Polar Views in Nephrology

Pro: Thresholds to define chronic kidney disease should not be age-dependent

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Current thresholds to define chronic kidney disease (CKD) are essentially based on two measures, estimated GFR (eGFR) and albuminuria. The first two stages (stage 1 and 2) are mainly defined by the presence of abnormal albuminuria (>30 mg/g creatinine). Conversely, overt CKD (stages 3–5) is defined by an eGFR < 60 mL/min/1.73 m² with addition of albuminuria level; in these patients, in fact, numerous studies have identified the adverse and independent prognostic implications of albuminuria when added to eGFR. The subject matter of this polar view is to evaluate whether low eGFR (<60 mL/min/1.73 m²) or high albuminuria (>30 mg/g creatinine) can also be considered adequate cut-off values for definition of CKD in advanced age.

To examine the relationship between age and kidney measures for CKD definition, two issues should be addressed. The first is represented by the assessment of kidney function in healthy subjects in function of age to establish whether eGFR below the threshold value (<60 mL/min/1.73 m²) is a process of physiologic senescence or a sign of renal pathology. The second one concerns the evaluation of the interaction between age and eGFR/albuminuria thresholds on the risk of death and end-stage renal disease (ESRD). We examined the main studies characterized by high number of participants and/or long-term follow-up that analysed the whole age spectrum including very elderly subjects, in different study settings, i.e. general population, high-risk patients and CKD patients, including those under nephrology care.

EGFR TO DEFINE CKD IN ELDERLY HEALTHY SUBJECTS

The assessment of kidney disease in subjects with advanced age in the range of initial renal dysfunction, that is, stage 3a (60–45 mL/min/1.73 m²), may generate confusing results because of the ‘physiologic’ eGFR decline associated with age. Indeed, the prevalence of the stage 3a is extraordinarily high in elderly US subjects (21.5% in age 70–79 years) and further increases in very elderly individuals (37.8% in age ≥80 years) [1]. The same holds true in Italy (13.5 and 29.2%, respectively) [1]. Noteworthy, diagnosis of CKD stage 3a in older subjects is mainly based on moderate and isolated reductions in eGFR since ~80% of them do not have albuminuria [1].

A preliminary question is whether it is possible to assess the threshold of eGFR below of which renal pathology, rather than physiologic senescence, occurs. Kidney living donors provide a unique opportunity to study normal aging; these subjects, in fact, undergo all diagnostic tests to ensure their healthy status and, moreover, examination of kidney tissue can also be available. Recently, Hallan et al. [2] and Glassock et al. [3] have carefully reviewed the recent Literature on kidney living donors and healthy subjects, examining the cross-sectional findings on the age-dependent relationship between functional and morphological abnormalities, but have reached opposite conclusions. According to Hallan et al. [2], ‘among the elderly, a eGFR below 60 indicates a pathological reduction in kidney function’, on the contrary, according to Glassock et al. [3], ‘a significant fraction of apparently normal aged individuals over the age of 60 years (more women than men) have eGFR values below 60 mL/min per 1.73 m²’. This discrepant position can be influenced by several factors including different methods in measuring or estimating GFR, histological
techniques, the low number of subjects of advanced age among living donors as well as by the heterogeneous (and not always mentioned) exclusion criteria for eligible living donors with mildly reduced measured GFR (mGFR).

Of note, in older subjects, there is no correlation between loss of kidney mass and mGFR. Indeed, among older kidney donors (>65 years), GFR, measured by inulin clearance, was normal (79 ± 4 mL/min/1.73 m²) but renal functional reserve, that is, the increase in GFR after maximal vasodilation induced by concurrent infusion of amino acids and dopamine, was markedly reduced [4]. This discrepancy may be ascribed to the greater score of atherosclerotic lesions and tubular atrophy, detected in healthy older subjects [4]. This is further testified by a large cross-sectional study involving 1203 kidney donors, in which age-related increase in the prevalence of glomerulosclerosis appears to be unrelated to the GFR measured by iothalamate clearance [5]. Furthermore, patients who have ischaemic renal disease may be unrecognized because of the presence of normal GFR. Indeed, a study that used inulin clearance to measure GFR found ischaemic renal atherosclerosis at renal arteriography despite normal mGFR [6]. This finding becomes even more critical when considering eGFR estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation, which is currently considered the most adequate method to evaluate renal function in clinical practice. Indeed, a recent study has shown that eGFR by CKD-EPI does not confirm mGFR value (urinary clearance of iothalamate) in 28% of cases, with a difference between the two measures as large as 17 mL/min/1.73 m² [7]. Therefore, the assessment of eGFR per se seems to be inadequate to discriminate among senescence, subclinical vascular disease or initial renal structural changes, conditions that, moreover, may also be combined in the same subject.

**ROLE OF AGE IN THE PREDICTION OF RISK OF END-STAGE RENAL DISEASE AND DEATH**

In our opinion, the best available method to verify whether age modifies the thresholds for CKD definition is represented by the evaluation of association between eGFR/albuminuria and ‘hard’ end-points, such as death and ESRD. This type of analysis has indeed been carried out and includes a large number of patients extracted from (A) general population, high-risk and CKD cohorts and (B) cohorts of CKD patients under nephrology care.

**General population and high-risk cohorts**

One of the key studies on the progression of renal disease and mortality by age is that by O’Hare et al. who evaluated the prognosis of over 600,000 subjects of Veterans Administration [8]. During follow-up, the percentage of subjects developing ESRD was much lower than that of subjects who died before ESRD (4.4 versus 21.8%). Both the absolute incidence of ESRD and the adjusted risk of ESRD decreased with aging only for subjects with eGFR < 60 mL/min/1.73 m²; on the contrary, incidence and adjusted risk of mortality augmented through the categories of increasing age as well as categories of decreasing eGFR. These data suggest that the lower risk of ESRD in elderly subjects can be due, at least in part, to their greater risk of mortality (the so-called ‘competitive risk’). However, a slower CKD progression may contribute to this finding; indeed, in that study, the probability of eGFR decline, greater than 3 mL/min/year, was lower in older patients than in their younger counterparts for eGFR categories less than 45 mL/min/1.73 m² [8].

Similar findings have been confirmed by a more extensive analysis of CKD Consortium on more than two million people, mainly extracted from general and high-risk cohorts, and categorized by age (18–54, 55–64, 65–74, and ≥75 years) [9]. In these cohorts, death remarkably overcame ESRD in subjects with CKD. In general and high-risk cohorts, mortality rate was, as expected, higher in older than in younger subjects; however, after full adjustment, mortality risk increased with eGFR decline within each age category but adjusted HRs were progressively lower at older age. Mortality risk consistently started to increase in the range of eGFR from 60 to 75 mL/min/1.73 m² and, specifically, in those aged ≥75 years, it reached statistical significance at eGFR value of 56 mL/min/1.73 m², therefore supporting the validity of the threshold of 60 mL/min/m² for defining CKD in the elderly. Furthermore, in the CKD cohorts included in this meta-analysis, the slopes for relative risk of mortality were largely parallel across age categories, indicating no age–eGFR interaction. When considering albuminuria, its interaction with age for the relative risk of death was in general less evident as compared with eGFR, even though a significant positive interaction was observed at high albuminuria levels.

Importantly, lower eGFR was always associated with excess mortality risk (absolute risk) that was higher in older as compared with middle-aged adults, independently from cohort considered (general population, high-risk subjects and CKD patients) [9]. Specifically, in the general population and high-risk cohorts, for eGFR 45 (versus 80) mL/min/1.73 m², extra death per 1000 person-years was 2–3 times greater in those aged ≥75 years as compared with other age categories. Similar trends were observed for albuminuria; the absolute risk differences of albuminuria 300 mg/g compared with 10 mg/g progressively increased across age categories (7.5, 12.2, 22.7 and 34.3 deaths per 1000 person-years for age 18–54, 55–64, 65–74 and ≥75 years, respectively) [10]. In CKD cohorts, this phenomenon was even more pronounced in older age for eGFR 15 (versus 50) mL/min/1.73 m². Similarly, in older individuals of a large cohort of veterans with diabetes, albuminuria was independently associated with an increased risk of death at all levels of eGFR after adjusting for potential confounders [11]; in younger individuals, this association was attenuated at lower levels of eGFR.

Taken together, these findings, obtained in different cohorts, indicate that relative risks of mortality for low eGFR and high albuminuria are attenuated among older participants in general and high-risk cohorts but not in CKD cohorts. However, for a specific eGFR value, attributable risk (that is, the difference of absolute risk between older and younger) is consistently higher in older age in all cohorts. Interestingly, also for traditional cardiovascular risk factors (blood pressure,
glucose and cholesterol), a similar pattern of risk estimate (attenuation of relative risk in the presence of an increase in absolute risk) has been found with age; nevertheless, no age-specific thresholds for these factors are currently accepted [10, 12].

With regard to the renal outcome, the same meta-analysis showed that the risk of ESRD similarly increased in all age groups with either eGFR decline below 60 mL/min/1.73 m² or increasing albuminuria [9]. Of note, however, the association of a given level of eGFR with risk of ESRD was attenuated in older versus younger subjects. This finding may depend, at least in part, on the remarkably higher risk of death before ESRD in advanced age, the so-called ‘competitive risk’.

Cohorts of CKD patients under nephrology care

The TArget Blood pressure LEvel (TABLE) study is a multicentre prospective investigation of CKD prognosis in the setting of nephrology care, as testified by the enrolment of patients with at least one year of care in the 25 participating renal clinics [13, 14]. This cohort included 1248 CKD patients stage 3–5 with a mean age of 67 years (interquartile range, 58–76), mean eGFR of 30 mL/min/1.73 m² and median proteinuria of 0.6 g/day (interquartile range, 0.2–1.3), followed for 5.2 years on median. As expected, these patients had a more advanced CKD (lower eGFR and higher proteinuria) with respect to the patients derived from the general population and, consequently, the prevalent hard end-point of this cohort was the achievement of ESRD [incidence rates were 8.3 per 100 patient-years (95% CI, 7.4 to 9.2) for ESRD and 5.9 per 100 patient-years (95% CI, 5.2 to 6.6) for all-cause death] [13, 14]. This result extends to nephrology practice the findings of randomized clinical trials in nephrology, such as Modification of Diet in Renal Disease and AASK that have also shown a greater rate of ESRD than mortality [15, 16]. Figure 1 shows incidence of ESRD and death before ESRD in three age categories (<65, 65–75 and >75 years) by CKD stage in the TABLE cohort. The increase in incidence of ESRD was proportional to level of renal dysfunction, and it was not affected by age. As expected, moreover, mortality increased with age but there was no difference in eGFR threshold levels among classes of age [14].

Notably, the older CKD patients of the TABLE cohort were mainly affected by hypertensive nephropathy whereas the prevalent diagnosis in younger patients was glomerular disease, therefore accounting for values of proteinuria lower in older than in younger patients. These differences in underlying renal disease may contribute to the relatively minor incidence of ESRD in older CKD patients [15, 16]. Similar findings have been reported in a retrospective study including 116 patients with moderate CKD regularly followed for at least 5 years in one nephrology clinic [17]. The authors found in patients aged >75 years that eGFR decline was negligible (<1 mL/min/year on average) and slower than younger patients [17]. As for the TABLE cohort, also in this study the prevalent diagnosis of elderly CKD patients was hypertensive nephrosclerosis while the prevalent diagnosis in younger patients was glomerulonephritis [17].

At variance with general and high-risk cohorts, in the TABLE study, we found a positive interaction between age and proteinuria for ESRD risk (P < 0.002) [14], that is, elderly patients with CKD stage 3–4 and significant proteinuria (>0.5 g/day) are at higher risk for ESRD versus their younger counterparts; in this regard, we hypothesized that the kidney of elderly patients is more vulnerable to the nephrotoxic effects of proteinuria likely due to the greater degree of renal fibrosis and ischaemia [4, 5]. Our finding on ESRD risk is indeed confirmed by Consortium in CKD cohorts [9].

Interestingly, besides proteinuria, we also evaluate all the potential interactions between age and modifiable risk factors in predicting ESRD and mortality [14]. However, these analyses disclosed the absence of any further interaction with age. Specifically, independently of age, risk of ESRD was predicted by lower body mass index and Hb and higher phosphate while mortality risk increased in the presence of higher uric acid and lower Hb levels. Therefore, CKD complications do not appear to be age-dependent.

C O N C L U S I O N S

On the basis of large longitudinal outcome studies, it is possible to hypothesize that the thresholds of low eGFR and high
albuminuria are generally appropriate to define CKD across all age subgroups in terms of patient survival. Thus, the levels of eGFR and albuminuria should be added in the cardiovascular risk charts for the general population where only traditional risk factors are considered so far.

As demonstrated by Consortium in CKD cohorts, and by our group in referred CKD patients, more complex is the analysis of the interaction between age and both eGFR and proteinuria when addressing the risk of ESRD. Of note, the complexity is not merely due to more restrictive policies for dialysis initiation in older patients [18]. Indeed, longitudinal findings on the relatively lower rate of treated ESRD in advancing age are in fact influenced by the competitive risk related to the increasing mortality before ESRD with age. In addition, the decline of eGFR is generally slower in older than younger CKD patients likely because older patients have vascular nephropathy as the prevalent cause of CKD with a relatively lower rate of treated ESRD in advancing age. Indeed, longitudinal analysis of the interaction between age and both eGFR and proteinuria when addressing the risk of ESRD. Of note, the association between age and nephroclerosis on renal biopsy among healthy adults. Ann Int Med 2010; 152: 561–567


**REFERENCES**


**OPPONENT’S COMMENT**

The crux of the controversy over the need for an age calibration of eGFR thresholds for defining what is and what is not CKD revolves around whether one attributes the ageing-associated changes in eGFR to a manifestation of a pathological process (a disease or diseases) involving the kidneys or a purely biological phenomenon linked to organ senescence per se. This is not an either/or distinction since the alternatives are not mutually exclusive. Epidemiological studies, often cited by Conte et al., are powerless to make an unambiguous declaration concerning pathology versus biology. However, the adoption of a single threshold of function (eGFR or albuminuria) dichotomizes populations into non-overlapping categories attached to labels. The PRO arguments of Conte et al. rest largely on epidemiological studies asserting that values for eGFR (or albuminuria) below (or above) a selected threshold are linked to enhanced relative risks of adverse events (e.g. death or ESRD) regardless of age. Such analyses are sensitive to the choice of a reference value for relative risk comparisons—has the proper reference value been selected? A ‘real-life’ illustration may help to focus the discussion. One female, age 30 years, has an eGFR of 65 mL/min/1.73 m2 and another female, age 75 years, has an eGFR of 55 mL/min/1.73 m2, both repeated twice over a 6-month period. Both subjects are non-diabetic and have normal urinalyses and equivalent blood pressure. Which one more likely has CKD that will have a material impact on life expectancy and morbidity? According to the non-age calibrated definitions, the younger subject does not have CKD while the older subject does have CKD. According to the CKD Consortium, the fully adjusted hazard ratio for all-cause mortality (using an eGFR of 80 mL/min/1.73 m2 for the same age as the reference group) is ~1.7–1.8 for the younger person and <1.2 for the older person—differences that are clinically significant. The adjusted HR for treated ESRD is increased to about the same extent for both subjects. The eGFR in the younger person is at the 5th percentile and in the older person is at the 25th percentile for age. I would posit that the younger person has been under-diagnosed as not having CKD and that the older person has been over-diagnosed and probably does not have CKD. I largely concur with Conte et al. that the addition of albuminuria, particularly above values of 300 mg albumin/gm creatinine, has utility in helping to define CKD, independently of the eGFR. I remain
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INTRODUCTION

After a lengthy period of deliberation, during which mountains of evidence were reviewed by a stellar group of experts, The Kidney Disease Improving Global Outcomes (KDIGO) clinical practice guidelines (CPGs) for the evaluation and management of chronic kidney disease (CKD) have been released (28 December 2012) for general use by physicians and public health agencies throughout the world [1]. These CPGs update, revise and amplify those published a decade earlier under the auspices of the National Kidney Foundation-Kidney Disease Quality Outcomes Initiative (NKF-KDOQI) [2]. Over the decade that elapsed between these two seminal publications, enormous attention has been lavished on the subject of generic CKD, a nosology created by the original recommendations of NKF-KDOQI in 2002 [2]. According to PubMed, over 36 000 articles have been published on the general subject of CKD in the last 10 years.

In the original 2002 K/DOQI version, CKD could be diagnosed in any individual, of any age over 20 years, with an estimated (e) or measured (m) glomerular filtration rate (GFR) of <60 mL/min/1.73 m² persisting for >3 months, even if there were no other outward signs of kidney disease, such as abnormal proteinuria (or albuminuria), urinary sediment findings (such as hematuria), imaging or pathological abnormalities, in a renal biopsy [2]. The 2012 KDIGO–CPG recommendations validates this universal eGFR threshold in a ‘one size fits all’ approach to diagnosing and defining CKD, irrespective of age (or gender), and adds a qualifier, in the form of albuminuria grading. This formulation of CKD, based in part on eGFR values, gives physicians a ‘Hobson’s Choice’ for identifying CKD, and effectively ordains that the elderly bear a high burden of such a diagnosis, with a prevalence rate as high as 50% in those over 75 years of age [3]. About two of every three individuals ‘diagnosed’ as having generic CKD in this schema will be older adults. Such a diagnosis will largely be the result of discovery of a ‘mild-to-moderate’ reduction in estimated GFR (eGFR) (45–59 mL/min/1.73 m²) without abnormal albuminuria [4]. It bears an emphasis that the universal ‘threshold’ for defining CKD, exclusively based on a renal function parameter such as eGFR, originally arose, not from evidence, but from supposition [2]. The ‘normal’ mGFR of a 20-year-old healthy adult (average of men and women—with men higher than women) was believed to be ∼120–125 mL/min/1.73 m², thus a GFR (mGFR or eGFR) of <60 mL/min/1.73 m² could be regarded as a decline of >50% from ‘healthy adult values’. Subsequent studies clearly demonstrated that eGFR, calculated from any of several creatinine-based estimating equations, was relatively inaccurate and imprecise at normal levels of GFR, and that the eGFR (creatinine) was negatively biased relative to the mGFR, by as much as 10–20.

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