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Rate of Kidney Function Decline Associates with Increased Risk of Death

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The current classification scheme for chronic kidney disease (CKD) does not differentiate between patients who show a progressive course of CKD and those whose kidney function remains stable over a long period. There is an association of faster progression of CKD with worse mortality, suggesting that an individual’s slope of estimated GFR (eGFR) over time could help us refine the prognosis for patients with any given stage of CKD. Many questions still need to be answered before the mainstream application of the slopes of eGFR is possible.

The estimation formula-based CKD classification by the Kidney Disease Outcomes Quality Initiative (K/DOQI)\(^1\) has proved to be an eye opener to the medical community and has raised awareness about the common frequency of decreased eGFR and the high mortality associated with lower eGFR.\(^2\)–\(^5\)

The immediate impact of this awareness has been a significant increase of clinical referrals to nephrologists from various practitioners\(^6\) who suddenly discovered that many of their patients had CKD,\(^7\) a condition that became easy to diagnose but whose management still befuddles many nonspecialists. Those of us on the receiving end of these consultations have quickly come to realize that some patients who are labeled as having CKD received a misdiagnosis because of deficiencies in our estimation formulas or of standardization of serum creatinine measurements,\(^8\) and many patients, of course, who indeed have a GFR of <60 ml/min per 1.73 m\(^2\) display a stable and asymptomatic course with no change in metabolic disturbances characteristic of CKD. How to deal with the latter group has been a challenge from both a prognostic and a therapeutic point of view.

Prognostic studies that show decreased kidney function to associate with increased mortality are mostly based on a static definition of CKD and bundle together patients who might have had progressive or nonprogressive disease.\(^2\)–\(^5\) More important, though, nephrologists assessing patients with mild and nonprogressive CKD are often faced with questions about how much to treat, because interventions aimed at delaying progression are obviously moot and the utility of therapies targeting mild metabolic derangements of CKD is questionable.

A practical solution to these deficiencies of the static K/DOQI classification for CKD is to identify patients with progressive loss of kidney function by using past serial measurements of their serum creatinine. Plotting slopes of 1/creatinine or eGFR versus time has long been a tool of nephrologists, and slopes have been used as an outcome variable in clinical studies, yet they have attracted surprisingly little attention as independent predictors of clinical outcomes such as mortality or risk for ESRD.

The study by Al-Aly et al.\(^10\) in this issue of *JASN* fills a void in this sense because it expands\(^11\)–\(^14\) to a select group of patients with early stage 3 CKD (estimated GFR 45 to 60 ml/min per
1.73 m²) the findings of previous studies that examined the slopes of eGFR as predictors of outcomes. The authors report a U-shaped association between calculated slopes of eGFR and all-cause mortality: Patients who seem to have gain in kidney function, more likely a decrease in serum creatinine as a result of illness, and patients with progressive loss of kidney function both display higher mortality compared with patients with age-appropriate slopes of eGFR, with worse outcomes seen with the most severe loss of kidney function.10

The study by Al-Aly et al.10 could have some immediate and far-reaching practical implications. With the spreading use of electronic medical records, serial measurements of serum creatinine are now readily available to an increasing number of practitioners, and incorporating slopes of eGFR into the assessment of CKD could make it relatively easy for primary care providers to identify patients who are at high risk for progression to ESRD or mortality and thus need a referral to a nephrologist. This not only would ease consultant workload but also could prevent the unnecessary anguish of many patients who under the current classification scheme are labeled with a blanket diagnosis of stage 3 CKD and face hypothetically ominous outcomes.

Despite the obvious potential practical benefits of using eGFR slopes, there are still a number of unanswered questions that need study before mainstream application of this approach. First, the reason for the observed higher mortality in the group that progresses faster is unclear: The slopes in the study by Al-Aly et al.10 provide prognostic information, but there is no etiologic link between steeper slopes and higher mortality. Establishing such a link is important if one wants to use slopes of eGFR not only to identify at-risk patients but also to trigger specific therapies aimed at preventing such outcomes. Because worsening kidney function can have a number of adverse consequences (including but not limited to worse BP control, various biochemical abnormalities, and higher levels of uremic toxins), the higher mortality seen in patients with steeper slopes could be the result of various complications in a time-dependent manner. The study by Al-Aly et al.10 does not offer more detailed insight into such mechanisms of action; this will need to be done in future studies.

Second, if we wanted to expand the static K/DOQI definition of CKD by incorporating information about the trajectory of renal function in individual patients, then this would require additional measurements of serum creatinine. Fluctuations in serum creatinine levels as a result of laboratory or biological variability that is unrelated to CKD could make it difficult to discern individuals with truly progressive disease. Furthermore, it is unknown how many serial serum creatinine measurements are needed and at which time intervals they need to be obtained to establish reliably a slope that is representative of the single-patient course of CKD.

Third, slopes generated using eGFR seem to underestimate progression that is defined by slopes generated using measured GFR.15 The practical impact of this observation is unclear. Fourth, the study of Al-Aly et al.10 examined patients with rheumatoid arthritis and mild CKD. Whether these findings can be corroborated in studies that are more representative of the broader CKD population remains to be seen.

In summary, the study by Al-Aly et al.10 raises awareness about the importance of the progressive nature of CKD and suggests that the incorporation of slopes of eGFR into the evaluation of CKD could lead to a refinement in risk stratification that may have important practical benefits. Likewise, an argument could be made for including measures of albuminuria in any new revision of the classification scheme for CKD.16 The study by Al-Aly et al.10 nevertheless should stimulate further research on how best to implement this slope concept in clinical practice and to determine which therapeutic interventions it should trigger.

DISCLOSURES
None.

REFERENCES
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Blood Pressure and Mortality among ESRD Patients: All Patients Are Not Created Equal

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The annual risk for mortality is extremely high for patients who have ESRD and are treated with dialysis in the United States, and cardiovascular disease persists as their most common cause of death. Hypertension affects the majority of hemodialysis patients, and most have what would be considered uncontrolled hypertension. However, appropriate BP targets for these patients remain uncertain and have largely been extrapolated from studies conducted of the general population. The Kidney Disease Outcomes Quality Initiative (KDOQI) Work Group on this subject offered an opinion of “a reasonable goal is predialysis BP <140/90 mmHg,” but the evidence to support their statement was reported as weak. The weakness of this conclusion stems partly from the exclusion of patients with ESRD from randomized trials involving antihypertensive drugs and BP targets, thereby leaving nephrologists to rely on observational data for guidance on the best approach to manage BP in dialysis patients.

Adding to the problem, these epidemiologic data are not always in agreement in their reported relationship between BP and mortality, and their findings vary on a number of factors, including when BP was analyzed (before versus after dialysis), whether early (1 to 2 years) versus late (>3 years) mortality was assessed, and whether pulse pressure was included in the analysis. Moreover, studies often presume that all patients with ESRD are alike despite their differences in age, gender, race, ethnicity, comorbid illnesses, socioeconomic status, and geographic location, just to name a few.

In this issue of JASN, Myers et al. critically examine three important patient factors—age, race, and diabetes status—to determine whether they modify the relationship between BP and mortality among dialysis patients. Studied patients were new to hemodialysis, had survived at least 150 days from their first outpatient dialysis, had recorded predialysis BP, and were followed for a median of 1.5 years.

Several findings in this study are worthy of comment. First, the increased mortality among dialysis patients that associated with low systolic BP (SBP) in other studies was most pronounced among older patients and those with diabetes. It is probable that older patients and those with diabetes had a greater burden of severe cardiac disease (that was not measured) than their counterparts, which would place them at increased risk for death. Second, Myers et al. also observed that high SBP was associated with mortality only among younger hemodialysis patients, a finding that was independent of race or diabetes, suggesting that younger people with ESRD may be more similar to the general population in their risk factors for death. Third, Meyers et al. confirmed the long-known survival advantage for black patients who are on dialysis to be limited to older patients.

Although this is certainly one of the best observational studies to pay attention to how outcomes are different in certain patient groups, more guidance is needed. Perhaps we should be less aggressive with BP in older patients or those with diabetes and more aggressive with younger patients, but how should we treat a patient with comorbid illnesses, systolic dysfunction, high intradialytic weight gain, intradialytic hypotension, and medication nonad-