Classification of Chronic Kidney Disease: A Step Forward

Chronic kidney disease (CKD) is common and harmful but treatable, and it is recognized as a worldwide public health problem (1, 2). Approximately 23 million U.S. adults have CKD, for a prevalence of 11.5% (3). Kidney failure and cardiovascular disease (CVD) are generally considered to be the most important outcomes, but the risks for each outcome vary widely among patients, and clinicians need guidance to prioritize their clinical decisions.

"Chronic kidney disease" is a general term for heterogeneous disorders of kidney structure and function. The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines (4) define CKD as follows, regardless of clinical diagnosis: kidney damage (usually defined as an albumin–creatinine ratio [ACR] $\geq$ 30 mg/g) or a glomerular filtration rate (GFR) less than 60 mL/min per 1.73 m^2 (usually estimated from the serum creatinine level) for at least 3 months. Severity is traditionally classified according to GFR, but several landmark studies (5–11) have shown that a higher level of proteinuria (ascertained by ACR or dipstick protein testing) is a risk factor for CKD progression and mortality independent of estimated GFR. The organization Kidney Disease: Improving Global Outcomes (KDIGO) recently sponsored a collaborative meta-analysis and international conference that examined these studies, as well as others that confirmed and extended their findings. The organization recommended retaining the KDOQI definition of CKD, revising the classification to include clinical diagnosis and albuminuria stages in addition to GFR stages, and using these stages to develop risk categories (**Figure**, *top*) (12, 13). In this issue, Tonelli and colleagues (14) compared the utility of a new classification by risk categories (**Figure**, *bottom*) with that of the current classification by KDOQI GFR stages and considered the implications for referral to nephrologists.

The development cohort included 949 323 patients (102 701 with urinary ACR) from the Alberta Kidney Disease Network between 2002 and 2006; 1% of patients experienced CKD progression (the composite outcome of kidney failure, treated by dialysis or transplantation, or doubling of serum creatinine level) and 5.2% died during a median follow-up of 38 months. The validation cohort included 14 358 patients from the Third National Health and Nutrition Examination Survey (NHANES III) between 1988 and 1994; 14.7% of patients died during a median follow-up of 104 months. In the development cohort, the investigators computed unadjusted incidence rates of both outcomes for combinations of GFR and albuminuria stages and formed risk categories by aggregating stages according to risk. In both cohorts, the investigators compared the accuracy of predictions made by using risk categories with those made by using GFR stages. Reclassification by risk categories was judged to be more accurate if a higher proportion of patients without the outcome were classified to a lower level or a higher proportion of patients with the outcome were classified to a higher level. Reclassification was judged to be less accurate if the opposite results occurred. Net reclassification is the difference of the proportion of more accurate and less accurate reclassifications.

In both cohorts, most patients with CKD were reclassified to a lower (less severe) level. Net reclassification was more accurate for prediction of CKD progression (33% and 2% in the Alberta Kidney Disease Network ACR and dipstick testing subgroups, respectively) but less accurate for mortality (−8% and −21% in the ACR and dipstick testing subgroups and −18% in the NHANES III cohort). In all groups, reclassification was more accurate for those without subsequent events but less accurate for those with subsequent events. For example, a strategy of referring patients in risk categories 3 or 4 to nephrologists versus those in GFR stages 3 or 4 would lead to 3.9 million versus 16.3 million referrals in the United States. Although 5.3 million patients who survived (3.3%) would be correctly reclassified from GFR stages 3 or 4 to risk categories 1 or 2 and would not be referred, 3.1 million patients who died (18%) would be incorrectly reclassified from stages 3 or 4 to risk categories 1 or 2 and also would not be referred. However, because more patients survived than died during the follow-up interval, more patients were correctly than incorrectly reclassified. Tonelli and colleagues suggest that using risk categories rather than GFR stages would reduce unnecessary referrals, but at the cost of not referring or delaying referral for some patients who would later die.

The strengths of this study include a large, well-characterized development cohort and the use of an objective method to derive risk categories and an independent cohort to evaluate mortality outcomes. Its limitations include the short duration of follow-up, lack of data on CKD progression in NHANES III, and selection of the thresholds for referral. The KDOQI guidelines recommended referring all patients with CKD stage 4 but not all with CKD stage 3, as was performed here. A comparison with a more restricted group of patients with CKD stage 3 would have been more informative. Although referral is a concern for nephrologists and those who examine use of health resources, recommendations for referral can vary widely among communities and even more so among countries, and the relationship of referral to patient outcomes is not well understood (15).

The ultimate goal of a classification system for CKD should be to facilitate clinical decisions that improve patient outcomes. Clinical diagnosis, concurrent complications, and prognosis are key factors in clinical decision-making. Important adverse outcomes include not only CKD progression and mortality but also infections, impairment in cognitive and physical function, and medical

Figure. **Risk categories for kidney and mortality outcomes, by GFR and albuminuria or proteinuria stage.**

Composite Ranking by Adjusted Relative Risks (KDIGO, 2009)

			Albuminuria Stage				
			A1		A2	A3	
			Optimal and High-Normal		High	Very High and Nephrotic	
GFR Stage	Description	Range, *mL/min per 1.73 m²*	<10 mg/g	10–29 mg/g	30–299 mg/g	300–1999 mg/g	≥2000 mg/g
G1	High and optimal	>105					
		90–104					
G2	Mild	75–89					
		60–74					
G3a	Mild to moderate	45–59					
G3b	Moderate to severe	30–44					
G4	Severe	15–29					
G5	Kidney failure	<15					

Composite Ranking by Unadjusted Absolute Risks (Tonelli et al, 2010)

			Description and Range of Proteinuria Stages, ACR or Dipstick		
			Normal	Mild	Heavy
GFR Stage	Description	Range, *mL/min per 1.73 m²*	10–29 mg/g or Negative	30–300 mg/g or Trace to 1+	>300 mg/g or ≥2+
1	High and optimal	>90			
2	Mild	60–89			
3a	Mild to moderate	45–59			
3b	Moderate to severe	30–44			
4	Severe	15–29			
5	Kidney failure	<15			

ACR = albumin–creatinine ratio; CKD = chronic kidney disease; GFR = glomerular filtration rate; KDIGO = Kidney Disease: Improving Global Outcomes. **Top.** Risk categories based on a composite ranking of 5 outcomes by the Chronic Kidney Disease Prognosis Consortium for the KDIGO Conference, London, 2009. The lowest-risk categories (no CKD) are not shaded; moderate-, high-, and very high–risk categories are shaded from lightest to darkest green. Modified from Kidney International and reproduced from Levey and colleagues (13) with permission of KDIGO. **Bottom.** Risk categories based on a composite ranking of 2 outcomes by Tonelli and colleagues (14). Risk group 0 (no CKD) is not shaded, and groups 1 2, 3 and 4 are indicated with progressively darker shades of green. For comparison with the KDIGO figure, we have added a sixth GFR category (<15 mL/min per 1.73 m^2), shaded darkest green.

errors (16–19). In our view, Tonelli and colleagues have provided a rigorous evaluation of incorporating more detailed information on proteinuria for prognosis and for guiding referral. However, for the following reasons, we would not recommend substituting risk categories for the current GFR and albuminuria stages or relying on risk categories alone to predict clinical outcomes.

First, decreased GFR and albuminuria are associated with different, concurrent complications of CKD that require differences in management. Management of patients with decreased GFR includes adjusting drug dosages and avoiding drugs with kidney toxicity; detecting and treating anemia, bone and mineral disorders, malnutrition, and neuropathy; and, in late stages, preparing for dialysis and transplantation. Management of patients with albuminuria includes therapy with angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers and a lower-than-usual blood pressure goal to slow kidney disease progression, and in patients with the nephrotic syndrome, restriction of dietary sodium and the use of diuretics and possibly anticoagulants. Although some of these complications overlap, retaining separate GFR and albuminuria stages would probably facilitate management. By analogy, hypertension and hypercholesterolemia are each associated with increased risk for CVD and could be combined into categories of risk for referral to specialists, but these conditions are considered separately as indications for drug therapy.

In addition, risk varies considerably on the basis of both clinical diagnosis and factors other than kidney disease, such as age, sex, race, presence or absence of CVD risk factors, and history of CVD. Tonelli and colleagues did not consider these factors in their analyses; we suspect that the nonkidney factors would affect predictions of mortality more than predictions of kidney disease progression. Quantitative risk prediction for a given patient would require use of computer-based instruments to consider multiple risk factors that are specific for each outcome of interest. The widespread use of CVD risk prediction for guiding CVD risk factor management suggests that this approach may be useful (20).

We conclude that adding albuminuria stages to GFR stages enables better description of CKD for prognosis and management. The KDIGO organization has convened a work group to update the KDOQI classification for CKD. Grouping of GFR and albuminuria stages into risk categories may be a useful means of communication for clinicians, patients, and the public (**Figure**) but requires more study to determine accuracy for a range of outcomes. Future studies should develop and validate quantitative risk prediction instruments and evaluate their utility for management of CKD.

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