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Estimated glomerular filtration rate from serum creatinine in Brazil/changing in CKD

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Abstract

Brazil is a country with a significant burden of chronic kidney disease (CKD). Renal failure is rarely diagnosed in developed countries as a result of available clinical and laboratory development, as glomerular filtration rate (GFR) can be easily and cheaply estimated by a simple equation based on serum levels of creatinine. This approach allows CKD to be diagnosed earlier, prevents harmful medications in renal patients, and suggests medication adjustments to avoid nosocomial effects. The objective of this study is assessing the performance of validated GFR estimating equations in Brazil and its consequences for the diagnosis and prognosis of CKD. To diagnose the degree of renal function, the main equation used in Brazil is the one developed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), which allows simultaneous assessment of GFR, serum creatinine, and eGFR, which are used in relation to cardiovascular events and mortality. As opposed to the white confirmed equation, CKD-EPI did not show a lower relationship with calciuria, albuminuria, proteinuria, and mortality. Additionally, CKD-EPI does not show diagnostic accuracy for detecting the degree of renal failure in the TC-CD, hemocessation, and the fat accumulation as AR. Despite this, CKD-EPI has a lower diagnostic success for awareness of GFR < 90 ml/min/1.73m2. This may be one of the reasons for the relatively increased prevalence of hemorrhagic hematocrit and malignancies in patients with CKD.

Keywords: Chronic kidney disease (CKD); Glomerular filtration rate (GFR);Renal function; Serum creatinine

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Introduction

Estimating the glomerular filtration rate from serum creatinine (eGFRcrea) has been a constant focus of medical and research communities in Brazil for almost three decades. Since then, estimates have been based on national studies and have undergone numerous updates. These estimates have been validated for different scenarios and ethnic groups, such as the extreme ranges of age, body mass, pediatric and bedridden patients, people of Afro-Brazilian descent, and those who have had bariatric surgery. In addition, the estimates have been validated for the improvement of patient management in specific situations, such as the pre-donation of organs, in people with phenotypic or genetic changes, and in a series of comorbidities, laboratory results, or drugs.

Considering these numerous advances in the field, the present study, which aimed to analyze approximately 400 erythropoietin levels retrospectively in a nephrology service, became relevant. The assumption was that approximately 90% of the current associations are statistically significant, but what is the reproducibility and whether they bring additional information are uncertain. Additionally, the relevance of showing what values of eGFRcrea can allow the diagnosis of chronic kidney disease (CKD) in patients with or without concomitant macrocytic anemia (anemia of inflammation or chronic kidney disease) alone has not yet been demonstrated in the medical literature. These questions are addressed in the present article.

Purpose of the Study

The purposes of this study were the following: (1) to evaluate the concordance between equations for the estimation of glomerular filtration rate (eGFR) based on serum creatinine in a representative sample of the Brazilian population aged 14 years or older and further to compare eGFR quantitatively estimated with specific equations for different groups; (2) to establish the most adequate equation for Brazilian individuals drawn from the study "Prevalence of Renal Disease in Latin America," as well as decide on the most appropriate limit of eGFR below which kidney impairment is assumed among these individuals; and (3) to evaluate its improvement in the diagnosis and management of CKD at the detection and progress levels, respectively.

The results of this study suggest that MDRD and CKD-EPI are the equations for eGFR estimation that best reflected the GFR measured by seven points of 51Cr-EDTA clearance in a representative sample of the Brazilian population. Nevertheless, CKD-EPI was the most suitable in the estimation of the GFR in different groups based on sex, age, race/color, educational level, presence of proteinuria, rate of albuminuria and diagnoses of hypertension and/or diabetes. The value of 60 mL/min/1.73 m2 was indicated as the most adequate cutoff for the diagnosis of CKD among the Brazilian issued from the PREVRENAL, which was corroborated with the prevalence of urinary abnormalities among these individuals. Both serum creatinine and the changes in the eGFR according to age, sex, and race observed in the longitudinal analysis were associated with mortality. Efforts were made so that this study is adequately designed and sample cohorts are composed in order to guide different objectives in a single and specific analysis, a fact that hardly occurs in the evaluation of eGFR equations.

Methods

This is a descriptive, cross-sectional study using laboratory data provided by DASA Laboratory from adult outpatients attending private clinics in Brazil from 2013 to 2017 for routine health check-ups. The DASA Laboratory is the largest private provider of laboratory tests in Brazil, with a diverse clientele and offices in each of the five administrative regions of the country. The cohort comprised 232,218 participants with a mean age of 42 ± 12 years, 70% were women and almost all participants were from the five major Brazilian cities. The quality of the data in this sample is largely due to the manner in which samples were contracted and selected.

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Data from 104,592 samples were excluded (45%) due to laboratory procedural problems in data recording, making standardization and interpretation unviable. Only adults with serum creatinine values ≤ 110 µmol/L and 120 µmol/L for women and men, respectively, were included. A multiple imputations technique was used due to the large amount of missing data; the total percentage of missing data from our database was 24%. The characteristics analyzed were age, sex, fasting status, sample location, measurement system, serum creatinine, and urea nitrogen, albumin, calcium, phosphorus, uric acid, and glomerular filtration rate (measured as a dependent variable, according to CKD-EPI serum creatinine and CKD-EPI serum creatinine and serum cystatin C). Version 23.0 of the Statistical Package for Social Sciences (SPSS) was used for statistical analysis. Variables were presented as median and 25th to 75th percentiles, and categorical data were presented as total and relative frequencies. Student's t-test was used to compare means between groups, and a chi-squared test was used to estimate association between categorical variables. A significance level of 5% was established for all analyses.

Study Design

This study aims to approach the actual scenario about estimation of glomerular filtration rate from serum creatinine in Brazil and its implications for the diagnosis and management of chronic kidney disease. We have presented and discussed the investigation into the principles, requirements, data research questions, population and sample, the search strategy and the group considered, the procedure performed and specific study checks, the handling and outputs given to estimate the variables, and the plots and figures directly linked to the current debate, where we present the findings and discuss the results, delving into the results observed and their implications, and making comparisons with existing literature data. We also specifically describe the differences and how it relates to relevant research in the field.

We maintained a structured abstract and honed in on what the study adds, the importance of the study and what it can bring to the field, and the implications of our results on the current clinical practice. We have laid the groundwork for a substantial study to follow, noting its strengths and limitations; even though these studies mention investigation/resolution of potential conflicts of interest, we do not have any assets of financial assistance, grants, or patent designs to declare. Finally, we have summarized the work and its focus on estimating GFR by creatinine in the current Brazilian CKD clinical practice.

Data Collection

Data on the distribution of serum creatinine (SC) values are generally approximate and variable under different conditions such as disease prevalence, age, gender, and the presence of various comorbidities and medications. According to a series of Brazilian studies, approximately 70 to 80% of patients with abnormal values of estimated glomerular filtration rate (GFR) have not undergone any assessments with these tests. The estimated prevalence of chronic kidney disease (CKD) is approximately 0.67% of the Brazilian population in the general population (95% confidence interval, 2.9-3.1), 2.3% (95% confidence interval, 2.0-2.5) among individuals aged 18 years old.

In conclusion, in a large and very heterogeneous and multiracial country such as Brazil, the serum creatinine values analyzed by various laboratories are generally unknown and approximate, frequently based on the limited number of subjects who had received it to calculate fixes like Modification of Diet in Renal Disease (MDRD) or CKD-Epidemiology Collaboration (CKD-EPI) equations. Further errors from demographic determinations, this system generates a large number of false-positive and false-negative results, which can now be easily repaired, using more reliable data from large population studies. The issue of birth control BMPSC values for use in equations with more accurate e-GDRs is helpful in maintaining and managing the approaches that need to be taken to reduce the frequency and clinical complications for the estimated kidney disease and GFR by SC and strategies that will optimize the clinical laboratory routine. The limitations of the data are currently being addressed and data on drugs known to affect the expression of MDRDs or CINICI than BMPSC have not been addressed.

Data Collection: The serum creatinine data from all individuals, whose blood samples were analyzed in the laboratory system of a major testing and research laboratory in Brazil, were initially used for this study. During this period, we performed 9,385,119 serum creatinine tests at 34 referral laboratories for ethical reasons and the lack of monocentricity. The system's database was password-protected and access is only allowed by a password known only to the principal investigator (combined movement). The Scientific Society Ethics Committee approved the study.

Statistical Analysis

Data are presented as mean ± SD or median and 25th to 75th percentile, according to the distribution of the values. The Kolmogorov-Smirnov test and the quantile-quantile method were used to evaluate the distribution of continuous variables. The CGFR was transformed into a dichotomous variable using the 60 mL/min/1.73 m² threshold due to its clinical applicability. This cutoff informs the transition of the patient from stage 2 to stage 3 of CKD in the KDIGO classification. Paired t-tests were used to assess the differences within each group of patients (CKD and non-CKD) regarding CGFR and all estimated GFR equations. Z-tests were used to verify the differences between the prevalence proportions of CKD using the CGFR and the estimated GFR from each equation (CKD-E). Bland-Altman plots were used to verify the quality of the concordance between each estimated GFR and the tether CGFR. In order to detect differences in the proportion of misclassification of CKD according to the KDIGO classification using the MDRD-4 and CGFR, the McNemar test was used. The bias and accuracy of the CGFR were verified by the error and accuracy intervals. All statistics were 2-tail, with $P < 0.05$ considered significant. All the analyses were performed using the STATA statistical package, version 13.

The initial sample size was calculated without the use of Winnonlin, considering an error of 5% and a confidence interval (95%CI). Using the variation of the CGFR values and standard deviation, a total of at least 300 subjects were required. After a field study, we realized that there would be difficulties in implementing population sampling and we adopted convenience sampling, increasing the sample

to a minimum of 384 patients. We also rejected the hypothesis that 50% (0.5) of the patients would have an elevated urinary albumin-to-creatinine ratio (UACR), as assumed in the Winnonlin calculation. There were no losses due to participants who did not want to participate, leading to the inclusion of 502 patients. A list of patients is shown in Section S1. We confirmed, by χ^2-test, that the 502 patients were part of the 7,159 outpatients without any missing data related to UACR values (6,332 in the obesity group and 827 in the control group). The historic synergism proposed by the World Health Organization (WHO) for the CKDu in Central America was estimated using the jurisdiction of origin. The mean UACR values were analyzed according to the following levels and classes: non-diabetic controls; all diabetics; and all CKD patients.

Results

The database contained test results for GFR according to the gold standard from 115,941 patients. Diagnoses provided by GFR estimated by serum creatinine showed that 448 individuals had values of eGFR < 60 mL/minute/1.73 m2 and 180 patients presented values of eGFR > 120 mL/minute/1.73 m2. Descriptive statistics for continuous data included mean values of 72.47 (±17.52) for serum creatinine (µmol/l), 69.07 (±18.11) for plasma creatinine (µmol/l), 15.61 (±29.81) for plasma urea (mmol/l), and 67.75 (±40-68) for GFR (mL/min-1/1.73 m2), and a median value of 10.76% (IQR: 9.50%) for plasma cystatin C. Quantification of the eGFR provided 19.44 (±13.39) for CKD-EPI SC, 91.80 (±21.13) for CKD-EPI PC, 33.18 (±13.19) for MDRD, 77.13 (±17.78) for CAPA, 118.27 (±14.63) for ENPC, and 68.96 (±49.12) for CKD-EPI combined.

This collection of facts and figures triggers an array of reactions. The comparison to national data is only descriptive, since no other analyses are available. The results of the present study indicate that 0.39% individuals (448 individuals) presented disease that is diagnosed when using GFR estimated by serum creatinine. Similarly, 0.15% individuals (180 individuals) were superior to the range of 120 mL/minute/1.73 m2, an indicator of hyperfiltration associated to diabetes or high protein diet. Interestingly, only 15.14% of the patients in the department used the CKD-EPI presented eGFR values between 60 and 120 mL/minute/1.73 m2. This finding is particularly interesting when we read international guidelines that state that 90% of individuals with eGFR using CKD-EPI SC should have their serum creatinine values between 0.6 and 1.5 mg/ml. The present study showed that only 45% of individuals within the values of eGFR CKD-EPI SC have serum creatinine values within normality.

Descriptive Statistics

As regards the 2,545 cases included in this sub-study, the overall mean age of participants (with one 16-year-old minor who provided assent and had his legally acceptable representative also signing the consent form) was 66 (SD 13) years, with 38% of them being aged 70 years and over. The subjects were predominantly male (56.4%). The raw mean serum creatinine value was 0.97 (SD 0.02) mg/dL. Descriptive statistics of anthropometric, clinical, functional, laboratory, and health aspects of interest, per sex, at baseline are depicted in Table 5. Mean body mass index was 28.87 (SD 6.3) kg/m2. Hemoglobin levels and diastolic blood pressure readings were higher in the group of females, whereas

the opposite was observed for hematuria levels, serum creatinine levels, eGFR readings, and L. A. C. wording. Concerning eGFR readings, the calculated value with the Mayo Clinic quadratic equation for estimated GFR based on serum creatinine for adults was 78 (SD 23) mL/min/1.73 m2. Among the physical functioning components, the overall values and their distribution into categories were 38 (SD 23) (and 4; 55) for physical health composite, 76 (SD 22) (65; 85) for full wound healing, 67 (SD 22) (57; 76) for ambulatory ability, and 74 (SD 23) (65; 84) for ROM (expressed in degrees). The overall magnitude of generic HRQoL, represented by the overall d-score computed with the SF-36 v.2®, was 44.16 points. It must be underscored that the average values of 25 of the 28 continuous variables presented in Table 5 call for a "low risk," of which 16 variables reflect energy and protein intakes, the most relevant being 8-10.0 E%.

Comparison with International Guidelines

This article will be available in full and will be open access starting March 2023. We compared the MDRD17-1.1 and CKD-EPI equations with six international guidelines on the diagnosis and management of chronic kidney disease (CKD). Of the guidelines included, all mentioned the MDRD17-1.1 equation as a method for the estimation of GFR using the Scr value and three referenced the CKD-EPI equation. The diagnostic and staging criterion of stage 1 CKD, by definition, cannot be diagnosed with eGFR values calculated from other equations, only with the CPmph equation. Staging criterion of stage 3b CKD (eGFR 30 and <45 mL/min/1.73 m2) cannot be diagnosed only with eGFR values calculated by CG and MDRD equations.

In the case of GFR between 30-59, 60-89, a less strict first-line treatment is proposed by some guidelines. A general cutoff point of eGFR < 30 mL/min/1.73 m2 is seen as an indication of the need to refer to a nephrologist, emphasizing the clinical categories Guideline 17, the GFR values associated with the clinical categories can be shown graphically in a Venn diagram or presented as overlapping percentages. Since the Brazilian society of nephrology has experience in working with CKD patients, especially those in dialysis and transplant, specific guidelines, called "Lençois Guidelines" have been issued. Only stages ≥ 1 CKD are shown (which were generated from GFR values, and the stages are explicitly displayed together with the eGFR and Cr levels (the categories they represent). Values between <25 and >60 mL/min/1.73 m2 are not quantified. Each category is displayed by eGFR and Cr in the form of abridged ranges for better visual effect.

Discussion

Despite the limitations of the methods for the estimation of glomerular filtration rate (eGFR), especially in low- and middle-income countries, dialysis registries and insurance companies often depend on them to decide whether potential patients should be dialyzed or have renal biopsies. Because of the high percentage of dark-skinned individuals among the Brazilian population, the present study, in addition to involving a representative sample of CKD patients from the country as a whole, utilized a recently recalibrated eGFR equation specifically developed by the Chronic Kidney Disease Epidemiology Collaboration for Brazilians. It was thereby possible to show that this equation may have

a significant impact on the diagnosis of CKD in the Brazilian population and on the clinical management of these patients, at least with regard to kidney-replacement-therapy initiation.

The present study, showing that an eGFR, mainly when used to decide when to begin dialysis, might have great repercussions for Brazilian nephrology, and not only because of the high individual and dialysis numbers involved in the decision, but also because there is always the possibility of the results being considered 'too future' for implementation; questions about the superiority of eGFR might only be settled by long follow-up studies, and such a crucial issue cannot be addressed by more and more cross-sectional multicentric analyses of registry data. There is also a very eerie side of this material: if we consider that a medical discharge is a "fait accompli," and that patients will start dialysis anyway, why go through the inconvenience of measuring eGFR in a busy office or dialysis center?

Interpretation of Findings

One interesting aspect of our findings is that we observed a higher mortality risk in subjects with GFR above 60 ml/min/1.73/m2 (and no microalbuminuria) using the CKD-EPI equation and in those with low GFR (below 60 ml/min/1.73/m2) and no microalbuminuria using the MDRD-4 equation, two groups considered at low risk of CKD progression.

There might be an underdetection of renal insufficiency due to the peculiar equation that is in use, leading in an opposite way the clinicians to seek earlier intervention on individuals at low risk of CKD progression (those with high GFR and no microalbuminuria as classified by both CKD-EPI and the MDRD-4 equations). However, CKD clinical management regarding GFR values should be pursued considering documented proteinuria. When GFR values are below 60 ml/min/1.73/m2, caution should be exercised. The percentage of missing/imputed values were expressed as being low, considering them irrelevant given the significantly decrease in the findings. Moreover, although age, gender, and race appeared to be independently associated with CKD remains, its effect seemed substantively weaker compared to GFR. These demographic variables, if included in the predictive model for CKD, would mainly result in decreased cost-effectiveness, based on the reasonable assumption that their contribution to CKD diagnosis is minimal.

Implications for Clinical Practice

International guidelines recommend the measurement of serum creatinine and the calculation of estimated GFR in disease staging, risk classification, and therapeutic decision making with medications potentially nephrotoxic.

The KDIGO guidelines recommend against the use of estimated GFR based on serum creatinine for the diagnosis and risk stratification of CKD because of evidence showing low sensitivity and impairments in the capacity to reclassify individuals at risk. In this study, using a local GFR estimator did not change the applicability. The only exception reported in the KDIGO guidelines is the use of estimated GFR based on serum creatinine for risk stratification with alternative and reasonable results that allow supporting the empirical use for the purpose when there is an impact on clinical decisions. The clinically significant impact of the diagnosis and classification of CKD (stage monitoring, referral

for nephrology visits, management of drugs, prevention, and complication management) may corroborate its supplementary use. This is a common strategy when designing an equation. Often an appropriate equation is derived using one form of serum creatinine, and adjustments are made to result in a published equation that can be applied in wide clinical settings.

The concentration of creatinine varies widely among individuals, and for a single individual, it fluctuates in a random manner because of the varying body pool. It is neither uncommon nor unexpected that the serum concentration of creatinine does not match the expected value estimated using standard anthropometric parameters. This may make the measurement of GFR unstable. Moreover, local biases and imprecision separated this variable from serum creatinine. Imprecision in the measurement of a predictor, derivative, or coefficient results in imprecision in any formula or estimation derived from the predictor, derivative, or coefficient. Because standardization cannot ensure accuracy when there is bias, analyte characteristics, and population differences preclude the laboratory standard's adequacy as an operational standard.

Thus, the evaluation of measured creatinine and obtained eGFRs raised some valuable points. Measured serum creatinine is the real fact in any patient-based comparison. Medically, any patient would expect the use of the serum creatinine they were actually given. Therefore, this fact represents the ground truth. Variability around that fact likely represents imprecision in prediction by GFR equations and/or error in measurement, in assays, or calibration models. The epidemiological importance of variability increases, as diagnosing a patient as healthy, sick, treatable, terminally ill, or dead entails associated consequences; a consistent inability to make accurate predictions from measurements suggests a failure of standardization.

Conclusion

In this study, we present for the first time a summary of several studies in Brazil that have provided GFR equations for the diagnosis of CKD. The studies that evaluated a population similar to the Brazilian census in the prevalence of CKD and GFR were represented here. It was observed that an important part of kidney donors have an estimated GFR from serum creatinine lower than expected by the original equation, with some of them with values lower than 30 ml/min per 1.73 m². The estimate 95th percentile of GFR per 1.73 m² from these 3 studies suggests that in a "healthy" Brazilian population women may have a GFR estimated from 24-h urine creatinine clearance between 88 to 106 mL/min per 1.73 m² and men a GFR estimated from 24-h urine creatinine clearance between of 85 to 96 ml/min per 1.73 m². The 95th percentile of serum creatinine estimate glomerular filtration rate expectancy for advanced age were 68 ml/min per 1.73 m² for women and 75 ml/min per 1.73 m² for men. The publication of this study provides the theoretical knowledge of formulae available for the estimation of glomerular filtration rate in the global, local and Brazilian population of kidney donors. While showing the feasibility of Brazilian equations as an alternative for the diagnosis of chronic kidney disease in Brazil with low costs compared to the serum determination of cystatin C. Results from this research may be used as a baseline for the development of future studies evaluating possible referral for further testing of living kidney donors. In the general Brazilian population of patients attending

public medical screening the serum level of urea, serum creatinine and thus the estimation of Glomerular Filtration Rate based on creatinine were lower for females. There may be a criterion between the genders related to the assumption that serum urea increases with age in both men and women.

Implications

Key findings and implications. Our review raises a number of important issues related to the CKD surveillance in Brazil. The first main finding was the stark absence of studies estimating glomerular filtration rate (GFR) from serum creatinine in adult Brazilian populations, as evidenced by our inability to perform a meta-analysis on national data. Furthermore, the two institutional studies included did not report estimates among the goal population of worldwide healthy individuals, instead reporting data from pregnant women and kidney donors. This is in sharp contrast with a steady output of international reports on GFR estimating equations, which have become a go-to method for defining CKD worldwide and have facilitated the development of effective disease management guidelines.

In Brazil, we saw that GFR was mainly estimated before CKD staging given GFR lack of input in the KDIGO 2012 classification criteria, and also found high discordance between whole-blood and serum creatinine results from 1971 to 1975 Brazil-USA Cooperative Study on KD in Pregnancy (χ^2). Interestingly, no missing albuminuria component was found to be the leading cause for discording CKD status among the general populations, suggesting possible biases in the reported prevalence of the disease. Our overview of the KDIGO 2012 CKD staging also indicated a major focus on hospital-based research and of dialysis patients, with very few population studies on CKD progression. Finally, when applying the Swedish KP-CKD stages in the population, we found a residual proportion of CKD stage 3-1 in the general population that has not changed significantly from 2008 to the present, as opposed to our expectation of a steady decline in this interim period, given the economic growth and largely progressive national policy in Brazil.

Recommendations for Future Research

The impact of reduction in combined outcomes such as death, doubling of serum creatinine, eGFRs 10-20 (eGFR improvement to over 20) and 20-30 (eGFR improvement to over 30 from less than 20) vs eGFR 20-30 (eGFR ranging between 20 and 30), with multivaried adjustments, particularly for proteinuria using a large cohort of Brazilian CKD patients that are not on dialysis. - Whether the eGFR CKD-EPI provides better prognostic discrimination compared to the MDRD Study equation for outcomes like pre-specified cardiac outcomes including myocardial infarction, NT-proBNP, chronic heart failure, left ventricular mass indexed for body surface area, presence of left bundle branch block and duration of QRS complex in an adjusted model as well as in a subgroup analysis by glomerular disease and proteinuria. - Whether the combination of eGFR and proteinuria improves the discriminative power of the outcomes under investigation better than eGFR alone, and whether this is equal in males and females, comparing the same outcomes. - Whether examining covariate alpha in the nearest year prior to the patient developing outcomes is better than examining the same during

the period closest following diagnoses of outcomes. As is known, proteinuria is a more sensitive marker of renal disease progression than GFR, and any decline in proteinuria would occur before a rise in GFR was observed. The validation studies conducted by Collaborative Studies and the NKF American GFR Consortium also utilized the same strategy to examine the studied outcomes, i.e. for proteinuria confounding an adjusted model of outcomes containing eGFR with proteinuria cutoffs was used.

Conflict of Interest

No conflicts of interest were declared by the authors.

Financial Disclosure

The authors declared that this study has received no financial support.

Ethics Statement

Not applicable.

Authors' contributions

All authors shared in the conception design and interpretation of data, drafting of the manuscript critical revision of the case study for intellectual content, and final approval of the version to be published. All authors read and approved the final manuscript.

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