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), 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. 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. 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 conditions associated with CKD and describing clinical outcomes (death, transplantation, and renal dialysis) over a 5 1/2-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 clini-
Table 1. Relevant Patient Characteristics, Disease Stages, and Glomerular Filtration Rates (GFRs) at Baseline*

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>GFR, 60-89; No Proteinuria (n = 14,202)</th>
<th>Stage 2 GFR, 60-89; Proteinuria (n = 17,411)</th>
<th>Stage 3 GFR, 30-59 (n = 11,278)</th>
<th>Stage 4 GFR, 15-29 (n = 777)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at index, mean (SD), y</td>
<td>61.4 (14.1)</td>
<td>60.8 (14.9)</td>
<td>71.6 (11.9)</td>
<td>73.6 (13.6)</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>43.8</td>
<td>56.5</td>
<td>37.5</td>
<td>35.9</td>
</tr>
<tr>
<td>Follow-up, mean, mo</td>
<td>11.9</td>
<td>11.9</td>
<td>11.9</td>
<td>11.5</td>
</tr>
<tr>
<td>Year 1</td>
<td>11.4</td>
<td>11.3</td>
<td>11.1</td>
<td>9.1</td>
</tr>
<tr>
<td>Year 2</td>
<td>10.7</td>
<td>10.3</td>
<td>10.1</td>
<td>7.0</td>
</tr>
<tr>
<td>Year 3</td>
<td>10.0</td>
<td>9.3</td>
<td>9.2</td>
<td>5.3</td>
</tr>
<tr>
<td>Year 4</td>
<td>8.5</td>
<td>7.8</td>
<td>7.6</td>
<td>3.9</td>
</tr>
<tr>
<td>Total observation time, mean (SD), mo</td>
<td>53.9 (14.3)</td>
<td>49.8 (17.9)</td>
<td>51.1 (16.5)</td>
<td>37.6 (20.8)</td>
</tr>
</tbody>
</table>

* 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.

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. 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-
Across all stages, hyperlipidemia increased 2- to 3-fold patients who survived or disenrolled from the health plan.

cept stage 4, where the prevalence was similar to that of line in those who died than in survivors for all stages ex-

prevalence for these 4 comorbidities was also highest in patients who survived or disenrolled. The increase in
mildia was higher both at baseline and end point than among

disease of coronary artery dis-

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

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>No Comorbidities</th>
<th>Coronary Artery Disease</th>
<th>Congestive Heart Failure</th>
<th>Hyperlipidemia</th>
<th>Hypertension</th>
<th>Diabetes Mellitus</th>
<th>Anemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR, 60-89, no proteinuria (n = 10 629)*</td>
<td>54.0 (−27.4)</td>
<td>8.5 (10.3)</td>
<td>1.4 (5.8)</td>
<td>14.2 (16.2)</td>
<td>29.7 (23.5)</td>
<td>11.5 (9.1)</td>
<td>4.9 (16.9)</td>
</tr>
<tr>
<td>Stage 2 disease (n = 1102)</td>
<td>40.7 (−27.4)</td>
<td>13.0 (14.6)</td>
<td>3.9 (10.7)</td>
<td>16.5 (18.6)</td>
<td>36.8 (27.7)</td>
<td>29.0 (16.1)</td>
<td>6.4 (24.0)</td>
</tr>
<tr>
<td>Stage 3 disease (n = 7238)</td>
<td>36.6 (−25.5)</td>
<td>15.5 (14.6)</td>
<td>5.4 (12.6)</td>
<td>15.5 (17.1)</td>
<td>46.9 (24.5)</td>
<td>15.1 (10.8)</td>
<td>7.6 (28.3)</td>
</tr>
<tr>
<td>Stage 4 disease (n = 216)</td>
<td>25.0 (−22.2)</td>
<td>19.0 (14.3)</td>
<td>12.5 (19.4)</td>
<td>13.4 (19.9)</td>
<td>55.6 (21.7)</td>
<td>18.5 (11.6)</td>
<td>28.2 (37.5)</td>
</tr>
<tr>
<td>GFR, 60-89, no proteinuria (n = 1446)*</td>
<td>47.9 (−21.8)</td>
<td>10.0 (11.2)</td>
<td>10.1 (18.0)</td>
<td>7.5 (6.8)</td>
<td>31.4 (13.5)</td>
<td>16.3 (7.4)</td>
<td>14.7 (39.9)</td>
</tr>
<tr>
<td>Stage 2 disease (n = 339)</td>
<td>41.0 (−23.3)</td>
<td>17.4 (12.1)</td>
<td>13.6 (20.6)</td>
<td>7.4 (7.4)</td>
<td>33.1 (15.0)</td>
<td>28.3 (11.8)</td>
<td>14.8 (42.1)</td>
</tr>
<tr>
<td>Stage 3 disease (n = 2736)</td>
<td>29.9 (−18.1)</td>
<td>24.4 (13.3)</td>
<td>22.2 (21.6)</td>
<td>9.8 (6.6)</td>
<td>45.3 (13.5)</td>
<td>21.6 (7.6)</td>
<td>17.5 (42.2)</td>
</tr>
<tr>
<td>Stage 4 disease (n = 355)</td>
<td>20.3 (−14.9)</td>
<td>29.3 (12.4)</td>
<td>32.7 (23.6)</td>
<td>13.0 (5.6)</td>
<td>50.1 (16.1)</td>
<td>30.0 (5.5)</td>
<td>33.8 (39.4)</td>
</tr>
<tr>
<td>GFR, 30-59, no proteinuria (n = 11 278)</td>
<td>63.3 (−27.4)</td>
<td>13.3 (11.2)</td>
<td>10.1 (18.0)</td>
<td>7.5 (6.8)</td>
<td>31.4 (13.5)</td>
<td>16.3 (7.4)</td>
<td>14.7 (39.9)</td>
</tr>
<tr>
<td>Stage 2 disease (n = 339)</td>
<td>60.8 (−23.3)</td>
<td>17.4 (12.1)</td>
<td>13.6 (20.6)</td>
<td>7.4 (7.4)</td>
<td>33.1 (15.0)</td>
<td>28.3 (11.8)</td>
<td>14.8 (42.1)</td>
</tr>
<tr>
<td>Stage 3 disease (n = 2736)</td>
<td>49.9 (−18.1)</td>
<td>24.4 (13.3)</td>
<td>22.2 (21.6)</td>
<td>9.8 (6.6)</td>
<td>45.3 (13.5)</td>
<td>21.6 (7.6)</td>
<td>17.5 (42.2)</td>
</tr>
<tr>
<td>Stage 4 disease (n = 355)</td>
<td>39.3 (−14.9)</td>
<td>29.3 (12.4)</td>
<td>32.7 (23.6)</td>
<td>13.0 (5.6)</td>
<td>50.1 (16.1)</td>
<td>30.0 (5.5)</td>
<td>33.8 (39.4)</td>
</tr>
<tr>
<td>GFR, 15-29, no proteinuria (n = 777)</td>
<td>74.8 (−36.8)</td>
<td>63.3 (−27.4)</td>
<td>13.3 (11.2)</td>
<td>7.5 (6.8)</td>
<td>31.4 (13.5)</td>
<td>16.3 (7.4)</td>
<td>14.7 (39.9)</td>
</tr>
<tr>
<td>Stage 2 disease (n = 77)</td>
<td>60.8 (−23.3)</td>
<td>17.4 (12.1)</td>
<td>13.6 (20.6)</td>
<td>7.4 (7.4)</td>
<td>33.1 (15.0)</td>
<td>28.3 (11.8)</td>
<td>14.8 (42.1)</td>
</tr>
<tr>
<td>Stage 3 disease (n = 630)</td>
<td>49.9 (−18.1)</td>
<td>24.4 (13.3)</td>
<td>22.2 (21.6)</td>
<td>9.8 (6.6)</td>
<td>45.3 (13.5)</td>
<td>21.6 (7.6)</td>
<td>17.5 (42.2)</td>
</tr>
<tr>
<td>Stage 4 disease (n = 51)</td>
<td>39.3 (−14.9)</td>
<td>29.3 (12.4)</td>
<td>32.7 (23.6)</td>
<td>13.0 (5.6)</td>
<td>50.1 (16.1)</td>
<td>30.0 (5.5)</td>
<td>33.8 (39.4)</td>
</tr>
</tbody>
</table>

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

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).

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

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mortality, and inflammation is an important factor of re-
reactive protein, is also a risk factor for cardiovascular
increases the risk of death. However, anemia may be a
anemia accelerates the progression of heart disease and
patients who died are consistent with the hypothesis that
as a shorter period of observation. There was also a higher
these data do not suggest that changes should be made
to current treatment recommendations in CKD, further
research designed to help disentangle the associations be-
between anemia, heart disease, and inflammatory pro-
tizations pharmacological treatment. If this is the case, the
greater prevalence of cardiovascular risk factors in sur-
vivors represents successful treatment and a subsequent
decrease in mortality. In our analysis, survivors were
greater prevalence of these cardiac conditions among study pa-
tients at both baseline and end of observation than among
As we cannot isolate cause of death in our data, it is likely that cardiac disease is predominantly re-
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 sur-
vived or disenrolled. Further, the increase in prevalence of these 4 comorbidities over the 5½-year obser-
vation 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 pa-
tients with CKD 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
carnistion and inflammation is an important factor of re-
duced 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 mor-
tality. Finally, some evidence suggests that treatments for
these comorbidities, such as angiotensin-converting en-
zyme inhibition, also decrease red cell production.3 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 be-
tween anemia, heart disease, and inflammatory pro-
terculosis 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
who 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
mortality, as has been found in the dialysis popula-
tion.5 Although each of these risk factors was identified
through diagnoses extracted from medical records, we
have no reason to believe that recording was less regu-
lar for one of these outcome groups. Thus, any bias
resulting from our definition would likely be equally dis-
bursed 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 ini-
tiating pharmacological treatment. If this is the case, the
greater prevalence of cardiovascular risk factors in sur-
vivors 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 manage-
ment 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 hy-
pertension 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 signifi-
cantly and may cease to add measurable risk.6-13 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 near-
ly 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 popu-
lation 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

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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

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Patients With CKD (n = 27,998)</th>
<th>Control Patients (n = 27,998)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>Change</td>
</tr>
<tr>
<td>None</td>
<td>44.4</td>
<td>−24.1</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>13.1</td>
<td>11.5</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>6.0</td>
<td>10.4</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>13.6</td>
<td>14.1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>37.4</td>
<td>21.2</td>
</tr>
<tr>
<td>Diabetes</td>
<td>15.8</td>
<td>9.2</td>
</tr>
<tr>
<td>Anemia</td>
<td>8.6</td>
<td>24.5</td>
</tr>
</tbody>
</table>

*Values are given as percentage.

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millions of patients with CKD.7 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.

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

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in previous studies to be a risk factor for progressive renal dysfunction and increased cardiovascular mortality, 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%). 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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REFERENCES


