Current CKD Definition Takes into Account Both Relative and Absolute Risk

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LETTER TO THE EDITOR www.jasn.org

Age-Dependent Definition of CKD

I read the online article by Delanaye *et al.*[1] calling for age-dependent definitions of CKD and the two accompanying editorials[2,3] with great interest. As a pediatric nephrologist, I do not have a stake in the details of the adult argument. However, as a nephrologist, I also recognize the importance of clinically relevant definitions of CKD stages and I was struck by one of the arguments advanced by Chertow and Beddhu[2] who advise caution before tampering with the current scheme. They take exception to the claim by Delanaye *et al.* that overdiagnosis of CKD in the elderly could lead to inappropriate care, including diagnostic evaluation and treatment of nonexistent kidney disease. Chertow and Beddhu assert that the elderly are less likely to get clinically indicated care for cardiac disease and other conditions that require contrast-enhanced imaging. In fact, this well documented observation reinforces the call for change by Delanaye *et al.* because inappropriate care is bidirectional—overzealous evaluation of patients who are healthy and insufficient testing of patients who are presumed sick, in this case with CKD. Rethinking the threshold GFR to define CKD may have the potential to be helpful, not only in the geriatric population but across the life span if that includes the older end of the pediatric spectrum.

DISCLOSURES

None.

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Delanaye *et al.*[1] propose that GFR thresholds to define CKD should depend on age. Specifically, people aged≥65 years with GFR 45–59 ml/min per 1.73 m^2 and albumin-creatinine ratio<30 mg/g should not be classified as having CKD. This is not a new proposal. It has been discussed many times, including by the Kidney Disease Outcomes Quality Initiative in 2002 and Kidney Disease Improving Global Outcomes (KDIGO) work groups in 2009 and 2012.[2] Each time, the consensus was that the GFR threshold for the definition of CKD should be age-independent.

Delanaye *et al.* now reopen the discussion, suggesting that the GFR threshold for the CKD definition should be determined only by relative risks for mortality. They cite data from the CKD Prognosis Consortium, the largest meta-analysis, showing that the relative hazard of mortality for eGFR 45–59 versus 75–89 ml/min per 1.73 m^2 with albumin-creatinine ratio<30 mg/g was lower at older age. However, they do not mention the higher absolute risk of mortality (two to four times higher at the oldest compared with youngest group).[3] Absolute risk is more important than relative risk to patients and providers. The threshold for CKD should also take into account outcomes beyond mortality such as ESKD, AKI, heart failure, and hospitalization which are often more specific and sensitive

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consequences of CKD, and have substantial excess risk in older age.

Many other diseases, such as hypertension and diabetes, follow a similar pattern of higher prevalence at older age with smaller relative risks but higher attributable risks of mortality and complications. Yet, the hypertension and diabetes guidelines define these diseases independently of age while recommending evaluation and management personalized to age and other factors. Similarly, the KDIGO guideline recommends an age-independent definition but personalized evaluation and management.

The CKD definition has been stable since 2002, enabling great progress in the field. The age-independent GFR threshold has been widely accepted by nephrology societies across the world, endorsed by the World Health Organization, and incorporated into the International Classification of Disease Coding System. At each deliberation, the expanding evidence base has supported the original definition. We think that changing the GFR threshold at older age on the basis solely of relative risk of mortality while ignoring the higher absolute risk for mortality and other outcomes is a narrow view that impedes progress. We believe it is time, as a nephrology community, to move the discussion to optimizing management and discovering new therapies.

DISCLOSURES

None.

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Authors' Reply

We agree with Trachtman[1] regarding the potential benefits for both young and elderly with age-based eGFR thresholds. We disagree with the points raised by Coresh *et al.*[2] First, despite the cited guidelines, there is not widespread consensus among practicing nephrologists that elderly patients with an eGFR of 45–59 ml/min per 1.73 m^2 and no albuminuria have diseased kidneys.[3] Further, primary care guidelines fail to see clinical benefit with this classification.[4] Second, although absolute risks are often important, humans have a limited lifespan and it is not clear that an hazard ratio of 1.2 for risk translates into clinically meaningful life years lost.[5] The statistical prognostic models relating eGFR to outcomes were on the basis of relative risk and the "heat maps" were on the basis of relative risk. The eGFR level associated with lowest risk (absolute or relative) declines with older age and this is not accounted for in the CKD definition. As with any epidemiologic study, a small hazard ratio of 1.2 could easily be due to bias (high-risk rather than just general population cohorts were used in the CKD prognosis consortium analyses) or residual confounding (such as systemic microvascular disease or lower nephron endowment linked to other complications of lower birthweight). Third, a causal pathway linking the age-related decline in eGFR to an increased risk of nonrenal outcomes is lacking. We concur that older patients with a low-normal GFR have less renal reserves putting them at increased risk for kidney failure, but this is too rare of an event to justify a disease label. High BP and glucose can be lowered with medications with a demonstrable clinical benefit, but there is no evidence that eGFR can be increased for a clinical benefit. A fairer comparison would be pulmonary function tests, which are reported with age-appropriate reference ranges due to the age-related decline in pulmonary function.[6] We hope that the CKD prognosis consortium and Kidney Disease Improving Global Outcomes will reconsider the age-related decline in eGFR for the purposes of identifying persons with diseased kidneys.

DISCLOSURES

None.

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