Frequency of Cardiovascular Risk Factors and Metabolic Syndrome in Patients with Chronic Kidney Disease

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Objective: Metabolic syndrome is a clustering of cardio-metabolic risk factors. Cardiovascular disease is the main cause of morbidity and mortality in end-stage renal disease. The aim of this study was to elucidate the frequency of traditional and novel cardiovascular and metabolic syndrome risk factors in patients with chronic kidney disease. Identification of these risk factors will allow for precautions to be taken earlier to prevent cardiovascular diseases and metabolic syndrome in chronic kidney disease patients.

Methods: A total of 214 patients (91 females, 123 males, mean age 56.1 ± 14.4 years) with chronic kidney disease who were followed in the Nephrology Department of Istanbul Goztepe Training and Research Hospital were included in the study. Anthropometric and biochemical measurements for cardiovascular risk factors and metabolic syndrome parameters were recorded. Glomerular filtration rates (GFR) were estimated using the Cockcroft Gault formula. Metabolic syndrome was defined according to International Diabetes Federation criteria.

Results: Thirty-seven percent of patients with chronic renal failure were found to have three or more major cardiovascular risk factors. Seventy percent of patients were found to have metabolic syndrome. The mean numbers of major cardiovascular risk factors and metabolic syndrome parameters in patients with different GFR stages were: 1.8 ± 1.0 , 2.6 ± 1.2 (GFR <15 mL/min per 1.73 m², n=102); 2.4 ± 1.0 , 3.0 ± 1.0 (GFR 15-29 mL/min per 1.73 m², n=51); 2.5 ± 1.1 , 3.3 ± 1.0 (GFR 30-59 mL/min per 1.73 m², n=39); 2.4 ± 1.1 , 3.5 ± 0.7 (GFR 60-89 mL/min per 1.73 m², n=22), respectively ($P=.001$).

Conclusion: Although the frequency of cardiovascular risk factors and metabolic syndrome were high in patients with chronic kidney disease, they were negatively correlated with the stage of renal failure.

Keywords: Cardiovascular risk factors; Chronic kidney disease; Metabolic syndrome

Chronic kidney disease (CKD) is a major health problem. Patients with end-stage renal disease are characterized by higher mortality rates than the general population.¹ Mortality from cardiovascular disease (CVD) is 10 to 20 times higher among patients treated with long-term hemodialysis or peritoneal dialysis than in the general U.S. population.² The burden of classic and novel cardiovascular (CV) risks in

individuals with earlier-stage kidney dysfunction is understudied in the general population.³ The majority of deaths are due to CVD in end-stage renal disease patients, and CVD is also a significant cause of morbidity and acute hospitalization in these patients.⁴ As a result, a combination of complications of CKD and accelerated CVD in these patients results in high rates of death. Some traditional CV

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Table 1. Number, gender and age of the patients according to GFR groups.

GFR	N (%)	Male	Female	Age, y
		n (%)	n (%)	Mean $\pm$ SD
<15	102 (47.7)	60 (58.8)	42 (41.2)	53.0 $\pm$ 15.1
15-29	51 (23.8)	25 (49.0)	26 (51.0)	60.1 $\pm$ 14.3
30-59	39 (18.2)	24 (61.5)	15 (38.5)	59.3 $\pm$ 12.1
60-89	22 (10.3)	14 (63.6)	8 (36.4)	54.5 $\pm$ 14.2
Total	214 (100)	123 (57.5)	91 (42.5)	56.0 $\pm$ 14.6

GFR: glomerular filtration rate; SD: standard deviation.

risk factors are male gender, hypertension, diabetes mellitus, high low-density (LDL) cholesterol, low high-density (HDL) cholesterol, physical inactivity, high body mass index (BMI), and obesity. These are evident in patients with or without renal disease.⁵

Metabolic Syndrome has been recognized as a possible risk factor for renal damage, and the increased prevalence of both metabolic syndrome and renal disease justifies the increasing interest within the nephrology community toward metabolic syndrome as another possible inducing cause of CKD, although the available evidence of a direct causal relationship between metabolic syndrome and development of renal disease is scanty so far.⁶ Kurella et al⁷ concluded that metabolic syndrome is a risk factor for the development of diabetes and CVD; however, no prospective studies have examined metabolic syndrome as a risk factor for CKD. Recently, a few population-based studies have been published.⁸⁻¹⁰

An increasing number of patients with CKD either require renal replacement therapy or may suffer from concomitant cardiovascular events. Improvement of CV risk factors may enhance the health quality of patients with CKD and decrease morbidity and mortality rates. The aim of this study was to determine metabolic syndrome frequency and CV risk factor profiles of patients with varying degrees of renal failure.

Methods

Data of the participants were collected from the Nephrology

Department of Istanbul Goztepe Training and Research Hospital, Turkey. A total of 214 patients with CKD (91 females, 123 males, mean age 56.10 $\pm$ 14.4 years) were included in the study. Patients followed in the Nephrology Department were evaluated with respect to their demographic, anthropometric data, physical examination, laboratory findings, and therapeutic details to assess the presence of CV risk factors and metabolic syndrome. Participants were enrolled from 2005 to 2007. The study was designed as a retrospective chart review. Glomerular filtration rates (GFR) were estimated using the Cockcroft Gault formula: (140-age) $\times$ weight (kg) / 72 $\times$ serum creatinine (mg/dL) $\times$ 0.8 (if female). Patients with GFR <90 ml/min per 1.73 m² body surface area were included in the study. Kidney function was classified on the basis of the five estimated GFR ranges suggested by the National Kidney Foundation Practice Guidelines for Chronic Kidney Disease.¹¹ Four groups of patients were analyzed according to their GFR levels and assigned to GFR stages according to the National Kidney Foundation¹¹ as follows: Stage 2, kidney damage (diagnosed with imaging studies and urine tests [eg, proteinuria]) with mildly decreased GFR (60-89 ml/min per 1.73 m²); Stage 3, moderately decreased GFR (30-59 ml/min per 1.73 m²); Stage 4, severely decreased GFR (15-29 ml/min per 1.73 m²); and Stage 5, kidney failure GFR (<15 ml/min per 1.73 m²).

The total number of CV risk factors were determined according to the following items: current cigarette smoking, hypertension (systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg and/or being on antihypertensive therapy), high LDL-cholesterol (>160 mg/dL), low HDL-cholesterol (<35 mg/dL), diabetes mellitus (fasting plasma glucose $\geq$ 126 mg/dl and/or being on antidiabetic therapy), and BMI $\geq$ 30 kg/m².

Metabolic syndrome is defined according to the existence of three or more of the following criteria: (1) abdominal obesity with waist circumference >94 cm for men or >80 cm for women; (2) triglyceride $\geq$ 150 mg/dL; (3) HDL-cholesterol <40 mg/dL for men or <50 mg/dL for women; (4) blood pressure $\geq$ 130/85 mmHg, (5) fasting plasma glucose $\geq$ 100 mg/dL.¹²

Table 2. Association between cardiovascular risk factors and GFR stages.

CV Risk Factors	GFR				P*
	<15 n (%)	15-29 n (%)	30-59 n (%)	60-89 n (%)	
Hypertension (n=171)	67 (65.7)	46 (90.2)	39 (100)	19 (86.4)	.001
Hyperlipidemia (n=60)	20 (19.6)	16 (31.4)	16 (41.0)	8 (36.4)	.048
Diabetes mellitus (n=70)	30 (29.4)	16 (31.4)	17 (43.6)	7 (31.8)	.449
Smoking (n=31)	14 (13.7)	8 (15.7)	6 (15.4)	3 (13.6)	.980
Low HDL (n=82)	40 (39.2)	24 (47.1)	11 (28.2)	7 (31.8)	.173
Obesity (n=41)	8 (7.8)	13 (25.5)	10 (25.6)	8 (36.4)	.001

GFR: glomerular filtration rate; CV: cardiovascular.

*chi-square test

Table 3. Association between the number of the cardiovascular risk factors and GFR stages.

CV risk factors (n)	GFR				Total (%)
	<15 n (%)	15-29 n (%)	30-59 n (%)	60-89 n (%)	
0	12 (11.8)	-	-	1 (4.5)	13 (6.1)
1	30 (29.4)	11 (21.6)	9 (23.1)	4 (18.2)	54 (25.2)
2	34 (33.3)	17 (33.3)	10 (25.6)	7 (31.8)	68 (31.8)
3	23 (22.5)	15 (29.4)	11 (28.2)	6 (27.3)	55 (25.7)
4	3 (2.9)	7 (13.7)	8 (20.5)	4 (18.2)	22 (10.3)
5	-	1 (2.0)	1 (2.6)	-	2 (0.9)
Total	102 (100)	51 (100)	39 (100)	22 (100)	214 (100)

GFR: glomerular filtration rate; CV: cardiovascular.

*Likelihood ratio: $P=.004$

Statistical analysis was performed by SPSS 12.0 (Statistical Package for Social Sciences, Chicago IL, USA). Results were expressed as mean, standard deviation, and median. Categorical data were represented as numbers and percents. For the purpose of analysis of the differences between groups Mann-Whitney U-test, Kruskal-Wallis test and Mann-Whitney U-test with Bonferroni correction for post hoc analysis were used. Alpha significance was analysed by application of Bonferroni correction. Chi-square test was used to analyze associations in discrete variables between the groups. We considered P values of $<.05$ to be statistically significant.

Results

A total of 214 patients were included in the study (91 females, 123 males, mean age 56.10 ± 14.4 years). Ninety-nine of the patients (45.46%) were receiving either peritoneal dialysis or hemodialysis. Mean waist circumference was 95.05 ± 15.23 cm (52-150 cm); mean BMI was 25.7 ± 5.3 kg/m² (15.2-45.4 kg/m²). One-hundred fifty-five (70.1%) patients were receiving antihypertensive therapy, 53 (24.0%) patients were

receiving antilipemic therapy, and 45 (20.4%) patients were receiving antidiabetic therapy.

The number, gender, and age of the patients according to their GFR groups are shown in table 1. Participants with estimated GFR values between 15-29 ml/min per 1.73 m² and 30-59 ml/min per 1.73 m² were older than the participants with GFR <15 ml/min per 1.73 m² ($P=.010$, $P=.022$, respectively).

Association Between GFR Stages and Cardiovascular Risk Factors

Hypertensive patients constituted 86.4% of the study group, 27% of the patients were hyperlipidemic, and diabetic patients constituted 32.6% of total patients. Thirty-two (14.5%) patients were current smokers, and HDL-cholesterol was lower than 40 mg/dL in 86 (40%) patients. Estimated BMI was higher than 30 kg/m² in 41 patients.

The patients with GFR values between 30-59 ml/min per 1.73 m² were obviously more prone to have hypertension than the

Table 4. Association between metabolic syndrome parameters and GFR stages.

MS parameters	GFR				P*
	<15 n (%)	15-29 n (%)	30-59 n (%)	60-89 n (%)	
Waist circumference Female >80 cm; Male >94 cm (n=136)	46 (45.1)	37 (72.5)	33 (84.6)	20 (90.9)	.001
HDL-cholesterol Female <50 mg/dl; Male <40 mg/dl (n=105)	48 (47.1)	31 (60.8)	16 (41.0)	10 (45.5)	.238
Blood pressure $\geq 130/85$ mmHg and/or being on antihypertensive therapy (n=184)	76 (74.5)	48 (94.1)	39 (100)	21 (95.5)	.001
Fasting plasma glucose ≥ 100 mg/dl and/or being on antidiabetic therapy (n=118)	48 (47.1)	27 (52.9)	27 (69.2)	16 (72.7)	.034
Triglyceride ≥ 150 mg/dl (n=85)	52 (51.0)	11 (21.6)	13 (33.3)	9 (40.9)	.001

GFR: glomerular filtration rate; MS: metabolic syndrome.

*chi-square test

Table 5. Association between the number of metabolic syndrome parameters and GFR stages.

MS parameters, n	GFR				Total
	<15	15-29	30-59	60-89	
0	3 (2.9%)	-	-	-	3 (1.4%)
1	14 (13.7%)	4 (7.8%)	3 (7.7%)	-	21 (9.8%)
2	28 (27.5%)	10 (19.6%)	3 (7.7%)	3 (13.6%)	44 (20.6%)
3	34 (33.3%)	22 (43.1%)	17 (43.6%)	6 (27.3%)	79 (36.9%)
4	17 (16.7%)	11 (21.6%)	12 (30.8%)	13 (59.1%)	53 (24.8%)
5	6 (5.9%)	4 (7.8%)	4 (10.3%)	-	14 (6.5%)
Total	102 (100%)	51 (100%)	39 (100%)	22 (100%)	214 (100%)

GFR: glomerular filtration rate; MS: metabolic syndrome.

*Likelihood Ratio: $P=.003$

patients with GFR values between 15-29 ml/min per 1.73 m² and 60-89 ml/min per 1.73 m² ($P<.001$) (table 2). But, fewer patients had hypertension in the GFR <15 ml/min per 1.73 m² group than other GFR groups. The group of patients with GFR <15 ml/min per 1.73 m² were less likely to have hyperlipidemia than other groups ($P=.048$). No difference was found between other GFR groups according to hyperlipidemia ($P>0.05$). There was also no significant difference between GFR groups with regard to being diabetic, a current smoker, or having low HDL-cholesterol level ($P>.05$). The association between GFR groups and BMI was significant in GFR 60-89 ml/min per 1.73 m² group and other groups ($P=.001$). In the GFR <15 ml/min per 1.73 m² group, obesity was significantly lower than the other groups ($P=.001$).

Participants with one and two CV risk factors were more likely to have lower GFR (table 3). As GFR increased, the total number of patients who had more CV risk factors increased. So, there was a positive correlation between increasing GFR and the number of CV risk factors ($P=.004$).

Association Between GFR Stages and Metabolic Syndrome

The number of the patients with waist circumference larger than 80 cm in women and 94 cm in men, and with GFR <15 ml/min per 1.73 m² was less than the patients with other GFR stages ($P<.001$). However, there was no significant difference between patients with GFR 15-29 ml/min per 1.73 m², 30-59 ml/min per 1.73 m², and 60-89 ml/min per 1.73 m² when they were evaluated according to waist circumference. When HDL-cholesterol was evaluated as a metabolic syndrome

parameter, no significant difference was found among any GFR stages ($P=.238$). Patients with GFR values between 15-29 ml/min per 1.73 m², 30-59 ml/min per 1.73 m², and 60-89 ml/min per 1.73 m² were more prone to have hypertension than patients with GFR <15 ml/min per 1.73 m² ($P<.001$). Hyperglycemia was more frequent in patients with GFR values between 30-59 ml/min per 1.73 m² and 60-89 ml/min per 1.73 m² than the patients in other GFR stages ($P=.034$). Triglyceride levels were significantly higher in the patients with GFR <15 ml/min per 1.73 m² than in the patients in other GFR groups ($P=.001$) (table 4).

The number of metabolic syndrome parameters was positively correlated with increasing GFR (table 5). This association was considered statistically significant ($P=.003$). Odds ratio of the risk factors were represented in table 6. Median number of CV risk factors and metabolic syndrome parameters increased with GFR (table 7).

Discussion

As GFR increases, the total number of the patients having more CV risk factors increases, and metabolic syndrome is significantly lower in patients with GFR <15 ml/min per 1.73 m². When risk factors for CVD and metabolic syndrome parameters were evaluated individually, we found that triglyceride levels increased with decreasing GFR. Elevated serum triglyceride is caused by the accumulation of triglyceride rich lipoproteins such as very low density protein and intermediate density lipoprotein.¹³

Patients whose LDL-cholesterol levels are higher than 160 mg/dL are more likely to have higher GFR than patients who have normal LDL-cholesterol levels. Sarnak et al¹⁴ similarly described the relationship between dyslipidemia and GFR, particularly regarding hypertriglyceridemia. As GFR declines, triglyceride levels increase. Kasiske et al¹⁵ concluded that hemodialysis patients with GFR <15 ml/min per 1.73 m² tend to have LDL-cholesterol levels similar to the general population. In end-stage renal disease patients, LDL-cholesterol is usually reduced or within the normal range.¹⁶

About 86% of our patients were hypertensive and/or on antihypertensive therapy, similar to the studies of Coresh et al¹⁷ and Buckalew et al.¹⁸ About 77% of the patients were

Table 6. Odds ratio of cardiovascular risk factors in groups GFR <30 and ≥30.

CV Risk Factor	P*	OR	CI
Hypertension	.001	6.844	2.03 – 23.07
Hyperlipidemia	.020	2.108	1.12 – 3.97
Diabetes mellitus	.192	1.509	0.81 – 2.80
Smoking	.810	1.110	0.47 – 2.60
Low HDL	.031	0.484	0.25 – 0.94
Obesity	.008	2.612	1.27 – 5.36

GFR: glomerular filtration rate; CV: cardiovascular; OR: odds ratio;

CI: confidence interval

*chi-square test

Table 7. Mean and median number of the cardiovascular risk factors and metabolic syndrome parameters.

GFR	N	CV risk factors (n)		MS parameters (n)	
		Mean $\pm$ SD	Median	Mean $\pm$ SD	Median
<15	102	1.8 $\pm$ 1.0	2	2.6 $\pm$ 1.2	3
15-29	51	2.4 $\pm$ 1.0	2	3.0 $\pm$ 1.0	3
30-59	39	2.5 $\pm$ 1.1	3	3.3 $\pm$ 1.0	3
60-89	22	2.4 $\pm$ 1.1	2	3.5 $\pm$ 0.7	4
Total	214	2.1 $\pm$ 1.1	2	2.9 $\pm$ 1.1	3

Kruskal-Wallis test: $P=.001$.

GFR: glomerular filtration rate; CV: cardiovascular; MS: metabolic syndrome; SD: standard deviation

using one or two antihypertensive agents. Most commonly used antihypertensive agents were calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers (40%, 24%, and 18% respectively). While 95% of the patients with GFR values of 60-89 ml/min per 1.73 m² had hypertension, only 75 % of patients with GFR of <15 ml/min per 1.73 m² had hypertension. The prevalence of hypertension increases as GFR increases. There is a positive relationship between hypertension and GFR. Although Sarnak et al¹⁴ declared an inverse relationship with systolic blood pressure and level of GFR, diastolic blood pressure was not significantly associated with GFR. The study called the Modification of Diet in Renal Disease Study (MDRD)¹⁸ included subjects with GFR values between 25-55 ml/min per 1.73 m² as well as those between 13-24 ml/min per 1.73 m². Patients with GFR values between 30-59 ml/min per 1.73 m² had the highest rate of hypertension either systolic or diastolic. This group of patients were older than the patients with GFR <15 ml/min per 1.73 m². Foley et al³ did not find any association between higher levels of blood pressure and low GFR stage. Wheeler et al¹⁹ concluded that patients with more severely impaired renal function had lower diastolic pressure, in contrast to Sarnak et al¹⁴ who found no significant association between diastolic blood pressure and GFR. In our study population, patients who were on renal replacement therapy were more lean than the patients in the other groups, so this might influence our results on hypertension.

Approximately 33% (n=70) of the patients in our study had diabetes mellitus, while 24% had diabetic kidney disease (n=51). Tonelli et al²⁰ reported that about 37.5% of CKD patients had diabetes mellitus and the presence of diabetes was associated with CVD in CKD stages 1 through 4. Diabetes mellitus is the cause of end-stage renal disease in approximately 40% of cases in the United States. Diabetic patients were equally distributed among GFR stages. In our study, mean fasting plasma glucose of the diabetic patients was 168.4 mg/dL $\pm$ 87.6mg/dL and mean HbA1c level of these patients was 8 $\pm$ 3.0%. Mean fasting plasma glucose of the nondiabetic patients was 98.9 $\pm$ 22.2 mg/dL, and mean HbA1c level was 5.7 $\pm$ 1.3%. Menon et al²¹ concluded that HbA1c was associated with increased mortality in nondiabetic kidney disease and a predictor of all-cause mortality. Despite this association between strict glycemic control and reduction in CVD mortality, morbidity rates have not been examined with randomized trials.

Approximately 14% of our patients were current smokers. In the CHOICE study, about 18% of the patients were current smokers on dialysis.²² Smoking has been linked to progression of kidney disease and of CVD in patients with reduced GFRs.^{23,24}

Patients with GFR <15 ml/min per 1.73 m² and 15-29 ml/min per 1.73 m² had lower HDL-cholesterol levels than patients in the other GFR groups. But this result was not found to be statistically significant ($P>.05$). This result was parallel to the results of Wheeler et al,¹⁹ who concluded that patients with more severely impaired renal function had lower HDL-cholesterol levels. Despite an HDL-cholesterol level cut-off value of 35 mg/dL in the MDRD study, Sarnak et al¹⁴ found that HDL-cholesterol was positively correlated with GFR stage.

Chen et al²⁵ examined a subsample of the National Health and Nutrition Examination Survey (NHANES) III population for the association between metabolic syndrome and risk for CKD. They compared the proportion of the participants with CKD among those with or without each component of metabolic syndrome. They concluded that elevated blood pressure, serum triglyceride, and plasma glucose were significantly associated with increased prevalence of CKD. Low HDL-cholesterol and abdominal obesity were significantly associated with increased prevalence of CKD. The patients in this study were not classified according to their GFR stages. Patients with GFR<15 ml/min per 1.73 m² were more malnourished than the patients in the other groups, so they had lower waist circumference and their fasting plasma glucose levels were lower than the patients with GFR <30 ml/min per 1.73 m². Diabetic patients were prone to hypoglycemia due to advanced renal failure.

We found that the number of CV risk factors and metabolic syndrome parameters increased with increasing GFR. Subjects with one and two risk factors were especially more likely to have lower GFR levels. Our patients were from the Nephrology Department, so patient distribution was in a homogenous manner according to their GFR stages. Because uremia is a major risk factor for accelerated and atherosclerotic CV complications, dialysis procedures through bioincompatibility constitute an additional risk factor.²⁶ Tonelli et al²⁰ reported that CVD was common in the predialysis population, and its prevalence increased with more severe kidney failure.

However, that study population consisted of patients who had creatinine clearances of 75 ml/min per 1.73 m² or less but were not on dialysis therapy. Patients with GFR <15 ml/min per 1.73 m² were less obese and had the lowest waist circumference, so there was not a strong association with other CV risk factors and metabolic syndrome parameters. Our data showed that patients were undertreated for their hypertension, high LDL-cholesterol, and diabetes (eg, HbA1c level was 8.4±3.0%).

In the ARIC (Atherosclerosis Risk in Communities) study,²⁷ patients were classified according to their GFR stages, but patients with GFR<15 ml/min per 1.73 m² were not included in the study, and patients with GFR values between 15-59 ml/min per 1.73 m² constituted only 2% of the study population. When basic characteristics of the patients were evaluated, atherosclerotic CVD risk factors were found to be higher in the group with lower baseline GFR. In our study, 48% of the patients had GFR<15 ml/min per 1.73 m², and all patients were followed by the physicians in the Nephrology Department.

When the results were evaluated totally, patients with GFR >30 ml/min per 1.73 m² had more hypertension, hyperlipidemia, and obesity. Lower BMI and cholesterol levels in patients with GFR<30 ml/min per 1.73 m² were assumed to be due to malnutrition. These factors can be responsible for unfavorable outcomes in these patients with a spectrum of hemodialysis related risk factors named malnutrition-inflammation complex syndrome (MICS). Recent research has shown that several components of MICS, alone or in combination, are predictors of mortality in hemodialysis patients.²⁸ Kalantar-Zadeh et al²⁹ estimated the relative risk of mortality in a hypothetical model that was based on the state of nutrition and serum cholesterol levels. It appeared that in underweight patients mortality is influenced by hypocholesterolemia. Takeda et al³⁰ also failed to show an association between hypertension and mortality in hemodialysis patients. Fleischmann et al³¹ concluded that conventional risk factors over at least a two-year period did not readily account for the higher mortality of a group of predominately African-American patients on hemodialysis. It is also claimed that greater fluid retention between two subsequent hemodialysis treatment sessions is associated with higher risk of all-cause and cardiovascular death.³² Heart failure is the most common cause of early death in patients on dialysis.³³ So, end-stage renal disease patients do not die as often of myocardial infarctions, but rather from sudden cardiac death and congestive heart failure.

Conclusion

The results of this study indicate that the number of the CV risk factors and metabolic syndrome frequency increases with increasing GFR. High frequency of CV risk factors among these patients suggests that cardiovascular disease begins in earlier stages of renal failure; therefore, implementation of risk factor reduction strategies earlier and aggressively in the course of renal failure may provide an opportunity to prevent

CVD in CKD patients who also suffer from dialysis-related risk factors.

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