

# Relationship between Nephrologist Care and Progression of Chronic Kidney Disease

Lori A. Orlando, MD, MHS; William F. Owen, MD; and David B. Matchar, MD

## Abstract

**Background:** Since chronic kidney disease (CKD) affects 11% of the United States population, and its incidence is rising, experts recommend early referral to nephrologists in the hope that it may delay the onset of end-stage disease and improve survival. However, limitations in the capacity of currently practicing nephrologists may prevent widespread early referral.

**Objective:** To examine the relationship between disease progression and timing of nephrology referral.

**Study Design and Data Collection:** We retrospectively identified 1,553 veterans at the Durham, North Carolina VA hospital between January 1998 and December 1999 who had CKD, defined as two outpatient serum creatinines  $\geq 1.4$  mg/dL at least three months apart. Our endpoint was a composite of progression to the next CKD stage or death. We compared the time to the composite endpoint for each CKD stage and for early CKD (stages 1-3) to advanced CKD (stages 4 and 5) using a Cox proportional hazards model for two groups: those with primary care only (PCP-only) and those with primary and nephrology care (nephrology).

**Results:** Ninety-two percent had hypertension, 52% diabetes, 49% coronary artery disease, and 89% proteinuria. Angiotensin-converting enzyme inhibitors and anti-lipid medications were used by 52% and 39%, respectively. The median number of days spent in each CKD stage and the proportion of each groups reaching the composite endpoint are—stage 1: 1,149 days, 68% of the PCP-only group and 73% of the nephrology group; stage 2: 1,206 days, 60% and 65%; stage 3: 1,158 days, 69% and 63%; and stage 4: 794 days, 86% and 72%. Adjusted survival curves for the composite endpoint were similar between the two groups for CKD stages 1 (HR 1.08 for nephrology versus PCP-only) and 2 (HR 1.20); however for CKD stages 3 (HR 0.80,  $p < 0.05$ ) and 4 (HR 0.75,  $p < 0.05$ ), the nephrology group gained 316, 215, and 120 more days of progression-free survival, respectively.

**Limitations:** The major limitation is difficulty accounting for unmeasured bias in specialty referrals. We were unable to analyze stage 5-to-dialysis due to the small number of individuals with the outcome.

**Conclusion:** Our data suggest that an appropriate time for nephrology comanagement of patients with CKD may be stage 3; however, prospective studies are needed to clarify the role and timing of nephrology referral.

**Keywords:** chronic kidney disease, provider, kidney disease

## Background

Chronic kidney disease (CKD) affects 11% of the United States population, about 20 million people.<sup>1</sup> Improving the management of CKD has been shown to increase survival in those with CKD, delay the development of end-stage renal disease (ESRD), and improve morbidity and mortality once ESRD develops.<sup>2</sup> Slowing the rate of progression and delaying ESRD are now more important than ever as the incidence of CKD and ESRD is increasing, in large part due to the increasing

prevalence of CKD risk factors such as the aging of the population, hypertension, and diabetes mellitus.<sup>3</sup> This is true at both the national and state level. For example, in 2003 the point prevalence of ESRD in North Carolina was 14,635 with an incidence of 3,207—this makes us one of the top ten states for prevalence and incidence. Even more concerning, the prevalence increased 280% in the ten years between 1993 and 2003, slightly higher than the national average of 250%.<sup>4</sup>

ESRD accounts for \$20 billion per year in Medicare expenditures. With the increase in its incidence, expenditures are

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projected to reach \$42 billion per year by 2010.<sup>5</sup> Given concerns over the rising impact of CKD on the health of the general population and increasing expenditures for dialysis care, researchers have begun to investigate the impact of care in the pre-ESRD period on ESRD outcomes. Several of these studies have suggested that nephrology referral early in the pre-ESRD course may improve the morbidity and mortality on dialysis.<sup>6</sup> These studies, while methodologically limited by dichotomizing and varying the definition of early referral (from one month to one year predialysis), and the use of dialysis populations (not generalizable to predialysis populations), provided preliminary evidence in favor of early referral to sub-specialists.

Based upon these preliminary studies, experts have recommended early referral to nephrologists for all CKD patients. However, widespread implementation has been limited by the disparity between the capacity of currently practicing nephrologists and the number of CKD patients.<sup>7</sup> Since this disparity exists and the preliminary studies were methodologically limited, researchers have begun to investigate in more detail the impact and timing of nephrology care on renal-related outcomes.

In view of the conundrum between an inadequate number of subspecialists to deliver care and uncertainty about when their intervention may be of the greatest benefit, we examined the relationship between the severity of CKD, the presence of subspecialty care, and progression of CKD in a pre-ESRD population.

## Methods

We performed a retrospective observational database study of 1,553 veterans with CKD at the Durham, North Carolina Veterans Administration Hospital (VA). Our primary objective was to identify whether care provided by a nephrologist increases the time spent in any chronic kidney disease stage (ie, slows progression). The Durham VA Internal Review Board (IRB) approved this study.

We identified subjects by searching the local VA laboratory database for patients with serum creatinine concentrations measured between January 1, 1998 and December 31, 1999. Patients with two values  $\geq 1.4$  mg/dL, the upper limit of normal for our laboratory, during outpatient lab visits at least three months apart were included in the study. Patients were excluded if they were not followed in our primary care or nephrology clinics or if renal replacement therapy was initiated within 90 days of the first identified serum creatinine measurement.

## Measures

For every subject in the cohort, we obtained all serum creatinine, calcium, phosphorus, albumin, hemoglobin, low density lipoprotein (LDL), hemoglobin A1C (HgA1c), and urine protein quantification values in the laboratory database between the inclusion date and December 31, 2004. Creatinine measurements were converted into an estimated glomerular filtration rate (GFR) using the modified Modification by Diet of Renal Disease Study formula

( $GFR = \exp[5.228 - 1.154 \times \ln(\text{Scr}) - 0.203 \times \ln(\text{age}) - 0.299$  (if female)  $- 0.192$  (if black)])<sup>8</sup> and assigned a CKD stage using the Kidney Disease Outcomes Quality Initiative (KDOQI) CKD staging guidelines.<sup>9</sup> Specifically, stage 1 = GFR  $\geq 90$  mL/min with proteinuria, stage 2 = GFR  $< 90$  mL/min and  $\geq 60$  mL/min with proteinuria, stage 3 = GFR  $< 60$  mL/min and  $\geq 30$  mL/min, stage 4 = GFR  $< 30$  mL/min and  $\geq 15$  mL/min, and stage 5 = GFR  $< 15$  mL/min or renal replacement therapy. The values for calcium, phosphorous, albumin, hemoglobin, HgA1c, and LDL were each averaged over three-month periods during follow-up. CKD-related complications included hypocalcemia (serum calcium  $< 8.5$  mg/dL), hyperphosphatemia (serum phosphorus  $> 4.5$  mg/dL), hypoalbuminemia (serum albumin  $< 4$  g/dL), and anemia (serum hemoglobin  $< 12$  mg/dL), and were defined here according to the Renal Physicians Association's and KDOQI evidence-based guidelines.<sup>10</sup> Complications were considered present if  $\geq 50\%$  of the averages exceeded the recommended goal. HgA1c (goal  $\leq 7.0\%$ ), LDL (goal  $\leq 100$ mg/dL), and blood pressure values (goal  $\leq 135/85$ mmHg), also defined according to the above guidelines, were handled in the same manner. We used this method in order to evaluate the relationship between chronic exposure to CKD-related complications and/or poorly controlled comorbidities and long-term outcomes, such as disease progression and death.

We obtained data from the local pharmacy database on angiotensin converting enzyme inhibitors (ACEIs), angiotensin 2 receptor blockers (ARBs), erythropoietin, and lipid lowering agents prescribed during the study period. Prescriptions from the VA pharmacy are generally considered to be excellent indicators of medication usage since most veterans do not obtain drugs outside of the VA pharmacy and, due to the copay, do not request refills for medications not being taken. Medications were only included in the analysis if they were prescribed for at least six months.

We also collected data for the study period from the national inpatient and outpatient VA databases maintained in Austin, Texas. Data collected included demographics, comorbid conditions, blood pressure, and resource use (number of clinic visits and hospitalizations). These databases are a cumulative index of admissions and discharges from all United States VA medical centers and have been validated for reliability.<sup>11</sup> Comorbid conditions, including the presence of diabetes mellitus, hypertension, left ventricular hypertrophy (LVH), coronary artery disease (CAD), and current tobacco use, were identified using ICD-9 codes, while patient encounters with primary care physicians or nephrologists, clinic visits, and hospitalizations were identified using clinic and provider encounter codes. Race was categorized as white versus nonwhite. The CKD stage at first visit to nephrology was defined as the stage at initiation of nephrology care. Initiation of renal replacement therapy was identified by using ICD-9 and clinic codes from all three (local, national inpatient, and national outpatient) sources, as well as chart reviews of all patients with at least one GFR  $< 31$  mL/min. Death was identified using the national VA benefits database maintained in Austin.

## Analysis

The date of the first GFR within the cohort identification period (January 1, 1998 and December 31, 1999) for each patient was identified as the index date (time 0). The date of each subsequent GFR was used to calculate the number of days from the index date in order to construct a time course of GFR and CKD stage for each patient. In an effort to reduce the effect of regression to the mean and laboratory imprecision, we identified the index GFR as the average GFR for the three months prior to index date and we assumed that an individual remained in their current CKD stage until two measurements at least three weeks apart were either both higher or both lower than the previous stage. When this occurred, a new stage was assigned based upon the GFR at the time of the first of the two measurements.

In order to assess the effect of nephrology care on CKD course, we created two groups: PCP-only and PCP with nephrology (nephrology). Individuals who had nephrology clinic visits were assigned to the nephrology group, whereas those followed by a primary care physician only were assigned to the PCP-only group. Baseline characteristics were compared between these two groups using the Student's T-test for continuous variables and the Mantel-Haenszel chi-square for categorical variables.

Survival curves were constructed using all patients in a given stage to determine the time spent in each stage (ie, from stage 1 to 2, stage 2 to 3, stage 3 to 4, etc.), and the time from pre-advanced CKD, stages 1-3, to advanced CKD (ACKD), stages 4 and 5. The time spent in a given stage was defined as the time period between the very first assignment to that stage and a composite endpoint of either first assignment to a higher stage or death. If neither endpoint was reached then patients were censored at the time of their last follow-up. If an individual advanced more than one stage between measurements, then the time to the endpoint was defined as one half of the interval observed. Since many patients progressed through several CKD stages, a single individual may be represented in more than one survival curve.

We used a Kaplan-Meier survival curve to calculate the unadjusted progression-free survival time for each stage and a Cox Proportional Hazards model to compare the adjusted and unadjusted progression-free survival times between the nephrology and PCP-only groups for each stage. The adjusted model included age in years, race (white versus nonwhite), ACEI (use versus non-use), ACEI started during the analyzed stage, Anti-lipid agents (use versus non-use), uncontrolled diabetes (versus controlled diabetes—as defined in the measures section for HgbA1c > 7%), current tobacco use (versus noncurrent or no use), and diabetes (versus no

diabetes), hypertension (versus no hypertension), cardiovascular disease (versus no cardiovascular disease), or proteinuria (versus no proteinuria). We excluded measures of control (other than diabetes) from the model because we were limited in the number of covariates we could analyze by the frequency of the outcome. We also excluded CKD-related complications and resource use because we could not distinguish between cause and effect with our study design. Only individuals followed by a nephrologist during the stage being analyzed were assigned to the nephrology group, and only those taking a medication during the specified stage were assigned the medication. Since ACEIs may acutely decrease and then stabilize GFR, we created an indicator variable for those who initiated an ACEI during the analyzed stage (ACEI started during stage) in order to distinguish between its short-term and long-term effects.

We incorporated the propensity to be seen by a nephrologist into our model in order to account for potential bias in patients referred to subspecialists. These continuous scores, which represent the probability that an individual received nephrology care based upon modeled characteristics, are incorporated into the Cox Proportional Hazards model as a covariate to balance observed characteristics between the two groups. We calculated a propensity score<sup>12</sup> for the probability of receiving nephrology care using a logistic regression model adjusted for age (in years), race (nonwhite versus white), diabetes (versus no diabetes), hypertension (versus no hypertension), cardiovascular disease (versus no cardiovascular disease), ACEI use (versus non-use), anti-lipid medication use (versus non-use), hypocalcemia (present versus not present), hyperphosphatemia (present versus not present), anemia (present versus not present), number of hospitalizations, and rate of progression prior to nephrology care (average change in GFR prior to first visit).

**Table 1.**  
**Characteristics of the Study Cohort and the Two Subgroups at Baseline**

	Total	Nephrology	PCP-only	p-value
Number	1,553	456	1,097	
Age (range)	70 (26-98)	68.7	70.3	0.01
Nonwhite race (%)	32%	33%	32%	0.77
Diabetes (%)	52%	58%	49%	0.002
Hypertension (%)	92%	98%	90%	< 0.001
Proteinuria (%)	89%	75%	58%	< 0.001
Current Tobacco use (%)	21%	21%	21%	1.0
Coronary Artery Disease (%)	49%	56%	57%	0.49
Left ventricular hypertrophy (%)	3%	3%	3%	1.0
Hyperlipidemia (%)	24%	25%	24%	0.60
Average stage at cohort entry	1.3	1.6	1.1	< 0.001

## Results

The baseline characteristics for our cohort and the two subgroups, PCP-only and nephrology, are reported in Table 1. Follow-up characteristics, including disease management and the development of CKD-related complications, are reported in

Table 2. Our cohort was composed of mostly elderly individuals. All were male and 33% were nonwhite. More than 90% had hypertension, 50% had diabetes and coronary artery disease, 50% used ACEIs, and 39% used anti-lipid medications. Only 3% used erythropoietin and less than 1% used ARBs, which reflects limitations on access to these two classes of drugs at our VA. The average stage at entry into the cohort was very early (1.3), and the average stage for referral was also early (1.6). When comparing those followed by nephrologists to those followed only by a PCP, individuals in the PCP-only group were older and were less likely to have diabetes, hypertension, hypoalbuminemia, or hyperphosphatemia. Management of diabetes, hypertension, and hyperlipidemia were similar between the PCP-only and nephrology groups and both groups had a similar number of days of follow-up, 1,310 for the nephrology group and 1,285 for the PCP-only group. Of the cohort of 1,553 individuals, only 133 (8%) were lost to follow-up.

The outcomes of the survival and Cox proportional hazard

individuals in stage 1 progressed to the next stage than died, an equal number progressed as died in stage 2, and more progressed than died during stages 3 through 5. At each stage, proportionally fewer individuals in the PCP-only group progressed to the next CKD stage, but more died, than in the nephrology group.

The hazard ratio, an estimate of the relative risk for each covariate, is shown in Table 4. For the stage 4 to 5 model we only incorporated age, race, ACEI use, and anti-lipid medication use because the small number of outcomes limited the number of covariates that could be included in the model. All other models were analyzed with all the prespecified covariates. Nephrology care at stages 3 and 4 and during early CKD improved survival (adjusted HR 0.80, 0.75, and 0.91, respectively). ACEIs transiently reduce GFR as signified by a hazard ratio of greater than 1 for the ACEI started during stage variable; however, long-term they are protective and reduce the rate of progression by almost 40% for stages 1-3 and for pre-ACKD to ACKD. Lipid-lowering agents appear to be protective, whereas diabetes appears to be harmful.

Both effects were present across all the stages analyzed. In addition, proteinuria appears to predict a more rapid disease course for pre-ACKD to ACKD. We did not perform the Cox Proportional Hazards analysis for the stage 5 to ESRD group because of its small size, and we excluded comorbid conditions from the stage 4 to 5 analysis because the small number of individuals who reached the endpoint limited the number of covariates that could be analyzed.

## Discussion

Our findings suggest that nephrologists' involvement in the care of individuals with CKD is associated with a prolonged course of early CKD and delayed onset of ESRD. Individuals who

were followed by a nephrologist in addition to their PCP spent significantly more time in CKD stages 3-5 than those followed only by their primary care providers. This finding lends support to current recommendations for initiation of care by a subspecialist and suggests that referrals may be most beneficial around stage 3.

While our study suggests that the addition of nephrology care around stage 3 may play an important role in prolonging disease course, it does not provide an explanation for why this occurs. In order to gain some insight, we evaluated the management of comorbidities and the presence of chronic CKD-related

analyses are presented in Tables 3 and 4 and the curves derived from Cox proportional hazard analysis for each stage are depicted in Figure 1. These show that individuals spent a median of 3.2 years per stage in stages 1, 2, and 3, but only 2.1 years in stages 4-5. There was no difference between the PCP-only and nephrology groups for the unadjusted time spent in stage 1 or stage 2; but for stages 3 through 5 and early to advanced CKD, those in the nephrology group spent 316, 251, 120, and 55 more days, respectively, in each stage than those in the PCP-only group. Of those who reached the composite endpoint, more

**Table 2.**  
**Characteristics of Management and CKD-related Complications during Follow-up of the Study Cohort and the Two Subgroups**

	Total	Nephrology	PCP-only	p-value
Number	1,553	456	1,097	
Days of follow-up (mean)	1,296	1,310	1,285	0.30
Hospitalizations, mean (range)*	2.6 (0-28)	2.8	2.5	0.03
Clinic visits, mean (range)*	141 (7-1,412)	170	129	< 0.001
Lipid lowering agent (%)	39%	43%	38%	0.58
ACEI (%)	52%	51%	52%	0.07
Blood pressure < 135/85(%) <sup>#</sup>	37%	41%	36%	0.06
HgA1c < 7% (%) <sup>#</sup>	39%	38%	40%	0.10
LDL < 100 mg/dL (%) <sup>#</sup>	33%	32%	36%	0.06
Calcium < 8.5 mg/dL (%) <sup>#</sup>	6%	6%	6%	0.82
Albumin < 4 g/dL (%) <sup>#</sup>	50%	59%	49%	< 0.001
Hemoglobin < 12 mg/dL (%) <sup>#</sup>	9%	10%	9%	0.63
Phosphorus > 4.5 mg/dL (%) <sup>#</sup>	6%	9%	5%	0.006

ACEI=angiotensin converting enzyme inhibitor; HgA1c=hemoglobin A1c; LDL=low density lipoprotein

\*This is the average and range of the total number of visits during the follow-up period per patient.

<sup>#</sup> Individual values for each patient were averaged over three-month periods during follow-up. If  $\geq 50\%$  of the averages exceeded the recommended goal then the patient was considered uncontrolled. Table reports % of patients who are uncontrolled.

Legend: Medication use is presented as the proportion of the group using the medication for at least six months during the study period. The management of diabetes, hypertension, and hyperlipidemia as well as the complications of CKD are presented as the proportion with 50% or more of their three-month averages outside of the recommended values.

**Table 3.**  
**Results of the Unadjusted Survival Analyses**

	Stage 1 to 2	Stage 2 to 3	Stage 3 to 4	Stage 4 to 5	Stage 5 to ESRD	Pre-ACKD to ACKD
Total Cohort (#)	1,217	887	416	86	26	1,530
CKD progression # (%)	583 (48%)	276 (31%)	70 (17%)	21 (24%)	6 (23%)	94 (6%)
died # (%)	255 (21%)	273 (31%)	205 (49%)	45 (52%)	7 (27%)	701 (46%)
composite endpoint # (%)	838 (69%)	549 (62%)	275 (66%)	66 (78%)	13 (50%)	750 (49%)
Median days spent in stage	1,149	1,206	1,158	794	709	1,961
PCP-only vs Nephrology p-value	0.41	0.32	< 0.001	0.03	NA	< 0.001
PCP-only group #	995	624	209	28	6	1,090
CKD progression # (%)	445 (45%)	156 (25%)	14 (7%)	4 (14%)	1 (17%)	27 (2%)
died # (%)	231 (23%)	217 (35%)	131 (63%)	20 (71%)	2 (33%)	509 (47%)
composite endpoint # (%)	676 (68%)	376 (60%)	145 (69%)	24 (86%)	3 (50%)	536 (49%)
median days spent in stage	1,168	1,247	895	558	655	1,936
Nephrology group #	222	263	207	58	20	440
CKD progression # (%)	138 (62%)	120 (46%)	56 (27%)	17 (29%)	5 (25%)	67 (15%)
died # (%)	24 (11%)	53 (20%)	74 (36%)	25 (43%)	5 (25%)	147 (34%)
composite endpoint # (%)	162 (73%)	173 (65%)	130 (63%)	42 (72%)	10 (50%)	214 (49%)
median days spent in stage	1,127	1,100	1,211	834	776	1,991

Legend: The number with composite endpoint is the number of individuals who either died or had CKD progression. The unadjusted median time to endpoint is the median time to either disease progression or death for that stage.

**Table 4.**  
**Adjusted Hazard Ratios (with 95% confidence intervals) from the Cox Proportional Hazards Analysis**

	Stage 1 to 2	Stage 2 to 3	Stage 3 to 4	Stage 4 to 5	Pre-ACKD to ACKD
Nephrology vs PCP-only	1.08 (0.91,1.29)	1.20 (0.99,1.45)	0.80 (0.61,0.90)*	0.75 (0.45,0.89)*	0.91 (0.76,0.99)*
Age per 1 year	1 (1.00,1.01)	1.01 (1.01,1.02)	1 (0.98,1.01)	1.02 (1.00,1.04)	1 (1.00,1.01)
Nonwhite vs White Race	0.71 (0.62,0.83)*	0.89 (0.73,1.08)	1.11 (0.83,1.44)	1.24 (0.70,2.10)	0.82 (0.69,0.96)*
ACEI use	1.1 (0.91,1.31)	0.62 (0.51,0.74)*	0.68 (0.56,0.98)*	0.96 (0.56,1.64)	0.53 (0.45,0.63)
ACEI started during stage	0.73 (0.61,0.88)*	1.13 (0.93,1.37)	1.03 (0.77,1.42)	2.14 (0.89,4.58)	NA
Anti-lipid agents use	0.64 (0.55,0.75)*	0.57 (0.45,0.71)*	0.54 (0.40,0.70)*	0.71 (0.39,1.38)	0.46 (0.38,0.54)*
Diabetes	1.32 (1.13,1.55)*	1.18 (0.97,1.43)	1.13 (0.86,1.50)	NA	1.31 (1.10,1.56)*
Hypertension	0.8 (0.66,1.35)	0.93 (0.72,1.57)	0.91 (0.77,1.53)	NA	0.85 (0.78,1.01)
Current Tobacco use	1 (0.82,1.13)	0.79 (0.63,1.00)	0.92 (0.69,1.30)	NA	0.84 (0.70,1.02)
Coronary Artery Disease	1.35 (1.14,1.61)*	1.52 (1.23,1.93)*	0.86 (0.64,1.17)	NA	1.54 (1.27,1.88)*
HgA1c > 7%	1.14 (0.91,1.43)	1.28 (1.01,1.63)*	1.53 (1.08,2.11)*	NA	1.33 (1.04,1.62)*
Positive Urine Protein	1 (1.00,1.00)	1 (1.00,1.00)	1.12 (0.91,1.15)	NA	1.46 (1.26,1.74)*

\*p < 0.05

ACEI = angiotensin converting enzyme inhibitor; HgA1c = hemoglobin A1c

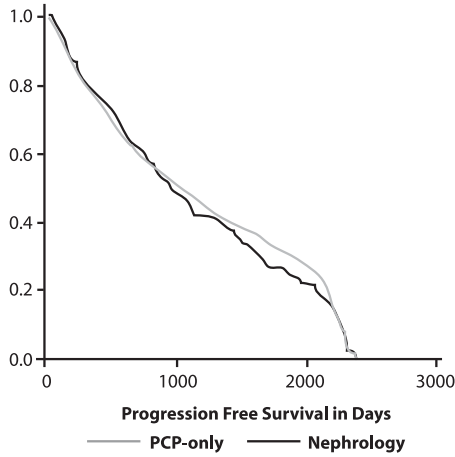
Legend: Hazard ratios > 1 indicate an increased risk of reaching the composite endpoint (death or CKD progression), whereas a hazard ratio < 1 indicates a reduced risk of reaching the composite endpoint. A value of 1 reflects no association between the covariate and the endpoint.

complications between the two groups during follow-up. Both the PCP-only and nephrology groups provided similar levels of control for diabetes, hypertension, hyperlipidemia, hypercalcemia, and anemia; however chronic hyperphosphatemia and

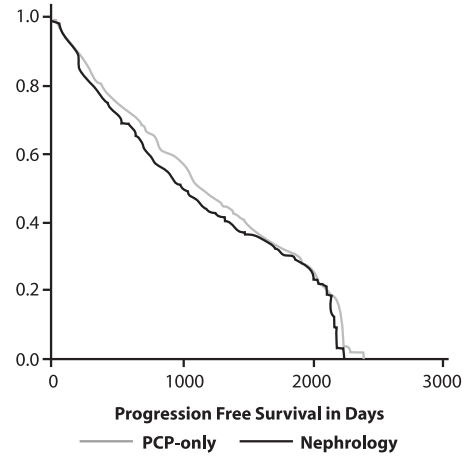
hypoalbuminemia were more common in the PCP-only group. In addition, there was greater use of ACEIs in the nephrology group; however, the 1% absolute difference is not clinically significant. It is not possible to distinguish between cause and effect

**Figure 1.**  
**Adjusted Kaplan Meier Survival Curves**

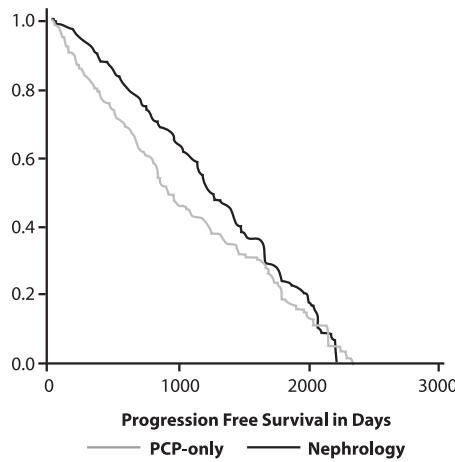
**Adjusted Survival Curve: Stage 1 to 2**



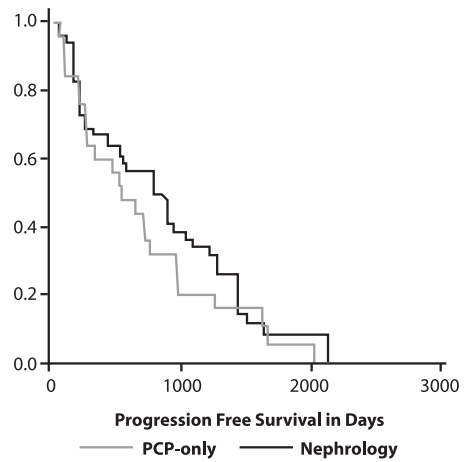
**Adjusted Survival Curve: Stage 2 to 3**



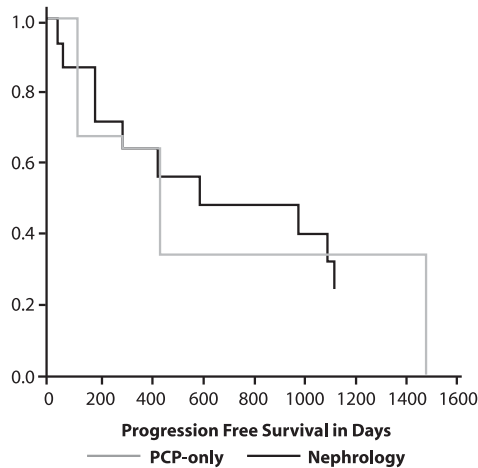
**Adjusted Survival Curve: Stage 3 to 4**



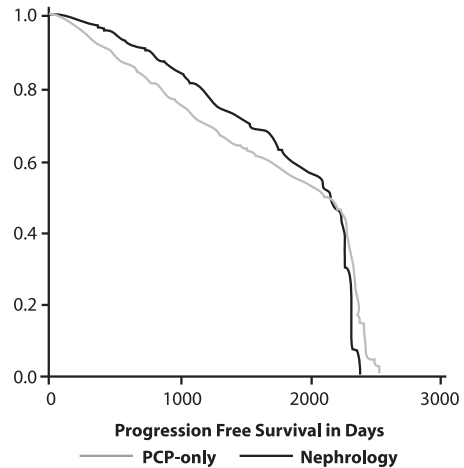
**Adjusted Survival Curve: Stage 4 to 5**



**Adjusted Survival Curve: Stage 5 to Dialysis**



**Adjusted Survival Curve: Early to Advanced CKD**



Legend: Graphs the survival curve (ie, time to the composite endpoint of death or CKD progression) for the nephrology (solid line) and PCP-only (dashed line) groups during each stage. The x-axis represents the time in days, and the y-axis reflects the proportion of the group that has not reached the endpoint. The curves display the proportion of the initial group that has not reached the endpoint over time. The median time for the group to reach the endpoint is reflected by the time point on the x-axis that corresponds with 0.5 on the y-axis.

with our study design; however, these findings are suggestive, and because nephrologists in practice will not be able to expand their capacity to accommodate all stage 3, 4, and 5 patients (almost nine million individuals), it is imperative that we perform well-designed prospective studies to further investigate the answer to these questions.

Similar to the results of a recently published study,<sup>13</sup> we found that mortality was profound, particularly at higher CKD stages. Only at stages 1 and 2 did fewer individuals die than progress, despite the fact that the percentage of individuals reaching the composite endpoint remained relatively similar across all stages (values for stage 4 and 5 are imprecise due to the few individuals in these two groups). When comparing the nephrology group to the PCP-only group across all stages, fewer individuals in the PCP-only group progressed to a higher stage; however more individuals died. This relationship may be related to a lower referral rate for individuals with comorbidities conferring an increased risk of death, such as cancer. The limitations of our data prevent us from examining this association in more detail.

Previous studies evaluating the impact of nephrology care on renal-related outcomes have focused upon the association between the morbidity and mortality of dialysis and the patterns of pre-ESRD care.<sup>14,15</sup> These retrospective studies consistently found that individuals referred to a nephrologist early had less morbidity and mortality than those referred late, however early referral was dichotomized (ie, before or after a prespecified cut-off time), the definition varied (one month to one year predialysis), and the findings were not generalizable to pre-ESRD populations. This is the first study to evaluate a CKD population in various stages of disease over an extended follow-up time. By performing a study to investigate the impact of nephrology care at each CKD stage, we were able to more closely assess the impact of a nephrologist on mortality and progression in those with pre-ESRD who receive medical care by primary care physicians. This is an important distinction since the impact of recommending early referral will be limited to those already receiving medical care. It will not affect those who receive no pre-ESRD medical care.

The retrospective design of our study raises the possibility that the difference in outcomes between the two groups may have been related to unmeasured variables or bias in patients referred to

nephrologists. We attempted to account for this possibility by using a propensity score to adjust the analysis. Propensity scores are able to improve upon statistical analysis in potentially biased populations, but they are still subject to the problems of unmeasured bias. The average stage at referral, 1.6, is quite low, indicating that most patients seen by subspecialists were referred during their earliest stages and that crossover between the nephrology and PCP-only groups at later stages was limited. The study design also prevented us from controlling loss to follow-up; however, only 133 of the original 1,553 individuals transferred out of the system, and there was excellent long-term follow up, averaging 3.5 years.

The population we studied limits the generalizability of our results to other veterans since VA populations may be different than non-VA populations and the patterns of care may also be different. In particular, patients tend to have more comorbidities with more severe disease. Referrals may take longer and follow-up by subspecialists may not be as close as in other systems. In addition, we were unable to determine if an individual received care from a non-VA nephrologist or if they received medications outside of the VA, although both are uncommon in our experience. To address this concern, we performed an informal survey of primary care providers at the Durham VA and a limited chart review for 50 patients in each group. The informal survey found that providers believed only 1-2% of their patients may obtain additional care outside of the VA and that less than 1% obtained medications outside the VA. The chart review did not identify any patients with either care or medications from outside the VA.

Our study suggests that the addition of subspecialty care to standard care by a PCP around CKD stage 3 may improve outcomes. However, well-designed prospective studies should be performed to further clarify the role and timing of nephrologist care in the management of patients with CKD. If the relationship is supported by additional studies, the reason for the phenomenon could have important clinical and health policy implications. If it is attributable to care that requires nephrology training or is otherwise only feasible in the context of a nephrology practice, then we will need to train more nephrologists. However, if some or all of the effect can be attributed to activities that can be incorporated into PCP practice, then PCPs will need to become more adept at these activities. **NCMJ**

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