Estimated Glomerular Filtration Rate (Egfr) In Elderly: A Comparison Between The Ckd-Epicreatinine And Biscreatinine Equations

Taxa da filtração glomerular estimada (tfge) em idosos: Comparação entre as equações ckd-epi-creatinina e bis-creatinina

DOI:10.34117/bjdv6n12-787

Recebimento dos originais: 10/12/2020
Aceitação para publicação: 04/01/2021

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ABSTRACT
Background: Aging is a risk factor for the development of chronic kidney disease (CKD). The estimation of the glomerular filtration rate (eGFR) is the most used method to assess renal function, influencing individualized therapeutic adjustment of medications eliminated by the kidneys. Objective: To compare the results obtained using two creatinine-based equations applied in older people: CKD-EPICreatinine and BISCreatinine; as well as evaluate the impact of these equations in the classification of the elderly in different stages of CKD. Materials and methods: An observational study was carried out in a long-term care facility, including subjects aged 70 years or older. Renal function was assessed by two equations: CKD-EPICreatinine and BISCreatinine. Statistical analysis included Kolmogorov-Smirnov, Wilcoxon, Spearman, and Bland-Altman tests. Staging of the level of renal function was performed according to the Kidney Disease: Improving Global Outcomes guidelines. Results: 73 patients with a mean age of 79.2 ± 6.1 years were evaluated. There was a significant decrease (p<0.001) in the eGFR obtained by the BISCreatinine equation in relation to CKD-EPICreatinine. Both equations showed strong correlation (r=0.96, p<0.001). The concordance analysis it was observed a bias of -13.6% (-33.5 to 6.3). From the mild-moderate reduction in renal function (3a stage), there was an increase in the number of elderly people classified in more advanced stages when assessed by BISCreatinine. Conclusion: BISCreatinine has been shown to underestimate the eGFR results, not showing full agreement from a clinical point of view for stratification of renal function with CKD-EPICreatinine in eGFR greater than 59 ml/min x 1,73m2.

Keywords: Glomerular filtration rate, elderly, aging, renal function.

RESUMO
Introdução: O envelhecimento é um fator de risco para o desenvolvimento da doença renal crônica (DRC). A estimativa da taxa de filtração glomerular (TFGe) é o método mais utilizado para avaliação da função renal, impactando no ajuste terapêutico individualizado de fármacos excretados via renal. Objetivo: Comparar os resultados da TFGe utilizando duas equações aplicadas na população idosa: CKD-EPI-Creatinina e BIS-Creatinina; assim como, avaliar o impacto dessas equações na classificação dos idosos nos diferentes estágios da DRC. Material e métodos: Foi realizado em estudo observacional em uma instituição de longa permanência para idosos, incluindo indivíduos com idade >70 anos. A função renal foi avaliada por meio de duas equações: CKD-EPI-Creatinina e BIS-Creatinina. A análise estatística foi realizada pelos testes de Kolmogorov-Smirnov, Wilcoxon, Spearman e Bland-Altman. O estadiamento de acordo com os níveis de função renal foi realizado segundo as diretrizes da Kidney Disease: Improving Global Outcomes. Resultados: Foram avaliados 73 idosos com idade média de 79.2 ± 6.1 anos. Houve diminuição significativa (p<0.001) da TFGe obtida pela equação a BIS-Creatinina em relação a CKD-EPI-Creatinina. As duas equações apresentaram forte correlação (r=0.96, p<0.001). Na análise da concordância, observou-se viés de -13.6% (-33.5 para 6.3). A partir da redução discreta-moderada da função renal (Estágio 3a) houve aumento do número de idosos classificados nos estágios mais avançados quando avaliados pela BIS-Creatinina. Conclusão: BIS-Creatinina demonstrou subestimar os resultados da TFGe, não exibindo concordância plena do ponto de vista clínico, para estratificação da função renal com a CKD-EPI-Creatinina, na TFGe maior que 59 ml/min x 1,73m2.

Palavras-chave: Taxa de filtração glomerular, idosos, envelhecimento, função renal.

1 INTRODUCTION

Aging, or senescence, is a natural and progressive biological process that implies changes in many organism systems (Denic, Glassock, & Rule, 2016). This process is a risk factor to the development of chronic kidney disease (CKD), considering that renal structure and function may be affected by senescence (Abdulkader, Burdmann, Lebrão, Duarte, & Zanetta, 2017).

CKD is characterized by functional abnormalities present for more than 3 months with significant clinical implications (KDIGO, 2013). Among them there is a reduction in the capacity of proximal and/or distal tubular filtration and secretion, resulting in a significant decrease in renal filtration, mainly in the elderly (Garasto et al., 2014), becoming necessary an individualized therapeutic adjustment of medications excreted by the kidneys (Denic et al., 2016).

The most reliable determination to assess renal function is the glomerular filtration rate (GFR), defined as the renal ability to purify a substance from the blood, expressed in milliliters per minute (Gounden, Bhatt, & Jialal, 2020). The gold standard for measuring GFR is the inulin renal clearance, nonetheless is an invasive procedure, which demands individual care and has a high cost, making it impractical (Raman, Middleton, Kalra, & Green, 2017).

In the laboratory practice, the biomarker used most frequently in the clinical assessment of renal system is the determination of serum creatinine (Porrini et al., 2019), and its use for the assessment of renal function is due to the low cost, laboratory availability, being frequently included in laboratory exam profiles (Miller & Jones, 2018). Creatinine is a product of the breakdown muscle creatinine phosphate, in other words, its production is dependent on muscle mass, which explains the variations related to factors like age, gender, race, and protein intake (Schaeffner et al., 2012; Van Pottelbergh et al., 2014). Thus, serum creatinine alone is an inconsistent indicator of renal function, being preferable its use associated with equations that estimate GFR (eGFR), including variables like age and gender (Bastos & Kirsztajn, 2011; Libório et al., 2012), making this method frequently used in elderly (Oscanoa, Amado, Romero-Ortuno, & Hidalgo, 2018).

The CKD evaluation and management guideline, the “Kidney Disease: Improving Global Outcomes (KDIGO)”, classify individuals in five stages based on eGFR: normal > 90 mL/min x 1,73m2 (stage 1), mildly decrease 89 - 60 ml/min x 1,73m2 (stage 2), mild to moderate decrease 59 – 45 ml/min x 1,73m2 (stage 3a), moderate to severe decrease 44 - 30 mL/min x 1,73m2 (stage 3b), severe decrease 29 – 15 mL/min x 1,73m2 (stage 4), kidney failure < 15 mL/min x 1,73m2 (stage 5) (KDIGO, 2013). The most popular formula to eGFR in clinical practice include Cockcroft Gault (CG), Modification of Diet in Renal Disease (MDRD), and CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), but its use in specific populations may be restrictive, mainly due to loss of accuracy in their results (Garasto et al., 2014; Libório et al., 2012; Vinodh Kumar & Mohan, 2017).

While CG does not take into account the factors that affect creatinine metabolism and secretion, the study population of MDRD did not includ any individual over 70 years (Raman et al., 2017). Yet, the CKD-EPI equation is considered the most precise in the temporal classification of CKD, mainly em subjects with eGFR close to reference and/or borderline values (Gaitonde, Cook, & Rivera, 2017).

Besides that, KDIGO recommends the use of CKD-EPI to estimate GFR, unless there is evidence that another equation performs better (Miller & Jones, 2018). For example, the BISCreatinine equation, developed by the Berlin Initiative Study (BIS), that demonstrates great symmetry in their results in older people (Schaeffner et al., 2012).

Although there is evidence available in the literature that supports the use of BISCreatinine equation in subjects 70 years or older, CKD-EPICreatinine also remains a recommended equation for the elderly (Corsonello et al., 2018). Therefore, it becomes important to interpret the possible differences between these equations in the elderly population, especially concerning the assessment of renal function and its time-dependent classification, because of possible CKD. Thus, the objective of this study was to compare the results obtained by the BISCreatinine and CKD-EPICreatinine equations; as well as evaluate the impact of these equations on the classification of the elderly at different stages of CKD.

2 MATERIALS AND METHODS

An observational study was carried out, with subjects residing in a long-term care facility (LTCF), in the city of Ponta Grossa – Paraná, Brazil, between March 2018 and March 2019.

The authorization term was provided by the legal responsible of the elderly residents in the LTCF. This study was approved by the Ethics Committee of the State University of Ponta Grossa, opinion n. 2.745.328. This research was carried out in accordance with the Declaration of Helsinki.

Only individuals over 70 years old who had a medical request for serum creatinine were selected for the study. Personal information (age, sex, and race) of the research participants were obtained from medical records provided by the LTCF

Venous blood puncture was performed according to the protocol, by an enabled pharmacist; the samples were processed in the University Laboratory of Clinical Analysis of the State University of Ponta Grossa (LUAC – UEPG). Serum creatinine concentrations were obtained by the kinetic-colorimetric method in the automated device CT 300i (Wiener Lab. Group®). If the serum creatinine values were obtained by the conventional method, the results were standardized according to the reference method, considered the gold standard for determining creatinine and traceable to the ID-MS (*Isotope Dilution Mass Spectrometry*), by the following equation: [ID-MS_Creatinine (mg/dL) = (conventional_Creatinine – 0.067)/1.065].

Renal function was assessed by eGFR, obtained by two equations:

- The *Chronic Kidney Disease Epidemiology Collaboration* group developed the CKD-EPICreatinine equation (Levey et al., 2009):

Female			Male	
Race	Creatinine (Cr)	Formula	Creatinine	Formula
Black	≤ 0.7	$GFR = 166*(Cr/0.7)^{-0.329} * 0.993^{age}$	≤ 0.9	$GFR = 163*(Cr/0.9)^{-0.411} * 0.993^{age}$
Black	> 0.7	$GFR = 166*(Cr/0.7)^{-1.209} * 0.993^{age}$	> 0.9	$GFR = 163*(Cr/0.9)^{-1.209} * 0.993^{age}$
White or other	≤ 0.7	$GFR = 144*(Cr/0.7)^{-0.329} * 0.993^{age}$	≤ 0.9	$GFR = 141*(Cr/0.9)^{-0.411} * 0.993^{age}$
White or other	> 0.7	$GFR = 144*(Cr/0.7)^{-1.209} * 0.993^{age}$	> 0.9	$GFR = 141*(Cr/0.9)^{-1.209} * 0.993^{age}$

- The Berlin Initiative Study group developed the $BIS_{Creatinine}$ ["BIS-1"= $3736*Creatinine^{-0.87}*Age^{-0.95}$], and for female participants, the eGFR must be multiplied by 0.82 (Schaeffner et al., 2012).

Subsequently, the eGFR results for the two equations were evaluated by reference values and staging for adults, according to KDIGO: normal > 90 mL/min x $1,73m^2$ (stage 1), mild decrease 89 - 60 ml/min x $1,73m^2$ (stage 2), mild to moderate decrease 59 – 45 ml/min x $1,73m^2$ (stage 3a), moderate to severe decrease 44 - 30 mL/min x $1,73m^2$ (stage 3b), severe decrease 29 – 15 mL/min x $1,73m^2$ (stage 4), kidney failure < 15 mL/min x $1,73m^2$ (stage 5) (KDIGO, 2013).

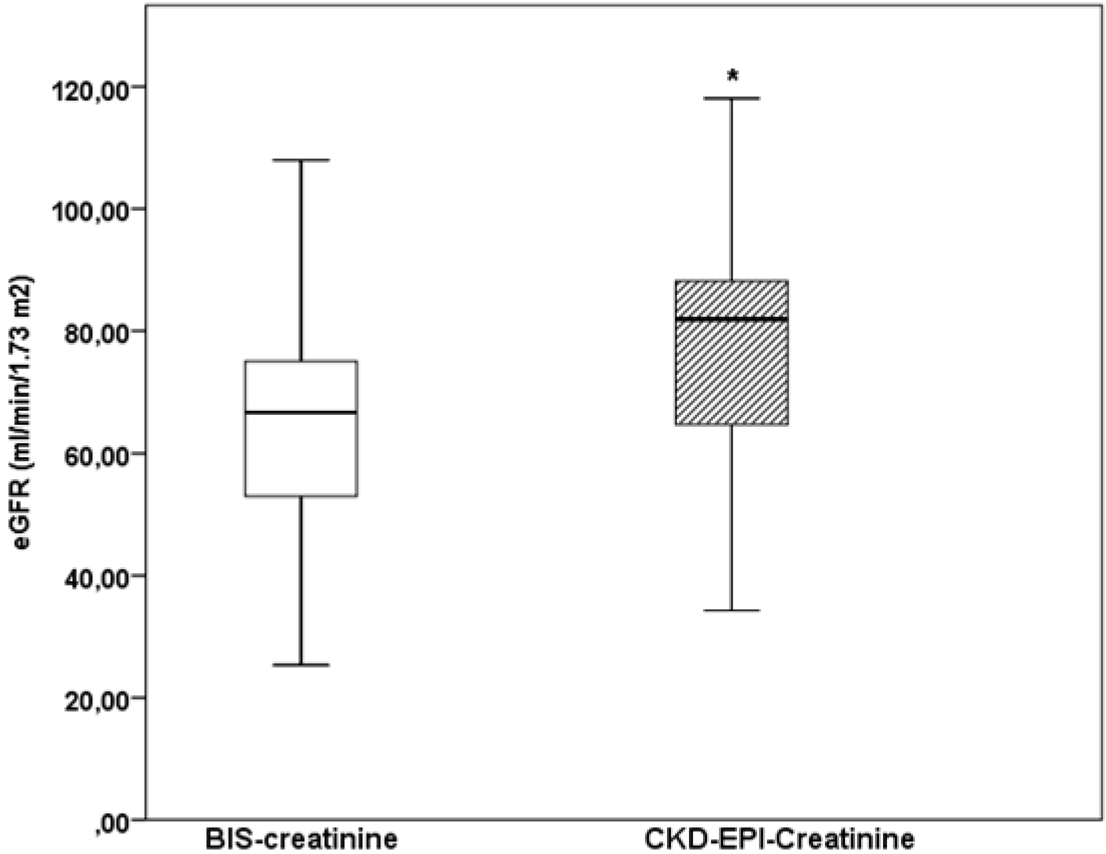
2.1 STATISTICAL ANALYSIS

Normality was assessed by the *Kolmogorov-Smirnov* test. If normality was confirmed, data were shown as mean and standard deviation (mean ± SD), as for age variable. Nonetheless, when normality is not confirmed, as for variable eGFR, data were shown as median and interquartile range. The comparison between the results of eGFR, obtained by $BIS_{Creatinine}$ and $CKD\text{-}EPI_{Creatinine}$ equation, was performed by the Wilcoxon test. The correlation between the two equations was analyzed using Spearman's correlation coefficient. The Bland-Altman plots were used to detect bias between the two equations, showing the difference (in percentage) of the values in the axis [($CKD\text{-}EPI_{Creatinine}$ – $BIS_{Creatinine}$)/mean %] versus the average of the two measurements, with analysis of the limits of agreement. The distributions of the CKD stages based on the two eGFR equations, according to the KDIGO classification, were presented in number and percentage. Data were analyzed by the MedCalc® program, version 19.0.3 (MedCalc Software, Ostend, Belgium), and the significance level was pre-fixed in $p < 0.05$.

3 RESULTS

A total of 73 subjects with a mean age of 79.2 ± 6.1 years were evaluated, 44 (60.3%) of whom were female and 29 (39.7%) of whom were male. In the evaluation of eGFR, the $BIS_{Creatinine}$ equation presented median values of 66.6 (52.8 – 75.1) ml/min/1.73 m^2; whereas CKD-EPI$_{Creatinine}$ evidenced values of 81.9 (64.0 – 88.5) ml/min/1.73 m^2, showing a significant difference between the results ($p<0.001$) (Figure 1).

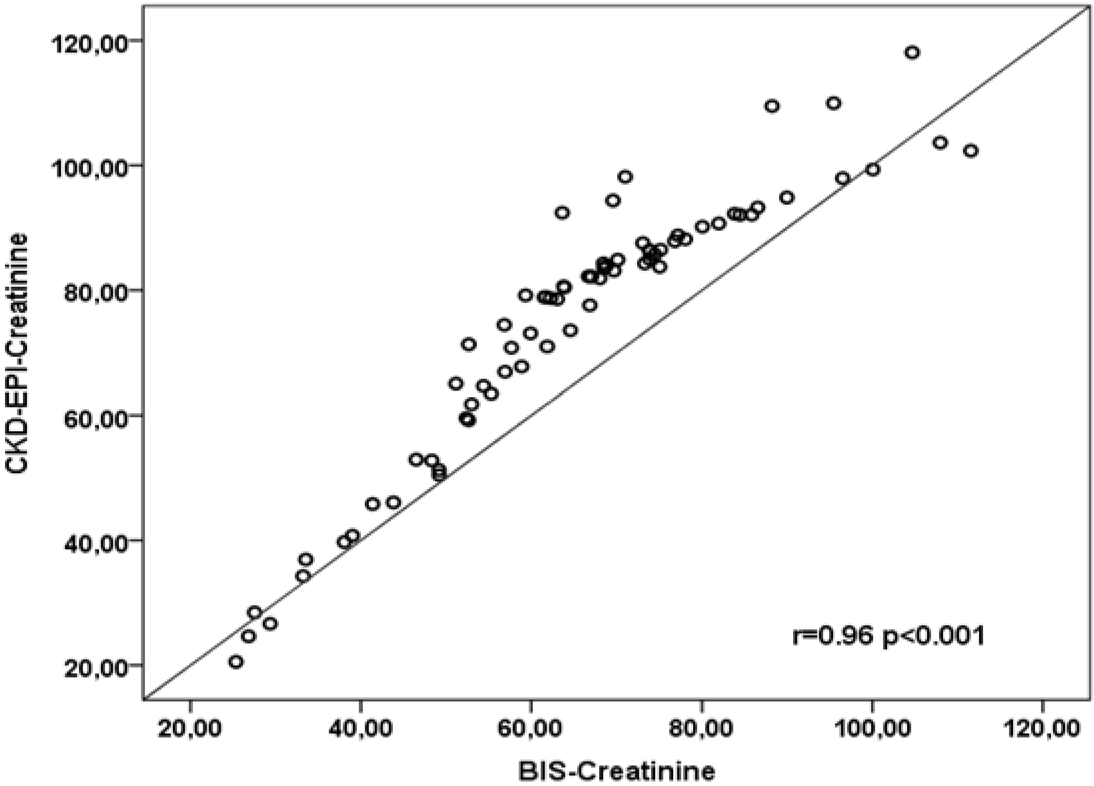
Figure 1 – Median and interquartile range of the estimated glomerular filtration rate (eGFR) of the elderly, according to the BIS$_{Creatinine}$ and CKD-EPI$_{Creatinine}$ equations.



*statistical difference between the two equations ($p<0.05$).
CDK-EPI, Chronic Kidney Disease Epidemiology. BIS, Berlim Initiative Study.

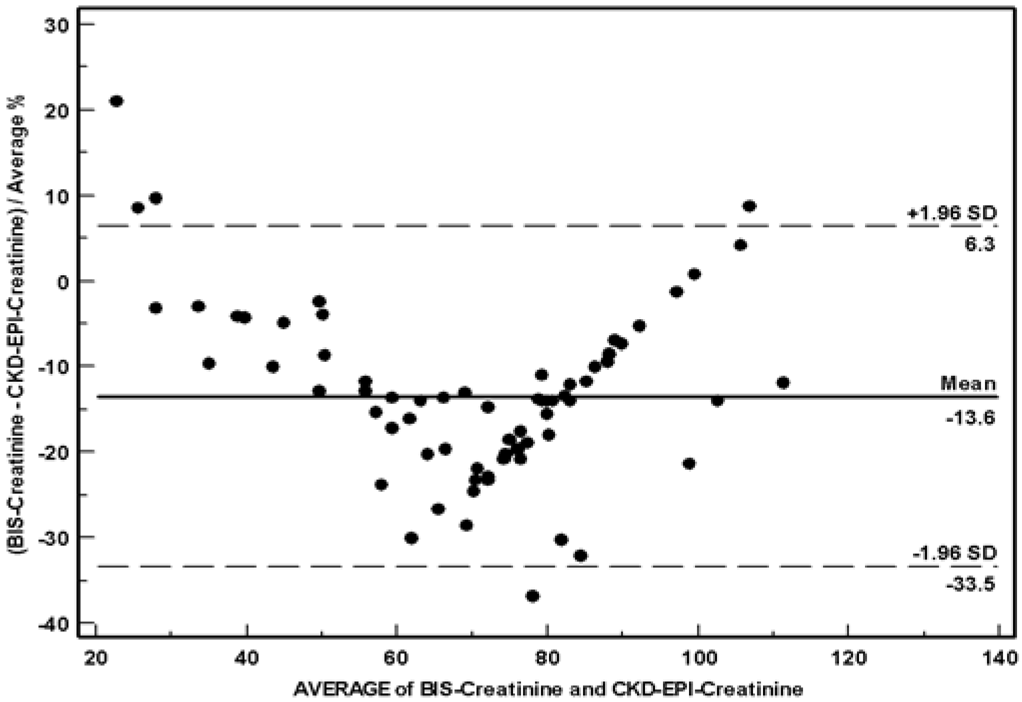
Furthermore, correlation and concordance between the BIS$_{Creatinine}$ and CKD-EPI$_{Creatinine}$ equations in the elderly population were evaluated. Both equations showed strong correlation ($r=0.96$, $p<0.001$) (Figure 2). However, the concordance analysis showed a mean difference between the two equations of -13.6% (-33.5 to 6.3), and the values can be underestimated by up to 33.5% or overestimated by up to 6.3%, with a variation of approximately 19.9% (Figure 3).

Figure 2 - Spearman's correlation to the values of glomerular filtration rate (eGFR) by BISCreatinine and CKD-EPICreatinine equations in the elderly evaluated in the study.



CDK-EPI, Chronic Kidney Disease Epidemiology. BIS, Berlim Initiative Study.

Figure 3 – Concordance analysis between the CKD-EPI$_{Creatinine}$ and BIS$_{Creatinine}$ equations. Bland-Altman plots (upper and lower dotted lines represents the concordance level (mean ± 1.96 DP); continuous line represents the mean difference between the two equations evaluated in the study.



CDK-EPI, Chronic Kidney Disease Epidemiology. BIS, Berlim Initiative Study.

The staging of CKD based on eGFR equations, according to the KDIGO classification, are shown in Table 1. As the $BIS_{Creatinine}$ equation demonstrated an underestimation of the results, the modification of the classification of stages in relation to the results of $CKD\text{-}EPI_{Creatinine}$ is shown in Table 2. It was observed that from the mild to moderate decrease in renal function (stage 3a) there was a change in the diagnosis when the eGFR was calculated using $BIS_{Creatinine}$, thus highlighting the increase in elderly people classified with more advanced stages, than when evaluated by CKD-EPI (Table 2).

Table 1 – Classification of chronic kidney disease by the eGFR according to the equations evaluated in the study.

Renal function KDIGO	$CKD\text{-}EPI_{Creatinine}$ (n=73) n (%)	$BIS_{Creatinine}$ (n=73) n (%)
Normal > 90 mL/min x 1,73m^2 (Stage 1)	17 (23.3)	7 (9.6)
Mildly decreased 89 – 60 ml/min x 1,73m^2 (Stage 2)	41 (56.1)	40 (54.8)
Mildly to moderately decreased 59 – 45 ml/min x 1,73m^2 (Stage 3a)	7 (9.6)	16 (21.9)
Moderately to severely decreased 44 – 30 mL/min x 1,73m^2 (Stage 3b)	4 (5.5)	6 (8.2)
Severely decreased 29 – 15 mL/min x 1,73m^2 (Stage 4)	4 (5.5)	4 (5.5)
Kidney failure < 15 mL/min x 1,73m^2 (Stage 5)	0 (0)	0 (0)

TFGe, taxa de filtração glomerular estimada
KDIGO, *Kidney Disease Outcomes Quality Initiative*
BIS, *Berlim Initiative Study*
CDK-EPI, *Chronic Kidney Disease Epidemiology*

Table 2 – Distribution of the number of elderly people according to the stages of chronic kidney disease classified by the eGFR using $BIS_{Creatinine}$ in relation to $CKD\text{-}EPI_{Creatinine}$

$CKD\text{-}EPI_{Creatinine}$ Kidney Function (KDIGO)							
$BIS_{Creatinine}$	Stage 1	Stage 2	Stage 3a	Stage 3b	Stage 4	Stage 5	Total
Stage 1	**7**	*10*	0	0	0	0	17
Stage 2	0	**30**	*11*	0	0	0	41
Stage 3a	0	0	**5**	*2*	0	0	7
Stage 3b	0	0	0	**4**	0	0	4
Stage 4	0	0	0	0	**4**	0	4
Stage 5	0	0	0	0	0	0	0
Total	7	40	16	6	4	0	73

The numbers in bold indicates the elderly who have not changed their stage evaluated by the two equations.
The numbers in italics indicate the elderly who changed stages due to the $BIS_{Creatinine}$ in relation to the $CKD\text{-}EPI_{Creatinin}$. KDIGO, *Kidney Disease Outcomes Quality Initiative*
BIS, *Berlim Initiative Study*
CDK-EPI, *Chronic Kidney Disease Epidemiology*

4 DISCUSSION

eGFR based on serum creatinine level is a fast and low-cost determination to assess kidney function, being important in the therapeutic management of drugs excreted by the kidneys, mainly in the elderly, in view of the possible toxicity caused by the accumulation of these drugs or their active metabolites (Houlind et al., 2018).

The results of this study demonstrated significantly decreased values of eGFR when obtained by the $BIS_{Creatinine}$ equation in relation to the $CKD\text{-}EPI_{Creatinine}$. Despite having a strong correlation (r = 0.96), the high bias (- 13.6%) may demonstrate disagreement from the point of view of the patient's clinical evaluation in the face of the two equations, as demonstrated in the results of stratification of kidney function. Thus, the results obtained by $BIS_{Creatinine}$ may be underestimated in relation to $CKD\text{-}EPI_{Creatinine}$, corroborating the information obtained so far (Bustos-Guadaño et al., 2017; Houlind et al., 2018).

It is observed that there are differences between the two equations and that these result in different stratifications according to the kidney function. Of the 17 individuals classified in stage 1 using $CKD\text{-}EPI_{Creatininr}$, 10 were reclassified in stage 2 when evaluated by $BIS_{Creatinine}$; of the 41 classified in stage 2, 11 were reclassified in stage 3a; of the 7 individuals classified in stage 3a, 4 were reclassified in stage 3b. Bustos-Guadaños et al. (2017) report that the estimate based on $BIS_{Creatinine}$ results in a greater number of individuals with severe CKD according to KDIGO, as it allocates more patients in stages 3b and 4. The present study showed that the classification change does exist, but reallocated more subjects in stages 2 and 3a. This divergence may be explained by the age difference of the studied populations, considering that Bustos-Guadaños et al. (2017) worked with an older population (85-98 years old) and that the kidney function tends to reduce with age advance (Denic et al., 2016).

Should be highlighted that $BIS_{Creatinine}$ is an equation validated to estimate the GFR in the elderly, especially in cases of normal or mild to moderately decreased kidney function, decreasing the wrong classification of subjects with GFR greater than or less than 60 mL/min/1,73m^2 (Schaeffner et al., 2012). Nevertheless, the results of this study raise the hypothesis that BIS-Creatinine may identify the elderly with decreased kidney function earlier when compared to $CKD\text{-}EPI_{Creatinine}$.

Corsonello et al. (2018) claim that although the $CKD\text{-}EPI_{Creatinine}$ equation is considered a reference to assess kidney function, it may produce unsatisfactory results in the elderly population (Corsonello et al., 2018). Koppe et al. (2013) report that $CKD\text{-}EPI_{Creatinine}$ was purposely developed in a population with better kidney function, that intentionally included healthy individuals, which explains the better performance in greater values of eGFR (Koppe, Klich, Dubourg, Ecochard, & Hadj-Aissa, 2013). They also affirm that $BIS_{Creatinine}$ tends to be the most reliable way to estimate the GFR in the elderly due to the consistency of the research design that developed it, which include creatinine dosage by the enzymatic method traceable to the ID-MS (*Isotope Dilution Mass Spectrometry*) and its comparison with the gold standard for determining GFR, in a wide population with a mean age of 78.5 years and mild to moderate decrease in kidney function, showing greater concordance and correlation with the inulin clearance, mainly in subjects with eGFR greater than 30mL/min/1,71m^2 (Koppe et al., 2013).

Oscanoa et al. (2018) performed a systematic review, with 1295 studies, demonstrating to estimate of GFR in the elderly, the $BIS_{Creatinine}$ equation seems to be more precise than $CKD\text{-}EPI_{Creatinine}$, mainly in individuals older than 70 years. The $BIS_{Creatinine}$ precision may be greater than $CKD\text{-}EPI_{Creatinine}$, especially in the elderly with GFR ≥ 60 ml/min/1,73 m^2 (Oscanoa et al., 2018). It should be noted that the results of the present study demonstrated changes in the distribution of the number of elderly people according to the stages of CKD assessed by $BIS_{Creatinine}$ in relation to $CKD\text{-}EPI_{Creatinine}$ in subjects with eGFR greater than 59 ml/min x 1,73m^2.

Selistre et al. (2019) mention that each equation has better performance in the population in which the study was developed. They also report that, although the study population in CKD-EPI-Creatinine is quite heterogeneous in terms of age group and that only 13% of the individuals studied were 60 years or older, the study showed satisfactory performance of this equation in elderly patients with different levels of GFR (Selistre et al., 2019).

This present study has some limitations, a gold standard was not used to measure GFR and the sample was composed exclusively of institutionalized elderly.

5 CONCLUSION

Based on the results obtained by the present study, it is evident that eGFR by $BIS_{Creatinine}$, in patients over 70 years of age, underestimates the results and does not show full correlation, from the clinical point of view to the stratification of kidney function with $CKD\text{-}EPI_{Creatinine}$, recommended by KDIGO, in eGFR greater than 59 ml/min x 1,73m^2.

The choice of the method used to evaluate eGFR in the elderly has a great impact in the clinical practice, especially in the use of drugs that undergo excretion and/or clearance by the kidneys or have a possible toxicity effect, considering that the same subject may be classified at different stages of kidney function according to the equation used. Thus, the results of the present study demonstrate the need to establish specific guidelines for the elderly population.

ACKNOWLEDGMENTS

The authors are grateful to the Asilo São Vicente de Paulo (Long-Term Care Facility - LTCF) and to LUAC – University Laboratory of Clinical Analysis of the State University of Ponta Grossa (UEPG), for allowing this study to be carried out.

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