Cystatin C improves the diagnosis and stratification of chronic kidney disease, and the estimation of glomerular filtration rate in diabetes

V. Rigalleau a,*, M.-C. Beauvieux b, e, F. Le Moigne b, e, C. Lasseur c, e, P. Chauveau c, e, C. Raffaitin a, e, C. Perlemoine a, e, N. Barthe d, e, C. Combe c, e, H. Gin a, e

Nutrition-diabétologie, hôpital Haut-Lévêque, avenue de Magellan, 33600 Pessac, France
Biochimie, hôpital Haut-Lévêque, avenue de Magellan, 33600 Pessac, France
Néphrologie, hôpital Pellegrin, place Amélie-Raba-Léon, 33000 Bordeaux, France
Médecine nucléaire, hôpital Pellegrin, place Amélie-Raba-Léon, 33000 Bordeaux, France
Université de Bordeaux-II Victor-Segalen, 33000 Bordeaux, France

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Abstract

Aims. – Estimation of glomerular filtration rate (GFR) is recommended to diagnose and stratify chronic kidney disease (CKD). Can cystatin-C (cysC) assay improve the results in diabetic patients?

Methods. – In 124 diabetic patients with a wide range of GFR, as determined by 51Cr-EDTA clearance (i-GFR), we estimated ‘e-GFR’ by: the recommended Cockcroft–Gault (CG) formula and Modification of Diet in Renal Disease (MDRD) study equation; the new Mayo Clinic quadratic (MCQ) equation; the recently proposed composite estimation including both serum creatinine and cysC; and a simplified approach dividing the MDRD by cysC if less than 1.10 mg/L.

Results. – The highest diagnostic accuracy (receiver operating characteristic [ROC] curves) and the highest proportions of well-stratified patients were obtained by cysC and the MDRD which, however, underestimated i-GFR for patients without CKD (−17%, P < 0.001). The CG overestimated GFR in KDOQI stages 1 and 2, ignored stage 5 and was the least accurate. The MCQ equation overrepresented stage 2, overestimating GFR at this stage (+23%, P < 0.005). The composite estimation (54.7 ± 27.0 mL per minute 1.73 m2) correlated best with i-GFR (56.1 ± 35.3; r = 0.90, P < 0.001), and did not significantly differ from it across the entire population and within each Kidney Disease Outcome Quality Initiative (KDOQI) stage but was also biased (Bland–Altman procedure). Simply dividing the MDRD by cysC if less than 1.10 mg/L produced a comparable performance and eliminated the bias.

Conclusion. – The recommended creatinine-based estimations of GFR need to be improved. CysC assay helps in the diagnosis and stratification of CKD and leads to better estimates of GFR in diabetic patients without any substantial increase in complexity.

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Résumé

La cystatine C améliore le diagnostic et la stratification de l’atteinte rénale et l’estimation de la fonction rénale chez les patients diabétiques.

Objectif. – Il est nécessaire d’avoir une estimation le débit de filtration glomérulaire (DFG) pour porter le diagnostic et préciser le stade d’une maladie rénale chronique. Le dosage de cystatine C (CysC) facilite-t-il ce travail chez les patients diabétiques ?

Méthodes. – Chez 124 patients diabétiques présentant un large éventail de DFG mesuré par clairance du 51Cr-EDTA, nous avons estimé « DFGc » par : les formules recommandées Cockcroft et Gault (CG) et Modification of Diet in Renal Disease (MDRD) ; l’équation quadratique de la Mayo Clinic (MCQ) ; une estimation composite récemment proposée et incluant à la fois la créatininémie et CysC ; une approche simplifiée en divisant simplement le résultat de MDRD par CysC si inférieur à 1,10 mg/L.

Résultats. – Les meilleures efficacités diagnostiques (courbes ROC) et les stratifications les plus exactes ont été obtenues avec CysC et l’équation MDRD, mais cette dernière sous-estimait le DFG des patients indemnes d’atteinte rénale (−17%, P < 0.001). La formule CG surestimait le DFG

Abbreviations: AER, albumin excretion rate; CG, Cockcroft–Gault; CKD, chronic kidney disease; cysC, cystatin C; e-GFR and i-GFR, estimated and isotopic glomerular filtration rate; MCQ, Mayo Clinic quadratic equation.

* Corresponding author.
E-mail address: vincent.rigalleau@wanadoo.fr (V. Rigalleau).
1. Introduction

Diabetes is the primary cause of chronic kidney disease (CKD) and, since 2001, most of the patients requiring dialysis in the US have been diabetic [1]. The National Kidney Foundation (NKF) recommends stratification of CKD into stages 1 to 5 [2], based on glomerular filtration rate (GFR) as estimated by the Cockcroft–Gault formula (CG) [3] or the Modification of Diet in Renal Disease (MDRD) study equation [4]. The American Diabetes Association also recommends these equations to diagnose CKD in diabetic patients, based on their estimated GFR (e-GFR; threshold: 60 mL per minute per 1.73 m²) and albumin excretion rate (AER; threshold: 30 mg per 24 h) [5].

However, the GFR-predictive equations are far from perfect. Only 65% of the 2095 patients studied by Froissard et al. were correctly stratified by e-GFR [6]. Their validity may be even lower in diabetic patients due to the influence of body weight [7] and glucose control [8]. Previously, we have reported that only 60% of 200 diabetic subjects were correctly stratified by the MDRD or the more recent Mayo Clinic quadratic (MCQ) equations and was only 50% using the CG [10]. Because it is more accurate [11], not biased by body weight [7] and more precise when glucose control is poor [8], the MDRD appears to be preferable. Nevertheless, it underestimates normal-to-high GFR levels [12], so better results have been reported with the CG in recent onset type 1 [13] and type 2 [14] diabetes. Estimations may, therefore, be adequate for diabetic patients with versus without renal impairment [15], further emphasizing the importance of the initial diagnosis of CKD, which cannot be solely based on the AER because approximately 20% of diabetic patients present a low GFR without albuminuria [16].

Cystatin C (cysC) is a promising new marker of renal function [17]. CysC is produced at a constant rate by nucleated cells, is freely filtered and almost completely degraded, but not secreted, by proximal tubular cells; extrarenal factors that may modulate creatinine would therefore have less impact on cysC [18]. Numerous reports have highlighted its value in the detection of early renal impairment in diabetic subjects [18–20], making it a good candidate for making the initial diagnosis of CKD in diabetes. Of particular interest, Rule et al. recently proposed cysC thresholds for the stratification of CKD in the nondiabetic population and derived a composite GFR estimation based on both serum creatinine (sCr) and cysC, which was highly correlated with the results of 460 iohalumate-clearance determinations [21]. Can cysC improve the diagnosis and stratification of CKD in diabetic patients? Is the composite estimate a better reflection of their GFR, and can it be simplified?

In 124 diabetic patients, we determined GFR by 51Cr-EDTA clearance and compared the diagnostic accuracy (ROC curves) and stratification by sCr, cysC and the creatinine-based estimations (CG, MDRD, MCQ). We also performed regression analysis, the Bland–Altman procedure and accuracy analysis (mean absolute differences as percentage) to compare the creatinine-based estimations with the Rule et al. composite equation and a simplified GFR estimation based on the MDRD, corrected by dividing it by cysC in patients without CKD.

2. Subjects, materials and methods

2.1. Subjects

We recruited 124 adult diabetic patients attending our clinical unit (service de nutrition-diabétique, hôpital Haut-Lévêque, Pessac, France) for evaluation of their diabetes and nephropathy. The majority were men (n = 78) and had type 2 diabetes (n = 88), aged 62 ± 13 years (range: 19–83) with a 27.5 ± 4.6 kg/m² BMI (range: 15.6–40.7) and AER of 575 ± 864 mg per 24 h (range 5–4000). Of the patients with type 2 diabetes, 55% were treated with insulin. Arterial pressure was 144 ± 19 mmHg systolic and 81 ± 9 mmHg diastolic; 89% were being treated with antihypertensive drugs, with the majority (53%) requiring more than two different antihypertensive agents.

2.2. Analytical methods

sCr was determined by a multiparameter analyzer (Olympus AU 640, Olympus Optical, Tokyo, Japan), using the Jaffé method, with bichromatic measurements according to the manufacturer’s specifications; the analyzer was calibrated and controlled every day. The same procedure was followed through-
out the study. The results were obtained in micromole per liter and converted into milligram per deciliter to perform the predictive equations. Serum cysC (mg/L) was determined on a nephelometric analyzer (Behring Nephelometer 2, La Défense, Paris, France) using particle-enhanced immunonephelometry (N Latex Cystatin C, Dade Behring, Marburg, Germany). Clearance of the radionuclide marker was measured after intravenous injection of 51Cr-EDTA (Cis Industries, Gif/Yvette, France). All patients were studied in the morning at 9 a.m. after a light breakfast. After a single bolus of 100 μCi (3.7 MBq) of 51Cr-EDTA, a total of four venous blood samples were drawn at 75, 105, 135 and 165 minutes and urinary samples collected at 90, 120, 150 and 180 minutes, as previously described [22]. 51Cr-EDTA radioactivity was measured by a gamma counter (COBRA 2, model 05003, Packard Instruments, Meriden, CT).

2.3. Estimation of renal function

Single sCr and cysC measurements were performed the day before the isotope measurement of GFR (i-GFR) to calculate the: 1) creatinine-based formula: 1a) CG formula [3] as follows:

\[
CG = \frac{140 - \text{age (years)} \times \text{body weight (kg)} \times 0.85 \text{ (if female)}}{72 \times \text{sCr (mg/dL)}}
\]

As this equation was originally designed to estimate creatinine clearance expressed in milliliter per minute, the results were adjusted for body surface area, as calculated by Dubois’ formula [23]. For the following MDRD and MCQ equations, and composite estimations of GFR, the results are expressed as milliliter per minute per 1.73 m².

We used the simplified equation [4]:

1b) MDRD = \([186 \times \text{sCr (mg/dL)}]^{-1.154} \times \text{[age (years)]}^{-0.203} \times 0.742 \text{ (if female)} \times 1.210 \text{ (if African–American)},

1c) MCQ = \exp [1.911 + 5.249/\text{SCr (mg/dL)} - 2.114/\text{SCr (mg/dL)}^2 - 0.00686 \times \text{age (years)} - 0.205 \text{ (if female)}] [9];

2) composite e-GFR based on both sCr and cysC [21] where:

\[
\text{composite} = \frac{1}{[166.8 \times \text{(cysC)}^{1.30} \times [273 \times \text{(sCr)}]^{-1.22} \times \text{age}^{-0.299} \times 0.738 \text{ (if female)}]};
\]

3) simplified approach based on MDRD and cysC, where the MDRD was used in subjects with CKD if cysC greater or equal to 1.10 mg/L, and divided by cysC if less than 1.10 mg/L in those without CKD.

2.4. Stratification of CKD

According to the KDOQI guidelines of the NKF, CKD is stratified into stages 1 (GFR greater than or equal to 90 and AER greater than 30 mg per 24 h), 2 (GFR is 60–89 and AER greater than 30 mg per 24 h), 3 (GFR: 30–59), 4 (GFR: 15–29) and 5 (GFR less than 15). Those with a GFR greater than 60 mL per minute per 1.73 m² and AER less than 30 mg per 24 h were only considered to be ‘at increased risk’ due to diabetes. The cysC thresholds were less than or equal to 0.80 mg/L (stage 1), 0.80–1.09 (stage 2), 1.10–1.86 (stage 3), 1.87–3.17 (stage 4) and greater than 3.17 (stage 5), as reported by Rule et al. for native kidney disease using a similar assay [21].

2.5. Statistical analysis

The sensitivity and specificity of sCr, cysC and creatinine-based e-GFR by the CG, MDRD and MCQ equations in the diagnosis of moderate renal failure (GFR less than 60 mL per minute per 1.73 m²) were assessed from nonparametric receiver operating characteristic (ROC) curves, generated by plotting sensitivity versus one-specificity, giving the ideal test for a sensitivity equal to one and a specificity equal to one. Areas under the curve (AUC) were calculated and compared according to the procedure of Hanley and McNeil [24]. The proportions (%) of subjects correctly diagnosed as having (or not) CKD by sCr (thresholds: 120 and 150 μmol/L), cysC (threshold: 1.10 mg/L) and e-GFR by CG, MDRD and MCQ (threshold: 60 mL per minute per 1.73 m²) and those correctly stratified based on cysC and e-GFR were also compared. The results of the predictive equations (CG, MDRD, MCQ, composite and simplified approach with MDRD divided by cysC if cysC less than 1.10 mg/L) were compared with isotope-derived GFR by correlations, paired t-tests and the Bland–Altman procedure. The precision of the equations was assessed by the absolute differences between their results and those from isotope-measured GFR. The calculations were performed using SPSS software, version 10.0. Results are presented as means ± S.D. and P < 0.05 was considered significant.

3. Results

The GFR was 56.1 ± 35.3 mL per minute per 1.73 m² (range 8.5–164), sCr was 148 ± 79 μmol/L (range 64–492) and cysC was 1.56 ± 0.84 mg/L (range 0.49–5.48).

3.1. Diagnosis of moderate renal failure

The ROC curves are presented in Fig. 1a (sCr and cysC) and 1b (CG, MDRD, MCQ). The best AUC was with cysC (0.958, P < 0.05 versus sCr and CG), followed by the MCQ and MDRD (0.941 and 0.938, respectively, both not significant versus cysC, and P < 0.05 versus CG). The worst AUC was with the CG (0.866, P < 0.05 versus all others except sCr [0.904]). It is worth noting that the difference between the MDRD and sCr alone did not reach significance; therefore, estimating GFR by the recommended CG and MDRD had no clear advantages, whereas there were advantages using the cysC (P < 0.05 versus sCr) and MCQ (P = 0.05 versus sCr) equations.

A total of 76 patients had an i-GFR less than 60 mL per minute per 1.73 m². The percentages of correct diagnoses of CKD according to GFR less than 60, and non-CKD according to GFR greater than 60, were 89% with cysC (P < 0.05 versus all others except the MDRD), 88% with the MDRD (P < 0.05 versus all of the following except MCQ), 81% with the MCQ, 80% with sCr (threshold: 120 μmol/L), 77% with the CG and 71% with sCr (threshold: 150 μmol/L).
3.2. The consequences of diagnosing CKD by the MDRD equation versus cysC

CysC and the MDRD equation performed similarly (ROC curve analysis, rate of correct diagnoses) in the diagnosis of CKD, but the MDRD had a tendency to underestimate GFR (−17%, \( P < 0.001 \)) in patients without CKD (Table 1). On the other hand, a diagnosis of CKD using cysC greater than or equal to 1.10 mg/L did not underestimate normal GFR. In fact, it allowed an estimation of GFR by the composite formula, which performed similarly to the MDRD in patients with CKD, but with smaller underestimations in patients without CKD (−7%, \( P = 0.054 \)). More simply, dividing the MDRD by cysC eliminated any underestimation of GFR in patients without CKD.

3.3. Stratification of CKD

The overall proportions of correctly stratified patients were 72.6% with cysC, 66.9% with the MDRD, 62.9% with the MCQ and 54% with the CG (\( P < 0.05 \) versus all others except the MCQ). Table 2 shows the number of patients, with their estimated and measured GFRs, in each KDOQI stage. The CG overestimated GFR in stages 1 and 2 and ignored stage 5. The MDRD underestimated GFR in stages 1 and 2 and overrepresented stage 3. The MCQ overestimated GFR in stage 2 and 3 and overrepresented stage 2. The stratification by cysC levels led to a scatter effect that did not differ substantially from the distribution by i-GFR. The composite equation tended to underestimate GFR in stages 1 (\( P = 0.07 \)) and 2, whereas the simplified approach did not.

3.4. Estimates of renal function

The mean creatinine-based e-GFR significantly differed from i-GFR, being overestimated by the CG and MCQ and underestimated by the MDRD, whereas the differences with cysC,

<p>| Table 1 |
| Glomerular filtration rates (GFR) and estimations (e-GFR) in the patients diagnosed with chronic kidney disease (CKD) or not, based on MDRD estimations and cystatin-C (cysC) levels |</p>
<table>
<thead>
<tr>
<th>MDRD-based diagnosis</th>
<th>CKD</th>
<th>Non-CKD</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
<td>87</td>
<td>37</td>
</tr>
<tr>
<td>i-GFR (mL/min/1.73 m(^2))</td>
<td>38.1 ± 18.5</td>
<td>98.3 ± 28.9</td>
</tr>
<tr>
<td>MDRD</td>
<td>38.5 ± 14.0</td>
<td>81.7 ± 14.6</td>
</tr>
<tr>
<td>( r )</td>
<td>0.77</td>
<td>0.52</td>
</tr>
<tr>
<td>( P ) vs i-GFR</td>
<td>NS</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>CysC-based diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>( n )</td>
</tr>
<tr>
<td>i-GFR</td>
</tr>
<tr>
<td>MDRD</td>
</tr>
<tr>
<td>( r )</td>
</tr>
<tr>
<td>( P ) vs i-GFR</td>
</tr>
<tr>
<td>Composite</td>
</tr>
<tr>
<td>( r )</td>
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<tr>
<td>( P ) vs i-GFR</td>
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<tr>
<th>Simplified approach</th>
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<tbody>
<tr>
<td>MDRD</td>
</tr>
<tr>
<td>e-GFR</td>
</tr>
<tr>
<td>( r )</td>
</tr>
<tr>
<td>( P ) vs i-GFR</td>
</tr>
</tbody>
</table>

MDRD, Modification of Diet in Renal Disease study; i-GFR, isotope measurement of GFR; NS, not significant.
including estimates, were not statistically significant. Its accuracy was similar to that with MDRD and cysC including e-GFR and all were more precise than the MCQ equation (P < 0.05) and CG (P < 0.001). However, the MCQ was more accurate than the CG (P < 0.005). The MDRD, composite and, to a lesser extent, the MCQ were all biased, according to the Bland–Altman procedure, and underestimated a high GFR. Interestingly, dividing the MDRD by cysC if less than 1.10 mg/L according to the simplified approach corrected such a bias. (Table 3 and Fig. 2)

Fig. 2 shows the measured GFR according to their estimations for the 106 diabetic patients with CKD, categorized by their predicted KDOQI stage. The recommended estimations failed when GFR was greater than 60, with CG leading to overestimation and MDRD to underestimation. The MCQ corrected this only for stage 1 CKD, but overestimated the GFR in stages 2 and 3, whereas the application of cysC prevented this tendency.

For the 18 patients without CKD (AER less than 30 mg per 24 h and i-GFR greater than or equal to 60 mL per minute per 1.73 m²), the actual i-GFR (88.4 ± 20.2 mL per minute per 1.73 m²) did not significantly differ from its estimates (CG: 88.3 ± 31.2, r = 0.58; MCQ: 90.8 ± 21.4, r = 0.66; com-
None of the strategies that we tested provided a better estimation than the MDRD equation in renal-insufficient (GFR less than 60 mL per minute per 1.73 m²) diabetic patients. Yet, the MDRD underestimates normal-to-high GFRs, as already reported in nondiabetic [6,27,28] and diabetic [13,14] populations. This is of particular concern in diabetic nephropathy, where the initial stages involve glomerular hyperfiltration [13,14,29]. Because of these important initial stages, it is essential to correctly estimate GFRs greater than 60 mL per minute per 1.73 m² in diabetic patients, as the high-GFR underestimation leads to later underestimation of GFR decline, rendering using the MDRD for monitoring kidney function questionable in diabetes [29,30]. This bias may explain several unexpected results from epidemiological studies using the MDRD in nonrenal-insufficient subjects: two-fold higher rates of CKD in diabetic women [31]; better life expectancy in older aged patients with mild renal failure [32]; and diverging correlations between renal function and cardiovascular risk factors [33]. For these reasons, the use of the MDRD should be reserved for renal-insufficient patients, or its bias needs to be corrected when applied to other conditions.

The MCQ equation was recently derived from a population that included kidney donors to reduce such a bias [9]. Although less accurate than the MDRD, it allows a more homogeneous stratification [10]. In contrast to the CG and MDRD, we found that using the MCQ to diagnose CKD was more accurate than basing the diagnosis solely on an sCr greater than 120 μmol/L. The GFR bias, however, persisted, with a deleterious influence for CKD stages 2 and 3. Nevertheless, the lesser bias of the MCQ should be an advantage in epidemiological studies including subjects with normal renal function, and for the follow-up of patients with declining renal function, but further research is probably necessary to determine whether these advantages are sufficient to replace the MDRD by the MCQ.

Our study confirms the value of cysC, which performed the best in the diagnosis and stratification of CKD in our study population. However, its differences with the MDRD did not reach statistical significance for these parameters. One practical advantage is that basing the diagnosis of CKD on cysC avoids the erroneous estimation of GFR in diabetic patients without CKD that tends to result with the MDRD. In day-to-day clinical practice, such patients represent the vast majority of the diabetic population: 95% of 6247 patients studied by Middleton et al. had sCr less than 150 μmol/L, and 27.5% had a MDRD less than 60 mL per minute per 1.73 m², apparently overestimating the true proportion of cases of CKD [31]. In addition to the scientific uncertainty, falsely labelling diabetic patients as renal-insufficient may have medical (use of metformin), emotional and financial consequences. The cost of one cysC determination is now approximately 10 €. The second advantage is that cysC is better at estimating GFR. Some formulas based on cysC alone have already been proposed for type 1 [34] and type 2 [35] diabetic patients, although their advantage over the MDRD was not evident in those studies. Our regression analysis gives an explanation for those disappointing results: the inclusion of demographic parameters such as age and gender markedly improved the correlation between one per sCr and GFR and this

4. Discussion

Despite being recommended, simple and widely used, the CG formula is not an ideal tool for the diagnosis and stratification of CKD in diabetes. More of our patients were correctly diagnosed as CKD on the simple basis of sCr greater than 120 μmol/L, than by calculating an e-GFR less than 60 mL per minute per 1.73 m² with the CG and almost half of our patients were wrongly KDOQI-stratified by the formula. Its correlation with i-GFR and its accuracy were also poor. An important explanation for this poor performance is that the CG estimates GFR as proportional to body weight: omitting weight from the calculation improved its correlation to GFR [15]. This bias is now increasing as the mean BMI of the patients undergoing dialysis is increasing twice as fast as the BMI in the general US population [25] and a high BMI appears to be an important risk factor for end-stage renal disease [26]. For these reasons, the CG formula should be abandoned, or at least corrected, in the future.

Fig. 2. Isotope measurement of GFR as a function of e-GFR in the 106 diabetic patients with chronic kidney disease, categorized by their Kidney Disease Outcomes Quality Initiative (KDOQI) stratification.

<table>
<thead>
<tr>
<th>e-GFR (mL/min/1.73m²)</th>
<th>Cockcroft &amp; Gault</th>
<th>MDRD</th>
<th>Mayo clinic quadratic</th>
<th>Composite</th>
<th>Simplified</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 60</td>
<td>82.6 ± 16.3, r = 0.67</td>
<td>MDRD/cysC: 91.6 ± 26.9, r = 0.67</td>
<td>120 &lt; GFR ≤ 180</td>
<td>120 &lt; GFR ≤ 180</td>
<td>120 &lt; GFR ≤ 180</td>
</tr>
<tr>
<td>&gt; 90</td>
<td>16.6, r = 0.60, P &lt; 0.001</td>
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improvement was less apparent with cysC presumably because it does not depend on body composition [36]. For this reason, we chose to test the composite estimation proposed by Rule et al. [21], which includes both sCr and cysC. The results did not differ from the i-GFR, unlike those seen with the CG, MDRD and MCQ, and also had the highest correlation coefficient and the best precision. No significant difference between the composite estimation and the i-GFR was detected for each KDOQI stage (Table 2), but this calculation requires a computer and does not resolve the problem of the GFR-related biases, as shown by the Bland–Altman procedure.

Our simplified approach can be performed in day-to-day clinical practice to:

- determine sCr and cysC;
- diagnose CKD if cysC greater or equal to 1.10 mg/L;
- estimate GFR by the MDRD (as recommended) in patients with CKD, as nothing is better in such patients;
- estimate GFR by MDRD/cysC in other patients (without CKD).

This approach also corrected the MDRD bias, which we consider an important finding: a biased estimation of GFR precludes an accurate follow-up of GFR changes. Recent reports have also shown the value of cysC for GFR follow-up [37]. The main limitation of our study was that dividing the MDRD estimation by cysC if less than 1.10 mg/L needs to be validated by other groups and, if possible, with even better results.

Conflicts of interest

The authors declare no conflicts of interest.

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