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Comparison of the new and traditional CKD-EPI GFR estimation equations with urinary inulin clearance: A study of equation performance

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ABSTRACT

Background: Diagnosis, prognostication and treatment in chronic kidney disease is often informed by an estimate of the glomerular filtration rate (GFR). Commonly used GFR estimation (eGFR) equations are based on serum creatinine (Cr) concentrations and display suboptimal precision and accuracy. Newer equations incorporating additional endogenous markers such as β-Trace Protein (BTP), β_2-Microglobulin (B2M) and cystatin C (cysC) have been developed but require validation.

Methods: This prospective cohort study evaluated the performance of 6 eGFR equations developed by the chronic kidney disease - epidemiology collaboration group (CKD-EPI) against urinary inulin clearance GFR in patients recruited from outpatient nephrology clinics.

Results: Mean biases were negligible and similar between equations. The eGFR-EPI Cr/cysC had the best precision and accuracy of all the equations and the best agreement with inulin mGFR when classifying participants into GFR categories. The BTP and B2M equations displayed the worst precisions and accuracies and showed the least consistent performance across levels of GFR. Thus, the eGFR-EPI Cr/cysC is the least biased, most precise and has the highest accuracy as compared to other eGFR-EPI equations.

Conclusions: The BTP and B2M equations are the worst performing of the eGFR-EPI equations, and no benefit is observed with the addition of BTP or B2M to Cr/cysC.

1. Introduction

The glomerular filtration rate (GFR) is considered the best marker of overall kidney function [1]. Clinically, the GFR is used to diagnose and manage kidney disease, to dose adjust renally-excreted medications and to predict risk of end stage kidney disease (ESKD) [2]. In the research setting, the GFR often serves as an outcome measure in clinical trials and is used to determine prevalence of chronic kidney disease (CKD) in epidemiologic studies [3–5]. GFR can be estimated using endogenous markers or measured using exogenous markers. The latter is rarely done due to issues with cost, availability and inconvenience [1]. As such, GFR is far more frequently estimated, with a plethora of equations having been developed over the years using a variety of endogenous filtration markers.

The most common biomarker used to estimate GFR is creatinine (Cr). Despite its widespread use, Cr is not an ideal biomarker for GFR estimation as it can be secreted by the tubules, and its serum concentration is influenced by many factors that are unrelated to GFR [6]. There are also significant analytical issues with Cr assay non-specificity [7,8]. Although all contemporary equations include demographic modulators of Cr concentrations, there remains substantial imprecision in GFR estimation with both significant under and overestimation of the measured GFR (mGFR) [9].

To improve GFR estimation, several alternate markers have been studied, such as cystatin C (cysC), β-Trace Protein (BTP), and β_2-Microglobulin (B2M). A number of estimation equations incorporating

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Table 1
CKD-EPI eGFR equations[a].

eGFR-EPI equation	Year	Equation
Cr	2009	eGFR = 141 x $\min(Cr/\kappa,1)^{\alpha}$ x $\max(Scr/\kappa, 1)^{-1.209}$ × 0.993^{Age} x 1.018 (if female) x 1.159 (if black) Where κ = 0.7 if female or 0.9 if male Where α = −0.329 if female or − 0.411 if male
cysC	2012	eGFR = 133 x $\min(cysC/0.8,1)^{-0.499}$ x $\max(cysC/0.8,1)^{-1.328}$ × 0.996^{Age} x 0.932 (if female)
Cr/cysC	2012	eGFR = 135 x $\min(Cr/\kappa,1)^{\alpha}$ x $\max(Cr/\kappa,1)^{-0.601}$ x $\min(cysC/0.8,1)^{-0.375}$ x max(cysC/0.8,1)-0.711 × 0.995Age x 0.969 (if female) x 1.08 (if black) Where κ = 0.7 if female or 0.9 if male Where α = −0.248 if female or − 0.209 if male
BTP	2016	eGFR = 55 x $BTP^{-0.695}$ × 0.998^{Age} x 0.899 (if female)
B2M	2016	eGFR = 133 x $B2M^{-0.852}$
BTP/B2M	2016	eGFR = 96 x $BTP^{-0.278}$ x $B2M^{-0.588}$

[a] For all equations, Cr is the plasma creatinine (in mg/dL), cysC is the serum cystatin C (in mg/l), BTP is the serum β-Trace Protein (in mg/l), and B2M is the serum β_2-Microglobulin (in mg/l).

these, alone or in combination, have been developed [10–14]. The biomarker gaining the most prominence is cysC, with the 2012 Kidney Disease: Improving Global Outcomes (KDIGO) CKD guidelines recommending the use of the chronic kidney disease epidemiology collaboration (CKD-EPI) cysC or Cr/cysC equation in certain circumstances where eGFR accuracy is important or when CKD diagnosis using Cr alone is uncertain [2]. More recently, the CKD-EPI collaboration has developed equations using the additional biomarkers BTP and B2M (Table 1) [11]. The aim of this study was to evaluate the performance of all six CKD-EPI GFR estimation equations (eGFR-EPI) against the gold standard urinary inulin clearance in patients with CKD.

2. Methods

2.1. Participants

Stable adult CKD patients were recruited for this prospective cohort study in outpatient general nephrology, CKD, and transplant clinics at Kingston Health Sciences Center (KHSC) (Kingston, Ontario, Canada). The study was approved by the Queen's University Health Sciences Research Ethics Board. Each patient provided willing, informed consent prior to being enrolled. Exclusion criteria were: known allergy to iodine, inulin, shellfish or contrast dye; pregnancy or breastfeeding; known impaired bladder emptying; likely death from co-morbid disease within 3 months; and likely need for dialysis or repeat transplant within 3 months. A negative plasma beta-HCG test was required for women of childbearing age prior to testing.

2.2. Urinary inulin clearance

Subjects were asked to hydrate orally at 5–10 ml/kg of body weight prior to study arrival with an additional 10–15 ml/kg of body weight of oral hydration administered upon arrival. Throughout the study, subjects continued oral hydration to ensure urinary flow rate > 3 ml/min. Each arm was outfitted with a heparin lock. An intravenous bolus of 50 mg/kg of body weight of 25% inulin (Innutest, Fresenius Kabfa) was administered over 5 mins. After the bolus, an inulin infusion was initiated at 2000 mg/h. After a 1 h period for equilibration in the plasma, subjects provided three consecutive timed one-hour urine samples. Hand-held ultrasound was used to determine the post-void residual (PVR). If the emptying was deemed inadequate (PVR > 20% of pre-bladder volume), the subjects were asked to void again. If subjects were still unable to void adequately, the study was stopped and they were censored from the final data.

At 1, 2, 3, and 4 h after initiation of the inulin infusion, blood samples were taken from the contralateral arm to the infusion. Immediately after sampling, the samples were centrifuged at 3000 rpm for 10 min at 4 °C. The plasma was separated from the sample and placed on ice until being transferred to a −80 °C freezer for storage. Colorimetric methods were used to determine inulin concentration in the plasma and urine samples. A fructose specific reagent, resorcinol, was used with a modified method to that of Walser, Davidson and Orloff [15]. Urinary clearance was calculated for each of the 1-h periods, using the following equation: Inulin Clearance = ($Urine_{inulin}$ * $Urine_{Volume}$) / $Plasma_{inulin}$ where U_{inulin} is the concentration of inulin in the urine, U_{volume} is the urine flow rate and P_{inulin} is the average plasma inulin concentration of the pre and post urine collection plasma samples. The final GFR was the mean of the urinary clearance values for the 3 collection periods. GFR values were then corrected for body surface area using the Dubois method [16].

2.3. Estimated GFR with endogenous markers

Plasma for Cr and serum for BTP, cysC, and B2M were obtained at baseline immediately prior to inulin bolus. The Abbott Diagnostics enzymatic assay which is IDMS traceable was used to measure Cr on an Abbott Architech Plus 6000 at KHSC. CysC, B2M, and BTP were measured on a BN Dade Behring Prospec analyzer using the Siemens' PENIA assays (Siemens Healthcare Diagnostics) at the Children's Hospital of Eastern Ontario (CHEO) (Ottawa, Canada). The measured values of the biomarkers were then used, along with demographic characteristics, to calculate eGFR-EPI with each of the six equations. The average of the results for the eGFR-EPI Cr/cysC and eGFR-EPI BTP/B2M was calculated.

2.4. Analysis

Performance of each eGFR equation was evaluated by calculating bias (mean and median difference of eGFR – inulin mGFR), mean percent bias [(eGFR – inulin mGFR)/inulin mGFR] *100), precision (standard deviation (SD) of the mean bias and interquartile range (IQR) of the median bias), and accuracy (percentage of eGFR estimates that fell within 10% and 30% of the inulin mGFR [P10 and P30]). Root mean squared error (RMSE) was also calculated as a measure of accuracy. This analysis was repeated after subdividing patients into mGFR subgroups (< 30, 30–59 and ≥ 60 ml/min/1.73 m^2). Paired *t*-tests were used to compare the biases of the eGFRs, F-tests to compare the precisions, and McNemar's test was used to compare the P30 accuracies. The relationship between paired eGFR and mGFR values was also examined by modified Bland Altman analysis. The proportion of patients in KDIGO GFR categories was calculated for each equation and the inulin mGFR [2]. For each equation, the proportion of patients correctly classified into mGFR category was also determined for the entire cohort and for each GFR category separately. Weighted Cohen's kappa was used to compare the agreement between each eGFR method and mGFR in classifying subjects into KDIGO GFR categories.

Table 2
Patient demographics and clinical characteristics.

Characteristic	Value
Age, mean y ± SD	60.2 ± 14.5
Female sex n (%)	33 (40)
White race n (%)	79 (95)
Kidney transplant recipient n (%)	14 (17)
BSA (m^2) ± SD	2.0 ± 0.3
BMI (kg/m^2) ± SD	29.9 ± 6.6
Mean Cr ± SD (μmol/l)	219.2 ± 128.7
Mean cysC ± SD (mg/l)	2.1 ± 1.0
Mean BTP ± SD (mg/l)	1.7 ± 1.0
Mean B2M ± SD (nmol/l)	500 ± 288
Median inulin mGFR (P25-P75) (ml/min/1.73 m^2)	28.9 (18.5–47.8)
Median eGFR-EPI Cr (P25-P75) (ml/min/1.73 m^2)	28.0 (16.0–48.5)
Median eGFR-EPI cysC (P25-P75) (ml/min/1.73 m^2)	31.4 (19.8–54.0)
Median eGFR-EPI Cr/cysC (P25-P75) (ml/min/1.73 m^2)	37.1 (26.1–49.4)
Median eGFR-EPI BTP (P25-P75) (ml/min/1.73 m^2)	33.6 (21.5–47.8)
Median eGFR-EPI B2M (P25-P75) (ml/min/1.73 m^2)	33.6 (21.8–50.7)
Median eGFR-EPI BTP/B2M (P25-P75) (ml/min/1.73 m^2)	29.9 (17.5–47.8)

3. Results

3.1. Participant characteristics

Eight-six participants completed the study protocol. Three were excluded from the final analysis due to missing data. Participant characteristics are shown in Table 2. The median mGFR was 28.0 (P25-P75, 18.5–47.8) ml/min/1.73 m^2 while the median eGFR-EPIs ranged from 28.0 to 37.1 ml/min/1.73 m^2. Ninety-five percent were white and 17% were kidney transplant recipients.

3.2. Equation performance

3.2.1. Entire cohort

Performance results for the eGFR equations are found in Table 3. For the entire cohort, mean biases were similar and approaching zero for all equations. The eGFR-EPI Cr/cysC precision was significantly better than that of all the other equations. The three BTP/B2M had the worse precisions. Accuracy (P30) was higher for the three Cr and cysC based equations (range 77–89%) than for the three BTP and B2M equations (range 57–67%). Accuracy based on RMSE was also higher for the three Cr and cysC based equations (range 0.08–0.10) than for the three BTP and B2M equations (range 0.13–0.17). Of all, the eGFR-EPI Cr/cysC equation had the highest accuracy (P30, 90%), which was significantly higher than all the other equations. (P value range < 0.001 to $P = .01$) except for Cr alone ($P = .08$) and the 4-marker average ($P = .09$). The eGFR-EPI Cr/cysC equation also had the highest accuracy based on RMSE (0.08).

3.2.2. By mGFR Subgroup

For participants with an mGFR < 30 ml/min/1.73 m^2 ($n = 44$), mean biases were higher for the 3 eGFR-EPI BTP and B2M equations (range 5.4–8.6 ml/min/1.73 m^2) than those of the Cr and cysC equations (range 0.3–2.5 ml/min/1.73 m^2). The eGFR-EPI Cr/cysC equation had the lowest bias which was significantly better than all equations and the 4-marker average other than Cr alone ($P = .8$). The eGFR-EPI Cr/cysC was the most precise (SD 4.6 ml/min/1.73 m^2), which was significantly better than all the other equations except for Cr alone ($P = .1$). The eGFR-EPI Cr/cysC equation was significantly more accurate (P30, 80%) than all equations other than Cr alone ($P = .4$), CysC alone ($P = .07$) and the 4-marker average ($P = .09$).

For participants with an mGFR of 30–59 ml/min/1.73 m^2 ($n = 23$), mean biases were similar between equations. The eGFR-EPI Cr/cysC equation was significantly more precise than the other equations. While it had the highest accuracy (P30, 100%), the eGFR-EPI Cr/cysC equation was not significantly more accurate than the other equations (range $P = .1$ to $P = .3$) or the 4-marker average ($P = 1$).

For participants with mGFR ≥60 ml/min/1.73 m^2 ($n = 15$), the three eGFR-EPI BTP and B2M-based equations had very high mean biases (range, −17.1 to −15.2 ml/min/1.73 m^2) as compared to the 3 eGFR-EPI Cr and cysC equations (range, −0.8 to 5.5 ml/min/1.73 m^2). The eGFR-EPI Cr equation was the least biased but this was not significantly different from the eGFR-EPI Cr/cysC equation. ($P = .07$). The precision of the eGFR-EPI Cr/cysC equation was not significantly better than any equation (range P = .1 to $P = .4$) except for BTP alone ($P = .007$). The accuracy of the eGFR-EPI Cr/cysC equation was not significantly different than the accuracies of the other equations or the 4-marker average (range $P = .25$ to P = 1).

Fig. 1 plots the mean percent bias for each equation by mGFR decile. The BTP and B2M equations overestimate mGFR to a greater degree at higher mGFRs, and underestimate mGFR to a greater degree at lower mGFRs as compared to the Cr and cysC equations, which are more consistent across the range of GFRs. Bland Altman analysis shown in Fig. 2 demonstrates very wide limits of agreement for the BTP equations with overestimation of GFR at lower mGFR and underestimation at higher GFRs. The combination Cr/cysC shows the most consistent estimation across mGFR.

3.3. GFR categories

Fig. 3, and Supplemental Table 1 show the distribution of KDIGO GFR categories by each equation and by inulin mGFR [2]. As expected given their biases, the three BTP and B2M equations classify fewer subjects into the G1 and G5 categories and more in the G3 and G4 categories as compared to the Cr and cysC equations. Table 4 documents the proportion of patients correctly classified into mGFR category by equation. The eGFR-EPI Cr/cysC equation had the best agreement with mGFR with an overall correct classification percentage of 85% and a weighted kappa statistic of 0.88. The eGFR-EPI Cr and eGFR-EPI cysC equations both had an overall correct classification percentage of 77% and weighted kappa statistics of 0.82 and 0.81. The eGFR-EPI BTP/B2M equation correctly classified 66% (weighted kappa statistic 0.68), while the BTP and B2M alone equations correctly classified the fewest subjects (55%) and had the lowest weighted kappa statistic of 0.56.

4. Discussion

This study is the first to evaluate all the eGFR-EPI equations with traditional and novel markers against a gold standard inulin clearance. We show that the combination Cr/cysC equation provides the best overall estimate of mGFR with the lowest bias, highest precision and accuracy, and greatest classification ability as compared to all other eGFR-EPI equations. This superior performance holds across GFR categories. The BTP and B2M equations display the worst performance with significantly poorer precision at all levels of GFR. Averaging the Cr/cysC and BTP/B2M equations does not improve or even worsens performance as compared to Cr/cysC equation alone.

The improved performance of the combination eGFR-EPI Cr/cysC over the single marker equations have been shown by others in diverse populations [12,17–19]. The BTP and B2M equations have not been well studied. In the equations' internal validation study ($n = 1171$, mean mGFR 48 ± 22 ml/min/1.73 m^2), equation performance was similar to our findings, with the worst performance seen for the BTP alone equation and the best for the combination Cr/cysC equation [11]. Biases were comparable between studies. Precisions and accuracies are also very similar in magnitude and worst for the BTP equation (IQR 15 and 12 ml/min/1.73 m^2) and best for the Cr/cysC equation (IQR 9.3 and 7.8 ml/min/1.73 m^2). The P30 accuracy of the combination equation Cr/cysC was 89% and identical to that of the current study. The accuracy of the BTP alone equation was inferior to that seen in the internal validation study (P30 76% vs 57%). This is likely in part the

Table 3
Performance of eGFR-EPI compared to inulin mGFR.

	eGFR-EPI	Mean bias ml/min/1.73m^2	Precision (SD) ml/min/1.73m^2	Median bias ml/min/1.73m^2	Precision (IQR) ml/min/1.73m^2	P10	P30	RMSE
All (n = 83)	Cr	−0.1	8.2**	−0.6	8.3	35	80	0.10
	cysC	2.1*	8.1$^{\alpha}$	1.7	8.4	37	77$^{\delta}$	0.10
	Cr/cysC	0.2	6.3	0.4	7.8	40	89	0.08
	BTP	1.4	14.5$^{\beta}$	5.0	12.1	22	57$^{\beta}$	0.17
	B2M	0.1	11.7$^{\beta}$	2.4	9.9	28	67$^{\beta}$	0.13
	BTP/B2M	−0.1	11.7$^{\beta}$	2.2	10.7	28	67$^{\beta}$	0.13
	4-marker	0.1	7.0	0.2	8.0	38	80	0.09
Inulin mGFR < 30 ml/min/1.73m^2 (n = 44)	Cr	0.4	5.5	−0.1	6.8	27	71	0.13
	cysC	2.5$^{\beta}$	6.2$^{\delta}$	2.0	5.5	30	64	0.12
	Cr/cysC	0.3	4.6	0.4	6.6	32	80	0.10
	BTP	8.6$^{\beta}$	6.4$^{\delta}$	6.3	7.7	9	36$^{\beta}$	0.20
	B2M	5.5$^{\beta}$	6.4$^{\delta}$	4.8	6.2	20	50†	0.16
	BTP/B2M	5.4$^{\beta}$	6.3$^{\delta}$	4.7	6.2	30	50†	0.15
	4-marker	2.8$^{\beta}$	5.1	2.7	5.3	32	64	0.11
Inulin mGFR 30–59 ml/min/1.73m^2 (n = 23)	Cr	−0.4	8.4$^{\delta}$	−1.9	10.0	39	87	0.08
	cysC	−1.0	9.5$^{¥}$	−1.8	13.2	35	87	0.09
	Cr/cysC	−2.0	5.5	−3.0	8.1	43	100	0.06
	BTP	−0.4	10.2*	0.2	14.0	39	83	0.10
	B2M	0.0	9.6$^{¥}$	−0.4	8.1	43	83	0.09
	BTP/B2M	−0.5	9.4$^{¥}$	0.6	11.1	26	83	0.09
	4-marker	−1.2	6.2	−1.8	10.2	39	100	0.06
Inulin mGFR ≥ 60 ml/min/1.73m^2 (n = 15)	Cr	−0.8	13.8	−2.8	14.1	53	93	0.08
	cysC	5.5	9.6	3.8	16.5	60	100	0.05
	Cr/cysC	3.2	10.0	3.9	11.1	60	100	0.05
	BTP	−17.1$^{\beta}$	20.0$^{¥}$	−10.3	28.4	33	80	0.12
	B2M	−15.7$^{\beta}$	12.7	−14.0	12.0	27	93	0.11
	BTP/B2M	−15.2$^{\beta}$	13.6	−12.8	20.4	27	93	0.10
	4-marker	−6.0$^{\beta}$	9.0	−3.8	7.8	53	100	0.05

All comparisons to eGFR-EPI Cr/cysC.
* P = .002.
** P = .009.
$^{\alpha}$ P = 0.01.
$^{\beta}$ P < 0.0001.
$^{\delta}$ P = 0.02.
† P = .04.
$^{¥}$ P = .007.

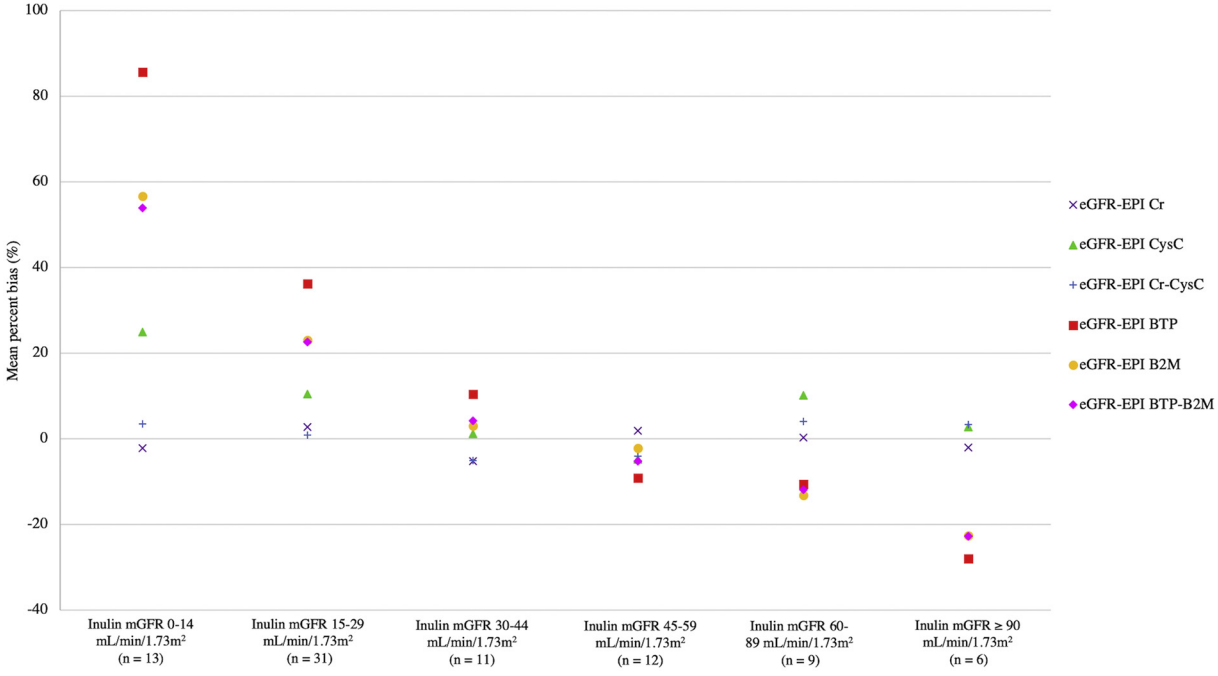

Fig. 1. Mean percent bias for each equation by mGFR KDIGO category.

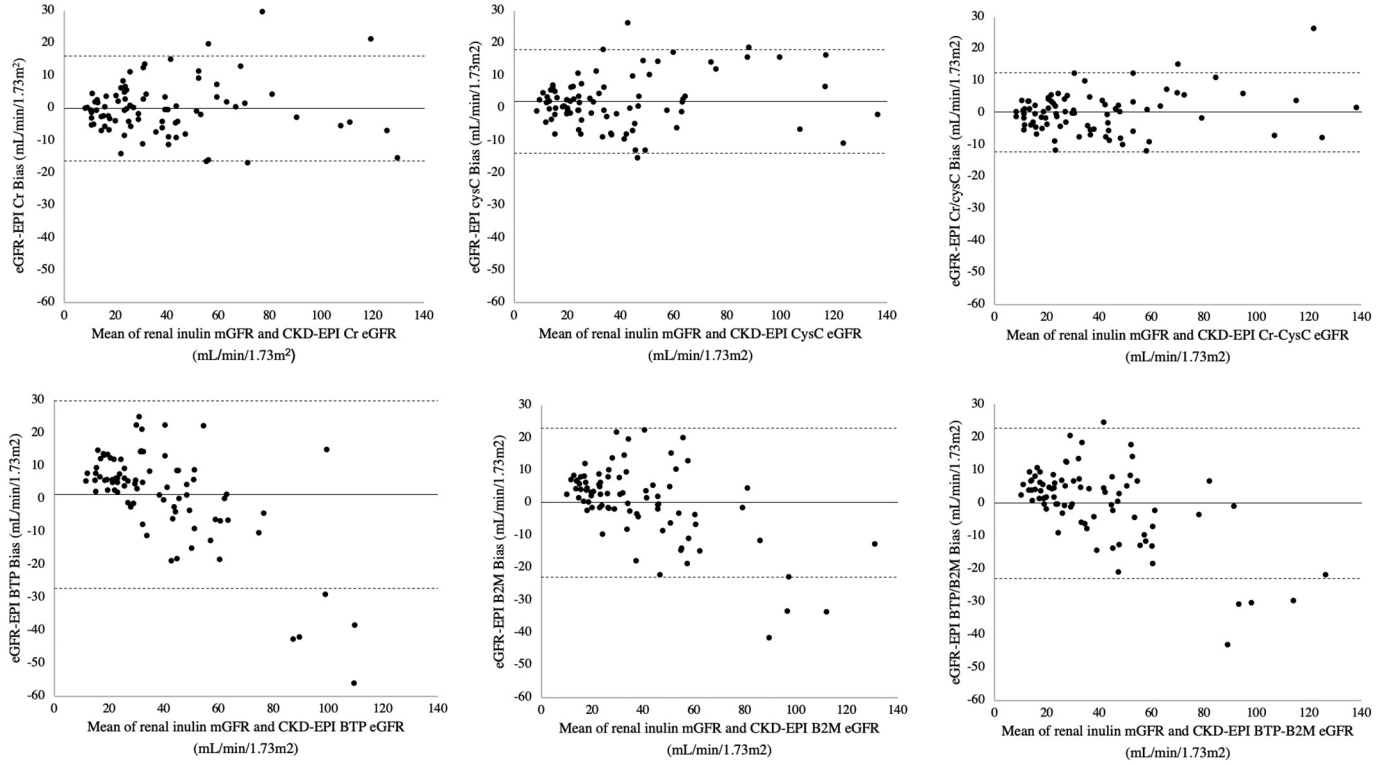

Fig. 2. Bland Altman analysis. Solid line is mean bias and hatched lines are upper and lower limits of agreement.

result of the higher overall GFR of the internal validation study. The authors do not present equation performance by GFR subgroups in the internal validation study. The studies do deviate on BTP equation performance at the highest levels of GFR (GFR > 100 ml/min/1.73 m^2). Examination of the plotted data reveals significant GFR overestimation in the internal validation study but significant GFR underestimation in the current study when GFR is high. However, both studies are limited by low patient numbers, making it difficult to draw any firm conclusions. It should also be noted that any assay interference will have a dramatic impact on GFR estimation when analyte concentrations are low (as in these patients) due to the inverse relationship between analyte concentration and GFR [7].

One other study has compared the novel equations to plasma iohexol clearance (single sample only protocol) in 126 elderly subjects with a mean mGFR of 54 ml/min/1.73m^2 [17]. The BTP and B2M equations were less precise and less accurate than the Cr/cysC equation.

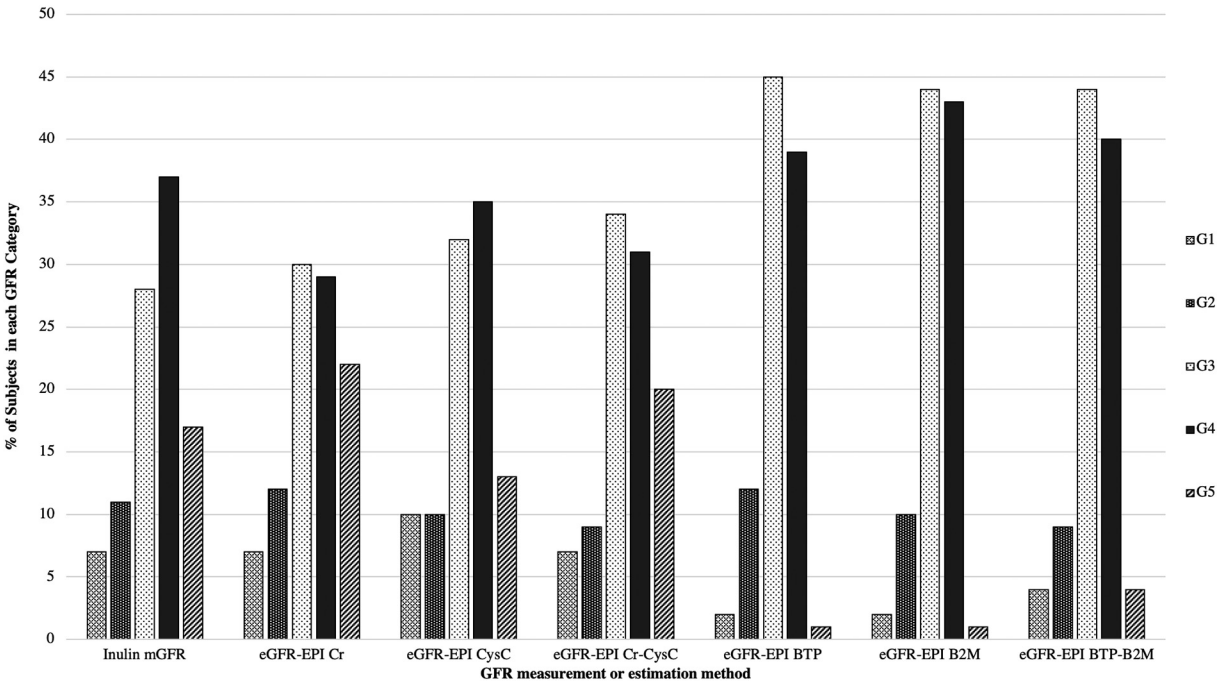

Fig. 3. CKD GFR categories by inulin mGFR and by CKD-EPI eGFR.

Table 4
Proportion of patients classified into the correct KDIGO mGFR category.

	All (n = 83)	G1 (*n* = 6)	G2 (*n* = 9)	G3 (n = 23)	G4 (*n* = 31)	G5 (*n* = 13)
eGFR-EPI Cr % (95% CI)	77 (67–86)	83	78	78	68	93
eGFR-EPI cysC % (95% CI)	77 (65–84)	100	67	87	74	62
eGFR-EPI Cr/cysC % (95% CI)	85 (75–91)	100	78	96	74	92
eGFR-EPI BTP % (95% CI)	55 (43–65)	17	56	87	58	8
eGFR-EPI B2M % (95% CI)	55 (43–65)	33	22	83	68	8
eGFR-EPI BTP/B2M % (95% CI)	66 (54–75)	50	33	96	77	23
4-Marker average % (95% CI)	79 (68–87)	83	56	96	81	62

They do not provide bias and precision data by GFR subgroups nor any plotted data. However the P30 accuracy of the subgroup with eGFR < 45 ml/min/1.73m^2 was similar at 57–65% to that of the current study [17]. A larger study in the elderly (n = 566) with a mean plasma iohexol mGFR of 60.4 ml/min/1.73 m^2 is the only study so far showing similar performance of the BTP equation to the Cr/cysC equation [20]. The authors speculate that this may because their elderly cohort more closely resembled the cohort used to derive the eGFR-EPI BTP equation (older and more diabetics) than the eGFR-EPI Cr/CysC equation [20]. The same patient cohort was used to evaluate the multimarker FAS equations and, in that study, adding BTP to Cr and cysC also did not improve iohexol GFR estimation [14]. Similar findings have been shown in a pediatric population with inulin GFR [21].

The poor performance of the BTP and B2M equations is perhaps not surprising. Unlike Cr, BTP is not inert. It is thought to act as a ligand involved in the transport of lipophilic molecules [10]. It is also an enzyme involved in prostaglandin metabolism, catalyzing the conversion of PGH2 to PGD2 [10]. PGD2 has a number of important physiologic functions and is involved in the regulation of sleep induction, nociception, inflammation, vasodilation, bronchoconstriction and platelet aggregation, amongst others [10]. As such, there are likely many non-GFR determinants of BTP concentrations that are not captured by the demographic variables included in the equations [10,22,23]. In addition to age and gender, factors that have been identified include serum albumin levels, urine protein excretion and weight [22,23]. There may also be genetic factors at play. In a genome-wide association analysis of the ARIC study, a locus upstream of the BTP gene accounted for 5% and 6% of the differences in serum BTP concentrations in European Americans and African Americans [24]. From an analytical prospective, there are also no higher order measurement procedures or reference materials available for BTP [25]. We have recently shown differences in the Siemens' BTP assay when measured contemporaneously in different laboratories and in the same laboratory over time suggesting lot to lot differences in assay components [25].

B2M, a low molecular weight protein found on every nucleated cell, is freely filtered by the glomerulus and then almost entirely reabsorbed at the proximal tubules, where it is subsequently catabolized into its constituent amino acids [26]. B2M accumulates in the serum when GFR is impaired [11]. However, serum B2M concentrations can be increased in conditions other than CKD including neoplastic and inflammatory conditions ranging from multiple myeloma to rheumatoid arthritis [27]. Systolic blood pressure, age, gender, total cholesterol, smoking and urine protein excretion have been shown to be associated with serum B2M independently of GFR [23,28]. Like BTP, there are no higher order reference materials or methods for B2M. Thus, analytical issues may impact on the accuracy of GFR estimation using B2M in different centers and over time as has been shown with Cr, cysC and BTP based GFR estimation [7,25,29–31].

Study strengths include the use of urinary inulin clearance for GFR measurement and the simultaneous assessment of all equations. Limitations include the small patient size, the lack of individuals with better preserved GFR and the absence of racial heterogeneity.

5. Conclusions

It is hoped that multi-marker equations will lead to improved GFR estimation by averaging out the impact of independent non-GFR determinants on the eGFR in individual patients [11,32]. The results of this study indicate that the combination eGFR-EPI Cr/cysC equation is superior to the 5 other eGFR-EPI equations studied, with lower bias and greater precision, accuracy and improved classification ability. The addition of BTP/B2M eGFR to Cr/cysC eGFR did not improve GFR estimation. Further studies are needed to generalize these findings to other populations, such as non-white and those with preserved GFR.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cca.2018.11.019.

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