Effect of Smoking on the Estimated Glomerular Filtration Rate of Chronic Kidney Disease Patient Prior to Dialysis Initiation

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Abstract

Introduction. Smoking is prevalent among Filipinos, but little is known about whether this is associated with the rapid decline of the renal function among patients with existing chronic kidney disease (CKD). The purpose of this study is to investigate whether or not there is a direct relationship of smoking to the progression of CKD requiring patient to be on dialysis/renal replacement therapy.

Methods. A cross-sectional, retrospective study design was used. All CKD 5_D patients of the Amang Rodriguez Memorial Medical Center (ARMMC) Hemodialysis (HD) Unit in the month of July to August, 2019 were included, if they are $\geq$ 18yo, regardless of their co-morbidities. Excluded are those with acute kidney injury (AKI), and iatrogenic, surgical or trauma complications that cause renal dysfunction. Charts were reviewed and 55 patients qualified. Smoking status were grouped according to the US Centers for Disease Control (CDC) smoking definitions, either never, former and current smoker. Estimated glomerular filtration rate (eGFR) Creatinine were computed using the CKD-Epi formula 3-yr, 2-yr, 1-yr and 0-yr prior to HD. The main outcome measure was whether and what among the smoking status hastens the progression of CKD. Descriptive statistical analyses were done along with one-way variance, two-way variance, and chi-square.

Results. Most of the smokers were males ($p \leq 0.001$). Most of the participants had diabetes as the primary illness. All of the participants had same endpoint of having eGFR < 15 at the time of dialysis initiation. There was a significant progressive decrease from eGFR3 to eGFR0 in all smoking status. Current smokers have the highest significant reduction in eGFR ($p \leq 0.001$).

Conclusion. Smoking hastens the progression of CKD among Filipinos. With that, we support the smoking cessation campaign of the ARMMC and the DOH. In addition, further work up is suggested to determine the primary mechanistic pathway of smoking that affects the renal cells.

Keywords: Chronic Kidney Disease, Smoking Status, eGFR

Introduction

Chronic Kidney Disease (CKD) is the presence of either kidney damage and a decreased GFR (Glomerular Filtration Rate) <60 ml/min/1.73 m^2 that is existing for more than 3 months. Markers of kidney damage might be in the form of albuminuria, presence of urinary sediments, signs of tubular damage, morphologic or structural abnormalities or any history of renal transplant.[1]

CKD has notable impact on the global morbidity and mortality. Although commonly as progressive complication of hypertension and diabetes mellitus, it has an indirect impact by increasing the risks associated with the major causes of death.[2]

According to the WHO (World Health Organization) Global Burden Diseases 2015 data, it is estimated that there were 1.2 million patients who died from renal failure which shows an increase of 32% since 2005 era. In 2010, about 2.3 to 7.1 million patients who died with ESRD (End Stage Renal Disease) without the benefit of chronic dialysis.[2] Local Statistical data from the NKTI (National Kidney and Transplant Institute) states that, kidney diseases, particularly end-stage renal disease

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(ESRD), is already the 7th leading cause of death among Filipinos. Approximately one Filipino develops chronic kidney disease every hour. More than 5,000 Filipino are currently undergoing dialysis and about 1.1 million people worldwide are on Renal Replacement Therapy (RRT).[3] In 'Amang' Rodriguez Memorial Medical Center (ARMMC), there were recorded almost 516 CKD patients admitted for the past three years with an almost equal percentage of males and females.[4]

According to the US Center for Disease Control (CDC), globally, tobacco use causes > 7 million deaths a year.[5] On the other hand, Philippine Global Adult Tobacco Surveys (GATS) data shows only 15.9% Filipino adults currently smoke tobacco – 40.3% among males and 5.1% among females. Smoking declined by close to 50% among females.[6]

Statistical data had shown that smoking is related direct and indirectly to the depression of renal function. Among smokers, mortality and morbidity due to kidney failure was increased by two-fold. Evidence shows that smoking causes endothelial dysfunction, oxidative stress, inflammation that further worsen the kidney injury.[7]

Cigarette smoking, a proven risk factor for atherosclerotic disease, may increase the amount of albuminuria in both in diabetic and non-diabetic populations whereas the effects of smoking on estimated Glomerular Filtration Rate (eGFR) still lacks evidence and suggest further studies.[7]

A cross-sectional study done by Ishizaka et. al among Japanese men suggests that whether or not smoking is protective long-term or deleterious acutely, it does not proportionate on long-term renal prognosis and they further suggest future studies.[8]

In this study, we investigated whether there is a direct relationship of cigarette smoking to the progression of CKD requiring patient to be on dialysis/RRT. Currently there is no known local study correlating the effect of smoking on the decline of renal function.

Methodology

The study was done in ARMMC HD unit in Marikina City, Philippines. ARMMC caters not only to the people of Marikina, but also the neighboring towns. It is a referral center since it is the nearest tertiary medical center in Eastern Rizal. The unit has 10 hemodialysis machines, and 8 of it are regularly used, both for the in-patients and out-patients. A regular monthly maintenance and water analysis is done to assure the safety of those who use the machines.

All CKD patient who underwent hemodialysis in July and August 2019 at ARMMC HD unit were included in the study. They are 18 years old and above, both male and female. The primary diseases or the reason of their renal failure was also determined for comparison since it is the major contributor to the progression CKD and also for future references. The four most common primary diseases of out participants were Hypertension, Diabetes Mellitus, Chronic Glomerulonephritis and Obstructive causes. All of the 55 participants qualified using the inclusion criteria, three of them expired within the study period.

Data collection was done through chart reviews and history taking. Records were reviewed to validate the current age, date of dialysis initiation, age on HD initiation, primary disease and its duration, and their smoking habits and history. Data gathered were re-confirmed by asking the participants themselves during their scheduled dialysis.

Participant's smoking status was defined and grouped according to the US CDC classification of smoking status definitions.[9] They were separated into one of the following:

1. *Never smoker:* an adult who has never smoked, or who has smoked less than 100 cigarettes in his or her lifetime;
2. *Former smoker:* An adult who has smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of interview or who had quit for more than 1 month, and
3. *Current smoker:* An adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes or who had quit smoking for 1 month or less

The duration they stopped smoking prior to dialysis was also determined for future reference.

All of the participants were already baseline CKD 5_D at the time of dialysis initiation with an eGFR < 15 ml/min/1.73m^2 (labeled in the study as eGFR0) during the study. Records were reviewed and participants were asked to confirm their serum creatinine values 1-year, 2-years and 3-years prior to dialysis initiation. With the said information, eGFR-1 year prior (eGFR1), 2-years prior (eGFR2) and 3-years prior (eGFR3) to dialysis initiation was computed using the CKD-Epi Formula. The CKD-Epi equation is the recommended formula by the International Society of Nephrology. The Kidney Disease Improving Global Outcomes (K-DIGO) committee promulgated this for estimating the GFR because it has better accuracy and addresses the ethnicity coefficient as compared to the Modification of Diet in Renal Disease (MDRD) Study Equation which uses predictable clinical variables.[10]

Data collected was tabulated using Google Sheets and was secured with password for privacy purposes. Only the researcher, adviser and the biostatistician had access to these data.

A cross-sectional, retrospective study design was used in this study. The outcome (CKD 5_D) and the exposures (smoking status) was measured at the same time. Participants in this study were selected using the inclusion and exclusion criteria.

The data collected was processed and analyzed using the Statistical Package for Social Sciences (SPSS) 20.0 software and GraphPad Prism. Descriptive statistics of the

Table I. Clinical Characteristics and Laboratory Data of All Subjects Enrolled

Variables	Never Smoker (n=19)	Former Smoker (n=10)	Current Smoker (n=26)	P value
Age (mean±SD)	42±17.44	59.50±10.36	48.12±13.12	0.012*
Sex (n) Male Female	 4 15	 6 4	 24 2	0.001*
Pack Years	---	15.65±13.74	13.12±9.41	0.001*
Primary Disease HPN DM CGN Obstructive	 3 6 8 2	 2 7 1 0	 6 10 10 0	0.191
Disease Duration (mean±SD)	4.95±4.31	9.30±6.26	5.81±3.53	0.042
Age in HD (mean±SD)	40.84±17.41	58.40±9.80	45.92±13.71	0.012*
eGFR 0 (mean±SD)	<15	<15	<15	0.000*
Creatinine1 (mean±SD)	225.26±75.01	172±62.86	163.27±65.07	0.012*
eGFR 1 (mean±SD)	31.06±22.93	38.78±18.14	48.98±21.60	0.027*
Creatinine2 (mean±SD)	159.47±68.11	132±66.80	119.62±45.91	0.084
eGFR 2 (mean±SD)	50.54±35.52	57.22±27.41	70.86±28.63	0.095
Creatinine3 (mean±SD)	108.95±35.42	103.50±36.06	94.92±23.96	0.314
eGFR 3 (mean±SD)	69.30±32.78	69.18±24.93	87.16±25.32	0.071

* with significant differences ($p<0.05$)

data were determined by frequencies, percentages, mean ± standard deviation. Distributions of participant characteristics by smoking status were compared by one-way analysis of variance (ANOVA) for continuous variables, and by the chi-square test for categorical variables. Two-way ANOVA was used to compare the differences of three eGFR values and the three smoking status. Probability levels of lower than 0.05 were considered statistically significant based on a two-sided test.

Results

Baseline Clinical Characteristics. The mean age of the participants was 49±13.3 and among them the mean age of those who never smoker was lower as compared to the former and current smokers. Among of the 55 participants, 19 were never smokers and 36 had smoking history. Significantly most of the smokers were males ($p > 0.001$) with a mean pack year of 14.38 ± 11.57. Most of the participants had diabetes as the primary illness, others had hypertension, chronic glomerulonephritis and obstructive uropathy with a mean disease duration of 6.6 ± 4.72 years. The mean age when participants were started on dialysis was 48.38 ± 13.64 years. eGFR was higher in current smokers than in never smokers and former smokers in 1 year prior to HD but was not statistically significant ($p=0.27$). eGFR2 and eGFR3 showed no significant differences among the three smoking statuses. All of the participants had the same endpoint of having eGFR <15 ml/min/1.73m^2 at the time of dialysis initiation (*Table I*).

Participants' eGFR0, eGFR1, eGFR2 and eGFR3 were compared to the smoking status. Results revealed that current and former smokers had higher eGFR3, eGFR2 and eGFR1 as compared to the Never smoker who had a lower eGFR to begin with (*Figure 1*). Results also revealed that there is no difference between eGFR and smoking status in eGFR3 and eGFR2. As shown in the whisker plot, the mean ± SD is even higher in current smoker and

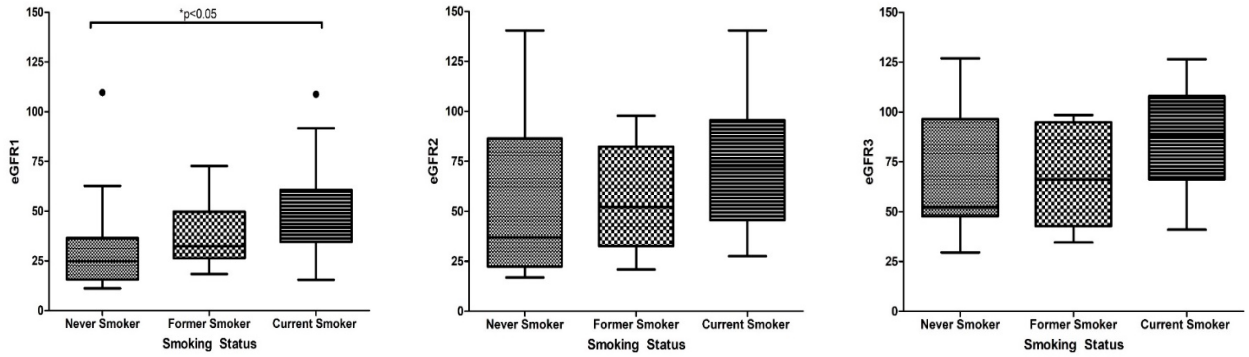

Figure 1. eGFR1 (left), eGFR2 (middle) and eGFR3 (right) according to Smoking Status

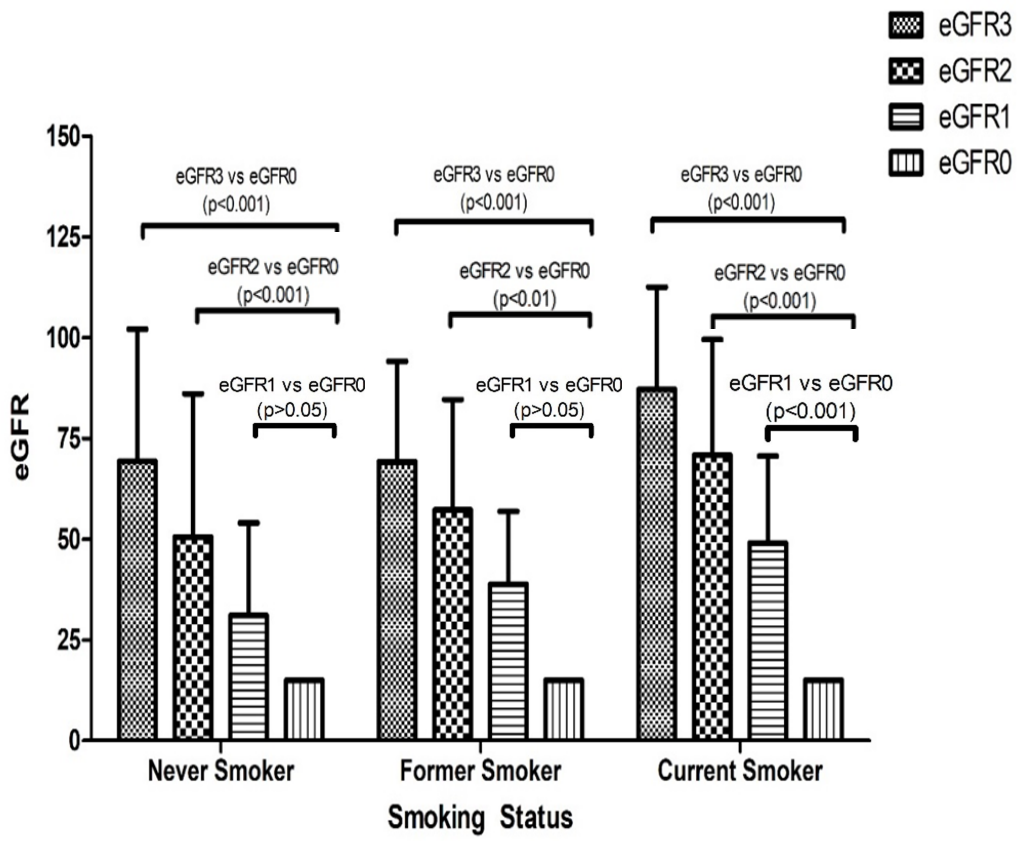

Figure 2. Decline in eGFR through Year 0 to Year 3 according to Smoking Status

former smokers as compared to the never smoker, however, statistical significance was not achieved. In eGFR1, current smoker has higher eGFR than never smoker with a $p < 0.05$. in eGFR0, samples all have a standard error of zero since all values of eGFR are 15. One-way ANOVA cannot be analyzed at this time.

Decline in eGFR. There was a significant progressive reduction in estimated GFR from year 3 (eGFR3) to year 0 (eGFR0) in all smoking status. Among the three, current smokers have the highest significant reduction in eGFR from year 3 to year 0 ($p<0.001$), year 2 to year 0, and year 1 to year 0. No significant reduction was noted in the eGFR of all smoking status from year 3 (eGFR3) to year 1 (eGFR1), eGFR3 to eGFR2 and eGFR2 to eGFR1 prior to HD.

There was a significant progressive reduction in estimated GFR from year 3 (eGFR3) to year 0 (eGFR0) prior to HD in never smoker, former smoker, and current smokers as shown in *Figure 2*. (p values are highlighted in red in the table below. All three smoking status have significant reduction from year 3 to year 0 prior to HD (all p<0.001). Among the three, current smokers have the highest significant reduction in eGFR from year 3 to year 1 prior to HD ($p<0.001$).

There was a significant progressive reduction in estimated GFR from year 2 (eGFR2) to year 0 (eGFR0) prior to HD in never smoker, former smoker, and current smokers as shown in Figure 3. (p values are highlighted in red in the table below. All three smoking status have significant reduction from year 2 to year 0 prior to HD, the highest being in never and current smokers ($p<0.001$). No significant values were noted in former and never smokers.

We also see that there was a significant progressive reduction in eGFR from year 1 (eGFR1) to year 0 (eGFR0) prior to HD in current smokers. No significant statistical difference were noted in former and never smokers.

Decline in eGFR VS Smoking Status per Primary Disease. Decline in eGFRs were compared to the smoking status per primary disease entity, namely hypertension, diabetes, chronic glomerulonephritis, and obstructive causes. Analysis shows no significant difference in the decline of eGFR either never smoker, former smoker and current smoker among participants with Hypertension ($p = 0.643$), Diabetes ($p = 0.963$), and Chronic Glomerulonephritis ($p = 0.649$). However, variance analysis for participants with Obstructive causes cannot be performed due to limited number of variables and sample size (2 participants).

Discussion

This study was made to determine the possible effect of smoking, either formerly or currently smoking on the eGFR of CKD patients of ARMMC Hemodialysis Unit. CKD is multifactorial in general and a lot of variables might be contributory to disease progression. Tobacco smoking in any form is associated with atherosclerotic cardiovascular disease by causing endothelial dysfunction and promoting oxidative stress. As proven in some animal studies, it promotes mesangial cell proliferation, and podocyte injury worsening the severity of kidney injury.[7] CKD and progressive decline in renal function are highly variable even if the individuals have the same underlying and degree of functional impairment. Variability of risk is typical on such complex diseases, which means that the multifactorial factors may be involved in the disease process and progression.[11] Knowing that, measures should be done and determined to prevent or even delay disease progression of CKD.

This study showed that smoking is inversely proportional to the eGFR value. Three smoking statuses were compared: never smoker, current smoker and former smokers. As seen in the clinical characteristics, some smokers, both current and former, had a higher eGFR, 3-years, 2-years, and 1-year prior to dialysis initiation as compared to the never smokers who are mostly already had a noticeable kidney injury to begin with. This means that some smokers included in the study still had a good kidney function on the start of year measurement. There is no significant difference in the eGFR3 and eGFR2 in all three-smoking status. Statistical significance was noted on comparing eGFR3 and eGFR1, most notably among current smokers, with a $p < 0.001$. This means that during this period, there are already signs of progressive renal damage, as seen by a drop in the eGFR from a previously normal kidney function. Further deterioration of kidney damage was shown on comparing the eGFR3 and eGFR0. Current smokers had the highest change in the eGFR among the three smoking status, which means they had the fastest decline in the eGFR.

In this study, it is noted that there is no difference in the decline of eGFR among smoking status in all primary diseases, as all of them will decline eventually regardless of the smoking status. This clearly proves the progressive nature of the disease, which could be multifactorial. But the fact that smoking hastens the disease progression cannot be ignored as shown in the analyses above.

A cross-sectional study done by Ishizaka et. al, concluded that cigarette smoking decreases the prevalence of low eGFR.[8] Comparing it to our study, an opposite result was achieved. Our study shows the deleterious effect of smoking among Filipino patients with CKD. There might be a multifactorial variable that affects the study and cause the differences, like the race, environmental, cultural and behavioral factors. But further study is suggested to consider the other variables.

Our study has some limitations. First, we only use the eGFR Creatinine as an estimate of the renal function. There are other markers of kidney damage such as presence of albuminuria, urinary sediments, electrolyte disturbances and structural deformities. These parameters can be used for predicting the prognosis of renal damage. Second, smoking habits was obtained subjectively by history taking and queries. This could affect the study if there are inconsistencies in the subject's response. Currently there are measurable variables with regards to smoking, such as cotinine level that could be measured in blood, urine, saliva, hair and nails. It is the most widely use biomarker in the US.[5] Third, due to the time and resources limitation, a small sample size was used. A cohort, prospective study using a bigger sample size or using the general population could be an alternative method to better achieve statistical values.

In conclusion, smoking hastens the progression of CKD to ESRD among Filipinos. With that, we support the smoking cessation campaign of the ARMMC and the DOH. We suggest to do further study using linear correlation with the Pack-Year and the decline in eGFR. In addition, further work up is suggested to determine the primary mechanistic pathway of smoking that affects the renal cells.

Conflict of Interest. The authors declare no affiliations with any organization or sect that had financial nor non-financial interest in the subject matter or materials discussed.

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APPENDICES

Descriptives

		N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
						Lower Bound	Upper Bound		
Age	Never Smoker	19	42.00	17.436	4.000	33.60	50.40	18	71
	Former Smoker	10	59.50	10.363	3.277	52.09	66.91	45	75
	Current Smoker	26	48.12	13.116	2.572	42.82	53.41	21	69
	Total	55	48.07	15.363	2.072	43.92	52.23	18	75
Disease Duration (years)	Never Smoker	19	4.95	4.314	.990	2.87	7.03	1	15
	Former Smoker	10	9.30	6.255	1.978	4.83	13.77	1	20
	Current Smoker	26	5.81	3.533	.693	4.38	7.23	1	15
	Total	55	6.15	4.572	.617	4.91	7.38	1	20
Age Started on HD	Never Smoker	19	40.84	17.405	3.993	32.45	49.23	16	69
	Former Smoker	10	58.40	9.834	3.110	51.37	65.43	45	74
	Current Smoker	26	45.92	13.717	2.690	40.38	51.46	18	68
	Total	55	46.44	15.551	2.097	42.23	50.64	16	74
Creatinine 1 Year Prior	Never Smoker	19	225.26	75.009	17.208	189.11	261.42	70	350
	Former Smoker	10	172.00	62.858	19.877	127.03	216.97	90	310
	Current Smoker	26	163.27	65.068	12.761	136.99	189.55	80	400
	Total	55	186.27	72.949	9.836	166.55	205.99	70	400
eGFR 1	Never Smoker	19	31.06	22.932	5.261	20.01	42.11	11	110
	Former Smoker	10	38.78	18.142	5.737	25.80	51.76	18	73
	Current Smoker	26	48.98	21.602	4.236	40.26	57.71	16	109
	Total	55	40.94	22.640	3.053	34.82	47.06	11	110
Creatinine 2 Years Prior	Never Smoker	19	159.47	68.107	15.625	126.65	192.30	60	280
	Former Smoker	10	132.00	66.800	21.124	84.21	179.79	60	280
	Current Smoker	26	119.62	45.911	9.004	101.07	138.16	60	250
	Total	55	135.64	59.931	8.081	119.43	151.84	60	280
eGFR 2	Never Smoker	19	50.54	35.520	8.149	33.42	67.66	17	141
	Former Smoker	10	57.22	27.412	8.668	37.61	76.83	21	98
	Current Smoker	26	70.86	28.631	5.615	59.30	82.43	28	141
	Total	55	61.36	31.830	4.292	52.76	69.96	17	141
Creatinine 3 Years Prior	Never Smoker	19	108.95	35.417	8.125	91.88	126.02	60	200
	Former Smoker	10	103.50	36.059	11.403	77.70	129.30	60	150
	Current Smoker	26	94.92	23.962	4.699	85.24	104.60	60	170
	Total	55	101.33	30.687	4.138	93.03	109.62	60	200
eGFR 3	Never Smoker	19	69.30	32.780	7.520	53.50	85.10	30	127
	Former Smoker	10	69.18	24.925	7.882	51.35	87.01	35	99
	Current Smoker	26	87.16	25.320	4.966	76.93	97.39	41	127
	Total	55	77.72	28.981	3.908	69.89	85.56	30	127
Pack Years	Never Smoker	19	.00	.000	.000	.00	.00	0	0
	Former Smoker	10	15.65	13.744	4.346	5.82	25.48	2	40
	Current Smoker	26	13.12	9.407	1.845	9.32	16.91	2	35
	Total	55	9.05	10.830	1.460	6.12	11.97	0	40

ANOVA

		Sum of Squares	df	Mean Square	F	P Value
Age	Between Groups	2006.555	2	1003.278	4.858	.012
	Within Groups	10739.154	52	206.522		
	Total	12745.709	54			
Disease Duration (years)	Between Groups	129.751	2	64.875	3.377	.042
	Within Groups	999.086	52	19.213		
	Total	1128.836	54			
Age Started on HD	Between Groups	2032.755	2	1016.377	4.793	.012
	Within Groups	11026.772	52	212.053		
	Total	13059.527	54			
Creatinine 1 Year Prior	Between Groups	44680.109	2	22340.055	4.787	.012
	Within Groups	242680.800	52	4666.938		
	Total	287360.909	54			

eGFR 1	Between Groups	3584.731	2	1792.366	3.868	.027
	Within Groups	24093.876	52	463.344		
	Total	27678.607	54			
Creatinine 2 Years Prior	Between Groups	17601.837	2	8800.918	2.595	.084
	Within Groups	176350.891	52	3391.363		
	Total	193952.727	54			
eGFR 2	Between Groups	4744.330	2	2372.165	2.469	.095
	Within Groups	49965.902	52	960.883		
	Total	54710.232	54			
Creatinine 3 Years Prior	Between Groups	2216.816	2	1108.408	1.185	.314
	Within Groups	48635.294	52	935.294		
	Total	50852.109	54			
eGFR 3	Between Groups	4394.056	2	2197.028	2.789	.071
	Within Groups	40960.838	52	787.708		
	Total	45354.894	54			
Pack Years	Between Groups	2421.458	2	1210.729	16.093	.001
	Within Groups	3912.179	52	75.234		
	Total	6333.636	54			

Multiple Comparisons

Bonferroni

Dependent Variable	(I) Smoking Status	(J) Smoking Status	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
						Lower Bound	Upper Bound
Age	Never Smoker	Former Smoker	-17.500*	5.614	.009	-31.39	-3.61
		Current Smoker	-6.115	4.337	.494	-16.85	4.61
	Former Smoker	Never Smoker	17.500*	5.614	.009	3.61	31.39
		Current Smoker	11.385	5.347	.114	-1.84	24.61
	Current Smoker	Never Smoker	6.115	4.337	.494	-4.61	16.85
		Former Smoker	-11.385	5.347	.114	-24.61	1.84
Disease Duration (years)	Never Smoker	Former Smoker	-4.353*	1.712	.042	-8.59	-.12
		Current Smoker	-.860	1.323	1.000	-4.13	2.41
	Former Smoker	Never Smoker	4.353*	1.712	.042	.12	8.59
		Current Smoker	3.492	1.631	.111	-.54	7.53
	Current Smoker	Never Smoker	.860	1.323	1.000	-2.41	4.13
		Former Smoker	-3.492	1.631	.111	-7.53	.54
Age Started on HD	Never Smoker	Former Smoker	-17.558*	5.689	.010	-31.63	-3.48
		Current Smoker	-5.081	4.395	.759	-15.95	5.79
	Former Smoker	Never Smoker	17.558*	5.689	.010	3.48	31.63
		Current Smoker	12.477	5.419	.076	-.93	25.88
	Current Smoker	Never Smoker	5.081	4.395	.759	-5.79	15.95
		Former Smoker	-12.477	5.419	.076	-25.88	.93
Creatinine 1 Year Prior	Never Smoker	Former Smoker	53.263	26.689	.154	-12.76	119.29
		Current Smoker	61.994*	20.619	.012	10.99	113.00
	Former Smoker	Never Smoker	-53.263	26.689	.154	-119.29	12.76
		Current Smoker	8.731	25.420	1.000	-54.16	71.62
	Current Smoker	Never Smoker	-61.994*	20.619	.012	-113.00	-10.99
		Former Smoker	-8.731	25.420	1.000	-71.62	54.16
eGFR 1	Never Smoker	Former Smoker	-7.722	8.410	1.000	-28.53	13.08
		Current Smoker	-17.927*	6.497	.024	-34.00	-1.85
	Former Smoker	Never Smoker	7.722	8.410	1.000	-13.08	28.53
		Current Smoker	-10.205	8.010	.625	-30.02	9.61
	Current Smoker	Never Smoker	17.927*	6.497	.024	1.85	34.00
		Former Smoker	10.205	8.010	.625	-9.61	30.02
Creatinine 2 Years Prior	Never Smoker	Former Smoker	27.474	22.751	.698	-28.81	83.76
		Current Smoker	39.858	17.576	.083	-3.62	83.34
	Former Smoker	Never Smoker	-27.474	22.751	.698	-83.76	28.81
		Current Smoker	12.385	21.670	1.000	-41.22	65.99
	Current Smoker	Never Smoker	-39.858	17.576	.083	-83.34	3.62
		Former Smoker	-12.385	21.670	1.000	-65.99	41.22
eGFR 2	Never Smoker	Former Smoker	-6.683	12.110	1.000	-36.64	23.28
		Current Smoker	-20.325	9.356	.103	-43.47	2.82
	Former Smoker	Never Smoker	6.683	12.110	1.000	-23.28	36.64
		Current Smoker	-13.642	11.535	.727	-42.18	14.89

Creatinine 3 Years Prior	Current Smoker	Never Smoker	20.325	9.356	.103	-2.82	43.47
		Former Smoker	13.642	11.535	.727	-14.89	42.18
	Never Smoker	Former Smoker	5.447	11.948	1.000	-24.11	35.01
		Current Smoker	14.024	9.230	.404	-8.81	36.86
	Former Smoker	Never Smoker	-5.447	11.948	1.000	-35.01	24.11
		Current Smoker	8.577	11.380	1.000	-19.58	36.73
	Current Smoker	Never Smoker	-14.024	9.230	.404	-36.86	8.81
		Former Smoker	-8.577	11.380	1.000	-36.73	19.58
eGFR 3	Never Smoker	Former Smoker	.120	10.965	1.000	-27.01	27.25
		Current Smoker	-17.862	8.471	.119	-38.82	3.09
	Former Smoker	Never Smoker	-.120	10.965	1.000	-27.25	27.01
		Current Smoker	-17.982	10.444	.273	-43.82	7.85
	Current Smoker	Never Smoker	17.862	8.471	.119	-3.09	38.82
		Former Smoker	17.982	10.444	.273	-7.85	43.82
Pack Years	Never Smoker	Former Smoker	-15.650*	3.389	.000	-24.03	-7.27
		Current Smoker	-13.115*	2.618	.000	-19.59	-6.64
	Former Smoker	Never Smoker	15.650*	3.389	.000	7.27	24.03
		Current Smoker	2.535	3.228	1.000	-5.45	10.52
	Current Smoker	Never Smoker	13.115*	2.618	.000	6.64	19.59
		Former Smoker	-2.535	3.228	1.000	-10.52	5.45

*. The mean difference is significant at the 0.05 level.

Appendix for Fig 1

eGFR3 vs Smoking Status

ANOVA Table	SS	df	MS		
Treatment (between columns)	4394	2	2197		
Residual (within columns)	40961	52	788		
Total	45355	54			
Bonferroni's Multiple Comparison Test	Mean Diff.	t	Significant? P < 0.05?	Summary	95% CI of diff
Never Smoker vs Former Smoker	0.12	0.011	No	ns	-27 to 27
Never Smoker vs Current Smoker	-18	2.1	No	ns	-39 to 3.1
Former Smoker vs Current Smoker	-18	1.7	No	ns	-44 to 7.9

eGFR2 vs Smoking Status

ANOVA Table	SS	df	MS		
Treatment (between columns)	4744	2	2372		
Residual (within columns)	49966	52	961		
Total	54710	54			
Bonferroni's Multiple Comparison Test	Mean Diff.	t	Significant? P < 0.05?	Summary	95% CI of diff
Never Smoker vs Former Smoker	-6.7	0.55	No	ns	-37 to 23
Never Smoker vs Current Smoker	-20	2.2	No	ns	-43 to 2.8
Former Smoker vs Current Smoker	-14	1.2	No	ns	-42 to 15

eGFR1 vs Smoking Status

ANOVA Table	SS	df	MS		
Treatment (between columns)	3585	2	1792		
Residual (within columns)	24094	52	463		
Total	27679	54			
Bonferroni's Multiple Comparison Test	Mean Diff.	t	Significant? P < 0.05?	Summary	95% CI of diff
Never Smoker vs Former Smoker	-7.7	0.92	No	ns	-29 to 13
Never Smoker vs Current Smoker	-18	2.8	Yes	*	-34 to -1.9
Former Smoker vs Current Smoker	-10	1.3	No	ns	-30 to 9.6

*- significant; ns – not significant

eGFR0 vs Smoking Status

	Never Smoker	Former Smoker	Current Smoker
Number of values	19	10	26
Minimum	15	15	15
25% Percentile	15	15	15
Median	15	15	15
75% Percentile	15	15	15
Maximum	15	15	15
Mean	15	15	15

Std. Deviation	0.0	0.0	0.0
Std. Error	0.0	0.0	0.0
Lower 95% CI	15	15	15
Upper 95% CI	15	15	15

Appendix for Figure 2

Table Analyzed	Data 1			
Two-way ANOVA				
Source of Variation	% of total variation	P value		
Interaction	12.39	< 0.0001		
eGFR	24.54	< 0.0001		
Smoking Status	15.89	< 0.0001		
Source of Variation	P value summary	Significant?		
Interaction	***	Yes		
eGFR	***	Yes		
Smoking Status	***	Yes		
Source of Variation	Df	Sum-of-squares	Mean square	F
Interaction	4	30199	7550	10
eGFR	2	59828	29914	41
Smoking Status	2	38726	19363	26
Residual	156	115016	737	
Number of missing values	69			
Bonferroni posttests				
eGFR3 vs eGFR2				
Smoking Status	eGFR3	eGFR2	Difference	95% CI of diff.
Never Smoker	69	51	-19	-46 to 8.0
Former Smoker	69	57	-12	-49 to 25
Current Smoker	87	71	-16	-39 to 6.6
Smoking Status	Difference	t	P value	Summary
Never Smoker	-19	2.1	P > 0.05	ns
Former Smoker	-12	0.98	P > 0.05	ns
Current Smoker	-16	2.2	P > 0.05	ns
eGFR3 vs eGFR1				
Smoking Status	eGFR3	eGFR1	Difference	95% CI of diff.
Never Smoker	69	31	-38	-65 to -11
Former Smoker	69	39	-30	-67 to 6.5
Current Smoker	87	49	-38	-61 to -15
Smoking Status	Difference	t	P value	Summary
Never Smoker	-38	4.3	P < 0.05	*
Former Smoker	-30	2.5	P < 0.05	*
Current Smoker	-38	5.1	P<0.001	***
eGFR3 vs eGFR0				
Smoking Status	eGFR3	eGFR0	Difference	95% CI of diff.
Never Smoker	69	15	-54	-81 to -28
Former Smoker	69	15	-54	-91 to -17
Current Smoker	87	15	-72	-95 to -49
Smoking Status	Difference	t	P value	Summary
Never Smoker	-54	6.2	P<0.001	***
Former Smoker	-54	4.5	P<0.001	***
Current Smoker	-72	9.6	P<0.001	***
eGFR2 vs eGFR1				
Smoking Status	eGFR2	eGFR1	Difference	95% CI of diff.
Never Smoker	51	31	-19	-46 to 7.3
Former Smoker	57	39	-18	-55 to 18
Current Smoker	71	49	-22	-45 to 1.0
Smoking Status	Difference	t	P value	Summary
Never Smoker	-19	2.2	P > 0.05	ns
Former Smoker	-18	1.5	P > 0.05	ns
Current Smoker	-22	2.9	P < 0.05	*
eGFR2 vs eGFR0				
Smoking Status	eGFR2	eGFR0	Difference	95% CI of diff.
Never Smoker	51	15	-36	-62 to -8.8
Former Smoker	57	15	-42	-79 to -5.3
Current Smoker	71	15	-56	-79 to -33
Smoking Status	Difference	t	P value	Summary

Never Smoker	-36	4.0	P<0.001	***
Former Smoker	-42	3.5	P<0.01	**
Current Smoker	-56	7.4	P<0.001	***
eGFR1 vs eGFR0				
Smoking Status	eGFR1	eGFR0	Difference	95% CI of diff.
Never Smoker	31	15	-16	-43 to 11
Former Smoker	39	15	-24	-61 to 13
Current Smoker	49	15	-34	-57 to -11
Smoking Status	Difference	t	P value	Summary
Never Smoker	-16	1.8	P > 0.05	ns
Former Smoker	-24	2.0	P > 0.05	ns
Current Smoker	-34	4.5	P<0.001	***

ns – not significant; * - p<0.05; ** - p<0.01; *** - p <0.001

Decline in eGFR VS Smoking Status per Primary Disease

Hypertension

Descriptives

Decline in eGFR

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Never Smoker	3	40.33	21.008	12.129	-11.85	92.52	19	61
Former Smoker	2	28.00	7.071	5.000	-35.53	91.53	23	33
Current Smoker	6	32.50	12.865	5.252	19.00	46.00	14	52
Total	11	33.82	14.020	4.227	24.40	43.24	14	61

ANOVA

Decline in eGFR

	Sum of Squares	Df	Mean Square	F	Sig.
Between Groups	205.470	2	102.735	.467	.643
Within Groups	1760.167	8	220.021		
Total	1965.636	10			

Post Hoc Tests

Multiple Comparisons

Dependent Variable: Decline in eGFR
Bonferroni

(I) Smoking Status1	(J) Smoking Status1	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Never Smoker	Former Smoker	12.333	13.541	1.000	-28.50	53.17
	Current Smoker	7.833	10.489	1.000	-23.80	39.46
Former Smoker	Never Smoker	-12.333	13.541	1.000	-53.17	28.50
	Current Smoker	-4.500	12.111	1.000	-41.02	32.02
Current Smoker	Never Smoker	-7.833	10.489	1.000	-39.46	23.80
	Former Smoker	4.500	12.111	1.000	-32.02	41.02

Diabetes

Descriptives

Decline in eGFR

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Never Smoker	6	31.83	21.255	8.677	9.53	54.14	16	73
Former Smoker	7	31.71	20.621	7.794	12.64	50.79	10	66
Current Smoker	10	29.60	15.785	4.992	18.31	40.89	11	61
Total	23	30.83	17.938	3.740	23.07	38.58	10	73

ANOVA

Decline in eGFR

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	26.642	2	13.321	.038	.963
Within Groups	7052.662	20	352.633		
Total	7079.304	22			

Post Hoc Tests

Multiple Comparisons

Dependent Variable: Decline in eGFR
Bonferroni

(I) Smoking Status1	(J) Smoking Status1	Mean Difference (I-J)	Std. Error	Sig.	95% Confidence Interval	
					Lower Bound	Upper Bound
Never Smoker	Former Smoker	.119	10.447	1.000	-27.18	27.41
	Current Smoker	2.233	9.697	1.000	-23.10	27.57
Former Smoker	Never Smoker	-.119	10.447	1.000	-27.41	27.18
	Current Smoker	2.114	9.254	1.000	-22.06	26.29
Current Smoker	Never Smoker	-2.233	9.697	1.000	-27.57	23.10
	Former Smoker	-2.114	9.254	1.000	-26.29	22.06

Chronic Glomerulonephritis

Post hoc tests are not performed for Decline in eGFR because at least one group has fewer than two cases.

Descriptives

Decline in eGFR

	N	Mean	Std. Deviation	Std. Error	95% Confidence Interval for Mean		Minimum	Maximum
					Lower Bound	Upper Bound		
Never Smoker	8	38.63	27.959	9.885	15.25	62.00	3	90
Former Smoker	1	28.00	.	.	.	.	28	28
Current Smoker	10	49.60	31.546	9.976	27.03	72.17	1	94
Total	19	43.84	29.087	6.673	29.82	57.86	1	94

ANOVA

Decline in eGFR

	Sum of Squares	df	Mean Square	F	Sig.
Between Groups	800.251	2	400.126	.444	.649
Within Groups	14428.275	16	901.767		
Total	15228.526	18			

Obstructive

One-way Analysis of variance cannot be performed due to limited variables and sample size.

DEFINITION OF TERMS

1. **Never smoker,** an adult who has never smoked, or who has smoked less than 100 cigarettes in his or her lifetime;
2. **Former smoker:** An adult who has smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of interview or who had quit for more than 1 month
3. **Current smoker:** An adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes or who had quit smoking for 1 month or less[9].
4. **Chronic Kidney Disease**- presence of either kidney damage and a decreased GFR that is existing for more than 3 months, and it refers to all the 5 stages of kidney damage (CKD 1 to 5)[1].
5. **End Stage Renal Disease**- refers to the last stage of Chronic Kidney Disease (CKD 5). They are designated as CKD 5_D (dialysis) or CKD 5_T (kidney transplant)[13].