Comparison of formulas for calculating estimated glomerular filtration rate and its diagnostic thresholds for chronic kidney disease in older adults: a cross-sectional study

Abstract

Objective: To evaluate and compare the CKD-EPI, BIS1 and MDRD formulas and diagnostic thresholds of 45 and 60 ml/min/1.73m² in older patients. Method: A cross-sectional, descriptive, analytical observational study was conducted. Patients aged ≥65 years treated at a referral outpatient clinic between January 2020 and June 2022, were assessed. Patients with only one creatinine level or with transient GFR abnormalities were excluded. Results: The GFR estimates using the CKD-EPI formula were higher than both the BIS1 and MDRD formulas in patient groups aged 65-74 years and 75-84 years. In the group of patients aged 85-94 years, the CKD-EPI showed no difference when compared with the MDRD, yielding higher estimates only compared with the BIS1. Greater dispersion was found between the CKD-EPI and BIS1, showing less agreement between these formulas, as confirmed by the Kappa test (76.7%), while there was almost perfect agreement between the CKD-EPI and MDRD. Conclusion: The BIS1 formula showed stronger correlation of the decrease in eGFR with advancing age, reflecting the physiological renal aging process and serving as a potentially useful tool for estimating GFR in older adults. The formula can help provide a more accurate diagnosis of CKD and aid planning of interventions to slow the progression of CKD and predict the risk of mortality from cardiovascular diseases.

Keywords: Chronic Renal Failure. Glomerular Filtration Rate. Aged. Diagnosis.
INTRODUCTION

Chronic kidney disease (CKD) is defined by structural change in the kidney or a glomerular filtration rate (GFR) <60 ml/min/1.73m² for a period of ≥3 months. The detection and timely management of decline in kidney function can slow the progression of CKD to more severe forms, such as end-stage kidney disease.

Estimated GFR (eGFR) is often employed in clinical practice as a standardized measure, with several biomarkers used for this purpose, such as insulin or iohexol levels (exogenous markers), and creatinine or cystatin C (endogenous markers). Currently, creatinine is the most commonly used measure due to its accuracy and low cost, and is estimated with formulas such as the Modification of Diet in Renal Disease (MDRD) and Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations.

Diagnosing CKD in older adults can be challenging because, besides aging-related physiological decline in GFR and changes in body composition (lower muscle mass and bone density plus increased adipose tissue), there is a growing incidence of type 2 diabetes mellitus (DM2), systemic arterial hypertension (SAH), other conditions, and non-communicable diseases contributing to a rise in the prevalence of CKD.

In addition, the classification of CKD across different age groups using the MDRD and CKD-EPI formulas has limitations, raising doubts as to whether the changes in GFR are due to the aging process alone. In an effort to address this limitation, the Berlin Initiative Equation (BIS) was recently developed and specifically adapted for older individuals. Validated equations for estimating GFR in this age group were lacking, especially in cases of normal or only moderately-reduced kidney function, where an age-calibrated formula can reduce incorrect classification of individuals with GFR <60 mL/min/1.73m² or >60 mL/min/1.73m².

Assessing GFR is vital in clinical practice and has always posed a challenge. It is paramount to interpret signs, symptoms and laboratory anomalies which may be an indication of kidney disease and to determine drug dosing and help detect, control and estimate CKD progression and prognosis. Thus, early recognition of high-risk populations with decreased kidney function is important in CKD. Assessment based on 24-hour creatinine clearance has practical limitations and can lead to errors in classification due to pre-analytical and analytical interference and limitations. In an attempt to attain an estimate as close as possible to the true GFR, a number of different formulas for estimating GFR have been developed, including the CKD-EPI, MDRD and BIS equations.

Therefore, the objective of the present study was to assess and compare the CKD-EPI, BIS and MDRD equations for calculating GFR in older adults and the diagnostic threshold of 45 and 60 ml/min/1.73m² for CKD in these patients.

METHOD

An analytical, descriptive, cross-sectional study was conducted based on data from medical records of patients treated at the nephrology outpatient clinic of the Center for Medical Specialties of CESUPA (CEMEC) in Belém city, Pará state, Brazil between January 2020 and June 2022. The study population was selected by convenience sampling.

The sample size was calculated for a 95% confidence interval and 5% margin of error. The ideal sample size for identifying the association investigated was estimated at 231 patients for a more heterogeneous sample with a statistical power of 50%, and at 173 patients for a more homogenous population with a statistical power of 80%.

The study included patients of both genders, aged ≥65 years (matching age for validating BIS formula and used in previous studies), who had at least 2 serum creatinine measurements registered in their medical records, with a time interval of ≥3 months between readings. Patients that had transient changes in GFR were excluded.

The variables collected (age, gender, self-reported race, and creatinine values) and comorbidities were
analyzed according to data from medical records (Systemic Arterial Hypertension - SAH; type 2 Diabetes Mellitus – DM2; Cardiovascular Disease – CVD; Obesity and Dyslipidemia).

Laboratory serum creatinine values were determined using the kinetic colorimetric method, while estimated GFR (eGFR) were calculated using the MDRD, CKD-EPI (CKD EPI 2021) and BIS 1 equations3,5,11.

The variables were extracted, summarized and compiled into tables and/or figures using descriptive statistics according to the nature of the variables and distributions. The normality of the variables was assessed using the Shapiro-Wilk test. Difference between the groups with and without comorbidities for numeric variables was tested using the Mann-Whitney test, whereas age groups were evaluated using the Kruskall-Wallis test, with application of Dunn’s post-hoc test in the event of rejection of the null hypothesis. Related (same age for each formula) groups were compared using Friedman’s test, with Dunn’s post-hoc test when p<0.05.

The association between independent groups (with and without comorbidities; dichotomous diagnostic thresholds) and dichotomous variables was investigated using Fisher’s Exact test and, where these were polychotomous (diagnostic thresholds with > 2 categories), the association was investigated using the G test followed by Residuals Analysis for chi-squared when independence was rejected.

Agreement among the results of the formulas investigated was assessed using Fleiss’ Kappa test (categorical variable) or the Intraclass Correlation Coefficient (numeric variable). Also, Bland Altman plots were employed to illustrate the relationship between the GFRs estimated by the formulas analyzed. The level of statistical significance adopted for the statistical tests was set at 5% (0.05) for rejection of the null hypothesis.

Data were collected from medical records after approval of the project by the research ethics committee of the Centro Universitário do Estado do Pará (CESUPA), under Permit no. 5.308.765.

DATA AVAILABILITY

The full dataset underpinning the study results is available upon request from the corresponding author Lucas Lobato Acatauassu Nunes.

RESULTS

A total of 574 medical records of patients treated at the nephrology outpatient clinic were initially analyzed, with selection of 254 patients for inclusion in the study. Participants had a mean age of 75.7±6 years (range 65-103 years) (95%CI: 74.1–76.1), mean creatinine level of 1.6±1.0 mg/dl (95%CI: 1.4–1.7) and 61.8% were female (95%CI: 55.7–67.6). With regard to comorbidities presented by the patients studied, 88.6% (n=225) had systemic arterial hypertension (SAH); 48.8% (n=124) type II Diabetes Mellitus (DM2); 67.7% (n=172) dyslipidemia; 30.7% (n=78) obesity and 23.2% cardiovascular disease (CVD).

Figure 1 depicts the distribution of individual measurements and median values for GFR estimated using the formulas CKD-EPI (Median=47.3; IQR=34.4–61.9), BIS1 (Median=42.9; IQR=34.1–53.8) and MDRD (Median=44.4; IQR=32.0–57.5), providing a comparison of formulas and revealing significant differences between the values obtained by the CDK-EPI versus the BIS1 (p<0.001) and the CDK-EPI versus the MDRD (p<0.001), but no difference for the MDRD versus the BIS1 (p=0.889).
A comparison of estimated GFR (eGFR) by age group and formula is depicted in Figure 2. The 65-74 years age group contains a higher number of patients and exhibits a statistically significant difference among all 3 formulas. In the 75-84 years group, a statistical difference was found only for the CKD-EPI vs. BIS1 and the CKD-EPI vs. the MDRD. The GFRs estimated by the CKD-EPI formula were higher across all age groups than the values obtained using the other formulas.

Regarding the distribution of patients according to the cut-off points for GFR thresholds, there was high agreement of values estimated by the CKD-EPI and BIS1 (Agreement=76.7%; Kappa=0.629) formulas and almost perfect agreement between the CKD-EPI and MDRD (Agreement=87.8%; Kappa=0.808) and between the BIS1 and MDRD (Agreement=82.6%; Kappa=0.712) formulas.

The analysis of the graphical pattern showing dispersion of differences among the formulas (Figure 3) suggests lower agreement between the CKD-EPI and BIS1 formulas, with higher mean difference from zero relative to the other comparisons (Mean of differences=4.71, 95%CI = -7.71 to 17.13; Figure 3A). Furthermore, the results of comparing the CKD-EPI versus BIS1 (Figure 3A) and the CKD-EPI versus MDRD (Figure 3B) show that the positive difference between the formulas widens with increasing mean, the opposite pattern to that seen when comparing the BIS1 versus the MDRD (Figure 3C).

Examining estimated crude values, the intraclass correlation coefficient (ICC) of comparing CKD-EPI versus BIS1 was equal to 0.956 (95%CI=0.846–0.980; p<0.001). CKD-EPI versus MDRD was 0.978 (95%CI=0.962–0.986; p<0.001) and MDRD versus BIS1 was 0.964 (95%CI=0.948–0.974; p<0.001).

**Figure 1.** Median values (median +P95) and comparison of GFR values (mL/min/1.73m²) estimated by CDK-EPI, BIS1 and MDRD formulas. Belém, Pará state, 2023.

eGFR: estimated Glomerular Filtration Rate; p<0.001 (Friedman’s test). Source: study protocol, 2023.
Figure 2. Comparison of eGFR (mL/min/1.73 m²) obtained by CKD-EPI, BIS1 and MDRD formulas in 65-74 years (1A), 75-84 years (1B) and 85-94 years (1C) age groups. Belém, Pará state, 2023.

Friedman’s test (Dunn). Source: study protocol, 2023.
Figure 3. Bland-Altman plot for mean and 95% Confidence Interval of agreement of GFR values (mL/min/1.73m²) estimated by CKD-EPI, BIS1 and MDRD formulas. Belém, Pará state, 2023.

Analysis of graphical pattern of dispersion for comparisons of CDK-EPI versus BIS1 (Figure 3A), CDK-EPI versus MDRD (Figure 3B) and BIS1 versus MDRD (Figure 3C).
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Comparison of GFR (mL/min/1.73m²) estimated using the CKD-EPI, BIS1 and MDRD formulas and the comorbidities analyzed showed significantly lower values for all formulas in patients with SAH, DM2 and CVD, and no difference in those with and without dyslipidemia or across different BMI categories (Table 1).

Comparing the difference in frequency of CKD diagnoses using the current criteria of eGFR <60 mL/min/1.73m² versus eGFR <45 mL/min/1.73m², fewer patients were diagnosed by all formulas when applying the lower limit, with 28.7% of cases defined as not having CKD using the CKD-EPI, 29.1% by the MDRD and 29.5% by the BIS1 equation.

Regarding the eGFR thresholds of 45 and 60 mL/min/1.73m², both calculated by the CKD-EPI, BIS1 and MDRD formulas, a comparison of patients classified above and below the defined cut-off points by comorbidity is presented in Table 2. For estimates using the BIS1 formula, there was a significant association between the presence of SAH and CVD in patients with eGFR <45 (p=0.002 and p=0.036, respectively) and <60 mL/min/1.73m² (p=0.024 and p=0.012, respectively) and between the presence of DM2 and eGFR <45 mL/min/1.73m² (p=0.044).

Table 1. Comparison of eGFR (mL/min/1.73m²) according to comorbidity and formula. Belém, Pará state, 2023.

<table>
<thead>
<tr>
<th>Condition</th>
<th>CKD-EPI Median (IQR)</th>
<th>p-value*</th>
<th>BIS 1 Median (IQR)</th>
<th>p-value*</th>
<th>MDRD Median (IQR)</th>
<th>p-value*</th>
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<tbody>
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<td>SAH</td>
<td></td>
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<tr>
<td>Yes (n=225)</td>
<td>45.8 (31.9 – 59.6)</td>
<td>&lt;0.001</td>
<td>40.5 (33.3 – 52.3)</td>
<td>&lt;0.001</td>
<td>43.3 (30.9 – 55.9)</td>
<td>&lt;0.001</td>
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<tr>
<td>No (n=29)</td>
<td>60.7 (48.8 – 74.2)</td>
<td></td>
<td>54.1 (43.9 – 61.4)</td>
<td></td>
<td>59.1 (47.5 – 67.9)</td>
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<td>DM2</td>
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<td></td>
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<tr>
<td>Yes (n=124)</td>
<td>41.6 (30.6 – 59.5)</td>
<td>0.008</td>
<td>40.0 (31.9 – 53.1)</td>
<td>0.026</td>
<td>39.1 (29.1 – 54.2)</td>
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<td>No (n=130)</td>
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<td>46.1 (37.6 – 54.7)</td>
<td></td>
<td>49.0 (38.1 – 59.7)</td>
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<td>Dyslipidemia</td>
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<td>Yes (n=172)</td>
<td>47.2 (34.8 – 62.0)</td>
<td>0.905</td>
<td>42.5 (34.5 – 54.1)</td>
<td>0.472</td>
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<td>No (n=82)</td>
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<td>46.0 (31.1 – 58.9)</td>
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<td>CVD</td>
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<tr>
<td>Yes (n=59)</td>
<td>40.8 (28.4 – 53.0)</td>
<td>0.006</td>
<td>38.3 (29.4 – 47.8)</td>
<td>0.005</td>
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<tr>
<td>No (n=195)</td>
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<td>44.4 (36.2 – 54.7)</td>
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<td>Normal BMI</td>
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<td>Yes (n=176)</td>
<td>47.6 (34.7 – 62.0)</td>
<td>0.736</td>
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<td>No (n=78)</td>
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<td></td>
<td>43.2 (31.1 – 58.7)</td>
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</table>

DISCUSSION
The results of the present study showed the overall relationships among the 3 formulas for calculating eGFR, revealing reassignments in CKD diagnoses based on eGFR and reclassifications in staging of some patients, with greater dispersion between CKD-EPI and BIS1 indicating lower agreement of these equations.

This lower agreement is likely explained by the fact that the BIS1 formula yielded lower estimated values across all analyses that decreased with advancing age, due to different levels of influence of comorbidities.
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and to intrinsic factors such as sex and muscle mass between these formulas\textsuperscript{6,9,10,16-20}. This result may point to greater utility of this formula for differentiating between a physiological or pathological decline in eGFR among older patients and is consistent with a previous systematic review suggesting the BIS1 formula may be more accurate than the CKD-EPI for calculating eGFR in older adults\textsuperscript{21,22}.

A 2020 cohort study of 7,845 outpatients aged >70 years with CVD showed reclassification of CKD stages in approximately 35\% of participants, with CKD prevalence increasing from 35.4\% to 55.5\% when using the BIS-1 compared to the CKD-EPI\textsuperscript{6}.

Similar studies have also shown that BIS1 values were lower in older adults compared with GFR calculated using the CKD-EPI and MDRD formulas\textsuperscript{16,18}. It is important to note that the BIS1 formula was developed and validated in a sample of people aged over 70 years\textsuperscript{6,23}, whereas the serum creatinine-based CKD-EPI included only a small percentage of older adults\textsuperscript{3}.

By contrast, in participants aged 85-94 years, no statistically significant differences between the MDRD and CDK-EPI equations were found. Thus, almost perfect agreement occurs predominantly in this age group, a finding replicated in previous studies\textsuperscript{14,24}. Other studies of individuals aged > 85 years have also shown that the BIS1 offered greater accuracy than both the CKD-EPI and MDRD\textsuperscript{14}.

Given that different stages of CKD can require different therapeutic approaches, not only in the context of CKD but also its comorbidities, these disagreements can further complicate the health care needs found for older patients, such as incorrect dosing of drugs owing to the need to adjust for renal function, the use of diagnostic mediums such as contrast, and the start of renal replacement therapy\textsuperscript{25-27}.

In addition to comparing different formulas for estimating GFR, this study analyzed different thresholds for defining CKD in older adults. Results showed a stronger association for eGFR <45 mL/min/1.73m\textsuperscript{2}, calculated using the BIS1 formula, with the comorbidities SAH, DM2 and CVD. This threshold led to a higher percentage of people with comorbidities diagnosed with CKD, particularly when determined by increased mortality or greater risk of progression to end-stage renal failure, since the association of CKD with SAH, DM2 and CVD is clear\textsuperscript{1,28,31}.

A 2021 cohort study of a Canadian population reported that the use of the same eGFR threshold (60 mL/min/1.73m\textsuperscript{2}) for all ages can lead to overestimation of diagnosed cases of CKD in older adults and result in unnecessary interventions\textsuperscript{32}. A systematic cohort review conducted in 2010 showed that eGFR < 60 mL/min/1.73m\textsuperscript{2} was associated with increased mortality and higher risk for end-stage renal disease\textsuperscript{33}. However, many authors have cited that the reference group used to support this result was inadequate, concluding that the mortality risk in older patients with eGFR of 45–60 and >60 mL/min/1.73m\textsuperscript{2} was similar, with the former being slightly higher, where significant change in mortality of this group only occurs when eGFR is < 45 mL/min/1.73m\textsuperscript{2}\textsuperscript{14,22,24,34,35}.

Accurate assessment of eGFR is useful in clinical practice for identifying possible cardiovascular outcomes. A study of a general population in China found that the use of serum creatinine-based eGFR, combined with albuminuria or otherwise, improved cardiovascular prediction, particularly for cardiovascular mortality and heart failure\textsuperscript{25}. Thus, correctly calculating eGFR in older adults is paramount, where existing comorbidities and commonly used drugs should also be taken into account\textsuperscript{15} and different classifications of renal function in older adults have direct important clinical implications\textsuperscript{4,28}.

The present study has some limitations. First, the analysis was based on a single center and relatively small sample. Second, equations that use cystatin C for calculating GFR were not adopted, and direct measurements of GFR to serve as a gold standard for comparing the eGFR derived from the formulas were not performed.

CONCLUSION

The BIS1 formula yielded lower eGFR values, favoring its use in the older population. The formula can be used in conjunction with the diagnostic threshold of 45 mL/min/1.73m\textsuperscript{2} for reclassification of CKD patients, leading to more accurate diagnosis of CKD in older patients. Adoption of this approach
Calculation of estimated GFR in older adults can have a major impact on the public health system and on patient prognosis, given that the criteria of 45 ml/min/1.73m² showed stronger associations with comorbidities, particularly SAH, DM2 and CVD. Long-term studies should be conducted to validate the BIS1 for the Brazilian population and compare morbidity-mortality outcomes in patients diagnosed using different thresholds and equations.

AUTHORSHIP

• Daniel Chagas Barreto - Involved in study conception and design; data collection; data interpretation; writing of original draft and approval of final version for publication.
• Juan Lucca Farias - Involved in study conception and design; data collection; data interpretation; writing of original draft and approval of final version for publication.
• Ismari Perini Furlaneto - Involved in study conception and design; data interpretation; writing of article, critical review and approval of final version for publication.
• Lucas Lobato Acatauassu Nunes - Involved in study conception and design; data interpretation; writing of article, critical review and approval of final version for publication.

REFERENCES


