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

Eunjeong Kang1†, Seung Seok Han2†, Jayoun Kim3, Sue Kyung Park4, Wookyung Chung5, Yun Kyu Oh6, Dong-Wan Chae7, Yong-Soo Kim8, Curie Ahn2 and Kook-Hwan Oh2*

Abstract

Background: Serum creatinine (Cr) and cystatin C (CysC) can both be used to estimate glomerular filtration rate (eGFRCr 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 eGFRCr 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 eGFRCr were classified into three groups: two groups with stable eGFRCr (stable with high eGFRCr and stable with low eGFRCr) and one group with decreasing eGFRCr. 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 eGFRCr but stable & low eGFR CysC; n = 55) were younger and had greater proteinuria values than the agreement group (stable & low eGFRCr 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 eGFRCr 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
† Eunjeong Kang and Seung Seok Han co-first authors
2Department 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

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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\textsubscript{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\textsubscript{CysC}) may reflect GFR more accurately than eGFR with Cr (eGFR\textsubscript{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\textsubscript{Cr} as an initial assessment of renal function, and eGFR\textsubscript{CysC} as a confirmation of CKD in certain circumstances when eGFR\textsubscript{Cr} is less accurate, with an evidence level of 2B. eGFR\textsubscript{CysC} may be also used in adult patients with eGFR\textsubscript{Cr} of 45–59 ml/min/1.73 m\textsuperscript{2} who do not have markers of kidney damage, with an evidence level of 2C [4]. Nevertheless, the utility of eGFR\textsubscript{CysC} and conditions under which eGFR\textsubscript{CysC} differs from eGFR\textsubscript{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\textsubscript{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\textsubscript{CysC} and we identified certain patients had a discrepancy trend between eGFR\textsubscript{Cr} and eGFR\textsubscript{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\textsubscript{Cr} and eGFR\textsubscript{CysC} ≥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\textsubscript{Cr} and eGFR\textsubscript{CysC} ≥4 times (Fig. 1).

![Fig. 1 Flow diagram of the study. eGFR, estimated glomerular filtration rate; Cr, creatinine; CysC, cystatin C](image-url)
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.

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/m²)                | 24.5 ± 3.4       |
| Body surface area (m²)                 | 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 m²)                  |                  |
| eGFR<sub>cr</sub>                      | 58.5 ± 28.9      |
| eGFR<sub>cysc</sub>                    | 58.4 ± 31.2      |
| eGFR<sub>cr<cysc</sub>                 | 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

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 $\chi^2$ 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 eGFRCr 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<sub>cr<cysc</sub>) 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 (KC11O1MI0441), 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 $53.2 \pm 12.1$ 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 $58.5 \pm 28.9$ mL/min/1.73 m$^2$, $58.4 \pm 31.2$ mL/min/1.73 m$^2$, and $58.0 \pm 30.6$ 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 eGFR$_{Cr}$ (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](image_url)  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.
were small numbers of patients in the D and SH groups with eGFR\textsubscript{CysC}.

**Conditions related to discrepant trends between eGFR\textsubscript{Cr} and eGFR\textsubscript{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\textsubscript{Cr}, eGFR\textsubscript{CysC}, and eGFR\textsubscript{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\textsubscript{Cr} and eGFR\textsubscript{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\textsubscript{Cr}, eGFR\textsubscript{CysC}, and eGFR\textsubscript{CrCysC} were 57.5 ± 29.6 mL/min/1.73 m\textsuperscript{2}, 57.1 ± 31.4 mL/min/1.73 m\textsuperscript{2}, and 56.9 ± 31.1 mL/min/1.73 m\textsuperscript{2}, respectively.

The trajectory patterns of eGFR\textsubscript{Cr} and eGFR\textsubscript{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).
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 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 (%) |                     |                     |        |
| Low (53)                 | 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/m²)  | 24.4 ± 4.0           | 24.7 ± 3.3          | 0.514  |
| Body surface area (m²)   | 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 (%) | 81.8                 | 80.3                | 0.924  |
| eGFR (ml/min/1.73 m²)    |                      |                     |        |
| 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                |        |

**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.
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

### Table 3: Analysis to identify conditions related to discrepant trends of eGFR_Cr and eGFR_CysC

| Variables                        | Model 1 OR (95% CI) | P       | Model 2 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 (53)                         | 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           |         |                     |         |
| 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_Cr_CysC                     | 1.07 (1.04–1.10)    | < 0.001 | 1.07 (1.05–1.09)    | < 0.001 |

**Model 1:** Adjusted for age, sex, eGFR_Cr-CysC 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
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 ± 3.4 kg/m², which was lower than that of another CKD cohort (32.1 ± 7.9 kg/m² 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<sub>Cr</sub> 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<sub>Cr</sub> and eGFR<sub>CysC</sub>. 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<sub>CysC</sub>, our results may constitute the basis of future updates.

Conclusions
In conclusion, we identify conditions related to discrepant trends of eGFR<sub>Cr</sub> and eGFR<sub>CysC</sub>. 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; SL: Stable with high eGFR; D: Decreasing eGFR

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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.

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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.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 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 (KC1101M0044), 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
1Department of Internal Medicine, Ewha Womans University Seoul Hospital, Ewha Womans University College of Medicine, Seoul, South Korea.
2Department of Internal Medicine, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, South Korea.
3Medical Research Collaborating Center, Seoul National University College of Medicine, Seoul, South Korea.
4Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, South Korea.
5Department of Internal Medicine, Gachon University Gil Medical Center, Incheon, South Korea.
6Department of Internal Medicine, Seoul National University Boramae Medical Center, Seoul, South Korea.
7Department of Internal Medicine, Seoul National University Bundang Hospital, Seongnam, South Korea.
8Department of Internal Medicine, The Catholic University of Korea, Seoul St. Mary’s Hospital, Seoul, South Korea.

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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, Thyssell 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, Thyssell 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):713–45.
5. Al-Aly Z, Balsabramanian S, McDonald JR, Scherer JR. 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 extraction cohorts: the Minnesota business and professional men study and the Zutphen study. J Am Heart Assoc. 2015;4(3):e003138.
7. Gill TM, Gahbauer EA, Han L, Allone 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. Kuswahana 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, Paikov ME, Taylor L, Gupta I, Todd-Stephens J, Maynard C, Rodriguez RA, Murtugh 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, Bowie B, Xian H, Balsabramanian 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 HL, 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. Blilou-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. Heine G, Schepfer M. A solution to the problem of separation in logistic regression. Stat Med. 2002;21(16):2409–19.
18. Heine 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. Fisser 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, Portel 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):664–12.
24. Suredenz J, Indulekh K, Aravinth 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, Girai 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, Unalacik 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): CR9–101.
27. Shilpak MG, Matsushita K, Arnlov J, Inker LA, Katz R, Polkinghorne KR, Rotenberg 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(12):932–43.
28. Zahrans 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, Florenni M, Padinri 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. Tkocz M, Nowicki M, Lukarnovicz J. Increased cystatin C concentration in urine of nephrotic children. Pediatri 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.

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