value
Intercept	105.11	58.17	-	-
Age	0.92	0.22	2.5(0.72-8.70)	0.08
BMI	0.18	0.70	1.20 (1.00-1.44)	0.04*
Creatinine	-1.27	1.35	1.12 (0.80-1.57)	0.48
PCR	1.20	0.67	0.80 (0.62-1.03)	0.08
eGFR	0.33	0.24	0.99 (0.91-1.06)	0.17
Albumin	8.96	4.61	0.28(0.09-0.68)	0.02*
Calcium	0.94	0.19	0.81(0.41-1.60)	0.56
Phosphate	-7.33	2.95	2.32(1.40-3.83)	0.001*
Uric Acid	2.25	1.09	0.93(0.71-1.23)	0.64
iPTH	-0.02	0.016	0.99(0.99-1.00)	0.24
Total Cholesterol	0.06	0.64	1.06(0.95-1.19)	0.28
Triglycerides	-0.01	0.14	0.98(0.96-1.00)	0.19
LDL	-0.06	0.66	0.93(0.83-1.06)	0.34
HDL	-0.05	0.67	0.94(0.83-1.07)	0.41
Ejection Fraction	0.41	0.43	1.50 (0.64-3.52)	0.34

*p value <0.05 is considered as statistically significant

Discussion:

CKD is an established risk factor for CVD.[26] There are considerable clinical and biochemical risk factors prevalent in CKD directly associated with increased CVD events.[26] In addition, a common etiology has been linked for CVD and CKD.[27] There is an ongoing dilemma whether the same ongoing inflammatory process contribute to both the progression of kidney dysfunction and LVH. Studies have outlined that angiotensin II, a potent growth factor promotes LVH and fibrosis as well as glomerular sclerosis all via the AT1 receptor respectively. This leads to the prediction for a common cause for CKD and CVD.[27-28] It is the subject for further research to delineate the fact that whether advancing kidney disease itself promotes conditions under which there are enhanced effects of angiotensin II and other cytokines. One school of thought suggest that the complex interplay of cytokines like interleukins 6 and 10, tumour necrosis factor, tissue growth factor beta, vascular endothelial growth factor (VEGF) etc. along with the persistent acute phase reaction and low level inflammation which occurs as kidney failure progresses in conjunction with malnutrition leads to heart failure, atherosclerosis and death.[27] Further, genotype is also important in determining the outcome of kidney dysfunction in patients with CKD.[29-30]

Our study depicts the prevalence of hypertension (83%), dyslipidemia (55%) and diabetes (33%) with no significant difference between CKD stage 3, 4 and 5ND in the study population. In contrast to our finding, a study reported from Japan[9] have shown a higher prevalence of hypertension, dyslipidemia and diabetes from CKD stage 3 to 5. This could be due to the difference in age as their patients[9] were older (68+14 years) with significantly ($p<0.001$) increasing age, while our patients were younger (52.03±13.64 years) with significantly decreasing ($p<0.01$) age from CKD stage 3 to 5. Similarly, the prevalence of hypertension (96.1%), dyslipidemia (67.1%) and diabetes (30.3%) in pre-dialysis CKD in Nigeria also showed no difference between CKD stages and their patients were much younger (48.00±15.28 years).[31]

Comparison of the occurrence of other traditional risk factors like smoking, obesity, male gender, history of CVD and LVH individually and in totality in the present study, a higher prevalence of traditional risk factors was observed in Stage 3 CKD but the difference between the stages was insignificant. This finding was supported by a study reported from China by Zhang et al[32] which depicts occurrence of increased traditional CVD risk factors even in individuals with mildly decreased eGFR.[32]

CVD events like myocardial infarction, stroke and all-cause mortality are highly prevalent in early CKD.[26] These events significantly increases with decreasing eGFR due to increasing prevalence of CKD specific non- traditional CVD risk factors like albuminuria, anemia, hyperparathyroidism, metabolic bone disease, hyperhomocysteinemia, malnutrition, apolipoprotein isoforms, inflammation, endothelial dysfunction and oxidative stress[26,32] and with every 10 ml/min/1.73m^2 reduction of eGFR, the risk of cardiovascular mortality increased by five times.[5] So timely evaluation and intervention to control these risk factors from early CKD is necessary to decrease CVD mortality and morbidity.

In the present study, we have evaluated and compared the prevalence of proteinuria, anemia, hypoalbuminemia, hyperuricemia, hyperphosphatemia and hyperparathyroidism as nontraditional CVD risk factor in CKD stage 3-5 and their association with LVH. Proteinuria, a marker of CKD, reflects endothelial dysfunction, coagulopathy, inflammation and greater severity of the target end-organ damage particularly in patients with diabetes and hypertension.[8] Studies have demonstrated a strong association of proteinuria with CVD even at early stage with persistent microalbuminuria, and have suggested that changes in proteinuria is a useful predictor of future outcomes.[33] The Prevention of Renal and Vascular End stage Disease (PREVEND) study found that a 2-fold increase in urine albumin to creatinine ratio was associated with 30% increase in risk for cardiovascular mortality.[33-34] Proteinuria, present in 99% of our CKD population is much higher than reported by Iimori et al9 (56.3%) in Japan. Moreover, our study reveals that there is a significant increase in proteinuria across the CKD stages ($p<0.001$) which was almost double in CKD stage 5 than stage 3 respectively. This could be

due to high prevalence of proteinuric kidney disease affecting younger age group in this part of the world.[35]

Anemia is one of the earliest finding in CKD patients which worsens with declining kidney function, both due to nutritional and erythropoietin deficiency.[36] Hemoglobin had significantly ($p<0.001$) reduced and prevalence of anemia had significantly ($p<0.001$) increased from CKD stage 3 to 5ND in our patients. This is in accordance to the Chronic Renal Insufficiency Cohort (CRIC) study which reported that the level of hemoglobin decreased with decreasing eGFR.[37] A study from Nepal also showed higher prevalence of anemia with increasing CKD stage although overall prevalence in their patients was much lower (47.85%) compared to the present study (78%) which could be due to inclusion of patients from CKD stages 1 to 5 in their study.[11] Chronic anemia may result in an increased cardiac output and ventricular dilation initially, with LVH and arterial remodeling subsequently leading to arteriosclerosis. Both of these factors are associated with future CVD risk.[38]

Serum albumin in CKD is strongly and independently associated with kidney function. There is a decline in albumin concentration in CKD especially in elderly patients, independent of clinical risk factors like albuminuria and negative acute phase reactant.[39] Significant reduction of serum albumin from stage 3 to 5 pre-dialysis CKD patients observed in present study ($p<0.03$) is similar to other studies in abroad[9] and in Nepal.[12] However, hypoalbuminemia, a marker of malnutrition, found in 93% of our study population with no difference between the CKD stages contradicts the prevalence of 35.5% reported from Nigeria by Adejumo et al[31] with significant increase of hypoalbuminemia from CKD stage 3 to stage 5.

Hyperuricemia is also considered to be a risk factor for CVD events and all-cause mortality.[21] The prevalence of hyperuricemia in present study (71%) is much higher than reported prevalence of 57.9% in pre-dialysis CKD patients by Adejumo et al[31] and there is no significant difference in hyperuricemia among the stages of CKD in both the studies. Studies have shown that the risk of CVD events and all-cause mortality increases by about 10% with every mg/dl rise in uric acid.[21]

Altered metabolism of phosphate and parathyroid hormone is a known consequence of CKD. The severity of hyperphosphatemia and hyperparathyroidism rises with increasing severity of CKD and both are linked with increased CVD events. Hyperphosphatemia is associated with increased risk for death, cardiovascular events and vascular calcification among patients with and without kidney disease[40] and high iPTH is associated with CVD events even in CKD stage 3 and 4.[41] Hyperphosphatemia has direct effect on vascular and cardiac valve calcification, modulation of key hormones fibroblast growth factor-23 and calcitriol although the exact mechanism of CVD due to high phosphate is still poorly understood.[40] PTH acts on specific PTH receptors on cardiomyocytes and results in cardiac hypertrophy and fibrosis, myocardial calcium deposition and valvular calcification.[42] Researches have shown that there is a linear association between PTH levels and mortality, and the increased risk was apparent even when iPTH levels were just above the normal limit.[43] Serum phosphate, iPTH, hyperphosphatemia and hyperparathyroidism had shown linear rise with increasing CKD stage.[9] Our study exhibits similar result except the prevalence of hyperparathyroidism which was present only in CKD stage 5. An earlier study reported from our institute also revealed a significant rise of serum phosphate with negative correlation with eGFR ($p<0.001$) and significantly higher prevalence of hyperphosphatemia ($p<0.001$) in stage 5 CKD.[12] However, the prevalence of hyperphosphatemia was much lower (42%) in our study than reported before from Nepal (63.6%)[12] and abroad (63.2%).[31] The lower prevalence of hyperparathyroidism affecting only 12% of CKD stage 5 in our study compared to 55.1% in Japanese CKD population[9] might be because of the cut off levels of parathyroid hormone used for risk stratification. The present study defined hyperparathyroidism as CVD risk only if iPTH was >600pg/ml whereas Iimori et al9 had defined it to be >65pg/ml.

Framingham Risk Score uses traditional risk factors to predict the risk for CVD events after 10 years in general population and guides the treatment of modifiable risk factors to decrease the risk. However, this equation is considered not to be sufficient to predict the CVD risk in CKD as the nontraditional risks with proven CVD events are not included in this equation and traditional risk factors may have different risk relationship both qualitatively and quantitatively with CVD in CKD compared with the general population.8 On predicting the CVD events in our study population by Framingham risk equation, high risk of developing CVD in 10 years was in 53%, 27% and 30% of the study population in stage 3, 4 and 5 respectively and remaining were in intermediate risk or low risk with no significant statistical difference among the stages of CKD although all people with CKD are considered to be high risk for CVD.[44] The various risk factors, traditional and non-traditional tend to have an additive effect and hasten atherosclerosis and progression of CKD[1] and development of CKD-CVD module should assess traditional and non-traditional CV risk factors including left ventricular hypertrophy, serum albumin, hemoglobin, phosphate, and urate.[45] On assessment of the prevalence of cumulative risk factors in present study, we found similar number of traditional risk factors in all CKD stages and significantly higher nontraditional risk factors in CKD stage 5 ($p<0.01$) indicating increasing CVD risk with advancing CKD and this could be the cause of increased CVD events in these patients.[9]

LVH is an independent predictor of future cardiac event[46] and prevalence of LVH rises with severity of kidney disease.[47] LVH was present in 53% of our patients with no difference between the CKD stages which indicates that the presence of CVD complications are prevalent since early stage of CKD. Age, hypertension, diabetes, smoking, serum calcium and iPTH levels have strong correlation with LVH in CKD.[48] However, multiple-logistic regression analysis for determination of association of LVH (Table 5) in our study population depicted the risk factors increased BMI, decreased serum albumin and increased phosphate levels as significant predictor for LVH.

The limitation of this study is use of non-probability sampling technique and enrollment of all consecutive patients with inclusion criteria during the study period. We also could not evaluate all potential CVD risk factors in patients with CKD and CVD outcome except LVH due to resource constraints.

Conclusion:

CVD risk factors were highly prevalent with similar traditional risk factors and risk of future CVD events in CKD patients similar to the normal population. Moreover, nontraditional risk factors increased with increasing CKD stages and high BMI, low serum albumin and high phosphate level predicted LVH in our pre-dialysis CKD patients. Thus, timely diagnosis and intervention of the modifiable risk factors even in early stage of CKD could alter the cardiovascular risk and prevent future CVD events.

Recommendation:

This study can be taken as a baseline for a multicenter prospective study to establish a causal relationship of CVD risk factors with the development of cardiovascular events and for interventional studies to find out the beneficial effects of early treatment of these

risk factors with CVD outcome in the CKD patients.

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Availability of data and materials:

Datasets generated and/or analyzed during the current study are not publicly available due to the unavailability of disclosure of patient's identification but are available from the corresponding author on reasonable request.

Ethics approval and consent to participate:

This study was initiated only after approval and obtaining the ethical clearance from Institutional Review Board (IRB, NAMS). All the study participants were enrolled only after obtaining the written informed consent.

References

1. Gansevoort RT, Correa-Rotter R, Hemmelgarn BR et al. Chronic kidney disease and cardiovascular risk: epidemiology, mechanisms, and prevention. Lancet 2013; 382: 339–352.
2. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney International Supplements. 2013; 3: 136–150.
3. Mark PB. Strategies to manage cardiovascular risk in chronic kidney disease. Nephrol Dial Transplant.2018; 33: 23–25.
4. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification, and stratification. Am J Kidney Dis 2002; 39: S1.
5. Manjunath G, Tighiouart H, Coresh J et al. Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. Kidney International. 2003; 63: 1121–1129.
6. Foley R, Wang C, Collins AJ. Cardiovascular risk factor profiles and kidney function stage in the US general population: the NHANES III study. Mayo Clin Proc 2005; 80: 1270.
7. Amaresan MS. Cardiovascular disease in chronic kidney disease. Indian J Nephrol. 2005; 15: 1–7.
8. Sarnak MJ, Levey AS, Schoolwerth AC et al. Kidney Disease as a Risk Factor for Development of Cardiovascular Disease. A Statement from the American Heart Association Councils on Kidney in Cardiovascular Disease, High Blood Pressure Research, Clinical Cardiology, and Epidemiology and Prevention. Circulation. 2003; 108: 2154-2169.
9. Iimori S, Noda Y, Okado T et al. Baseline characteristics and prevalence of cardiovascular disease in newly visiting or referred chronic kidney disease patients to nephrology centers in Japan: a prospective cohort study. BMC Nephrology. 2013; 14(152): 1-11.
10. Kalra S, Sharma P, Sharma AP et al. Prevalence of Cardiovascular Risk Factors in Patients with Chronic Kidney Disease. Journal, Indian Academy of Clinical Medicine. 2009; 10(1 & 2): 23-6
11. Poudel B, Yadav B, Jha B et al. Prevalence and association of anemia with CKD: A hospital based cross sectional study from Nepal. Biomedical Research. 2013; 24 (1): 99-103
12. Rajbhandari A, Agrawal RK, Baral A et al. Estimation of Serum Vitamin D, Calcium and Phosphorus in Chronic Kidney Disease. Medical Journal of Shree Birendra Hospital. 2017; 16: 30-36
13. Shlipak MG, Fried LF, Cushman M, Manolio TA, Peterson D, Stehman-Breen C et al. Cardiovascular Mortality Risk in Chronic Kidney Disease: Comparison of Traditional and Novel Risk Factors. JAMA. 2005;293:1737-1745.
14. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies [published correction appears in Lancet. 2004 Mar 13; 363(9412):902]. Lancet. 2004; 363(9403):157-163. doi:10.1016/S0140-6736(03)15268-3.
15. Levey AS, Bosch JP, Lewis JB et al. A More Accurate Method to Estimate Glomerular Filtration Rate From Serum Creatinine: A New Prediction Equation. Modification of Diet in Renal Disease Study Group. Ann Intern Med. 1999 ;130(6):461-70
16. Whelton PK, Carey RM, Aronow WS et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: Executive summary: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018; 71: 1269–1324.
17. Scheuner MT, Setodji CM, Pankow JS et al. Relation of familial patterns of coronary heart disease, stroke, and diabetes to subclinical atherosclerosis: The Multi-Ethnic Study of Atherosclerosis. Genet Med. 2008; 10(12): 879–887.
18. National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III) final report. Circulation. 2002;106:3143–421
19. Miettinen H, Haffner SM, Lehto S et al. Proteinuria Predicts Stroke and Other Atherosclerotic Vascular Disease Events in Nondiabetic and Non–Insulin-Dependent Diabetic Subjects. Stroke 1996;27(11);2033-2039
20. Vlagopoulos PT, Tighiouart H, Weiner DE et al. Anemia as a Risk Factor for Cardiovascular Disease and All-Cause Mortality in Diabetes: The Impact of Chronic Kidney Disease. J Am Soc Nephrol. 2005;16: 3403–3410
21. Chen J-H, Chuang S-Y, Chen H-J et al. Serum Uric Acid Level as an Independent Risk Factor for All-Cause, Cardiovascular, and Ischemic Stroke Mortality: A Chinese Cohort Study. Arthritis & Rheumatism. 2009; 61(2):225-232.
22. Block GA, Klassen PS, Lazarus JM et al. Mineral Metabolism, Mortality, and Morbidity in Maintenance Hemodialysis. J Am Soc Nephrol. 2004;15: 2208–2218
23. Zand L, Kumar R. Serum Parathyroid Hormone Concentrations and Clinical Outcomes in ESRD: A call for Targeted Clinical Trials. Seminars in Dialysis. 2016;29(3):184-188.
24. Weiner DE, Tighiouart H, Elsayed EF et al. The Relationship Between Nontraditional Risk Factors and Outcomes in Individuals With Stage 3 to 4 CKD. Am J Kidney Dis. 2008;51:212-223
25. Chen S-C, Su H-M, Tsai Y-C et al. Framingham Risk Score with Cardiovascular Events in Chronic Kidney Disease. PLoS ONE 2013; 8(3): e60008.
26. Yuan J, Zou X-R, Han SP et al. Prevalence and risk factors for cardiovascular disease among chronic kidney disease

patients: results from the Chinese cohort study of chronic kidney disease (C-STRIDE). BMC Nephrology.2017;18 (23): 1-12

27. Wright J, Hutchison A. Cardiovascular disease in patients with chronic kidney disease. Vascular Health and Risk Management. 2009;5:713–722
28. Willenheimer R, Dahlof B, Rydberg E, Erhardt L. AT1-receptor blockers in hypertension and heart failure: clinical experience and future directions. Eur Heart J. 1999;20(14):997–1008.
29. Iwai N, Ohmichi N, Nakamura Y, Kinoshita M. DD genotype of the angiotensin-converting enzyme gene is a risk factor for left ventricular hypertrophy. Circulation. 1994;90(6):2622–2628.
30. Staessen JA, Wang JG, Ginocchio G, Petrov V, Saavedra AP, Soubrier F, et al. The deletion/insertion polymorphism of the angiotensin converting enzyme gene and cardiovascular-renal risk. J Hypertens. 1997;15(12 Pt 2):1579–1592.
31. Adejumo OA, Okaka EI, Madumezia G et al. Assessment of some cardiovascular risk factors in predialysis chronic kidney disease patients in Southern Nigeria. Niger Med J. 2015;56(6):394-399
32. Zhang LX, Zuo L, Wang Fet al. Cardiovascular Disease in Early Stages of Chronic Kidney Disease in a Chinese Population. J Am Soc Nephrol. 2006; 17: 2617–2621.
33. Hillege HL, Fidler V, Diercks GFH et al. Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group. Urinary Albumin Excretion Predicts Cardiovascular and Noncardiovascular Mortality in General Population. Circulation. 2002;106:1777-1782
34. Currie G, Delles C. Proteinuria and its relation to cardiovascular disease. International Journal of Nephrology and Renovascular Disease 2014;7:13–24.
35. Khakurel S, Agrawal RK, Hada R. Pattern of end stage renal disease in a tertiary care center. JNMA J Nepal Med Assoc. 2009;48(174):126-130
36. O'Mara NB. Anemia in patients with chronic kidney disease. Diabetes Spectrum. 2008; 21(1): 12-19.
37. Lash JP, Go AS, Appel LJ et al. Chronic Renal Insufficiency Cohort (CRIC) Study: Baseline Characteristics and Associations with Kidney Function. Clin J Am Soc Nephrol 4: 1302–1311, 2009.
38. Sarnak MJ, Tighiouart H, Manjunath G et al. Anemia as a Risk Factor for Cardiovascular Disease in the Atherosclerosis Risk in Communities (ARIC) Study. J Am Coll Cardiol 2002;40(1):27–33.
39. Lang J, Katz R, Ix JH et al. Association of serum albumin levels with kidney function decline and incident chronic kidney disease in elders. Nephrol Dial Transplant. 2018; 33: 986–992. doi: 10.1093/ndt/gfx229.
40. Kendrick J, Kestenbaum B, Chonchol M et al. Phosphate and Cardiovascular Disease. Adv Chronic Kidney Dis. 2011; 18(2): 113–119.
41. Lishmanov A, Dorairajan S, Pak Y et al. Elevated serum parathyroid hormone is a cardiovascular risk factor in moderate chronic kidney disease. Int Urol Nephrol. 2012;44(2):541-547.
42. Pontoriero G, Cozzolino M, Locatelli F et al. CKD Patients: The Dilemma of Serum PTH Levels. Nephron Clin Pract 2010; 116: c263–c268.
43. Kovesdy CP, Kalantar-Zadeh K. Bone and mineral disorders in pre-dialysis CKD. Int Urol Nephrol 2008; 40:427–440.
44. Sharma SK, Zou H, Togtokh A et al. Burden of CKD, Proteinuria, and Cardiovascular Risk Among Chinese, Mongolian, and Nepalese Participants in the International Society of Nephrology Screening Programs. American Journal of Kidney Diseases. 2010; 56(5): 915-927
45. Major RW, Cheng MRI, Grant RA et al. Cardiovascular disease risk factors in chronic kidney disease: A systematic review and metaanalysis. PLoS ONE. 2018;13(3): e0192895. https://doi.org/10.1371/journal.pone.0192895
46. Okwuosa TM, Soliman EZ, Faye Lopez et al. Left Ventricular Hypertrophy and Cardiovascular Disease Risk Prediction and Reclassification in Blacks and Whites: The ARIC Study. Am Heart J. 2015 Jan; 169(1): 155–161.e5.
47. Sambi RS, Gaur AK, Hotchandani R, et al. Patterns of left ventricular hypertrophy in chronic kidney disease: an echocardiographic evaluation. Indian Heart J. 2011; 63(3):259-268.
48. Stack AG, Saran R. Clinical correlates and mortality impact of left ventricular hypertrophy among new ESRD patients in the United States. Am J Kidney Dis. 2002; 40:1202– 1210.