SHORT REPORT

Comparison of 24-hour urinary creatinine clearance and estimated glomerular filtration rate based on a panel of filtration markers in patients with chronic kidney disease

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Abstract

Diagnosis and management of chronic kidney disease (CKD) requires accurate assessment of glomerular filtration rate (GFR). In practice, GFR is typically estimated by equations based on creatinine concentration in blood, but creatinine is affected by non-GFR factors such as age and sex. Alternative filtration markers such as cystatin C, beta-trace protein (BTP), and beta-2 microglobulin (B2M) may be less dependent on age and sex, but equations combining these markers have not been investigated in patients with chronic kidney disease (CKD). In this cross-sectional study of 50 patients with CKD stage 3–4, we compared kidney function estimates based on creatinine, cystatin C, BTP, B2M, or a combination of markers. Compared to the creatinine/cystatin C combination equation, the panel equation yielded a mean difference of only 2.8 ml/min/1.73 m^2, indicating that switching to the panel equation would be unlikely to affect management.

KEYWORDS
beta-2 microglobulin, beta-trace protein, chronic kidney disease, creatinine, cystatin C, estimated glomerular filtration rate, panel equation

1 | INTRODUCTION

It is estimated that 8%–16% of people worldwide suffer from chronic kidney disease (CKD),[1] defined as markers of kidney damage or glomerular filtration rate (GFR) less than 60 ml/min/1.73 m^2 for at least 3 months.[2] Patients with CKD are susceptible to inappropriate prescribing of medications that require dose adjustment based on kidney function.[3] Nearly all adverse drug reactions caused by renally excreted medications are dose related and avoidable with appropriate dose adjustment,[4] but there remains debate about how to do this in practice.

Urinary creatinine clearance (UC$_{Cre}$) approximates GFR based on renal elimination of creatinine, a metabolic byproduct in muscle tissue that is freely filtered at the glomerulus. UC$_{Cre}$ is sometimes used for assessing kidney function and dosing renally excreted medications, but UC$_{Cre}$ tends to overestimate GFR because creatinine is partially secreted by renal tubules.[5] Alternatively, GFR can be estimated from creatinine concentration in blood using a standardized

equation that accounts for known patient factors. The Cockcroft–Gault equation (CG_{Cre}) accounts for patient age, sex, and weight, but it remains an imprecise correlate of GFR across patient groups.[6] Most clinical settings use the creatinine-based Chronic Kidney Disease Epidemiology Collaboration equation ($CKD\text{-}EPI_{Cre}$), which adjusts for age and sex and is more accurate than CG_{Cre}.[7] However, all creatinine-based equations have the same fundamental drawback that creatinine concentration is influenced by non-GFR determinants such as dietary intake and endogenous production by muscle tissue.[8] Patients with decreased muscle mass, such as those affected by frailty[9] or amputation,[10] are at risk for overestimation of kidney function with $CKD\text{-}EPI_{Cre}$, potentially leading to underdiagnosis and undertreatment of CKD.

Cystatin C, beta-trace protein (BTP), and beta-2 microglobulin (B2M) are alternative filtration markers for estimating GFR.[11] A cystatin C-based equation ($CKD\text{-}EPI_{Cys}$) is more accurate than $CKD\text{-}EPI_{Cre}$ among patients with low muscle mass,[12] but cystatin C concentration is affected by other non-GFR factors such as obesity, inflammation, smoking, proteinuria, and glucocorticoid use.[13-16] Equations adapted for BTP ($CKD\text{-}EPI_{BTP}$) and B2M ($CKD\text{-}EPI_{B2M}$) are less accurate than $CKD\text{-}EPI_{Cre}$ or $CKD\text{-}EPI_{Cys}$, but they may be less dependent on age and sex.[17] An equation combining creatinine and cystatin C ($CKD\text{-}EPI_{Cre\text{-}Cys}$) is superior to both $CKD\text{-}EPI_{Cre}$ and $CKD\text{-}EPI_{Cys}$ in certain patient populations,[18] while an equation combining all four markers ($CKD\text{-}EPI_{Panel}$) performed even better than $CKD\text{-}EPI_{Cre\text{-}Cys}$ in a development cohort.[19] Given the importance of accurate GFR assessment for diagnosis and management of CKD, current guidelines recommend measuring cystatin C in patients with a creatinine-based estimated GFR of 45–59 ml/min/1.73 m².[2] There is limited knowledge about how the addition of BTP and/or B2M would affect GFR estimates in patients with CKD, and we are not aware of any studies comparing $CKD\text{-}EPI_{Panel}$ to $CKD\text{-}EPI_{Cre}$ or $CKD\text{-}EPI_{Cre\text{-}Cys}$ in this population.

2 | METHODS

2.1 | Study design, setting, and participants

This was a cross-sectional study of 51 patients previously described by Boesby et al.[20] Patients in this cohort were recruited between April 2010 and June 2011 from outpatient clinics at Rigshospitalet or Herlev Hospital in Copenhagen, Denmark. Inclusion criteria were age 18–80 years, CKD stage 3–4 defined as eGFR 15–59 ml/min/1.73 m² according to $CKD\text{-}EPI_{Cre}$, and hypertension defined as untreated BP >130/80 mmHg or use of an anti-hypertensive medication. A full list of exclusion and withdrawal criteria can be found in the original study. Patients were subsequently excluded from the current study in case of eGFR ≥60 ml/min/1.73 m² according to $CKD\text{-}EPI_{Cre}$ after remeasuring creatinine with standardized equipment.

2.2 | Measurements and outcomes

Potential non-GFR factors affecting filtration marker concentration were selected based on previously described associations. These included age, sex, smoking, diabetes, obesity, inflammation, and proteinuria. Body mass index (BMI) and cholesterol were chosen as a marker of obesity, while C-reactive protein (CRP) and soluble urokinase plasminogen activator receptor (suPAR) were chosen as markers of acute and chronic inflammation, respectivel. Demographic information was obtained at the time of the initial study, and patient samples were collected and stored at −80°C. With the exception of cholesterol, all plasma and urine markers were remeasured for the current study using standardized equipment (Table S2). GFR was estimated by UC_{Cre}, CG_{Cre}, $CKD\text{-}EPI_{Cre}$, $CKD\text{-}EPI_{Cys}$, $CKD\text{-}EPI_{BTP}$, $CKD\text{-}EPI_{B2M}$, $CKD\text{-}EPI_{Cre\text{-}Cys}$, or $CKD\text{-}EPI_{Panel}$ (Table S1). UC_{Cre} and CG_{Cre} were adjusted for body surface area according to the DuBois and DuBois formula. CKD classification was determined by international staging guidelines[2]: ≥60, 45–59, 30–44, 15–29, or <15 ml/min/1.73 m².

2.3 | Statistics

Summary statistics are presented as mean with standard deviation for continuous variables or number with percent of patients for categorical variables. Differences between eGFR equations were evaluated by mixed linear regression. To explore associations between potential non-GFR factors and each outcome, a series of linear regressions was performed and are presented in the Supporting Information. A value of $p < .05$ was considered statistically significant. All analysis was performed in SAS Studio version 3.8 (SAS Institute INC, Cary NC, United States).

3 | RESULTS

3.1 | Patient characteristics

Of the 51 patients described in the original study, one patient was excluded due to eGFR ≥60 ml/min/1.73 m² according to $CKD\text{-}EPI_{Cre}$. Patient characteristics for the remaining 50 patients are shown in Table 1. Mean age was 58.4 years, 13% of patients were female, and mean eGFR according to $CKD\text{-}EPI_{Cre}$ was 34.5 ml/min/1.73 m².

3.2 | Comparison of eGFR equations

Mean GFR according to each eGFR equation and differences between equations are shown in Table 2. UC_{Cre} yielded the highest GFR with a mean of 47.4 ml/min/1.73 m². Compared to UC_{Cre}, eGFR was lower according to CG_{Cre} (difference of −5.9 ml/min/1.73 m²) and $CKD\text{-}EPI_{Cre}$ (difference of −12.8 ml/min/1.73 m²). Among CKD-EPI equations, $CKD\text{-}EPI_{Cre}$ yielded the lowest mean eGFR

TABLE 1 Patient characteristics for 50 patients with CKD

	Value, Mean ± SD or n (%)
Demographics	
Age (years)	58.4 ± 13.0
Female	13 (26)
Current smoker	6 (12)
Diabetes	12 (24)
Weight (kg)	89.1 ± 17.1
Height (m)	1.74 ± 0.08
Body mass index (kg/m^2)	29.3 ± 4.8
Body surface area (m^2)	2.03 ± 0.21
GFR[a] (ml/min/1.73 m^2)	34.5 ± 10.6
Type of chronic kidney disease	
Polycystic kidney disease	10 (20)
Glomerulonephritis[b]	9 (18)
Hypertensive nephropathy[c]	3 (6)
Partial or complete nephrectomy[d]	3 (6)
Diabetic nephropathy	2 (4)
Other[e]	4 (8)
Unknown	19 (38)
Blood and urine markers	
Plasma creatinine (mg/dl)	2.1 ± 0.6
Plasma cystatin C (mg/L)	1.9 ± 0.5
Plasma beta-trace protein (mg/L)	1.4 ± 0.5
Plasma beta-2 microglobulin (mg/L)	4.6 ± 2.2
Plasma cholesterol (mg/dl)	190 ± 39
Plasma C-reactive protein (mg/L)	3.0 ± 3.8
Plasma suPAR (ng/ml)	4.8 ± 1.5
Proteinuria (g/day)	0.9 ± 1.5

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; suPAR, soluble urokinase plasminogen activator receptor.

[a]Estimated according to CKD-EPI$_{Cre}$.

[b]Includes focal segmental glomerulosclerosis ($n = 4$), membranous glomerulonephritis ($n = 3$), IgA nephropathy ($n = 1$), and membranoproliferative glomerulonephritis ($n = 1$).

[c]Includes hypertensive glomerulonephropathy and nephrosclerosis.

[d]Due to renal cancer.

[e]Includes chronic pyelonephritis, interstitial nephritis, reflux nephropathy, and renal artery stenosis (all $n = 1$).

(34.5 ml/min/1.73 m^2), and CKD-EPI$_{BTP}$ yielded the highest mean eGFR (42.4 ml/min/1.73 m^2). Mean eGFR was similar between CKD-EPI$_{Cre}$, CKD-EPI$_{Cre-Cys}$, and CKD-EPI$_{Panel}$ (maximum difference of 3.3 ml/min/1.73 m^2).

Distribution across CKD stages for each eGFR equation is shown in Table S3. Other than one patient with GFR <15 ml/min/1.73 m^2 after remeasuring creatinine, all patients would be classified as CKD stage 3–4 according to CKD-EPI$_{Cre}$, in agreement with the original study inclusion criteria. Switching from CKD-EPI$_{Cre}$ to UC$_{Cre}$ would result in 10 patients (20%) with GFR <60 ml/min/1.73 m^2 being reclassified as GFR ≥60 ml/min/1.73 m^2, while switching to CKD-EPI$_{Cre-Cys}$ or CKD-EPI$_{Panel}$ would result in two patients (4%) or four patients (8%), respectively, being reclassified as GFR ≥60 ml/min/1.73 m^2.

3.3 | Exploratory analysis for potential non-GFR factors

Associations between potential non-GFR factors and filtration marker concentration are shown in Table S4. After correction for multiple hypothesis testing, significant associations remained between smoking status and cystatin C concentration, and between suPAR and cystatin C, BTP, and B2M concentration. Associations between potential non-GFR factors and eGFR equations are shown in Table S5. After correction for multiple hypothesis testing, significant associations remained between BMI and CG$_{Cre}$, between smoking status and CKD-EPI$_{Cys}$, and between suPAR and CKD-EPI$_{Cys}$, CKD-EPI$_{BTP}$, CKD-EPI$_{B2M}$, and CKD-EPI$_{Panel}$.

4 | DISCUSSION

4.1 | Discrepancies between eGFR and implications for clinical practice

Overall, mean eGFR was highest according to UC$_{Cre}$ and lowest according to CKD-EPI$_{Cre}$, with a difference of 12.8 ml/min/1.73 m^2. Despite the well-documented inaccuracies of UC$_{Cre}$, particularly in patients with low GFR, this method continues to be used for monitoring of kidney function and drug dosing in clinical settings worldwide. Our findings highlight the large discrepancy between UC$_{Cre}$ and eGFR and emphasize the importance of moving away from UC$_{Cre}$ as an indicator of kidney function. In contrast, mean difference in eGFR between CKD-EPI$_{Cre-Cys}$ and CKD-EPI$_{Panel}$ was only 2.8 ml/min/1.73 m^2, which is similar to normal biological variation in eGFR[21] and unlikely to be clinically relevant for most patients.

We found that switching from CKD-EPI$_{Cre}$ to CKD-EPI$_{Cre-Cys}$ or CKD-EPI$_{Panel}$ would result in two patients (4%) or four patients (8%), respectively, with GFR <60 ml/min/1.73 m^2 being reclassified as GFR ≥60 ml/min/1.73 m^2, and one patient (2%) with GFR <15 ml/min/1.73 m^2 being reclassified as GFR ≥15 ml/min/1.73 m^2. Accurate CKD classification has important implications for dosing of renally excreted medications. Approximately 23% of patients with CKD in Danish hospitals have at least one medication dosed higher than recommended according to renal function.[22] Common examples of such medications in this population include analgesics, antidiabetics, and antihypertensives. Internationally, Tesfaye et al. estimate that the prevalence of inappropriate prescribing among patients with CKD ranges from 9% to 81%.[3]

TABLE 2 Comparison of mean GFR according to different methods

	Mean GFR $\pm$ SE (ml/min/1.73 m²)	Difference (95% CI) from given method		
		UC$_{Cre}$	CKD-EPI$_{Cre}$	CKD-EPI$_{Cre-Cys}$
UC$_{Cre}$	47.4 $\pm$ 2.6	N/A	+12.8 (+9.7 to +15.9)	+12.3 (+9.4 to +15.2)
CG$_{Cre}$	41.5 $\pm$ 1.6	−5.9 (−9.5 to −2.3)	+7.0 (+5.3 to +8.6)	+6.4 (+4.3 to +8.6)
CKD-EPI$_{Cre}$	34.5 $\pm$ 1.5	−12.8 (−15.9 to −9.7)	N/A	−0.5 (−1.7 to +0.6)
CKD-EPI$_{Cys}$	37.4 $\pm$ 2.1	−9.9 (−13.1 to −6.7)	+2.9 (+0.6 to +5.3)	+2.4 (+1.2 to +3.6)
CKD-EPI$_{BTP}$	42.4 $\pm$ 1.9	−4.9 (−8.8 to −1.1)	+7.9 (+5.5 to +10.3)	+7.4 (+5.4 to +9.3)
CKD-EPI$_{B2M}$	42.2 $\pm$ 2.1	−5.2 (−8.4 to −2.0)	+7.6 (+5.2 to +10.1)	+7.1 (+5.4 to +8.8)
CKD-EPI$_{Cre-Cys}$	35.1 $\pm$ 1.7	−12.3 (−15.2 to −9.4)	+0.5 (−0.6 to +1.7)	N/A
CKD-EPI$_{Panel}$	37.8 $\pm$ 1.8	−9.6 (−12.5 to −6.6)	+3.3 (+2.0 to +4.6)	+2.8 (+2.3 to +3.2)

Abbreviations: BTP, beta-trace protein; B2M, beta-2 microglobulin; CG, Cockcroft-Gault; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; Cre, creatinine; Cys, cystatin C; GFR, glomerular filtration rate; UC, urinary clearance.

Due to the limited size of our cohort, it is difficult to draw conclusions about potential dosing discrepancies when switching between eGFR equations. In any case, these discrepancies must be weighed against the cost and complexity of measuring additional filtration markers. Future research should clarify the value of using CKD-EPI$_{Panel}$ in other patient groups at high risk of inaccurate kidney function estimates based on creatinine and/or cystatin C. Until this cost–benefit analysis is performed, we suggest using measured GFR as a confirmatory test for individual patients that require a more accurate kidney function assessment.

4.2 | Non-GFR factors: insights and future directions

The decision to measure GFR with a gold standard will depend on its clinical relevance for individual patients and a suspicion that estimated GFR will be inaccurate. As expected, we found that cystatin C, BTP, and B2M concentration were less affected by age and sex compared to creatinine. However, these filtration markers were significantly associated with plasma suPAR levels. There is ongoing work investigating suPAR as a marker of systemic chronic inflammation,[23] so its association with cystatin C, BTP, and B2M may indicate a role of these markers in chronic inflammatory pathways. A similar study of non-GFR factors in older patients identified a significant influence of CRP on cystatin C and B2M, but not BTP.[24] We did not observe any significant associations with CRP, which supports the hypothesis that suPAR and CRP reflect different aspects of inflammation.

5 | CONCLUSIONS

In this cohort of patients with CKD, switching from UC$_{Cre}$ to an eGFR equation would have clinically relevant consequences, whereas switching between CKD-EPI$_{Cre}$, CKD-EPI$_{Cre-Cys}$, and CKD-EPI$_{Panel}$ would be unlikely to affect management. These findings suggest there is no reason to favor CKD-EPI$_{Panel}$ over CKD-EPI$_{Cre-Cys}$ in this

patient population, although larger studies are needed to support this conclusion. Systemic chronic inflammation indicated by suPAR level explained some of the variation in GFR estimates based on cystatin C, BTP, and B2M, but future studies using measured GFR as comparison are needed to determine the effect of suPAR on eGFR accuracy. Our study has several notable limitations. First, the study included only 50 patients with CKD stage 3–4 and hypertension, which limits generalizability. Second, the study did not include a gold standard measurement of GFR, so it was not possible to evaluate the accuracy of eGFR equations relative to measured GFR. Finally, the study did not include markers of muscle mass, and no patients were taking glucocorticoids during the study, so we could not evaluate the influence of these factors on filtration marker concentration.

AUTHOR CONTRIBUTIONS
REI, LB, DH, and MBH were involved in research idea and study design. LB, DH, and MBH were involved in data acquisition. EI was involved in statistical analysis. All authors contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for their own contributions, and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

DISCLOSURE
The authors declare no conflict of interest.

ETHICS STATEMENT
The study from which this data was collected is registered at www.clinicaltrials.gov (identifier: NCT01100203) and was approved by the Danish Data Protection Agency and the Ethics Committee for the Capital Region in Denmrak. The study was conducted in accordance

with the Helsinki Declaration, and written informed consent was obtained from all participants prior to inclusion.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.