Can modifications of the MDRD formula improve the estimation of glomerular filtration rate in renal allograft recipients?

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Abstract

Background. Two modifications of the MDRD equation [the Mayo Clinic (MC) equation and Rule’s refitted (RR) MDRD formula] were proposed to overcome disadvantages of the original MDRD formula to calculate glomerular filtration rate (GFR). Additionally, a correction factor for the original MDRD formula has been introduced to adapt this formula to creatinine values measured by the isotope-dilution mass spectrometry (IDMS) method. Although precise determination of GFR is of central importance in renal transplant recipients, these equations have not been tested in these patients so far.

Methods. Considering the impact of different creatinine calibrations, we analysed the MC equation and the RR-MDRD formula in comparison with the old as well as the re-expressed (IDMS traceable) MDRD equation and the Cockcroft–Gault (C–G) formula in 126 consecutive patients after kidney transplantation with respect to correlation, bias, precision, accuracy and ROC analysis. GFR was determined as technetium-diethylenetriamine pentaacetic acid (⁹⁹mTc-DTPA-clearance).

Results. After adjustment to IDMS creatinine determination, the performance of the re-expressed MDRD formula improved considerably in comparison to the original MDRD equation. In comparison with the re-expressed MDRD formula bias of the MC formula and the RR-MDRD formula were significantly smaller (2.31 and −0.35 vs. 3.82 ml/min/1.73m²). However, precision and correlation of these formulae did not differ significantly from one another, but all equations showed a higher precision than the C–G formula (P ≤ 0.006 each). The accuracies within 30% of true GFR of the MC (79.4%) and the RR-MDRD equation (84.9%) were significantly higher than those of the re-expressed MDRD formula (72.2%; P < 0.03).

Conclusion. In comparison to the original and the re-expressed MDRD formula, calculation of GFR by the MC equation and the RR-MDRD formula led to improved diagnostic performance in renal transplant recipients after adjustment of creatinine. In quotidian work both formulae can be applied to these patients. Nonetheless, to determine GFR exactly, gold standard techniques are mandatory.

Keywords: accuracy; bias; DTPA-clearance; glomerular filtration rate; IDMS; Mayo Clinic equation

Introduction

The commonly recommended MDRD (Modification of Diet in Renal Disease) formula to estimate glomerular filtration rate (GFR) has been validated in patients with different renal diseases. However, in patients after kidney transplantation, its diagnostic performance has been shown to deteriorate [1]. Thus, a recommendable GFR equation is still lacking.

Recently, Rule et al. [2] suggested two modified MDRD equations to overcome some of the disadvantages of the original MDRD formula. Their first formula is also known as the new ‘Mayo Clinic Equation’ and has been used in several recent studies [3,4]. In contrast to the MDRD study cohort which included only patients with diminished renal function (GFR < 60 ml/min), the study of Rule et al. [2] comprised 580 healthy persons and 320 patients with chronic kidney diseases. Covering the whole range of GFR thus the Mayo Clinic (MC) equation potentially could serve as a tool to identify patients with renal insufficiency.

The second formula was proposed to optimize the MDRD formula in patients with known renal disease. This modification was termed as the Rule’s refitted
MDRD formula (RR-MDRD) [2]. This RR-MDRD formula and the MC equation are based on creatinine values which were determined at the Mayo Clinic Laboratory.

Interestingly, in the study of Rule et al. [2] 31% (n = 99) of the patients with chronic kidney disease were kidney transplant recipients. Thus, it is of considerable interest whether these equations are suitable for GFR determination in renal transplant recipients too.

Based on improved knowledge regarding the impact of creatinine calibration on GFR estimation with creatinine-based formulae, Levey and co-workers proposed a variant of the MDRD formula which is traceable to the gold standard of creatinine determination (isotope-dilution mass spectrometry, IDMS) [5]. Since no data are available for patients after kidney transplantation, the IDMS traceable (re-expressed) MDRD equation was included in our analysis and compared with the Cockcroft–Gault (C–G) formula, the original MDRD, the MC and the RR-MDRD equation with the aim to identify the best performing equation for renal transplanted patients.

Subjects and methods

In 126 consecutive patients (53 female, 73 male; 96.8% Caucasian) attending our outpatient department, GFR measurements were prospectively performed. True GFR was determined as technetium-dithylenetriamine pentaacetic acid (99mTc-DTPA) clearance with a single injection technique based on the method proposed by Russell et al. [6]. Lack of increase or decrease of >15% of creatinine within 2 weeks before and after the investigation was considered as an inclusion criterion. The study was approved by the local Ethics Committee and performed in accordance with the ethical guidelines of the revised Helsinki Declaration of 1996. Written informed consent was obtained from each patient.

Average patient age was 49.0 (46.6–51.3; range: 19–72) years and the time frame of investigation was 74.1 (61.3–86.9; range 3–278) months after transplantation. Thirty-six measurements were performed within 12 months after RTx, 56 between 1 and 10 years and 34 more than 10 years after RTx.

Immunosuppression was based on a calcineurin inhibitor regimen in 120 patients (73 cyclosporin A, 47 tacrolimus) and on sirolimus in six patients. Virtually all patients (98.4%) were treated with corticosteroids and 64 patients additionally received mycophenolate-mofetil (MMF, n = 59) or azathioprine (n = 5).

Creatinine was determined on a Dimension RxLTM clinical chemistry analyser (Dade Behring, Marburg, Germany) with an assay based on a modification of the kinetic Jaffé reaction [7]. The intra-assay coefficient of variation (CV) was 0.03, while the inter-assay CV was 0.05. The assay was adjusted for calibration with the IDMS method. The calibration equation was:

$$\text{creatinine}_{\text{IDMS}} = \text{creatinine}_{\text{Dade}} + 0.0399/1.009.$$  

This formula was used to counteract a small negative bias of 0.93% (0.013 mg/dl) which was found with the Dade Behring assay.

The GFR was calculated simultaneously on the basis of the following formulae:

$$\text{MDRD formula} = 186 \times [\text{serum \, creatinine} \, (\text{mg/dl})]^{-1.154 \times [\text{age}]^{-0.203} \times [0.742 \times [\text{patient is female}] \times [1.21 \, \text{if patient is African-American}]}.$$  

$$\text{C-G formula} = \text{[140-\text{age (years)} \times \text{weight (kg)/72} \times \text{serum creatinine} \, (\text{mg/dl}) \times (0.85 \, \text{if patient is female}) \times (0.767 \, \text{if patient is female}] \times [1.21 \, \text{if patient is African-American}]}.$$  

Creatinine values were used as IDMS calibrated data and as values converted to the Cleveland Clinical Laboratory using an equation proposed by A.S. Levey to convert the IDMS adapted values to the values of the Cleveland Clinical Laboratory (IDMS calibrated creatinine = 0.95 x original MDRD study creatinine) [18]. Furthermore, an additional increase in creatinine by 0.23 mg/dl to each value was calculated to convert the data of the Beckman modified kinetic Jaffé reaction of the Cleveland Clinical Laboratory to the uncompensated Jaffé reaction of the Mayo Clinic Laboratory as suggested by Rule et al. [10]. Consequently, the equation we used for conversion of creatinine from IDMS to the Mayo Clinic Laboratory in our study was the following: creatinineMayo Clinic = (creatinineIDMS/0.95 mg/dl) + 0.23 mg/dl.

Statistics

Diagnostic performance was determined by calculation of linear correlation, bias (mean difference from true GFR), precision (SD of bias) [11] and accuracy. Accuracy was measured as the proportion of GFR estimates within 30% and 60% deviation of the true GFR [12]. Furthermore, a second graphical analysis according to Bland and Altman [13] was used to assess accuracy. F-tests were performed for comparison of the SD of the mean difference and McNemar’s test to compare the degree of accuracy.

To compare diagnostic sensitivity and specificity of the different formulae a receiver operating characteristic (ROC) analysis was performed at several GFR levels (30 and 60 ml/min/1.73m2). Data are given as mean and 95% confidence intervals unless indicated otherwise. P-values <0.05 were considered significant. Bland and Altman plots and ROC analysis were performed with Medcalc® Software, Mariakerke, Belgium.

Results

Mean GFR was 39.4 (36.7–42.2) ml/min/1.73m2 in our cohort. The results of the different GFR estimates are given in Table 1. The use of the re-expressed MDRD formula resulted in a significant reduction of bias (8.19 vs 3.8 ml/min/1.73 m2, P < 0.0001). Whereas precision and accuracy within 50% of true GFR were also
improved but did not reach significance, the accuracy within 30% showed a significant improvement compared with the original MDRD formula ($P=0.004$).

When IDMS calibrated creatinine values were applied to the MC formula a pronounced overestimation of GFR occurred (mean difference: 16.4 ml/min/1.73m²). Consequently, precision (15.9 ml/min/1.73m²) and accuracy (50%: 59.5%) were poor. However, after conversion of the creatinine values to the Mayo Clinic Laboratory, bias, precision and accuracy improved dramatically. Similar results were found for the RR-MDRD formula. Thus, the following comparison is based on the results of the re-expressed MDRD equation and the C–G formula on the one hand (using IDMS creatinine) and on the MC and the RR-MDRD formula on the other hand (using creatinine values converted to the Mayo Clinic Laboratory).

The estimates of the re-expressed MDRD and the C–G formula differed significantly from true GFR ($P<0.0001$). However, to a lesser extent, the MC formula was also found to overestimate true GFR significantly ($P=0.012$). In contrast, the RR-MDRD equation did not differ from true GFR. Consequently, all formulae differed significantly from one another.

The correlation coefficients of the MC, the RR-MDRD and the re-expressed MDRD equations with the GFR were comparable (0.84, 0.83 and 0.82, respectively). However, correlation coefficients of the C–G equation (0.73) differed significantly from all other formulae ($P<0.05$ each).

Although the bias of the re-expressed MDRD was significantly lower than the bias of the C–G equation ($P<0.0001$), it was significantly higher than the biases of the MC equation and the RR-MDRD formula. In contrast, bias of the MC equation was significantly larger than for the RR-MDRD formula ($P<0.0001$). When compared with the other equations, the bias of the C–G equation was poorest ($P<0.0001$).

The calculated precisions of the MC, the RR-MDRD, the re-expressed MDRD formula and the C–G equation were 10.1, 9.1, 10.2 and 12.7 ml/min/1.73m², indicating best precision for the RR-MDRD formula. However, the precision of the MC, the RR-MDRD and the re-expressed MDRD formula did not differ significantly from one another. Nevertheless, precision of the re-expressed MDRD was statistically significant and better than the precision of the C–G formula ($P=0.006$; $F$-statistics 1.5705). Similarly, the MC formula and the RR-MDRD equation showed a better precision than the C–G formula ($P<0.006$; $F$-statistics 1.574 and $P<0.0001$; $F$-statistics 1.9453).

The overall accuracies within 50% of true GFR of the MC as well as the RR- and the re-expressed MDRD formula were significantly higher than the accuracy of the C–G formula ($P<0.0001$, Table 1). Yet, in this respect, none of the equations were found to be significantly better than the other ones.

Accuracy within 30% of the true GFR was significantly higher for the RR-MDRD formula than for the re-expressed MDRD formula ($P=0.0008$).
Likewise, the 30% accuracy of the MC equation was superior to that of the re-expressed MDRD formula \( (P = 0.027) \). The RR-MDRD and the MC formula did not show statistical differences in the accuracy within 30% of true GFR. Nevertheless, the re-expressed MDRD formula as well as the MC equation showed a significantly higher accuracy than the C–G formula \( (P < 0.0001 \text{ each}) \).

Furthermore, to determine the accuracy of the estimates Bland and Altman plots were used. This technique was applied to display the agreement between estimated and measured GFR values by calculating the span between \(-1.96 \text{ SD}\) and \(+1.96 \text{ SD}\) of the mean difference (Figure 1A–D). The smallest span was observed for the RR-MDRD formula (35.9 ml/ min/1.73 m²), which was somewhat lower than the values of the MC formula and the re-expressed MDRD formula (both 39.9 ml/min/1.73m²). The corresponding value of the C–G formula was considerably higher (50.0 ml/min/1.73m²).

Diagnostic sensitivity and specificity of each formula was determined by ROC analysis. At cut off levels of 30 and 60 ml/min/1.73 m², the re-expressed and the RR-MDRD formula and the GFR are plotted in figure 1A, Rule’s refitted MDRD and GFR in figure 1B, MC formula and GFR in figure 1C and C&G and GFR in figure 1D.

Highest sensitivity (85.3%) was calculated for the MC formula to diagnose a GFR <60 ml/min/1.73m². Whereas, highest specificity (94.1%) was shown for the re-expressed and RR-MDRD formulae. Highest sensitivity (100%) but lowest specificity (80.7%) to detect a GFR <30 ml/min/1.73m² was found for the C–G formula. In contrast, highest specificity (89.8%) but lowest sensitivity (92.1%) was calculated for the MC formula at a decision point of GFR <30 ml/min/1.73m². However, these differences did not reach statistical significance.

**Discussion**

This analysis was undertaken to answer several questions regarding the estimation of GFR in renal allograft recipients. First, the MC formula, which was
proposed to calculate GFR over the whole range of renal function, was tested in a kidney transplanted cohort with predominantly reduced renal function. Second, the RR-MDRD formula proposed to estimate GFR in patients with known renal disease was evaluated in renal allograft recipients.

Third, Levey et al. [5] published the re-expressed MDRD formula to allow comparison between the method of creatinine determination of the Cleveland Clinical Laboratory and the IDMS method recently. To our knowledge, this is the first validation of the re-expressed MDRD formula in a kidney transplanted cohort. The comparison of the original and the re-expressed MDRD formula showed a significant improvement with respect to bias and accuracy. It seems reasonable to believe that the confusing results regarding over- and underestimation of GFR when using the MDRD formula during recent years may be resolved after creatinine calibration to IDMS creatinine as suggested in an excellent review published recently by Stevens et al. [14]. Thus, the re-expressed MDRD now provides a slight overestimation of true GFR (+3.8 ml/min/1.73 m²) but this should be tolerable to estimate GFR of renal transplant recipients in quotidian work. Nevertheless, precision is still unsatisfactory and accuracy is far from an ideal GFR equation, which should reach 90% within 10% accuracy of true GFR as suggested by the NKF [12].

The performance of the C–G equation was disappointing. It should be pointed out that the C–G formula was originally used to predict creatinine clearance but not GFR. Tubular secretion of creatinine results in an overestimation of GFR and may therefore hamper the use of the C–G equation in patients after kidney transplantation.

In contrast to the MDRD formula, which is based on a cohort of patients with known renal disease and reduced renal function, the MC formula was developed by including potential healthy kidney donors and patients with chronic kidney disease. Thus, the MC formula could in fact be the ideal formula to estimate GFR in a patient where renal disease is unknown.

However, in a series of 162 potential kidney donors and 882 patients with chronic kidney disease stages 1 and 2, Froissart et al. [15] analysed the MC equation and found an overestimation of true GFR in both cohorts. Moreover, Cirillo et al. [3] found a high and systematic overestimation, especially in patients with GFR levels >60 ml/min/1.73 m². Similar results were found in our study when creatinine determination was based on IDMS standard. After conversion to the Cleveland Clinical Laboratory, the performance of the GFR estimation improved but underwent a further enhancement after conversation of the creatinine values to the Mayo Clinic Laboratory. Following that step, the diagnostic performance of the MC formula was in part superior or at least similar to the re-expressed MDRD formula. Thus, the studies mentioned above may be considerably biased by differences in methods of creatinine determination. Although the MC formula is lacking adequate evaluation in patients with unknown chronic kidney disease, the results of the ROC analysis suggest that the MC equation may be used as a screening parameter. In addition, here, we demonstrate that the MC formula can reliably be applied in patients after kidney transplantation.

Rule et al. attempted to improve the original MDRD study equation for patients with chronic kidney diseases and termed the resulting equation ‘refitted MDRD’. A further evaluation of this equation has not been undertaken so far.

Our analysis shows—after stepwise creatinine conversion—that the RR-MDRD provides best performance with respect to bias, precision and accuracy. Therefore, the RR-MDRD formula can be used as an alternative approach to the MDRD equation in patients after kidney transplantation.

However, some drawbacks of our study ought to be mentioned. First, conversion of our creatinine values to the Mayo clinic laboratory method has not been performed directly. However, to our knowledge, no conversion formula of the Mayo Clinic Laboratory to the IDMS creatinine had been published at the time when the study of Rule et al. took place. Thus, we converted the creatinine of the MDRD laboratory to the Mayo Clinic Laboratory by adding 0.23 mg/dl as proposed by Rule in previous studies, due to the use of the uncompensated Jaffé method [10,16]. However, it could be argued that this addition affects low
creatinine values more than higher creatinine values. Nevertheless, the differences between creatinine determination by different methods are mainly based on susceptibility to non-creatinine chromogens. In this regard, it is known that measurement of lower creatinine values is more likely to be affected by non-creatinine chromogens than that of higher values [17]. Thus, our approach may be adequate. Even so, a confirmed conversion factor between the IDMS and the Mayo Clinic Laboratory is mandatory, assumed that GFR estimations as proposed by Rule and coworkers will become widely used.

In summary, the calibration of creatinine to the IDMS method significantly enhances the performance of the MDRD formula. Nonetheless, re-expressed MDRD was outperformed by the MC and the RR-MDRD formula. Thus, both may be reliably used in a transplant cohort. However, none of these formulae can replace gold standard techniques to exactly determine GFR.

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