

## Research paper

# Comparison of commonly used creatinine-based GFR estimating formulas in elderly female non-diabetic patients with chronic kidney disease

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## ABSTRACT

**Introduction:** Measuring glomerular filtration rate (GFR) with the isotopic method is a gold standard. However, it is an elaborate and expensive procedure, so in everyday practice GFR is estimated with creatinine-based formulas. Despite the number of studies, it remains unclear which GFR estimating equation is the most accurate, especially in increasing elderly population.

**Aim:** The aim of this study was to compare the commonly used formulas to assess which one of them should be used in elderly female non-diabetic patients suffering from chronic kidney disease (CKD).

**Material and methods:** 336 non-diabetic females aged 70 and more were qualified to the study. On the basis of serum creatinine concentration, estimated GFR (eGFR) was estimated using various formulas.

**Results and discussion:** The eGFR and CKD stages differ significantly depending on the used formula. The modification of diet in renal disease equation (MDRD) formula showed slightly, but still significantly, better correlation with creatinine concentration in serum than the CKD epidemiology collaboration equation. The Cockcroft-Gault equation formula was significantly inferior to above mentioned equations. The receiver operating characteristic curves showed that MDRD is the most sensitive equation and the differences between formulas compared in pairs were significant.

**Conclusions:** Due to its highest correlation with creatinine and its highest sensitivity and specificity, the MDRD formula seems to be the most accurate equation to estimate GFR in elderly non-diabetic females.

## 1. INTRODUCTION

Glomerular filtration rate (GFR) is widely acknowledged as the best marker of kidney function.<sup>1</sup> Its assessment is crucial, as it is used to calculate drugs dosages, and, most importantly, detecting kidney diseases, including chronic kidney disease (CKD). Measuring GFR with the isotopic method, even though it is the most accurate, is an elaborate, expensive and time-consuming procedure. For that reason, GFR is routinely estimated (estimated GFR – eGFR) by creatinine concentration in the serum.<sup>1–4</sup> Common methods for estimating GFR include creatinine-based formulas, such as the Cockcroft–Gault (CG) equation, the modification of diet in renal disease (MDRD) equation and the CKD epidemiology collaboration (CKD-EPI).<sup>5</sup> These formulas are derived from regression analysis, where the GFR level depends on both creatinine concentration in the serum and other variables, such as sex, age, weight, race, which impact serum concentration of creatinine irrespectively of GFR, as they are surrogates for its production in muscles.<sup>5</sup>

However, none of these formulas seems to be universal. For example, the MDRD equation is said to be the best for diabetic patients, as showed by Schwandt et al.<sup>6</sup> The CKD-EPI equation appears to be the most precise in some multi-ethnic Asian populations.<sup>3,7</sup> Moreover, a study by Liu et al. shows that none of these equations seems to be accurate in the Chinese adults and that in this group the Xiangya equation should be used.<sup>8</sup>

## 2. AIM

As showed above, despite the number of studies, it remains unclear which of these formulas is the most accurate, especially in increasing elderly population. Given that there are only a few studies comparing these equations in elderly patients, most of which were performed on small groups, we aimed to compare commonly-used formulas to assess which one of them should be used in elderly females without diabetes.

## 3. MATERIAL AND METHODS

Data used in the following analysis was obtained from 336 female non-diabetic outpatients from Poland aged 72–98 years, suffering from CKD (also described in details in another study)<sup>9</sup> recognized according to Kidney Disease: Im-

proving Global Outcomes (KDIGO) 2012 guidelines.<sup>10</sup> Only these patients who had their creatinine concentration measured twice in the interval of 3 months were included in the analysis. The excluding criteria were conditions that may influence GFR in selected group of patients: age under 70, cancer, diabetes, NYHA IV heart failure, severe liver damage, chronic inflammatory diseases, cachexia, disorders of the thyroid function and steroid therapy.

Correlation coefficient between eGFR calculated by using given formula and the concentration of creatinine in the serum was used as determinant of quality of estimating eGFR and the stage of CKD (classified according to KDIGO 2012).<sup>10</sup> Also, the correlation between eGFR estimated with given formula and the CKD stage was used as a determinant of ability of this formula to predict CKD stage.

The Shapiro–Wilk test was used to examine the normality of distribution of compared values. Due to the failure of meeting the criteria for normal distribution of compared values ( $P < 0.001$  for each), nonparametric tests were used to compare them. To compare all, the Friedman’s ANOVA test was used if the variables were dependent, and if they were independent – the Kruskal–Wallis’s ANOVA test was used. The Wilcoxon test was used to compare in pairs. The same nonparametric tests were used to compare the distribution of CKD stages. Spearman correlation was used to estimate the degree of correlation between calculated values of eGFR and serum creatinine concentration. Estimated correlations were transformed with Fisher  $z$ -transformation and then compared with  $t$ -test.

The receiver operating characteristic (ROC) curves were used to indicate the most sensitive GFR estimating formula. The criterion was at least CKD stage 2 diagnosis (eGFR  $< 90$  mL/min/1.73 m<sup>2</sup>).

Given that there are about 4 millions people suffering from CKD in Poland<sup>11</sup> and, basing on the analyzed literature, at least 30% of them are diabetic and great (unknown exactly) part is under the age of 65<sup>6,7,12–16</sup>, the minimal size of the probe was estimated at 97 ( $n = 336$ ) with assumption that the accepted maximal error was 10% and the level of significance was 5%.

## 4. RESULTS

### 4.1. Characteristic of the examined group

Table 1 shows detailed characteristics of the examined group. Due to very small groups, patients with stage 4 and 5 of CKD

**Table 1. Characteristics of the examined group ( $n = 336$ ).**

Characteristics	CKD stage				<i>P</i> value
	All	1	2	3	
Age, y	77.13 ± 4.54	76.03 ± 4.37	77.64 ± 4.60	79.63 ± 3.31	
Creatinine, μmol/L	64.85 ± 16.02	52.28 ± 6.75	69.92 ± 7.78	98.35 ± 13.21	
MDRD, mL/min/1.73 m <sup>2</sup>	84.44 ± 23.54	103.73 ± 20.80	73.02 ± 9.13	51.29 ± 10.68	<0.001
CKD-EPI, mL/min/1.73 m <sup>2</sup>	82.05 ± 16.97	95.17 ± 8.26	76.84 ± 9.25	50.54 ± 7.00	
CG, mL/min/1.73 m <sup>2</sup>	90.33 ± 24.66	105.65 ± 23.60	81.93 ± 16.93	59.33 ± 10.99	

Comments: numbers are given as mean ± SD.

**Table 2. The number of patients in each stage of CKD in the examined group.**

CKD stage	MDRD	CKD-EPI	CG	<i>P</i> value
1	125	147	172	<0.0001
2	179	165	144	<0.0001
3	37	27	26	<0.0001
4	1	1	0	–
5	3	5	3	–

**Table 3. Analysis of Spearman correlation between creatinine and eGFR calculated by using the MDRD, CKD-EPI and CG formulas depending on the stage of CKD.**

CKD stage	MDRD	CKD-EPI	CG
1	–0.9895	–0.8423	–0.4402
2	–0.9862	–0.9716	–0.5021
3	–0.9900	–0.9474	–0.4025

were skipped in the below presentation, however they were involved in the “All” group in conducted calculations.

Table 2 shows the number of patients in each stage of CKD depending on the used eGFR formula.

#### 4.2. Comparison of eGFR and CKD stages depending on the used equation

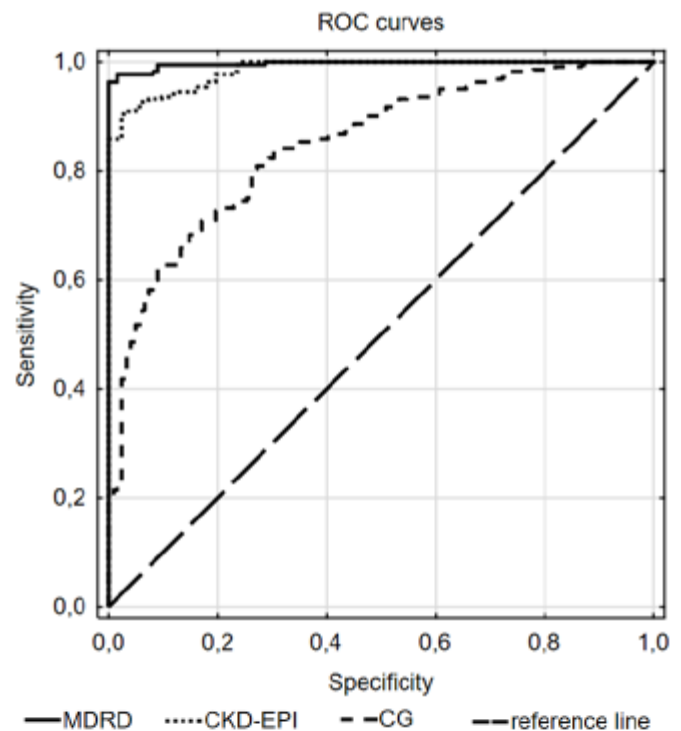
Distributions of creatinine and GFR estimated by using the MDRD, CG and CKD-EPI formulas did not fulfill the criteria of normality in the Shapiro–Wilk test ( $P < 0.001$  for each).

The Friedman’s ANOVA analysis showed significant ( $P < 0.001$ ) differences, both between the values of eGFR and marked CKD stages depending on the used equation. According to the Wilcoxon test’s results, the values of eGFR were significantly different for pairs of equations: MDRD and CG, CG and CKD-EPI ( $P < 0.001$ ). The difference between MDRD and CKD-EPI was insignificant ( $P = 0.187$ ). Comparison in pairs of CKD stages depending on the used formula showed significant differences for each pair ( $P < 0.05$ ).

#### 4.3. Analysis of correlation between eGFR or CKD stages and creatinine depending on the used equation

Analysis of Spearman correlation showed the strongest correlation between creatinine and eGFR when using the MDRD equation ( $R = -0.9823$ ), then the CKD-EPI equation ( $R = -0.9612$ ) and, lastly, the CG equation ( $R = -0.7206$ ). All of them were significant with  $P < 0.05$ . The differences for each pair of correlations were also significant ( $P < 0.001$ ).

Analysis of Spearman correlation based on the stage of CKD (stages 1–3) in these patients was also conducted. For stages 4 and 5 the analysis was withdrawn, as there were too few patients in these stages of CKD. The observed correlations were significant with  $P < 0.05$ , except from some analysis in groups with stage 3 of CKD because of a small number of patients. Nevertheless, the differences between



**Figure 1. The ROC curves assessing sensitivity of eGFR equation to determine CKD.**

each pair of correlation in all CKD stages were significant ( $P < 0.01$ ). Table 3 shows detailed results of the analysis.

#### 4.4. Analysis of ROC curves for eGFR formulas

ROC curves analysis showed that the most sensitive GFR estimating formula diagnosing at least 2nd stage of CKD was MDRD with area under curve (AUC) of 0.9969, then CKD-EPI with AUC of 0.9847 and the last was CG with AUC of 0.8475. The ROC curves were presented on the Figure 1. The differences between equations compared in pairs were significant with  $P < 0.001$  for each.

## 5. DISCUSSION

Our study generated three major findings:

- (1) The MDRD equation seems to be the most accurate GFR estimating formula.
- (2) The advantage of the MDRD over the CKD-EPI formula is only slight, but still significant.
- (3) The CG formula was characterized by only moderate sensitivity and accuracy in recognizing CKD.

In the literature, there are very few studies comparing commonly used eGFR estimating formulas, especially in white European female elderly patients. Most of the performed examinations took place in Asia. What is more, most of the studies, in contrast to ours, qualified patients who were under age of 65 years or diabetic. None of the found studies was performed only on female patients and the comparison between both sexes were carried out very rarely.

Our observations were consistent with the outcomes of comparison of the MDRD, CKD-EPI and CG formulas performed by Denkinger et al. on group of European patients.<sup>6</sup> However, in this study, in contrast to ours, all of the patients suffered from diabetes. The mentioned examination showed that especially in patients in age above 70 years, the MDRD equation was the most accurate. MDRD was also the best formula to estimate GFR in more severe stages of CKD (3, 4 and 5). It may suggest that MDRD would be a better equation to qualify patients for hemodialysis.<sup>17</sup> In stages 1 and 2 of CKD, the accuracy of MDRD and CKD-EPI seemed to be similar. Notwithstanding, in younger patients qualified to this study (aged 18–40) the CKD-EPI was visibly better than the MDRD.<sup>6</sup> Also, examination performed by Liu et al. in group of elderly Chinese patients seems to confirm slight advantage of the MDRD over the CKD-EPI. However, in this group the most accurate GFR estimating equation was the Xiangya formula, which was newly designed especially for this population and was characterized by better correlation with renal function examined with use of <sup>99m</sup>Tc-DTPA than any other commonly used equation.<sup>18</sup> Similarly as in pediatric group or in Chinese patients, it may be considered to elaborate new or modified equation that could be used in elderly females. Moreover, other study performed on Chinese elderly patients showed that the new equations, such as full-age-spectrum formula (FAS) and Berlin initiative study (BIS1), are more accurate than both MDRD and CKD-EPI in comparison to <sup>99m</sup>Tc-DTPA. However, almost the third part of patients in this study was diabetic and one of its inclusion criterion was eGFR < 60 mL/min/1.73 m<sup>2</sup>, so the examined population differed significantly from ours.<sup>12</sup>

The differences in CKD stages prediction ability of these equations were also observed between males and females in some studies. These studies demonstrate that in general population the CKD-EPI was characterized by smaller bias in female, while the MDRD was more accurate in males.<sup>6,13,14</sup> However, our results showed that this dependence does not happen in female advanced in age, where both equations had similar accuracy with slight but significant advantage of the MDRD.

The number of other publications also showed that probably the best creatinine-based equation in general population is the CKD-EPI.<sup>7,14–16,19,20</sup> However, the differences between CKD-EPI and MDRD were often very slight and the advantage of CKD-EPI was not significant in patients with CKD staged 3 or more.<sup>7,16,20</sup> Furthermore, for population of elderly patients, like in our examined group, the advantage of CKD-EPI has not been proved and most of examined patients were under age of 65 years or at least part of tested population suffered from diabetes.<sup>7,12–16</sup> In fact, there was only one examination that comparing eGFR equations, performed on the group of 398 elderly patients truly similar to ours. In this group, the mean age was 80 but in contrast to ours 19% of the patients suffered from diabetes, what could influence on the outcome. Its results showed the advantage of the CKD-EPI over the MDRD, but this predominance was very slight and significant only in stages 1 and 2 of CKD.<sup>20</sup> Additionally, pa-

tients were qualified less often to CKD stage 3 or more based on CKD-EPI what is consistent with our results.<sup>13</sup>

Furthermore, some authors suggest that in these patients, none of the tested formulas is exact enough and only the isotopic method with <sup>99m</sup>Tc-DTPA should be used in elderly patients.<sup>21,22</sup> However, due to the limitation of this method, it should be concluded from these studies that the outcomes of eGFR estimated from creatinine level in serum in this group of patients have to be assessed very carefully. Some other scientists suggest that before use isotope-based method it may be worth to consider the formulas basing on cystatin C or both cystatin C and creatinine due to its better predicting ability of CKD than the formulas based only on creatinine which secretion is changing while ageing.<sup>23</sup>

The CG was characterized by the lowest prediction ability and it tended to overestimate the GFR from the analyzed equations. These limitations in use of CG were also observed in other studies, where CG also demonstrated lower accuracy than the MDRD or CKD-EPI.<sup>6,18,21</sup>

The limitation of the study was the relatively small size of the examined group, especially in CKD stages 4 and 5 groups. However, the group was estimated to be big enough to draw significant conclusions.

## 6. CONCLUSIONS

From the carried-out analysis, it should be concluded that the most accurate and the most sensitive and specific GFR estimating equation in elderly female patients is MDRD. The MDRD formula seems to have a high ability to explain creatinine concentration in serum no matter the stage of CKD.

### Conflict of interest

None declared.

### Funding

None declared.

### Ethics committee approval

Ethics committee approval for this study was obtained (approval No KB Cm UMK 683/2015).

### Informed consent

Informed consent was obtained from the patients for publication of this research report.

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