Impact of Age and Overt Proteinuria on Outcomes of Stage 3 to 5 Chronic Kidney Disease in a Referred Cohort

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Background and objectives: Population-based studies have reported outcomes and risk factors for patients with chronic kidney disease (CKD), defined primarily by decreased estimated GFR (eGFR). They are characterized by old age, low proteinuria level, and stage 3 CKD. However, many patients referred to nephrologists are younger and have overt proteinuria and advanced CKD. This study evaluated the association between outcomes and those factors among referred CKD patients.

Design, setting, participants, & measurements: We retrospectively reviewed 461 referred patients with stage 3 to 5 CKD from January 2003 to December 2007. Key outcomes were death and ESRD. Patients were followed from the time of first serum creatinine measurement to December 2009.

Results: The median age of subjects was 67.0 years, and median follow-up was 3.2 years. Overt proteinuria was present in 57.0% of subjects. For stage 3, 4, and 5 CKD, cumulative mortality and probability of ESRD at 3 years was 9.5 and 6.5%, 11.2 and 27.8%, and 16.5 and 79.1%, respectively. Using proportional-hazards regression models, age was a determinant for death, whereas overt proteinuria was strongly associated with ESRD. Among stage 3 CKD patients older than 65 years without overt proteinuria, the incidence of death before renal replacement therapy (RRT) was 2.8/100 patient-years and none had ESRD. In patients with advanced CKD and overt proteinuria, the incidence of ESRD was substantially higher than that of death before RRT.

Conclusions: Stratification by age, proteinuria level, and CKD stage could predict the competing outcomes of death before RRT and ESRD among CKD patients.

had one or more outpatient determinations of serum creatinine levels, and none had previously received RRT. Patients were followed from the time of first serum creatinine measurement. We used the new Japanese equation for GFR estimation [estimated GFR (eGFR) (ml/min per 1.73 m^2) = 194 × Serum creatinine^{−1.094} × Age^{−0.287} × 0.739 (if female)] (22).

Entry criteria included eGFR <60 ml/min per 1.73 m^2, which presumed the presence of CKD based on a clinical history of deterioration. We excluded patients with malignancy at the first consultation, those who had already received RRT, those who refused RRT, and those who received immunosuppressive agents for renal disease. Patients were referred to family doctors if they were clinically stable and determined to be at low risk, to dialysis centers if maintenance hemodialysis were started, or to kidney transplantation centers if they were eligible for a transplant. They were followed up as long as possible through collaboration between referred institutions by letters. Patient follow-up ended on December 31, 2009 or on the day when they underwent renal transplantation. Patients were considered lost to follow-up if no contact was documented for more than 6 months. This was a retrospective observational study approved by the Ethics Committee of Rinku General Medical Center.

**Baseline Demographics and Comorbidities**

Baseline clinical and laboratory variables included age, sex, diabetes (The International Classification of Diseases, Tenth Revision [ICD-10 codes E10–E14], hypertension (ICD-10 codes I10–I15), prior CVD, smoking history, eGFR, overt proteinuria, and hemoglobin, at referral. CVD was defined as a combination of a cardiac event and stroke (ICD-10 codes I60–I67). A cardiac event was defined as the combination of sudden death (ICD-10 codes I46.1, I46.9), ischemic heart disease (ICD-10 codes I20–I25), and heart failure (ICD-10 code I50). Overt proteinuria was defined as urinary protein-creatinine ratio ≥1.0 g protein/g creatinine, or urine dipstick ≥2+ if urinary protein-creatinine ratio was unavailable. We also extracted use of renin-angiotensin system (RAS) inhibitors at baseline or within 3 months after referral. Information on smoking habits was obtained through a standard questionnaire.

**Outcomes**

The primary endpoints were all-cause death and ESRD requiring chronic RRT. Causes of death were extracted from medical records, and chronic RRT was defined as use of RRT more than 2 months. The secondary outcome was hospitalization for cardiac events and stroke. We recorded only the first event of each endpoint. For survival analysis, we used death during the entire follow-up period as an outcome, regardless of RRT use. We also calculated the incidence of the competing outcomes of death before RRT and ESRD among stratified patients. These outcomes were ascertained by hospital medical records and questionnaire surveys.

**Statistical Analysis**

Descriptive statistics are presented as medians with interquartile ranges. Continuous variables were compared using the Kruskal-Wallis test, and post hoc analysis was performed by Mann-Whitney U tests. Categorical variables were compared using the chi-square test. Patients lost to follow-up were regarded as censored at the date of the last documented contact in the following survival analyses.

Three-year cumulative mortality was estimated using the Kaplan-Meier method and compared using the log-rank test. Univariate and multivariate Cox proportional hazard regression analysis of death was conducted for those aged 46 to 85 years to evaluate the effects of several clinical variables and cardiovascular risk factors at baseline.

Contrary to all-cause mortality, cumulative probability of ESRD calculated using Kaplan-Meier method and associations between baseline variables and ESRD evaluated with Cox model were obviously biased, since patients who died before developing ESRD requiring RRT had subsequently no probability of progression to ESRD, indicating that ESRD and all-cause mortality were competing risk events. Consequently, cumulative probability of ESRD was estimated using the competing risk method and compared using the Gray test in the presence of death as a competing risk (23). The substantially higher cumulative probability of ESRD among patients with stage 5 CKD showed an initial steep rise and then followed by a near-plateau, violating the proportional hazard assumption, which was tested by a time-constant interaction term. Thus, univariate and multivariate competing risk regression of ESRD was conducted for patients aged 46 to 85 years with stage 3 and 4 CKD to evaluate the association between baseline characteristics and ESRD, using Fine and Gray model (24).

In multivariate model, the association between age and overt proteinuria with each primary outcome was adjusted using different models with forced entry. Effect modifications among age, overt proteinuria, and eGFR were assessed incorporating their simple interaction terms into multivariate models. To avoid multicollinearity, correlation analyses were performed among variables in each model based on phi coefficient for two nominal variables, correlation ratio (eta) for one nominal and one continuous variable, and Spearman’s correlation coefficient for two continuous variables. The validity of the proportional-hazards assumption was tested by adding a time-dependent interaction variable for each of the predictors in the models. The assumption of linearity was checked in the model for the continuous variable by cubic splines (25). Finally, the outcomes of death before RRT and ESRD were re-analyzed stratifying all patients by age, overt proteinuria, and CKD stages.

A P value <0.05 for two-sided tests was considered significant, and confidence intervals (CI) reported are 95% intervals. P values were adjusted by the method of Holm in multiple testing (26). Missing data in smoking history and proteinuria were both 1.7%, which were imputed using multiple imputation method with five data sets (27). All analyses were conducted with the use of STATA/SE 11.0 for Windows (STATA Corp. LP, College Station, TX).

**Results**

Between January 2003 and December 2007, 461 patients (62% men) with a median age of 67 years (range, 57 to 76 years) met the inclusion criteria. Of these, 189 patients (41.0%) with stage 3 CKD, 144 (31.2%) with stage 4, and 128 (27.8%) with stage 5 had median observational periods of 2.9 years (range 2.0 to 4.5), 3.4 years (2.3 to 4.7), and 3.2 years (1.9 to 4.4), respectively. During follow-up, 12 (4.0%) of 303 patients were lost at our institution. We referred 158 patients to other medical institutions, and 22 patients (13.9%) of those were lost.

Baseline characteristics of the population stratified by CKD stages are shown in Table 1. More than two-thirds of patients with CKD stage 3 and 4 were male, while 55.5% of those with stage 5 CKD were female. Patients with stage 4 and 5 CKD had a higher prevalence of hypertension and prior CVD compared with patients with stage 3 CKD. As CKD stage progressed, the hemoglobin level decreased and the prevalence of overt proteinuria increased. RAS inhibitors were used in approximately
60% of patients with stage 3 and 4 CKD, and in 47.7% of those with stage 5 CKD.

During the follow-up period, 168 patients experienced ESRD, including 12 patients (7.1%) with stage 3 CKD, 53 (31.5%) with stage 4 CKD, and 103 (61.3%) with stage 5 CKD. The incidence of death, cardiac events, and stroke (per 100 patient-years) increased as CKD stage progressed (Figure 1). The 3-year cumulative mortality for each CKD stage is shown in Figure 2. At 3 years after referral, the estimated mortality rates were 9.5% for those with stage 3 CKD, 11.2% for stage 4 CKD, and 16.5% for stage 5 CKD. There was no statistically significant differences in mortality among the 3 CKD groups (P = 0.096 by the Log-rank test). The 3-year cumulative probability of ESRD for each CKD stage is shown in Figure 3. At 3 years, the estimated rates of ESRD were 6.5% for stage 3 CKD, 27.8% for stage 4 CKD, and 79.1% for stage 5 CKD (Holm-adjusted P < 0.001).

Univariate regression analyses showed that older age, lower hemoglobin level, and prior CVD were significantly associated with death, whereas male gender, overt proteinuria, lower eGFR, lower hemoglobin level, diabetes, hypertension, and smoking history were significantly associated with ESRD (Table 2). Hazard ratios (with 95% CIs) for all-cause mortality and subhazard ratios (with 95% CIs) for ESRD among age and overt proteinuria are given for three different statistical models that include important clinical variables and cardiovascular risk factors (Table 3). After adjustment with respective models, age remained a significant risk factor for death whereas overt proteinuria was a strong predictor of ESRD. Age was also negatively associated with ESRD in Model 3.

We then stratified all patients by CKD stage, age (65 years), and the presence or absence of overt proteinuria level. The incidence of death before RRT and ESRD among each group was shown in Figure 4 with logarithmic scale. Among stage 3 CKD patients older than 65 years without overt proteinuria, that is, the representative population of general

![Figure 1. Incidence of death from any cause, cardiac events, and stroke during all study periods.](image1.png)

![Figure 2. Cumulative mortality among the three CKD groups.](image2.png)

### Table 1. Demographic and clinical data for 461 patients at each stage of CKD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Stage 3 (n = 189; 41.0%)</th>
<th>Stage 4 (n = 144; 31.2%)</th>
<th>Stage 5 (n = 128; 27.8%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 (56 to 74)</td>
<td>69 (60 to 76)</td>
<td>67 (58 to 77)</td>
<td>0.056</td>
</tr>
<tr>
<td>Male (%)</td>
<td>69.3</td>
<td>67.4</td>
<td>44.5&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m²)</td>
<td>43.6 (36.1 to 51.7)</td>
<td>22.0 (17.9 to 26.1)</td>
<td>9.7 (7.2 to 12.2)</td>
<td>N/A</td>
</tr>
<tr>
<td>Overt proteinuria (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>37.6</td>
<td>62.7&lt;sup&gt;a&lt;/sup&gt;</td>
<td>80.3&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>12.9 (11.5 to 14.3)</td>
<td>10.9 (9.8 to 12.1)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.6 (8.8 to 10.4)&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>31.8</td>
<td>41.7</td>
<td>39.1</td>
<td>0.148</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>76.7</td>
<td>92.4&lt;sup&gt;a&lt;/sup&gt;</td>
<td>95.3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior CVD (%)</td>
<td>20.1</td>
<td>31.3</td>
<td>26.6</td>
<td>0.064</td>
</tr>
<tr>
<td>Smoking history (%)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>45.7</td>
<td>48.9</td>
<td>39.7</td>
<td>0.308</td>
</tr>
<tr>
<td>RAS inhibitor (%)</td>
<td>59.3</td>
<td>63.9</td>
<td>47.7&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Continuous and categorical values are presented as median (interquartile range) and percentage of total, respectively. P values were adjusted by the method of Holm in multiple testing. Pt, patients; RAS, renin-angiotensin system; N/A, not applicable.

<sup>a</sup>Significant difference versus stage 3 CKD.

<sup>b</sup>Significant difference versus stage 4 CKD.

<sup>c</sup>n = 453 due to missing data.
CKD patients, the incidence of death before RRT was 2.8 in 100 patient-years and none of them experienced ESRD. For patients with more advanced CKD and overt proteinuria, the incidence of ESRD was substantially higher than that of death before RRT.

Discussion

The present study describes how the characteristics of CKD patients referred to nephrologists in Japan differ from those in the general population. Previous population-based studies in the United States have shown that the prevalence of patients with stage 3 CKD and stage 4 to 5 CKD was about 7.7% and 0.35% (15), with a mean age of 66.5 to 71.6 and 70.1 to 73.6 years, respectively (11,13). Among those with stage 3 and 4 CKD, the prevalence of macroalbuminuria was 6.1% and 42.4%, respectively (15). Similar characteristics were also described in Japanese general CKD patients. The prevalence of stage 3 CKD and stage 4 to 5 CKD in a general Japanese population is about 10.4% and 0.2%, respectively (16). The prevalence of the elderly (older than 70 years) and positive proteinuria is 57.7% and 7.7% in stage 3 CKD, and 70.1% and 52.9% in stage 4 to 5 CKD, respectively (16). In contrast to these population-based studies, our patients were younger and were more likely to have advanced CKD and overt proteinuria. Thus the outcomes in the present study of referred patients differed from outcomes in population-based studies in terms of higher ESRD and lower mortality.

This discrepancy of outcomes was elucidated by proteinuria and age, both of which have attracted attention as predictors among CKD patients (28–30). As shown in the present study, proteinuria and age contributed differently to CKD outcomes. Proteinuria and albuminuria are accepted markers of kidney damage, and are associated with lower eGFR and an increased risk of subsequent ESRD (31–39). On the other hand, age is inversely associated with ESRD and positively associated with death (7,40–43). The stratification of heterogeneous CKD patients by those factors and CKD stage could be a simple strategy for the selection of patients who should be intensively treated by nephrologists. Whether this strategy could be applied to a more general population or not needs to be studied in future.

The incidence of outcomes among our older patients with stage 3 CKD without proteinuria were similar to those in a population-based study (13), and the incidence of ESRD was substantially higher than that of death before RRT among those with more advanced CKD and overt proteinuria. There are a few reports that describe the outcomes in non-general CKD patients, all of whom had stage 4 CKD (43–44). However, results from these reports are not consistent. One cohort study from the United Kingdom showed that crude mortality and the percentage of ESRD at 5 years were 47.5% and 24.7%, respectively (43), which is consistent with the population-based study (13). On the other hand, a study from Canada indicated that 7% of patients died, and 25% started RRT during the first 2 years of follow-up (44), which is similar to our results. In the UK cohort study, the median age (71.4 years) and the prevalence of proteinuria (62.1%) were similar to those in the population-based studies.

Table 2. Univariate Cox regression analysis of death and ESRD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death HR (95% CI)</th>
<th>P</th>
<th>ESRD a HR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td>1.98 (1.45 to 2.69)</td>
<td>&lt;0.001</td>
<td>0.78 (0.59 to 1.03)</td>
<td>0.078</td>
</tr>
<tr>
<td>Male</td>
<td>0.95 (0.57 to 1.61)</td>
<td>0.861</td>
<td>1.86 (1.01 to 3.45)</td>
<td>0.048</td>
</tr>
<tr>
<td>eGFR (per 10 ml/min per 1.73 m²)</td>
<td>0.85 (0.70 to 1.02)</td>
<td>0.079</td>
<td>0.31 (0.21 to 0.46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Overt proteinuria</td>
<td>1.22 (0.71 to 2.08)</td>
<td>0.471</td>
<td>9.10 (4.20 to 19.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>0.79 (0.69 to 0.89)</td>
<td>&lt;0.001</td>
<td>0.74 (0.66 to 0.84)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.80 (0.46 to 1.37)</td>
<td>0.407</td>
<td>2.06 (1.24 to 3.43)</td>
<td>0.005</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.22 (0.69 to 7.09)</td>
<td>0.180</td>
<td>10.7 (1.52 to 76.0)</td>
<td>0.017</td>
</tr>
<tr>
<td>Prior CVD</td>
<td>2.30 (1.35 to 3.93)</td>
<td>0.002</td>
<td>1.26 (0.72 to 2.21)</td>
<td>0.424</td>
</tr>
<tr>
<td>Smoking history</td>
<td>1.48 (0.88 to 2.49)</td>
<td>0.144</td>
<td>2.04 (1.22 to 3.41)</td>
<td>0.006</td>
</tr>
<tr>
<td>RAS inhibitors</td>
<td>0.66 (0.39 to 1.10)</td>
<td>0.110</td>
<td>0.78 (0.47 to 1.29)</td>
<td>0.326</td>
</tr>
</tbody>
</table>

aPatients with stage 5 CKD were excluded.
On the other hand, patients in our study and the Canadian study were younger and showed better survival (median age of 69 years and 6.6% estimated mortality at 2 years; mean age of 67.3 years and 6.6% mortality at 2 years, respectively) (44), resulting in a higher incidence of ESRD because these outcomes are competing risk events. Although the prevalence of overt proteinuria in our study was much higher than other studies, indicating that they had more progressive CKD, the incidence of ESRD was similar to Canadian study, probably because of higher rate of RAS inhibitor use in our study than the Canadian study (63.9% versus 48.1%). Thus, the outcomes among advanced CKD patients could be predicted based on age and overt proteinuria, in addition to eGFR at baseline.

Several limitations of our study should be noted. First, although most baseline characteristics were obtained, this was a retrospective observational study and we lost 7.4% of patients to follow-up. Among 22 losses at stage 3 CKD, median age was 63 years (range, 49 to 69) and four patients (18%) had overt proteinuria. Among 11 losses at stage 4 CKD, median age was 76 years (range, 53 to 78) and six patients (55%) had overt proteinuria. There were no statisti-

Table 3. Association of age and overt proteinuria with death and ESRD

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death HR 95% CI</th>
<th>P</th>
<th>ESRD SHR 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 10 years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1a</td>
<td>2.05 (1.49 to 2.82)</td>
<td>&lt;0.001</td>
<td>0.87 (0.64 to 1.18)</td>
<td>0.364</td>
</tr>
<tr>
<td>Model 2a</td>
<td>1.87 (1.35 to 2.60)</td>
<td>&lt;0.001</td>
<td>0.81 (0.60 to 1.10)</td>
<td>0.170</td>
</tr>
<tr>
<td>Model 3a</td>
<td>1.70 (1.20 to 2.41)</td>
<td>0.003</td>
<td>0.67 (0.49 to 0.92)</td>
<td>0.013</td>
</tr>
<tr>
<td>Overt proteinuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1a</td>
<td>1.38 (0.78 to 2.45)</td>
<td>0.270</td>
<td>6.03 (2.73 to 13.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 2a</td>
<td>1.39 (0.78 to 2.47)</td>
<td>0.265</td>
<td>5.55 (2.56 to 12.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Model 3a</td>
<td>1.13 (0.62 to 2.05)</td>
<td>0.697</td>
<td>4.97 (2.23 to 11.1)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Model 1a: Overt proteinuria, sex, and estimated glomerular filtration ratio.
Model 1b: Age, sex, and estimated glomerular filtration ratio.
Model 2a/b: Model 1a/b + prior cardiovascular disease, diabetes and hypertension.
Model 3a/b: Model 2a/b + smoking history, hemoglobin and renin-angiotensin inhibitors.

"Patients with stage 5 CKD were excluded.

Figure 4. Incidence of death before renal replacement therapy and end-stage renal disease stratified by age, overt proteinuria, and CKD stages. *No incidence.

(13,43,45).
cal differences in age and proteinuria between lost patients and those not lost ($P = 0.091$ and $P = 0.072$ in stage 3, and $P = 0.85$ and $P = 0.49$ in stage 4, respectively). Only one of 128 patients at stage 5 CKD was lost. Therefore, these lost patients were not supposed to have significant influence on our results. Second, because of the small study size, it is likely that our study had insufficient power to draw any conclusions about the prognosis and risk factors. Several variables that are supposed to be established risk factors of death (sex, diabetes, hypertension, and smoking history) were not statistically identified in our study. However, considering the prevalence of stage 4 to 5 CKD in Japanese general adult population (0.2%) (16) and the population of Izumisano city and neighboring four municipalities (78,291 and total of 162,143 in the 2005 national population census (46), respectively), our patients with stage 4 to 5 CKD in this study were supposed to account for majority of those in this area, although this study was a dynamic population cohort. We also investigated the prevalence of those who initiated RRT at our institution among four major dialysis centers in this area during this study period, and found it to be 68.7%. Third, we did not evaluate primary kidney disease. It is possible that the lack of primary kidney disease as a confounder made the impact of age and overt proteinuria on ESRD stronger than expected in our analysis. However, it is quite difficult to include precise diagnoses as a variable in analyses because clinical diagnosis is often ambiguous and incorrect, and renal biopsy is rarely performed for advanced CKD patients. Moreover, sometimes there are coexisting kidney diseases, such as nephrosclerosis and diabetic nephropathy. On the other hand, our stratification strategy with age, proteinuria, and CKD stage is simple and practical. Fourth, the study population consisted of only Japanese subjects without malignancy. Previous studies have also described longer survival and lower CVD event rates in Japanese high-risk population than those in other countries (47). These factors might contribute to the better survival in our study.

Conclusion

In the present study, we showed different backgrounds and outcomes in CKD patients referred to nephrologists compared with patients included in population-based studies. Advanced CKD and overt proteinuria were common among referred patients. Proteinuria and age contributed differently to CKD outcomes. Stratification of heterogeneous CKD patients by those factors and CKD stage could be a simple strategy for predicting the competing outcomes and for the selection of patients who should be intensively treated by nephrologists.

Acknowledgments

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Disclosures

None.

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