Editorial

Carmine Zoccali* and Mario Plebani

Extrapolated normative GFR data for living kidney donation

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The estimated glomerular filtration rate (eGFR) threshold to be applied for the definition of chronic kidney disease (CKD) is one of the most debated clinical research areas in nephrology. Before commenting the study by Delanaye et al. on normative data of measured GFR (mGFR) in elderly kidney donors published in this issue of the *Journal* [1], it is useful to briefly summarize the terms of this debate.

In the late 90s Levey et al. developed a GFR formula based on the MDRD study which was more accurate than measured creatinine clearance. The formula was subsequently refined and the last version of the same formula (the CKD-Epi) is now almost universally adopted. However, dissent on the consistent application of the formula in all adults independently of age still lingers. Pierre Delanaye is one of the most acute opponents of the universal, age-independent application of this formula. He objects that because the relative mortality risk in the elderly with CKD stage 3a may be less than that in younger populations, the definition of CKD should be based on appropriately age-stratified eGFR thresholds. For this purpose he produced age-specific GFR thresholds based on percentiles [2]. A recent analysis by Liu et al. [3] in the Alberta Clinical data base supports Delanaye's contention. Although based on robust epidemiological data, this contention should be tempered by some considerations. The background absolute mortality risk is higher in the elderly than in the young population, which should reduce the relative mortality risk in the elderly population with CKD stage 3a. The GFR-estimating equations were mainly derived in CKD populations. This may cause more misclassification of eGFR when these equations are applied to populations

where the GFR measurements include values higher than those in the CKD populations where the equations were derived. This possibility is suggested by the observation that in a large cohort of elderly individuals in Tuscany participants with measured (rather than estimated) creatinine clearance 60–90 mL/min/1.73 m² had a 70% excess risk of death as compared to those with creatinine clearance >90 mL/min/1.73 m² [4]. Furthermore, although the relative death risk by the eGFR is lower at stage 3a than at stage 3b CKD, the general population absolute risk is similar because stage 3a (excess risk of death 20%) is about four times more prevalent than stage 3b (excess risk for death 80%) in the USA [5] and in an European country like Italy [6]. Both absolute and relative risk are of relevance in public health and one cannot be interpreted without the other [7]. The debate on the eGFR threshold is not confined to age. Indeed social and biological arguments exist against the use of the race coefficient of this formula. A new formula based on creatinine and cystatin C, but without race, resulted more accurate and led to smaller differences between Black and non-Black individuals than the corresponding new equations with either creatinine or cystatin C alone [2].

Well beyond the ongoing debate about CKD stages definition, the fact remains that the GFR declines with aging and that this phenomenon is of relevance in some clinical decisions which apply to elderly people, like in kidney transplantation. Graft survival in old recipients by old cadaveric donors is very close to that of young recipients by young cadaveric donors and graft survival in these age-matched categories is superior to that in age-unmatched transplants [8].

Accurate evaluation of health status and renal function is fundamental in kidney transplantation from healthy donors. The GFR is the key parameter for the screening of suitable living candidates to donation. Current guidelines recommend that the GFR be initially measured with the creatinine-based formula and eventually confirmed with an exogenous tracer or with measured creatinine clearance or with the creatinine-cystatin based formula [9]. Measurement of the GFR with exogenous tracers is complex and laborious and there are differences among the techniques presently

***Corresponding author: Prof. Carmine Zoccali**, Renal Research Institute, New York, NY, USA; and Associazione Ipertensione Nefrologia e Trapianto Renale (IPNET) c/o Nefrologia e CNR, Grande Ospedale Metropolitano, 89124 Reggio Calabria, Italy, Phone: 0039 3407354062, E-mail: carmine.zoccali@tin.it. <https://orcid.org/0000-0002-6616-1996>

Mario Plebani, Department of Medicine-DIMED, University of Padova, Padova, Italy. <https://orcid.org/0000-0002-0270-1711>

accepted as golden standards. For example, likely because tubular reabsorption, the urinary clearance of ^{51}Cr -EDTA underestimates inulin clearance by 5–15% [10]. Diethylenetriaminopenta-acetic acid (DTPA) labeled with $^{99\text{m}}\text{Tc}$, an analog of EDTA, is freely filtered at glomerular level and tubular reabsorption is negligible. However, this radio-tracer undergoes also extrarenal elimination and DTPA may dissociate from $^{99\text{m}}\text{Tc}$ and bind to plasma proteins, thereby leading to underestimation of the GFR [11]. Iohexol measurement should be ideally done with high performance liquid chromatography (HPLC) [12] but the technique is time consuming and expensive. Data collected among living donors candidates show that the (measured) GFR (mGFR) undergoes a steady decline over time [13]. However, data on the mGFR in donors older than 60 years are very limited because the proportion of elderly donors is small. This proportion was about 10% in a Mayo Clinic series of 1,203 donors collected between 1999 and 2009 [6]. Subsequent surveys registered an increase of elderly donors [14] and it is likely that this proportion may further increase in the years ahead. In 2020 in the EUROTRANSPLANT Registry, 16% of living kidney donations came from individuals older than 65 years [15]. In such delicate donations the GFR is almost always based on golden standard measurements. Given the virtual absence of solid normative data of the mGFR, pragmatical approaches are needed to optimize the evaluation of renal function in elderly donors.

In the present study, Delanaye et al. [1] resorted to the same technique they applied for the identification of the age-dependent CKD threshold, i.e. calculated age-percentiles of mGFR in a population of about 2000 French and Belgian living kidney donors <65 years. Here the issue at stake was not CKD staging but that of pragmatically extrapolating a mGFR reference range for elderly kidney donors. Extrapolated results were then validated in an internal cohort of 147 donors ≥ 65 years and in an external cohort of 329 donors and healthy subjects ≥ 65 years. Percentages within the extrapolated 5–95th percentile (P5–P95) were calculated in these validation populations. Remarkably, in the external validation cohort, only five individuals (1.5%) had mGFR lower than the extrapolated P5 and only 25 (7.6%) higher than P95 while the vast majority, i.e. 200 and 99 (90.9%) had a mGFR between P5–P95. Thus, normative mGFR data generated by extrapolation beyond 65 years in a large population of European living kidney donors nicely overlapped with actual mGFR data in a reasonably large group of living kidney donor and healthy individuals older than 65 years.

Delanaye et al. deserve credit for proposing age-specific GFR percentiles in living kidney donation. The

current KDIGO guidelines consider the GFR 90 mL/min/1.73 m² or higher as an acceptable level of kidney function for donation. Such a level is higher than the median extrapolated GFR in the age range 65–80 years in Delanaye's study (Figure 1). Thus, the application of this (conservative) threshold would exclude about 50% of potential healthy donors. In this guideline a GFR lower than 60 mL/min per 1.73 m² forbids kidney donation but candidates with a GFR ranging from 60 to 89 mL/min per 1.73 m² can be still considered, provided that the decision to donate "... be individualized based on age and health profile ...". 60 mL/min/1.73 m² coincides with the 10th percentile GFR at 65 years (Figure 1) implying that the vast majority of healthy individuals (the 90%) at this age are suitable candidates to donation on the basis of the GFR. The British Transplantation Society has already adopted age- and gender-dependent GFR thresholds [16]. By this approach 80 years old males with a GFR > 58 mL/min/1.73 m² and females with a GFR > 49 mL/min/1.73 m² are considered as suitable donors. These levels are very close to the 10th mGFR age-percentile (Figure 1) suggesting that a 50 mL/min/1.73 m² GFR is not a barrier for kidney donation for about the 90% of 80 years old potential kidney donors in Britain. Extending this reasoning to other elderly age-strata, the use of age-specific GFR percentiles may allow a pondered discussion with the elderly kidney donor and the kidney recipient in the specific psychological, social and clinical context where transplantation is being considered.

Even though the dimension of the internal and external population used for data validation is limited, it should be recognized that data of the kind are sparse in the transplant literature. The present study is indeed one of the largest focusing on normative GFR data in living donors based on mGFR rather than on eGFR. On the other hand we should be aware that extrapolation is an exploratory technique which may be affected by the diversity of data in different databases. Extrapolated values can be unreliable, especially when there are disparities in the existing data sets. As remarked by Delanaye et al. the mGFR-age trajectory estimated in the present study is based on cross-sectional data while the actual mGFR decline with the aging process needs to be identified on the basis of longitudinal observations. The fact that the GFR in the generation and validation data sets was measured by the ^{51}Cr -EDTA and the Iohexol and inulin clearance is an issue that might have affected the results in a non-easily predictable manner. Indeed, GFR measurements by these highly intercorrelated filtration markers show not trivial differences [17]. Overall, given the paucity of GFR data in the old and in the very old population, the approach by Delanaye et al. of extrapolating age specific GFR percentiles is sound and the extrapolated kidney

Measured GFR
(mL/min/1.73m²)

Figure 1: Extrapolated 50 and 10th measured GFR percentile across age as reported in Table 2 in the Delanaye et al. study. The graph is commented in main text.

function range can be provisionally used in clinical practice. However, the need of establishing age-specific normal ranges for the measured GFR, the approach already taken by the British Transplantation society [16], should be more resolutely pursued. Additional international efforts are needed to produce normal intervals of the mGFR across age strata in the old. Over 3,000 GFR measurements have been collected in living kidney donors by the British Transplantation Society. Like in the French-Belgian population used in this study, it is most likely that the number of elderly donors be small also in Britain. Combining British and European (French-Belgian) data would be useful to improve the estimate of the normal interval of the measured GFR in the age range beyond 65 years. Furthermore, the British data base could be used to further validate in a much larger external population the age-specific GFR ranges extrapolated by Delanaye on the basis of the French-Belgian population of living kidney donors. Such an international collaboration would undoubtedly increase the evidence-base to be applied in the screening of elderly kidney donors, a population inherently at high risk where decisions are complex and much often difficult to be taken.

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