CKD Classification: Time to Move Beyond KDOQI

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The number of patients with ESRD is increasing worldwide. Despite recent advances in our understanding of the uremic state and improvements in the science and technology of renal replacement therapy, the morbidity and mortality of these patients is unacceptably high: More than 20% per year. Moreover, the health care cost of treating ESRD exceeds $17 billion annually in the United States alone.[1]

These observations led the nephrology community a few years ago to recognize chronic kidney disease (CKD) as an important public health problem while emphasizing the need for timely treatment for prevention of ESRD. Among a large number of initiatives aimed at increasing early awareness of CKD, the National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guidelines for classification and staging of CKD receives most attention and acceptance.[2] In addition to a working definition, KDOQI proposes a classification system based on severity determined by level of kidney function, calculated from the estimated GFR (eGFR), irrespective of the cause of kidney disease.

The KDOQI CKD definition and classification are widely accepted in clinical practice and influential in epidemiologic studies worldwide. Nevertheless, the classification is the subject of increasing scrutiny by investigators,[3] regulators, and even members of the original KDOQI workgroup.[4] A controversial aspect of KDOQI is the high prevalence of CKD imposed by the classification system itself. Use of KDOQI leads to prevalence estimates of combined stages 1 and 2 CKD ranging from 2.9 to 7.0% in the general population.[5] In other studies, stage 3 CKD prevalence is 4.2 to 4.3%. The resultant inference that approximately one in 10 individuals has CKD seemed improbable to many practicing nephrologists and investigators, with far-reaching implications to the nephrology community based on recommendations that such individuals be identified, studied, and, when necessary, treated.[6,7] Differences in prevalence rates of the various CKD stages also raise important questions regarding the identification of risk factors associated with progression of CKD to end stage. Among these is the observation that prevalence rates of stage 3 CKD is now 10 to 20 times more than prevalence rates of stages 4 and 5 CKD.[7]

In this issue of *JASN*, Hallan *et al.*[8] report results from a large population-based study in which the combined influence of eGFR and albuminuria is examined as a predictor of ESRD in 65,589 adults who participated in the Nord-Trøndelag Health (HUNT-2) Study between 1995 and 1997. In 124 patients who progressed to ESRD after 10.5 yr of follow-up, a number of demographic and clinical variables were entered into a "best clinical model" that associates significantly with progression to ESRD; however, the addition of eGFR and albuminuria alone nullifies all of the other significant associations within the best clinical model, whereas both eGFR and albuminuria remain independently and strongly associated with progression to ESRD by multivariate analysis.

A striking observation is the strong synergistic effect of excess risk for progression to ESRD when eGFR and albuminuria are used in combination. The investigators further provide time-dependent receiver operating characteristic analyses that show that considering both the urinary albumin/creatinine ratio and eGFR substantially improves diagnostic accuracy with an area under the curve (AUC) of 0.936. Interestingly, including data from the best clinical model did not improve this AUC significantly. The overall conclusion of this study is reduced eGFR should be complemented by semiquantification of urinary albumin to predict optimally progression to ESRD.

Several important aspects of this elegant study by Hallan *et al.*[8] deserve mention. First, in addition to being one of the largest prospective cohorts exploring risk for progression to ESRD, the investigators should be commended for their meticulousness in executing the study and analyzing their data. The use of multiple urine samples and applying multiple imputation methods to missing samples, stringent confirmation of ESRD cases, and use of sensitivity analyses to validate results all are noteworthy strengths of this study. Second, the results have significant public health implications. An important aspect of KDOQI staging is not only to define the prevalence of the disease but also to develop an algorithm recommending referral for further evaluation of CKD.

Specifically, KDOQI recommends evaluation of a patient for kidney disease only when GFR is <60 ml/min per 1.73 m^2 in the presence of a risk factor. This somewhat arbitrary recommendation leads to excessive use of health care resources, such as unnecessary close monitoring of substantial numbers of individuals. For example, referral to a nephrologist on the basis of current stages 3 to 4 CKD by KDOQI would include 4.7% of the general population to identify 69.4% of all individuals expected to progress to ESRD.[2] Alternatively, referral to a nephrologist on the basis of the classification system suggested in this new study[8] would include 1.4% of the general population without losing predictive power—that is, this smaller number of individuals would still detect 65.6% of those expected to progress to ESRD. To depict the beneficial aspect of combined measurement of eGFR and albuminuria, the authors use a complex approach: The partial AUC for false-pos-

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itive rates. Their data indicate for most, if not all, screening populations evaluated that combining the albumin-to-creatinine ratio and eGFR substantially improves discrimination, whereas the additional effect of adding the best clinical model variables is marginal. Finally, the predictive importance of albuminuria in general[3] is once again emphasized in this study.[8] This is an important observation in lieu of speculation that microalbuminuria is a manifestation of a systemic disturbance affecting all microcirculations and therefore not a sufficient diagnostic criterion for CKD.[7] Albuminuria in this study is a continuous risk factor for progression to ESRD with no lower limit and at all levels of eGFR.[8] It will be interesting to see whether the results still hold with urine dipstick assessment, a very important practical point.

The study by Hallan *et al.*[8] should also be interpreted with some cautions. The HUNT-2 study population is a homogeneous group of individuals who were exclusively white and relatively young and had limited comorbid conditions, perhaps limiting generalizations. Because the study did not have a repeat assessment of kidney function, it is also not possible to assess individual rates of progression of kidney disease, which might have significant implications in terms of risk for ESRD. Despite the comprehensive and sometimes complex statistical approach, an analysis of observed *versus* predicted cases of ESRD or a net risk reclassification improvement analysis would provide more straightforward practical information.[9] It should also be emphasized that this study must be interpreted only in the context of predicting progression to ESRD. These results by no means imply that a similar impact would be observed for other clinically important outcomes or that appropriate measures are not available to prevent additional renal injury. Finally, addition of albuminuria testing is not necessarily the only recommended modification of KDOQI guidelines. For example, in a retrospective study, Eriksen and Ingebretsen[10] showed that changing the chronicity criterion to 6, 9, or 12 mo reduces the number of patients with CKD relative to a 3-mo criterion, with consequent differing rates of progression to kidney failure or death.

The study by Hallan *et al.*[8] provides us much optimism that important modifications to the original KDOQI guidelines for staging of CKD could offer significant improvements in predicting progression to ESRD. The time has come to apply these modifications to the current guidelines. Until we do so, the focus should remain on appropriate management of CKD and associated conditions independent of staging.

DISCLOSURES

None.

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See related article, "Combining GFR and Albuminuria to Classify CKD Improves Prediction of ESRD," pages 1069–1077.

Lessons from Geographic Variations in Predialysis Nephrology Care

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Inadequate access to nephrology subspecialists among patients with advanced chronic kidney disease (CKD) is one of the major public health problems of our discipline. Depending on its

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