

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 (C_{cr}) 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 C_{cr} 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 C_{cr} and MDRD4 for women ($r = 0.7790$) and men ($r = 0.8009$), and between C_{cr} 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 C_{cr} 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 C_{cr} .

Key words: glomerular filtration rate, Cockcroft–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, iothexol 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 (C_{cr}), 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 C_{cr} 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 C_{cr} . Hence C_{cr} is considered a better indicator of renal function than the serum creatinine level (10). Problems in measuring C_{cr} primarily emanate from 24 hour urine collection, which can initiate gross errors in C_{cr} determination due to subjective or objective mechanisms. Herein, prediction equations determining C_{cr} and GFR based on the determination of serum concentrations of creatinine (S_{cr}) 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 (MRDR) developed in a multi-centre American study present the most widely used prediction equations for determination of C_{cr} 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 C_{cr} 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:

$$GFR_{CG} = \{[(140 - \text{age}/\text{years}) \times \text{weight}/\text{kg}]/[72 \times S_{cr}/\mu\text{mol/l}]\} \times (0.85 \text{ for women})$$

2. The MDRD4 formula:

$$GFR_{MDRD4} = 175 \times S_{cr}/\mu\text{mol/l}^{-1.154} \times \text{age}/\text{years}^{-0.203} \times 1.212 \text{ (for black people)} \times 0.742 \text{ (for women)}$$

3. The CKD-EPI formula:

$$GFR_{CKD-EPI} = 141 \times \min(S_{cr}/k, 1)^a \times \max(S_{cr}/k, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018 \text{ (for women)} \times 1.159 \text{ (for black people)}$$

S_{cr} is serum creatinine [$\mu\text{mol/l}$]

k is 0.7 for women and 0.9 for men

a is -0.329 for women and -0.411 for men

min. indicates the minimum of S_{cr}/k or 1

max. indicates the maximum of S_{cr}/k or 1

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 and 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 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.

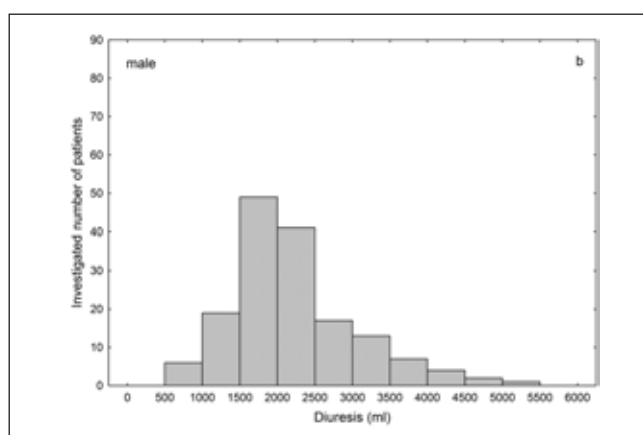
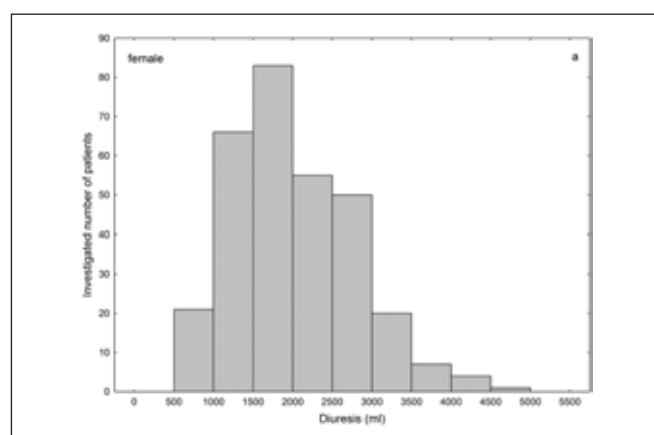


Fig. 1. Diuresis of investigated patients; women and men

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 40–49 year age group

Women

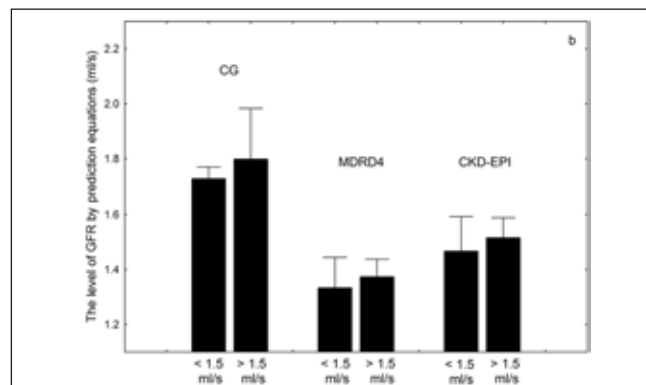
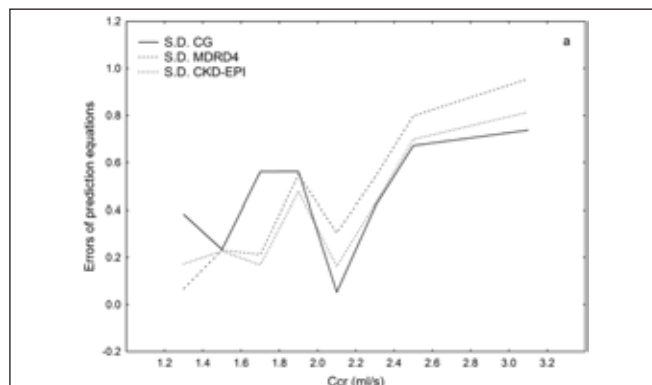
Correlation analysis of prediction equations with C_{cr} show a moderate degrees of correlation with MDRD4 ($r=0.5910$), CG ($r=0.5750$) and CKD-EPI ($r=0.5520$). The moving average suggested by prediction equation error tended to increase with increasing C_{cr} . Significant differences were established 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, $p=0.001$).

The interval 30–39 years:

Women



Men

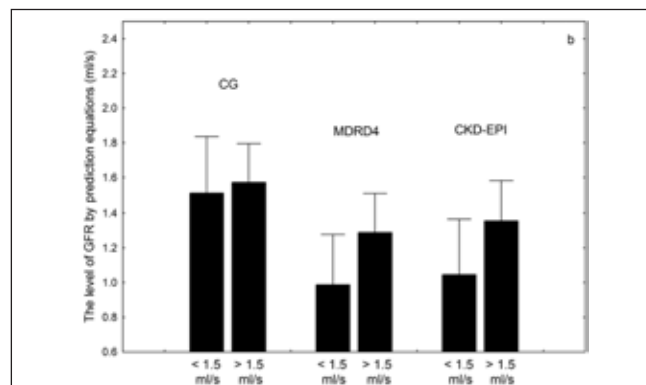
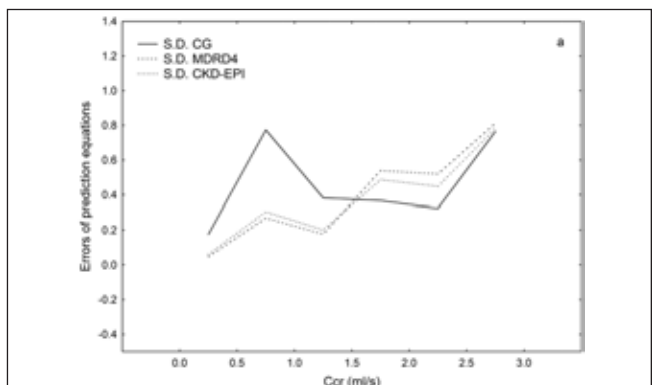
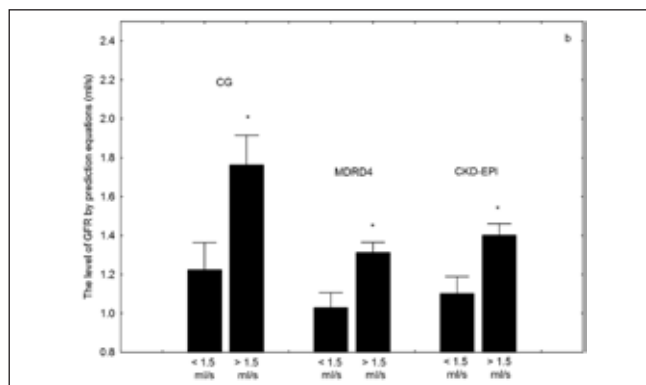
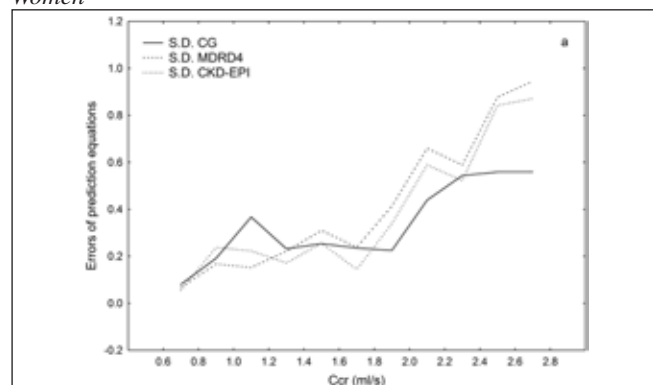


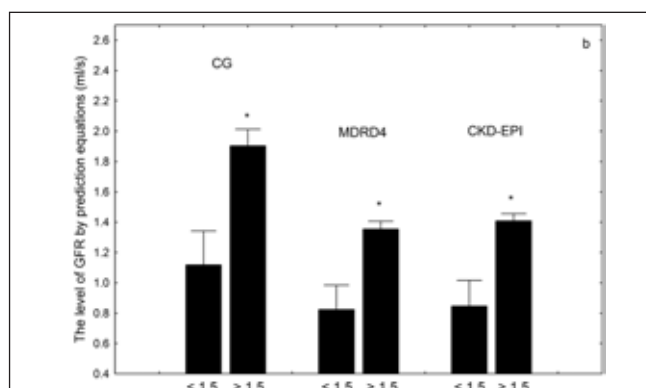
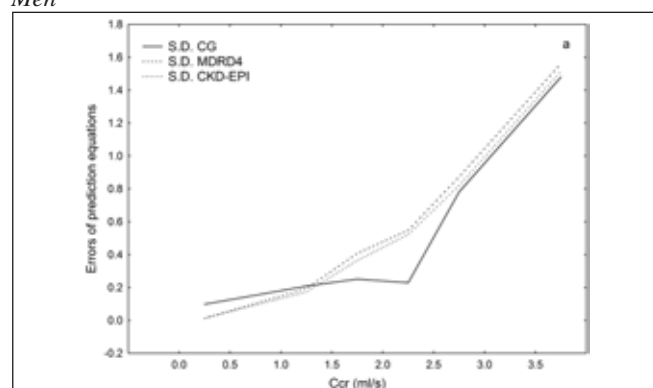
Fig. 2 a) Errors in the CG, MDRD4 and CKD-EPI prediction equations. The moving average of the absolute value of S.D.M. **b)** Comparison of GFR calculated by using prediction equations CG, MDRD4 and CKD-EPI for $GFR < 1.5$ ml/s and > 1.5 ml/s. Bars and error bars represent the mean \pm S.E.M.; *denotes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

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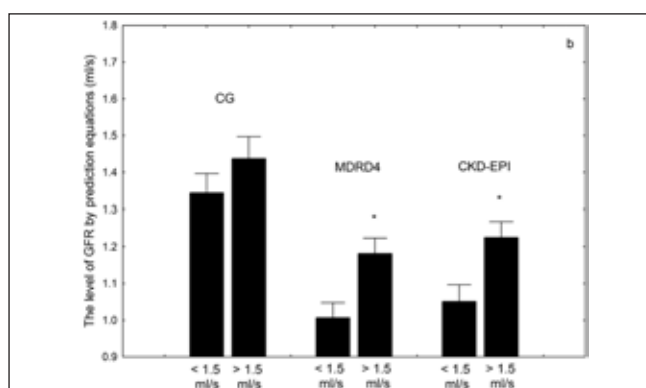
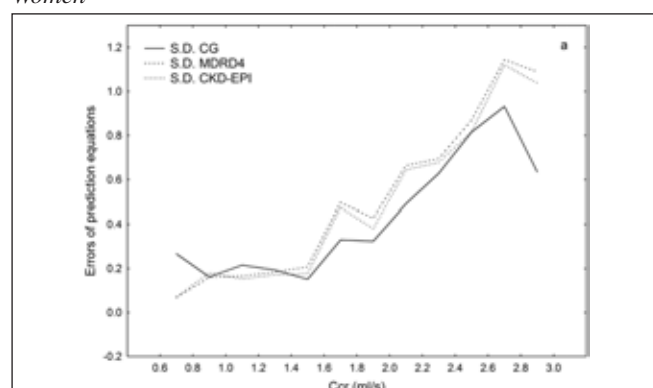
The interval 40–49 years:
Women



Men



The interval 50–59 years:
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Men

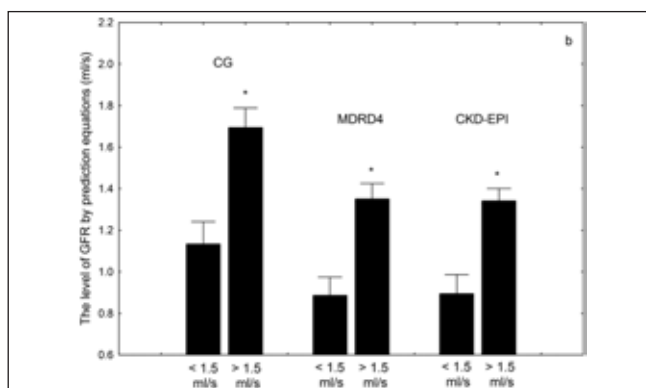
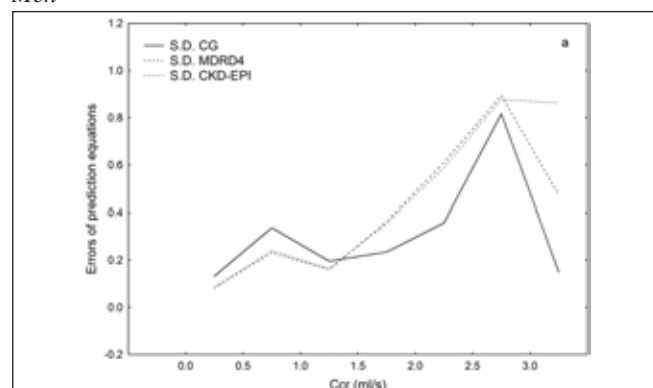
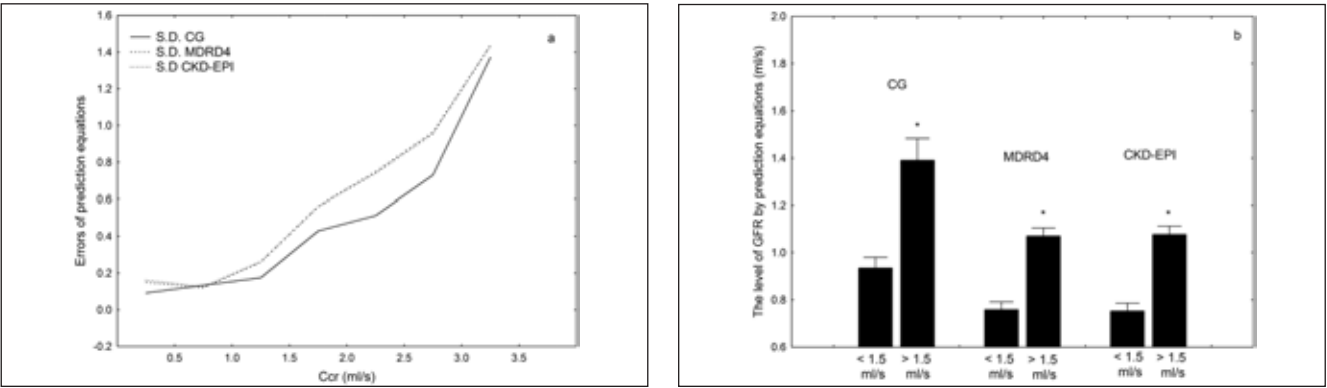
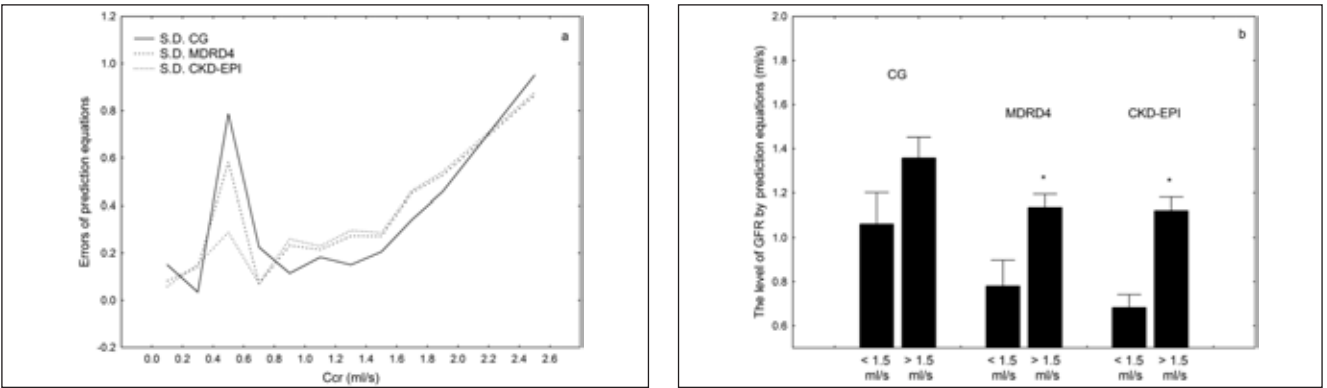


Fig. 2. (cont. from page 36)

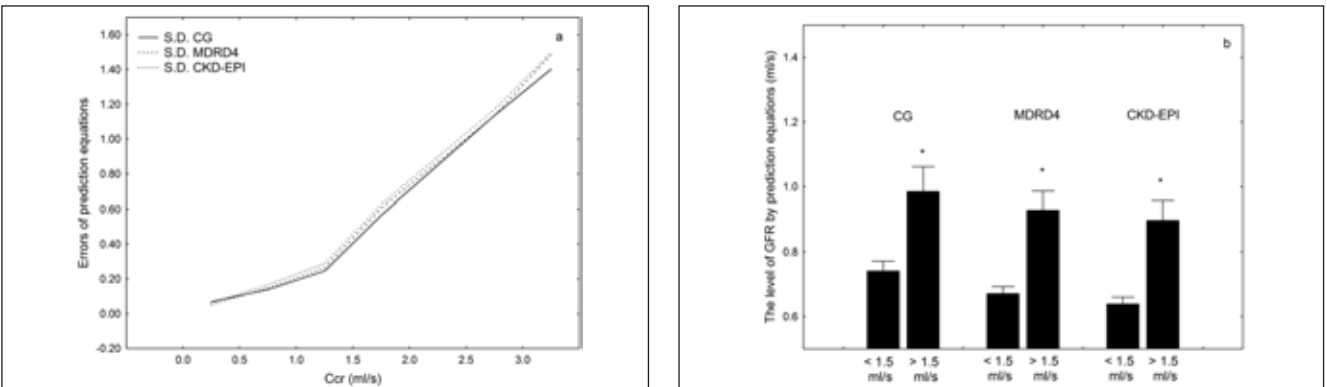
The interval 60–69 years:
Women



Men



The interval 70–79 years:
Women



Men

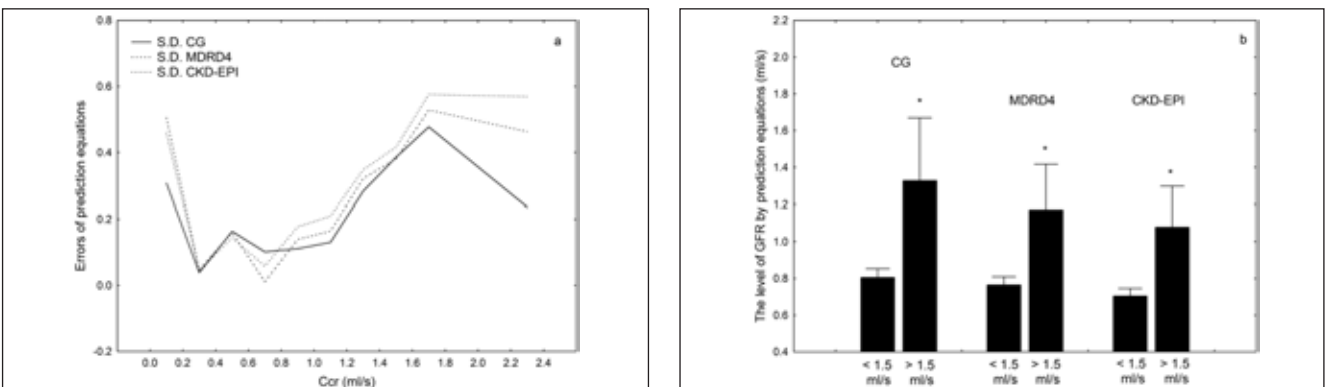


Fig. 2. (cont. from page 37)

The 50–59 year age group

Women

Correlation analysis of prediction equations and C_{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_{cr} (MDRD4 – $r=0.7366$; CKD-EPI – $r=0.7177$ and CG – $r=0.0622$). 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_{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_{cr} revealed a high degree of correlation for MDRD4 ($r=0.8009$) and CKD-EPI ($r=0.8002$) 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 declined 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_{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_{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 slightly 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_{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_{cr} , with the aim to use prediction equations CG, MDRD4 and CKD-EPI to estimate GFR levels from S_{cr} . Many studies have estimated clearance of inulin (C_{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_{cr} estimation with prediction equations; because C_{in} estimation is complicated in continuous inulin intravenous administration and adjustment by cystatin C is more expensive (6, 18). S_{cr} is a good indicator of renal function, but the conclusion of authors is that S_{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_{cr} and the MDRD4 prediction equation for women ($r=0.7790$) and men ($r=0.8009$), and between C_{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_{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_{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_{in} and CG and MDRD4 prediction equations for subjects aged 46 ± 16 years. In addition, our study also confirms the finding between C_{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 C_{cr} regulation (28, 29). Since the Pearson coefficient of correlation did not provide adequate comparison of C_{cr} 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 afford “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 C_{cr} ; 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 C_{cr} 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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