

In Defense of Age-Based Estimated GFR Thresholds to Define CKD



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The release of the 2024 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines¹ on the evaluation and management of chronic kidney disease (CKD) was highly anticipated by the nephrology community. In these new recommendations, estimated glomerular filtration rate (eGFR) remains one of the main variables for establishing a diagnosis of CKD. A notable change in the updated recommendations is that, for children and adolescents, it is recommended that an eGFR < 90 ml/min per 1.73 m² can be flagged as “low.” Although the 2024 recommendations continue to use a single eGFR threshold of 60 ml/min per 1.73 m² to define CKD, this represents an important recognition by the KDIGO workgroup that “normal” GFR changes with age.¹ In this editorial, we present arguments supporting an age-adapted definition of CKD and highlight the limitations of arguments

justifying a single threshold of 60 ml/min per 1.73 m².²

GFR Changes With Age

Among healthy people (without albuminuria), GFR increases from birth to about 2 years of age, remains fairly constant from 2 to 40 years, and declines gradually thereafter.^{2–4} The average “peak” GFR among healthy adults (which occurs before the age of 40 years) varies by study and measurement method, but most recent studies suggest that the median GFR among healthy young adults is approximately 105 ml/min per 1.73 m².² Age-related decreases in GFR are universal after 40 years of age and have been observed in every individual studied in works conducted in Europe, the USA, and other countries around the world.^{2,3,5} Detailed biopsy studies suggest that the decline is due to loss of nephrons over time.⁵ Because GFR decline with age is universal, many healthy elderly people have a GFR < 60 ml/min per 1.73 m². For example, the median GFR among men aged 75 to 79 years is 75 ml/

min per 1.73 m², and among women aged 75 to 79 years, it is 70 ml/min per 1.73 m².³

Importance of GFR Thresholds in CKD

The reason the identification of a (or several) GFR threshold(s) is important is that this allows people with a GFR known to be associated with adverse outcomes to be “flagged” for health care professionals, ensuring appropriate referrals and timely intervention to slow progression of CKD. Most electronic health records and laboratories now highlight creatinine values corresponding to GFR < 60 ml/min per 1.73 m².

Both the 2013 and the 2024 KDIGO recommendations highlight the associations between eGFR < 60 ml/min per 1.73 m² and adverse outcomes, including all-cause and cardiovascular mortality, relying exclusively on the CKD Prognosis Consortium data.^{1,6} Although the sample size is impressive, the CKD Prognosis studies had limitations and do not reflect all existing data.² The justification in the CKD Prognosis studies for using an eGFR between 90 and 104 ml/min per 1.73 m² as the reference (a GFR at or above the 90th percentile for healthy elderly people) is unclear. Other studies revealed that the risk of adverse outcomes was minimized at eGFR of 60 to 75 ml/min per 1.73 m² among those aged >65 years without albuminuria.^{2,7} The fact that eGFR > 104 ml/min per 1.73 m² was associated with significantly higher risks of death and cardiovascular events was largely ignored, though this likely reflects either hyperfiltration or overestimation of true GFR in frail people with low muscle mass, at least among older people; in the very elderly, even eGFR of 90 to 104 ml/min per 1.73 m² may indicate hyperfiltration.

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Although the 2024 KDIGO guidelines acknowledge that the association between eGFR and adverse outcomes was weaker among those aged > 65 years than among those aged <65 years and even identifies those with CKD 3a by eGFR determined using creatinine and no or minimal albuminuria as having risk similar to the reference group, the statistical significance of the differences is emphasized.^{1,6} In a sample of over 20 million, even minute differences are likely to be statistically significant. Furthermore, the assertion that a stronger association between eGFR (determined using creatinine and cystatin C) and adverse outcomes among those aged >65 years supports the 60 ml/min per 1.73 m² cut-off is flawed. eGFR determined using both creatinine and cystatin C provides a more accurate estimate of measured GFR than eGFR determined using either creatinine or cystatin C; this is because combining these biomarkers compensates for the limitations of each. eGFR determined using creatinine will overestimate measured GFR in people with inflammation-related protein-energy wasting because creatinine is lower in people with muscle wasting. In contrast, eGFR determined using cystatin C will underestimate measured GFR in people with inflammation because cystatin C is elevated in inflammatory states.⁸ Given that inflammation is associated with adverse outcomes, the stronger association between eGFR determined using creatinine and cystatin C and adverse outcomes among those aged >65 years is likely driven not by GFR but by inflammation. Indeed, the stronger association between cystatin C and adverse outcomes than between creatinine and adverse outcomes is well-known. Equally important is the fact that the vast majority of laboratories and practitioners use

creatinine-based equations to estimate GFR due to the limited availability of cystatin C. The threshold used to flag eGFR associated with adverse outcomes should be determined using the same measure that is most widely used in practice.

Although basing the eGFR threshold to be flagged as “low” on the association with adverse outcomes is logical, application of this principle appears inconsistent. It is puzzling that defenders of a universal threshold of <60 ml/min per 1.73 m² (determined based on the association with adverse outcomes) are strangely unconcerned by strong evidence that younger adults with modestly decreased eGFR (70–80 ml/min per 1.73 m²) also have elevated risks of adverse outcomes.⁹ Among 8.7 million adults aged 18 to 65 years, eGFR ≤10th percentile for age was associated with a significantly higher risk for all-cause mortality, major adverse cardiac outcomes, and kidney failure. Failure to flag GFRs that are low for age, (but not <60 ml/min per 1.73 m²) has real, and potentially irreversible, consequences for younger adults; fewer than 40% of adults aged 18 to 39 years had a repeat examination of eGFR within a year, only 5% had albuminuria assessed, and fewer than 4% were referred to a nephrologist.⁹ Although CKD is less common in younger people than older people, early intervention could prevent the progression of CKD and have an enormous impact on health and quality of life over the many potential years of life in younger people.

Age-adapted GFR thresholds, based either on age-specific percentiles of estimated or measured GFR or age-adapted thresholds such as 75, 60 and 45 ml/min per 1.73 m² for people younger than 40 years, 40 and 60 years, and older than 65 years respectively² are an

alternative approach to identifying people with GFR low enough to put them at risk for adverse outcomes.

Just as a single eGFR threshold of 60 ml/min per 1.73 m² results in under identification of pathology in younger adults, it also results in overdiagnosis of CKD in the elderly. An age-adapted CKD definition reduces the prevalence of CKD by as much as 50% among people aged >65 years. Far from “minimizing” the burden of CKD, age-adapted eGFR thresholds should be viewed as a more personalized approach, emphasizing both the normal physiology of aging and the real risks associated with reduced GFR.

Hope for Recognition of the Importance of Age in Future KDIGO Guidelines?

Although we are disappointed that age-adapted thresholds defining CKD were not proposed in the 2024 KDIGO guidelines, we are optimistic that the new guidelines may open the doors to consideration of an age-adapted definition of CKD in the future. As noted, the practice point stating “An eGFRcr level <90 ml/min per 1.73 m² can be flagged as ‘low’ in children and adolescents over the age of 2 years”¹ clearly indicates a recognition that a normal GFR is well above 60 ml/min per 1.73 m² in healthy children and adolescents, and that ignoring GFR between 60 and 89 ml/min per 1.73 m² represents a missed opportunity to delay or prevent CKD progression. It is unknown whether a threshold of 90 ml/min per 1.73 m² versus a threshold of 75 ml/min per 1.73 m² (proposed by some²) is the correct choice. The choice was justified based on evidence that eGFR of 60 to 89 ml/min per 1.73 m² is associated with a rate of reaching kidney failure or a 50% decline in eGFR within 10 years of approximately 10% for nonglomerular

CKD and approximately 40% for glomerular CKD and with increased risks of impaired linear growth and of hyperparathyroidism.¹ The problem of pediatric patients with “low” GFR being “cured” on their 18th birthday was not addressed. GFR percentiles or age-adapted thresholds would solve this problem.

Future work should consider the value, including potential harms, of maintaining a fixed GFR threshold of 60 ml/min per 1.73 m² to define CKD. This is particularly important in the elderly, in whom overdiagnosis of CKD may have negative impacts.²

Another important recognition in the 2024 KDIGO guidelines of the importance of age is the recommendation to predict the absolute risk of kidney failure in patients with CKD with risk scores such as the Kidney Failure Risk Equation.¹ In all these scores, age is a key variable in determining risk. A discussion of the strengths and the limitations of these scores is beyond the scope of the current editorial. However, all such scores have the advantage of providing a meaningful and personalized absolute risk of kidney failure, in contrast with heat maps that focus on relative risk at the population level.

The new KDIGO guidelines represent an enormous effort of a dedicated volunteer workgroup to summarize and interpret a vast body of evidence to provide guidance regarding best practices.¹ Our criticism does not negate the incredible value of these guidelines. Rather, we hope to emphasize that such guidelines always represent a work-in-progress, evolving continuously with new scientific data. This is why they are both so important and successful.

DISCLOSURE

All the authors declared no competing interests.

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