Combining GFR and Albuminuric to Classify CKD Improves Prediction of ESRD

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ABSTRACT

Despite the high prevalence of chronic kidney disease (CKD), relatively few individuals with CKD progress to ESRD. A better understanding of the risk factors for progression could improve the classification system of CKD and strategies for screening. We analyzed data from 65,589 adults who participated in the Nord-Trøndelag Health (HUNT 2) Study (1995 to 1997) and found 124 patients who progressed to ESRD after 10.3 yr of follow-up. In multivariable survival analysis, estimated GFR (eGFR) and albuminuria were independently and strongly associated with progression to ESRD: Hazard ratios for eGFR 45 to 59, 30 to 44, and 15 to 29 ml/min per 1.73 m² were 6.7, 18.8, and 65.7, respectively (P < 0.001 for all), and for micro- and macroalbuminuria were 13.0 and 47.2 (P < 0.001 for both). Hypertension, diabetes, male gender, smoking, depression, obesity, cardiovascular disease, dyslipidemia, physical activity and education did not add predictive information. Time-dependent receiver operating characteristic analyses showed that considering both the urinary albumin/creatinine ratio and eGFR substantially improved diagnostic accuracy. Referral based on current stages 3 to 4 CKD (eGFR 15 to 59 ml/min per 1.73 m²) would include 4.7% of the general population and identify 69.4% of all individuals progressing to ESRD. Referral based on our classification system would include 1.4% of the general population without losing predictive power (i.e., it would detect 65.6% of all individuals progressing to ESRD). In conclusion, all levels of reduced eGFR should be complemented by quantification of urinary albumin to predict optimally progression to ESRD.

Since the publication of the Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines on the classification of chronic kidney disease in 2002,1 several studies based on this classification system have shown very high prevalence estimates of chronic kidney disease (CKD) in the general population (10 to 13%).2,3 Screening for CKD is therefore increasingly suggested4-6; however, only a small proportion of patients with stage 3 to 4 CKD progress to ESRD.5 There is an ongoing discussion on whether the current CKD criteria are appropriate.6-8 Developing a risk score to identify better the patients who are at increased risk for ESRD would be of major importance for the current efforts to establish clinical guidelines and public health plans for CKD.4,5,10

Several predictors of progression to ESRD


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have been identified,9 but their independent predictive power has not been well studied either in the general population or in high-risk subgroups. Intuitively, a low estimated GFR (eGFR) is an important risk factor for ESRD, and eGFR is the backbone of the current CKD classification. High urine albumin is a well-established major risk factor for progression.9 Only a few studies have examined the renal risk as a function of the combination of eGFR and albuminuria.11–14 These studies are of restricted value, however, because of exclusion of patients with diabetes13; inclusion of men only12; inclusion of only patients with diabetes13; or absence of information on potentially important risk factors, such as smoking, obesity, dyslipidemia, and cardiovascular disease.11,14

CKD screening beyond patients with known hypertension or diabetes has been proposed,1–4 but such screening programs have remained unsatisfactory because of their limited predictive power. We used the data of the Second Nord-Trøndelag Health Study (HUNT 2), Norway, to improve such prediction. HUNT 2 is a large population-based study with a high participation rate.15 Our aim was to examine how accurately subsequent progression to ESRD could be predicted by a combined variable of baseline eGFR and urine albumin. We also tested whether further potential renal risk factors provided additional independent prediction.

RESULTS

After 10.3 yr of follow-up of 65,589 patients, 58 started on renal replacement therapy (RRT) and 132 others died of advanced CKD. We excluded four patients who died of acute-on-chronic renal failure, nine of acute renal failure, 38 with stages 3 to 4 CKD, and 15 for whom adequate information on renal function was missing; therefore, 124 patients with documented progression to ESRD were included. Baseline characteristics of our study participants are summarized in Table 1. The prevalence of stages 3 and 4 CKD at baseline was 4.4 and 0.1%, respectively, in patients who did not progress and 46.0 and 23.4%, respectively, in patients who did progress to ESRD.

Table 2 shows the age-adjusted hazard ratios (HRs) of all potential risk factors for progression to ESRD available. Increased risk was significantly associated with male gender, low physical activity, presence of diabetes, higher values of body mass index and waist circumference, higher values of systolic and diastolic BP, treatment with antihypertensive drugs, lower values of HDL cholesterol concentration, and higher values of triglyceride and glucose concentration. No significantly increased risk was associated with low education, depression, current smoking, prevalent cardiovascular disease, or higher values of total cholesterol. A “best clinical model” was then

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All (n = 65,589)</th>
<th>No Progression to ESRD (n = 65,465)</th>
<th>Progression to ESRD (n = 124)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr; mean [SD]; n = 65,589)</td>
<td>50.1 (17.3)</td>
<td>50.1 (17.3)</td>
<td>70.8 (13.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male gender (%; n = 65,589)</td>
<td>46.8</td>
<td>46.8</td>
<td>62.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low education (%; n = 61,369)b</td>
<td>70.7</td>
<td>70.6</td>
<td>86.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Depression (%; n = 58,423)c</td>
<td>10.6</td>
<td>10.6</td>
<td>26.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Current smoking (%; n = 64,395)</td>
<td>28.0</td>
<td>28.0</td>
<td>17.6</td>
<td>0.012</td>
</tr>
<tr>
<td>Low physical activity (%; n = 57,881)d</td>
<td>20.1</td>
<td>20.1</td>
<td>42.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes (%; n = 64,693)</td>
<td>3.3</td>
<td>3.3</td>
<td>18.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CVD (%; n = 64,624)e</td>
<td>7.9</td>
<td>7.9</td>
<td>25.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BMI (kg/m2; mean [SD]; n = 64,306)</td>
<td>26.4 (4.1)</td>
<td>26.4 (4.1)</td>
<td>28.0 (5.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Waist circumference (cm; mean [SD]; n = 64,022)</td>
<td>86.5 (11.8)</td>
<td>86.5 (11.8)</td>
<td>94.1 (13.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Systolic BP (mmHg; mean [SD]; n = 64,708)</td>
<td>137.9 (21.8)</td>
<td>137.9 (21.8)</td>
<td>160.6 (24.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg; mean [SD]; n = 64,708)</td>
<td>80.3 (12.3)</td>
<td>80.3 (12.2)</td>
<td>87.3 (15.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Antihypertensive medication (%; n = 64,649)</td>
<td>11.1</td>
<td>11.0</td>
<td>46.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol (mg/dl; mean [SD]; n = 65,158)</td>
<td>228.2 (48.9)</td>
<td>228.2 (50.3)</td>
<td>252.4 (58.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dl; mean [SD]; n = 65,155)</td>
<td>53.2 (15.1)</td>
<td>54.1 (15.5)</td>
<td>46.4 (15.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mg/dl; median [range]; n = 65,158)</td>
<td>131 (12–696)</td>
<td>131 (12–696)</td>
<td>187 (35–363)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose (mg/dl; median [range]; n = 65,158)f</td>
<td>93 (41–558)</td>
<td>94 (41–558)</td>
<td>102 (61–348)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine (mg/dl; mean [SD]; n = 65,158)</td>
<td>1.0 (0.2)</td>
<td>1.0 (0.2)</td>
<td>1.7 (0.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>eGFR (ml/min per 1.73 m2; mean [SD]; n = 65,158)</td>
<td>94.2 (21.5)</td>
<td>94.3 (21.5)</td>
<td>49.8 (23.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ACR (mg/g; median [range]; n = 9703)</td>
<td>7 (0.4–2437)</td>
<td>7 (0.4–1558)</td>
<td>136 (94.4–2437)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

a The “no progression” and “progression” groups are compared using χ2 test or two-sample t test. BMI, body mass index; CVD, cardiovascular disease. 
b Fewer than 12 yr in school. 
c Eight points or more on the depression part of the Hospital Anxiety and Depression Score. 
d Less than 1 h of light activity per week in participants’ leisure time. 
e Self-reported history of myocardial infarction, angina pectoris, or stroke. 
f Measured at random.
identified by manual forward selection of the significant age-adjusted variables. In this multivariable analysis, age, gender, physical activity, diabetes, systolic BP, antihypertensive mediation, and HDL cholesterol remained as significant predictors \( (P < 0.016) \); however, they all turned out to be NS after inclusion of eGFR and albumin-to-creatinine ratio (ACR). For example, patients with diabetes had an age-adjusted HR of 2.68 and of 1.80 in the multivariable “best clinical model,” but after accounting for eGFR and ACR, the HR was not different from 1.00. Evidently, the major predictors of future ESRD were low eGFR and high ACR. Patients with eGFR 45 to 59 ml/min per 1.73 m² had a multiadjusted HR of 6.67 compared with those with eGFR \( \geq 60 \) ml/min per 1.73 m². The HR associated with eGFR 30 to 44 and 15 to 29 ml/min per 1.73 m² was 18.8 and 65.7, respectively. Compared with patients with normalalbuminuria, the presence of micro- or macroalbuminuria conferred a 13.0 and 47.2 times higher risk for progressing to ESRD, respectively. Figure 1 shows that after adjustment for age, gender, and eGFR, the risk associated with increasing ACR was continuous with no lower limit (\( i.e. \), the association continued even into the range of normoalbuminuria).

A positive interaction between eGFR and ACR was observed. Patients with eGFR \( \geq 60 \) ml/min per 1.73 m² and normoalbuminuria had an age-adjusted HR of 34.8 (95% confidence interval [CI] 11.4 to 107.1) compared with the reference group with eGFR \( \geq 60 \) ml/min per 1.73 m² and normoalbuminuria. Patients with eGFR \( \geq 60 \) ml/min per 1.73 m² and micro- or macroalbuminuria had an HR of 36.4 (95% CI 12.4 to 107.0). The expected HR for patients with both risk factors should be 71.2, but the observed HR was 570.5 (95% CI 199.7 to 1630.0). Therefore, the relative excess risk due to interaction was 500.3 (95% CI 59.8 to 940.6), and an attributable portion of 0.877 (95% CI 0.826 to 0.928) indicate that 88% of the joint effect of low eGFR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Age-Adjusted Variables</th>
<th>Best Clinical Model</th>
<th>Best Clinical + eGFR + ACR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR 95% CI P</td>
<td>HR 95% CI P</td>
<td>HR 95% CI P</td>
</tr>
<tr>
<td>Age (per 10 yr)</td>
<td>1.72 1.48 to 1.99 &lt;0.001</td>
<td>1.15 0.98 to 1.35 0.073</td>
<td>1.24 0.83 to 1.86 0.296</td>
</tr>
<tr>
<td>Male gender</td>
<td>2.13 1.50 to 3.07 &lt;0.001</td>
<td>2.22 1.49 to 3.31 &lt;0.001</td>
<td>1.24 0.83 to 1.86 0.296</td>
</tr>
<tr>
<td>Low educationa</td>
<td>1.09 0.61 to 1.94 0.768</td>
<td>1.32 0.91 to 1.92 0.39</td>
<td>0.92 0.56 to 1.49 0.735</td>
</tr>
<tr>
<td>Depression</td>
<td>1.74 1.15 to 2.63 0.009</td>
<td>1.71 1.13 to 2.60 0.012</td>
<td>1.23 0.81 to 1.87 0.337</td>
</tr>
<tr>
<td>Current smoking</td>
<td>2.68 1.68 to 4.27 &lt;0.001</td>
<td>1.80 1.11 to 2.90 0.016</td>
<td>0.87 0.53 to 1.43 0.585</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.26 0.82 to 1.93 0.288</td>
<td>1.06 0.22 to 1.10 0.004</td>
<td>1.38 1.19 to 1.61 &lt;0.001</td>
</tr>
<tr>
<td>BMI (per 1-kg/m²)</td>
<td>1.15 0.98 to 1.35 0.073</td>
<td>2.22 1.49 to 3.31 &lt;0.001</td>
<td>1.24 0.83 to 1.86 0.296</td>
</tr>
<tr>
<td>Waist circumference (per 10-cm)</td>
<td>1.15 0.98 to 1.35 0.073</td>
<td>2.22 1.49 to 3.31 &lt;0.001</td>
<td>1.24 0.83 to 1.86 0.296</td>
</tr>
<tr>
<td>Systolic BP (per 10-mmHg)</td>
<td>1.16 1.02 to 1.32 0.018</td>
<td>2.38 1.62 to 3.50 &lt;0.001</td>
<td>1.08 0.69 to 1.68 0.731</td>
</tr>
<tr>
<td>Diastolic BP (per 10-mmHg)</td>
<td>2.98 2.08 to 4.32 &lt;0.001</td>
<td>1.71 1.13 to 2.60 0.012</td>
<td>1.23 0.81 to 1.87 0.337</td>
</tr>
<tr>
<td>Antihypertensive treatment</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>Cholesterol (per 40-mg/dl)</td>
<td>1.09 0.96 to 1.25 0.197</td>
<td>2.38 1.62 to 3.50 &lt;0.001</td>
<td>1.08 0.69 to 1.68 0.731</td>
</tr>
<tr>
<td>HDL cholesterol (per 4-mg/dl)</td>
<td>0.85 0.81 to 0.91 &lt;0.001</td>
<td>0.90 0.85 to 0.95 &lt;0.001</td>
<td>0.96 0.91 to 1.02 0.129</td>
</tr>
<tr>
<td>Triglycerides (per 80-mg/dl)</td>
<td>1.25 1.16 to 1.35 &lt;0.001</td>
<td>0.90 0.85 to 0.95 &lt;0.001</td>
<td>0.96 0.91 to 1.02 0.129</td>
</tr>
<tr>
<td>Glucose (per 20-mg/dl)</td>
<td>1.10 1.04 to 1.16 &lt;0.001</td>
<td>0.90 0.85 to 0.95 &lt;0.001</td>
<td>0.96 0.91 to 1.02 0.129</td>
</tr>
<tr>
<td>Renal function (ml/min per 1.73 m²)</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>eGFR &gt;60</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>eGFR 45 to 59</td>
<td>11.50 6.56 to 20.20 &lt;0.001</td>
<td>6.70 3.78 to 11.90 &lt;0.001</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>eGFR 30 to 44</td>
<td>52.60 29.60 to 93.40 &lt;0.001</td>
<td>18.80 10.30 to 34.40 &lt;0.001</td>
<td>65.60 35.20 to 122.10 &lt;0.001</td>
</tr>
<tr>
<td>eGFR &lt;30</td>
<td>299.50 165.60 to 541.80 &lt;0.001</td>
<td>52.60 29.60 to 93.40 &lt;0.001</td>
<td>18.80 10.30 to 34.40 &lt;0.001</td>
</tr>
<tr>
<td>ACR normal</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
<td>1.00 1.00</td>
</tr>
<tr>
<td>microalbuminuria</td>
<td>18.50 9.90 to 34.70 &lt;0.001</td>
<td>13.00 6.76 to 25.1 &lt;0.001</td>
<td>47.50 19.8 to 109.0 &lt;0.001</td>
</tr>
<tr>
<td>macroalbuminuria</td>
<td>193.70 94.60 to 396.70 &lt;0.001</td>
<td>13.00 6.76 to 25.1 &lt;0.001</td>
<td>47.50 19.8 to 109.0 &lt;0.001</td>
</tr>
</tbody>
</table>

*Age-adjusted HRs associated with all available potential risk factors based on Cox regression analysis are given. A best clinical model was then identified by manual forward selection among the significant variables. Finally, eGFR and ACR were added to the best clinical model.

*Fewer than 12 yr in school.

*Eight points or more on the depression part of the Hospital Anxiety and Depression Score.

*Less than 1 h of light activity per week in participants’ leisure time.

*Self-reported history of myocardial infarction, angina pectoris, or stroke.

*ACR ranging from 20 to 200 mg/g in men and 30 to 300 mg/g in women.
and increased albuminuria was due to interaction between the two risk factors. This strong synergistic effect indicates that eGFR and ACR give better risk stratification when used in combination.

Table 3 shows the HRs of progression to ESRD associated with a new 12-category variable based on the combined effect of eGFR and ACR. Cox regression analysis showed that within each ACR category, lower eGFR categories were associated with a higher risk. Likewise, progressively higher ACR categories were associated with a progressively higher risk within each eGFR category. Patients with macroalbuminuria and eGFR 15 to 29 ml/min per 1.73 m² had a 6957 times higher risk for ESRD compared with the reference category of patients with eGFR ≥60 ml/min per 1.73 m² and normal ACR. After multivariable adjustment, these patients had a 4146 times higher risk. Categories of low, medium, and high risk for progression to ESRD are indicated in Table 3 with footnote symbols (b, c, and d, respectively).

Figure 2 shows that the best clinical model (age, gender, physical activity, diabetes, systolic BP, antihypertensive medication, and HDL cholesterol) had a total area under the receiver operating characteristic (ROC) curve (AUC) of 0.864 (i.e., classified correctly 86.4% of pairs of patients in the general population who did and did not progress to ESRD). ACR alone performed substantially better (AUC 0.893), but eGFR alone had the best prediction (AUC 0.933). Combining ACR and eGFR increased the total AUC only marginally (0.936); however, using total AUC for evaluating the diagnostic accuracy of a test implies equal importance of true-positive and false-positive rates. For screening-related situations, the clinical relevant region of the curve is at low FP rates (<0.10).

Table 3. HRs for progression to ESRD by categories of eGFR and ACR

<table>
<thead>
<tr>
<th>Parameter</th>
<th>eGFR (ml/min per 1.73 m²)</th>
<th>≥60</th>
<th>45 to 59</th>
<th>30 to 44</th>
<th>15 to 29</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal ACR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unadjusted</td>
<td>1.0b</td>
<td>30.8 (9.3 to 102.2)b</td>
<td>76.0 (18.5 to 313.2)b</td>
<td>583.1 (120.5 to 2822.0)c</td>
<td></td>
</tr>
<tr>
<td>adjusted</td>
<td>1.0b</td>
<td>23.4 (6.7 to 82.1)b</td>
<td>51.9 (11.5 to 233.5)b</td>
<td>368.7 (69.2 to 1964.0)c</td>
<td></td>
</tr>
<tr>
<td>Microalbuminuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unadjusted</td>
<td>33.9 (11.2 to 102.6)b</td>
<td>227.4 (72.8 to 710.2)c</td>
<td>740.6 (246.7 to 2222.0)c</td>
<td>3833.0 (1265.0 to 11,611.0)d</td>
<td></td>
</tr>
<tr>
<td>adjusted</td>
<td>27.3 (8.8 to 84.5)b</td>
<td>146.5 (42.7 to 502.7)c</td>
<td>448.9 (133.7 to 1508.0)c</td>
<td>2202.0 (632.5 to 7669.0)d</td>
<td></td>
</tr>
<tr>
<td>Macroalbuminuria</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>unadjusted</td>
<td>306.6 (50.3 to 1871.0)c</td>
<td>1108.0 (285.8 to 4297.0)c</td>
<td>3167.0 (1066.0 to 9403.0)d</td>
<td>6957.0 (2286.0 to 21,165.0)d</td>
<td></td>
</tr>
<tr>
<td>adjusted</td>
<td>196.3 (27.6 to 1397.0)c</td>
<td>641.1 (143.6 to 2862.0)c</td>
<td>2036.0 (594.3 to 6973.0)d</td>
<td>4146.0 (1187.0 to 14,824.0)d</td>
<td></td>
</tr>
</tbody>
</table>

*Numbers are unadjusted HR (95% CI) and HR after adjustment for age, gender, systolic BP, antihypertensive medication, diabetes, HDL cholesterol, and physical activity in a Cox regression analysis. Microalbuminuria was ACR ranging from 20 to 200 mg/g in men and 30 to 300 mg/g in women.

bLow risk for progression to ESRD.

*Medium risk for progression to ESRD.

dHigh risk for progression to ESRD.
Table 4. Diagnostic accuracy of prognostic markers for progression to ESRD in different populations selected for screening

<table>
<thead>
<tr>
<th>Prognostic Marker</th>
<th>Screening Strategies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diabetes/ Hypertension</td>
</tr>
<tr>
<td></td>
<td>TPR0.03 pAUC</td>
</tr>
<tr>
<td>Best clinical model</td>
<td>0.155 0.603</td>
</tr>
<tr>
<td>ACR</td>
<td>0.459 0.752</td>
</tr>
<tr>
<td>eGFR</td>
<td>0.453 0.754</td>
</tr>
<tr>
<td>eGFR + ACR</td>
<td>0.579 0.807</td>
</tr>
<tr>
<td>eGFR + ACR + best clinical model</td>
<td>0.612 0.820</td>
</tr>
</tbody>
</table>

aTPR0.03, true-positive rate (i.e., sensitivity) at a fixed false-positive rate (FPR) of 0.03; pAUC, partial area under the clinically relevant part of the ROC curve (FPR 0.00 to 0.10) transformed to values between 0.5 and 1.0.35 Analogous to ordinary ROC analysis, a perfect test would have pAUC = 1.0, whereas a test with no ability to discriminate between those progressing to ESRD and those not progressing would have pAUC = 0.5. Best clinical model includes age, gender, physical activity, diabetes, systolic BP, antihypertensive treatment, and HDL cholesterol.
bBritish CKD guidelines recommend screening of individuals with hypertension, diabetes, autoimmune diseases, CVD, or postrenal obstruction.4

Table 5. Diagnostic effectiveness of different algorithms for detecting patients progressing to ESRD

<table>
<thead>
<tr>
<th>Referral Criteria</th>
<th>Screening Strategy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Diabetes/ Hypertension</td>
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<tr>
<td></td>
<td>DR (%) Pop. (%) NNTF</td>
</tr>
<tr>
<td>CKD</td>
<td>50.2 3.7 38.4</td>
</tr>
<tr>
<td>stages 3 to 4</td>
<td>44.2 2.1 25.3</td>
</tr>
<tr>
<td>stages 4</td>
<td>11.3 0.4 1.2</td>
</tr>
<tr>
<td>eGFR-ACR</td>
<td>moderate or high risk</td>
</tr>
<tr>
<td></td>
<td>high only</td>
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</tbody>
</table>

aDR, detection rate (i.e., the proportion of all participants in the HUNT 2 study experiencing ESRD during the next 10.3 yr included for intensive follow-up); Pop., proportion of the total adult population included for intensive follow-up; eGFR-ACR moderate risk = GFR 15 to 29 and normal ACR, or eGFR 30 to 59 and microalbuminuria, or eGFR ≥60 and macroalbuminuria in Table 3; eGFR-ACR high risk = eGFR 15 to 29 and microalbuminuria, or eGFR 15 to 44 and macroalbuminuria in Table 3.
several clinical trials, patients with macroalbuminuria and eGFR 15 to 29 ml/min per 1.73 m² would still have an HR of 730 (95% CI 170 to 3103; Table 3). Likewise, the detection rates for future ESRD in the general population were still similar for stages 3 to 4 CKD versus moderate/high-risk eGFR–ACR model for referral (62.2 versus 58.8%), whereas the number of patients referred to a specialist were more than three-fold lower with the latter referral criteria (Table 5).

**DISCUSSION**

In this large population-based sample, we identified the combination of eGFR and albuminuria as a powerful predictor of progression to ESRD. This model did not improve significantly by addition of further variables. Our predictor was more effective than the current K/DOQI CKD classification system because the latter does not include albumin as a predictor in stages 3 to 4 CKD.

Several methodologic aspects of our study deserve discussion. First, the validity of ESRD as a primary outcome may pose problems in epidemiologic research. Many patients with ESRD die from cardiovascular causes before being taken on dialysis, but we were able to include these by linkage to the Cause of Death Registry. In addition, a few patients with eGFR <15 ml/min per 1.73 m² remained alive without dialysis throughout a 10.3-yr study period. They pose a potential cause of misclassification bias because most cases would come from the low-risk groups; however, sensitivity analyses showed that our results would still be valid even if the reference category contributed >200% extra cases of ESRD, an extent of misclassification that is very unlikely. We were also able to validate the diagnosis of ESRD in all cases included—a major strength of this study—and the incidence of study participants who started RRT was identical to the mean incidence for Norway. Another limitation is that only a subgroup of HUNT 2 participants were invited to deliver urine for albumin testing. To avoid bias and loss of statistical power, however, we used multiple imputation proposed by statisticians for this particular purpose rather than using the traditional complete-case analysis. In large populations (n > 1000) and with 20 databases imputed, as in our study, this technique has been shown to handle up to 90% missing values with a validity and precision of the imputed values almost identical to the “true” values. To avoid potential artifacts, we measured ACR in three nonfrozen urine samples within 5 d. This is highly recommended and could give more accurate results than a single measurement. Other limitations may be attributed to the imprecision of the Modification of Diet in Renal Disease (MDRD) formula in the range of normal values leading to risk category misclassification of some participants. The homogeneous study population decreases the generalizability of our results to other ethnic groups. In addition, selection bias is always a potential problem in observational studies, but the participation rate of HUNT 2 was among the highest ever reported in such large-scale studies.

The combination of eGFR and proteinuria was assessed in some studies that used small cohorts, specific populations, or dipstick testing, but studies specifically measuring albuminuria and covering the complete range of urine albumin values in a white general population with hard end points have not yet been reported. Iseki et al. studied 95,255 Japanese patients and found that dipstick proteinuria and eGFR 30 ml/min per 1.73 m² were associated with a 1000 times higher risk for future dialysis compared with no proteinuria and eGFR ≥60 ml/min per 1.73 m². In a small cohort of black patients (n = 1094) with hypertension and nephrosclerosis, Lea et al. documented that the risk for progression extends down into the range of microalbuminuria. None of these studies adjusted for other variables. Ishani et al. were the first to explore the eGFR–proteinuria combination in a multivariable analysis using data from 12,866 men at high risk for heart disease. Patients with macroalbuminuria and eGFR <60 ml/min per 1.73 m² had 33 times higher risk for progressing to RRT compared with those with negative dipstick and eGFR ≥60 ml/min per 1.73 m². Verhave et al. studied 6022 individuals who were from the general population and had eGFR >60 ml/min per 1.73 m² and found that increasing albumin excretion, even in the normal range, was associated with increasing risk for renal function loss. Using the same population, Brantsma et al. showed that even for eGFR 30 to 59 ml/min per 1.73 m² microalbuminuria or worse was associated with higher annual loss of renal function. Our study confirms that urine albumin is a continuous risk factor for progression to ESRD—a much more relevant end point—with no lower limit and at all levels of eGFR.

How does the predictive power of this study compare with that of past studies? Previously suggested screening strategies can detect 44 to 100% of all patients with stages 3 to 4 CKD in the general population, but, of these, only a small minority will progress to ESRD. Consequently, using these algorithms, the health system would be overwhelmed with an excessive number of patients who actually do not need treatment by a nephrologist. It has therefore been increasingly questioned whether the currently available CKD classification system is appropriate. Inclusion of albuminuria even at eGFR <60 ml/min per 1.73 m² for the assessment of the risk for progression of CKD has been suggested; however, our study is the first to address and quantify systematically the predictive power of such a classification system using a large population-based cohort with hard end points. Our study documents that adding information on urine albumin to patients with stages 3 to 4 CKD substantially increases the predictive power to identify individuals at high risk for progression. We emphasize that a large proportion of patients with stage 3 CKD are at low risk for progression as long as the urine albumin concentration is low. At the same level of eGFR, the risk rises substantially when micro- or macroalbuminuria is present.

Our study shows that including additional variables beyond
CONCISE METHODS

The HUNT 2 study is a Norwegian large-scale general health study. From 1995 through 1997, all individuals who resided in Nord-Trøndelag county and were aged ≥20 yr were invited. The population is stable (net out migration of 0.3% per year) and ethnically homogeneous (97% white). The participants answered a comprehensive questionnaire, underwent clinical examination, and donated a blood sample. A planned missing data design was used for expensive or bothersome examinations (e.g., repeated measurements of urine albumin concentration). A more detailed description of the objectives, methods, and participation in the HUNT 2 study has been given elsewhere. The participants gave informed consent, including linkage to central national registries. This study was approved by the Regional Committee for Medical Research Ethics, the Norwegian Data Inspectorate, and the Ministry of Health.

Of 92,939 individuals invited, 27,350 did not respond; thus, 70.6% of the entire adult population participated. All participants reported on current and former health, illness in the family, education, and risk factors such as smoking and physical inactivity. Three consecutive standardized BP measurements were recorded in the sitting position at 1-min intervals using an automatic oscillometric method (Dinamap 845XT; Critikon, Tampa, FL). Blood was obtained from all participants, immediately centrifuged and refrigerated, and analyzed within 2 d using a Hitachi 911 autoanalyzer (Hitachi, Mito, Japan).

GFR was estimated with the MDRD Study equation for standardized serum creatinine values:

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egFk = 175 \times \left[ \text{serum creatinine (mg/dL)} \right]^{-1.154} \times \text{age}^{-0.203} \times 0.742 \times \text{women} \]

The original Jaffe-based creatinine values were recalibrated providing isotope dilution mass spectrometry traceable values. By doing so, eGFR values for the HUNT 2 study have been shown to be unbiased in the normal range and for all age groups. Individuals with eGFR <15 ml/min per 1.73 m² at baseline (n = 15) were excluded, and individuals with eGFR values ≥160 ml/min per 1.73 m², which is unlikely to be physiologic, were given a value of 160 ml/min per 1.73 m² (n = 541).

Among the 65,589 participants, 8360 had hypertension and were taking BP-lowering drugs or were patients with diabetes. These patients were asked to deliver spot urine samples on three consecutive mornings, and 88.6% returned all requested urine samples. Nonresponders were not statistically different from those who delivered all urine samples regarding important variables such as age, gender, cardiovascular disease, weight, BP, lipids, and serum creatinine. A random 5% sample of individuals without diabetes and hypertension (n = 2861) were also asked to deliver urine samples; 75.6% returned all requested urine samples. Nonresponders were not statistically different regarding the variables mentioned already except for a younger age (44 vs 49 yr; P = 0.001). Urine albumin concentration in refrigerated urine samples (5°C) was measured within 5 d using an immunoturbidimetric method (Dako A/S, Glostrup, Denmark; lower detection level 1 mg/L), and the mean urine ACR was used as an expression for albumin excretion.

The study outcome was ESRD. In Norway, all live births are given a national identification number, enabling record linkage of all study participants to the Norwegian Renal Registry, which is >99.9% complete regarding start of RRT (T. Leivestad, registry director, personal communication, May 2008) and to the Cause of Death Registry. We used CKD death, defined as those who had a CKD diagnosis (International Classification of Diseases, 10th Revision diagnosis N00 through N19 excluding N10 and N17) as the immediate cause of death or underlying cause of death on their death certificate to find individuals who had ESRD and did not start RRT. Two experienced nephrologists manually searched the deceased individuals’ records available from the hospital and/or the general practitioner. Cases with “acute-on-chronic” renal failure were excluded. ESRD was defined as starting RRT or death with advanced renal failure (i.e., a documented CKD diagnosis and a documented stable eGFR <15 ml/min per 1.73 m² or other indications for RRT before death).

Statistical analyses were performed using Stata 10.0 (Stata Corp., College Station, TX). In general, there were few missing data (<2% for most variables; Table 1), but repeated measurements of ACR were, by study design, available only in a subgroup. Multiple imputation is now considered the standard method for handling this type of data, whereas complete case analysis would yield too imprecise as well as biased results. The multiple imputation technique estimates the mean and uncertainty of the missing data in individuals using all information from the actually observed data in a proper way. Using the Stata command “ice,” we created 20 complete data sets to achieve maximum accuracy. Subsequently, the Stata command “micombine” was used together with standard statistical methods, giving unbiased risk estimates with correct CIs. For most individuals without diabetes and hypertension, data were missing completely at random, and for those who did not return urine samples as requested, data were assumed to be missing at random, thus meeting the assumptions of

eGFR and ACR in a renal risk model will not substantially improve risk prediction and can therefore be omitted for cost’s and simplicity’s sake. In addition, eGFR and ACR complement each other very well, leading to a strong interaction and a strong predictive power. Roughly, ACR is a marker of the rate of progression, whereas eGFR is a marker of how advanced the disease process is. This by no means negates the importance of, for example, hypertension, diabetes, and smoking as modifiable factors in the progression of CKD, because ability to predict future ESRD should not be equated with causality. As an added benefit of this approach—although not directly tested in this analysis—a previous study using the same data set showed that the combination of eGFR and ACR significantly improved cardiovascular risk prediction at all age levels but particularly in the elderly, for whom the predictive power of traditional risk factors is attenuated.

We conclude that in the general population, eGFR and urine albumin excretion, even in the range of microalbuminuric values, are the most powerful predictors of ESRD known to date. They exhibit strong interaction, and all levels of eGFR should be complemented by information on urine albumin to improve classification and prognostication. Future renal risk scores and CKD classification systems based on these two variables will be a simple and powerful tool improving our ability to handle efficiently the large group of patients with CKD.
of the method. ACR was log-transformed and not used as predictor in
the imputation of other missing variables, study outcome (ESRD) was
included in the imputation model, and the time variable was
log-transformed. Regression modeling revealed interactions be-
tween gender and both BP and diabetes; therefore, these two interac-
tions were included in the imputation model.

Cox proportional hazard regression analysis was used to evaluate the
influence of renal risk factors on progression to ESRD. We checked for
crossover and other nonproportional survival patterns and for linearity in continuous variables. Binary variables were coded
as 0/1, and ordinal variables were coded as integer values. All individ-
uals were passively observed (i.e., further clinical examinations or
blood samples were not performed) until January 1, 2006; death; or
starting RRT, whichever occurred first. Age-adjusted associations for
all available variables were evaluated, and a best clinical model was
built by entering significant variables into a multivariable model using
stepwise forward selection. Finally, eGFR and ACR were added to the
previous best clinical model, and, in all further analyses, we consis-
tently adjusted the eGFR-ACR results for the best clinical model vari-
able. Interaction on an additive scale was used to evaluate whether
eGFR and ACR are more effective for risk stratification when used
together rather than separately. Two-sided P < 0.05 was considered signif-
ificant. A composite variable with 12 categories combining four eGFR
categories and three ACR categories was used to evaluate the com-
bined effect of these two variables. Microalbuminuria was defined as
ACR 20 to 200 mg/g in men and 30 to 300 mg/g in women, and
macroalbuminuria was defined as ACR >200 mg/g in men and >300
mg/g in women. The continuous relationship of higher ACR with
future ESRD was explored using fractional polynomial models ad-
justed for eGFR, gender, and age. Because relative risk–based meth-
ods are not well suited for classifying or predicting risk in individuals,
we used time-dependent ROC curves for survival data. In popula-
tion-based screening, the clinical relevant region of the ROC curve is
at low false-positive rates. We calculated the partial area under the
ROC curve for false-positive rates between 0.00 and 0.10. For dis-
eases with a low prevalence and/or with no confirmative test available,
false-positive rates of 0.03 and lower are often recommended to avoid
errors with a low prevalence and/or with no confirmative test available,
together rather than separately. Two-sided

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DISCLOSURES

None.
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