Kang et al. BMC Nephrology (2020) 21:280
https://doi.org/10.1186/s12882-020-01932-4

BMC Nephrology

RESEARCH ARTICLE Open Access

Discrepant glomerular filtration rate trends from creatinine and cystatin C in patients with chronic kidney disease: results from the KNOW-CKD cohort

Eunjeong Kang[1†], Seung Seok Han[2†], Jayoun Kim[3], Sue Kyung Park[4], Wookyung Chung[5], Yun Kyu Oh[6], Dong-Wan Chae[7], Yong-Soo Kim[8], Curie Ahn[2] and Kook-Hwan Oh[2*]

Abstract

Background: Serum creatinine (Cr) and cystatin C (CysC) can both be used to estimate glomerular filtration rate ($eGFR_{Cr}$ and $eGFR_{CysC}$). However, certain conditions may cause discrepancies between eGFR trends from Cr and CysC, and these remain undetermined in patients with chronic kidney disease (CKD).

Methods: A total of 1069 patients from the Korean CKD cohort (KNOW-CKD), which enrolls pre-dialytic CKD patients, whose Cr and CysC had been followed for more than 4 years were included in the sample. We performed trajectory analysis using latent class mixed modeling and identified members of the discrepancy group when patient trends between $eGFR_{Cr}$ and $eGFR_{CysC}$ differed. Multivariate logistic analyses with Firth's penalized likelihood regression models were performed to identify conditions related to the discrepancy.

Results: Trajectory patterns of $eGFR_{Cr}$ were classified into three groups: two groups with stable $eGFR_{Cr}$ (stable with high $eGFR_{Cr}$ and stable with low $eGFR_{Cr}$) and one group with decreasing $eGFR_{Cr}$. Trajectory analysis of $eGFR_{CysC}$ also showed similar patterns, comprising two groups with stable $eGFR_{CysC}$ and one group with decreasing $eGFR_{CysC}$. Patients in the discrepancy group (decreasing $eGFR_{Cr}$ but stable & low $eGFR_{CysC}$; $n = 55$) were younger and had greater proteinuria values than the agreement group (stable & low $eGFR_{Cr}$ and $eGFR_{CysC}$; $n = 706$), differences that remained consistent irrespective of the measurement period (4 or 5 years).

Conclusions: In the present study, we identify conditions related to discrepant trends of $eGFR_{Cr}$ and $eGFR_{CysC}$. Clinicians should remain aware of such potential discrepancies when tracing both Cr and CysC.

Keywords: Chronic kidney disease, Creatinine, Cystatin C, Estimated glomerular filtration rate, Trajectory pattern

* Correspondence: khoh@snu.ac.kr
[1]Eunjeong Kang and Seung Seok Han co-first authors
[2]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea
Full list of author information is available at the end of the article

Background

Accurate measurements of glomerular filtration rate (GFR) are important in nephrology. Because actual GFR is difficult to measure and expensive when used for screening, GFR is often estimated using serum creatinine ($eGFR_{Cr}$). However, serum creatinine (Cr) is affected by non-GFR determinants such as muscle mass, body size, diet, and nutritional status [1]. Recently, cystatin C (CysC), which is a 13.3 kDa protein serine protease inhibitor produced by all nucleated cells, was proposed as a marker for estimating GFR [2, 3]. Because CysC is less influenced by muscle mass than other measures, eGFR with CysC ($eGFR_{CysC}$) may reflect GFR more accurately than eGFR with Cr ($eGFR_{Cr}$) in patients with muscle wasting, chronic disease, and limb amputation [1]. The Kidney Disease Improving Global Outcomes guidelines for the evaluation of chronic kidney disease (CKD) recommends using $eGFR_{Cr}$ as an initial assessment of renal function, and $eGFR_{CysC}$ as a confirmation of CKD in certain circumstances when $eGFR_{Cr}$ is less accurate, with an evidence level of 2B. $eGFR_{CysC}$ may be also used in adult patients with $eGFR_{Cr}$ of 45–59 ml/min/1.73 m^2 who do not have markers of kidney damage, with an evidence level of 2C [4]. Nevertheless, the utility of $eGFR_{CysC}$ and conditions under which $eGFR_{CysC}$ differs from $eGFR_{Cr}$ are unknown.

Intra-individual dynamic change in laboratory measurements provides better prognostic information than cross-sectional data alone [5]. In this respect, trajectory analysis has been applied to evaluate clinical parameters such as blood pressure [6], disability and functional decline [7, 8], and body mass index [9]. Variability in renal function is commonly observed in clinical settings [5]. Previously, trajectory analysis of eGFR demonstrated that CKD patients with catastrophic declining patterns had high rates of co-morbidities and mortality [10, 11].. However, the trajectory patterns of $eGFR_{CysC}$ have not been evaluated. The KNOW-CKD (KoreaN cohort Study for Outcomes in patients With Chronic Kidney Disease), a representative Korean CKD cohort, had traced values of $eGFR_{CysC}$, and we identified certain patients had a discrepancy trend between $eGFR_{Cr}$ and $eGFR_{CysC}$. To identify conditions related to discrepancies, we traced the patterns of both types of eGFR results. To enhance accuracy, both Cr and CysC were measured using calibrations traceable to the international standard reference material.

Methods

Study population

Study subjects were selected among participants in the KNOW-CKD, which is a representative prospective Korean pre-dialytic CKD cohort that began enrolling patients in 2011, wherein kidney transplant recipients were not included. The detailed design and method of the KNOW-CKD were described previously [12]. Briefly, a total of 2238 participants were enrolled in the KNOW-CKD study. Both serum Cr and CysC were measured at baseline, 6 months and 1 year after enrollment, and thereafter once per year. Patients who measured both $eGFR_{Cr}$ and $eGFR_{CysC} \geq 5$ times from baseline were included. Patients who died during the follow-up period ($n = 25$) and those without baseline CysC ($n = 7$) were excluded. Consequently, 1069 patients were analyzed in the present study. For sensitivity analysis, we defined another group that included patients for whom clinicians measured both $eGFR_{Cr}$ and $eGFR_{CysC} \geq 4$ times (Fig. 1).

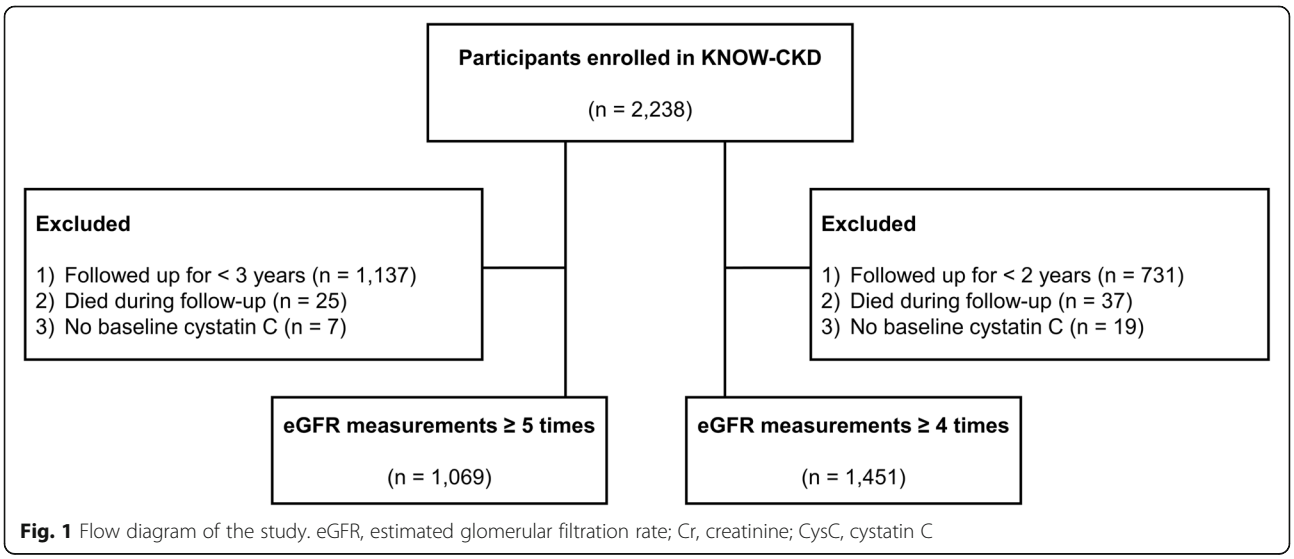

Fig. 1 Flow diagram of the study. eGFR, estimated glomerular filtration rate; Cr, creatinine; CysC, cystatin C

Table 1 Baseline characteristics of study participants

Variables	Total ($n = 1069$)
Age (years)	53.2 ± 12.1
Male (%)	60.4
Age-adjusted Charlson comorbidity index (%)	3.9 ± 1.8
Low (≤3)	58.7
Moderate (4–5)	27.2
High (6–7)	12.3
Very high (≥8)	1.8
Diabetes mellitus (%)	26.5
Hypertension (%)	96.4
Systolic blood pressure (mmHg)	126.1 ± 14.6
Diastolic blood pressure (mmHg)	76.4 ± 10.3
Body mass index (kg/m^2)	24.5 ± 3.4
Body surface area (m^2)	1.7 ± 0.2
Systolic blood pressure (mmHg)	126.1 ± 14.0
Diastolic blood pressure (mmHg)	76.4 ± 10.3
Cause of chronic kidney disease (%)	
Diabetic nephropathy	15.4
Non-diabetic nephropathy	84.6
eGFR (ml/min/1.73 m^2)	
$eGFR_{Cr}$	58.5 ± 28.9
$eGFR_{CysC}$	58.4 ± 31.2
$eGFR_{CrCysC}$	58.0 ± 30.6
Laboratory findings	
Hemoglobin (g/dL)	13.21 ± 1.85
Blood urea nitrogen (mg/dL)	
Uric acid (mg/dL)	6.90 ± 1.86
Phosphorus (mg/dL)	
Total bilirubin (mg/dL)	
Albumin (g/dL)	4.26 ± 0.35
uPCR (mean, interquartile range)	0.4 (0.1–1.0)
< 0.3 g/g (%)	45.0
0.3–0.9 g/g (%)	30.6
1.0–3.0 g/g (%)	18.8
≥ 3 g/g (%)	5.6
uACR (mean, interquartile range)	272.4 (49.7–705.1)
< 30 mg/g (%)	19.2
30–299 mg/g (%)	33.4
≥ 300 mg/g (%)	47.4
ESRD event (%)	69.0

eGFR Estimated glomerular filtration rate; *Cr* Creatinine; *CysC* Cystatin C; *uPCR* Urine protein/creatinine ratio; *uACR* Urine albumin creatinine ratio

Variable measurements

Data for all of the covariates were collected at the time of enrollment including age, sex, comorbidities (diabetes, hypertension, age-adjusted Charlson comorbidity index), body mass index, body surface area, waist and hip circumference, systolic and diastolic pressures, and laboratory findings including white blood cell count, hemoglobin, platelet count, blood urea nitrogen, uric acid, calcium, phosphorus, alkaline phosphatase, total bilirubin, total cholesterol, low density lipoprotein, high density lipoprotein, triglyceride, fasting glucose, albumin, spot urine protein/creatinine ratio (uPCR), and spot urine albumin/creatinine ratio (uACR).

Blood and random voided urine (if possible, second urine in the morning) were collected. All of the samples were measured at a central laboratory (Lab Genomics, Gyeonggi-do, South Korea). Serum Cr was measured by the Jaffe rate blank method using alkaline picrate in a central laboratory and an assay traceable to isotope dilution mass spectrometry (IDMS) (ADVIA® Chemistry Creatinine 2, Siemens, Germany). Serum CysC was measured with a latex-particle enhanced immunoturbidimetric assay (ADVIA® Chemistry Cystatin C Reagents, Siemens, Germany) with calibration traceable to international reference material [13, 14]. The eGFR was estimated by serum Cr or/and CysC using the CKD Epidemiology Collaboration (CKD-EPI) equation [15]. Because of ethical issues and data protection regulations, data that support the findings of the present study cannot be made publicly available.

Statistical analysis

All statistical analyses were carried out using R (version 3.5.2; The R Foundation for Statistical Computing, Vienna, Austria). Continuous and categorical variables were presented as means±standard deviation and proportions, respectively. We used one-way analysis of variance and the χ^2 test for comparisons of continuous variables and categorical variables, respectively. For trajectory analysis, we applied latent class mixed modeling (lcmm R package) and the R code is provided in the Supplemental materials. We calculated the entropy, Akaike's information criteria and Bayesian information criteria for goodness-of-fit statistics and these were described in the Supplemental materials. Subsequently, we defined the discrepancy group as having decreasing $eGFR_{Cr}$ but stable $eGFR_{CysC}$ and the agreement group as having both stable $eGFR_{Cr}$ and $eGFR_{CysC}$.

To identify factors related to discrepant trends, Firth's penalized likelihood ratio method was used to account for rare events because of potential bias to the maximum likelihood estimator [16–18]. To identify independent conditions related to discrepant trends, univariate and multivariate logistic regression models with backward elimination method were applied. Adjusted variables in multivariate analysis conducted with or without the stepwise conditional method included age, sex, eGFR calculated with Cr and CysC ($eGFR_{CrCysC}$) that

represented a renal function, and variables that had *P*-values < 0.1 in univariate analysis. Statistical significance was set as $P < 0.05$ using two-tailed tests.

Ethics statement

The study protocol was approved by the Institutional Review Board at each participating clinical center [Seoul National University Hospital (1104–089-359), Seoul National University Bundang Hospital (B-1106/129–008), Yonsei University Severance Hospital (4–2011-0163), Kangbuk Samsung Medical Center (2011–01-076), Seoul St. Mary's Hospital (KC11OIMI0441), Gil Hospital (GIRBA2553), Eulji General Hospital (201105–01), Chonnam National University Hospital (CNUH-2011-092), and Busan Paik Hospital (11–091)]. Written informed consent was obtained from each patient. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

Baseline characteristics

Baseline characteristics of total enrolled participants were described in Table 1. The mean age of these patients was 53.2 ± 12.1 years and 646 (60.4%) were male. Patients with diabetes and hypertension comprised 283 (26.5%) and 1031 (96.4%) patients, respectively. Mean values for $eGFR_{Cr}$, $eGFR_{CysC}$, and $eGFR_{CrCysC}$ were 58.5 ± 28.9 mL/min/1.73 m^2, 58.4 ± 31.2 mL/min/1.73 m^2, and 58.0 ± 30.6 mL/ min/1.73 m^2, respectively. Median values for uPCR and uACR were 0.4 g/g (0.1–1.0 g/g) and 272.4 mg/g (49.7–705.1 mg/g), respectively. The numbers of patients with uACR 3000 mg/g and uPCR > 3 g/g were 30 (2.8%) and 60 (5.6%), respectively.

Trajectory patterns of $eGFR_{Cr}$ and $eGFR_{CysC}$

The relationship between baseline $eGFR_{Cr}$ and $eGFR_{CysC}$ is shown as a Bland-Altman plot (Supplemental Figure 1). The mean value of difference was 0.148, and standard deviation was 11.327. The correlation coefficient (r) between $eGFR_{Cr}$ and $eGFR_{CysC}$ was 0.93. We identified three distinct trajectory patterns for $eGFR_{Cr}$ (Fig. 2): two groups with stable $eGFR_{Cr}$ (stable with high $eGFR_{Cr}$ [SH] and stable with low $eGFR_{Cr}$ [SL]) and one group with decreasing $eGFR_{Cr}$ (D). Trajectories of $eGFR_{CysC}$ also showed similar patterns, with two groups with stable $eGFR_{CysC}$ (SH and SL) and one group with decreasing $eGFR_{CysC}$ (D). Baseline characteristics according to the group of $eGFR_{Cr}$ and $eGFR_{CysC}$ were described in Supplemental Table 1. Particularly, 69% of the ESRD events were occurred in the decreasing eGFRCr (D) group. We conducted cross-tabulation using these groups (Fig. 3). Most patients (97.6%; $n = 1043$) were classified into the SL group in $eGFR_{CysC}$, followed by the SH (1.31%, $n = 14$) and D (1.12%, $n = 12$) groups. There

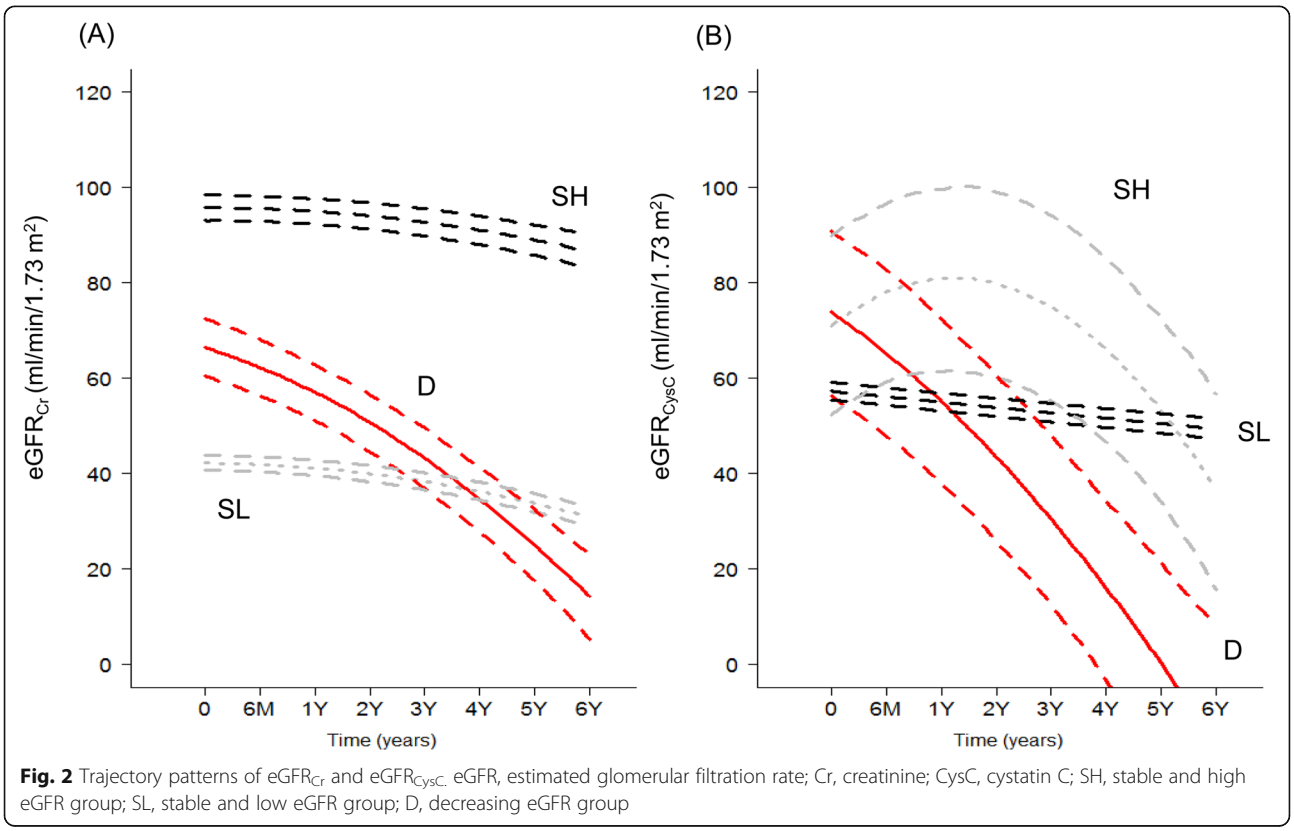

Fig. 2 Trajectory patterns of $eGFR_{Cr}$ and $eGFR_{CysC}$. eGFR, estimated glomerular filtration rate; Cr, creatinine; CysC, cystatin C; SH, stable and high eGFR group; SL, stable and low eGFR group; D, decreasing eGFR group

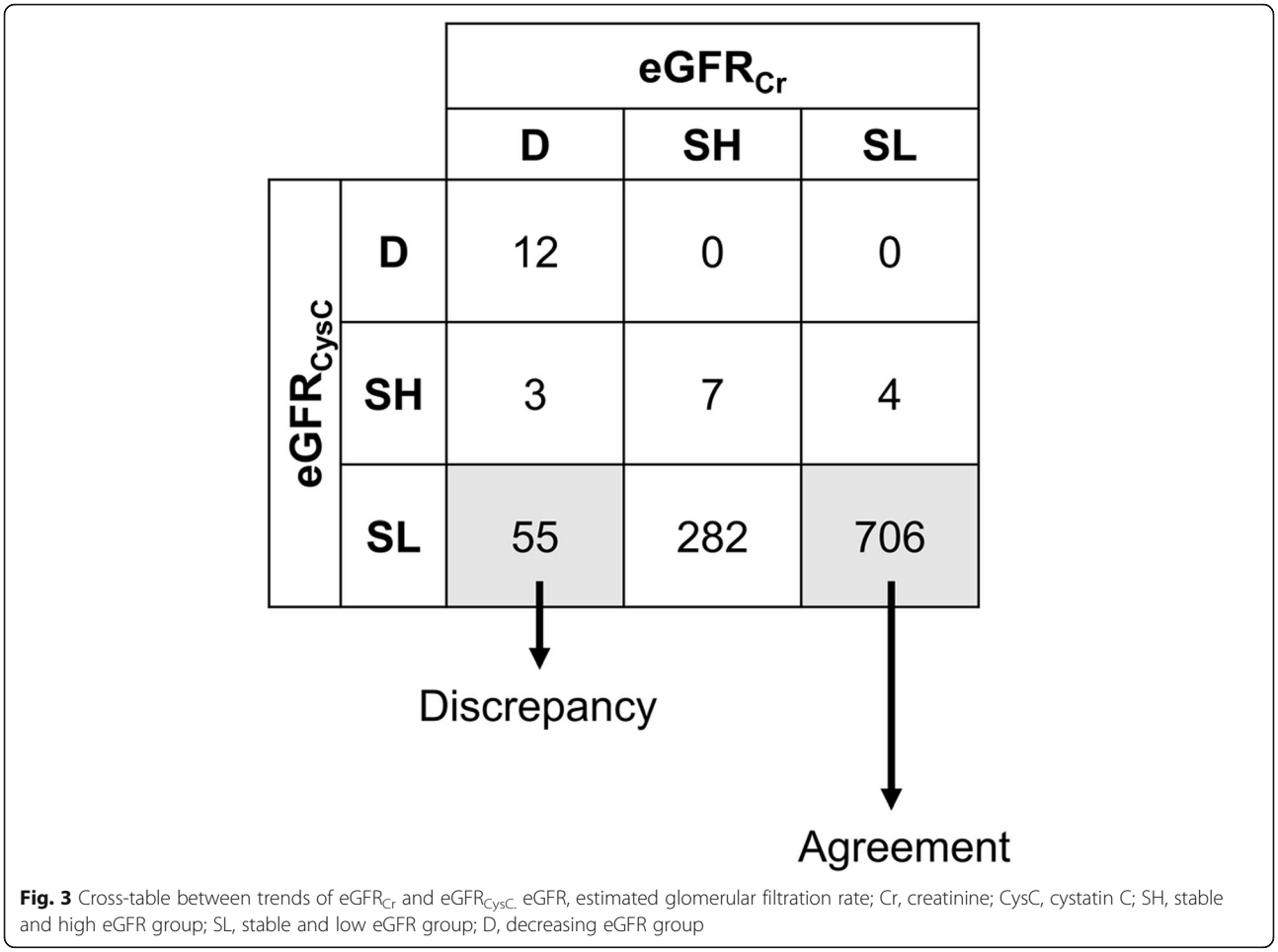

Fig. 3 Cross-table between trends of $eGFR_{Cr}$ and $eGFR_{CysC}$. eGFR, estimated glomerular filtration rate; Cr, creatinine; CysC, cystatin C; SH, stable and high eGFR group; SL, stable and low eGFR group; D, decreasing eGFR group

were small numbers of patients in the D and SH groups with $eGFR_{CysC}$.

Conditions related to discrepant trends between $eGFR_{Cr}$ and $eGFR_{CysC}$

Table 2 summarizes baseline characteristics according to discrepant trends. The patients in the agreement group were older than those in the discrepancy group. There were no differences in underlying disease, including diabetes and hypertension, or body mass index. Body surface area was greater in the discrepancy group than in the agreement group. Proteinuria values represented by uPCR and uACR and baseline renal function evaluated by $eGFR_{Cr}$, $eGFR_{CysC}$, and $eGFR_{CrCysC}$ were higher in the discrepancy group than in the agreement group.

When the discrepancy group was set as the dependent variable, younger age and proteinuria were selected as predictors of discrepancies between trends of $eGFR_{Cr}$ and $eGFR_{CysC}$. When the backward elimination method was applied (model 2 in Table 3), age and proteinuria remained significant for predicting the discrepancy of trends. These results remained consistent in the subgroup analyses according to the age and proteinuria (Supplementary Tables 4, 5).

Sensitivity analysis with patients for whom eGFRs were measured ≥4 times

The sensitivity analysis was conducted in patients for whom eGFRs were measured more than 4 times (n = 1451). The results for most baseline features were similar to those of the previous patient group (Supplemental Table 6). Their mean age was 53.2 ± 12.1 years old and 59.5% of enrolled patients were male. Diabetic patients accounted for 29.3%. Mean values of $eGFR_{Cr}$, $eGFR_{CysC}$ and $eGFR_{CrCysC}$ were 57.5 ± 29.6 mL/min/1.73 m^2, 57.1 ± 31.4 mL/min/1.73 m^2, and 56.9 ± 31.1 mL/ min/1.73 m^2, respectively.

The trajectory patterns of $eGFR_{Cr}$ and $eGFR_{CysC}$ were classified into 3 groups (Supplemental Figure 1), and there were discrepancies between trends similar to those observed in the main analysis (Supplemental Figure 2). In multivariate analysis, young patient age, proteinuria, and other variables such as male sex and large body surface area had tendencies for discrepancy compared with the counterpart groups (Supplemental Table 7).

Table 2 Baseline characteristics according to discrepancy between the trends of $eGFR_{Cr}$ and $eGFR_{CysC}$

	Discrepancy ($n = 55$)	Agreement ($n = 706$)	P
Age (years)	44.8 ± 10.3	56.8 ± 10.7	< 0.001
Male (%)	61.8	62.2	0.957
Age-adjusted Charlson comorbidity index (%)	2.4 ± 1.7	4.0 ± 1.7	< 0.001
Low (≤3)	74.5	42.9	
Moderate (4–5)	21.8	36.5	
High (6–7)	3.6	18.1	
Very high (≥8)	0	2.4	
Diabetes (%)	27.3	31.4	0.622
Hypertension (%)	98.2	98.9	1.000
Systolic blood pressure (mmHg)	128.0 ± 13.0	125.9 ± 14.7	0.306
Diastolic blood pressure (mmHg)	78.4 ± 10.7	75.7 ± 10.1	0.062
Body mass index (kg/m^2)	24.4 ± 4.0	24.7 ± 3.3	0.514
Body surface area (m^2)	1.8 ± 0.2	1.7 ± 0.2	0.036
Systolic blood pressure (mmHg)	128.0 ± 13.0	125.9 ± 14.7	0.306
Diastolic blood pressure (mmHg)	78.4 ± 10.7	75.7 ± 10.1	0.062
Cause of chronic kidney disease (%)			0.924
Non-diabetic nephropathy	81.8	80.3	
Diabetic nephropathy	18.2	19.7	
eGFR (ml/min/1.73 m^2)			
$eGFR_{Cr}$	66.4 ± 16.6	41.9 ± 15.2	< 0.001
$eGFR_{CysC}$	58.2 ± 19.72	41.6 ± 17.9	< 0.001
$eGFR_{CrCysC}$	61.0 ± 18.3	40.8 ± 16.1	< 0.001
Laboratory findings			
Hemoglobin (g/dL)	13.4 ± 1.7	12.9 ± 1.9	0.029
Blood urea nitrogen (mg/dL)	20.8 ± 5.8	20.2 ± 8.6	< 0.001
Uric acid (mg/dL)	6.8 ± 1.7	7.4 ± 1.7	0.020
Phosphorus (mg/dL)	3.5 ± 0.5	3.6 ± 0.6	0.041
Total bilirubin (mg/dL)	0.7 ± 0.3	0.7 ± 0.3	0.087
Albumin (g/dL)	4.2 ± 0.3	4.2 ± 0.3	0.967
uPCR (mean, interquartile range)	0.5 (0.2–1.5)	0.4 (0.1–1.0)	0.054
< 0.3 g/g (%)	30.9	41.3	0.011
0.3–0.9 g/g (%)	27.3	33.1	
1.0–3.0 g/g (%)	27.3	20.6	
≥ 3.0 g/g (%)	14.5	5.0	
uACR (mean, interquartile range g)	427 (120–1206)	295 (72–744)	0.040
< 30 mg/g (%)	7.3	14.5	0.202
30–299 mg/g (%)	32.7	36.1	
≥ 300 mg/g (%)	60.0	49.4	

eGFR Estimated glomerular filtration rate; *Cr* Creatinine; *CysC* Cystatin C; *uPCR* Urine protein/creatinine ratio; *uACR* Urine albumin creatinine ratio

Discussion

Information about eGFRs trends may be more helpful to predict prognosis than single measurements of eGFR. Although CysC has been used as an additional parameter to calculate GFR, $eGFR_{CysC}$ trends have not been evaluated and compared to those of $eGFR_{Cr}$. In the present study, we first compared $eGFR_{Cr}$ and $eGFR_{CysC}$ trends and found that certain factors such as young age and proteinuria were related to discrepancies in trends between two eGFRs.

Table 3 Analysis to identify conditions related to discrepant trends of $eGFR_{Cr}$ and $eGFR_{CysC}$

	Model 1		Model 2	
Variables	OR (95% CI)	*P*	OR (95% CI)	*P*
Age	0.92 (0.89–0.95)	< 0.001	0.92 (0.89–0.95)	< 0.001
Male	1.60 (0.61–4.26)	0.343		
Age-adjusted CCI				
Low (≤3)	Reference			
Moderate (4–5)	1.30 (0.53–3.12)	0.563		
High (6–7)	1.66 (0.28–7.28)	0.541		
Very high (≥8)	2.48 (0.02–30.54)	0.608		
Body surface area	2.01 (0.18–20.83)	0.562		
Diastolic blood pressure	1.01 (0.98–1.04)	0.579		
Hemoglobin	0.90 (0.71–1.13)	0.350		
Blood urea nitrogen	0.99 (0.92–1.05)	0.661		
Uric acid	0.91 (0.74–1.12)	0.379		
Phosphorus	0.83 (0.42–1.62)	0.590		
Total bilirubin	2.00 (0.52–7.35)	0.307		
uPCR (g/g)				
< 0.3	Reference		Reference	
0.3–0.9	1.69 (0.49–5.26)	0.392	1.53 (0.68–3.45)	0.305
1.0–3.0	4.54 (0.95–21.44)	0.058	3.32 (1.43–7.84)	0.006
≥ 3.0	17.87 (3.14–102.19)	0.001	12.38 (4.07–37.39)	< 0.001
uACR (mg/g)				
< 30	Reference			
30–299	2.53 (0.74–10.73)	0.145		
≥ 300	1.55 (0.27–10.19)	0.630		
$eGFR_{CrCysC}$	1.07 (1.04–1.10)	< 0.001	1.07 (1.05–1.09)	< 0.001

Model 1: Adjusted for age, sex, $eGFR_{CrCys}$ and the variables which had *P* value less than 0.1 in univariate analysis
Model 2: Model 1 with backward elimination method
CCI Charlson comorbidities index; *OR* Odds ratio; *CI* Confidence interval; *uPCR* Urine protein/creatinine ratio; *uACR* Urine albumin/creatinine ratio; *eGFR*, estimated glomerular filtration rate; *Cr* Creatinine; *CysC* Cystatin C

In the present study, we identified young age as a condition related to discrepancies between two eGFR trends, and the possible mechanisms are described as follows. There was a non-linear association between age and CysC concentration [19], and the increment rates of CysC levels were accelerated in patients aged over 50–60 years [20, 21]. Serum Cr remained relatively constant in healthy individuals between 20 and 70 years old [22]. Because there is a gap between the time point of increasing Cr and CysC, age may be a factor underlying discrepancies between eGFR trends. Additionally, when the CKD-EPI equation was developed, a large number of young patients were included from various diabetic cohorts [23], so that the proportions of younger diabetic patients differed from those in more recent studies (≤40 years, 11%; and 41–50 years, 20% in the KNOW-CKD cohort vs. ≤40 years, > 40% in the CKD-EPI-developing cohort). Such baseline differences might affect the non-GFR determinants of CysC because CysC is associated with insulin resistance, obesity, hypertension, and oxidative stress, which in turn are closely dependent on diabetes [24–26]. Inflammation could be a reason for the discrepancy between trends of $eGFR_{Cr}$ and $eGFR_{CysC}$, as inflammation is a representative determinant of CysC [27]. Although a wide ranges of inflammatory markers were not measured in the study cohort, young and old participants might have different inflammatory milieu that affects $eGFR_{CysC}$ trends. Because these hypotheses have not been thoroughly tested, further evaluations regarding the mechanisms underlying this phenomenon are needed.

Most filtered CysC is reabsorbed and metabolized by the proximal tubule cells [28, 29]. Previous study identified that the concentration of CysC was influenced by urine protein excretion, an influence stronger than that of Cr [30]. Similarly, several studies suggest that heavy proteinuria influenced renal handling of CysC [31, 32]. The association between urinary CysC and proteinuria

was predominant in pediatric cases with nephrotic syndrome compared with controls [32]. Proteinuria itself decreases the tubular uptake of low molecular weight proteins, including CysC, primarily throughout the competition for a common transport mechanism in the preclinical model [31]. The present findings regarding the relationship between proteinuria and discrepant trends might be attributable to these factors.

Non-GFR determinants are well-known for serum Cr and CysC, respectively. A representative non-GFR determinant for Cr is muscle mass. Body mass index is a simple index for body composition but does not distinguish between excess fat, muscle, and bone mass [33, 34]. In the present study, we did not detect the independent significance of body mass index underlying the discrepancy between eGFR trends, although a dependent relationship with body surface area was detected. This difference might be because body mass index and body surface area do not reflect muscle mass. In the present study, the mean body mass index was $24.5 \pm 3.4\ kg/m^2$, which was lower than that of another CKD cohort ($32.1 \pm 7.9\ kg/m^2$ in CRIC) [35]. In this respect, population-related factors also hamper the distinctive relationship between body mass index and muscle mass and thus, the effects of body mass index and body surface area might disappear in the final analysis.

The study has some limitations that deserve attention. The number of subjects was modest, although the statistical power was sufficient. Particularly, we could not compare the discrepant trends between some groups with low patient numbers. The study sample was entirely comprised of East Asians and CKD-EPI eGFR equations were not validated in the Korean population. As noted above, non-$eGFR_{Cr}$ determinants such as muscle mass differed from those of individuals of European descent, which warrants further study to identify other significant conditions. The present findings were obtained from patients with non-dialytic CKD, and thus, the application of results to healthy individuals or the general population is limited. Standard measurements of GFR such as inulin excretion rate were not available for the study cohort, and such data would be useful to determine which trend was more accurate.

The results of the present study demonstrate discrepant conditions between trends from $eGFR_{Cr}$ and $eGFR_{CysC}$. Although further studies are needed to confirm our findings in other independent cohorts, clinicians should remain aware that discrepant conditions may occur when both Cr and CysC are used to evaluate and trace renal function. Because the present guidelines do not urge caution when determining the condition of $eGFR_{CysC}$, our results may constitute the basis of future updates.

Conclusions

In conclusion, we identify conditions related to discrepant trends of $eGFR_{Cr}$ and $eGFR_{CysC}$. Clinicians should remain aware of such potential discrepancies when tracing both Cr and CysC.

Supplementary information

Supplementary information accompanies this paper at https://doi.org/10.1186/s12882-020-01932-4.

Additional file 1.

Abbreviations

Cr: Creatinine; CysC: Cystatin C; eGFR: Estimated glomerular filtration rate; GFR: Glomerular filtration rate; KNOW-CKD: KoreaN cohort study for outcomes in patients with chronic kidney disease; CKD: Chronic kidney disease; uPCR: Spot urine protein/creatinine ratio; uACR: Spot urine albumin/creatinine ratio; IDMS: Isotope dilution mass spectrometry; CKD-EPI: Chronic kidney disease epidemiology collaboration; SH: Stable with high eGFR; SL: Stable with low eGFR; D: Decreasing eGFR

Acknowledgements

Not applicable.

Financial disclosure

The authors have nothing to disclose.

Conflict of interest

The authors have nothing to disclose.

Declarations

Nothing to declare.

Authors' contributions

Study design: SSH, KHO and CA, Acquisition of Data: SKP, WC, YKO, DWC, YSK, and KHO, Data analysis: EK, SSH and JK, Writing the manuscript: EK and SSH, Review, revision and final approval: SSH and KHO. All authors have read and approved the manuscript.

Funding

This study was supported by the research program funded by the Korea Center for Disease Control and Prevention (2011E3300300, 2012E3301100, 2013E3301600, 2013E3301601, 2013E3301602, and 2016E3300200). The study was supervised by the CKD Advisory Committee composed of members from the KCDC and the Korean Society of Nephrology (KSN, NCT01630486 at http://www.clinicaltrials.gov). The funders had no role in study design, data collection or analysis, decision to publish, or preparation of the manuscript.

Availability of data and materials

The dataset can be available that is within the perspective of the scientific objectives of KNOW-CKD and researchers who approved by the KNOW-CKD investigators can be accessed the data (http://www.know-ckd.org/ckd/main/main.html).

Ethics approval and consent to participate

The study protocol was approved by the Institutional Review Board at each participating clinical center [Seoul National University Hospital (1104–089-359), Seoul Navtional University Bundang Hospital (B-1106/129–008), Yonsei University Severance Hospital (4–2011-0163), Kangbuk Samsung Medical Center (2011–01-076), Seoul St. Mary's Hospital (KC11OIMI0441), Gil Hospital (GIRBA2553), Eulji General Hospital (201105–01), Chonnam National University Hospital (CNUH-2011-092), and Busan Paik Hospital (11–091)]. Written informed consent was obtained from each patient.

Consent for publication

Not applicable.

Competing interests
None.

Author details
[1]Department of Internal Medicine, Ewha Womans University Seoul Hospital, Ewha Womans University College of Medicine, Seoul, South Korea. [2]Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea. [3]Medical Research Collaborating Center, Seoul National University College of Medicine, Seoul, South Korea. [4]Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, South Korea. [5]Department of Internal Medicine, Gachon University, Gil Medical Center, Incheon, South Korea. [6]Department of Internal Medicine, Seoul National University Boramae Medical Center, Seoul, South Korea. [7]Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea. [8]Department of Internal Medicine, The Catholic University of Korea, Seoul St. Mary's Hospital, Seoul, South Korea.

Received: 16 January 2020 Accepted: 6 July 2020
Published online: 16 July 2020

References

1. Levey AS, Fan L, Eckfeldt JH, Inker LA. Cystatin C for glomerular filtration rate estimation: coming of age. Clin Chem. 2014;60(7):916–9.
2. Grubb A, Simonsen O, Sturfelt G, Truedsson L, Thysell H. Serum concentration of cystatin C, factor D and beta 2-microglobulin as a measure of glomerular filtration rate. Acta Med Scand. 1985;218(5):499–503.
3. Simonsen O, Grubb A, Thysell H. The blood serum concentration of cystatin C (gamma-trace) as a measure of the glomerular filtration rate. Scand J Clin Lab Invest. 1985;45(2):97–101.
4. Inker LA, Astor BC, Fox CH, Isakova T, Lash JP, Peralta CA, Kurella Tamura M, Feldman HI. KDOQI US commentary on the 2012 KDIGO clinical practice guideline for the evaluation and management of CKD. Am J Kidney Dis. 2014;63(5):713–35.
5. Al-Aly Z, Balasubramanian S, McDonald JR, Scherrer JF, O'Hare AM. Greater variability in kidney function is associated with an increased risk of death. Kidney Int. 2012;82(11):1208–14.
6. Tielemans SM, Geleijnse JM, Menotti A, Boshuizen HC, Soedamah-Muthu SS, Jacobs DR Jr, Blackburn H, Kromhout D. Ten-year blood pressure trajectories, cardiovascular mortality, and life years lost in 2 extinction cohorts: the Minnesota business and professional men study and the Zutphen study. J Am Heart Assoc. 2015;4(3):e001378.
7. Gill TM, Gahbauer EA, Han L, Allore HG. Trajectories of disability in the last year of life. N Engl J Med. 2010;362(13):1173–80.
8. Lunney JR, Lynn J, Foley DJ, Lipson S, Guralnik JM. Patterns of functional decline at the end of life. Jama. 2003;289(18):2387–92.
9. Kuwahara K, Honda T, Nakagawa T, Yamamoto S, Hayashi T, Mizoue T. Body mass index trajectory patterns and changes in visceral fat and glucose metabolism before the onset of type 2 diabetes. Sci Rep. 2017;7:43521.
10. O'Hare AM, Batten A, Burrows NR, Pavkov ME, Taylor L, Gupta I, Todd-Stenberg J, Maynard C, Rodriguez RA, Murtagh FE, et al. Trajectories of kidney function decline in the 2 years before initiation of long-term dialysis. Am J Kidney Dis. 2012;59(4):513–22.
11. Xie Y, Bowe B, Xian H, Balasubramanian S, Al-Aly Z. Estimated GFR trajectories of people entering CKD stage 4 and subsequent kidney disease outcomes and mortality. Am J Kidney Dis. 2016;68(2):219–28.
12. Oh KH, Park SK, Park HC, Chin HJ, Chae DW, Choi KH, Han SH, Yoo TH, Lee K, Kim YS, et al. KNOW-CKD (KoreaN cohort study for outcome in patients with chronic kidney disease): design and methods. BMC Nephrol. 2014;15:80.
13. Inker LA, Schmid CH, Tighiouart H, Eckfeldt JH, Feldman HI, Greene T, Kusek JW, Manzi J, Van Lente F, Zhang YL, et al. Estimating glomerular filtration rate from serum creatinine and cystatin C. N Engl J Med. 2012;367(1):20–9.
14. Blirup-Jensen S, Grubb A, Lindstrom V, Schmidt C, Althaus H. Standardization of Cystatin C: development of primary and secondary reference preparations. Scand J Clin Lab Invest Suppl. 2008;241:67–70.
15. Levey AS, Stevens LA. Estimating GFR using the CKD epidemiology collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. Am J Kidney Dis. 2010;55(4):622–7.
16. FIRTH D. Bias reduction of maximum likelihood estimates. Biometrika. 1993; 80(1):27–38.
17. Heinze G, Schemper M. A solution to the problem of separation in logistic regression. Stat Med. 2002;21(16):2409–19.
18. Heinze G. A comparative investigation of methods for logistic regression with separated or nearly separated data. Stat Med. 2006;25(24):4216–26.
19. Odden MC, Tager IB, Gansevoort RT, Bakker SJ, Katz R, Fried LF, Newman AB, Canada RB, Harris T, Sarnak MJ, et al. Age and cystatin C in healthy adults: a collaborative study. Nephrol Dial Transplant. 2010;25(2):463–9.
20. Fliser D, Ritz E. Serum cystatin C concentration as a marker of renal dysfunction in the elderly. Am J Kidney Dis. 2001;37(1):79–83.
21. Finney H, Newman DJ, Price CP. Adult reference ranges for serum cystatin C, creatinine and predicted creatinine clearance. Ann Clin Biochem. 2000; 37(Pt 1):49–59.
22. Delanaye P, Cavalier E, Pottel H. Serum Creatinine: not so simple! Nephron. 2017;136(4):302–8.
23. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604–12.
24. Surendar J, Indulekha K, Aravindhan V, Ganesan A, Mohan V. Association of cystatin-C with metabolic syndrome in normal glucose-tolerant subjects (CURES-97). Diabetes Technol Ther. 2010;12(11):907–12.
25. Servais A, Giral P, Bernard M, Bruckert E, Deray G, Isnard Bagnis C. Is serum cystatin-C a reliable marker for metabolic syndrome? Am J Med. 2008; 121(5):426–32.
26. Demircan N, Gurel A, Armutcu F, Unalacak M, Aktunc E, Atmaca H. The evaluation of serum cystatin C, malondialdehyde, and total antioxidant status in patients with metabolic syndrome. Med Sci Monit. 2008;14(2): Cr97–101.
27. Shlipak MG, Matsushita K, Arnlov J, Inker LA, Katz R, Polkinghorne KR, Rothenbacher D, Sarnak MJ, Astor BC, Coresh J, et al. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med. 2013;369(10):932–43.
28. Zahran A, El-Husseini A, Shoker A. Can cystatin C replace creatinine to estimate glomerular filtration rate? A literature review. Am J Nephrol. 2007; 27(2):197–205.
29. Orlando R, Mussap M, Plebani M, Piccoli P, De Martin S, Floreani M, Padrini R, Palatini P. Diagnostic value of plasma cystatin C as a glomerular filtration marker in decompensated liver cirrhosis. Clin Chem. 2002;48(6 Pt 1):850–8.
30. Liu X, Foster MC, Tighiouart H, Anderson AH, Beck GJ, Contreras G, Coresh J, Eckfeldt JH, Feldman HI, Greene T, et al. Non-GFR determinants of low-molecular-weight serum protein filtration markers in CKD. Am J Kidney Dis. 2016;68(6):892–900.
31. Thielemans N, Lauwerys R, Bernard A. Competition between albumin and low-molecular-weight proteins for renal tubular uptake in experimental nephropathies. Nephron. 1994;66(4):453–8.
32. Tkaczyk M, Nowicki M, Lukamowicz J. Increased cystatin C concentration in urine of nephrotic children. Pediatr Nephrol. 2004;19(11):1278–80.
33. Freedman DS, Wang J, Maynard LM, Thornton JC, Mei Z, Pierson RN, Dietz WH, Horlick M. Relation of BMI to fat and fat-free mass among children and adolescents. Int J Obes (Lond). 29(1):2005, 1–8.
34. Gallagher D, Visser M, Sepulveda D, Pierson RN, Harris T, Heymsfield SB. How useful is body mass index for comparison of body fatness across age, sex, and ethnic groups? Am J Epidemiol. 1996;143(3):228–39.
35. Wang J, Thornton JC, Russell M, Burastero S, Heymsfield S, Pierson RN Jr. Asians have lower body mass index (BMI) but higher percent body fat than do whites: comparisons of anthropometric measurements. Am J Clin Nutr. 1994;60(1):23–8.

Publisher's Note