Nephrol Dial Transplant, 2025, **40**, 1455–1457
https://doi.org/10.1093/ndt/gfaf087
Advance access publication date: 7 May 2025

EDITORIAL

Kidney aging and chronic kidney disease—another perspective

Richard J. Glassock[1], Andrew D. Rule[2], Aleksandar Denic[2] and Pierre Delanaye[3,4]

[1]Department of Medicine, Geffen School of Medicine at UCLA, Los Angeles, CA, USA
[2]Division of Nephrology and Hypertension, Mayo Clinic, Rochester, MN, USA
[3]Department of Nephrology-Dialysis-Transplantation, University of Liège, CHU Sart Tilman, Liège, Belgium
[4]Department of Nephrology-Dialysis-Apheresis, Hôpital Universitaire Carémeau, Université de Montpellier, Nîmes, France
Correspondence to: Richard J. Glassock; E-mail: rjglassock@gmail.com

It is a given that the average age of the global population is increasing and that this demographic phenomenon will place a heavy burden on society and its health care enterprises, particularly in those countries with few resources to cope with the diseases that often accompany the aging processes. The World Health Organization has recently recognized this impending predicament by implementation of the United Nations Decade of Healthy Aging (2021–2030). Chronic Kidney Disease (CKD), as presently defined by the Kidney Disease Improving Global Outcomes (KDIGO) organization as an eGFR <60 ml/min/1.73 m^2, is predominately a disease of aging.

In the context of the matrix juxtaposing aging and CKD, it behooves all of us to think carefully about distinguishing good health from disease everywhere and for everyone as the inevitable process of aging occurs. In a provocative essay in this issue of *Nephrology Dialysis and Transplantation*, Ortiz and colleagues from the Japanese Society of Nephrology (JSN) and the European Renal Association (ERA) propose a conceptual framework for and a call to action on the achievement of kidney health in aging and aged societies all around globe [1]. CKD is rapidly becoming a treatable condition, most notably in the fields of diabetes, glomerulonephritis, and genetic diseases. It is logical that early detection and prompt management may in many instances delay or even prevent advanced CKD, including kidney failure.

However, we have concerns about how the diagnosis of CKD is made and how the risk of adverse outcomes of so defined CKD is assessed. These dual concerns arise from a consideration of the fundamental normal physiology of the kidney in aging humans. These concerns, in our opinion, need to be deeply considered as an integral part of the framework proposed the JSN and ERA, lest a substantial portion of the aging population receive an inaccurate "diagnosis" of CKD that lacks the consequences of a progressive disease resulting in meaningful increases in morbidity and mortality.

USE OF A NON-AGE-ADAPTED GLOMERULAR FILTRATION RATE (GFR) ESTIMATE FOR DEFINING CKD

A slow, but relentless, reduction in nephron number and GFR is a characteristic of normal, healthy aging [2]. This process occurs via global sclerosis of glomeruli predominately in the superficial cortex with atrophy of the attached tubule with surrounding interstitial fibrosis. Over time, the sclerosed glomeruli and foci of atrophic tubules further atrophy and become less detectable on histology such that the cortical parenchyma does not appear to sufficiently reflect the loss of nephrons. The most normal populations with kidney histology available are living kidneys donors and otherwise "healthy" patients who undergo a nephrectomy for tumor. In these, populations nephron number decreases from ~1.5 million to 750 000 from 20 to 90 years of age in a fairly linear manner with no sudden drop at a particular age [3] (Fig. 1). As a result, many people >65 years of age develop an eGFR <60 ml/min/1.73 m^2 (for three consecutive months or longer), the absolute (and arbitrary) single threshold of GFR used by KDIGO to operationally define CKD. The exact language used by KDIGO to define CKD implies that abnormalities of kidney function must have "implications for health." But this assertion remains quite vague, and is not taken into account either in epidemiological studies or in clinical practice.

The single nephron GFR and glomerular volume does not increase throughout the age range, suggesting that unlike CKD, kidney aging does not lead to glomerular hypertrophy and hyperfiltration [3, 4] (Fig. 1). Our published data suggesting there may be an increase in the oldest age group of living kidney donors (70–75 years) was limited by sample size and likely selection factors that require older donors to "hyperfilter" to be allowed to donate [4]. Increases in snGFR are seen in donors with obesity or with a family history of end-stage kidney disease (i.e. living related donor). Likewise, in patients with disease-related nephron loss, remaining glomeruli need to increase snGFR to compensate for nephron loss. Another piece of evidence for applying age-based thresholds comes from a study that found patients with more glomerulosclerosis or interstitial fibrosis/tubular atrophy within the range expected for their age did not have an increased risk of developing progressive CKD [5]. Patients who had nephrosclerosis, higher than expected for age, did have a higher risk of developing progressive CKD.

Since healthy aging, in the absence of co-morbidity (such as diabetes, obesity, hypertension), does not induce abnormal albuminuria, most of these older subjects will be defined as having CKD Stage 3A/A1 using the KDIGO matrix structure of GFR and Albuminuria classification. But these are healthy people "medicalized" by a "diagnosis"—stemming from a misunderstanding

Received: April 19, 2025; Editorial decision: May 3, 2025

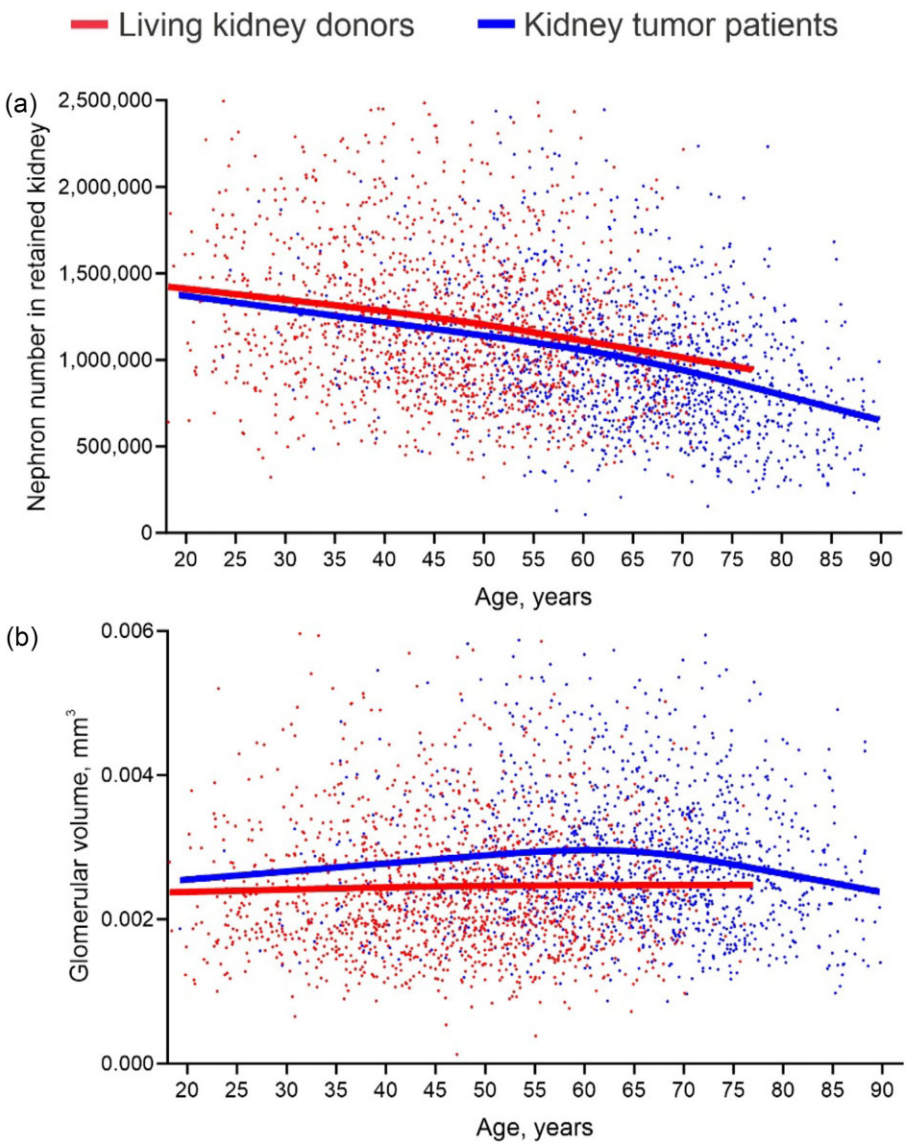

Figure 1: Trends in (**a**) nephron number and (**b**) glomerular volume with age among healthy adults (living kidney donors) and adults with common age-related comorbidities (kidney tumor patients) [3].

of normal physiology. What is needed to correct this flaw is an age-adapted rather than single fixed thresholds of GFR for a definition of CKD, [6] similar to how pulmonary function tests are reported. Fundamentally, age-adapted GFR thresholds for CKD definition are based on the universal observation that GFR declines with age in healthy individuals. This finding has been consistently confirmed in both cross-sectional and, more pertinently, longitudinal studies, utilizing reference methods or biomarkers to measure or estimate GFR [6, 7]. The decline of GFR with aging is universal, and was most recently shown in a large cohort of healthy European subjects [2].

The proposal of age-adapted GFR thresholds is often considered as 'too complex' and, as written by Ortiz et al. could lead to chaos. In fact, the age-adapted thresholds propose three thresholds instead of one: <75 ml/min/1.73 m² for individuals younger than 40 years, <60 ml/min/1.73 m² for those aged 40 to 65 years, and <45 ml/min/1.73 m² for those older than 65 years. Are three numbers significantly more complex than one? We do acknowledge that implementing such trichotomized thresholds could lead the issue of the "birthday paradox." For example, a 60-year-old individual with a stable eGFR of 55 ml/min/1.73 m² could be reclassified from having CKD to no CKD on turning 65 years. But, such a paradox also applies to the 2024 KDIGO guidelines, which clearly state that the GFR threshold should be 75 ml/min/1.73 m² in children and adolescents up to 18 years. Also, this issue can be mitigated by the relatively simple step of using GFR percentiles. Such percentiles have been well established in the literature across various continents, using both estimated and measured GFR [2, 6, 7]. Ortiz and colleagues argue that nephrologists would be the only specialists using such percentiles. This is not entirely correct. For straightforward parameters such as height or weight, pediatricians routinely use percentiles. Rheumatologists and Endocrinologists also utilize percentiles when interpreting bone mineral density results. With the assistance of clinical laboratories, it would be simple and straightforward in 2025 to automatically provide a percentile for age with each eGFR result. Moving from the single, threshold to age-adapted thresholds or percentiles might be considered a philosophical question of whether aging is a disease per se, but such a change in definition of CKD would lead to a substantial decrease in CKD prevalence among the elderly, and

equally importantly, an increase in CKD prevalence (and thus enhanced detection) among younger populations [7]. Nonetheless, there would still be more CKD in older than younger populations as is expected with most chronic disease.

CONSTRUCTION OF RELATIVE-RISK "HEAT MAPS" FOR ADVERSE OUTCOMES (MORTALITY, KIDNEY FAILURE, CVD) USING FIXED AND NOT AGE-ADAPTED REFERENCE VALUES OF GFR

The estimation of the risks of adverse outcomes (mortality, kidney failure, CVD, etc.) associate with any given value of GFR or albuminuria is a main feature of the KDIGO and CKD Consortium meta-analyses of CKD at any age in adults [8]. However, the hazard ratio calculations are made relative to a range of GFR values (90–104 ml/min/1.73 m^2) that are high for older adults [8]. In our opinion, analyses that do not adapt the reference value to the "normal" mean GFR (or eGFR) of each age category (age 40–65 years, 65–75 years, 75–85 years, and >85 years) can lead to significant over-estimation of risk. Meta-analysis of eGFRcr used to support a single threshold for CKD based on an increased mortality risk have been shown on reanalysis to support age-adapted thresholds for mortality risk [10].

A solution proposed has been to use cystatin C-based eGFR (alone or in combination with serum creatinine) as there is a more consistent increased risk of adverse outcomes (especially CVD risk) with cystatin C-based eGFR across the age spectrum [9]. Unlike the elevation in creatinine, that is relatively specific to loss of GFR, elevation in cystatin C occurs in other disease processes. A recent mechanistic study identified both endogenous and exogenous glucocorticoids activate the cystatin C gene and cystatin C recruits TREM2 macrophages, which play a role in a variety of diseases including inflammation, lipid metabolism, atherosclerosis, and cancer [10]. This elevation of cystatin C in other diseases processes inflates the risk of adverse outcomes with lower eGFRcys compared to lower eGFRcr and lower measured GFR. For purposes of diagnosing CKD, much more caution should be warranted with cystatin C-based eGFR than was provided by the KDIGO guidelines.

It is well recognized that medicine is moving toward personalized and precision approaches to diagnosis and management. With the advent of large data collections and artificial intelligence, this transition is becoming increasingly feasible. In nephrology, should we persist in a paradigm with one singular, generalized GFR threshold for the CKD definition, irrespective of such important factors such as age, sex, or body mass? This excessively standardized approach continues largely due to its apparent simplicity, and maybe, the inertia imposed by the status quo. Introducing GFR percentiles into CKD definition and age-adjusted reference values of GFR for assessment of population risks for adverse events represents a significant step toward personalized medicine. Such a shift could not only enhance diagnostic accuracy, but also harmonize CKD definitions and prognosis with established physiological principles.

CONFLICT OF INTEREST STATEMENT

None declared.

REFERENCES

1. Ortiz A, Kramer A, Rychlik I *et al.* Maintain kidney health in aging societies: a JSN and ERA call to action. *Nephrol Dial Transplant* 2025; gfaf068. https://doi.org/10.1093/ndt/gfaf068
2. Astley ME, Chesnaye NC, Hallan S *et al.* Age- and sex-specific reference values of estimated glomerular filtration rate for European adults. *Kidney Int* 2025;**107**:1076–87. https://doi.org/10.1016/j.kint.2025.02.025
3. Denic A, Mullan AF, Alexander MP *et al.* An improved method for estimating nephron number and the association of resulting nephron number estimates with chronic kidney disease outcomes. *J Am Soc Nephrol* 2023;**34**:1264–78. https://doi.org/10.1681/ASN.0000000000000124
4. Denic A, Mathew J, Lerman LO *et al.* Single-nephron glomerular filtration rate in healthy adults. *New Engl J Med* 2017;**376**:2349–57. https://doi.org/10.1056/NEJMoa1614329
5. Asghar MS, Denic A, Mullan AF *et al.* Age-based versus young adult thresholds on kidney biopsy and prognostic implications for CKD. *J Am Soc Nephrol* 2023;**34**:1421–32. https://doi.org/10.1681/ASN.0000000000000171
6. Delanaye P, Jager KJ, Bokenkamp A *et al.* CKD: a call for an age-adapted definition. *J Am Soc Nephrol* 2019;**30**:1785–805. https://doi.org/10.1681/ASN.2019030238
7. Jonsson AJ, Lund SH, Eriksen BO *et al.* The prevalence of chronic kidney disease in Iceland according to KDIGO criteria and age-adapted estimated glomerular filtration rate thresholds. *Kidney Int* 2020;**98**:1286–95. https://doi.org/10.1016/j.kint.2020.06.017
8. Grams ME, Coresh J, Matsushita K *et al.* Estimated glomerular filtration rate and adverse outcomes: an individual–participant meta-analysis. *JAMA* 2023;**330**:1266–77.
9. Denic A, Glassock RJ, Rule AD. Structural and functional changes with the aging kidney. *Adv Chronic Kidney Dis* 2016;**23**:19–28. https://doi.org/10.1053/j.ackd.2015.08.004
10. Kleeman SO, Thakir TM, Demestichas B *et al.* Cystatin C is glucocorticoid responsive, directs recruitment of Trem2+ macrophages, and predicts failure of cancer immunotherapy. *Cell Genom* 2023;**3**:100347. https://doi.org/10.1016/j.xgen.2023.100347

Received: April 19, 2025; Editorial decision: May 3, 2025