USE OF SELECTED PREDICTION EQUATIONS (CG, MDRD4, CKD-EPI) IN IMPROVING GLOMERULAR FILTRATION RATE ASSESSMENT IN CLINICAL PRACTICE IN SLOVAKIA

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SUMMARY

Our study aimed to establish the best prediction equation for different age ranges in estimating Glomerular Filtration Rate (GFR) in clinical practice in Slovakia. The GFR by 24-hour creatinine clearance (Ccr) and the estimated GFR (eGFR) using the Cockcroft–Gault (CG), the four-variable Modification of Diet in Renal Disease (MDRD4) and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations were obtained in adults aged 30–80 (n = 433, 10-years intervals). The correlation between these prediction equations and Ccr was evaluated. Errors in prediction equations were detected by moving average and by comparisons of the formulas for GFR < 1.5 ml/s and > 1.5 ml/s. The best correlations were established between Ccr and MDRD4 for women (r = 0.7790) and men (r = 0.8009), and between Ccr and CKD-EPI for women (r = 0.7780) and men (r = 0.8002) in the 60–69 age range. High correlation was also established between Ccr and CG (r = 0.8655) and MDRD4 (r = 0.8713) for men in the 40–49 age range. With the exception of the 30–40 age range, a low prediction error was observed for each age range in both genders when GFR was < 1.5 ml/s. We recommend utilization of the MDRD4 and CG equations for men (40–49 years) and MDRD4 and CKD-EPI for women and men (60–69 years), as preferred substitutes for Ccr.

Key words: glomerular filtration rate, Cockroft–Gault equation, MDRD 4 equation, CKD-EPI equation, creatinine clearance

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INTRODUCTION

According to statistics from the US and others countries, the number of patients diagnosed with kidney disease doubled between 2003 and 2010, and the latest Slovak Nephrological Society statistics recorded a rising trend in the incidence of chronic kidney disease. The serious consequences emanating from this condition significantly affect patients' quality of life and ultimately their mortality rate. Although glomerular filtration rate (GFR) is considered the best overall index of kidney function in health and disease, precise GFR measurement is invasive, time-consuming, expensive and technically difficult (1–4). GFR is estimated by clearance of the inulin, iohexol and ethylenediaminetetraacetic acid (EDTA) exogenous markers and by endogenous urea and creatine (5–7). The most commonly used method to evaluate GFR is by creatinine clearance (Ccr), where its rate is established by the amount of creatine completely cleared by the kidneys in 1 minute. Creatinine is a product of muscle creatine metabolism, and since it is filtered by the kidneys and not reabsorbed by renal tubules, it is ideal for determining GFR (8).

Serum creatinine concentration is a reflection of the glomerular filtration rate, and since its measurement is easily obtained and relatively inexpensive, this determination is often used as a screening measure of renal function and Ccr is commonly used in clinical medicine to assess GFR (9). Creatinine production from muscle creatine decreases with increasing age and loss of muscle mass, thus, serum creatinine can be deceptively low despite significant reduction in Ccr. Hence Ccr is considered a better indicator of renal function than the serum creatinine level (10). Problems in measuring Ccr primarily emanate from 24 hour urine collection, which can initiate gross errors in Ccr determination due to subjective or objective mechanisms. Herein, prediction equations determining Ccr and GFR based on the determination of serum concentrations of creatinine (Scr) and extrarenal factors including age, weight, gender, and ethnicity, are utilized to resolve problems connected with unreliable urine collection (11). Cockcroft and Gault (CG) and the Modification of Diet in Renal Disease equation (MDRD) developed in a multi-centre American study present the most widely used prediction equations for determination of Ccr and GFR (12, 13).

In addition, the new Chronic Kidney disease Epidemiology Collaboration equation (CKD-EPI) has been developed for the GFR estimation by the National Institutes of Diabetes, Digestive and Kidney Disease (3). This study focuses on the comparison of Ccr and prediction equations to assess the relative competence of the CG, MDRD4 and CKD-EPI formulas for differently aged patients in Slovakia, where the use of eGFR is not a common practice.
MATERIALS AND METHODS

Cohort Analysis and Sample Collection
The Cohort comprised 433 adults; 151 men (35%) and 282 women (65%) from the Haemodialysis Centre of the Partizánske Hospital in Slovakia. Participants were divided into the following age groups: 30–39 years (19 women and 10 men), 40–49 years (27 women and 20 men), 50–59 years (65 women and 40 men), 60–69 years (77 women and 45 men), and 70–79 years (94 women and 36 men). Patients with hypertension, diabetes and diagnosed renal disease were excluded from this study.

Serum samples from 24-hour urine collection by participants were evaluated by medical staff under specific laboratory conditions.

Creatinine Clearance ($C_{cr}$)
Creatinine measurement in urine and blood samples was detected by a non-enzymatic method using CREAT KIN 100 (Pliva-Lachema a.s., Czech republic). $C_{cr}$ determination was provided by the Selectra XL fully automatic analyzer, and GFR based on plasma creatinine concentration was calculated using the following three formulas:

1. The CG formula:
   $$\text{GFR}_{\text{CG}} = \frac{[140 - \text{age in years}] \times \text{weight in kg}/[72 \times \text{Scr in µmol/l}]}{0.85 \text{ for women}}$$

2. The MDRD4 formula:
   $$\text{GFR}_{\text{MDRD4}} = 175 \times \frac{\text{Scr in µmol/l}}{1.154 \times \text{age in years}^{-0.203} \times 1.212} \text{ for black people}$$
   $$\text{GFR}_{\text{MDRD4}} = 0.742 \text{ for women}$$

3. The CKD-EPI formula:
   $$\text{GFR}_{\text{CKD-EPI}} = 141 \times \min(\text{Scr in µmol/l}, 1)^{1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ for black people}$$
   $$\text{GFR}_{\text{CKD-EPI}} = 0.7 \text{ for women}$$
   $$\text{GFR}_{\text{CKD-EPI}} = 0.9 \text{ for men}$$
   $$\text{Age} = \min(\text{Scr in µmol/l}, 1)^{1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ for black people}$$
   $$\text{Age} = 0.329 \text{ for women}$$
   $$\text{Age} = 0.411 \text{ for men}$$

Estimation of GFR was established by the NKF’s Calculators for Health Care Professionals using the MDRD4, CKD-EPI and CG prediction formulae.

Statistical Analysis
Initial correlation was established between prediction equations CG, MDRD4, CKD-EPI and $C_{cr}$.

Statistical significance between prediction equations and $C_{cr}$ was evaluated by Pearson’s Correlation Coefficient, where correlations were divided into the following three intervals: low degree of correlation ($r=0–0.25$), moderate degree of correlation ($r=0.25–0.75$) and high degree of correlation ($r=0.75–1.0$). Standard deviations between prediction equations CG, MDRD4, CKD-EPI and $C_{cr}$ were computed, and the values for the standard deviations of equations overlying with moving average were extrapolated in charts.

For the purpose of this study, the cohort was divided into two groups: GFR < 1.5 ml/s (patients with chronic kidney disease by NKF) and GFR > 1.5 ml/s (patient with normal or increased GFR). The studied groups were tested for statistical consistency of errors in the CG, MDRD4 a CKD-EPI prediction equations.

Verification of the results between studied groups was evaluated by average and S.E.M. at three significance levels; *$p \leq 0.05$ (5%), **$p \leq 0.01$ (1%) and ***$p \leq 0.001$ (0.1%), and analyses were computed using Statistica 7 (Statsoft, Czech Republic).

RESULTS

Diuresis Assessment
Serum creatinine values were available from 457 individuals. In order to eliminate inaccuracies in 24-h urine collection, subjects with urine volumes < 0.6 l and > 5 l, and urinary creatinine < 4 or > 25 mmol/day were excluded. Characteristics of the cohort are detailed in the Methods section. The diuretic examination results did not provide a smooth distribution of values, with some sharp limits noted (Fig. 1). The commonly required measurements to the nearest 10 ml were present only in small numbers; with the most common diuresis reported to the nearest litre, half litre or 100 ml. Surprisingly, diuresis between 1,000–2,000 ml for women and 1,500–2,500 ml for men was detected in 50% of examined patients. This effect was most likely due to patient error; delivering estimates rather than accurate measurements. Such complications affected the accuracy of creatinine clearance in a classical manner.

![Fig. 1 Diuresis of investigated patients; women and men](image)
Correlation Analysis of Prediction Equations with $C_{cr}$, Moving Average of Errors of Prediction Equations and Comparison of Prediction Equation in the Interval GFR $>1.5$ and $<GFR$

The results of statistical analysis in 10-year age-group intervals are given in Fig. 2.

The 30–39 year age group

Women

Correlation analysis of prediction equations with $C_{cr}$ gave a low degree of correlation between CG and $C_{cr}$ ($r=0.1050$), while the MDRD4 formula ($r=0.3390$) and CKD–EPI formula ($r=0.3420$) delivered a moderate degree of correlation. The moving average suggested varying tendency of prediction equation error. Although it increased when $C_{cr}$ was above 2.1 ml/s; no significant differences between prediction equations and $C_{cr}$ were identified when $C_{cr}$ was above or below 1.5 ml/s.

Men

A moderate degree of correlation was established between all prediction equations and $C_{cr}$, with $r=0.6233$ for MDRD4, $r=0.6142$ for CKD–EPI and $r=0.3512$ for CG. Although the moving average suggested by prediction equation error also had a varying tendency; no significant difference between prediction equations was found, when $C_{cr}$ was above or below 1.5 ml/s.

The interval 30–39 years:

Women

![Graph showing errors in the CG, MDRD4 and CKD-EPI prediction equations.](image)

Men

![Graph showing comparison of GFR calculated by using prediction equations CG, MDRD4 and CKD-EPI for GFR $<1.5$ ml/s and $>1.5$ ml/s.](image)

The 40–49 year age group

Women

Correlation analysis of prediction equations with $C_{cr}$ show a moderate degrees of correlation with MDRD4 ($r=0.5910$), CG ($r=0.5750$) and CKD–EPI ($r=0.5520$). The moving average suggested by prediction equation error tended to increase with increasing $C_{cr}$. Significant differences were established for prediction equation error for CG (GFR $<1.5$ ml/s and $>1.5$ ml/s, $p=0.05$), MDRD4 (GFR $<1.5$ ml/s and $>1.5$ ml/s, $p=0.01$) and CKD-EPI (GFR $<1.5$ ml/s and $>1.5$ ml/s, $p=0.05$).

Men

Correlation analysis of prediction equations with $C_{cr}$ revealed a high degree of correlation between MDRD4 ($r=0.8713$) and CG ($r=0.8655$), while the CKD–EPI formula exhibited a moderate degree of correlation ($r=0.3512$). The prediction equation error was lower when $C_{cr}<$1.5 ml/s, but it had an intensive increase when $C_{cr}>1.5$ ml/s. Significant differences were established for prediction equation error for CG (GFR $<1.5$ ml/s and $>1.5$ ml/s, $p=0.01$), MDRD4 (GFR $<1.5$ ml/s and $>1.5$ ml/s, $p=0.001$) and CKD-EPI (GFR $<1.5$ ml/s and $>1.5$ ml/s, $p=0.001$).

Fig. 2 a) Errors in the CG, MDRD4 and CKD-EPI prediction equations. The moving average of the absolute value of S.D.M. b) Comparison of GFR calculated by using prediction equations CG, MDRD4 and CKD-EPI for GFR $<1.5$ ml/s and $>1.5$ ml/s. Bars and error bars represent the mean $\pm$ S.E.M; *denotes significant difference between the studied groups.

Contd. on the following pages
The interval 40–49 years:

Women

Men

The interval 50–59 years:

Women

Men

Fig. 2. (cont. from page 36)
The interval 60–69 years:

Women

Men

The interval 70–79 years:

Women

Men

Fig. 2. (cont. from page 37)
The 50–59 year age group

Correlation analysis of prediction equations and C\text{cr} revealed a moderate degree of correlation in each case: (MDRD4 − r = 0.5030; CKD-EPI − r = 0.4950; CG − r = 0.3520). The moving average suggested by prediction equation error was at a low level at 1.5 ml/s, but it tended to increase above this value. While significant differences were established for prediction equation error for MDRD4 (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.01) and CKD-EPI (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.05); no significant difference was found for CG at those levels.

Men

In this group, correlation analysis detected a moderate degree of correlation between each prediction equation and C\text{cr} (MDRD4 − r = 0.7366; CKD-EPI − r = 0.7177 and CG − r = 0.6622). The moving average had a low prediction equation error up to 1.5 ml/s and then a slightly increasing tendency. The prediction equation error for GFR over 2.5 ml/s had a sharply declining tendency. Significant differences were established for prediction equation error for CG (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.001), MDRD4 (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.001) and CKD-EPI (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.001).

The 60–69 year age group

Women

A high degree of correlations was established between prediction equations and C\text{cr} (MDRD4 − r = 0.7790; CKD-EPI − r = 0.7780), while the CG formula had a moderate degree of correlation (r = 0.6550). The curves of moving average show that prediction equation error up to 1.5 ml/s was at a low level, with a sharp tendency to increase above this value.

Significant differences were detected for prediction equation error for CG (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.001), MDRD4 (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.001) and CKD-EPI (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.001).

Men

Correlation analysis of prediction equations and C\text{cr} revealed a high degree of correlation for MDRD4 (r = 0.8009) and CKD-EPI (r = 0.8020) and a moderate degree for CG (r = 0.5776). The chart of moving average showing prediction equation error had a sharply increasing tendency from 0.2 to 0.4 ml/s and sharply declining from 0.4 to 0.6 ml/s. There was a low error level from 0.6 to 1.5 ml/s and then a slightly increasing tendency again from 1.5 ml/s. While significant differences were noted in prediction equation error for MDRD4 (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.05) and CKD-EPI (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.001), no significant difference was established for prediction equation CG (GFR < 1.5 ml/s and > 1.5 ml/s).

The 70–79 year age group

Women

A moderate degree of correlation between all prediction equations and C\text{cr} was found in this female group (MDRD4 − r = 0.6730; CKD-EPI − r = 0.6650; CG − r = 0.5400). From the moving average, we detected a low level of prediction equation error to 1.5 ml/s, with a sharply increasing tendency above this value. Significant differences between prediction equation error were established for CG (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.01), MDRD4 (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.001) and CKD-EPI (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.001).

Men

Moderate correlation was detected between all prediction equations and C\text{cr} (CG − r = 0.6381; CKD-EPI − r = 0.6277; MDRD4 − r = 0.6154). The chart of moving average showed sharply declining prediction equation error to 0.4 ml/s followed by a low error level from 0.4 to 1.2 ml/s, then sharply increasing tendency between 1.2 and 1.8 and finally sharply declining above this value. Significant differences were registered for prediction equation error for CG (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.01), MDRD4 (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.05) and for CKD-EPI (GFR < 1.5 ml/s and > 1.5 ml/s, p = 0.05).

DISCUSSION

The most common problem in C\text{cr} estimation remains centred on inaccurate 24 hour urine collection reports, and factors interfering with 24-hour urine accuracy cannot be offset by current analytical methods (14, 15). The accuracy of most delivered diuresis in our study was limited to levels of 1 litre, 0.5 litre or 100 ml, with a small number of measurements accurate at the 10 ml level. This caused suspicion concerning participants’ subjective estimation, rather than precise measurement.

This study yielded information on GFR estimation by C\text{cr}, with the aim to use prediction equations CG, MDRD4 and CKD-EPI to estimate GFR levels from S\text{cr}. Many studies have estimated clearance of inulin (C\text{in}) level and compared obtained values with eGFR estimation by prediction equations (16, 17). Other studies estimated GFR by creatinine and cystatin C and found that adjustments to both parameters were comparable (18, 19). In our study, we compared C\text{cr} estimation with prediction equations; because C\text{in} estimation is complicated in continuous inulin intravenous administration and adjustment by cystatin C is more expensive (6, 18). S\text{cr} is a good indicator of renal function, but the conclusion of authors is that S\text{cr} values are affected by factors including age, diet, muscle mass, and drugs, therefore, they should not be used as a standard in GFR determination (20–22). More recently, calculation of eGFR by empirical mathematical formulae, such as CG, MDRD and CKD-EPI, has been encouraged as a simple, rapid and reliable means of assessing kidney function.

Herein, correlation analysis produced the best correlations between C\text{cr} and the MDRD4 prediction equation for women (r = 0.7790) and men (r = 0.8009), and between C\text{cr} and CKD-EPI for women (r = 0.7780) and men (r = 0.8002) in the 60–69 year age group. We found a high correlation between C\text{cr} and the CG (r = 0.8655) and MDRD4 (r = 0.8713) prediction equations for men in the 40–49 year age group. High correlation between CG; MDRD4 prediction equations and C\text{cr} was reported in an adult Japanese population by Aizawa et al. (23). Egi et al. (24) and Botev et al. (17) registered similarly high correlations between C\text{cr}, CG and MDRD4 prediction equations for subjects aged 46±16 years. In addition, our study also confirms the finding between C\text{cr}, CG and MDRD4 prediction equations for men, and this suggests advantageous use of the MDRD4 and CKD-EPI formulae for men in the 60–69 age range. Our study is also consistent with the study of Zitta et al. (25), which concluded
that for routine purposes in cases of poor renal function eGFR methods are generally reliable.

Conclusions drawn by Schück et al. and Soares et al. (26, 27) as well as the results of our study show that prediction equations for determining GFR are not universally applicable for all patients, because equation accuracy improves in healthy populations without kidney disease. Age variation is also an important parameter because creatinine production experiences physiological decline with increasing age, so age becomes very important in Ccr regulation (28, 29). Since the Pearson coefficient of correlation did not provide adequate comparison of Ccr and prediction equations (30), our methodology was altered to comparison of prediction equation errors and comparison of significant differences between the three formulae for individual age ranges and gender, using GFR < 1.5 ml/s and > 1.5 ml/s in accordance with the NKF protocol. Despite using different formulae for men and women, and working with different levels of plasma creatinine and/or different aged groups (31), which further complicated this research, we were rewarded with greater accuracy.

Results of the moving average and significant differences in eGFR calculated by prediction equations in the interval GFR < 1.5 ml/s and GFR > 1.5 ml/s showed that the utility of prediction equations increased when GFR was < 1.5 ml/s for each age range, compared to GFR > 1.5 ml/s. An exception was noted for the 30–39 year age group in both genders, where the small number of female (n = 19) and male (n = 10) participants limited our results.

According to both Levey et al. (3) and Michels et al. (32), the CKD-EPI prediction equation is more accurate than the MDRD4 formula. These authors advised the use of CKD-EPI equation for patients with impaired renal function in order to reduce the number of false positive diagnoses to less than 1 ml/s/1.73 m².

The prediction equations have proven advantageous in Chronic Kidney Disease stages 2–5 in NKF classification (30). In summary, we contend that the prediction equations affording “first step” diagnosis in the following situations: MDRD4 and CKD-EPI for both genders in the 60–69 age group; and MDRD4 and CG for men in the 40–49 age group.

According to our results, we advise the incorporation of prediction equations as an additional examination of GFR. This will facilitate improvement and validation of kidney examinations in clinical practice in Slovakia regardless of patient age and gender.

CONCLUSIONS

Based on our statistical analysis of correlation, moving average and comparison of prediction equations in the GFR > 1.5, GFR < 1.5 interval, the following recommendations are highlighted to improve outcomes for nephrology patients:

1) Inclusion of prediction equations in clinical practice for the currently used Ccr; namely, the MDRD4 and CG equations for men aged 40–49 years, and the MDRD4 and CKD-EPI equations for both men and women aged 60–69 years;

2) The incorporation of these three prediction equations in clinical practice in Slovakia to form additional examination of Ccr for the gender and age groups not included in the previous sentence but examined in the Results section of this paper.

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REFERENCES


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