Opinion Paper

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Staging chronic kidney disease and estimating glomerular filtration rate: an opinion paper about the new international recommendations

Abstract: In January 2013, the international recommendations of the KDIGO (for "Kidney Disease: Improving Global Outcomes") to define chronic kidney disease (CKD) and classify patients in CKD stages have been published. In this opinion article, we will review and discuss the most important guidelines proposed about CKD staging and glomerular filtration rate (GFR) estimating. In particular, we question the choice of fixed knot values at 60 mL/min/1.73 m² to define CKD. We also question the strategies proposed to measure and use cystatin C results.

Keywords: creatinine; cystatin C; glomerular filtration rate.

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Introduction

Assessment of kidney function is one of the most frequent common practices in medicine. There are several ways to assess kidney function but one of the most frequently used is certainly to measure or estimate glomerular filtration rate (GFR). Measurement of GFR (e.g., by iohexol clearance) is relatively laborious even if we think the difficulties and costs have been systematically overestimated in recent scientific literature [1, 2]. Therefore, estimating GFR from biomarkers is still recommended and used in clinical practice. Nephrologists rely on the international recommendations of the Kidney Disease: Improving Global Outcomes (KDIGO) to define chronic kidney disease (CKD) and classify patients [3]. A new issue of these guidelines has been published in January 2013. In this opinion article, we will discuss and question several recommendations in the field of GFR estimation, underlining the points of special interest for the clinical laboratory.

Definition of CKD

In order to define CKD, the KDIGO guidelines use the following criteria: albuminuria, urine sediment electrolytes abnormalities, histological abnormalities, and history of kidney transplantation. Regarding estimated GFR (eGFR), CKD is defined by eGFR<60 mL/min/1.73 m² without any distinction of age. This recommendation is not graded [3]. However, other experts in the field have challenged this approach to CKD definition [4–6]. Indeed, renal physiologists know that GFR physiologically decreases with aging. There are strong arguments showing that measured GFR (mGFR) in healthy older subjects may be <60 mL/min/1.73 m² [4, 7, 8]. Omitting this physiological data will lead to overestimation of CKD prevalence in the general population, and especially in the elderly [9]. In those patients, the level of GFR is usually lower than in young people. A lower GFR value may without doubt be the reason for a higher susceptibly of acute kidney injury or future progress to CKD. We believe, however, that this is not a reason to call these subjects "patients" or "diseased". Also, and maybe more importantly for the nephrologist, a 30-year-old patient with a GFR of 65 mL/min/1.73 m² could be considered healthy although his GFR value is well below the percentile 10 of the normal GFR in this age range. We think that the CKD definition proposed by the KDIGO leads to an overestimation of CKD prevalence in the older people and a potentially underestimation of disease prevalence in young people [4]. We believe that the "variable" age must be taken into account in the CKD definition.

Staging CKD

The goal of the KDIGO guidelines is to propose international harmonization of CKD definition and staging which is undoubtedly a great advantage. The guidelines proposed to classify CKD by cause, albuminuria category and GFR category. In this paragraph, we will focus on the categorization of GFR. Six categories (G1 to G5, with G3 split in G3a and G3b) are proposed according to GFR levels (Table 1) [3]. The KDIGO underlines the fact that neither category G1 nor G2 can be considered as "disease" if there is no evidence of other kidney damage. However, even in the context of albuminuria or of single kidney (post nephrectomy), we think the usefulness and relevance of two different stages (G1 vs. G2) is clinically questionable. For clinicians following these types of nephrologic patients, what is the interest of knowing the patient to be in G1 or G2? Moreover, we think that defining stage 1 as GFR>90 mL/min/1.73 m² does not allow the consideration of important physiological concepts like hyperfiltration in obese and diabetic patients (GFR>120 mL/min/1.73 m²) [2, 10]. These criticisms must also be understood with our prior proposition to adapt normal GFR values to age.

We would also like to discuss the splitting of G3 in G3a (GFR>45 mL/min/1.73 m²) and G3b (GFR<45 mL/min/1.73 m²). Considering a cut-off at 45 mL/min/1.73 m² could be important. Indeed, authors have shown with GFR measured by a reference method that CKD-related complications (anemia, acidosis ...) begin around 45 mL/min/1.73 m² [11]. Regarding our concern about normal GFR values in the elderly, we don't question that an elderly subject with a GFR<45 mL/min/1.73 m² effectively suffers from CKD [4]. However, we make the difference between defining a new cut-off for stage 3 at 45 mL/min/1.73 m² instead of 60 mL/min/1.73 m² and splitting stage 3 into 3a and 3b. Splitting the stage 3 necessarily implies that diagnosing and differentiating the "subgroups" is possible. In this context, the range of 15 mL/min/1.73 m² (stage G3b is defined as 30–45 and stage 3a 45–60 mL/min/1.73 m²) could be too tight to be of clinical use. Indeed, we think there is little chance that any equation may correctly estimate GFR (and thus staging) with a precision of <15 mL/min/1.73 m². In the recent study published by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) consortium, the precision of the GFR equations (defined as IQR of the difference between measured and estimated GFR) was 10, 11, and 8 mL/min/1.73 m² in subjects with eGFR<60 mL/min/1.73 m² for the CKD-EPI creatinine, the CKD-EPI cystatin C, and the combined (creatinine and cystatin) CKD-EPI equation, respectively [12]. Thus this precision of approximately 10 mL/min/1.73 m² is probably too close to the difference of 15 mL/min/1.73 m² allowing stage 3a to be separated from stage 3b. In other words, it is not useful to split stages in subgroups if there is no method that accurately differentiates these subgroups.

Table 1 Chronic kidney disease classification.

GFR category	GFR, mL/min/1.73 m²	Term
G1	90	Normal or high
G2	60–89	Mildly decreased
G3a	45–59	Mildly to moderately decreased
G3b	30–44	Moderately to severely decreased
G4	15–29	Severely decreased
G5	<15	Kidney failure

CKD, chronic kidney disease; GFR, glomerular filtration rate. In the absence of evidence of kidney damage, neither GFR category G1 nor G2 fulfill the criteria for CKD.

Evaluation of GFR: creatinine and creatinine-based equations

GFR estimation is one of the main criterions to define CKD. The question "how to evaluate or estimate GFR" is thus crucial. In the last decades, several new equations have been proposed. These equations have been developed from "renal" biomarkers like the classical "serum creatinine" as well as the promising "cystatin C". We are now discussing the main guidelines proposed in the chapter "evaluation of GFR". We briefly remind the nomenclature of the KDIGO: level 1 is a recommendation and level 2 is a suggestion. Gradation from A to D is corresponding to the quality of evidence, from high to very low quality.

> *Guideline 1.4.3.1: "We recommend using serum creatinine and a GFR estimating equation for initial assessment."*

This guideline is the only one with such a high level of evidence (1A). Using serum creatinine for initial assessment is, of course, not questionable. Using systematically creatinine-based equations is yet less evident (see below).

> *Guideline 1.4.3.2: "We suggest using additional tests (such as cystatin C or a clearance measurement) for confirmatory testing in specific circumstances when eGFR based on serum creatinine is less accurate."*

The level of evidence for this recommendation is low (2B). Also, this guideline remains relatively vague, as circumstances where eGFR based on serum creatinine is less accurate are not clearly specified [3]. Nevertheless, knowing the intimate relationship between serum creatinine and muscular mass, we would hypothesize using additional testing in subjects with abnormal muscular mass. More importantly, the recommendation is not specific about the choice of such "additional tests". Cystatin C is a GFR biomarker known and studied from 1985 [13]. Cystatin C is freely filtrated by the glomerulus and then entirely reabsorbed by the proximal tubules, where it is almost entirely catabolized [14, 15]. The advantage of cystatin C over serum creatinine is often presented as the lack of dependency on muscular mass [16], even if this point has been challenged [17–19]. We will discuss the interest of cystatin C further. Additionally, the guidelines propose to use "clearance measurement" without any additional precision. This point is a source of frustration as several different types of clearances, including creatinine clearances, could be grouped in the words "clearance measurement" [1]. We think the choice of the additional testing will strongly depend on the reason why we need GFR. In situations where a degree of precision is needed or in patients where creatinine-based equations are suspected to be inaccurate, there is little interest to estimate GFR with another biomarker or creatinine clearance and we recommend using a reference method for measuring GFR. We believe that giving the same weight to cystatin C measurement as to the GFR reference method for confirmatory testing is misleading. Regarding our actual knowledge, it could be considered as a "positive" exaggeration of the potential role of cystatin C.

> *Guideline 1.4.3.3: "We recommend that clinicians use a GFR estimating equation to derive GFR from serum creatinine rather than relying on the serum creatinine concentration alone and understand clinical settings in which creatinine-based estimation is less accurate."*

One reason to recommend equations is that the same serum creatinine concentration does not mean the same in terms of GFR if gender, age and ethnicity are considered [20–23]. However, this recommendation totally ignores the interesting publications by Pottel et al. who proposed considering only serum creatinine and to adapt the results to different normal reference values in those different populations [24, 25]. Also important, we have no proof that using creatinine-based equations is better than using serum creatinine (or the inverse of serum creatinine) to estimate the GFR slope in the follow-up of our patients [2, 26].

> *Guidelines 1.4.3.4: "We recommend that clinical laboratories should measure serum creatinine using a specific assay with calibration traceable to the international standard reference materials and minimal bias compared to isotope-dilution mass spectrometry (IDMS) reference methodology."*

This recommendation for clinical laboratories is clear and the level of evidence is high (1B). The literature is abundant and a lot of authors have well described severe consequences of non-calibration on eGFR results [27, 28]. At this point, we would like to underline the fact that both the Modified Diet in Renal Disease (MDRD) study and CKD-EPI equations, which is favored by the KDIGO (see below), have been developed from samples measured mostly with the Jaffe assay not directly standardized to IDMS [29–31]. Traceability has been obtained indirectly and a posteriori [32, 33]. From a "Clinical Chemistry" perspective, we believe the way this standardization has been obtained in those studies is far from ideal [34, 35].

Moreover, the precision (i.e., the random error) of GFR equations, will strongly depend on the potential error of the main variable included, i.e., serum creatinine. Its role is particularly important bearing in mind that the remaining variables included in GFR equations (age, gender and ethnicity) have a potentially smaller risk of error. Due to the exponential relationship between serum creatinine and GFR [35], the erroneous effect is particularly present in the estimation of high GFR (low creatinine levels). From the laboratory's point of view, we are thus disappointed by the absence of recommendation regarding the better precision of the enzymatic assays in comparison to the Jaffe assay [36, 37]. The preference of the enzymatic method is relevant for the precision of the creatinine measurement and thus for the precision of the equations [37–39]. Moreover, we have to keep in mind that a French independent study has recently proven that enzymatic assays are truly IDMS traceable [36].

> *Guidelines 1.4.3.4 (followed): "We recommend that clinical laboratories should report eGFR in addition to the serum creatinine concentration in adults and specify the equation used whenever reporting eGFR."*

As nephrologist, we globally agree about this recommendation but clinical laboratories ought to be more careful because their responsibility is engaged and very high. Clinical Chemists should remind clinicians on a regular basis that equations are and remain an estimation, an approximation. A very interesting alternative proposed by Bjork et al. is to show GFR results as a probability for patients being at stage G1, G2 or G3 instead of showing a "pure" result [40].

Guidelines 1.4.3.4 (followed): "We recommend that clinical laboratories report eGFR in adults using the 2009 CKD-EPI creatinine equation. An alternative creatinine-based GFR estimating equation is acceptable if it has been shown to improve accuracy of GFR estimates compared to the 2009 CKD-EPI creatinine equation".

The recent guidelines have logically been largely influenced by the studies from the CKD-EPI consortium [3]: indeed, the leaders of the CKD-EPI consortium have participated in the redaction of the KDIGO recommendations, the "Evidence Review Team" was localized in Boston (where the CKD-EPI leaders work), and the equations discussed in the KDIGO are those published by the consortium [12, 30, 41]. However, it is unfortunate that the authors of the guidelines have omitted to discuss (and even to cite in the bibliography) other creatinine- or cystatin C-based equations proposed by other authors and developed with an accurate methodology. For example, we can cite the quadratic equations from the "Mayo clinic" [42, 43], the Lund-Malmö [44] and the Berlin Initiative Study (BIS) equations [45]. We acknowledge that the data provided and published by the consortium are impressive notably in terms of sample. However, because nobody (and no study) is perfect, we have also to underline some limitations of the main studies from the CKD-EPI consortium. The CKD-EPI equation is now favored by the CKD-EPI leaders and by the KDIGO guidelines. They thus recommend abandoning the MDRD study equation [3, 30]. They assert that this equation performs better than the prior MDRD study equation, which has been shown to underestimate mGFR in high or normal GFR levels, leading to an overestimation of CKD prevalence. Therefore, recommending the CKD-EPI equation at the population level (i.e., in epidemiologic studies) makes sense as its bias has been shown to be better in healthy subjects [30, 46]. At the individual level, this assertion is however questionable as the random error of the equation (i.e., the precision) is not shown to be better. In fact, considering the patient and the daily practice, the superiority of the CKD-EPI equation is solely evident and relevant in G1 subjects (>90 mL/min/1.73 m²), and not in the "key zone" around 60 mL/min/1.73 m² [30, 47–52]. We question thus the role of the CKD-EPI equation as the "point of reference" to potentially validate other equations.

Guidelines 1.4.3.4 (followed): "We recommend that serum creatinine concentration be reported and rounded to the nearest whole number when expressed as standard international units (µmol/L) and rounded to the nearest 100th of a whole number when expressed as conventional units (mg/dL). We recommend that eGFR should be reported and rounded to the nearest whole number and relative to a body surface area of 1.73 m² in adults using the units mL/min/1.73 m²."

With regard to the important issue of harmonization and standardization, we believe that it is time to favor standard international units. We fully agree with the proposed "rounding" as expressions like "100.56 mL/min/1.73 m²" are cumbersome and make no sense both from a clinical and biological point of view.

Guidelines 1.4.3.4 (followed): "We recommend eGFR levels <60 mL/min/1.73 m² should be reported as decreased."

Regarding the last part of the recommendation, we wonder why the guidelines recommend five CKD stages but ask the laboratory to simply report "decreased" without indicating a stage. It could be interpreted as a "*reductio ad absurdum*" of the complexity of the staging (five stages with one split stage), in particular for the general physician. Moreover, in "the MDRD area", several authors proposed that laboratories should display GFR results as ">60 mL/min/1.73 m²" without the absolute value because imprecision of the creatinine measurement results in a lower precision of the estimate for high GFR levels [38, 39]. This important issue for the clinical chemists has not been mentioned in the new guidelines. Even if the precision could theoretically be better with the CKD-EPI equation (simply because the exponent applied to creatinine in the high GFR levels is lower than in the MDRD equation) this improvement is not proven in clinical studies [51].

Evaluation of GFR: cystatin C

It is beyond the scope of this article to discuss all the potential or theoretical advantages, as well as the limitations of cystatin C as a marker for GFR estimation. Several review articles have been published on the topic, including in this journal [53–55]. One of the main limitation of cystatin C and cystatin C-based equations was the lack of standardization between assays leading to potential discrepancies similar to the ones observed in creatinine-based equations [56–59]. Standardization is however available since 2011 and this is considerable improvement for the topic "estimating GFR with cystatin C-based equations" [60]. This improvement is, however, not synonymous of "perfection" and, e.g., this new standardization is inferior to the IDMS-traceability observed for creatinine measurements. In other words, we have now a standardized calibrator, but we are still waiting for a "true" reference method to measure cystatin C, i.e., with mass spectrometry. Regardless of the limitations of the standardization, this process is an important improvement and necessary milestone for the implementation of cystatin C-based equations.

Equations based on standardized cystatin C (CKD-EPI cystatin C) or cystatin C and creatinine (combined CKD-EPI equation) have been proposed by the CKD-EPI consortium in 2012 [12]. The way of obtaining cystatin C calibration is, however, not unquestionable. The calibration has been done a posteriori (from samples frozen for more than 5 years) and indirectly. Cystatin C results may differ according to year of sampling as calibration of the Siemens assay has changed over time [12, 58].

The main conclusion of the CKD-EPI study with cystatin C-based equations is the superior performance of the combined equation over the CKD-EPI creatinine and CKD-EPI cystatin C equations. Interestingly, the better performance was obtained by an improvement in precision of the equation. In participants whose estimated GFR based on CKD-EPI creatinine was 45–74 mL/min/1.73 m², the combined equation improved the classification of measured GFR as either less or >60 L/min/1.73 m² (net reclassification index of 19.4%) and correctly reclassified 16.9% of those with an estimated GFR of 45–59 mL/min/1.73 m² as in fact having a GFR of >60 mL/min/1.73 m² [12]. From this observation, the guidelines 1.4.3.5 suggest the following strategy:

> *Guidelines 1.4.3.5: "We suggest measuring cystatin C in adults with eGFRcreat 45–59 mL/min/1.73 m² who do not have markers of kidney damage if confirmation of CKD is required: If eGFRcys/eGFRcreat-cys is also <60 mL/min/1.73 m², the diagnosis of CKD is confirmed; If eGFRcys/eGFRcreat-cys is >60 mL/min/1.73 m², the diagnosis of CKD is not confirmed.*

Such a strategy implies that cystatin C should be measured in a lot of patients in the general population (and not in specific ones). It is clearly a suggestion more than a recommendation because such a strategy is based on few studies. Clearly, at this point, other studies are necessary to confirm the clinical relevance, but also the cost-effectiveness, of such a strategy to screen CKD in the general, but also in more specific populations [61].

Other guidelines about the use of cystatin C remain unspecific and relatively vague. For instance, for the clinician, it remains still unclear which of the two CKD-EPI equations (combined or based only on cystatin C) should be used when. This important question needs future investigations.

Conclusions

In this opinion paper, we take the liberty to criticize the new KDIGO guidelines. A minimum of harmonization is indispensable for a classification, and probably at a given moment, arbitrary choices have to be made. Our main critics are finally about the arguments frequently proposed to justify these guidelines: e.g., the unique cut-off value of "normal GFR" at 60 mL/min/1.73 m², the choice of the CKD-EPI creatinine equation instead of the MDRD, or the preference for cystatin C instead of creatinine-based equations. Indeed, most of these arguments are epidemiological ones: eGFR<60 mL/min/1.73 m² is associated with higher mortality, CKD-EPI better predicts mortality than MDRD, and cystatin C also better predicts cardiovascular outcomes than creatinine [62–65]. These arguments are probably valid from both an epidemiological and predictive point of view but we believe that in clinical practice disease prediction for future population is not the primary role of the GFR estimation equation. Non-GFR determinants potentially play an important role in the "prediction" of the biomarkers and the statistics used seem to be of influence for such demonstrations (high risk of collinearity) [4, 66, 67]. It may be time for clinicians who are the ones taking care of patients to take their part in the debate and to propose alternatives.

We acknowledge that we might have been too severe in several occasions in this opinion paper. We know that guidelines elaboration has requested a lot of work and recommendations are the results of a lot of debate. It is almost always easier to destruct than to build. On the other side, guidelines are not carved in stone and discussion and debate are nutriments of science.

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