

Longitudinal Follow-up and Outcomes Among a Population With Chronic Kidney Disease in a Large Managed Care Organization

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Background: Chronic kidney disease is the primary cause of end-stage renal disease in the United States. The purpose of this study was to understand the natural history of chronic kidney disease with regard to progression to renal replacement therapy (transplant or dialysis) and death in a representative patient population.

Methods: In 1996 we identified 27 998 patients in our health plan who had estimated glomerular filtration rates of less than 90 mL/min per 1.73 m² on 2 separate measurements at least 90 days apart. We followed up patients from the index date of the first glomerular filtration rates of less than 90 mL/min per 1.73 m² until renal replacement therapy, death, disenrollment from the health plan, or June 30, 2001. We extracted from the computerized medical records the prevalence of the following comorbidities at the index date and end point: hypertension, diabetes mellitus, coronary artery disease, congestive heart failure, hyperlipidemia, and renal anemia.

Results: Our data showed that the rate of renal replacement therapy over the 5-year observation period was 1.1%, 1.3%, and 19.9%, respectively, for the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) stages 2, 3, and 4, but that the mortality rate was 19.5%, 24.3%, and 45.7%. Thus, death was far more common than dialysis at all stages. In addition, congestive heart failure, coronary artery disease, diabetes, and anemia were more prevalent in the patients who died but hypertension prevalence was similar across all stages.

Conclusion: Our data suggest that efforts to reduce mortality in this population should be focused on treatment and prevention of coronary artery disease, congestive heart failure, diabetes mellitus, and anemia.

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BASED ON CALCULATIONS FROM the Third National Health and Nutrition Examination Survey (NHANES III),¹ it is estimated that 20 million adults in the United States have chronic kidney disease (CKD). In contrast, the estimated prevalence of end-stage renal disease (ESRD) in the US population is 344 000.² This suggests that less than 2% of the CKD population progresses to renal replacement therapy (RRT).

Relatively little is known about the 98% of patients with CKD who do not advance to ESRD. Recently, the National Kidney Foundation (NKF) published its Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines that provide an evidence-based definition of CKD and a framework for staging the severity of CKD.¹ The objectives of the present work were to study the natural history of CKD in a large health maintenance organization (HMO) population in the context of that framework, examining the prevalence of comorbid con-

ditions associated with CKD and describing clinical outcomes (death, transplantation, and renal dialysis) over a 5½-year observation period.

METHODS

RESEARCH SETTING AND STUDY POPULATION

Participants were adult (>17 years old) members of Kaiser Permanente Northwest Division (KPNW), a large not-for-profit, group-model HMO that provides comprehensive, prepaid medical coverage to approximately 20% of the metropolitan population of Portland, Ore. Subscriber demographics are representative of the area population in ethnic makeup, with non-Hispanic whites representing about 78% of the population. The remainder of the population includes African Americans, Asians/Pacific Islanders, Native Americans, and persons of Hispanic descent. More than 18% of members are Medicare-eligible (>64 years old), and 8% are Medicaid members.

Kaiser Permanente Northwest Division maintains electronic administrative and clinical

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Table 1. Relevant Patient Characteristics, Disease Stages, and Glomerular Filtration Rates (GFRs) at Baseline*

Patient Characteristics	GFR, 60-89; No Proteinuria (n = 14 202)	Stage 2 GFR, 60-89; Proteinuria (n = 1741)	Stage 3 GFR, 30-59 (n = 11 278)	Stage 4 GFR, 15-29 (n = 777)
Age at index, mean (SD), y	61.4 (14.1)	60.8 (14.9)	71.6 (11.9)	73.6 (13.6)
Male sex, %	43.8	56.5	37.8	35.9
Follow-up, mean, mo				
Year 1	11.9	11.9	11.9	11.5
Year 2	11.4	11.3	11.1	9.1
Year 3	10.7	10.3	10.1	7.0
Year 4	10.0	9.3	9.2	5.3
Year 5	8.5	7.8	7.6	3.9
Total observation time, mean (SD), mo	53.9 (14.3)	49.8 (17.9)	51.1 (16.5)	37.6 (20.6)

*Disease was staged according to the National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines. GFRs were estimated in milliliters per minute per 1.73 m².

cal databases containing information on inpatient admissions, ambulatory contacts, pharmacy dispensations, laboratory tests, and outside claims and referrals. These databases are linked through unique health record numbers that are given to each member at the time of first enrollment in the health plan.

Laboratory tests are performed by a single regional laboratory using standardized methods that are periodically recalibrated against reference samples. We estimated glomerular filtration rates (GFRs) from serum creatinine values captured in KPNW's laboratory information system using the abbreviated Modification of Diet in Renal Disease Study (MDRD) formula³ as follows: estimated GFR (in milliliters per minute per 1.73 m²) = 186.3 × [serum creatinine]^{-1.154} × age^{-0.203} × [0.742 if a woman] × [1.21 if black].

Because data on race were not available, they were not included in the estimation of GFR. This missing variable had the effect of underestimating GFR by 21% for African Americans. However, less than 5% of our population is African American, so the overall population-level effect of this missing variable was minimal.

We identified all 42 293 HMO members who, in 1996, had an estimated GFR greater than 15 mL/min per 1.73 m² and less than 90 mL/min per 1.73 m² (index GFR), followed by a second GFR below 90 mL/min per 1.73 m² at the first creatinine measurement taken at least 90 days after the index GFR. We then staged the severity of their CKD based on the NKF K/DOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification.¹ The index GFR of patients with stage 4 disease (n=777) was estimated to be 15 to 29 mL/min per 1.73 m² and the index GFR of patients with stage 3 disease (n=11 278) was estimated to be 30 to 59 mL/min per 1.73 m². The NKF K/DOQI guidelines require that patients with stage 2 disease (GFR of 60-89 mL/min per 1.73 m²) also be checked for proteinuria. Although the current staging guidelines consider other renal markers, such as renal cysts, on radiologic examination in patients with polycystic kidney disease, we did not include them because these data were not readily obtainable and make up a small minority of renal markers. We defined proteinuria as urine protein of 1+ or greater by dipstick analysis, with leukocyte esterase less than 10/μL, measured within 6 months of the index GFR. About half (14 295) of the patients with a GFR of 60 to 89 mL/min per 1.73 m² did not have a qualifying urinalysis and were excluded from further analysis. Of the remaining 15 943 subjects, it was determined that 1741 had stage 2 disease. For comparison, we also included the 14 202 individuals with an index GFR of 60 to 89 mL/min per 1.73 m² in whom proteinuria was found to be absent. Our final case population totaled 27 998. A comparison group was selected by using a 1:1 age (year of birth) and sex

match from enrollees who did not meet the criteria for inclusion as a study patient and were eligible for at least 90 days from the index GFR of their matched case.

FOLLOW-UP AND END POINTS

Subjects were observed for up to 66 months from the date of their index GFR through June 30, 2001, or until death, disenrollment from the health plan, or advancement to RRT defined as initiation of dialysis or renal transplantation. Death and disenrollment were identified from HMO membership records. Transplant and dialysis were captured in the medical record.

DEMOGRAPHICS AND COMORBIDITIES

Sex and age at index date were extracted from HMO membership electronic records using the *International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM)* diagnosis and procedure codes. We identified diagnoses for coronary artery disease, congestive heart failure, diabetes mellitus, hypertension, and hyperlipidemia. We defined anemia as hemoglobin levels less than 12 g/dL with normal mean corpuscular volume. Comorbidities were considered present at baseline if they were charted at any time before or up to 3 months following the index date. Anemia was considered present at baseline if it was identified within 30 days of the index date. We further identified the comorbidities that were charted at any time prior to end of observation, and anemia that was measured at any time prior to end of observation.

RESULTS

The relevant baseline characteristics of the study subjects by GFR and disease stage are shown in **Table 1**. Age at index increased with stage while the percentage of male subjects declined with stage. Months of observation, in total and by year, were approximately similar for all stages except stage 4, for which observation time was substantially shorter.

Nearly half of subjects in stage 4 (mean ± 95% confidence bound, 45.7% ± 3.5%) died during observation (**Table 2**), a substantially higher proportion than in any other group. The mean ± 95% confidence bound proportion of subjects who died in stages 2 and 3 was 19.5% ± 1.9% and 24.3% ± 0.8%, respectively, while only 10.2% ± 0.5% of those in the comparison group (GFR, 60-89 mL/min per 1.73 m² without proteinuria) died, re-

Table 2. Study End points*

End Points	GFR, 60-89; No Proteinuria (n = 14 202)	Stage 2 GFR, 60-89; Proteinuria (n = 1741)	Stage 3 GFR, 30-59 (n = 11 278)	Stage 4 GFR, 15-29 (n = 777)
Disenrolled from plan	14.9	16.2	10.3	6.6
Died (prior to transplant/dialysis)	10.2	19.5	24.3	45.7
Received a transplant	0.01	0.2	0.2	2.3
Initiated dialysis	0.06	0.9	1.1	17.6
None of the above through June 30, 2001	74.8	63.3	64.2	27.8

*Glomerular filtration rates (GFRs) were estimated in milliliters per minute per 1.73 m². Other values are given as percentage of patients.

Table 3. Baseline Comorbidities and Change in Prevalence From Baseline to Follow-up in Patients With Chronic Kidney Disease

	Baseline (Change), %						
	No Comorbidities	Coronary Artery Disease	Congestive Heart Failure	Hyperlipidemia	Hypertension	Diabetes Mellitus	Anemia
Survived to June 30, 2001							
GFR 60-89, no proteinuria (n = 10 629)*	54.0 (-27.4)	8.5 (10.3)	1.4 (5.8)	14.2 (16.2)	29.7 (23.5)	11.5 (9.1)	4.9 (16.9)
Stage 2 disease (n = 1102)	40.7 (-27.4)	13.0 (14.6)	3.9 (10.7)	16.5 (19.8)	36.8 (27.7)	29.0 (16.1)	6.4 (24.0)
Stage 3 disease (n = 7238)	36.6 (-25.3)	15.5 (14.6)	5.4 (12.6)	15.5 (17.1)	46.9 (24.5)	15.1 (10.8)	7.6 (28.3)
Stage 4 disease (n = 216)	25.0 (-22.2)	19.0 (14.3)	12.5 (19.4)	13.4 (19.9)	55.6 (21.7)	18.5 (11.6)	28.2 (37.5)
Died Prior to June 30, 2001							
GFR 60-89, no proteinuria (n = 1446)*	47.9 (-21.8)	16.0 (11.2)	10.1 (18.0)	7.5 (6.8)	31.4 (13.5)	16.3 (7.4)	14.7 (39.9)
Stage 2 disease (n = 339)	41.0 (-23.3)	17.4 (12.1)	13.6 (20.6)	7.4 (7.4)	31.3 (15.0)	28.3 (11.8)	14.8 (42.1)
Stage 3 disease (n = 2736)	29.9 (-18.1)	24.4 (13.3)	22.2 (21.6)	9.8 (6.6)	45.3 (13.5)	21.6 (7.6)	17.5 (42.2)
Stage 4 disease (n = 355)	20.3 (-14.9)	29.3 (12.4)	32.7 (23.6)	13.0 (5.6)	50.1 (16.1)	30.0 (5.5)	33.8 (39.4)
Disenrolled Prior to June 30, 2001							
GFR 60-89, no proteinuria (n = 2116)*	57.8 (-18.0)	5.4 (5.0)	1.4 (3.0)	12.1 (8.4)	27.0 (13.5)	12.7 (5.1)	5.1 (9.6)
Stage 2 disease (n = 282)	41.8 (-19.1)	7.8 (6.7)	2.1 (6.1)	11.4 (6.7)	34.4 (16.0)	31.9 (8.9)	6.4 (14.2)
Stage 3 disease (n = 1160)	34.7 (-17.0)	15.5 (7.5)	5.9 (6.2)	14.3 (10.9)	47.8 (15.6)	18.0 (6.6)	8.3 (16.2)
Stage 4 disease (n = 51)	21.6 (-21.6)	23.5 (5.9)	9.8 (17.7)	21.6 (9.8)	47.1 (27.4)	23.5 (4.0)	31.4 (27.4)

*Glomerular filtration rates (GFRs) were estimated in milliliters per minute per 1.73 m².

ardless of hypertension status (not shown). The likelihood of renal replacement therapy, either transplant or dialysis, was near zero ($\leq 1.3\%$) for patients in all stages except stage 4, where $2.3\% \pm 1.1\%$ of patients received a transplant and $17.6\% \pm 2.7\%$ had dialysis initiated. Disenrollment from the health plan decreased with increasing stage, but was low in all stages over the 5½ years.

Table 3 shows the prevalence of comorbidities at index date and the change in prevalence that occurred during follow-up for patients who survived, died, and disenrolled from the health plan. For all comorbidities, the prevalence was higher at the end point of the study than at baseline for all stages of disease. Among patients who died in each stage, the prevalence of coronary artery disease, congestive heart failure, diabetes mellitus, and anemia was higher both at baseline and end point than among patients who survived or disenrolled. The increase in prevalence for these 4 comorbidities was also highest in those who died.

The prevalence of hyperlipidemia was lower at baseline in those who died than in survivors for all stages except stage 4, where the prevalence was similar to that of patients who survived or disenrolled from the health plan. Across all stages, hyperlipidemia increased 2- to 3-fold

in survivors compared with those who died. We further found that 26.6% of survivors, 13.7% of those who died, 15.5% of those who disenrolled, 39.3% of dialysis patients, and 50.0% of patients with a transplant had received at least 1 prescription for a statin (data not shown). The prevalence of hypertension at baseline was similar for all 3 end points across all stages. However, the prevalence of hypertension at end point increased considerably more in survivors than in patients who died or disenrolled.

Table 4 shows the comorbidities and change in prevalence from baseline to follow-up for patients with CKD and their controls. At baseline, 44.4% of patients with CKD and 73.7% of controls had no comorbidities. Patients with CKD were more likely to have disease in every category. They were also more likely to have accrued additional disease burden in every category, especially anemia (24.5% for patients with CKD vs 0.1% for controls) and congestive heart failure (10.4% for patients with CKD vs 5.2% for controls).

COMMENT

Most of the approximately 350 000 persons who have ESRD in the United States emerge from the estimated 20

Table 4. Baseline Comorbidities and Change in Prevalence From Baseline to Follow-up in Patients With Chronic Kidney Disease (CKD) and Controls Matched for Age and Sex*

Comorbidity	Patients With CKD (n = 27 998)		Control Patients (n = 27 998)	
	Baseline	Change	Baseline	Change
None	44.4	-24.1	73.7	-26.6
Coronary artery disease	13.1	11.5	6.2	7.4
Congestive heart failure	6.0	10.4	1.8	5.2
Hyperlipidemia	13.6	14.1	7.4	10.5
Hypertension	37.4	21.2	16.8	19.3
Diabetes	15.8	9.2	5.3	5.7
Anemia	8.6	24.5	2.1	0.1

*Values are given as percentage.

million patients with CKD.¹ The results reported in this study indicate that the population with ESRD is actually a highly specific group of patients who have progressive renal failure and survive to require dialysis; and that, even among those with advanced stage 4 disease, death prior to RRT is more than twice as likely as progression to ESRD.

Although we cannot isolate cause of death in our data, it is likely that cardiac disease is predominantly responsible. Cardiovascular disease is the most common cause of death among dialysis and transplant patients.⁴ We found higher baseline prevalence of coronary artery disease, congestive heart failure, diabetes mellitus, and anemia in patients who died than in patients who survived or disenrolled. Furthermore, the increase in prevalence of these 4 comorbidities over the 5½-year observation period was greatest in patients who died despite a shorter period of observation. There was also a higher prevalence of these cardiac conditions among study patients at both baseline and end of observation than among controls.

The high rates of heart disease and anemia in the patients who died are consistent with the hypothesis that anemia accelerates the progression of heart disease and increases the risk of death. However, anemia may be a marker for severity of CKD rather than a causative factor. Inflammation, as evidenced by a high level of C-reactive protein, is also a risk factor for cardiovascular mortality, and inflammation is an important factor of reduced erythropoiesis in this population.⁴ Additionally, if anemia is more prevalent in patients with congestive heart failure, coronary artery disease, and diabetes mellitus, the apparent association between death and anemia may be confounded by these diseases with a high mortality. Finally, some evidence suggests that treatments for these comorbidities, such as angiotensin-converting enzyme inhibition, also decrease red cell production.⁵ While these data do not suggest that changes should be made to current treatment recommendations in CKD, further research designed to help disentangle the associations between anemia, heart disease, and inflammatory processes might yield important clues for better patient care.

Contrary to common expectation, hypertension and hyperlipidemia were less common in patients who died before advancing to ESRD or RRT than in survivors. This finding is similar to findings in patients with ESRD for

whom high blood pressure was not associated with greater mortality. What is unclear from our data, however, is the extent to which low blood pressure may be a risk factor for mortality, as has been found in the dialysis population.⁶ Although each of these risk factors was identified through diagnoses extracted from medical records, we have no reason to believe that recording was less regular for one of these outcome groups. Thus, any bias resulting from our definition would likely be equally distributed between those who died and those who survived. It is possible that the greater prevalence of cardiovascular risk factors in survivors represents a higher rate of documentation of treatment. Clinicians might be more likely to record hypertension or hyperlipidemia when initiating pharmacological treatment. If this is the case, the greater prevalence of cardiovascular risk factors in survivors represents successful treatment and a subsequent decrease in mortality. In our analysis, survivors were more likely to have initiated statin therapy than those who died, which perhaps reflects the added cardioprotective effects of statin therapy that were recently reported.⁷ The finding that patients receiving RRT had the highest rates of statin use may be a consequence of closer management following ESRD diagnosis. Finally, the age of our population may be an important factor in the apparent lack of effect of the traditional cardiac risk factors of hypertension and hyperlipidemia. The mean age of our study population was 65 years. Previous studies have shown that in patients older than 65 years, the relative risk of mortality imparted by hypertension diminishes significantly and may cease to add measurable risk.⁸⁻¹³ Similarly, hyperlipidemia in epidemiologic studies in the elderly had no effect on cardiovascular mortality, and overall mortality was higher in patients with lower cholesterol levels.¹³

Although the population with stage 2 disease was nearly 11 years younger than the stage 3 population, the outcomes for stage 3 disease were remarkably similar to those of stage 2. The requirement of proteinuria in stage 2 disease appears to identify a population that is at greater risk for death and RRT. The risk of death was double and the risk of RRT was 10 times higher in the stage 2 population with proteinuria, compared with the population of patients who also had a GFR of 60 to 89 mL/min per 1.73 m² but no proteinuria. Proteinuria has been shown

in previous studies to be a risk factor for progressive renal dysfunction and increased cardiovascular mortality,^{14,15} which is consistent with our findings. The proteinuria requirement also identifies a population with a greater prevalence of diabetes mellitus, which may explain some portion of the excessive morbidity and mortality that we found in stage 2.

Although we did not determine the etiology of the renal disease in our study, the data provide indirect evidence that the prevalence of the different etiologies of kidney disease in the overall CKD population may be different from those of patients who progress to ESRD. Based on United States Renal Data System data from Oregon in 1999, the primary diagnosis for patients with renal disease initiating RRT was diabetes mellitus (43%).² In the present study, in all stages of CKD at baseline, the prevalence of diabetes mellitus was well below 43%, although a significant number of CKD patients with diabetes mellitus likely have alternative diagnoses for their primary renal disease.

An important limitation of our study was that only patients who sought medical care and had a creatinine measurement in 1996 were included. Thus, we cannot claim that the patients we identified represent the entire population with prevalent CKD. Our study population may represent a biased population in whom adverse outcomes would be more likely than in patients who did not seek medical care but had renal dysfunction. However, CKD is associated with advancing age, and elderly patients are more likely to access the health care system and have laboratory testing. The average age of our population was 65 years and the proportion of the entire health plan membership that received a creatinine measurement increased steadily with age (data not shown). These factors will have minimized whatever bias was introduced in our population selection process. Another limitation is that the criterion of 2 measurements at least 90 days apart added an "early survival" bias to the population, as some patients with CKD were excluded from the study because they died prior to having a second creatinine measurement after 90 days. Though minimal, this would result in an underestimation of mortality. One of our main findings, that death is far more likely than advancement to RRT, would only be strengthened by the elimination of the early survival bias.

In conclusion, the application of the NKF K/DOQI guidelines to our data indicate that previous reports describing patients having ESRD are not representative of patients with CKD. During our 5½-year observation period, only 3.1% of patients with stage 2 through stage 4 disease progressed to RRT while 24.9% died. Furthermore, the prevalence of comorbidities differed between patients who died and patients who survived. For example, our data suggest that the contribution of anemia and diabetes mellitus to mortality may be larger in CKD than other traditional cardiac risk factors. It remains unclear whether the high mortality rate in patients with CKD can be improved. Our data suggest that treatment and

prevention of coronary artery disease, congestive heart failure, diabetes mellitus, and anemia may be important elements of a strategy to improve outcomes in this population.

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