Cause-Specific Deaths in Non–Dialysis-Dependent CKD

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ABSTRACT

CKD is associated with higher risk of death, but details regarding differences in cause-specific death in CKD are unclear. We examined the leading causes of death among a non–dialysis-dependent CKD population using an electronic medical record-based CKD registry in a large healthcare system and the Ohio Department of Health mortality files. We included 33,478 white and 5042 black patients with CKD who resided in Ohio between January 2005 and September 2009 and had two measurements of eGFR<60 ml/min per 1.73 m^2 obtained 90 days apart. Causes of death (before ESRD) were classified into cardiovascular, malignancy, and non-cardiovascular/non-malignancy diseases and non–disease-related causes. During a median follow-up of 2.3 years, 6661 of 38,520 patients (17%) with CKD died. Cardiovascular diseases (34.7%) and malignant neoplasms (31.8%) were the leading causes of death, with malignancy-related deaths more common among those with earlier stages of kidney disease. After adjusting for covariates, each 5 ml/min per 1.73 m^2 decline in eGFR was associated with higher risk of death due to cardiovascular disease (hazard ratio [HR], 1.10; 95% confidence interval [95% CI], 1.08 to 1.12) and non-cardiovascular/non-malignancy diseases (HR, 1.12; 95% CI, 1.09 to 1.14) but not to malignancy. In the adjusted models, blacks had overall-mortality hazard ratios similar to those of whites but higher hazard ratios for cardiovascular deaths. Further studies to confirm these findings and explain the mechanisms for differences are warranted. In addition to lowering cardiovascular burden in CKD, efforts to target known risk factors for cancer at the population level are needed.

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CKD burden continues to grow and more than 20 million Americans are estimated to have CKD with varying levels of severity.[1] Several studies report that death prior to ESRD is much more common than progression to ESRD.[2,3] Go *et al.* reported a graded association between lower eGFR and higher risk of death, cardiovascular events, and hospitalization.[4] Subsequent studies have reported similar results of higher cardiovascular events and death, but cause-specific deaths in the non–dialysis-dependent CKD population are less well studied.[5]

The Center for Disease Control and Prevention (CDC) reports the leading causes of deaths in the general population every year by collecting cause-specific death from individual states. Diseases of the heart followed by malignancy are the leading causes of death in the general population.[6] Yet, the CKD population has greater comorbid conditions and thus the data from the general population might not be applicable to those with CKD. It is well known that CKD patients have more cardiovascular disease and hospitalizations.[4] Furthermore, patients with CKD are older and might sustain higher malignancy burden as cancer incidence increases with age. Few studies have reported higher incidence of various types of cancers among those with mild to moderate CKD.[7] Thus, better

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understanding of the causes of death in CKD could help focus efforts that target prevention strategies or disease management in those with CKD. Further, racial differences in reaching ESRD and death have been reported, but details about cause-specific deaths among various races remain unclear in CKD.[8–10]

We used a large electronic medical record-based CKD registry and Ohio state death data to examine if the risk for all-cause mortality increases with lower levels of kidney function. Further, we also aimed to compare the risks for each type of death (cardiovascular, malignancy, and non-cardiovascular non-malignancy) based on the stage of kidney disease, age, gender, race, and diabetes among the CKD population followed in our health system.

RESULTS

Patient characteristics

Our study population comprised 38,520 patients with CKD (Supplementary Figure 1). Mean age of the study population was 72.8±11.8 years with 43.7% being males and 13.1% blacks. Prevalence of diabetes, hypertension, malignancy, and coronary artery disease were 21.8%, 82.4%, 23.6%, and 19.4%, respectively. Mean eGFR was 46.5 ml/min per 1.73 m^2 with serum albumin of 4.1 mg/dl. Angiotensin converting enzyme inhibitors/angiotensin receptor blockers and statins were used among 61.3% and 54.5% of study participants. Other details of the study population are outlined in Table 1. Characteristics of patients based on age >65 versus <65 years, gender, and race are outlined in Supplementary Table 1.

Unadjusted and age-adjusted mortality rates

During a median follow-up of 2.3 years (25th percentile 1.1, and 75th percentile 3.5), 6661 died. The unadjusted mortality rate was 76.1 per 1000 years of follow-up (95% confidence interval [95% CI], 64.9 to 87.3) with higher rates among those >65 years, males, blacks, and those with advanced stages of kidney disease (Supplementary Table 2). Table 2 provides age-adjusted overall and cause-specific mortality rates/1000 years

Table 1. Characteristics of patients with CKD included in this analysis

Variables	All (*n*=38,520)	eGFR 45–59 (*n*=24,639)	eGFR 30–44 (*n*=10,816)	eGFR<30 (*n*=3695)
Age (years)	72.8 (11.8)	72.1 (11.3)	74.5 (11.8)	72.5 (14.1)
Male gender (*n*, %)	16818 (43.7)	10796 (43.8)	4393 (43.1)	1629 (44.1)
Blacks (*n*, %)	5042 (13.1)	2932 (11.9)	1368 (13.4)	742 (20.1)
Diabetes (*n*, %)	8385 (21.8)	5116 (20.8)	2309 (22.7)	960 (26.0)
Malignancy (*n*, %)	9100 (23.6)	6174 (25.1)	2234 (21.9)	692 (18.7)
Hypertension (*n*, %)	31742 (82.4)	20766 (84.3)	8117 (79.7)	2859 (77.4)
Hyperlipidemia (*n*, %)	29038 (75.4)	18974 (77.0)	7437 (73.0)	2627 (71.1)
Coronary artery disease (*n*, %)	7479 (19.4)	4642 (18.8)	2091 (20.5)	746 (20.2)
Congestive heart failure (*n*, %)	2812 (7.3)	1435 (5.8)	964 (9.5)	413 (11.2)
Body mass index (kg/m^2)[a]	29.3 (6.5)	29.4 (6.4)	29.3 (6.6)	29.3 (6.9)
BMI group (*n*, %)				
<18.5 kg/m^2	460 (1.2)	269 (1.1)	136 (1.3)	55 (1.5)
18.5–24.9 kg/m^2	8820 (22.9)	5530 (22.4)	2376 (23.3)	914 (24.7)
25–29.9 kg/m^2	13099 (34.0)	8578 (34.8)	3392 (33.3)	1129 (30.6)
≥30 kg/m^2	13971 (36.3)	9156 (37.2)	3569 (35.0)	1246 (33.7)
Missing	2170 (5.6)	1106 (4.5)	713 (7.0)	351 (9.5)
Smoker (*n*, %)				
No	28705 (74.5)	19092 (77.5)	7196 (70.6)	2417 (65.4)
Yes	2586 (6.7)	1680 (6.8)	654 (6.4)	252 (6.8)
Missing	7229 (18.8)	3867 (15.7)	2336 (22.9)	1026 (27.8)
eGFR (ml/min per 1.73 m^2)	46.5 (11.1)	53.4 (4.2)	38.6 (4.2)	22.2 (6.1)
Proteinuria (*n*, %)	4861(26.5)	2395(20.5)	1438(30.1)	1028(54.4)
Serum albumin (g/dl)[a]	4.1 (0.5)	4.1 (0.5)	4.0 (0.5)	3.9 (0.6)
Hemoglobin (g/dl)[a]	12.8 (1.8)	13.1 (1.7)	12.5 (1.8)	11.7 (1.8)
ACEI/ARB use (*n*, %)	23620 (61.3)	14715 (59.7)	6553 (64.3)	2352 (63.7)
Statins use (*n*, %)	20984 (54.5)	13536 (54.9)	5481 (53.8)	1967 (53.2)
Beta-blocker use (*n*, %)	21198 (55.0)	13084 (53.1)	5866 (57.6)	2248 (60.8)
Insurance (*n*, %)				
Medicare	31364 (81.4)	19851 (80.6)	8542 (83.9)	2971 (80.4)
Medicaid	258 (0.7)	127 (0.5)	82 (0.8)	49 (1.3)
Other	5763 (15.0)	3983 (16.2)	1260 (12.4)	520 (14.1)
Missing	1135 (2.9)	678 (2.8)	302 (3.0)	155 (4.2)

[a]Missing data for each of the following: BMI *n*=2170, proteinuria *n*=20,173; serum albumin *n*=7294, hemoglobin *n*=6258.
ACEI/ARB, Angiotensin converting enzyme inhibitors/angiotensin receptor blockers.

based on the various categories of eGFR and urine albumin-to-creatinine ratio (UACR).

Kidney function and causes of death

Overall, cardiovascular diseases (34.7%) and malignant neoplasms (31.8%) were the leading causes of death among our study population (Table 3). The proportion of deaths due to malignant neoplasms was higher among patients with eGFR 45–59 ml/min per 1.73 m^2 (CKD Stage 3a) while cardiovascular disease and non-cardiovascular/non-malignancy related deaths were higher among patients with lower eGFR categories. Supplemental Table 3 outlines the various types of malignancy-related deaths. In the Cox proportional hazards model examining eGFR as a continuous measure, higher eGFR was associated with better survival (Figure 1), but there was a non-linear effect where the survival benefit associated with each unit increase was stronger at lower levels of eGFR. Each 5 ml/min per 1.73 m^2 decline in eGFR was associated with higher risk due to cardiovascular disease (hazard ratio [HR] 1.11; 95% CI, 1.09 to 1.13), and non-cardiovascular/non-malignancy related deaths (HR 1.12; 95% CI, 1.10 to 1.14), but not malignancy-related deaths (HR 1.00; 95% CI, 0.98 to 1.02). Predicted three-year mortality risks due to various reasons are outlined in Figure 1. Similar results were noted in the categorical analysis based on the stages of CKD (Table 4). Associations between other covariates and cause-specific deaths are presented in Supplemental Table 4.

Cause-specific deaths for subgroups

Age >65 years versus age <65 years

In the Cox proportional hazards model, after adjusting for confounding variables, patients with CKD aged >65 years (versus age <65 years) had higher risk for all-cause deaths along with higher risk for deaths due to cardiovascular disease, malignancy, and non-cardiovascular/non-malignancy related deaths (Table 4).

Gender

After adjusting for covariates, males with CKD were at higher risk for overall deaths and had higher risk for deaths due to cardiovascular diseases, malignancy and non-cardiovascular/non-malignancy related deaths (Table 4).

Race

In the unadjusted model, blacks with CKD had higher risk of all-cause mortality and cardiovascular disease mortality, yet lower malignancy-related mortality compared with whites. However, after adjusting for covariates, blacks had similar risk for overall deaths and deaths due to malignancy but a higher risk of death due to cardiovascular diseases compared with whites (Figure 2).

Patients with diabetes versus non-patients with diabetes

After adjusting for covariates, patients with CKD and diabetes did not differ in their risk for all-cause deaths and cardiovascular deaths when compared with those without diabetes. However, patients with CKD and diabetes had lower risk for deaths due to malignancy and higher risk for non-cardiovascular/non-malignancy related deaths compared with those without diabetes (Table 4).

Sensitivity analyses

Results relating to additional sensitivity analyses are presented in the Supplemental methods/results section (Supplementary Tables 5 and 6).

DISCUSSION

Presence of CKD is associated with higher risk for death.[4,11,12] This report of cause-specific deaths among a large non–dialysis-dependent CKD population followed in our healthcare system documents that cardiovascular diseases and

Table 2. Age-adjusted mortality rates per 1000 years based on kidney function (eGFR and UACR)

eGFR	UACR<10	UACR 10-<30	UACR 30–300	UACR>300
All-cause deaths				
45–59 ml/min per 1.73 m^2	24.6 (19.9, 30.5)	29.0 (23.3, 36.1)	50.1 (41.8, 59.9)	82.2 (63.4, 106.6)
30–44 ml/min per 1.73 m^2	35.6 (26.1, 48.5)	55.8 (43.3, 72.0)	61.9 (49.9, 76.8)	70.1 (52.1, 94.2)
<30 ml/min per 1.73 m^2	54.4 (29.2,101.2)	59.5 (36.8, 96.0)	63.7 (44.0, 92.3)	99.9 (72.3, 138.0)
Cardiovascular deaths				
45–59 ml/min per 1.73 m^2	7.8 (5.4, 11.4)	10.8 (7.6, 15.3)	20.2 (15.3, 26.7)	35.3 (23.8, 52.4)
30–44 ml/min per 1.73 m^2	6.6 (3.3, 13.3)	17.7 (11.4, 27.5)	21.9 (15.4, 31.2)	31.1 (20.0, 48.3)
<30 ml/min per 1.73 m^2	20.5 (7.7, 55.0)	29.5 (15.2, 57.1)	22.4 (12.3, 41.0)	33.9 (19.6, 58.5)
Malignancy-related deaths				
45–59 ml/min per 1.73 m^2	9.4 (6.6, 13.4)	9.1 (6.1, 13.7)	13.3 (9.3, 19.1)	8.7 (3.9, 19.5)
30–44 ml/min per 1.73 m^2	12.3 (7.1, 21.3)	15.2 (9.1, 25.3)	13.2 (8.2, 21.4)	6.5 (2.4, 17.3)
<30 ml/min per 1.73 m^2	12.0 (3.0, 48.1)	4.0 (0.6, 28.1)	15.1 (6.7, 33.9)	11.2 (4.2, 29.9)
Non-cardiovascular/non-malignancy deaths				
45–59 ml/min per 1.73 m^2	6.6 (4.4, 9.9)	8.4 (5.7, 12.6)	15.8 (11.5, 21.7)	35.8 (24.2, 53.0)
30–44 ml/min per 1.73 m^2	17.0 (10.9, 26.5)	22.8 (15.4, 33.9)	25.4 (18.2, 35.5)	31.6 (20.3, 49.0)
<30 ml/min per 1.73 m^2	15.9 (5.1, 49.6)	23.8 (11.3, 50.3)	25.6 (14.4, 45.5)	50.6 (32.2, 79.6)

Table 3. Cause-specific deaths among those with non–dialysis-dependent CKD

Causes of death (*n*, %)	Overall (*n*=6661)	eGFR 45–59 (*n*=3308)	eGFR 30–44 (*n*=2261)	eGFR<30 (*n*=1092)
Cardiovascular diseases	2311 (34.7)	1017 (30.7)	862 (38.1)	432 (39.6)
Ischemic heart disease	1227 (18.4)	532 (16.1)	457 (20.2)	238 (21.8)
Heart failure	163 (2.4)	61 (1.8)	75 (3.3)	27 (2.5)
Cerebrovascular diseases	255 (3.8)	123 (3.7)	94 (4.2)	38 (3.5)
Other cardiovascular diseases	666 (10.0)	301 (9.1)	236 (10.4)	129 (11.8)
Malignant neoplasms	2117 (31.8)	1282 (38.8)	616 (27.2)	219 (20.1)
Non-cardiovascular/Non-malignancy				
Chronic lower respiratory disease	316 (4.7)	147 (4.4)	109 (4.8)	60 (5.5)
Diabetes mellitus	228 (3.4)	91 (2.8)	71 (3.1)	66 (6.0)
Nephritis, nephrotic syndrome and nephrosis	125 (1.9)	29 (0.9)	37 (1.6)	59 (5.4)
Alzheimer's disease	122 (1.8)	58 (1.8)	45 (2.0)	19 (1.7)
Influenza and pneumonia	113 (1.7)	48 (1.5)	43 (1.9)	22 (2.0)
Septicemia	95 (1.4)	47 (1.4)	33 (1.5)	15 (1.4)
Chronic liver disease and cirrhosis	66 (1.0)	26 (0.8)	27 (1.2)	13 (1.2)
Pneumonitis due to solids and liquids	50 (0.8)	22 (0.7)	18 (0.8)	10 (0.9)
Parkinson's disease	31 (0.5)	19 (0.6)	11 (0.5)	1 (0.1)
All other diseases	972 (14.6)	464 (14.0)	352 (15.6)	156 (14.3)
Non-disease related deaths[a]	115 (1.7)	58 (1.8)	37 (1.6)	20 (1.8)

[a]For example: homicide, suicide, accidents.

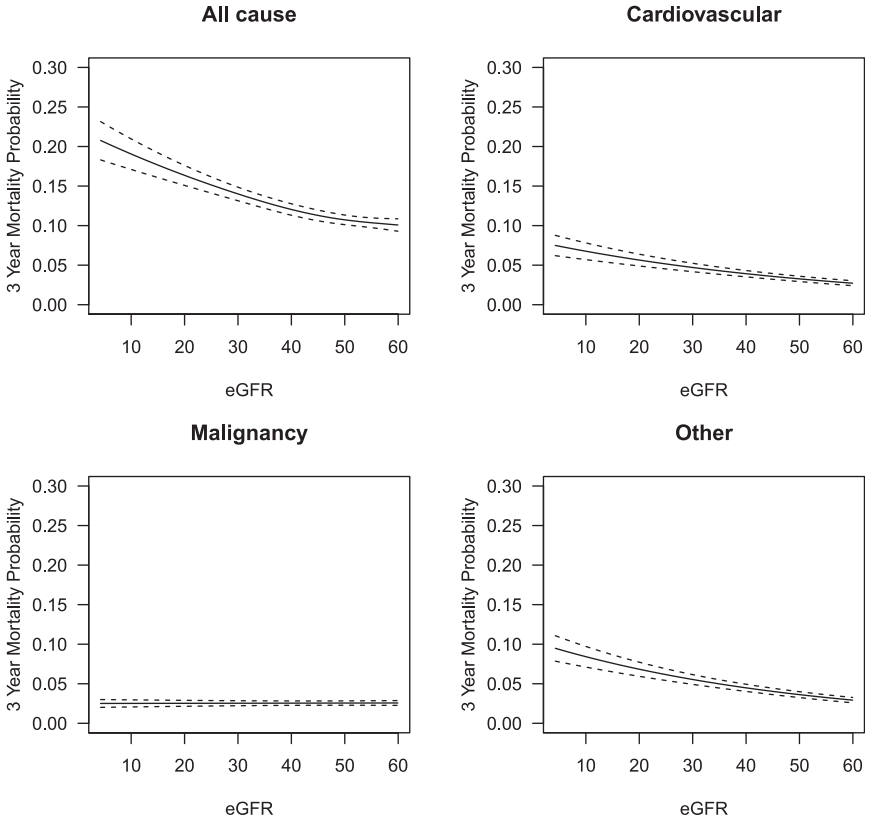

Figure 1. Predicted mortality due to all-cause, cardiovascular, malignancy, and other causes at three years in those with CKD.

malignancy are the leading causes of death and accounted for two-thirds of the deaths, a proportion higher than that reported in the general population (heart disease: 24.2%; malignant deaths: 23.3%). After accounting for underlying comorbid conditions, a decrement in eGFR was associated with an increased risk for overall, cardiovascular, non-cardiovascular/non-malignancy related deaths but not with malignancy-related deaths. Higher proportions of deaths in those with eGFR 45–59 ml/min per 1.73 m^2 were related to malignancy but cardiovascular deaths were the leading causes in those with lower eGFR categories. Even though blacks had similar risk as whites for all-cause mortality, they had higher risk for cardiovascular mortality and non-cardiovascular/non-malignancy related deaths.

Dialysis patients often die due to underlying cardiovascular causes, particularly sudden cardiac death.[13] Using data from the National Health and Nutrition Examination Survey, Muntner *et al.* reported 68% higher risk for cardiovascular mortality with eGFR<70 ml/min per 1.73 m^2 (versus >90 ml/min per 1.73 m^2).[14] A large meta-analysis of population-based cohorts reported increased risk for cardiovascular mortality with eGFR<60 ml/min per 1.73 m^2.[15,16] A secondary analysis of the Women's Health Initiative (*n*=1315) showed that eGFR<60 ml/min per 1.73 m^2 (versus >60 ml/min per 1.73 m^2) was associated with an increased risk for cardiovascular mortality but not for non-cardiovascular mortality.[17] Similarly, we noted higher cardiovascular mortality rates in those with lower levels of kidney function and among those aged >65 years and males. CKD is associated

Table 4. Associations between age, gender, diabetes and kidney function, and all-cause and cause-specific death in non–dialysis-dependent kidney disease

	Number of events	HR (95% CI) adjusted[a]
Age >65 years (n=29,501) versus <65 years (n=9019)		
All-cause mortality[b]	6661	1.73 (1.60 to 1.87)
Deaths due to cardiovascular disease	2311	2.45 (2.10 to 2.86)
Deaths due to malignancy	2117	1.31 (1.15 to 1.48)
Non-cardiovascular/non-malignancy death[c]	2118	1.86 (1.62 to 2.14)
Males (n=16,818) versus females (n=21,702)		
All-cause mortality[b]	6661	1.48 (1.41 to 1.56)
Deaths due to cardiovascular disease	2311	1.56 (1.43 to 1.71)
Deaths due to malignancy	2117	1.51 (1.38 to 1.65)
Non-cardiovascular/non-malignancy death[c]	2118	1.39 (1.27 to 1.53)
Patients with diabetes (n=8385) versus non-patients with diabetes (n=30,135)		
All-cause mortality[b]	6661	1.03 (0.96 to 1.10)
Deaths due to cardiovascular disease	2311	1.01 (0.90 to 1.13)
Deaths due to malignancy	2117	0.80 (0.70 to 0.92)
Non-cardiovascular/non-malignancy deaths[c]	2118	1.36 (1.21 to 1.53)
CKD Stage 3b (n=10,186) versus Stage 3a (n=24,639)		
All-cause mortality[b]	5569	1.21 (1.14 to 1.27)
Deaths due to cardiovascular disease	1879	1.35 (1.23 to 1.48
Deaths due to malignancy	1898	1.03 (0.93 to 1.14)
Non-cardiovascular/non-malignancy deaths[c]	1697	1.29 (1.17 to 1.42)
CKD Stages 4 and 5 (n=3695) versus Stage 3a (n=24,639)		
All-cause mortality[b]	4400	1.58 (1.46 to 1.70)
Deaths due to cardiovascular disease	1449	1.85 (1.64 to 2.09)
Deaths due to malignancy	1501	1.00 (0.86 to 1.16)
Non-cardiovascular/non-malignancy deaths[c]	1372	1.93 (1.71 to 2.18)

[a]Model includes age, race gender, diabetes, hypertension, hyperlipidemia, BMI group, albumin and hemoglobin, malignancy, coronary artery disease, congestive heart failure, insurance, Angiotensin converting enzyme inhibitors/angiotensin receptor blockers, statin, beta blocker, smoking, and CKD stage for all models except one model where age was substituted for age >65 to present categorical effect. HR shown were pooled using MIanalyze from five data sets created using multiple imputations.
[b]Includes all deaths related to non-disease causes.
[c]This does not include non-disease cause-related deaths.

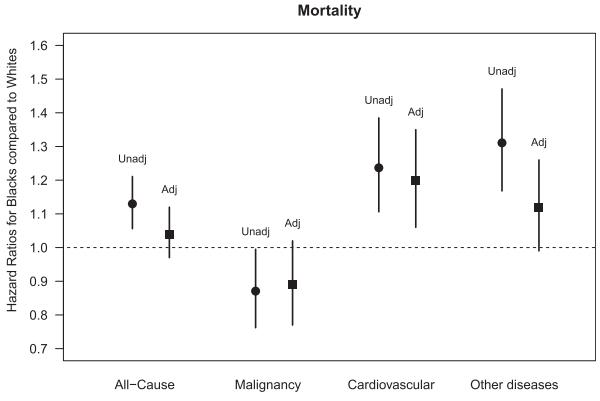

Figure 2. Risk for all-cause and major cause-specific deaths in blacks (versus whites).

with higher prevalence of both traditional and non-traditional cardiovascular risk factors (decline in kidney function *per se*) and as such may explain the observed associations.[18]

Nonetheless, malignancy accounted for nearly a third of the deaths and was the leading cause of death among those with stage 3a CKD. Recent studies have shown that the age-adjusted incidence rate of cancer is higher among those with CKD.[7,19] However, details about malignancy-related deaths are sparse, and a recent report from Taiwan indicated that patients with CKD had a higher mortality risk from liver, kidney, and urinary tract cancer.[20] Our results also highlight the leading causes of malignancy-related deaths (Supplemental Table 3) among the CKD population followed in our healthcare system. Overall, these higher numbers of cancer-related deaths could be attributed to the fact that a large proportion of patients receiving care for cancer at our healthcare system had underlying CKD or develop CKD during the treatment course. However, it is also important to note that the malignancy-related deaths have increased in the general population and whether our data reflect this pattern warrants further studies.

Studies examining the associations between CKD, ESRD, and death among blacks and whites had conflicting findings.[2,3,8,21] Weiner *et al.* reported that among those with CKD, blacks had relatively higher risk than whites (HR 1.76 versus 1.13) for all-cause mortality.[22] However, similar to us, the Kidney Early Evaluation Program and the most recent meta-analysis of several cohort studies did not report higher risk for

all-cause deaths for blacks.[15,23,24] Differences between these studies could be explained by the study timing (more recent studies showing narrowing of life expectancy gaps between races) and the differences between the confounders adjusted for in these studies.[25,26] While limited access to healthcare among blacks is reported to contribute to poor outcomes among blacks,[27] the number of office visits per year (a proxy for healthcare access) for blacks was in fact higher in our study population (median number of visits 5.7 for blacks versus 5.2 for whites). Blacks with albuminuria had higher risk for incident cardiovascular events and whether such differences in urinary protein excretion contribute to this higher risk is unclear.[28] Additionally, social determinants of health and other socio-economic factors likely could have played a role.[29] Cumulatively, our results argue for further studies to elucidate mechanisms underlying these higher cardiovascular deaths and the need for better monitoring and management of cardiovascular risk factors among blacks with CKD.

Risk for overall and other major causes of death was higher in those aged >65 years and among males suggesting the need to pay particular attention to screening and risk management in these subgroups. Lack of higher risk for all-cause deaths and cardiovascular mortality, and the lower risk for malignancy in those with diabetes and CKD is somewhat surprising. Recent studies in the general population showed that mortality rates among treated patients with diabetes is declining and such a trend might explain our findings.[30–32] The rates of deaths due to diabetes and respiratory diseases were higher in those with lower levels of kidney function. Given the smaller number of patients in individual subgroups, we could not conduct individual subgroup analysis. However, cumulatively, we noted higher risk for non-cardiovascular/non-malignancy related deaths with lower eGFR, highlighting the need for further studies.

The strengths of this study include a large CKD population which included those with two eGFR<60 ml/min per 1.73 m^2 and censored those who progressed to dialysis from a validated CKD registry and the availability of cause-specific death data from the Ohio State Department of Health. Even though our study is restricted to a single healthcare system, it is unlikely that CKD patients who live in the State of Ohio are substantially different from CKD patients cared for in other healthcare systems in other parts of the country. However, further studies using national databases are needed to know if there are differences and whether these data are generalizable (as we excluded patients belonging to races other than whites and blacks) and comparable to those with eGFR≥60 ml/min per 1.73 m^2. Proteinuria data were missing for about 50% of the study population; however, a sensitivity analysis restricting it to those with available urinary data showed similar findings. While we adjusted for several different confounding variables, we lacked details relating to screening procedures for cancer, treatment details for cancer, *etc*. It is also important to point out that we compared the risk for each type of death based on kidney disease and other characteristics. However, we did not examine the risk for underlying causes of death in various stages of kidney disease and based on other characteristics which could be examined in the future. Lastly, we obtained cause-specific deaths from the Ohio State Department of Health mortality files which provides data to the National Death Index for which there might be coding issues. However, these death indexes have been used by several studies in the past and are considered reliable.[33–35] Our internal validation process of those who died within our healthcare system also showed the reliability of these data.

In summary, our study found that cardiovascular diseases and malignancy were the leading causes of death among this non–dialysis-dependent CKD followed in a large healthcare system. A lower level of kidney function was associated with higher risk for cardiovascular mortality and deaths due to non-cardiovascular/non-malignancy diseases. Furthermore, blacks with non–dialysis-dependent CKD had a higher risk of cardiovascular deaths compared with whites. Additional studies among other CKD populations are needed to confirm these findings, and explain the mechanisms for the observed cause-specific death differences.

CONCISE METHODS

Patient population

We conducted an analysis using our preexisting electronic health record (EHR)-based CKD registry. The development and validation of it have been described in detail elsewhere.[36] Briefly, patients who had at least one face-to-face outpatient encounter with a Cleveland Clinic healthcare provider and had two eGFR values <60 ml/min per 1.73 m^2 more than 90 days apart between January 1, 2005, and September 15, 2009 were included. Patients aged <18 years old, and who were already diagnosed with ESRD needing dialysis or renal transplant were excluded. Patients who did not have ESRD prior to being included in the registry but subsequently developed ESRD or died during the study period are retained in the CKD registry. For this analysis, we included patients who met the following criteria: (a) had a valid social security number, (b) were residents of the State of Ohio, and (c) self-identified as either white or black (Supplementary Figure 1).

Kidney function

All serum creatinine measurements for the study population were performed in the same clinical laboratory by a Hitachi D 2400 Modular Chemistry Analyzer thereafter (Roche Diagnostics, Indianapolis, IN). CKD was classified into following stages: stage 3 CKD (eGFR 30–59 ml/min per 1.73 m^2), stage 4 CKD (eGFR 15–29 ml/min per 1.73 m^2), and stage 5 CKD (eGFR<15 ml/min per 1.73 m^2). We calculated eGFR using the CKD-EPI equation.[37] We further categorized stage 3 into CKD stage 3a (eGFR 45–59 ml/min per 1.73 m^2) and stage 3b (eGFR 30–44 ml/min per 1.73 m^2). To reflect clinical practice, patients who had a urine dipstick measurement, UACR, urine protein-to-creatinine ratio, and 24-hour urine studies were included to assess

whether they had proteinuria or not. The following cut-offs were considered in determining whether someone had proteinuria: presence of ≥1+ proteinuria in dipstick studies, >30 mg/g in those who had UACR and urine protein-to-creatinine ratio studies, and >30 mg proteinuria in 24-hour studies.

Covariates

Demographic details (age, gender, race, insurance details) were extracted from the EHR. Comorbid conditions such as diabetes mellitus, hypertension, coronary artery disease, malignancy, congestive heart failure, and hyperlipidemia were defined using prespecified criteria and were validated in an earlier publication.[36] These conditions existed prior to the second eGFR<60 ml/min per 1.73 m^2. We also extracted relevant laboratory data (serum albumin and hemoglobin) from the EHR.

Ascertainment of death and its causes

We linked our CKD registry with the Social Security Death Index and Ohio Department of Health mortality data to obtain details about mortality rates and cause-specific mortality details. The underlying cause of death was coded according to the *International Classification of Diseases*, Tenth Revision. We grouped the underlying causes of death as per the National Center for Health Statistics for each coding system except for some changes as outlined below. We classified deaths into the following four major categories along with reporting data for individual causes: (a) cardiovascular deaths, (b) malignancy, (c) non-cardiovascular/non-malignancy related and (d) other non–disease-related deaths (such as homicide/suicide/accidents). We defined cardiovascular deaths as deaths due to diseases of the heart, essential hypertension, cerebrovascular disease, atherosclerosis or other diseases of the circulatory system (*International Classification of Diseases*, Tenth Revision codes I00–I78). We also categorized the cardiovascular deaths into following clinically meaningful subcategories: ischemic heart disease (I20–I25), heart failure (I50), cerebrovascular diseases (I60s) and all other cardiovascular disease (include all others from I00 to I78 except I20–I25, I50, and I60). We have merged our CKD registry with the US Renal Data System (USRDS) to obtain details about those who transitioned to dialysis (up to September 15, 2009). To ensure that analysis represents only non–dialysis-dependent CKD, we censored patients at the time of transitioning to dialysis. All patients who survived until September 15, 2009 (last date USRDS data available) were censored on that date for mortality analyses.

Statistical analysis

We compared baseline characteristics among patients in various stages using chi-squared and ANOVA tests for categorical and continuous variables, respectively. Unadjusted mortality rates (per 1000 years of follow-up) were calculated overall and for various stages of CKD separately. We used a Poisson model to estimate age-adjusted death rates across Kidney Disease: Improving Global Outcomes risk groups. We tabulated the leading causes of pre-ESRD death overall and within various eGFR categories. We evaluated the relationship between eGFR categories, age >65, race, gender, and diabetes with various pre-ESRD mortality outcomes. We inspected log log plots for violations of the proportional hazards assumption. We fit separate univariable Cox proportional hazards models for each cause of death outcome (all-cause deaths, deaths due to cardiovascular disease, malignancy, and non-cardiovascular, non-malignant deaths). We then fit multivariable models for each mortality outcome including the following covariates: eGFR group, age, race, gender, diabetes, hypertension, hyperlipidemia, BMI, malignancy, coronary artery disease, congestive heart failure, insurance, use of Angiotensin converting enzyme inhibitors/angiotensin receptor blockers, statins and beta blockers, albumin, hemoglobin, and smoking. Nineteen percent of patients were missing serum albumin data, 16% were missing hemoglobin data, 19% were missing smoking status, 6% were missing BMI, and 3% were missing insurance. We used multiple imputations (SAS proc MI) with the Markov Chain Monte Carlo method and a single chain to impute five data sets with complete continuous and binary covariate data in a first step, and then in a second step we imputed insurance group on each of the five data sets using discriminant function analysis. All Cox models were performed on each of the five imputed data sets, and parameter estimates were combined using SAS MIanalyze. We also fit similar adjusted models with patients classified into age >65 versus <65, because prior research has shown age-related differences among the general population.[38] A separate analysis using eGFR as a continuous variable was also conducted. We tested the non-linearity of eGFR with restricted cubic splines. Methods relating to other additional sensitivity analyses are presented in the supplemental file (Supplementary methods and results).

All analyses were conducted using Unix SAS version 9.2 (SAS Institute, Inc., Cary, NC), and graphs were created using R 3.0.1 (The R Foundation for Statistical Computing, Vienna, Austria). The CKD registry and this study were approved by the Cleveland Clinic Institutional Review Board.

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DISCLOSURES

None.

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See related editorial, "Not All Deaths in CKD Are from a Broken Heart," on pages 2307–2308.

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