



EDITORIAL COMMENT

Epidemiology of chronic kidney disease: think (at least) twice!

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Abstract

The introduction of the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines has substantially contributed to the early detection of different stages of chronic kidney disease (CKD). Several recent studies from different parts of the world mention a CKD prevalence of between 8 and 13%. There are several reasons the CKD prevalence found in a study of a particular population is clearly overestimated. The structure of the population pyramid (young or older age) of the study sample may result in high or low CKD prevalence. The absence of using an isotope dilution mass spectrometry creatinine assay can be the source of high bias in CKD prevalence. In addition, using an arbitrary single threshold of estimated glomerular filtration rate (eGFR; <60 mL/min/1.73 m²) for classifying CKD leads to a substantial 'overdiagnosis' (false positives) in the elderly (>65 years of age), particularly in those without albuminuria (or proteinuria), haematuria or hypertension. It also results in a significant 'underdiagnosis' (false negatives) in younger individuals with an eGFR >60 mL/min/1.73 m² and below the third percentile for their age/gender category. The use of third percentile eGFR rates as a cut-off based on age/gender-specific reference values of eGFR allows the detection of these false positives and negatives. In the present article, we focus on an important and frequently omitted criterion in epidemiological studies: chronicity. Indeed, the two most important factors introducing a high number (up to 50%) of false positives are lack of confirming proteinuria and the absence of proof of chronicity of the eGFR found at first screening. There is an urgent need for quality studies of the prevalence of CKD using representative randomized samples of the population, applying the KDIGO guidelines correctly.

Key words: chronicity, chronic kidney disease, epidemiology

CKD. These three letters form one of the most used acronyms in the nephrology literature. Indeed, CKD (chronic kidney disease) is the common, general term used to describe the clinicopathologic state potentially leading to end-stage renal disease (ESRD), whatever the nature of the underlying pathophysiological process, from specific genetic or immune diseases (such as lupus nephritis) to more systemic insults (such as diabetic nephropathy) [1, 2]. In a very real sense, CKD is a generic term. This acronym, initially promoted by the US-based National

Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) [3] and later confirmed and extended by the Kidney Disease: Improving Global Outcomes (KDIGO) international guidelines [4], has the advantage that the same language is spoken everywhere. The term CKD has now replaced several other expressions that were used in the literature, including renal insufficiency, chronic renal failure and chronic renal disease [5, 6]. In these different nomenclatures, one word is common: 'chronic'. The chronicity of the kidney disease is clearly defined

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in the KDIGO guidelines for the evaluation of CKD [4] 'CKD is defined as abnormalities of kidney structure or function, present for ≥ 3 months, with implications for health' [4]. Thus, implicitly, this recommendation assumes that abnormalities are present at two different times, and so need to be measured at baseline and then confirmed at a subsequent time, specifically ≥ 3 months. As acknowledged by the KDIGO authors, the choice of the timing (3 months or 90 days) is a bit arbitrary, based more on clinical experience than clear evidence. This limit of 3 months has the advantage of being clear, explicit and easy to implement [4]. If the word 'abnormality' can encompass different concepts, certainly, the two most tested renal abnormalities, both in clinical practice and research, are the estimated glomerular filtration rate (eGFR), by creatinine-based equations, and the 'spot' urine albumin:creatinine ratio (UACR). *Sensu stricto*, CKD status can be attributed to a patient only if low eGFR and/or high UACR have been found at two different times, with at least a 3-month gap.

Focusing on the eGFR parameter, it is particularly intriguing that this chronicity criterion is often not considered in clinical research, and still less in renal epidemiology. The majority of published epidemiological studies consider the prevalence of CKD in general or specific populations [1, 7], but the vast majority of these studies have totally ignored the chronicity part of the CKD definition. In other words, nearly all studies have considered CKD for people with an eGFR < 60 mL/min/1.73 m² but measured only once. A study published in the current issue of *Clinical Kidney Journal* shares this important limitation [8]. However, this study is important, even though confined to a particular occupation (teachers), for several reasons. Good epidemiological data are scarce in Africa, especially in the sub-Saharan area [9–11]. Moreover, the study focuses on a relatively young and active population (46.3 \pm 8.5-years-old teachers) and they used the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation without the ethnic 'African American Black' coefficient factor, which seems misleading in African non-American populations [12, 13]. As expected in this young population, the prevalence of low eGFR (defined as eGFR < 60 mL/min/1.73 m²) with the CKD-EPI creatinine equation was relatively low, at 1.8%. We question if the prevalence of CKD would have been still lower if the chronicity criterion had been available. In other words, can we estimate the impact of confirming low GFR on the CKD prevalence in epidemiologic studies?

Based on the available literature, the impact of the confirmed diagnosis is far from negligible. In the National Health and Nutrition Examination Survey III, GFR was estimated by the Modification of Diet in Renal Disease (MDRD) equations. In a random sample of 98 patients with an eGFR < 60 mL/min/1.73 m², a second examination (in a median period of only 2 weeks) classified 77% of the same patients in the same category (stage 3A CKD). Thus 23% who would have been considered as 'diseased' had moved to 'healthy' after only a second creatinine measurement [14]. In 2006, Eriksen and Ingebretsen [16] published the results of patient and renal survival in the population of Tromsø, Norway, over a 10-year period. At that time, the population of Tromsø was $\sim 58\,000$ and 38 241 had one or more eGFR results available (by the MDRD non-standardized equation with coefficient 186 [15]) [16]. Among these 38 241 subjects, 6863 (17.9%) had an eGFR < 60 mL/min/1.73 m². The authors applied the chronicity criterion at 3 months. The CKD prevalence thus decreased to 3162 (8.3%), as 1526 (3.9%) had no second measurement and, importantly, 2175 (5.7%) had subsequent estimations > 60 mL/min/1.73 m². Therefore, considering only patients with second measurements available ($n = 5337$), it can be calculated

that 40.7% of subjects with a first eGFR < 60 mL/min/1.73 m² will not be confirmed as being CKD on the second estimation [16]. In another analysis from the same database (but using the standardized MDRD equation with coefficient 175 [17]), these authors also illustrated that the prevalence of CKD is influenced by the period of time used for the chronicity criterion [18]. If a 3-month period is considered, the prevalence of CKD was 3.2%, but it decreased to 2.0% if the chronicity criterion is obtained on a longer (i.e. 1-year) period [18].

Prospective longitudinal studies studying the slope of GFR in general or specific populations are scarce [19–22]. In 2015, Inker *et al.* [22] proposed such a study with longitudinal creatinine measurements (and eGFR by the CKD-EPI equation) of 3888 residents 31–59 years of age in Reykjavik, Iceland, with a mean follow-up of 25 ± 10 years and baseline eGFR > 60 mL/min/1.73 m². In this cohort, the authors calculated the lifetime risk for CKD stages 3–5. Interestingly, the authors used different CKD definitions. The first requires two consecutive measurements of eGFR < 60 mL/min/1.73 m² or one measurement of eGFR < 60 mL/min/1.73 m² if it was the last measurement of eGFR due to death or lack of subsequent creatinine measurement or ESRD. The second requires eGFR < 60 mL/min/1.73 m² on two occasions or eGFR < 60 mL/min/1.73 m² on the first measurement if the participant died before the second measurement or ESRD. The third requires eGFR < 60 mL/min/1.73 m² on two occasions or one eGFR < 45 mL/min/1.73 m² if it was at the last measurement of eGFR due to death or lack of subsequent creatinine measurement or ESRD. The fourth requires only one measurement of eGFR < 60 mL/min/1.73 m², irrespective of the results of follow-up measurements and was used for comparison with previous reports. Among these definitions, the first three integrate the notion of repeated measurement, whereas the last one is similar to definitions found in the majority of epidemiological studies. The results showed major discrepancies in lifetime CKD risk according to the definition used, and the differences are especially relevant with the fourth definition. For example, a woman who is currently 45 years of age has a lifetime risk of CKD stages 3–5 of 8.6, 7.8, 7.2 and 16.8% with definitions 1, 2, 3 and 4, respectively. In all analyses (men/women, different age categories and different follow-up), the CKD lifetime risk was systematically the highest with the definition including a single eGFR result. Other definitions can lead to variable results in terms of risk. We must keep in mind that the period of time between two consecutive measurements was also variable, but basically much longer (3–7 years) than the 3-month period required in the KDIGO definition [22]. The conclusions of this article must thus be interpreted with caution regarding the purpose of the current editorial, but these results perfectly illustrate that using a single eGFR result will lead to a significantly higher prevalence of CKD [22, 23].

The last study we want to discuss overcomes the shortcomings of the Inker *et al.* [22] study. In a seminal study, Benghanem Gharbi *et al.* [11] studied the prevalence of CKD in a randomized (voter list) cohort of 10 524 adult subjects in Morocco, representative of the general population. The authors strictly applied the CKD definition from the KDIGO guidelines, meaning that every low GFR (with the MDRD creatinine equation) should be confirmed after 3 months by a second measurement; chronicity was evaluated after 6 and 12 months. In this relatively young population, the prevalence of a decreased GFR (defined as eGFR < 60 mL/min/1.73 m²) was only 1.6%. Among these 'CKD' subjects, chronicity was tested in 78.9% ($n = 285$). When reinvestigated after 3 months (or later), 32% of stage 3A CKD and 7.8% of stage 3B subjects had an eGFR > 60 mL/min/1.73 m².

Based on both studies from Benghanem Gharbi et al. [11] and Eriksen and Ingebretsen [16], it can be suggested that 30–40% of patients labelled as CKD stage 3A when the diagnosis is based on only a single eGFR determination could actually move to 'normal' eGFR if the measurement is repeated after 3 months. These subjects could be considered as 'false-positive' CKD patients, questioning the validity of the majority of CKD epidemiological studies.

How can this high rate of false-positive diagnoses be explained? In the KDIGO perspective, the rationale of the 3-months threshold is to differentiate acute kidney disease (AKD) from CKD. In this view, the importance of fulfilling the chronicity criterion is unquestionable, as the care for CKD and AKD are very different. However, it seems unlikely that AKD explained very much of the 30% false-positive results, even if this assertion is based on lack of data. In part, these false-positive results can be explained by creatinine variability. As with any biological variable, creatinine can vary physiologically. In other words, if serum creatinine is repeatedly measured in the same individual under the same conditions with the same analytical methods, a variation [coefficient of variation (CV)] will be observed, i.e. the so-called intra-individual CV (CV_I) [24]. This is also the case for measured GFR which can vary in the same individual by 5–10% [25]. At this point, another source of variability must be added, i.e. the CV due to the analytical imprecision of the measurement, or analytical CV (CV_A). CV_A is dependent on the method (enzymatic or Jaffe) and specific assays used to measure serum creatinine. Both CV_I and CV_A determine the concept of critical difference or least significant change (LSC), which is defined as the smallest change over a limited period of time (classically some weeks) between results from the same individual that is not due to chance. We will consider the Jaffe methods for creatinine measurement, as these methods are most frequently used in the epidemiological studies [7]. Globally, for these methods, the LSC can be evaluated at ~20% [26, 27]. For a given man and woman age 60 years with a serum creatinine value of 1.2 and 0.9 mg/dL, respectively, the LSC concept implies that these values could normally vary from 0.96 to 1.44 and 0.72 to 1.08 mg/dL, respectively. Using the CKD-EPI equations and the same examples (1.2 and 0.9 mg/dL), the corresponding eGFR values will be 65 and 70 mL/min/1.73 m². However, because of normal variability of serum creatinine, the repeated eGFR results could be between 52 and 86 and 56 and 91 mL/min/1.73 m², respectively. In some cases, such physiologic variations of creatinine will lead to abnormal eGFR values (<60 mL/min/1.73 m²) [27]. The only way to prevent this variability is by repeating measurements, even over a short period of time. To be considered in the global context of clinical research, additional variability in repeated creatinine measurements can still occur if the samples are drawn at different moments of the day and/or in non-fasting conditions, as circadian variation and the influence of cooked meat intake on serum creatinine are both well known [1].

The confirmation of CKD by repeating measurements, notably of eGFR, is mandatory. However, some pitfalls must be discussed. First, as already discussed, the period of time considered for the application of the chronicity criterion (≥ 3 months) will influence the results: the longer the period between two measurements, the lower the CKD prevalence [18]. If a too long period of time is used for confirmation, there is a risk of increasing lost data for follow-up, the risk of increasing non-available data and also the risk of competing events, such as death in elderly populations. Second, according to the principle of regression toward the mean, if creatinine variability can

explain that some positive results (eGFR <60 mL/min/1.73 m²) become negative (eGFR >60 mL/min/1.73 m²) after a second test, there is the same risk that the first negative results are actually false negative and that repeated measurements would have been positive. However, because the first measurement is negative, this second measurement is not done. Therefore, to the best of our knowledge, the potential impact of these potentially false-negative results on the prevalence of CKD have not been studied. Third, in some retrospective analyses, with no systematic second measurement, there is a high risk of bias by indication. Indeed, in general, repeated creatinine measurements will be prone to be done in patients with CKD or at higher risk of CKD. This point is illustrated in a recent study from Sweden where the chronicity criterion could have been applied only in sicker subjects, leading to higher CKD prevalence in patients with repeated measurements. In this study, the authors also considered the time average value of different serum creatinine values, which is highly questionable and not justified by the authors [28].

Until now, we focused on eGFR abnormality, but the same reasoning can be applied to the UACR. Indeed, confirmation of albuminuria (or proteinuria) found at the first screening is another essential condition of the KDIGO guidelines before classifying an individual as having CKD or not. Many factors can influence albumin excretion, including obesity, age, sex, distant inflammation, high blood pressure, infection and drug use [29], resulting in wide fluctuations and hence false positivity of albuminuria. Several authors found a high percentage (>50%) of false-positive albuminuria at low values [urinary UACR 30–50 mg/g; dipstick proteinuria +], but less at higher values or dipstick ++ and +++ [11, 30, 31]. In the same way, CV_I or repeatability of UACR is very high (>50%), and this variability is higher in low UACR ranges (>100%) [32]. Together with the absence of proof of low eGFR chronicity, this non-confirmation of albuminuria (or proteinuria) in almost all epidemiological studies [7, 19] in the last 15 years results in false positivity of CKD prevalence of $\geq 50\%$ [11]. In addition, since creatinine excretion is in the denominator of the UACR equation, variations in creatinine excretion can influence the results independent of true albumin excretion rates. Low creatinine excretion (as in sarcopaenic elderly adults, chronic steroid myopathy or strict vegetarians) can spuriously elevate the UACR value and marked overexcretion of creatinine (muscle builders or obesity) can falsely lower the UACR values, leading to CKD misclassification in both circumstances [33, 34].

Large grey areas still exist in our knowledge of the true prevalence of CKD (according to its various causes) at the population level. Recent publications have questioned the purported 'epidemic' aspect of CKD [1]. But this topic is beyond the scope of this editorial; however, several other methodological aspects of CKD epidemiologic studies should be discussed and could explain, at least in part, the frequent overestimation of the prevalence of CKD in the current literature, namely, the choice of eGFR instead of measured GFR [25], the choice of the equations for eGFR [35], the choice of the biomarker [36, 37] and the choice of a unique threshold for CKD (at 60 mL/min/1.73 m²) instead of an age-calibrated threshold [36, 38]. Regarding this last point, we have advocated an age-sensitive threshold for CKD definition [36, 38], or better still, the use of third percentile eGFR creatinine levels based on age-/sex-specific reference values [11, 39]. This approach overcomes the false positives; that is, individuals with a still normal eGFR for their age (>3rd percentile), especially in case of an absence of renal damage (albuminuria, proteinuria or hematuria), who might correctly be considered as

not having CKD at all [11, 36, 38, 40, 41]. Of comparable importance is considering the young group of individuals with findings leading to a classification of no CKD, that is, no albuminuria (proteinuria) and a low eGFR for their age (<3rd percentile for age and sex category), but above the non-age-sensitive threshold of <60 mL/min/1.73 m² used in the KDIGO guidelines. Young and middle-aged adults with an eGFR of 60–74 mL/min/1.73 m² but without albuminuria/proteinuria or other signs of kidney damage may be better classified as ‘false negative’ CKD in our view [11, 42].

Among all these methodological parameters that have been briefly discussed, the application of the chronicity criterion is firmly and unequivocally mandatory in the diagnosis of CKD, as it is one of the important causes of false positive CKD diagnosis in case of non application. In epidemiology, like in life . . . before acting, think twice!

Conflict of interest statement

None declared.

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