Performance of the CKD-EPI and MDRD equations to estimate the glomerular filtration rate: a systematic review of Latin American studies

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Abstract

Background

Most commonly used equations to estimate the glomerular filtration rate (GFR) are the CKD-Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD). However, it is not clear which one shows a better performance in Latin America.

Objective

To assess the performance of both estimated GFR (eGFR) equations in Latin American countries. Methods In January 2019, we performed a systematic search in PubMed, Scopus, and “Biblioteca Regional de Medicina” (BIREME) to identify studies that reported eGFR using CKD-EPI and MDRD equations and compared them with a measured GFR (mGFR) using exogenous filtration markers, among adults from Latin American countries. Study selection, data extraction, and risk of bias evaluation were performed by two reviewers independently. We performed meta-analyses of P30, bias (using mean difference [MD] and its 95% confidence intervals [95% CI]), sensitivity, and specificity; and evaluated certainty of evidence using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.

Results

We included 12 papers, six of them were meta-analyzed (5 from Brazil and 1 from Mexico). Meta-analyses that compared CKD-EPI using creatinine measured with calibration traceable to isotope dilution mass spectrometry (CKD-EPI-Cr IDMS) and MDRD-4 IDMS did not show statistically significant differences in bias (5 studies, MD: 0.55 mL/min/1.73m 2 , 95% CI: -3.34 to 4.44), P30 (2 studies, MD: 4%, 95% CI: -4% to 13%), sensitivity (2 studies, 76% and 75%), and specificity (2 studies, 91% and 89%), with very low certainty of evidence for bias and P30, and low certainty of evidence for sensitivity and specificity.

Conclusions

We found that the performance of CKD-EPI-Cr IDMS and MDRD-4 IDMS do not differ significantly, although CKD-EPI-Cr IDMS tends to have a non-significant better performance in terms of P30. However, since most of the meta-analyzed studies were from Brazil, results may not be extrapolated to other Latin American countries. Trial registration CRD42019123434, PROSPERO. Registered 18 February 2019.

Introduction

Chronic Kidney Disease (CKD) is a public health problem; in 2014, 10.6% of adults aged over 30 years had stage 3–5 CKD (1). In 2017, CKD caused 35 800 000 disability-adjusted life-years (1.4% of all disability-adjusted life-years) worldwide (2), and 1 230 200 deaths (2.2% of all deaths) (3).

Assessing the glomerular filtration rate (GFR) is the cornerstone for performing an adequate screening, diagnosis and classification of CKD (4). However, the methods used to directly measure GFR (mGFR), requiring exogenous filtration markers, are laborious and costly. Thus, some equations are routinely used to obtain an estimated GFR (eGFR) from endogenous markers such as creatinine or serum cystatin C. The most commonly used equations are the CKD Epidemiology Collaboration (CKD-EPI) and the Modification of Diet in Renal Disease (MDRD)(5).

The MDRD equation originally used six variables (MDRD-6): serum creatinine, urea and albumin, age, sex, and ethnicity (6). A later version used only four variables (MDRD-4), excluding serum urea and albumin (7). Most recently, the MDRD-4 was re-edited to use creatinine measured with calibration traceable to isotope dilution mass spectrometry (IDMS) (8).

The CKD-EPI originally used the same four variables of the MDRD-4 (9). Later, other CKD-EPI equations were developed, which used serum cystatin C instead of creatinine (10), or used both serum creatinine and cystatin C (11).

Differences in the performance of these equations across certain ethnic groups have been reported (12–14), and attributed to differences in the production and excretion of creatinine (15) which, in turn, is related to diet (protein intake) and muscle mass (endogenous production of creatinine) that varies according to ethnicity (15, 16). Thus, it is possible that results from regions with different ethnic compositions such as Europe or North America, which are mostly Caucasian, cannot be extrapolated to Latin American populations that are composed of a mixture of Amerindians, Mestizos, Blacks, Asians, and Caucasians (17).

Given that Latin American stakeholders and practitioners require to know which equation has the best diagnostic performance in their specific context to better inform their decisions; we conducted a systematic review that compares the performance of the CKD-EPI and the MDRD equations to estimate the GFR in Latin American countries, and evaluated the certainty of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Methods

The study protocol was registered in PROSPERO (CRD42019123434). We performed a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines (18).

Literature search and study selection

In this systematic review, we included original observational studies that were performed in Latin American countries and compared both CKD-EPI and MDRD equations with mGFR (the gold standard, that used any exogenous filtration markers such as inulin, iohexol, iothalamate, 51Cr-EDTA, DTPA, among others) in adult populations (≥ 18 years). We did not exclude any study on the basis of language or any other criteria.

We carried out a literature search in PubMed and Scopus in January 2019, and in "Biblioteca Regional de Medicina" (BIREME) in February 2019. The search strategy for each database or virtual library is shown in Additional file 1.

Duplicated records were removed using the EndNote software. Later, two researchers (ABC and NBC) independently selected abstracts for full-text review and final inclusion, with any differences resolved by a third researcher (JHZT).

Also, we searched the lists of references of all included studies, and the lists of articles that cited each of the included studies (through Google Scholar) to identify other studies that fulfilled the inclusion criteria.

Data extraction

Two researchers (ABC and NBC) independently extracted data from each article that met the inclusion criteria using a standardized Microsoft Excel sheet, with any differences resolved by a third researcher (JHZT).

The following variables were extracted from each study: first author, year of publication, country, design (prospective or retrospective), population characteristics (inclusion and exclusion criteria, number of participants, sex, age, ethnic group, CKD diagnosis, and CKD etiology), intervention (type of MDRD and CKD-EPI equations), gold standard (exogenous filtration marker), mGFR, eGFR, and numerical results of diagnostic measures.

Main diagnostic measures were bias (defined as the mean of the difference between eGFR and mGFR), P30 (percentage of results of eGFR that did not deviate more than 30% from mGFR), and accuracy measurements (sensitivity, specificity, and area under the curve).

Other measures included: precision (defined as one standard deviation of bias, or as interquartile range), bias% (mean of the difference between eGFR and mGFR, in function of mGFR), P15, P10, combined root mean square error (CRMSE), Pearson coefficient, intraclass correlation coefficient, Kappa coefficient, and limits of agreement (defined as bias ± 2 standard deviations).

When there were doubts about some information reported in the studies, we sent an email to the authors in order to clarify the information.

Risk of bias and certainty of evidence

Two researchers (NBC and VEFR) assessed the four risk of bias domains of the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool (19): patient selection, index test, reference standard, and flow and timing. In case of disagreement, a consensus was achieved with a third researcher (JHZT).

We used the GRADE methodology (20) to report our certainty in the evidence of accuracy of diagnostic tests results. To show this certainty, we created tables of Summary of Findings (SoF) according to the GRADE specifications (21).

Statistical analyses

When possible, we performed meta-analyses of P30, bias, sensitivity, and specificity (when studies compared similar equations, showed their confidence intervals or standard deviations, or allowed to calculate these values).

For P30 and bias, we calculated mean differences (MD) and their 95% confidence intervals (95% CI). For sensitivity and specificity, we built a 2 × 2 table when possible. As there were less than four studies to meta-analyze, we could not perform a meta-analytical hierarchical regression for diagnostic accuracy, so we performed a meta-analysis of proportions using the exact binomial distribution. We assessed heterogeneity using an I^2 statistic and used random-effects models when I^2 was higher than 40%.

For bias and P30, we performed a subgroup analysis according to the presence of CKD (using the cut-off of 60 ml/min/1.73 m^2) since a previous systematic review showed that the eGFR equations performance varies across these subgroups (22). We could not perform a subgroup analysis for comorbidities since there was no more than one study that assessed the same version of the equation in any of the comorbidities groups. The data were processed using the Stata v14.0 software.

Results

Studies characteristics

In total, we identified 379 records after removing duplicates, of which we full-text reviewed 31 potentially eligible records, excluding 19 (reasons are detailed in Additional file 2) and including 12 (23–34). In addition, we did not identify new studies after searching the lists of references of all included studies, and the lists of articles that cited each of the included studies (through Google Scholar) (Fig. 1).

Characteristics of the 12 included studies are summarized in Table 1 and detailed in Additional file 3. The number of participants ranged from 14 to 354 in all studies. Two studies reported results from the same cohort (24, 34). One study (32) added data from two cohorts, one of which (30) was also included in our review and the other was not published as an original paper.

Table 1

Characteristics of the included studies

Author, Year	Country	Population / setting	N	% of Females	Age (mean in years)	CKD-EPI	MDRD	Diagnostic measures (P30, bias, sensitivity, or specificity)*	Gold standard	mGFR (mean in mL/min/1.73 m^2)
Arreola-Guerra, 2014	Mexico	Healthy/Hospital	97	41.2	35.8	CKD-EPI-Cr IDMS	MDRD-4 IDMS	Bias, P30	^{99m}Tc DTPA	102.7
Asnani, 2013	Jamaica	Homozygous sickle cell disease/Hospital	98	56	34	CKD-EPI-Cr	MDRD-4	Bias, P30	^{99m}Tc DTPA	94.91
Asnani, 2015	Jamaica	Homozygous sickle cell disease/Hospital	98	56	34	CKD-EPI-Cr, CKD-EPI-cystatin C	MDRD-4	Bias, P30	^{99m}Tc DTPA	94.9
Camargo, 2010	Brazil	Healthy/Hospital	55	47	56	CKD-EPI-Cr IDMS	MDRD-4 IDMS	Bias, P30	^{51}Cr-EDTA	98
		Type 2 diabetics/ Hospital	56	56	59	CKD-EPI-Cr IDMS	MDRD-4 IDMS	Bias, P30		106
David-Neto, 2016	Brazil	Elderly/Renal transplanted	70	40	65	CKD-EPI-Cr IDMS	MDRD-4 IDMS	Bias, P30	^{51}Cr-EDTA	47
Lopes, 2013	Brazil	Elderly/ Community	95	70	85.3	CKD-EPI-Cr IDMS, CKD-EPI cystatin C	MDRD-4 IDMS	Bias, P30, SE, SP	Iohexol	55
Lujan, 2012	Argentina	Healthy/ Potential donor	85	54	41	CKD-EPI-Cr IDMS	MDRD-4 IDMS	Bias, SE, SP	Non-radiolabeled iothalamate	116
Martinez-Martinez, 2013	Mexico	SLE/Hospital	14	100	32.5	CKD-EPI-Cr IDMS	MDRD-4 IDMS	Bias, P30	Non-radiolabeled iothalamate	Not mentioned
Silveiro, 2011	Brazil	Type 2 diabetics /Hospital	105	50	57	CKD-EPI-Cr IDMS	MDRD-4 IDMS	Bias, P30	^{51}Cr-EDTA	103
Trimarchi, 2012	Argentina	CKD, Healthy/ Hospital	300	42	Median: 48.6	CKD-EPI-Cr	MDRD-4		^{99m}Tc DTPA	For different stages of CKD: Control: 81.53 1: 95.26 2: 70.05 3: 45.59 4: 22.60 5: 11.18
Veronese, 2014	Brazil	Healthy, Type 2 diabetics, CKD/ Community, Hospital	354	55	53	CKD-EPI-Cr IDMS	MDRD-4 IDMS	Bias, P30, SE, SP	^{51}Cr-EDTA	87

CKD: chronic kidney disease; SLE: systemic lupus erythematosus, SE: sensitivity, SP: specificity, mGFR: measured glomerular filtration rate

Asnani 2013 and Asnani 2015 evaluated the same cohort

Veronese 2014 added data from two cohorts, one of which was Silveiro 2011

* In bold: diagnostic measures included in the meta-analyses

Author, Year	Country	Population / setting	N	% of Females	Age (mean in years)	CKD-EPI	MDRD	Diagnostic measures (P30, bias, sensitivity, or specificity)*	Gold standard	mGFR (mean in mL/min/1.73 m^2)
Zanocco, 2012	Brazil	CKD, Healthy/ Hospital	244	57	Males: 40.6 Females: 42.6	CKD-EPI-Cr IDMS	MDRD-4 IDMS	Sensitivity and specificity	Iohexol	61.31
CKD: chronic kidney disease; SLE: systemic lupus erythematosus, SE: sensitivity, SP: specificity, mGFR: measured glomerular filtration rate										
Asnani 2013 and Asnani 2015 evaluated the same cohort										
Veronese 2014 added data from two cohorts, one of which was Silveiro 2011										
* In bold: diagnostic measures included in the meta-analyses										

Regarding the country, six studies were conducted in Brazil (25–27, 30, 32, 33), two in Mexico (23, 29), two in Argentina (28, 31), and two reported results from the same cohort conducted in Jamaica (24, 34). Regarding the population, six studies were performed in healthy people (23, 25, 28, 31–33), one in candidates for living kidney donation (28), three in type 2 diabetics (25, 30, 32), two in the elderly (26, 27), one in people with systemic lupus erythematosus (SLE) (29), two from the same cohort in homozygous SS sickle cell disease (24, 34), and three in people diagnosed with CKD (31–33).

Nine studies compared MDRD-4 using IDMS (MDRD-4 IDMS) and CKD-EPI-Cr using IDMS (CKD-EPI-Cr IDMS) (23, 25–30, 32, 33), one compared MDRD-4 IDMS and CKD-EPI cystatin C (27), one compared MDRD-4 IDMS and CKD-EPI-Cr-cystatin C (27), three compared MDRD-4 without IDMS and CKD-EPI-Cr without IDMS (24, 31, 34), one compared MDRD-4 without IDMS and CKD-EPI cystatin C (34), and one compared MDRD-4 without IDMS and CKD-EPI-Cr-cystatin C (34). Of the nine studies that compared MDRD-4 IDMS and CKD-EPI-Cr IDMS, six could be included in the meta-analyses (five from Brazil and one from Mexico), since the others did not have enough information to estimate standard errors (Table 1).

Risk of bias

Using the QUADAS-2 tool, we found an uncertain risk of bias for most studies on patient enrolling, interpretation of index test results without knowledge of the reference standard, interpretation of reference standard without knowledge of the index test results, and the interval between index and reference standard test (Fig. 2).

Diagnostic outcomes

The results of each study are detailed in Additional file 4. Meta-analyses could only be performed for the comparison between CKD-EPI-Cr IDMS and MDRD-4 IDMS since other versions of the equations were not evaluated or were evaluated only in one study for the outcomes of interest.

Meta-analyses of bias and P30 are shown in Fig. 3. Meta-analyses of sensitivity/specificity (for the cut-off of GFR 60 ml/min/1.73 m^2) are shown in Fig. 4.

Regarding bias: meta-analyses of five studies (four performed in Brazil and one in Mexico) (23, 25–27, 32) showed no differences between these equations, although point estimates tend to favor slightly the CKD-EPI-Cr IDMS equation (MD: 0.55 mL/min/1.73 m^2, 95% CI: -3.34 to 4.44). For the record, the CKD-EPI-Cr IDMS advantage is higher (although still not significant) in populations with GFR ≥ 60 mL/min/1.73 m^2. In addition, these meta-analyses showed that both equations tend to over-estimate mGFR in people with CKD and to under-estimate it in people without CKD.

Regarding P30: meta-analyses of two studies (both performed in Brazil) (23, 25–27, 32) showed a P30 of 74% (95% CI: 57–90%) for CKD-EPI-Cr IDMS, and of 69% (95% CI: 59–78%) for MDRD-4 IDMS. However, the final mean difference was not compatible with a significant difference, although point estimates tend to favor slightly the CKD-EPI-Cr IDMS equation (MD: 4%, 95% CI: -4–13%). It should be noted that, the CKD-EPI-Cr IDMS advantage is higher (although still not significant) in populations with GFR ≥ 60 mL/min/1.73 m^2.

Regarding sensitivity and specificity, two studies (both performed in Brazil) (27, 32) showed similar sensitivity (76% for CKD-EPI-Cr IDMS and 75% for MDRD-4 IDMS) and specificity (91% for CKD-EPI-Cr IDMS and 89% for MDRD-4 IDMS).

Certainty of evidence

We used GRADE SoF tables to report the certainty of evidence. Regarding bias and P30, the certainty of evidence was very low for both CKD-EPI-Cr IDMS and MDRD-4 IDMS (Table 2). Regarding differences in true positives, true negatives, false positives, and false negatives between equations (obtained through sensitivity and specificity), the certainty of evidence was low (Table 3).

Table 2

Summary of findings of bias and P30

Question: How well is the performance of the CKD-EPI-Cr IDMS and MDRD-4 IDMS equations to diagnose CKD in adult populations (≥ 18 years) from Latin America?

Patient or population: Adults in Latin American countries
Settings: Included studies involved adults from community-dwelling and hospital-based patients (mean prevalence of CKD across included studies: 41%)
New test: CKD-EPI-Cr IDMS
Comparison test: MDRD-4 IDMS
Reference test: The measured glomerular filtration rate (mGFR) as gold standard was obtained by the Cr-EDTA single-injection method in four studies, Iohexol clearance in one study, and 99 m-Tc DTPA in one study.

Outcome	Number of studies (number of participants)	Test Result (95% CI)	Quality of the evidence (GRADE)
Bias			
CKD-EPI-Cr IDMS	5 (727)	-1.72 (-8.61 to 5.17)	⨁●●● VERY LOW [1,2,3,4]
MDRD4 IDMS		− 2.43 (-12.01 to 7.16)	⨁●●● VERY LOW [1,2,3,4]
P30			
CKD-EPI-Cr IDMS	2 (200)	73.78% (58.03 to 89.52)	⨁●●● VERY LOW [3,5]
MDRD-4 IDMS		68.83% (59.21 to 78.44)	⨁●●● VERY LOW [3,5]

GRADE Working Group grade of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimates of effect and may change the estimates.
Low quality: Further research is very likely to have an important impact on our confidence in the estimates of effect and is likely to change the estimates.
Very low quality: We are very uncertain about the estimates.

Bias: Defined as the mean of the difference between eGFR (by equations) and mGFR; P30: Defined as the percentage of results of eGFR that did not deviate more than 30% from mGFR; eGFR: estimated glomerular filtration rate; mGFR: measured glomerular filtration rate; CI: Confidence interval; CKD: Chronic Kidney Disease; CKD-EPI-Cr IDMS: CKD Epidemiology Collaboration equation using creatinine with isotope dilution mass spectrometry method to determine creatinine levels; MDRD-4 IDMS: Modification of Diet in Renal Disease (with four variables) equation with isotope dilution mass spectrometry method to determine creatinine levels.

[1]It was decided to decrease the level of evidence due to risk of bias because in more than 50% of the studies (it was uncertain if the gold standard and reference results were collected at the same time).

[2]It was decided to decrease the level of evidence due to high heterogeneity between the studies (I^2 higher than 90%).

[3]It was decided to decrease the level of evidence due to risk of bias (the gold standard was not the same in all the studies).

[4]It was decided to decrease the level of evidence due to imprecision (both equations could overestimate or underestimate the real value of the GFR).

[5]It was decided to decrease one level due to risk of bias (it was uncertain if the results of the gold standard and the reference were collected at the same time, and in one of the studies the results of all the participants were not analyzed).

Table 3

Summary of findings of sensitivity and specificity for the 60 mL/min/1.73 m^2 cut-off point

Question: How accurate are the CKD-EPI-Cr IDMS and MDRD-4 IDMS equations to diagnose CKD in adult populations (≥ 18 years) from Latin America?					
Number of Participants (Studies)	449 (2)	Pooled Sensitivity CKD-EPI-Cr IDMS	0.76 (95% CI: 0.69 to 0.83)	Pooled Sensitivity MDRD4-IDMS	0.75 (95% CI: 0.68 to 0.82)
		Pooled Specificity CKD-EPI-Cr IDMS	0.91 (95% CI: 0.88 to 0.94)	Pooled Specificity MDRD4-IDMS	0.89 (95% CI: 0.85 to 0.92)
Test Result	Number of results per 1 000 patients tested (95% CI)		Quality of the Evidence (GRADE)		
	Baseline risk across included studies: 41%				
	CKD-EPI-Cr IDMS	MDRD4-IDMS			
True positives (TP)	312 (283 to 340)	308 (279 to 336)	⨁⨁◯◯ LOW [1,2]		
TP absolute difference	4 more TP in CKD-EPI-Cr IDMS				
False negatives (FN)	98 (70 to 127)	102 (74 to 131)			
FN absolute difference	4 less FN in CKD-EPI-Cr IDMS				
True negatives (TN)	537 (519 to 555)	525 (502 to 543)	⨁⨁◯◯ LOW [1,2]		
TN absolute difference	12 more TN in CKD-EPI-Cr IDMS				
False positives (FP)	53 (35 to 71)	65 (47 to 88)			
FP absolute difference	12 less FP in CKD-EPI-Cr IDMS				

CI: Confidence Interval; CKD: Chronic Kidney Disease; CKD-EPI-Cr IDMS: CKD Epidemiology Collaboration equation using creatinine with isotope dilution mass spectrometry method to determine creatinine levels; MDRD4 IDMS: Modification of Diet in Renal Disease (with four variables) equation with isotope dilution mass spectrometry method to determine creatinine levels.

[1]It was decided to decrease the level of evidence due to risk of bias (in both studies, it is uncertain if a consecutive or random sample of patients was enrolled and if the results of the index test were interpreted without knowledge of the results of the gold standard)

[2]It was decided to decrease the level of evidence due to risk of bias (the gold standard was not the same in all the studies).

Discussion

Comparison with other studies

We performed meta-analyses of six studies conducted in Latin American countries that compared CKD-EPI-Cr IDMS and MDRD-4 IDMS. No clear differences between these equations were found for bias, P30, sensitivity, or specificity. However, point estimates showed a lower bias and a higher P30 (both non-statistically significant) using CKD-EPI-Cr IDMS in comparison with using MDRD-4.

A previous systematic review among patients in primary care settings searched for studies until 2017 and included 6 studies conducted in Latin American countries (all of which were included in our review) (22). This review found that in studies using IDMS, CKD-EPI-Cr IDMS had a lower bias (MD: 2.2 mL/min/1.73 m^2, 95% CI: 1.1 to 3.2) and higher P30 (MD: 2.7%, 95% CI: 1.6 to 3.8) than MDRD-4 IDMS. Considering this, it is possible that in our population, as well as in the population reported in the review, the CKD-EPI-Cr IDMS equation could really have a slightly better performance, which cannot be observed due to the lack of power (given the small sample size and high heterogeneity) and the absence of sufficient data to be considered in the meta-analysis of the other studies that evaluated bias and P30.

This presumed advantage of CKD-EPI-Cr IDMS over MDRD-4 IDMS was more evident in studies where the population did not have CKD (GFR ≥ 60 mL/min/1.73 m^2). A similar trend was found in a previous systematic review (22). This could be due to the fact that the CKD-EPI-Cr equation was developed in a study where the GFR mean was larger than in the study where the MDRD-4 equation was created (94.5 ml/min vs 39.8 ml/min respectively) (9).

How to better evaluate eGFR in LA populations

These equations may not be accurate for all racial groups due to their different muscle mass and, consequently, different excretion of creatinine (35). Thus, equations try to correct their estimations per race using different coefficients for white or black people but do not consider account other races.

Given this limitation, modifications of the formulas have been proposed for several ethnic groups, including Asian (36), Japanese (37), Chinese (38), Pakistanis (39), and African (12). However, previous attempts to modify the CKD-EPI-Cr formula for Latin American populations (40) and Brazilian population (33) found no significant improvements of the modified versus the original formula. This may be due to the fact that Latin American population do not include a single ethnic group, but a confluence of multiple ethnicities from diverse origins, and the profile of each population (in terms of percentage of European-descendant, Afro-descendent, or indigenous) may vary between and within countries and regions (41–43).

Given this ethnic heterogeneity, it is possible that the equations performance differs by country. However, of the six studies that could be meta-analyzed in our study, five were performed in Brazil, where the ethnic composition is different from other countries in the region. As an example, while around 60% of the Brazilian population is Caucasian and less than 0.5% is Amerindian (44), in Peru around 60% of the population identifies themselves as Mestizo, 25% as Quechua or Aymara (Amerindians), and only around 6% as Caucasians (45). This prevents conclusions being drawn on other Latin American countries where Amerindians represent an important proportion of the population. In this way, further studies comparing equations or trying to validate coefficients for other Latin American countries are needed.

Implications

Our results suggest that in Latin American populations, as in other populations, these equations do not vary greatly. However, CKD-EPI-Cr IDMS tends to have a non-significant better performance than the MDRD-4 IDMS in term of P30 and among people with GFR < 60 mL/min/1.73 m^2.

However, it is necessary to highlight that the certainty of evidence was very low or low, so further well-designed studies are needed. In addition, extrapolation to other Latin American countries is difficult because almost all meta-analyzed studies were performed in Brazil. Finally, all meta-analyzed studies used IDMS for creatinine calculation, which has to be taken into account in contexts that do not have IDMS.

Limitations and strengths

Some limitations should be considered: 1) Not all studies had enough information to perform a meta-analysis of the outcomes of interest, even after authors were consulted. 2) We have found differences in the characteristics of the included populations, but we were not able to perform subgroup analysis to understand how this differences affected the accuracy of the formulas (35). The influence of other factors, such as the different causes of CKD or taking of medicines was not studied either (46).

In spite of the limitations we believe our study is important as this is the first systematic review that has compared the GFR equations in Latin American countries, which performed a two-steps sensitive search (the first in two international databases and one local database, and the second in the references and articles that cited each of the articles included in the first step). In addition, we performed a comprehensive search including papers in Spanish and Portuguese, and the selection and extraction of data were performed in duplicate.

Conclusion

We performed a systematic review to assess the performance of the CKD-EPI and the MDRD equations to estimate the GFR in Latin American countries. We found 12 studies and could meta-analyze six of them (five were conducted in Brazil). We found that the performance of CKD-EPI-Cr IDMS and MDRD-4 IDMS do not differ significantly, although CKD-EPI-Cr IDMS tends to have a non-significant better performance in terms of P30 and among people with GFR ≥ 60 mL/min/1.73 m^2. However, since most of the meta-analyzed studies were from Brazil, results may not be extrapolated to other Latin American countries.

Abbreviations

BIREME
Biblioteca Regional de Medicina
CKD
Chronic Kidney Disease
CKD-EPI
CKD-Epidemiology Collaboration
CKD-EPI-Cr
CKD-Epidemiology Collaboration using Creatinine
CRMSE
combined root mean square error
eGFR
estimated GFR
GFR
Glomerular Filtration Rate

GRADE
Grading of Recommendations Assessment, Development and Evaluation
IDMS
Isotope Dilution Mass Spectrometry
MD
Mean Difference
MDRD
Modification of Diet in Renal Disease
MDRD-4
MDRD equation using four variables
MDRD-6
MDRD equation using six variables
mGFR
measured GFR
PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analysis
QUADAS-2
Quality Assessment of Diagnostic Accuracy Studies
SLE
systemic lupus erythematosus
SoF
Summary of Findings

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

ABC, SGL, JHZT, and ATR designed the study. ABC, NBC, and VEFR collected the data. ABC and ATR performed statistical analyses. All authors participated in the writing of the manuscript and approved its final version.

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Additional Files

File name: Additional file 1. File format: Additional file 1.docx

Title of data: Search strategy

File name: Additional file 2. File format: Additional file 2.docx

Title of data: Excluded studies

File name: Additional file 3. File format: Additional file 3.docx

Title of data: Characteristics of the included studies

File name: Additional file 4. File format: Additional file 4.docx

Title of data: Results of diagnostic outcomes according to CKD-EPI and MDRD equations

Figures

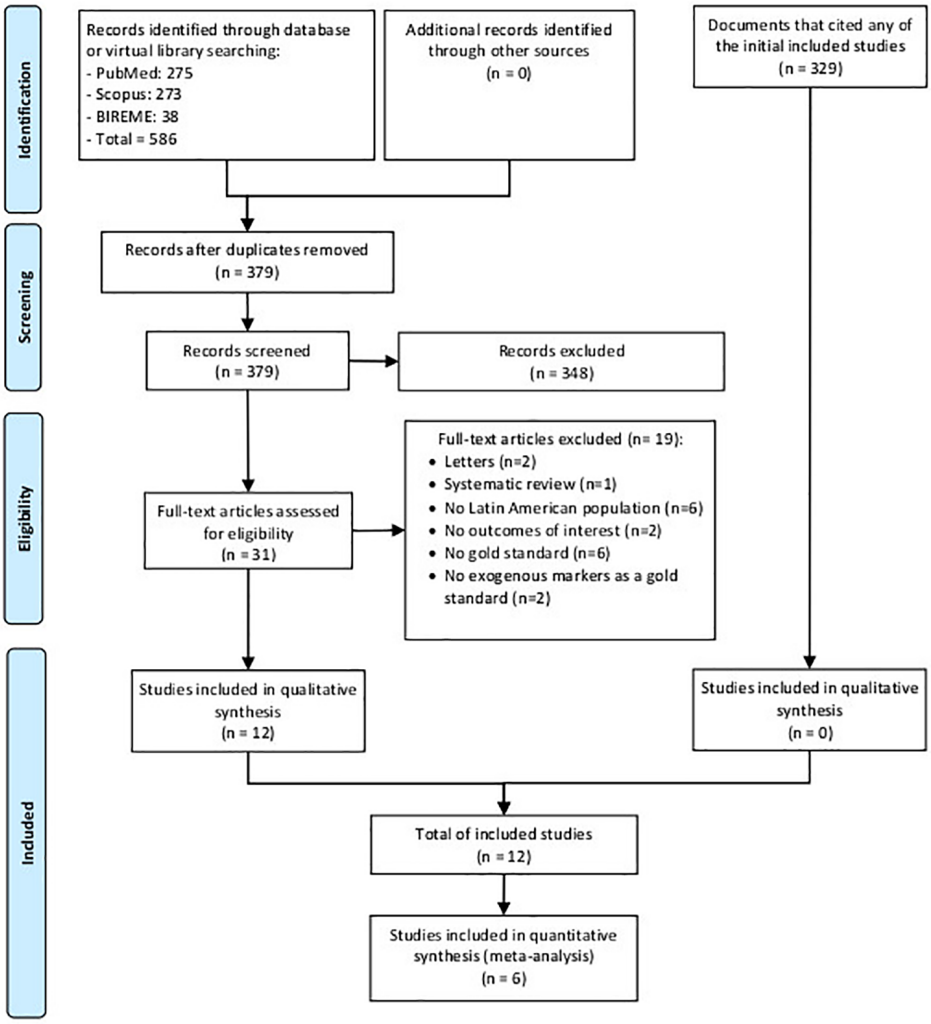
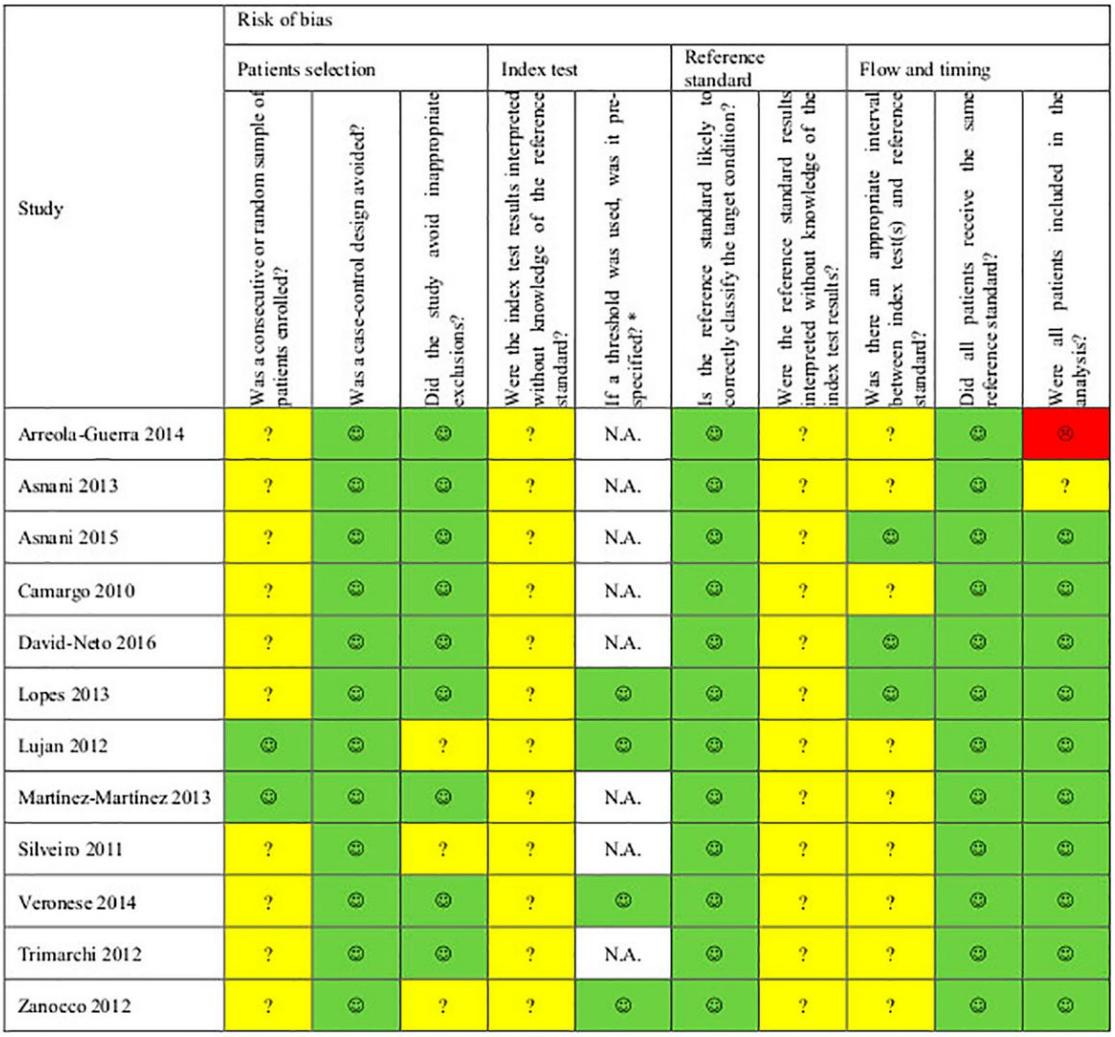


Figure 1

Flow diagram summarizing the process of literature search and selection



Study	Risk of bias									
	Patients selection			Index test		Reference standard		Flow and timing		
	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the reference standard?	If a threshold was used, was it pre-specified? *	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the index test results?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive the same reference standard?	Were all patients included in the analysis?
Arreola-Guerra 2014	?	☺	☺	?	N.A.	☺	?	?	☺	☹
Asnani 2013	?	☺	☺	?	N.A.	☺	?	?	☺	?
Asnani 2015	?	☺	☺	?	N.A.	☺	?	☺	☺	☺
Camargo 2010	?	☺	☺	?	N.A.	☺	?	?	☺	☺
David-Neto 2016	?	☺	☺	?	N.A.	☺	?	☺	☺	☺
Lopes 2013	?	☺	☺	?	☺	☺	?	☺	☺	☺
Lujan 2012	☺	☺	?	?	☺	☺	?	?	☺	☺
Martínez-Martínez 2013	☺	☺	☺	?	N.A.	☺	?	?	☺	☺
Silveiro 2011	?	☺	?	?	N.A.	☺	?	?	☺	☺
Veronese 2014	?	☺	☺	?	☺	☺	?	?	☺	☺
Trimarchi 2012	?	☺	☺	?	N.A.	☺	?	?	☺	☺
Zanocco 2012	?	☺	?	?	☺	☺	?	?	☺	☺

Figure 2

Risk of bias Green= Yes; Yellow= Unclear; Red= No; N.A= not applicable * Only applicable for studies that showed sensitivity/specificity

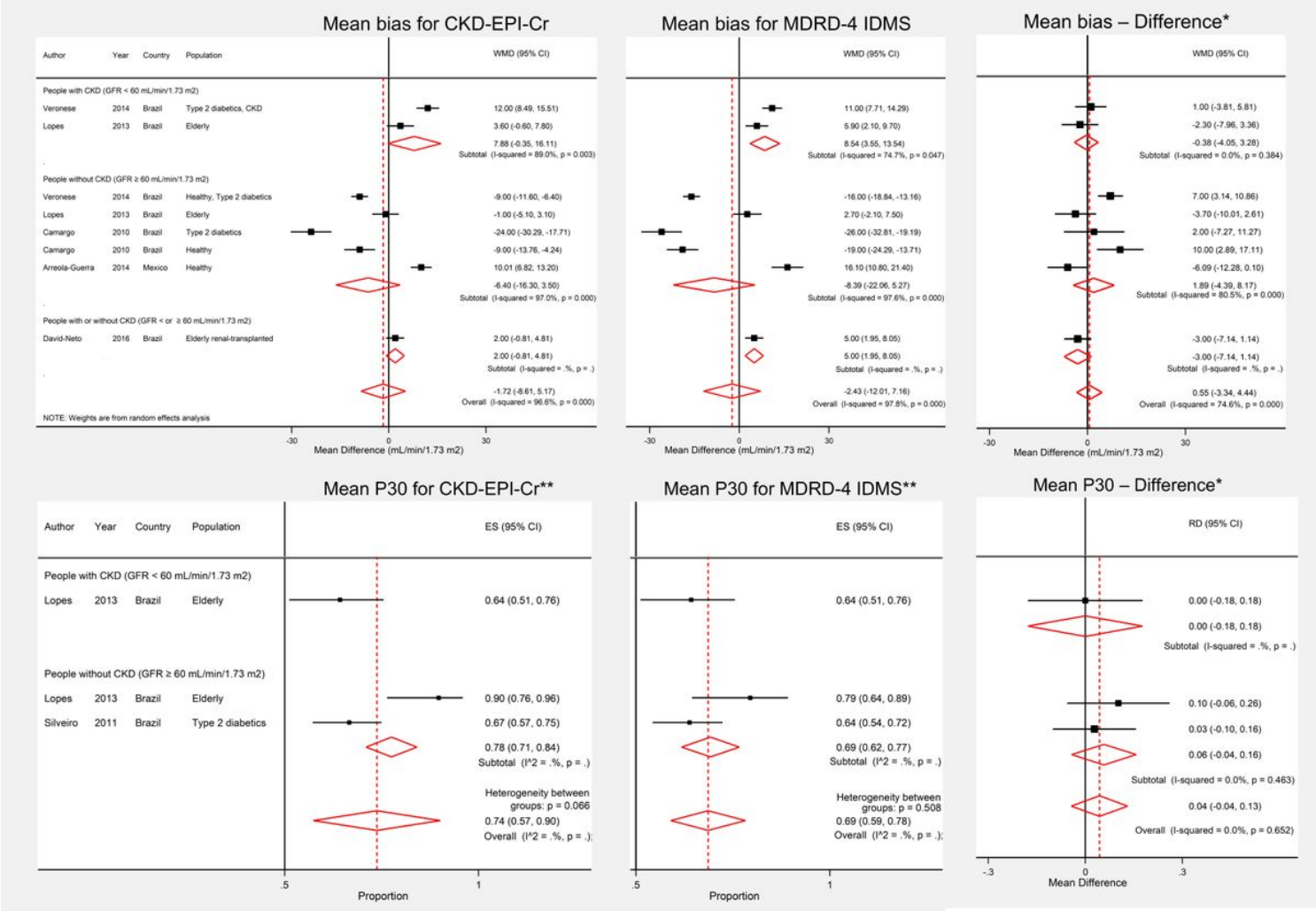


Figure 3

Forest plot for bias and P30 *The difference was calculated by subtracting CKD-EPI-Cr IDMS minus MDRD-4 IDMS values. **I2 could not be calculated given the small number of studies. The groups were separated according to the measured GFR reported in the studies. WMD= Weighted mean difference; ES= Effect size; RD= Risk differences

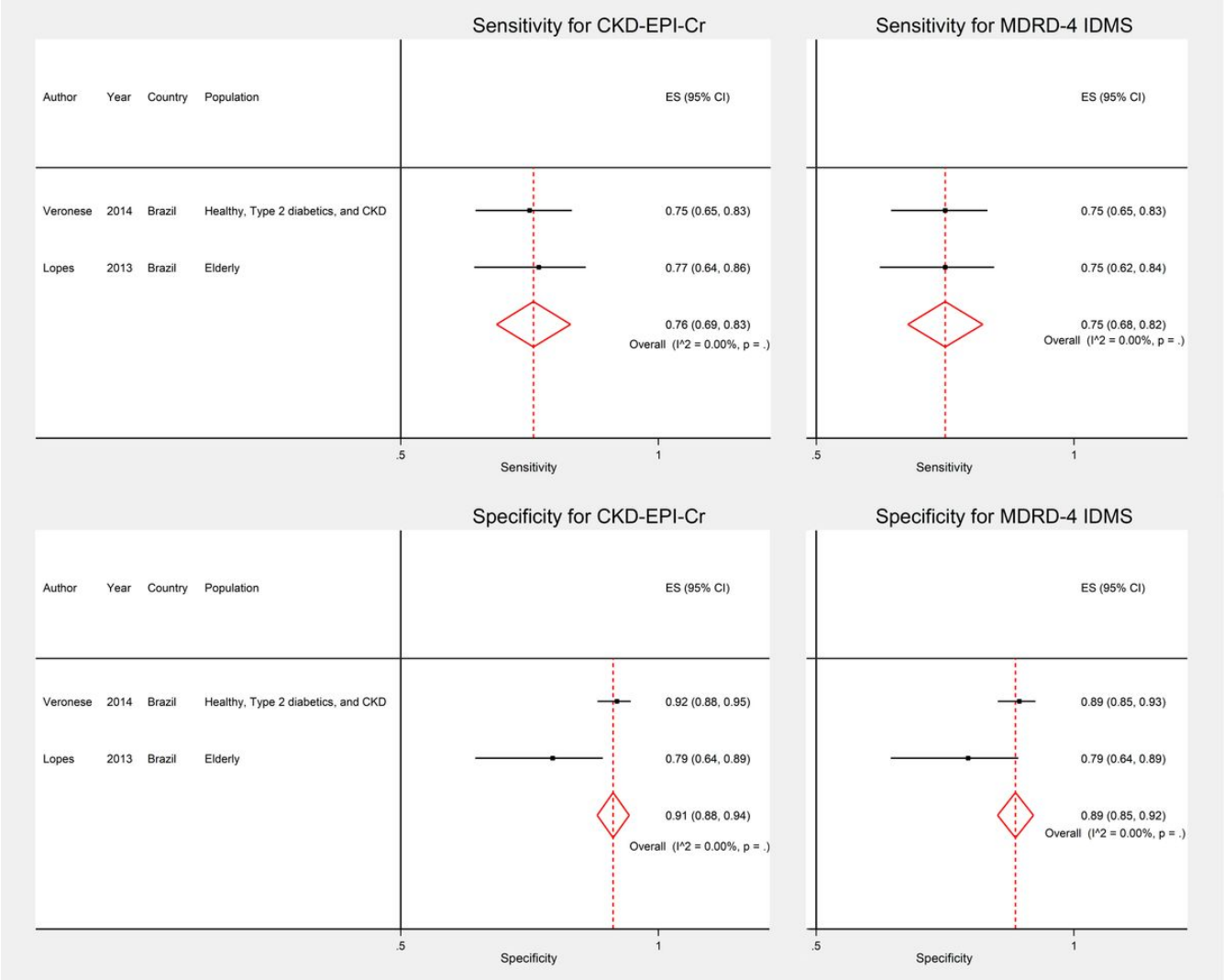


Figure 4

Forest plot for sensitivity and specificity (cut-off of GFR 60mL/min/1.73m2) ES= Effect size

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile2.docx
- Additionalfile3.docx
- Additionalfile4.docx
- PRISMA2009checklist.doc
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