

Concordance between estimated glomerular filtration rate using equations and that measured using an imaging method

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ABSTRACT

Background: Guidelines recommend estimating glomerular filtration rate (GFR) using creatinine-based equations (CBE). **Aim:** To evaluate the agreement between GFR measured using radionuclide imaging and estimated using creatinine-based equations. **Material and Methods:** In 421 patients aged 54 ± 17 years (47% women) GFR was estimated using the MDRD-4, CKD-EPI and the body surface adjusted Cockcroft Gault equation. GFR was also measured using a radionuclide imaging method with ^{99m}Tc-DTPA. The concordance between estimated and measured GFR was calculated using Lin's concordance coefficient and Bland and Altman plots. **Results:** Average GFR values obtained with CKD-EPI, MDRD-4, body surface adjusted Cockcroft Gault equation and ^{99m}Tc-DTPA imaging were 75.9 ± 26.6, 76.3 ± 28.8, 77.1 ± 31.6 and 77.9 ± 28.4 ml/min/1.73 m², respectively. There was no significant difference in means and 29% of participants had a GFR < 60 ml/min/1.73 m² by CKD-EPI. The correlation was good between equations, but acceptable when compared with the ^{99m}Tc-DTPA imaging. The weighted kappa between CBEs was good, but low when comparing CBEs with measured GFR. The Lin's concordance coefficient between estimated and measured GFR was low. **Conclusions:** GFR measured by ^{99m}Tc-DTPA radionuclide imaging has a low correlation and poor concordance with estimations using CBE.

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Key words: Glomerular Filtration Rate; Kidney Function Tests; Radionuclide Imaging; Renal Insufficiency, Chronic.

Concordancia entre la tasa de filtración glomerular estimada con ecuaciones y aquella medida mediante imágenes

Antecedentes: Las guías clínicas recomiendan estimar la tasa de filtración glomerular (TFG) usando ecuaciones basadas en la creatinina sérica. **Objetivo:** Estudiar la concordancia entre la TFG medida usando un método de imágenes usando radioisótopos y aquella estimada con ecuaciones. **Material y Métodos:** En 421 pacientes de 54 ± 17 años (47% mujeres), la TFG se estimó utilizando las

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ecuaciones MDRD-4, CKD-EPI y Cockcroft Gault ajustada para superficie corporal. La TFG se midió también con una técnica de imágenes usando ^{99m}Tc -DTPA. La concordancia entre la estimación y medición se calculó usando el coeficiente de concordancia de Lin y gráficos de Bland y Altman. **Resultados:** Los promedios de TFG obtenidos con CKD-EPI, MDRD-4, ecuación de Cockcroft Gault e imágenes con ^{99m}Tc -DTPA fueron $75,9 \pm 26,6$, $76,3 \pm 28,8$, $77,1 \pm 31,6$ y $77,9 \pm 28,4$ ml/min/1,73 m², respectivamente. No hubo diferencias significativas en los promedios y el 29% de los participantes tuvo una TFG < 60 ml/min/1,73 m². La correlación entre las ecuaciones fue buena, pero sólo aceptable cuando se comparó con la medición por imágenes. El kappa ajustado entre las ecuaciones fue adecuado, pero malo cuando se comparó las ecuaciones con la medición por imágenes. El coeficiente de Lin mostró una baja concordancia entre la estimación y medición de TFG. **Conclusiones:** La concordancia entre la estimación de TFG usando ecuaciones y su medición directa mediante imágenes es baja.

Palabras clave: Insuficiencia Renal Crónica; Pruebas de Función Renal; Cintigrafía; Tasa de Filtración Glomerular.

Chronic kidney disease (CKD) is a global public health problem. Approximately 500 million people worldwide have some degree of CKD^{1,2}. Glomerular filtration rate (GFR) is accepted as the best indicator of renal function, and its measurement in clinical practice is crucial, not only to diagnose CKD, but also to adequately stratify its severity, establish interventions and predict outcomes³⁻⁶. Traditionally, inulin clearance has been the gold standard to measure GFR, but it has important logistical difficulties for clinical massive use, even for experimental trial use. Clearance of some substances such as iothalamate, Cr-EDTA (Chromium-51 ethylenediamine tetraacetic acid), DTPA (diethylenetriaminepentaacetic acid) or iohexol, easier to detect in fluids and with simpler protocols, has become a benchmark equivalent of measured GFR (mGFR) gold standard without really being the most accurate methods⁷. These tools are difficult to use and expensive, and their repetitive use in the clinical setting is limited. Thus, they are mainly used for trials instead of renal inulin clearance. This systematically justifies the use of endogenous GFR markers, such as creatinine, and equations, to estimate GFR in the clinical practice³.

The method recommended by the *National Kidney Disease Education Program*, the *National Institute of Diabetes and Digestive and Kidney Diseases*, the *National Kidney Foundation* and the *American Society of Nephrology* to estimate GFR (eGFR) is based on the measurement of standar-

dized serum creatinine and its derived equations (MDRD-4 and CKD-EPI). All these equations lack an appropriate validation to the GFR in which they were applied, given that the method for measuring creatinine was not standardized in the different countries, and this introduced heterogeneity into the measurements^{8,9}.

Furthermore, estimates based on creatinine have several disadvantages, depend on multiple variables, and their accuracy is still under debate^{10,11}. CBEs have been validated and adjusted in the Japanese, American, Australian, Spanish and Chinese populations¹²⁻¹⁴. The performance of these in the Colombian population is unknown, and we will be limited to validate them in the absence of a gold standard test.

In Colombia, under special conditions in which error in the estimation of GFR with CBE is expected, we usually measure GFR with nuclear medicine using ^{99m}Tc -DTPA (Technetium-99 diethylenetriaminepentaacetic acid). This is a renal radiopharmaceutical marker available for nuclear imaging, which is filtered only by the glomerulus and, therefore, could be used to mGFR¹⁵. It is a simple and fast procedure, and although it is frequently used to study renovascular hypertension and obstructive uropathy, its availability is limited and is very expensive. The most commonly used and commercially available measurement method is the modified Gates method, which does not require blood or urine samples and only takes approximately 20 minutes¹⁶. Due to its convenien-

ce, it has been used in multiple clinical studies as a surrogate GFR marker¹⁷, and also as a gold standard in some studies on performance evaluation of CKD-EPI equation^{11,12,18-20}. Despite this, it is unknown whether this method is more accurate than CBE, and some studies have recently questioned its accuracy; for example, it is not recommended in international guidelines as a gold standard to generate or validate the use of equations. Within the expected biases are the hydration status, the degree of CKD, the presence of obesity or malnutrition, distance from the gamma camera to the patient, technical biases when selecting the area of the renal silhouette, and biases in the estimation of a geometrically asymmetric area²¹⁻²³. The objective of this study was to estimate the correlation and diagnostic concordance of eGFR by CBE, with that obtained by ^{99m}Tc-DTPA radionuclide imaging.

Methods

Study population and data collection

The study was carried out in 4 institutions in Bogotá, Colombia. A search was made with adult patients who underwent ^{99m}Tc-DTPA radionuclide imaging for standardized GFR measurement and who had a standardized serum creatinine value available for 2 weeks around the study indicated under physician clinical criteria, without GFR restriction. All possible sources of error in creatinine were excluded to adequately estimate GFR: acute kidney injury (AKI defined by KDIGO creatinine criteria), people at extremes of body mass index (BMI < 18 and > 35 kg/m²) and pregnant women; as well as the possible sources of error in the radionuclide imaging such as severe obesity with BMI greater than 35 kg/m², severe malnutrition with BMI < 18 kg/m², AKI, dehydration described in the medical record, more than 4 renal cysts per renal unit and obstruction of the urinary tract. All demographic data were collected, including dates, age, race, sex, weight, height, BMI, BSA, serum creatinine from which GFR is estimated by CKD-EPI equations, 4-variable MDRD, and Cockcroft Gault adjusted to BSA. The GFR result by radionuclide imaging was adjusted to 1,73 m² of BSA.

Measurement of serum creatinine and eGFR:

Serum creatinine was measured using an enzymatic technique (modular P Analyzer, Crea-

tinine plus assay, Roche Diagnostics, Mannheim, Germany). Serum levels were obtained from the laboratory database, as long as the sample had been collected and processed within two weeks of the radionuclide imaging. eGFR by MDRD was calculated using the 4-variable equation²⁴.

$$\text{eGFR MDRD-4} = 175 \times (\text{serum Cr})^{-1.154} \times (\text{age in years})^{-0.203} \times (0.742 \text{ if woman}) \times (1.210 \text{ if black race})$$

eGFR CKD-EPI was calculated using the equation developed in 2009⁸

$$= 141 \times \min(\text{serum Cr}/\kappa, 1)^{\alpha} \times \max(\text{serum Cr}/\kappa, 1)^{-1.209} \times (0.993^{\text{Age}^2}) \times (1.018 \text{ if woman}) \times (1.159 \text{ if black race})$$

Likewise, creatinine clearance was estimated by the Cockcroft Gault (CG) equation: (140 - Age * Weight * 0.85 if woman) / (72 * Creatinine(mg/dL)) and adjusted to a BSA of 1.73 m² to make a comparison between patients²⁵.

Radionuclide imaging of glomerular filtration with ^{99m}Tc-DTPA

It was performed by intravenous injection of ^{99m}Tc-DTPA (2-3 mCi or 74-111 MBq). Thirty minutes before starting the study, patients drank 500 ml of water to achieve adequate hydration and a urinary flow of at least 1-3 ml/min during the study. The study was performed with the patient in supine position on the gamma camera detection head. Flat dynamic images, obtained from the posterior projection of the upper abdomen region (kidney beds), were taken at 2 seconds per frame during the first minute (renal perfusion phase), 15 seconds per frame (4 frames per minute) for 6 minutes, and finally 13 frames each of 60 seconds during the rest of the study (parenchymal and excretion phases, respectively). The total duration of the study was 20-60 minutes, depending on the indication, and the GFR values were calculated with the Gates method.

Sample size

The minimum recommended sample size was taken to estimate Cohen's kappa coefficient of 5 non-proportional categories, considering a power of 80% and an alpha error of 0.05. Two pre-established kappa values were taken based on the literature: 0.5 and 0.6. The minimum sample size is 373 patients²⁶.

Study design and statistical analysis

We performed a correlation-concordance study for methods of GFR evaluation. The analysis was made with the Stata® 12.0 software for the Mac OS® package. Numerical data were expressed as medians or means and ranges or standard deviation according to distribution, and the categorical variables as numbers and percentages. The Wilcoxon rank sum test was used to compare non-normal variables and t-test for normal distribution. Correlation between eGFR by CBE and mGFR was evaluated using the Spearman correlation coefficient. Concordance was estimated using Cohen's kappa coefficient for two strata with a cut-off of 60 ml/min/1.73 m² and the weighted kappa estimation for 3 arbitrary strata and 5 strata, like CKD classification; however the patient did not have criteria for CKD diagnosis. The absolute precision of the result was estimated, defined as the difference between the value of the kappa coefficient and the lower limit of the confidence interval, using EPIDATA® 4.0 for MAC-OS®. Finally, Lin's concordance correlation coefficient was estimated, and it was expressed graphically with the limits of agreement of Bland-Altman. A p-value < 0.05 is assumed to be statistically significant.

Ethics

The research and ethics committee of each of the included centers approved the protocol.

Results

We found 618 radionuclide images with ^{99m}Tc-DTPA to measure glomerular filtration; 101 were discarded by exclusion criteria (extremes of body mass and acute kidney injury), and 96 by incomplete data. We analyzed 421 patients with studies performed between November 2008 and October 2017.

Demographic and clinical data of 421 included patients were summarized on Table 1. The majority of patients have normal eGFR. The 29.4% of patients has less than 60 ml/min/1.73 m² by CKD-EPI equations and only 4.2% less than 30 ml/min/1.73 m². Table 2 shows distribution according to each compared GFR method. The proportion of patients with eGFR less than 30 ml/min/1.73 m² was low.

The mean difference between CKD-EPI and

MDRD-4 was not significant (p = 0.85); it was not significant between CKD-EPI and BSA adjusted CG (p = 0.57), nor between CKD-EPI and that measured by ^{99m}Tc-DTPA (p = 0.31).

Figure 1 shows the distribution of the filtration measured by ^{99m}Tc-DTPA and that estimated by the different equations according to 5 strata like CKD classification using the CKD-EPI equation as recommended by guidelines. The distribution of values by equations are proportionally symmetric; however, we can see how values by mGFR with ^{99m}Tc-DTPA, had a disproportionate distribution compared with GFR by all equations

Table 1. Summary of demographic and clinical data

Variable	Value
Age, mean (SD), years	54 (±17.1)
Female, n (%)	155 (46.8)
Weight, mean (SD), Kg	68 (±13.9)
Height, mean (SD), cm	164 (±9.4)
BMI, mean (SD), Kg/m ²	25 (±4.14)
BSA, mean (SD), m ²	1.75 (±0.21)
Creatinine, mean (SD), mg/dL	1.16 (±1.05)
mGFR, mean (SD), ml/min/1.73 m ²	77.9 (±28.4)
eGFR, CKD-EPI mean (SD), ml/min/1.73 m ²	75.9 (±26.6)
eGFR MDRD-4 mean (SD), ml/min/1.73 m ²	76.3 (±28.8)
eGFR CG adjusted to BSA mean (SD), ml/min/1.73 m ²	77.1 (±31.6)

SD: standard deviation, Kg: kilograms, cm: centimeters, m: meter, mg milligrams, dL: deciliter. BMI: body mass index, BSA body surface area. eGFR: estimated glomerular filtration rate, mGFR: measured glomerular filtration rate, mL milliliters, min: minute.

Table 2. GFR distribution by equations and mGFR by ^{99m}Tc-DTPA

GFR ml/min/1.73 m ²	≥ 60	30-59	< 30
mGFR	74.1%	23.3%	2.6%
CKD EPI	70.5%	25.3%	4.27%
MDRD-4	71.9%	23.9%	4.2%
CG BSA	70.3%	25.7%	4%

BSA body surface area. eGFR: estimated glomerular filtration rate, mGFR: measured glomerular filtration rate, mL milliliters, min: minute.

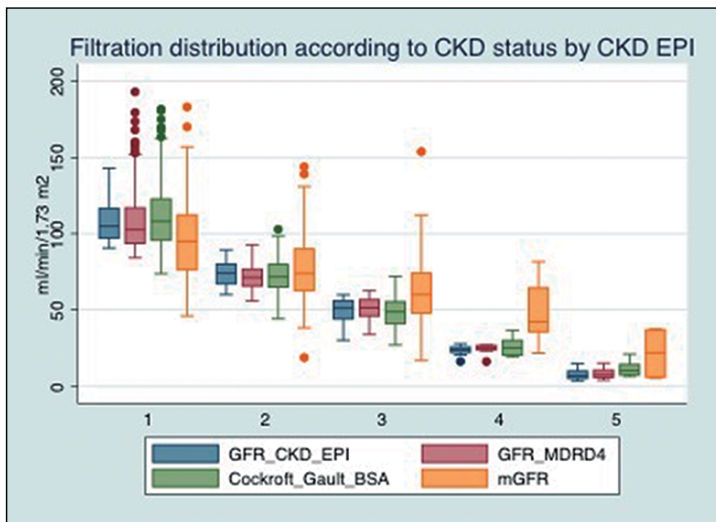


Figure 1. Box plot distribution of GFR based on 5 strata such as CKD classification by CKD-EPI equation. The figure shows the distribution of the values by each GFR method. The distribution of GFR measured by ^{99m}Tc -DTPA tends to leave the extremes of each degree of CKD classification according to CKD-EPI.

Table 3 shows a Spearman correlation between equations and mGFR by ^{99m}Tc -DTPA, There are high correlation between equations, but not between equations and mGFR.

The estimation of the concordance was made

Table 3. Correlation coefficient (Spearman)

	CKD-EPI	MDRD4	^{99m}Tc -DTPA
MDRD4	0.98	-	-
CGa	0.94	0.91	0.50
^{99m}Tc -DTPA	0.57	0.55	-

$p < 0.00001$. CKD-EPI: chronic kidney disease epidemiology collaboration equation. MDRD4: 4 variable modification of diet in renal disease equation. CGa: body surface adjusted Cockcroft Gault equation. ^{99m}Tc -DTPA: Technetium-99 diethylenetriaminepentaacetic acid.

by Cohen's kappa concordance coefficient for the cut point of \geq or $<$ 60 mL/min/1.73 m², and an almost perfect diagnostic agreement was obtained between MDRD-4 and CKD-EPI, considerable between CKD-EPI and CG BSA adjusted, considerable between MDRD-4 and CG BSA adjusted, and low concordance between mGFR and all the equations included in the evaluation (Table 4).

When stratifying according to 5 strata, like CKD classification, and according to arbitrary cut-off points of 30 and 60 mL/min/1.73 m², we confirmed the inadequate concordance between the glomerular filtration estimated by the equations and the mGFR, and its kappa worsens when it is stratified like CKD classification (5 strata) compared to only 2 strata ($p < 0.04$) (Tables 5 and 6).

Considering the sample of 421 patients, a CKD ratio of 29.8% with CKD EPI and 25.9% with mGFR and a Kappa coefficient of 0.41, the abso-

Table 4. Concordance for CKD diagnosis (Cohen's kappa coefficient)

	CKD-EPI	MDRD4	^{99m}Tc -DTPA
MDRD4	0.91 CI(0.87-0.96)	-	-
CGa	0.80 CI(0.73-0.86)	0.73 CI(0.66-0.81)	0.38 CI(0.28-0.48)
^{99m}Tc -DTPA	0.41 CI(0.31-0.50)	0.41 CI(0.31-0.51)	-

*CI: 95% confidence interval. All with p -value < 0.00001 . CKD-EPI: chronic kidney disease epidemiology collaboration equation. MDRD4: 4-variable modification of diet in renal disease equation. CGa: body surface adjusted Cockcroft Gault equation. ^{99m}Tc -DTPA: Technetium-99 diethylenetriaminepentaacetic acid.

Table 5. Concordance for 3 strata (Cohen's kappa coefficient)

	CKD-EPI	MDRD4	^{99m} Tc-DTPA
MDRD4	0.93 CI(0.89-0.97)	-	-
CGa	0.79 CI(0.72-0.85)	0.72 CI(0.65-0.79)	0.34 CI(0.24-0.43)
^{99m} Tc-DTPA	0.38 CI(0.28-0.47)	0.37 CI(0.28-0.46)	-

*CI: 95% confidence interval. All with p-value < 0.00001. CKD-EPI: chronic kidney disease epidemiology collaboration equation. MDRD4: 4 variable modification of diet in renal disease equation. CGa: body surface adjusted Cockcroft Gault equation. ^{99m}Tc-DTPA: Technetium-99 diethylenetriaminepentaacetic acid.

Table 6. Concordance for CKD classification in 5 strata (Cohen's kappa coefficient)

	CKD-EPI	MDRD4	^{99m} Tc-DTPA
MDRD4	0.89 CI(0.85-0.92)	-	-
CGa	0.75 CI(0.69-0.80)	0.66 CI(0.60-0.72)	0.24 CI(0.17-0.31)
^{99m} Tc-DTPA	0.29 CI(0.22-0.36)	0.28 CI(0.20-0.35)	-

*CI: 95% confidence interval. All with p-value < 0.00001. CKD-EPI: chronic kidney disease epidemiology collaboration equation. MDRD4: 4 variable modification of diet in renal disease equation. CGa: body surface adjusted Cockcroft Gault equation. ^{99m}Tc-DTPA: Technetium-99 diethylenetriaminepentaacetic acid.

lute accuracy (e) estimation was performed and a value of 0.096 was obtained, which is considered adequate and confirms a good sample size for the purpose of the study.

Finally, we estimate Lin's concordance correlation coefficient (CCC), and it was low for mGFR compared to eGFR with CKD-EPI ($\rho c = 0.57$

[95% confidence interval (CI): 0.507- 0.636 $p = 0.0005$]), with a slope of less than 1 and a positive interception (Figure 2). We observed an important dispersion of the data with clinical relevance in the limits of agreement of Bland-Altman of 50 ml/min/1.73 m², (Figure 3). The CCC between mGFR and all other equations was consistently low.

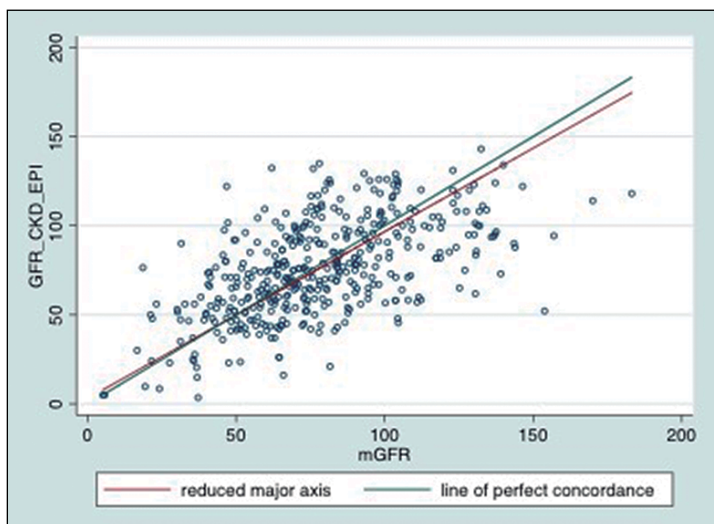


Figure 2. Lin's concordance correlation coefficient between CKD-EPI and ^{99m}Tc-DTPA. The figure shows a low CCC, with a slope of less than 1 and a positive interception. Interpreted as low agreement between GFR values measured by ^{99m}Tc-DTPA radionuclide image compared to that estimated by CKD-EPI equation.

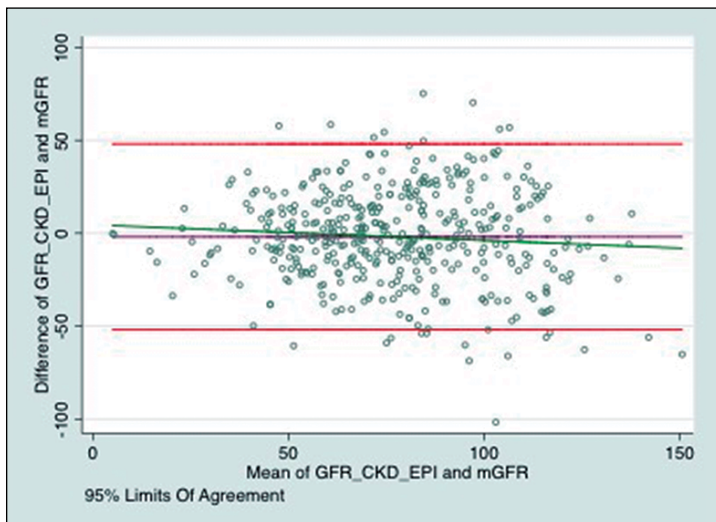


Figure 3. Bland-Altman limits of agreement. We can see that GFR average difference is small between CKD-EPI and ^{99m}Tc -DT-PA. However; it should be noted that this average difference is positive with low GFR values and negative with high GFR values. Likewise, the 95% limits of agreement are highly variable, equivalent to 50 ml/min/1.73 m². Which is obviously clinically relevant, and intolerable.

Discussion

The present study includes patients from several centers in Bogotá, with an adequate sample size and a representative GFR distribution, although a low proportion of patients with less than 30 ml/min/1.73 m². The Spearman correlation of the equations is adequate, due to its purely mathematical condition. However, it was bad for mGFR with respect to all eGFR equations. The study shows a low kappa concordance index for mGFR with ^{99m}Tc -DTPA radionuclide image versus eGFR with all CBEs. The same result was obtained with 3 and 5 strata like CKD classification, which indicates a low weighted agreement for diagnosis cut-off point and classification values if we considered a population with CKD. Finally a statistical test that considers both concordance and correlations such as Lin's coefficient confirms the low discriminatory capacity of mGFR compared with CKD-EPI and the others eGFR equations for defining any disease or classification based on GFR. These results are consistent with data from the literature, although some researchers are fortunate to include the gold standard^{5,6}.

A cross-sectional study conducted in Italy with 341 CKD patients, which sought to compare the accuracy and reliability of mGFR by ^{99m}Tc -DTPA dynamic renal radionuclide image (Gates method) and eGFR by the MDRD-4 and CKD-EPI equations, concluded that mGFR tends

to underestimate GFR in stages 1 and 2 of kidney disease and to overestimate it in stages 4 and 5 when compared with the equations, especially with CKD-EPI. Treatment with inhibitors of the renin-angiotensin axis and age less than 50 years accentuated the underestimation in early stages²⁷.

Ying-Chun Ma, et al. evaluated the performance of the ^{99m}Tc -DTPA radionuclide image in 482 CKD patients using the modified Gates method with the MDRD-4 abbreviated equation. In this study, plasma DTPA sampling (gold standard) was used, and an adequate correlation between the three measurements is shown. However, the MDRD-4 equation presented less bias and greater precision and accuracy compared with the radionuclide image. The results were consistent throughout the different stages of CKD¹⁷.

In some publications, ^{99m}Tc -DTPA dynamic renal radionuclide image is used as a reference standard to validate and determine the operative characteristics of the different creatinine-based equations³³⁻³⁵.^{11,12,28-30} However, Xie P. et al., following the results of their study conducted in China, recommended against using radionuclide image as a reference method in research that seeks to validate the CKD-EPI equation. That study compared mGFR by radionuclide image and that estimated by CKD-EPI with the measurement of plasma DTPA content as a gold standard; 149 CKD patients were included, and it was concluded

that both methods can be used to establish GFR, but that CKD-EPI is more accurate, especially at rates lower than 60 mL/min/1.73 m² ²¹. International guidelines do not consider ^{99m}Tc-DTPA radionuclide image as a method equivalent to the gold standard^{5,6}.

Limitations

- In Colombia, we do not have a gold standard test to directly measure the glomerular filtration rate as measured DTPA, Cr-EDTA, iothalamate or iohexol.
- Low proportion of patients with filtration less than 30 ml/min/1.73 m².
- Retrospective nature of the information.

Conclusions

Our analysis of diagnosis agreement between CBEs recommended by guidelines for CKD diagnostics and classification and mGFR by ^{99m}Tc-DTPA radionuclide imaging was low. Based on our study and previous literature, we do not recommend using mGFR by ^{99m}Tc-DTPA radionuclide imaging as a diagnostic test for disease diagnosis or classification based on GFR.

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