Predicting Renal Risk in the General Population: Do We Have the Right Formula?

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The widespread implementation of automated reporting of estimated GFR (eGFR) with each measurement of serum creatinine has resulted in the identification of large numbers of patients with previously undiagnosed chronic kidney disease (CKD). Epidemiologic studies have reported that CKD is relatively common, affecting up to 16.8% of the adult population (1), but it is clear that patients with CKD are a heterogeneous group with variable prognosis and only a minority progress to end-stage kidney disease (ESKD) (2). There is thus a need for methods to predict the risk for future progression of CKD. This will allow patients at high risk to be identified for treatment to slow progression and those at low risk to be reassured and spared unnecessary intervention. The need for risk stratification within CKD is particularly great among patients in the general population or primary care because the majority of patients with CKD are first identified in this setting and most are never referred to a nephrologist. Risk factors that predict CKD progression have been studied extensively in the past decade (3). Recognition that studies in disparate populations have reported similar risk factors led to the proposal that several important risk factors could be combined to develop a "renal risk score" to predict future risk for CKD progression, analogous to the Framingham risk score for predicting cardiovascular events (4). In the past 5 years, considerable progress has been made in developing such a risk score that is applicable to patients in the general population.

The first attempt was based on analysis of data from 8530 adult participants in the National Health and Nutrition Examination Surveys (NHANES) and sought to identify risk factors for prevalent CKD (defined as eGFR <60 ml/min per 1.73 m²). This produced a risk score that included age, female gender, hypertension, anemia, diabetes, peripheral vascular disease, history of cardiovascular disease, congestive heart failure, and proteinuria. Area under the receiver-operating characteristic (ROC) curve was 0.88, and a score of ≥4 yielded sensitivity of 92%, specificity of 68%, positive predictive value (PPV) of 18%, and negative predictive value (NPV) of 99%. Data from the Atherosclerosis Risk in Communities (ARIC) study were used for external validation (area under the ROC curve = 0.71) (5). Because this was a cross-sectional study, the risk score is useful for directing efforts to screen populations for CKD but gives no information about the future risk for CKD progression. Also, the utility of the score is somewhat weakened by reliance on two variables that require previous laboratory testing, namely anemia and proteinuria. Furthermore, the latter defines the presence of CKD regardless of GFR. The same group continued its efforts using a combined cohort of 14,155 participants who were aged ≥45 years and had a baseline eGFR of >60 ml/min per 1.73 m² from the ARIC study and Cardiovascular Health Study (CHS). A risk score was developed on two thirds of the combined cohort and validated on the remaining third. The primary outcome was reduction of eGFR to <60 ml/min per 1.73 m² during follow-up of up to 9 years. After identifying 10 predictors of incident CKD, they developed a simplified model based on eight categorical variables: Age, anemia, female gender, hypertension, diabetes, peripheral vascular disease, and history of congestive heart failure or cardiovascular disease. This gave an area under the ROC curve of 0.69, and a score of ≥3 yielded a sensitivity of 69% and a specificity of 58% but a PPV of only 17% (6). A similar study developed a risk score for incident CKD in 5168 Chinese participants. Age, BMI, diastolic blood pressure, type 2 diabetes, previous stroke, serum uric acid, postprandial blood glucose, hemoglobin A1c and proteinuria >100 mg/dL were included in two risk scores (one using clinical variables only and a second with all variables) that gave an area under the ROC curve of 0.77 for the derivation cohort and 0.67 for external validation data (7). Use of these scores identifies individuals at increased risk for developing CKD but does not allow stratification of the risk for future CKD progression.

In an attempt to achieve this, another group used data from 368 primary care practices in the United Kingdom. The derivation cohort comprised 775,091 women and 799,658 men who were aged 35 to 74 years and did not have recorded evidence of CKD. Two outcomes were studied during a period of up to 7 years: Moderate to severe CKD (defined as kidney transplantation, dialysis, diagnosis of nephropathy, proteinuria, or eGFR <45 ml/min per 1.73 m²) and ESKD (defined as kidney transplantation, dialysis, or eGFR <15 ml/min per 1.73 m²). Separate risk scores were developed for men and women. The final model...
for moderate to severe CKD included age, ethnicity, social deprivation, smoking, body mass index, systolic BP, diabetes, rheumatoid arthritis, cardiovascular disease, treated hypertension, congestive cardiac failure, peripheral vascular disease, use of nonsteroidal anti-inflammatory drugs (NSAIDs), and family history of kidney disease. In women, it also included systemic lupus erythematosus and history of kidney stones. The model for ESKD was similar but did not include NSAID use. Internal and external validation was performed yielding area under the ROC curve values of 0.818 to 0.878 (8). This study is limited by being observational and is therefore subject to significant bias. Only 56% of participants had had a serum creatinine level recorded at baseline; therefore, it is possible that some participants had undiagnosed CKD at inclusion. The combined outcome of “moderate to severe CKD” included too many disparate outcomes to make it clinically useful, but the ESKD outcome is relevant. Nevertheless, this study does illustrate the utility of developing a risk score that can be programmed into primary care computer systems to use commonly entered variables to alert practitioners to patients who are at increased risk for developing progressive CKD.

The study by Halbesma et al. (9) in this issue of CJASN represents the latest attempt to develop a renal risk score that is applicable to the general population. Data from 6809 participants in the Prevention of Renal and Vascular End-stage Disease (PREVEND) study were used to develop a risk score with the primary outcome of progressive CKD over 6.4 years, defined as the 20% most rapid decline in GFR and eGFR <60 ml/min per 1.73 m². The final risk score included baseline eGFR, age, albuminuria, systolic BP, C-reactive protein, and known hypertension and had an area under the ROC curve of 0.84. Internal validation was performed using a bootstrapping procedure. Initial analysis used eGFR derived from the Modification of Diet in Renal Disease (MDRD) equation, but this was repeated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation with similar results. This risk score does, however, suffer from a relatively low sensitivity and PPV. The proposed threshold score of ≥27 would identify 2.1% of the population as high risk but with a sensitivity of only 15.7% (suggesting that 84.3% of those with progressive CKD would be missed) and a PPV (risk for developing progressive CKD) of 28.1%, whereas the specificity and NPV are high at 98.4% and 96.7%, respectively. As discussed in the article, selecting a lower threshold would improve sensitivity with some reduction in specificity and could be used to select a group at intermediate risk for closer monitoring. The strengths of this study are that it focuses on predicting progressive CKD rather than all CKD (as in the study by Kshirsagar et al. [6]) and is not subject to the same potential bias as the study by Hippisley-Cox et al. (7) because all participants were evaluated in detail at baseline and during follow-up. The authors concede that their risk score may be limited by the fact that it was developed in a white population and that external validation is required before it can be widely applied.

Substantial and rapid progress has been made in developing renal risk scores, yet the goal of a simple, universally applicable scoring system that predicts clinically relevant renal outcomes in the general population remains to be achieved. Renal risk scores have been developed for referred patients who have diagnosed CKD and are under nephrology follow-up, but the applicability of these scores to the general population has yet to be assessed (10). All of the risk scores published to date suffer from one or more limitations but will be invaluable in designing future studies. Such studies should also investigate the benefit of novel biomarkers to predict renal risk as an alternative to the traditional risk factors studied to date. Further studies are required to investigate the health-economic costs versus benefits of improved early detection and risk stratification of CKD. Logic suggests that early detection would afford the greatest opportunity to intervene with renoprotective therapy and thus avoid progression to ESKD, but the majority of intervention studies have focused on more severe and advanced CKD. One prospective, randomized trial established the benefits of intensive medical and lifestyle intervention to prevent progressive CKD and cardiovascular disease in high-risk patients with diabetes and microalbuminuria (11), but further prospective studies are required to evaluate the benefit of this approach in patients without diabetes and with early-stage CKD. The development of a successful risk score would be a major step forward in meeting the challenge posed by the large number of patients who are at risk for developing CKD or have a new diagnosis of CKD and would go a long way to answering the concerns of those who have questioned the value of diagnosing CKD according to Kidney Disease Outcomes Quality Initiative (KDOQI) criteria (12). It is likely that further prospective studies will be required to meet this goal, but the potential benefits readily justify the effort and expense required.

Disclosures
None.

References


