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Clinical Research Article

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Performance of 4 Creatinine-based Equations in Assessing Glomerular Filtration Rate in Adults with Diabetes

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Abbreviations: 99mTc-DTPA, technetium-99m diethylenetriamine-pentaacetic acid; BMI, body mass index; CCC, concordance correlation coefficient; CKD-EPI, chronic kidney disease epidemiology collaboration; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; FAS, full age spectrum; HbA1c, Hemoglobin A1C; MDRD, modification of diet in renal disease; mGFR, measured glomerular filtration rate; r-LM, revised Lund–Malmö; RMAR, reduced major axis regression; SD, standard deviation.

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Abstract

Aims: To evaluate diagnostic performance of glomerular filtration rate (GFR) estimated by modification of diet in renal disease (MDRD), chronic kidney disease epidemiology collaboration (CKD-EPI), full age spectrum (FAS), and revised Lund–Malmö (r-LM) equations in adults with diabetes.

Methods: Individuals were included in this cross-sectional study if they had at least 1 measurement of technetium-99m diethylenetriamine-pentaacetic acid (^{99m}Tc-DTPA) GFR (mGFR) and serum creatinine (1487 patients with 2703 measures). GFR calculated by estimation equations was compared with mGFR. Diagnostic performance was assessed using concordance correlation coefficient (CCC), bias, precision, accuracy, reduced major axis regression (RMAR), and Bland–Altman plot. Analysis was repeated in subgroups based on sex, diabetes type, Hemoglobin A1C, and GFR level.

Results: Of all patients, 1189 (86%) had type 2 diabetes. Mean mGFR, MDRD, CKD-EPI, FAS, and revised Lund-Malmö eGFR were 66, 72, 74, 71, and 67 mL/min/1.73m^2, respectively. Overall, the r-LM had the highest CCC (0.83), lowest bias (–1.4 mL/min/1.73 m^2), highest

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precision (16.2 mL/min/1.73 m^2), and highest accuracy (P10 = 39%). The RMAR (slope, intercept) in r-LM, FAS, MDRD, and CKD-EPI was 1.18, –13.35; 0.97, –2.9; 1, -6.4, and 1.04, –11.3, respectively. The Bland–Altman plot showed that r-LM had the lowest mean difference and the narrowest 95% limit of agreement (–1.0, 54.1 mL/min/1.73 m^2), while mean difference was more than 5-fold higher in FAS, MDRD, and CKD-EPI (–5.2, –6.3, and –8.2, respectively).

Conclusions: In adults with diabetes the revised Lund-Malmö performs better than MDRD, CKD-EPI, and FAS in calculating point estimates of GFR.

Freeform/Key Words: CKD-EPI equation, diabetic kidney disease, diagnostic performance, estimated GFR, measure GFR, revised Lund–Malmö equation

Affecting about 40% of people with diabetes, diabetic kidney disease (DKD) is one of the most common complications of diabetes, which is increasing at an alarming pace worldwide (1, 2). DKD is the most common cause of dialysis or renal transplantation worldwide (2). Furthermore, DKD has been associated with higher cardiovascular and all-cause mortality rate, as well as higher disability adjusted life years in people with diabetes (2). Availability of novel medical interventions to halt or reduce disease progression necessitates prediction of at risk individuals and early diagnosis of those with the condition (3, 4). Hence, accurate diagnosis of DKD plays a crucial role in managing the condition.

Glomerular filtration rate (GFR) has been widely used as a surrogate of kidney function (5, 6). GFR measured by kidney or plasma clearance of exogenous compounds is considered the gold standard method for assessing GFR. However, these are invasive and resource-intensive procedures (7). Such limitations have led to the use of an alternate method, the estimated GFR (eGFR), using minimally invasive, widely available information such as age, sex, race, and serum creatinine (8). Since their introduction as a potential diagnostic tool, eGFR equations have undergone numerous alterations and modifications to produce estimates closer to gold standard measures (9). A crucial step in assessing newly developed equations is their validation in other populations (10).

Studies assessing agreement between measured GFR (mGFR) and the more commonly used eGFR equations, for example, modification of diet in renal disease (MDRD) and chronic kidney disease epidemiology collaboration (CKD-EPI), in people with diabetes have shown contradictory results (11-14). Furthermore, data regarding the more recent equations, for example, full age spectrum (FAS), revised Lund–Malmö (r-LM), and their agreement with mGFR in people with diabetes are scarce (15, 16). The current study aimed to investigate performance of 4 eGFR equations, namely MDRD, CKD-EPI, FAS, and r-LM, compared with mGFR in adults with diabetes.

Materials and Methods

Study participants

This observational study was conducted on people with type 1 or type 2 diabetes attending Austin Hospital between May 2002 and 2018. Austin Hospital is a large tertiary hospital in Melbourne, Australia, which has departments of endocrinology, nephrology, pathology, and nuclear medicine. Besides routine eGFR calculation and extensive complication screening, people with diabetes attending diabetes clinics have traditionally been offered to have their GFR measured more accurately by technetium-99m diethylenetriamine-pentaacetic acid (^{99m}Tc-DTPA) approximately every 5 years. To be included in this study, participants had to be >18 years old, diagnosed with type 1 or type 2 diabetes, and have at least 1 mGFR and serum creatinine within 3 months from mGFR collection date. Overall, 1487 patients with a total of 2703 mGFRs were included. This study was approved by the Austin Health Human Ethics Committee. The reported investigations have been carried out in accordance with the principles of the Declaration of Helsinki as revised in 2008.

Data collection and measurements

Data on patients' date of birth, sex, and type of diabetes were collected from electronic medical records. Patients' weight and height were recorded each time GFR was measured. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). All blood and urine samples were collected and analyzed by the Austin Health Pathology department. Routine chemistry was performed on a Hitachi 747/917, Beckman Synchron DxC800 or Roche Cobas 8000. Glucose was measured by hexokinase or glucose oxidase; total cholesterol, high-density lipoprotein, and triglycerides by timed end-point reactions (cholesterol esterase, modified cholesterol esterase, lipoprotein lipase respectively); creatinine by Jaffe reaction, and urine albumin by immunoturbidimetry. Low-density lipoprotein

was calculated using the Friedewald equation. Glycated hemoglobin (HbA1C) was measured by immunoassay on Roche Integra. Albumin excretion rate was calculated as the product of urine albumin concentration and urine volume per 1440 minutes.

GFR was measured based on the rate of plasma disappearance of a single intravenous injection of 120 MBq of ^{99m}Tc-DTPA (17). Before the injection, patients were hydrated with 500 mL of water. Three sequential serum samples were obtained over 3.5 hour following intravenous dose injection. The preinjection dose was calibrated for injection time. To rule out any extravasation of radiotracer at the injection site, an image (Arm Static) of the injection site was acquired. mGFR was then corrected for Brochner–Mortensen coefficient, sex (correction coefficient of 0.8 for men and 0.9 for women), and body surface area (using Dubois formula) (18). The corrected GFR for Brochner–Mortensen and sex will be referred as mGFR in this paper.

GFR was estimated by 4 estimation equations, namely the MDRD (19), CKD-EPI (20), FAS (21), and r-LM (Table 1) (22).

Statistical analysis

Baseline characteristics were reported as mean (standard deviation, SD) for continuous and frequency (%) for categorical variables. Albumin excretion rate was reported by median (interquartile range) due to high skewness. Analysis was conducted in total and subgroups based on sex (men/women), diabetes type (type 1/type 2), HbA1c level (HbA1c ≥ 69 mmol/mol [8.5%] and HbA1c < 69 mmol/mol [8.5%]), and eGFR categories (<30, 30-45, 45-60, 60-90, 90-120, ≥120, based on CKD-EPI equation as the common tool currently used in clinical practice).

Diagnostic performance of the 4 estimation equations were assessed via the following performance measures:

1. The agreement between mGFR and eGFR was assessed by concordance correlation coefficient (CCC) calculated by "concord" command in Stata. (23) The coefficient is interpreted as almost perfect (0.81-1), substantial (0.61-0.8), moderate (0.41-0.6), fair (0.21-0.4), and slight (0-0.2) (24).
2. Bias was calculated as median mGFR-eGFR.
3. Precision was assessed using interquartile range of bias as well as root mean square error (25).
4. Accuracy was defined as the proportion of eGFR within 10%, 30%, and 50% of mGFR (P10, P30, and P50, respectively) (26).
5. Precision and mean bias were further assessed by the Bland-Altman plot with reports on mean difference and 95% limit of agreement between mGFR and eGFR (27).
6. Fixed and proportional bias among the whole spectrum of GFR were evaluated by the reduced major axis regression (RMAR) graph with reports of its slope and intercept. Slope different from 1 is indicative of proportional bias, and in cases where slope is 1, the intercept different from 0 is indicative of fixed bias (28).

To facilitate comparison of performance of MDRD, CKD-EPI, FAS, and the r-LM, a radar chart of bias, precision, accuracy (P10, P30, P50), and CCC was drawn. Analysis was conducted using Stata version 14.0 (StataCorp LP, USA). All confidence intervals were estimated using bootstrap method with 1000 replications with 95% limit. There was no missing data of serum creatinine, sex, age, and mGFR.

Table 1. Glomerular filtration rate estimation equations

Name	Formula
Modification of diet in renal disease	$175 \times (\frac{S_{cr}}{88.4})^{-1.154} \times Age^{-0.203} \times 0.742$ (*if female*)
Chronic kidney disease epidemiology collaboration	Female & $S_{Cr} \leq 62$μmol/L: $144\times(S_{cr}/62)^{-0.329}\times0.993^{Age}$ Female & $S_{Cr} > 62$μmol/L: $144\times(S_{cr}/62)^{-1.209}\times0.993^{Age}$ Male & $S_{Cr} \leq 80$μmol/L: $141\times(S_{cr}/80)^{-0.411}\times0.993^{Age}$ Male & $S_{Cr} > 80$μmol/L: $141\times(S_{cr}/80)^{-1.209}\times0.993^{Age}$
Full age spectrum	$\frac{107.3}{\frac{S_{cr}}{Q_{Cr}}} \times [0.988^{(age-40)}$ *if age* $> 40]$
Revised Lund–Malmö	Q_{Cr} = the mean or median S_{cr} concentration of the corresponding age-/sex-matched healthy population $e^{X-0.0158\times age +0.438\times\ln(age)}$ Female & $S_{Cr} < 150$ μmol/L: $X = 2.50 + 0.0121 \times (150-S_{Cr})$ Female & $S_{Cr} \geq 150$ μmol/L: $X = 2.50-0.926 \times \ln(S_{Cr}/150)$ Male & $S_{Cr} < 180$ μmol/L: $X = 2.56 + 0.009\ 68 \times (180-S_{Cr})$ Male & $S_{Cr} \geq 180$ μmol/L: $X = 2.56-0.926 \times \ln(S_{Cr}/180)$

S_{cr}, serum creatinine. S_{cr} unit is μmol/L.

Results

From 1487 patients with mean age (SD) 62 (14) years, **591** were women (40%) and 1189 had type 2 diabetes (86%). From 2703 ^{99m}Tc-DTPA GFR measurements in 1487 patients, 40% were undertaken in women (n = 1607) and 82% were in people with type 2 diabetes (n = 2097). Mean (SD) BMI was 31 (6) kg/m^2, mean (SD) fasting serum glucose was 9.2 (3.5), mean (SD) HbA1c was 62 (14) mmol/mol (7.8% (1.3)), and mean serum creatinine 93.8 (39.7) µmol/L. Mean (IQR) albumin excretion rate in 24-hour urine was 12.4 (6.2, 42.6) µg/min and mean (SD) mGFR was 66 (25). Mean (SD) eGFR reported by MDRD, CKD-EPI, FAS, and r-LM were 72 (25), 74 (24), 71 (26), and 67 (21) mL/min/1.73 m^2, respectively (Table 2).

In general (Table 3 and Fig. 1), the r-LM had the highest concordance with mGFR; however, all equations had a CCC < 0.90 (CCC = 0.83, 0.81, 0.78, and 0.76 for r-LM, FAS, CKD-EPI, and MDRD, respectively). r-LM had the lowest bias (median difference with corrected mGFR = –1.4 mL/min/1.73 m^2) which was at least 3 times lower than the bias reported for FAS, MDRD, and CKD-EPI (median difference = –4.5, –6.0, –8.1 mL/min/1.73 m^2). Precision evaluated as interquartile range of bias ranged between 16.2 mL/min/1.73 m^2 in r-LM and 18.1 mL/min/1.73 m^2 in MDRD. Precision assessed via root mean square error ranged from 13.8 in rLM and 17.9 in MDRD. The r-LM had the highest accuracy (P50 = 96%, P30 = 83%, and P10 = 39%) followed by FAS, MDRD, and CKD-EPI.

As shown in Fig. 2, the RMAR slope and intercept ranged from 0.97, –2.92 in FAS to 1.18, –13.35 in the r-LM. All equations except MDRD (slope = 1) had both proportional and fixed bias. MDRD, CKD-EPI and FAS overestimated mGFR across the whole GFR range. However, r-LM overestimated GFR levels below 74.2 mL/min/1.73 m^2 and underestimated GFR values above 74.2 mL/min/1.73 m^2.

The Bland–Altman plot showed the lowest mean difference, 95% limit of agreement between mGFR and r-LM (–1.0, 54 mL/min/1.73 m^2). Mean difference between mGFR and other equations were more than 5-fold higher than r-LM (–5.2, –6.3, and –8.2 for FAS, MDRD, and CKD-EPI, respectively). However, CKD-EPI had a 95% limit of agreement close to r-LM (57.3 mL/min/1.73 m^2). In all 4 equations the Bland–Altman plot was more scattered in higher GFR levels (Fig. 3).

In men (Table 3), r-LM had the highest agreement, precision and accuracy while having the lowest bias (CCC = 0.83, RMSE = 12.9, P10 = 39%, P30 = 83%, P50 = 96%, median difference = –2.8). In women, although all equations had a similar agreement, precision and accuracy, CKD-EPI had a noticeably higher bias (median difference = –4.3, –0.5, 1.1, and –2.1 in CKD-EPI, FAS, r-LM, and MDRD, respectively). The reported bias of equations in women was generally lower than in men.

Similarly, in people with type 1 diabetes (Table 3), all equations had very similar agreement, precision and accuracy whereas bias was considerably lower in r-LM (median difference = –0.3). In people with type 2 diabetes, r-LM had a noticeably better agreement (CCC = 0.83), bias (median difference = –1.7), precision (RMSE = 13.6), and accuracy (P10 = 38%, P30 = 82%, and P50 = 95%). In those with HbA1c < 69 mmol/mol (8.5%), the r-LM showed considerably lower bias and higher precision and accuracy (median difference = –4.2, RMSE = 15.4, P10 = 37%, P30 = 79%, and P50 = 92%). In those with HbA1c ≥ 69 mmol/mol (8.5%), diagnostic performance of the r-LM seemed better than other equations. However, the low number of patients in this subgroup (n = 134) limits the interpretation of results.

Baseline characteristics of subgroups were reported in Table 4. Subgroup analysis based on eGFR (Table 5) revealed the superiority of r-LM in its agreement, bias, precision, and accuracy in eGFR levels > 60 mL/min/1.73 m^2. There was generally no considerable difference among the 4 equations in eGFR < 60 mL/min/1.73 m^2.

Discussion

This study investigated and compared performance of 4 creatinine-based eGFR equations with mGFR using various methods, namely bias, accuracy, precision, CCC, and RMAR in adults with diabetes. Results of this study showed that r-LM outperformed FAS, CKD-EPI, and MDRD in estimating GFR relative to mGFR. Analysis split by sex (men/women), type of diabetes (type1/type 2 diabetes), HbA1c level, and eGFR category showed the overall superiority of the r-LM equation. Therefore, we suggest using the r-LM equation to estimate GFR in adults with diabetes.

One of the potential causes for better performance of the r-LM and FAS compared to CKD-EPI and MDRD could be that they have used the more modern isotope dilution mass spectrometry (IDMS) traceable enzymatic method for measuring creatinine. This could have allowed for lower creatinine measurement error, which could lead to more accurate estimation equation (29). Another explanation for better performance of the r-LM in our study could be the similarity of methods used to measure GFR. In both r-LM development study and our study, GFR was measured by plasma clearance of exogenous markers, iohexol, and technetium-99m diethylenetriamine-pentaacetic acid (99mTc-DTPA), respectively. However, in MDRD and CKD-EPI, GFR was

Table 2. Characteristics of study participants

	All	Men	Women	*P*	Type 1 diabetes	Type 2 diabetes	*P*
Baseline characteristics							
n	1487	890	597	NA	199	1189	NA
Age (year)	62 (14)	62 (14)	62 (14)	.49	48 (16)	65 (11)	<.001
Sex (% women)	597 (40.1%)	0 (0.0%)	597 (100.0%)	<.001	86 (43.2%)	474 (39.9%)	.37
% with type 2 diabetes	1189 (85.7%)	715 (86.4%)	474 (84.6%)	.37	0 (0.0%)	1189 (100.0%)	<.001
Number of measurements	2703	1607	1096	NA	457	2097	NA
Age (year)	62 (13)	62 (13)	63 (13)	.025	50 (15)	65 (11)	<.001
Sex (% women)	40.5%	0	100%	<.001	204 (44.6%)	832 (39.7%)	.050
% with type 2 diabetes	82.1%	83.3	80.3	.050	0	100%	<.001
BMI (kg/m^2)	31 (6)	30 (5)	32 (7)	<.001	27 (4)	31 (6)	<.001
Fasting serum glucose (mmol/L)	9.2 (3.5)	9.3 (3.6)	9.2 (3.4)	.41	10.6 (4.9)	8.9 (3.0)	<.001
Total cholesterol (mmol/L)	4.3 (1.0)	4.2 (1.1)	4.5 (1.0)	<.001	4.6 (0.9)	4.2 (1.0)	<.001
HDL (mmol/L)	1.3 (0.4)	1.1 (0.4)	1.4 (0.4)	<.001	1.5 (0.5)	1.2 (0.4)	<.001
LDL (mmol/L)	2.3 (0.8)	2.3 (0.8)	2.4 (0.8)	.002	2.6 (0.7)	2.2 (0.8)	<.001
Triglyceride (mmol/L)[a]	1.4 (0.9, 2.0)	1.4 (0.9, 2.1)	1.4 (1.0, 2.0)	.60	0.8 (0.6, 1.2)	1.5 (1.1, 2.2)	<.001
HbA1c (%)	7.8 (1.3)	7.8 (1.4)	7.8 (1.2)	.65	7.8 (1.2)	7.8 (1.4)	.63
HbA1c (mmol/mol)	61.8 (14.5)	61.6 (15.2)	62.2 (13.4)	.66	61.3 (12.7)	62.1 (14.9)	.62
Serum creatinine (Umol/L)	93.8 (39.7)	102.7 (43.0)	80.9 (30.0)	<.001	84.2 (31.1)	96.4 (41.5)	<.001
Albumin excretion rate (µg/min)[a]	12.4 (6.2, 42.6)	17.7 (7.6, 65.2)	8.8 (5.1, 21.0)	<.001	8.2 (4.9, 18.5)	13.6 (6.6, 48.7)	<.001
mGFR	104 (49)	110 (50)	95 (46)	<.001	122 (46)	99 (48)	<.001
corrected mGFR[b]	66 (25)	64 (23)	70 (28)	<.001	78 (23)	63 (25)	<.001
MDRD eGFR	72 (25)	73 (24)	71 (26)	.043	80 (21)	70 (26)	<.001
CKD-EPI eGFR	74 (24)	75 (24)	74 (24)	.18	87 (22)	71 (24)	<.001
FAS eGFR	71 (26)	72 (25)	70 (27)	.10	85 (23)	68 (26)	<.001
Revised Lund–Malmö eGFR	67 (21)	67 (21)	68 (22)	.35	78 (18)	64 (21)	<.001

Values reported as mean (SD) unless mentioned otherwise. All GFR values are reported in mL/min/1.73 m^2.

NA, not applicable; BMI, body mass index; HDL, high density lipoprotein; LDL, low density lipoprotein; HbA1c, hemoglobin A1c; mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; FAS, full age spectrum

[a]Median (IQR).

[b]Measured GFR corrected for sex and Brochner–Mortensen coefficient.

Table 3. Validation of the Modification of Diet in Renal Disease (MDRD), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), the Full Age Spectrum (FAS), and the Revised Lund–Malmö equations in assessing GFR in people with diabetes based on their GFR category

	n	Agreement	Bias	Precision		Accuracy		
		CCC	Median mGFR–eGFR	IQR	RMSE	p10	p30	p50
All						p10	p30	p50
MDRD	2703	0.76 (0.74, 0.78)	−6.0 (−6.7, −5.2)	18.1 (17.0, 19.1)	17.9 (17.0, 18.9)	32% (30, 34)	74% (73, 76)	91% (89, 92)
CKD-EPI	2703	0.78 (0.76, 0.80)	−8.1 (−9.1, −7.3)	17.5 (16.3, 18.4)	16.8 (16.2, 17.4)	32% (30, 34)	73% (71, 75)	90% (89, 92)
FAS	2703	0.81 (0.79, 0.82)	−4.5 (−5.3, −3.8)	16.9 (16.1, 17.9)	16.2 (15.4, 17.0)	36% (34, 39)	79% (77, 81)	93% (92, 94)
R-LM	2703	0.83 (0.81, 0.84)	−1.4 (−2.0, −0.9)	16.2 (15.2, 17.1)	13.8 (13.3, 14.4)	39% (37, 41)	83% (81, 85)	96% (95, 96)
Men								
MDRD	1607	0.74 (0.71, 0.77)	−8.5 (−9.5, −7.4)	17.6 (16.4, 18.7)	17.7 (16.8, 18.5)	30% (27, 32)	71% (68, 73)	89% (87, 90)
CKD-EPI	1607	0.76 (0.73, 0.79)	−10.8 (−11.5, −10.0)	17.2 (16.3, 18.1)	17.4 (16.6, 18.2)	29% (26, 31)	69% (66, 71)	89% (87, 90)
FAS	1607	0.79 (0.77, 0.82)	−7.0 (−7.7, −6.2)	16.1 (15.1, 17.2)	16.1 (15.2, 17.0)	35% (32, 38)	76% (74, 79)	92% (91, 94)
R-LM	1607	0.83 (0.81, 0.85)	−2.8 (−3.8, −2.0)	14.8 (13.9, 15.7)	12.9 (12.2, 13.5)	40% (37, 43)	83% (81, 85)	95% (94, 96)
Women								
MDRD	1096	0.77 (0.74, 0.81)	−2.1 (−3.2, −0.7)	18.8 (17.4, 20.4)	18.2 (16.4, 20.5)	34% (32, 38)	80% (77, 83)	93% (92, 95)
CKD-EPI	1096	0.82 (0.79, 0.84)	−4.3 (−5.3, −3.3)	17.7 (16.3, 18.9)	15.8 (14.8, 16.7)	36% (33, 40)	79% (76, 82)	93% (91, 94)
FAS	1096	0.82 (0.79, 0.85)	−0.5 (−1.7, 0.6)	16.7 (15.5, 18.2)	16.3 (14.7, 18.0)	39% (35, 42)	83% (80, 85)	95% (94, 97)
R-LM	1096	0.81 (0.79, 0.84)	1.1 (−0.3, 2.4)	17.8 (16.1, 18.9)	15.2 (14.1, 16.2)	38% (34, 41)	83% (80, 86)	96% (95, 97)
Type 1 diabetes								
MDRD	457	0.68 (0.59, 0.76)	−2.5 (−4.5, −0.4)	21.2 (17.7, 24.6)	17.7 (15.8, 19.6)	37% (33, 42)	81% (76, 86)	94% (91, 96)
CKD-EPI	457	0.70 (0.62, 0.76)	−8.7 (−10.8, −6.1)	19.1 (16.6, 22.2)	18.4 (16.6, 20.3)	34% (29, 40)	77% (72, 83)	92% (89, 94)
FAS	457	0.72 (0.64, 0.78)	−6.2 (−7.9, −4.1)	19.4 (17.5, 22.9)	17.9 (15.9, 19.9)	37% (31, 42)	79% (75, 84)	93% (90, 96)
R-LM	457	0.75 (0.67, 0.81)	−0.3 (−2.1, 1.9)	18.1 (15.9, 20.3)	14.8 (13.1, 16.5)	43% (38, 49)	86% (81, 90)	96% (93, 98)
Type 2 diabetes								
MDRD	2097	0.76 (0.73, 0.78)	−6.7 (−7.5, −5.9)	17.5 (16.6, 18.7)	18.0 (16.9, 19.4)	30% (28, 32)	73% (70, 75)	90% (88, 91)
CKD-EPI	2097	0.78 (0.76, 0.80)	−8.1 (−9.1, −7.2)	17.1 (16.0, 18.3)	16.5 (15.8, 17.1)	31% (29, 33)	72% (69, 74)	90% (88, 91)
FAS	2097	0.81 (0.79, 0.83)	−4.1 (−4.9, −3.4)	16.7 (15.6, 17.5)	15.8 (14.9, 16.8)	36% (34, 38)	78% (76, 80)	93% (92, 94)
R-LM	2097	0.83 (0.81, 0.84)	−1.7 (−2.4, −1.0)	15.7 (14.7, 16.9)	13.6 (13.0, 14.3)	38% (36, 40)	82% (80, 84)	95% (94, 96)
HBA1c ≥ 69 (mmol/mol)								
MDRD	134	0.69 (0.58, 0.77)	−7.3 (−10.1, −4.1)	21.1 (14.1, 26.4)	20.0 (17.1, 22.8)	37% (29, 44)	72% (63, 79)	84% (78, 90)
CKD-EPI	134	0.69 (0.59, 0.77)	−10.9 (−12.5, −8.7)	18.2 (13.5, 22.4)	20.0 (17.4, 22.5)	31% (23, 38)	68% (59, 76)	84% (77, 90)
FAS	134	0.71 (0.62, 0.78)	−7.3 (−10.3, −3.8)	17.6 (13.7, 23.2)	19.9 (16.9, 22.9)	34% (26, 41)	72% (63, 79)	87% (80, 92)
R-LM	134	0.75 (0.65, 0.83)	−2.9 (−5.1, −1.0)	14.1 (11.5, 20.0)	16.1 (13.4, 18.6)	43% (35, 51)	77% (70, 84)	90% (84, 95)
HBA1c < 69 (mmol/mol)								
MDRD	397	0.69 (0.63, 0.74)	−9.4 (−10.8, −7.7)	18.6 (16.5, 21.3)	20.1 (18.4, 21.9)	25% (20, 29)	68% (64, 73)	86% (83, 89)
CKD-EPI	397	0.71 (0.65, 0.75)	−11.7 (−13.5, −10.2)	18.9 (16.7, 20.6)	19.4 (17.9, 21.0)	25% (21, 29)	63% (59, 68)	85% (82, 89)
FAS	397	0.74 (0.69, 0.78)	−7.4 (−9.3, −5.2)	17.8 (15.2, 19.6)	18.3 (16.4, 20.0)	30% (25, 35)	74% (70, 78)	89% (86, 92)
R-LM	397	0.77 (0.73, 0.81)	−4.2 (−6.3, −2.2)	16.1 (14.5, 18.1)	15.4 (13.8, 16.9)	37% (31, 41)	79% (75, 83)	92% (90, 95)

mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; FAS, full age spectrum; R-LM, revised Lund-Malmö; CCC, concordance correlation coefficient; IQR, interquartile range; RMSE, root mean square error; P10, P30, and P50, proportion of eGFR within 10%, 30%, and 50% of mGFR, respectively.

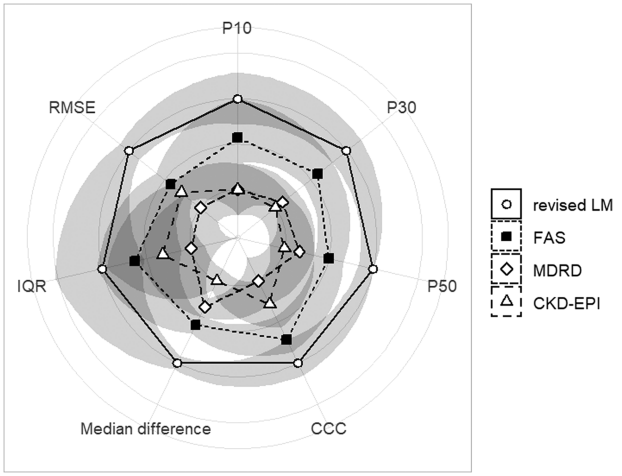

Figure 1. Comparison of diagnostic performance of 4 creatinine-based estimation equations compared with ^{99m}Tc-DTPA measured glomerular filtration rate in adults with diabetes. Radar chart shows bias, precision, accuracy (P10, P30, P50), and concordance correlation coefficient of estimation equations. Values closer to the center of the chart show poor performance, whereas values closer to the periphery of the chart show better performance. The shadows around the lines indicate the 95% confidence interval. IQR, interquartile range; RMSE, root mean square error; CCC, concordance correlation coefficient; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; FAS, full age spectrum; revised LM, revised Lund-Malmö.

measured by renal clearance of iothalamate (19, 20, 22). Methods relying on renal clearance of markers are prone to error due to reliance on bladder filling and emptying (30).

While many studies have assessed CKD-EPI and MDRD performance in estimating GFR in adults with diabetes (11, 12, 14, 31-33), few have validated FAS and r-LM in this population (15, 16, 34). A study on 475 Spanish adults with diabetes reported similar agreement and accuracy for r-LM, MDRD, and CKD-EPI (CCC = 0.92 in all 3 equations, P30 = 75%, 73%, and 72%) compared with iohexol mGFR (15). FAS in this study had a noticeably lower agreement and accuracy than the other 3 equations (CCC = 0.83, P30 = 49%). On the other hand, in a study on 215 Chinese adults with diabetes and chronic kidney disease (GFR measured with iohexol), FAS had lower bias and higher precision and accuracy than CKD-EPI and r-LM (median difference = 0.03, –1.92, –3.83; IQR = 13.64, 16.53, 15.57; P30 = 76%, 72%, 73%, respectively) (16). Another study on 729 Swedish adults with diabetes and GFR ≤ 30 mL/min/1.73 m^2 (GFR measured by plasma clearance of iohexol) showed that the r-LM had higher accuracy than CKD-EPI and MDRD (P30 = 72.5%, 66.6%, and 65.7%, respectively) (34).

While the r-LM had generally the same performance in both sexes, MDRD, CKD-EPI, and FAS showed better performance in women. Therefore, the difference between the r-LM and the other 3 equations was milder in women. However, MDRD and CKD-EPI (median difference = –2.1, –4.3 mL/min/1.73 m^2, respectively) still showed higher bias than FAS and r-LM (median difference = –0.5, 1.1 mL/min/1.73 m^2, respectively) in women. One possible reason for such outcome could be better performance of the proposed coefficients for women in MDRD and CKD-EPI equations. Regarding better performance of FAS in women further investigations are required (20, 21, 35).

All the 3 published studies in this field had used iohexol as the reference test for measuring GFR. Moreover, none of these studies used RMAR to evaluate performance and only 1 reported CCC to assess agreement between eGFR and mGFR. Furthermore, these 3 studies showed controversial results regarding performance of r-LM, FAS, CKD-EPI, and MDRD. Such variation in results of different studies highlights the importance of validating eGFR equations in different populations before their implementation in clinical practice. The conduct of validation studies helps in (1) choosing the best equation to be used in the target population, and (2) deciding whether an eGFR equation needs calibration before implementation (36). This study is the first to assess performance of r-LM, FAS, MDRD, and CKD-EPI in Australian adults with diabetes using ^{99m}Tc-DTPA as the reference test and RMAR as the performance evaluation tool. Our findings demonstrated that in Australian adults with diabetes, eGFR calculated by the r-LM was the closest to mGFR compared with MDRD, CKD-EPI, and FAS.

RMAR is 1 of the highly informative methods to assess agreement between 2 continuous measurement methods (28, 37). A RMAR slope different from 1 is indicative of proportional bias, and in cases where the slope is 1, the intercept different from 0 is indicative of fixed bias. In our study, the RMAR graph showed that the r-LM had the highest intercept and slope compared with the rest of the equations. This finding should be interpreted with caution as one might think the higher slope and intercept, the worse the performance compared with other equations. However, a closer look at the graph reveals that the fitted line for the r-LM was the closest to the perfect line for GFR between 40 and 100 mL/min/1.73 m^2 (in GFR levels around 74 mL/min/1.73 m^2, the equation estimations were almost the same as mGFR, Fig. 2). Therefore, the slope and intercept, per se, might not be a good indicator of diagnostic performance and should be considered along with the visual graph. The RMAR graph also showed that the r-LM overestimated GFR levels at the lower spectrum and underestimated GFR level at the higher spectrum. Similarly, Björk et al. in their paper on revising the Lund–Malmö equation reported that while the equation had the lowest bias (median percentage difference (eGFR – mGFR)/mGFR) in GFR between 30 and 89 (bias = 0.2), it overestimated GFR < 30 (bias = 3.8)

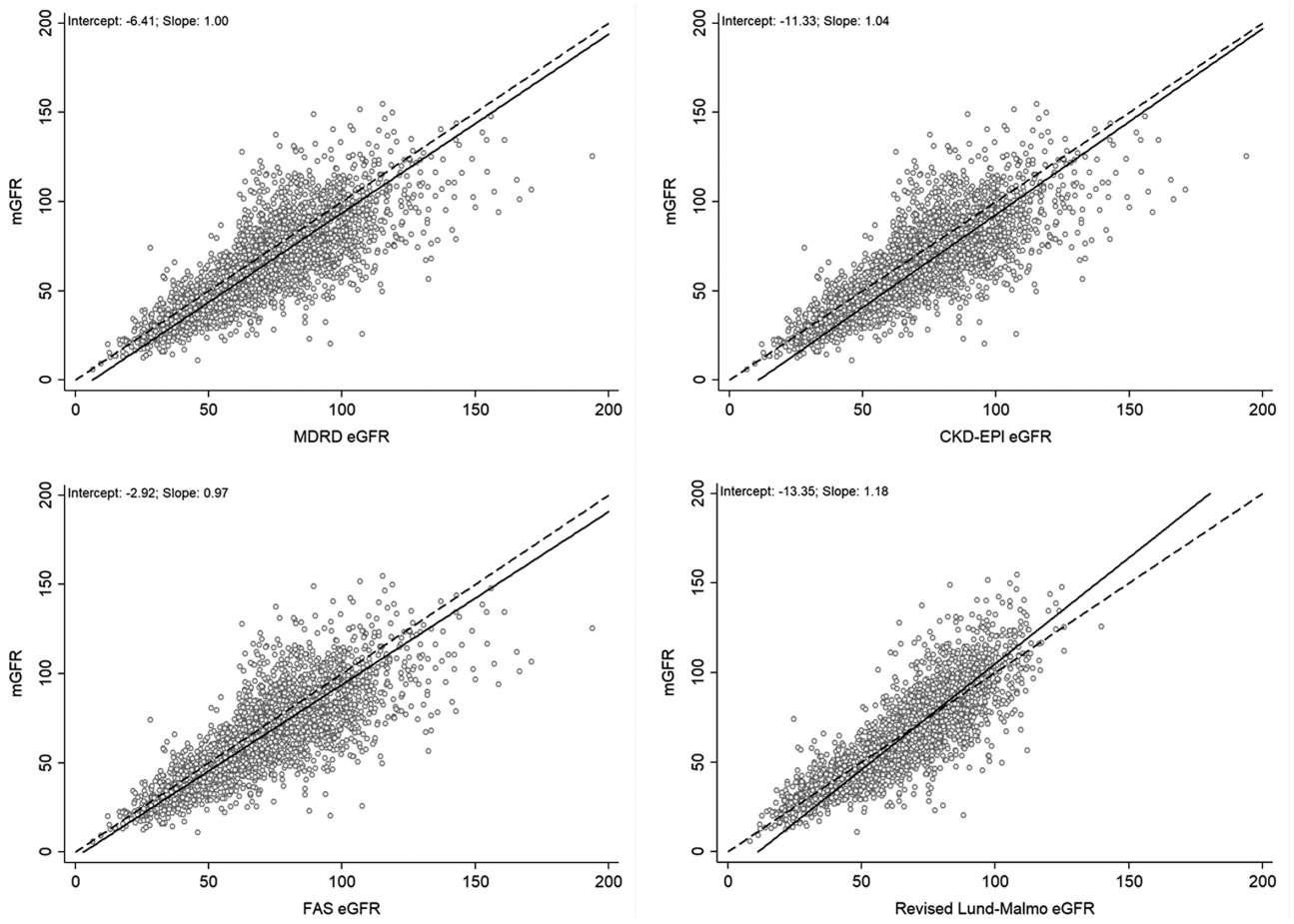

Figure 2. The reduced major axis regression of four creatinine-based estimation equations and ^{99m}Tc-DTPA measured glomerular filtration rate in adults with diabetes. The dashed line shows the line of perfect concordance, and the solid line shows the reduced major axis. MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; FAS, full age spectrum; revised LM, revised Lund–Malmö.

and underestimated GFR ≥ 90 (bias = –13.2). They discussed that the equation could not be further improved for GFR ≥ 90 without neglecting its negative effect on the equation accuracy at lower GFR level (22). Considering that DKD starts with a hyperfiltration phase, in a noticeable proportion of people with diabetes having an estimation equation with high precision and accuracy in the higher GFR levels would be of high importance (38).

Strengths and limitations

This study is the first to assess performance of r-LM, FAS, MDRD, and CKD-EPI in Australian adults with diabetes using ^{99m}Tc-DTPA as the reference test. The large study sample and utilizing more reliable methods, for example, RMAR, to compare mGFR with eGFR are the most important points of strength of the current study. As limitations, data on race, medications, and blood pressure of participants were not available to report.

Future direction

Assessing performance of these 4 equations in people without diabetes and comparing the results with those in people with diabetes would be of high importance to help understand whether these findings are exclusive to people with diabetes. Moreover, investigating performance of these equations from a categorical perspective using sensitivity, specificity, positive predictive value, and negative predictive value for diagnosing GFR categories would be of high benefit for clinical decision making. We also encourage future studies on comparison of these equations in estimating GFR change over time in people with diabetes.

Conclusion

As the first large study to investigate and compare performance of 4 recent creatinine-based eGFR equations with ^{99m}Tc-DTPA mGFR via bias, accuracy, precision,

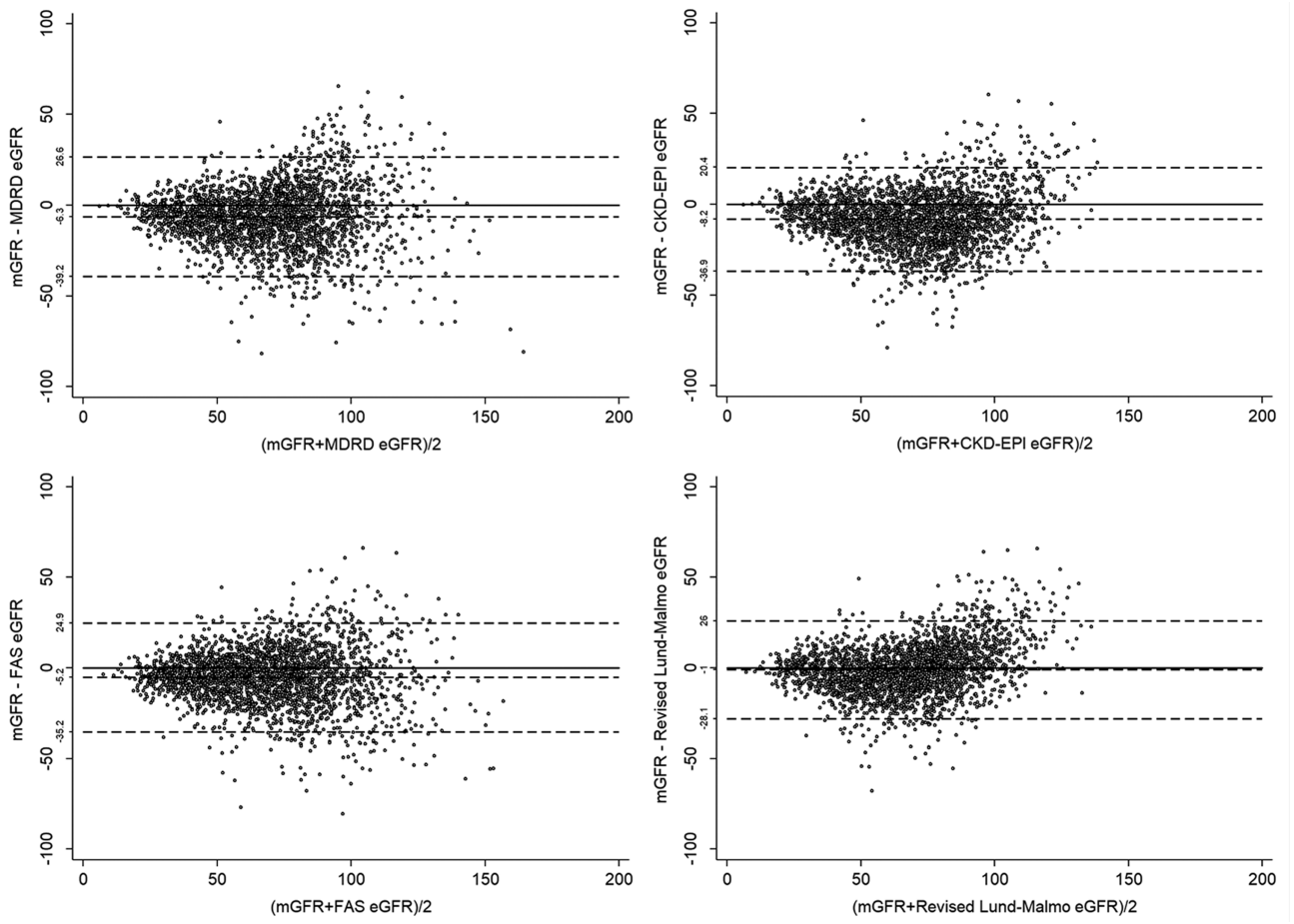

Figure 3. The Bland–Altman plot of four creatinine-based estimation equations and ^{99m}Tc-DTPA measured glomerular filtration rate in adults with diabetes. The solid line shows mean difference, and the dashed line shows the 95% limit of agreement. MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; FAS, full age spectrum; revised LM, revised Lund–Malmö.

CCC, and RMAR in adults with diabetes, we showed that r-LM outperformed CKD-EPI, MDRD, and FAS equations in estimating GFR at a single time point. Analysis split by sex (men/women), type of diabetes (type1/type 2), HbA1c level, and eGFR category showed the overall superiority of the r-LM equation. However, the equation needs further improvement and calibration, particularly for GFR levels higher than 100 and lower than 40 mL/min/1.73 m^2.

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Additional Information

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Data Availability: Restrictions apply to the availability of data generated or analyzed during this study to preserve patient confidentiality or because they were used under license. The correspond-

Table 4. Characteristics of study participants in subgroups

n	mGFR < 30	30 ≤ mGFR < 45	45 ≤ mGFR < 60	60 ≤ mGFR < 90	90 ≤ mGFR < 120	120 ≤ mGFR	HBA1c < 8.5%	HBA1c ≥ 8.5%
	192	397	570	1074	400	70	397	134
Age (year)	72.9 (10.3)	70.7 (9.2)	68.2 (9.7)	60.7 (11.2)	48.7 (12.9)	46.0 (10.9)	62.7 (13.1)	60.6 (13.3)
Sex (% women)	62 (32.3%)	156 (39.3%)	240 (42.1%)	380 (35.4%)	203 (50.7%)	55 (78.6%)	157 (39.5%)	55 (41.0%)
%with type 2 diabetes	169 (92.9%)	351 (91.2%)	493 (90.3%)	801 (79.2%)	230 (62.5%)	53 (86.9%)	314 (79.9%)	108 (81.2%)
BMI (kg/m^2)	30.6 (5.4)	30.8 (5.8)	30.8 (5.7)	30.6 (5.9)	30.4 (5.7)	33.2 (5.7)	30.9 (6.0)	32.8 (7.1)
Fasting serum glucose (mmol/L)	8.3 (3.2)	8.6 (3.5)	9.0 (3.3)	9.3 (3.4)	10.2 (3.8)	11.1 (3.7)	8.3 (2.9)	11.7 (4.3)
Total cholesterol (mmol/L)	4.1 (1.0)	4.0 (1.0)	4.2 (1.0)	4.3 (1.0)	4.7 (1.1)	4.9 (1.4)	4.0 (1.0)	4.3 (1.2)
HDL (mmol/L)	1.2 (0.4)	1.2 (0.5)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.2 (0.3)	1.3 (0.4)	1.2 (0.4)
LDL (mmol/L)	2.1 (0.8)	2.0 (0.8)	2.2 (0.8)	2.4 (0.8)	2.6 (0.8)	2.7 (1.0)	2.0 (0.9)	2.2 (1.0)
Triglyceride (mmol/L)[a]	1.5 (1.1, 2.2)	1.5 (1.1, 2.1)	1.4 (1.0, 2.0)	1.3 (0.8, 1.9)	1.3 (0.8, 2.2)	1.6 (1.2, 3.1)	1.3 (0.9, 1.9)	1.6 (1.2, 2.3)
HbA1c (%)	7.9 (1.3)	7.6 (1.1)	7.6 (1.2)	7.9 (1.5)	7.9 (1.5)	7.6 (0.9)	7.2 (0.7)	9.6 (1.1)
HbA1c (mmol/mol)	62.8 (14.4)	60.0 (12.1)	60.1 (12.9)	63.2 (16.0)	63.0 (16.0)	60.0 (9.9)	55.3 (7.9)	81.2 (12.3)
Serum creatinine (Umol/L)	178.9 (74.1)	122.9 (29.9)	95.4 (20.4)	79.2 (14.5)	68.2 (12.6)	55.3 (13.5)	92.7 (38.9)	89.1 (30.4)
Albumin excretion rate (µg/min)[a]	45.7 (9.9, 238.9)	28.6 (7.4, 116.9)	14.1 (6.4, 64.9)	10.1 (5.8, 25.3)	9.5 (5.7, 20.1)	9.5 (6.1, 31.0)	9.5 (4.9, 49.2)	19.4 (6.4, 90.1)
mGFR	34.2 (12.3)	54.3 (10.4)	77.9 (15.1)	117.5 (24.9)	167.5 (33.5)	214.6 (41.5)	97.9 (42.7)	106.3 (46.6)
corrected mGFR[b]	23.9 (4.9)	37.9 (4.3)	52.7 (4.4)	74.1 (8.3)	101.0 (7.9)	130.2 (8.7)	63.8 (24.4)	65.9 (24.2)
MDRD eGFR	34.1 (13.4)	48.0 (12.2)	63.5 (14.8)	81.1 (15.5)	96.8 (18.9)	117.9 (33.9)	73.3 (24.5)	75.3 (24.7)
CKD-EPI eGFR	33.6 (13.7)	48.6 (12.8)	65.3 (15.1)	84.1 (13.7)	100.0 (13.3)	110.0 (12.6)	75.1 (23.7)	77.7 (23.9)
FAS eGFR	33.3 (12.2)	46.0 (10.7)	60.2 (14.3)	79.4 (16.1)	100.1 (18.5)	121.8 (28.7)	71.7 (24.8)	75.0 (26.3)
Revised Lund–Malmö eGFR	30.2 (12.5)	44.8 (11.8)	59.6 (12.5)	75.4 (11.6)	89.7 (11.3)	102.1 (13.4)	67.7 (20.7)	70.2 (20.9)

Values reported as mean (SD) unless mentioned otherwise. All GFR values are reported in mL/min/1.73 m^2

NA, not applicable; BMI, body mass index; HDL, high-density lipoprotein; LDL, low-density lipoprotein; HbA1c, hemoglobin A1c; mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; FAS, full age spectrum.

[a]Median (IQR).

[b]Measured GFR corrected for sex and Brochner-Mortensen coefficient.

Table 5. Validation of the Modification of Diet in Renal Disease (MDRD), the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), the Full Age Spectrum (FAS), and the Revised Lund–Malmö equation in assessing GFR in people with diabetes based on their GFR category

	n	Agreement	Bias	Precision		Accuracy		
		CCC	Median mGFR–eGFR	IQR	RMSE	p10	p30	p50
120 ≤ eGFR								
MDRD	44	0.19 (0.06, 0.38)	–19.7 (–24.5, –13.1)	18.5 (12.9, 34.7)	38.8 (22.2, 57.0)	23% (12, 34)	77% (63, 90)	91% (80, 100)
CKD-EPI	44	0.06 (-0.04, 0.15)	–15.6 (–21.9, –8.8)	26.4 (11.5, 33.7)	19.8 (16.8, 22.8)	30% (15, 44)	89% (78, 98)	100% (100, 100)
FAS	44	0.21 (0.07, 0.36)	–25.4 (–31.4, –18.5)	16.1 (12.8, 28.5)	35.6 (25.4, 47.6)	16% (7, 27)	70% (54, 86)	93% (85, 100)
R-LM	44	0.45 (0.16, 0.63)	–0.0 (–5.1, 5.3)	19.1 (11.0, 27.0)	13.8 (10.0, 17.5)	59% (46, 72)	100% (100, 100)	100% (100, 100)
90 ≤ eGFR < 120								
MDRD	744	0.19 (0.13, 0.26)	–9.6 (–11.5, –7.2)	24.4 (22.3, 27.5)	22.7 (21.2, 24.2)	34% (30, 38)	74% (71, 78)	90% (87, 92)
CKD-EPI	744	0.21 (0.16, 0.25)	–12.5 (–14.0, –10.6)	20.8 (18.9, 22.6)	20.8 (19.5, 22.1)	33% (29, 37)	75% (71, 79)	91% (89, 93)
FAS	744	0.32 (0.26, 0.38)	–11.0 (–13.2, –8.8)	21.5 (19.6, 24.1)	21.4 (19.9, 22.7)	36% (32, 40)	77% (73, 81)	91% (89, 94)
R-LM	744	0.32 (0.27, 0.37)	–1.4 (–3.0, 0.2)	21.0 (18.9, 23.0)	16.9 (15.7, 18.1)	42% (38, 46)	88% (85, 90)	96% (94, 97)
60 ≤ eGFR < 90								
MDRD	1150	0.19 (0.14, 0.23)	–6.0 (–7.2, –4.5)	20.2 (18.5, 21.7)	17.1 (16.2, 18.0)	31% (28, 34)	75% (72, 78)	91% (90, 93)
CKD-EPI	1150	0.28 (0.24, 0.32)	–9.6 (–10.6, –8.1)	18.5 (17.2, 19.9)	17.2 (16.4, 18.0)	32% (29, 35)	72% (68, 75)	89% (87, 91)
FAS	1150	0.40 (0.36, 0.45)	–2.3 (–3.6, –1.5)	17.6 (15.9, 19.0)	14.4 (13.6, 15.3)	41% (37, 44)	82% (79, 84)	95% (94, 96)
R-LM	1150	0.36 (0.31, 0.39)	–1.7 (–2.9, –0.9)	17.6 (16.1, 19.0)	14.2 (13.4, 15.1)	40% (37, 43)	82% (80, 85)	96% (94, 97)
45 ≤ eGFR < 60								
MDRD	384	0.17 (0.11, 0.22)	–6.0 (–7.4, –4.8)	12.6 (11.0, 14.5)	11.2 (10.4, 12.0)	29% (25, 34)	73% (68, 78)	90% (87, 93)
CKD-EPI	384	0.19 (0.14, 0.24)	–6.9 (–8.5, –5.6)	12.7 (10.9, 14.1)	11.6 (10.8, 12.3)	30% (25, 35)	70% (65, 75)	90% (87, 93)
FAS	384	0.18 (0.12, 0.24)	–4.0 (–5.4, –2.5)	12.8 (11.4, 14.8)	10.4 (9.7, 11.3)	36% (31, 40)	78% (74, 83)	94% (91, 96)
R-LM	384	0.24 (0.18, 0.30)	–4.0 (–5.5, –2.1)	12.2 (10.9, 13.9)	10.0 (9.3, 10.8)	35% (30, 40)	80% (76, 85)	95% (93, 97)
30 ≤ eGFR < 45								
MDRD	276	0.20 (0.12, 0.28)	–2.9 (–4.4, –1.7)	12.8 (10.8, 14.1)	9.5 (8.7, 10.3)	31% (25, 36)	72% (67, 78)	90% (86, 94)
CKD-EPI	276	0.25 (0.17, 0.33)	–3.2 (–4.4, –1.1)	12.1 (10.0, 14.1)	9.1 (8.4, 9.9)	28% (22, 33)	73% (68, 78)	90% (87, 94)
FAS	276	0.24 (0.14, 0.33)	–2.3 (–3.8, –0.7)	12.6 (10.7, 14.1)	9.1 (8.3, 9.8)	27% (21, 32)	76% (72, 82)	92% (89, 96)
R-LM	276	0.30 (0.21, 0.40)	0.8 (–0.8, 2.4)	11.7 (9.7, 14.1)	8.9 (7.9, 9.8)	31% (26, 36)	78% (73, 82)	95% (92, 97)
eGFR < 30								
MDRD	105	0.39 (0.22, 0.59)	–1.3 (–2.5, –0.5)	6.8 (5.3, 8.8)	7.4 (5.2, 10.0)	33% (24, 43)	73% (65, 81)	92% (87, 97)
CKD-EPI	105	0.41 (0.24, 0.62)	–0.9 (–1.6, 0.2)	6.3 (5.0, 8.4)	7.2 (5.0, 9.9)	40% (31, 49)	75% (67, 83)	93% (88, 98)
FAS	105	0.39 (0.23, 0.56)	–2.0 (–3.5, –0.6)	6.4 (5.4, 9.2)	7.4 (5.3, 9.9)	31% (24, 40)	73% (64, 81)	90% (84, 96)
R-LM	105	0.33 (0.19, 0.54)	1.6 (0.5, 3.3)	6.9 (5.2, 8.8)	7.5 (4.9, 10.5)	30% (21, 39)	79% (70, 87)	96% (92, 100)

GFR was categorized based on estimations of the commonly used chronic kidney disease epidemiology collaboration (CKD-EPI) equation.

mGFR, measured glomerular filtration rate; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; CKD-EPI, chronic kidney disease epidemiology collaboration; FAS, full age spectrum; R-LM, revised Lund–Malmö; CCC, concordance correlation coefficient; IQR, interquartile range; RMSE, root mean square error; P10, P30, and P50, proportion of eGFR within 10%, 30%, and 50% of mGFR, respectively.

ing author will on request detail the restrictions and any conditions under which access to some data may be provided.

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