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Estimating Glomerular Filtration Rate in China: Is the European Kidney Function Consortium (EKFC) Equation the Solution?

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Abstract
The new European Kidney Function Consortium (EKFC) creatinine-based equation has been developed to be applicable over the entire age range (from 2 to 100 years) without any loss of performance in young adults and without loss of continuity in estimating glomerular filtration rate (GFR) between adolescents and adults. This goal is obtained by better taking into account the relationship between serum creatinine (SCr) and age in the estimating GFR model. This is accomplished by rescaling SCr, namely, dividing SCr by so-called Q value which is the median normal value of SCr concentration in a given healthy population. The better performance of the EKFC equation, compared to the current equations, has been shown in large European and African cohorts. Such good results are also suggested in cohorts from China, including in the current issue of *Nephron*. The good performance of the EKFC equation is observed, especially when the authors used a specific Q value for their populations notwithstanding GFR was measured by a controversial method. Using a population-specific Q value could make the EFKC equation universally applicable.

It sounds like a cliché, but China is one of the most populous countries on Earth and the prevalence of chronic kidney disease does not seem very different from other places in the world [1]. Estimating glomerular filtration rate (GFR) is thus of paramount importance. Nowadays, GFR is mostly estimated by different biomarkers used in different equations. Cystatin C is certainly a promising biomarker notably because its concentration seems more independent of demographic characteristics [2]. Indeed, serum creatinine (SCr) concentration, used for more than one century to evaluate kidney function has several drawbacks [3]. Among many limitations, the fact that creatinine concentration depends on population differences is problematic [4, 5]. Indeed, it means that the same equation will not be unbiased in all populations. The best and well-known example is the difference in creatinine concentrations between men and women, which implies the requirement for appropriately adjusting the equation when considered in men and women [2, 6, 7]. SCr is also potentially not the same in geographically, sociologically, or ethnically different populations. As a matter of fact, SCr is different, although GFR is identical, in Black US, White US, Black African, White European, and Black European subjects

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[5]. The reason why such variations in creatinine exists is not well understood but has nothing to do with "race" (even considering the word race in its only possible meaning which is race as a social concept). Indeed, SCr at the population level is clearly different between US Black and non-Black men but is very similar in Black and non-Black US women, questioning race as the underlying cause of it [4, 8]. Differences in creatinine generation also exist in Asia compared to other continents and potentially between Asian countries. This is illustrated by the variation in coefficients that have been proposed to "correct" for the estimation of GFR in the most used estimating GFR equation, namely, the Chronic Kidney Disease Epidemiology (CKD-EPI) equation. Of interest, these coefficients were different in China, Japan, or Korea [9–13]. All these correction factors are however misleading because they suggest that GFR must be corrected between Asian populations, whereas it seems probable that measured GFR is actually not (very) different between Asian populations. If a correction should be applied, it should be at the SCr level. This is one of the main characteristics of the European Kidney Function Consortium (EKFC) equation which has been developed to be used in every specific population, as long as a rescaling value for creatinine, the Q value, is known [6]. The Q value is the median normal value of SCr concentration in a given population [6, 14, 15]. As an example, the Q value in White European populations (older than 25 years) is 0.7 mg/dL for women and 0.9 mg/dL for men [14, 16]. The EKFC creatinine-based equation has been shown to have the lowest bias and higher accuracy in large White European populations, with the advantage to be applicable from children to old adults [6]. This EKFC equation is also applicable to other populations like African Black populations in West Africa, with the best performance obtained with population-specific Q values [5]. Q values are easy to establish, and different methodologies can be proposed. For example, the European White Q values have been obtained from large laboratory databases where serial creatinine measurements were omitted, assuming that the majority of results were from healthy people [14]. For Black European Q values, such a large sample was not available and Q values were thus deducted from smaller, but better phenotyped samples regarding their healthy status, such as a population of living kidney donors [5]. Using population-specific Q values was associated with improved performance in bias and accuracy for the EKFC equation in different populations [5]. This equation is also performing better in young adults and allows the continuity of estimating GFR over the complete age range (2–100 year), such a continuity being absent for the CKD-EPI equation and the currently recommended equation in children (with implausible jumps in eGFR at the adult transition) [6, 17]. In adults, the association between measured GFR and SCr according to age in healthy populations is also better modeled by EKFC than by CKD-EPI, as SCr concentration remains relatively constant with age whereas measured GFR is naturally decreasing with aging after 40 years [14, 18, 19]. The association between GFR and SCr is thus necessarily different before and after 40 years which is taken into consideration in the EKFC equation but not in the CKD-EPI equation [6, 20]. This observation probably explains, at least in part, the better performance of the EKFC equation in the Chinese population described by Ma and colleagues in the current issue of nephron [21]. Once again, the added value of the EKFC equation is especially relevant in young adults. In the whole population, the bias of the EKFC population is still positive, suggesting an overestimation of the EKFC equation, even if the bias is significantly lower than the CKD-EPI equation (and the authors used the 2009 CKD-EPI equation, the race-free 2021 CKD-EPI equation would overestimate still more GFR [22]). However, it must be mentioned here that Ma et al. used the European Q values in their main analysis, which are potentially not ideal for Chinese subjects. Two studies from China also showed a better performance for the EKFC equation as compared to CKD-EPI in a limited sample of 160 Chinese subjects and in a larger sample of elderly patients, even when these authors also considered European Q values [23, 24]. Indeed, different studies in the past have suggested that normal creatinine concentrations (and so Q values) in China could be lower than those in Europe [25, 26]. This is confirmed by Ma et al. [21] in their supplemental Tables. Applying such Chinese-specific Q values indeed decreases the overestimation observed in the study by Ma with a bias moving from 3.61 to an unbiased result of −0.36 mL/min/1.73 m^2 [21].

Even if the EKFC equation shows the best performance in the current cohort, it must be acknowledged that the accuracy of the equation remains relatively low, compared to the performance of the same equation in the US or European cohorts [6, 7]. This low performance is not specific to the current dataset, but this result is also observed in many other cohorts from China [10]. All the studies with low performance have also been realized with a poor quality method of measured GFR. Indeed, in China, GFR seems to be frequently "measured" with DTPA scan with the so-called Gates method [27]. The Gates' method assumes that there is a concentration of DTPA accumulating in kidneys shortly after injection

and that this accumulation is dependent on GFR. After 2–3 min of examination, an image is created. The GFR result is then given applying a linear regression analysis between the radioactive counts measured by a gamma-camera and GFR measured by a reference method. This method can propose an accurate "split renal function," expressed in a relative way (left and right kidney working for 52% and 48% of the total function, as an example) [28]. The problem is that the absolute GFR value given by this method is not accurate [29–31]. Other authors, also from China, have even shown that the results given by the DTPA scan method was less accurate than the results given by estimating equations [29]. The statement by Ma et al. that an intraclass correlation coefficient >0.75 between DTPA scan and DTPA plasma clearance was justifying the use of DTPA scan as a reference method is, in our opinion, incorrect.

If, in a validation study on estimating GFR equations, the reference method itself is not accurate and precise, it can explain the low performance of all the equations. A few Chinese studies on GFR used DTPA dual plasma clearance [11, 23, 24, 29, 32], probably better than the Gates method, but still relatively inaccurate [33]. We urgently are in need for more and large studies in China with recognized and unquestionable reference methods for measuring GFR, like inulin urinary clearance or (and probably easier to implement) iohexol plasma clearance [33–36].

The universality of the creatinine-based EKFC equation is theoretically applicable with the development of population-specific Q values. The study by Ma et al. is a first step, but the added value of the EKFC equation in Chinese populations could definitively be proven in studies with both a dedicated, population-specific Q value and an adequate reference method to measure GFR.

Conflict of Interest Statement

The authors have no conflict of interest to declare.

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Author Contributions

Pierre Delanaye wrote the first draft and Hans Pottel critically reviewed it.

References

1 Wang L, Xu X, Zhang M, Hu C, Zhang X, Li C, et al. Prevalence of chronic kidney disease in China: results from the sixth China chronic disease and risk factor surveillance. JAMA Intern Med. 2023;183(4):298–310.
2 Pottel H, Björk J, Rule AD, Ebert N, Eriksen BO, Dubourg L, et al. Cystatin C–based equation to estimate GFR without the inclusion of race and sex. N Engl J Med. 2023;388(4):333–43.
3 Delanaye P, Cavalier E, Pottel H. Serum creatinine: not so simple. Nephron. 2017;136(4):302–8.
4 Delanaye P, Pottel H, Glassock RJ. Americentrism in estimation of glomerular filtration rate equations. Kidney Int. 2022;101(5):856–8.
5 Delanaye P, Vidal-Petiot E, Bjork J, Ebert N, Eriksen B, Dubourg L, et al. Performance of creatinine-based equations to estimate glomerular filtration rate in White and Black populations in Europe, Brazil, and Africa. Nephrol Dial Transpl. 2023;38(1):106–18.
6 Pottel H, Björk J, Courbebaisse M, Couzi L, Ebert N, Eriksen BO, et al. Development and validation of a modified full age spectrum creatinine-based equation to estimate glomerular filtration rate. A cross-sectional analysis of pooled data. Ann Intern Med. 2021;174(2):183–91.
7 Inker LA, Eneanya ND, Coresh J, Tighiouart H, Wang D, Sang Y, et al. New creatinine- and cystatin C–based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737–49.
8 Shi J, Lindo EG, Baird GS, Young B, Ryan M, Jefferson JA, et al. Calculating estimated glomerular filtration rate without the race correction factor: observations at a large academic medical system. Clin Chim Acta. 2021;520:16–22.
9 Delanaye P, Cavalier E, Mariat C, Krzesinski JM, Rule AD. Estimating glomerular filtration rate in Asian subjects: where do we stand? Kidney Int. 2011 Sep;80(5):439–40.
10 Li D, Yin W, Yi Y, Zhang B, Zhao J, Zhu C, et al. Development and validation of a more accurate estimating equation for glomerular filtration rate in a Chinese population. Kidney Int. 2019;95(3):636–46.
11 Wang J, Xie P, Huang J, Qu Y, Zhang F, Wei LG, et al. The new Asian modified CKD-EPI equation leads to more accurate GFR estimation in Chinese patients with CKD. Int Urol Nephrol. 2016;48(12):2077–81.
12 Horio M, Imai E, Yasuda Y, Watanabe T, Matsuo S. Modification of the CKD epidemiology collaboration (CKD-EPI) equation for Japanese: accuracy and use for population estimates. Am J Kidney Dis. 2010 Jul;56(1):32–8. (Electronic)):32–8
13 Jeong TD, Lee W, Yun YM, Chun S, Song J, Min WK. Development and validation of the Korean version of CKD-EPI equation to estimate glomerular filtration rate. Clin Biochem. 2016;49(9):713–9.
14 Pottel H, Vrydags N, Mahieu B, Vandewynckele E, Croes K, Martens F. Establishing age/sex related serum creatinine reference intervals from hospital laboratory data based on different statistical methods. Clin Chim Acta. 2008 Oct;396(1–2):49–55.
15 Pottel H, Hoste L, Delanaye P, Cavalier E, Martens F. Demystifying ethnic/sex differences in kidney function: is the difference in (estimating) glomerular filtration rate or in serum creatinine concentration? Clin Chim Acta. 2012 Oct;413(19–20):1612–7.
16 Björk J, Nyman U, Delanaye P, Grubb A, Larsson A, Vranken L, et al. A novel method for creatinine adjustment makes the revised Lund–Malmö GFR estimating equation applicable in children. Scand J Clin Lab Invest. 2020;80(6):456–63.

17 Pottel H, Björk J, Bökenkamp A, Berg U, Åsling-Monemi K, Selistre L, et al. Estimating glomerular filtration rate at the transition from pediatric to adult care. Kidney Int. 2019 May;95(5):1234–43.
18 Delanaye P, Gaillard F, Van Der Weijden J, Mjoen G, Ferhman-Ekholm I, Dubourg L, et al. Age-adapted percentiles of measured glomerular filtration in healthy individuals: extrapolation to living kidney donors over 65 years. Clin Chem Lab Med. 2022;60(3):401–7.
19 Pottel H, Hoste L, Yayo E, Delanaye P. Glomerular filtration rate in healthy living potential kidney donors: a meta-analysis supporting the construction of the full age spectrum equation. Nephron. 2017;135(2):105–19.
20 Pottel H, Delanaye P, Schaeffner ESEES, Dubourg L, Eriksen BOBO, Melsom T, et al. Estimating glomerular filtration rate for the full age spectrum from serum creatinine and cystatin C. Nephrol Dial Transpl. 2017 Jan;32(3):497–507.
21 Ma Y, Wei L, Yong Z, Yu Y, Chen Y, Zhu B, et al. Validation of the European Kidney Function Consortium (EKFC) equation in Chinese adult population: an equation standing on the shoulders of predecessors. Nephron. 2023. In process.
22 Shen Y, Wu H, Liu X, Zhu J, Shao W, Wang B, et al. Comparison of the 2021 and 2009 chronic kidney disease epidemiology collaboration creatinine equation for estimated glomerular filtration rate in a Chinese population. Clin Biochem. 2023;116:59–64.
23 Zhao L, Li HL, Liu HJ, Ma J, Liu W, Huang J, et al. Validation of the EKFC equation for glomerular filtration rate estimation and comparison with the Asian-modified CKD-EPI equation in Chinese chronic kidney disease patients in an external study. Ren Fail. 2023;45(1):2150217.
24 Xia F, Hao W, Liang J, Wu Y, Yu F, Hu W, et al. Applicability of Creatinine-based equations for estimating glomerular filtration rate in elderly Chinese patients. BMC Geriatr. 2021;21(1):481–13.
25 Wang X, Xu G, Li H, Liu Y, Wang F. Reference intervals for serum creatinine with enzymatic assay and evaluation of four equations to estimate glomerular filtration rate in a healthy Chinese adult population. Clin Chim Acta. 2011 Sep;412(19–20):1793–7.
26 Zhang GM, Xia YJ, Guo XX, Zhu BL, Zhang GM, Ma XB, et al. Reference intervals for total bilirubin, ALT, AST and creatinine in healthy Chinese elderly. Med Sci Monit. 2014;20:1778–82.
27 Gates GF. Split renal function testing using Tc-99m DTPA. A rapid technique for determining differential glomerular filtration. Clin Nucl Med. 1983 Sep;8(9):400–7.
28 Piepsz A, Dobbeleir A, Erbsmann F. Measurement of separate kidney clearance by means of 99mTc-DTPA complex and a scintillation camera. Eur J Nucl Med. 1977 Sep;2(3):173–7.
29 Xie P, Huang JM, Liu XM, Wu WJ, Pan LP, Lin HY. (99m)Tc-DTPA renal dynamic imaging method may be unsuitable to be used as the reference method in investigating the validity of CDK-EPI equation for determining glomerular filtration rate. PLoS One. 2013;8(5):e62328,
30 Galli G, Rufini V, Vellante C, D'Errico G, Piraccini R. Estimation of glomerular filtration rate with 99Tc(m)-DTPA: a comparative assessment of simplified methods. Nucl Med Commun. 1997 Jul;18(7):634–41.
31 Moralidis E, Papanastasiou E, Didangelos T, Hilidis I, Siountas A, Arsos G. Determination of the glomerular filtration rate in patients with type 2 diabetes: an assessment of the agreement between 51Cr-EDTA plasma clearance and 99mTc-DTPA plasma clearance, 99mTc-DTPA renography and plasma creatinine prediction equation. Diabetes Res Clin Pract. 2020;161:108079.
32 Liu W, Zhao L, Huang J, Wei LG, Guan MC, Gao F, et al. The Xiangya equation could not replace the Asian modified CKD-EPI equation in estimating glomerular filtration rate in Chinese patients with chronic kidney disease. Int Urol Nephrol. 2022;54(11):3025–31.
33 Soveri I, Berg UB, Björk J, Elinder CGG, Grubb A, Mejare I, et al. Measuring GFR: a systematic review. Am J Kidney Dis. 2014 Sep;64(3):411–24.
34 Delanaye P, Melsom T, Ebert N, Bäck SE, Mariat C, Cavalier E, et al. Iohexol plasma clearance for measuring glomerular filtration rate in clinical practice and research: a review. Part 2: why to measure glomerular filtration rate with iohexol? Clin Kidney J. 2016 Oct;9(5):700–4.
35 Xie D, Shi H, Xie J, Ding Y, Zhang W, Ni L, et al. A validation study on eGFR equations in Chinese patients with diabetic or non-diabetic CKD. Front Endocrinol. 2019;10:581.
36 Chen N, Shi H, Zhang L, Zuo L, Xie J, Xie D, et al. GFR estimation using a panel of filtration markers in shanghai and beijing. Kidney Med. 2020;2(2):172–80.