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Original Article

# Cystatin C to Creatinine-Based Estimated Glomerular Filtration Rate Ratio Predicts Mortality and Dialysis Risk in Older Patients with Chronic Kidney Disease

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SUMMARY

*Background:* This study investigated the discordance between cystatin C- and creatinine-based estimates of glomerular filtration rate (eGFR) (EKFCcys/EKFCcre) to predict adverse outcomes in older adults.
*Methods:* Older patients with chronic kidney disease (CKD) (mean age 76.7) from 2018 to 2020 were enrolled. Cystatin C, creatinine, and clinical data were assessed at baseline and followed up until death, dialysis, or administrative censorship. The subjects were stratified according to tertiles of the EKFCcys/EKFCcre ratio. The subhazard ratios (sHR) and time ratios were measured using competing risk regression and the cause-specific accelerated failure time (CS-AFT) model. Sensitivity analysis including models with cystatin-to-creatinine (Cys/Cre) ratios was also performed.
*Results:* In 369 older patients, the incidence rates of mortality and dialysis were 2.7 and 7.0 per 1000 patient-months, respectively. The incidences of mortality and dialysis were higher in the lowest tertile (0.9 vs. 4.2 per 1000 patient-month and 6.1 vs. 7.0 per 1000 patient-months, respectively) than in the highest tertile group. In the competing risk regression, the lowest tertile had a higher risk of mortality (sHR [95% CI] = 6.78 [2.34–19.68], $p < 0.05$). In CS-AFT, compared to the highest tertile group, the lowest tertile group exhibited an altered median survival time of 0.27 (0.11–0.68) and 0.36 (0.20–0.67), which is approximately 73% and 64% decrease in median survival time to mortality and dialysis, respectively (ps < 0.05). The results of the sensitivity tests were consistent.
*Conclusion:* The lowest tertile of the cystatin C-to-creatinine based eGFR ratio is a risk factor for clinical outcomes in older patients with CKD.



## 1. Introduction

Chronic kidney disease (CKD) is a global public health concern. The risks of mortality, morbidity, and hospitalization are associated with CKD stage.[1] The current CKD staging is predominantly based on the estimated glomerular filtration rate (eGFR) and proteinuria. However, creatinine-based eGFR, the most common method used to estimate GFR, is inaccurate in several clinical settings.[2] The creatinine levels have been shown to be influenced by non-GFR determinants, including extrarenal excretion of creatinine by the gastrointestinal tract, muscle mass and dietary intake, as well as organic anion transporters.[3] Several middle-molecular-weight proteins, such as factor D, beta-2 microglobulin, and cystatin C, have been used to measure GFR.[4] The correlation between the measured GFR and eGFR, combined with cystatin C and creatinine, was better than that with creatinine alone.[2,5] The cystatin C-based estimated glomerular eGFR may be a confirmatory test for specific circumferences. The renal clearance of creatinine and cystatin C is different owing to the differences in their molecular weights. Several factors other than GFR have been shown to affect cystatin C levels, including inflammatory status, nutritional status, diabetes, and hyperthyroidism.[6] Increased thickness of the glomerular basement membrane or shrinkage of glomerular filtration pores negatively affects cystatin C filtration, whereas creatinine filtration remains relatively unaffected.

Shrunken pore syndrome (SPS) is a phenotype of renal dysfunction assessed using the ratio of cystatin C-based to creatinine-based eGFR.[8] The cystatin-to-creatinine (Cys/Cre) ratio, regarded as a sarcopenia index, is negatively associated with mortality, whereas the cystatin C-to-creatinine-based eGFR ratio is positively correlated with mortality.[8,9] SPS has been reported as a risk factor for mortality, osteoporosis, heart failure, and severe GFR decline.[7,8,10–12] This has been observed in healthy populations, pregnant women, critically ill patients, inpatients, and after cardiac surgery.[7,8,13,14] Because heart failure and osteoporosis are common in older individuals, we postulate that SPS is highly prevalent in this population. Although SPS is associated with a high risk of mortality, the mechanisms underlying this association remain unclear. Previous studies have demonstrated an association between SPS and adverse events by using a proportional hazard model.[10,11,15,16] Other hazard models were used because the proportional hazard assumption criteria were not satisfied.

This study aimed to evaluate the association between cystatin C- and creatinine-based eGFR ratios and adverse events in older patients, using competing risk regression and a cause-specific accelerated failure time model (CS-AFT). We analyzed multiple risk

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factors for death or the need for dialysis at baseline, including demographic data, underlying diseases, and laboratory data, in a regional hospital. We compared these results with those of the Cys/Cre ratio. The impact of these factors on mortality or dialysis initiation was assessed for three years.

## 2. Materials and methods

### *2.1. Participants, study design, and data source*

This observational cohort study enrolled 939 adults from the pre-end-stage renal disease (ESRD) care plan, a project of the National Health Insurance Program (NHIP), to improve the quality of care for end stage renal disease (ESRD) in Taoyuan General Hospital since 2013. Creatinine is a major biomarker of kidney function, and cystatin C testing was introduced in 2018. Patients with an estimated glomerular filtration rate ($eGFR_{MDRD}$) < 60 ml/min/ 1.73 $m^2$ were enrolled in the pre-ESRD care plan. We retrospectively reviewed the medical records of the enrolled patients, including their laboratory and demographic data (age, sex, body weight, and height), medications, and outcomes. All disease records were coded based on the International Classification of Diseases, 10th Version, Clinical Modification (ICD-10-CM) in the electronic medical records of the Taoyuan General Hospital. Care, examination, and procedure codes were obtained. The baseline period was defined as 90 days after enrollment. Cystatin C levels were measured at the baseline. The end of the baseline period was the initiation of the cohort period and was followed until the date of dialysis commencement, mortality, or administrative censoring on December 31, 2020. Patients who underwent cystatin C and creatinine tests on the same day were included in this study. Those without cystatin C measurement (n = 420), length of follow-up of less than 28 days (n = 31), history of AKI (ICD-10-CM: N17.X) (n = 39) during the cohort period and those younger than 65 years (n = 80) at baseline were excluded (Figure 1). Consequently, a total of 369 eligible patients were included in the analysis.

### *2.2. Ethics*

This study adhered to the Declaration of Helsinki (2000) of the World Medical Association, and the study protocol was reviewed and approved by the Institutional Review Board of Taoyuan General Hospital (TYGH.109013).

### *2.3. Outcome ascertainment*

Demographic data, comorbidities, biochemical data, and date of death were obtained from electronic medical records. Dialysis was confirmed on the basis of the codes for ambulatory care expenditure by visit. Participants who were lost to follow-up without confirmation of death were censored at the last follow-up date. Participants who survived the administration censoring date were censored on December 31, 2020.

### *2.4. Study exposure*

The study exposure was the discordance between cystatin C- and creatinine-based eGFR, as reflected by the EKFCcys/EKFCcre ratio. These equations were developed by the European Kidney Func-

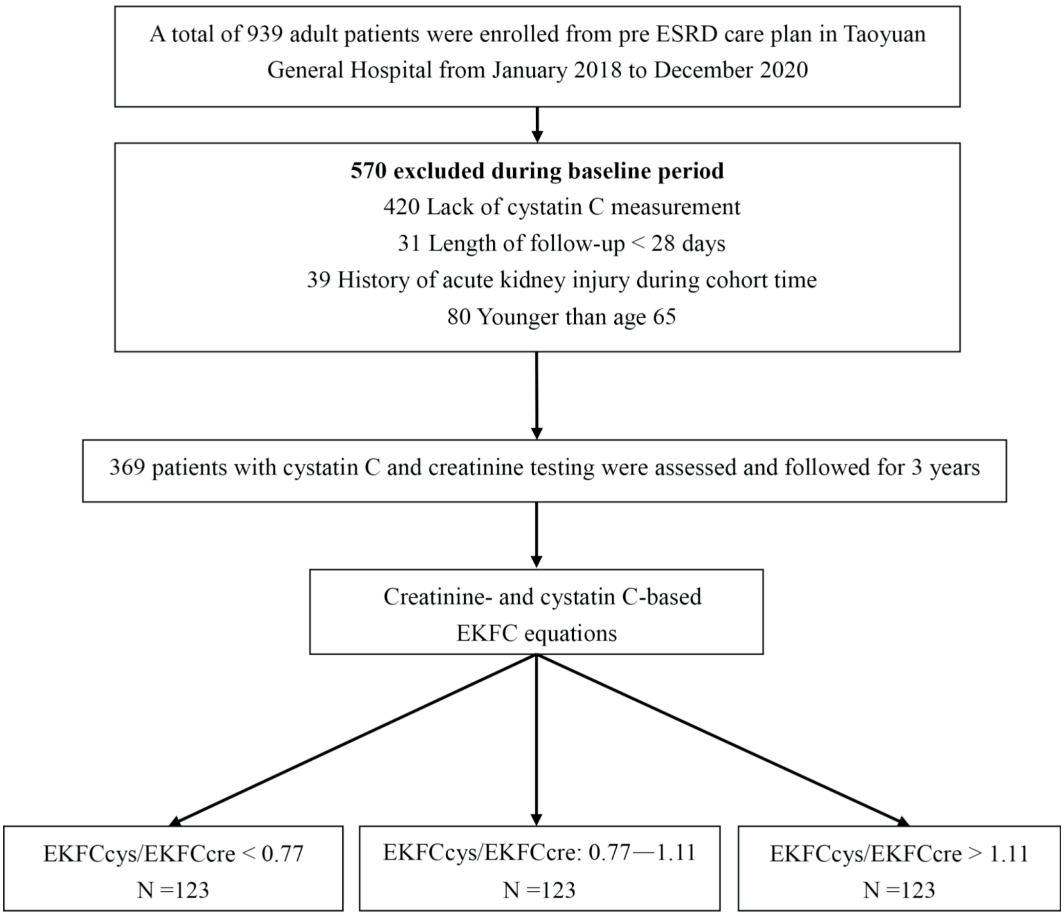


**Figure 1.** Dataflow. Abbreviations: EKFCcre & EKFCcys: creatinine- and cystatin-based equations, developed by European Kidney Function Consortium; ESRD: end stage renal disease.

tion Consortium to estimate GFR.[17] No consensus on the cutoff ratio of EKFCcys/EKFCcre or the normalization constant for cystatin C (Qcys) has been reported. The study population was categorized into three groups according to tertiles of the EKFCcy/EKFCcre ratio. Qcys was defined as 0.82 according to a previous study.[18] The difference between the cystatin C- and creatinine-based eGFR, abbreviated as GFRdiff, was also calculated.

### *2.5. Comorbidities ascertainment and laboratory data measurement*

Laboratory tests were performed by the Department of Laboratory Medicine at Taoyuan General Hospital, using standardized and automated methods. Hemoglobin was obtained by direct current detection using a microscope. Serum creatinine levels were measured using an enzymatic IDMS traceable method, whereas cystatin C levels were measured using a latex-enhanced immunoturbidimetric assay (ALINITY; Abbott Laboratories, Irving, Texas, USA). Serum albumin levels were determined using the bromocresol green assay. Cholesterol and the urine protein-to-creatinine ratio (UPCR) were also obtained. Diabetes mellitus (DM) was diagnosed according to ICD-10-CM codes E08–E14 and hypertension (HTN) was diagnosed according to ICD-10-CM codes I10–I16. Renin-angiotensin system blockade (RASb), diuretics, and steroids were also recorded according to the prescription claims data.

### *2.6. Statistical analysis*

Continuous variables with a normal distribution are summarized as mean $\pm$ SD unless otherwise stated. Variables with a non-normal distribution are expressed as medians (interquartile range [IQR]). Normality was assessed using the Kolmogorov–Smirnov test. Pearson's chi-square test, one-way analysis of variance (ANOVA), or the Kruskal–Wallis test was used to determine the differences among the three groups. The discordance and correlation between the eGFR estimations are also shown. As mortality may be a competing event for other outcomes, we conducted a competing risk regression for mortality and dialysis using Fine and Gray's proportional sub-hazard models. To confirm the robustness of this conclusion, we compared Cys/Cre and EKFCcys/EKFCcre using the area under the receiver operating characteristic curve (AUROC) and replaced creatinine with EKFCcre as a confounder in the sensitivity analysis. Once the proportional hazard assumptions were not satisfied for all confounders, the CS-AFT was introduced.[19] AFT is a parametric estimate, whereas the proportional hazard (COX) model is a semi-parametric estimate. The AFT hazard is assumed to have a continuous distribution, such as a log-normal, exponential, general gamma, or Weibull distribution.[19] Based on the information criterion, the Weibull distribution is preferred. As competing events may accelerate or decelerate time-to-event, we conducted a CS-AFT to assess the association between the parameters and time-to-event. All statistical analyses and plots were performed using STATA 16.0 (StataCorp. College Station, Texus, USA) and "R" software version 4.3.1. Statistical significance was set at $p < 0.05$. significant.

## 3. Results

### *3.1. Demographical characteristics and clinical outcomes*

The cohort of the 369 older subjects were followed up for a median of 20.7 months, ranging from 1 to 36.0 months, after the baseline period. The mean age of participants was 76.7 years. The incidence of all-cause mortality and dialysis commencement were 2.7 and 7.0 per 1000 patient-month. The median time to mortality and dialysis was 25.3 and 16.8 months. The ratio of EKFCcys/EKFCcre ranged from 0.28 to 3.03, whereas the correlation between two estimators was fair (r = 0.428) The GFRdiff was -2.7 (20.5 to -25.9) ml/min/1.73 $m^2$ (Figure 2). The agreement between EKFCcys and EKFCcre was good, as only 4.8% were outliers, according to the limits of agreement.

### *3.2. Comparisons among 3 groups with different ratio of cystatin C- and creatinine-based equations*

Table 1 shows comparisons among the three groups with different ratios of EKFCcys/EKFCcre. Compared to highest tertile, the lowest tertile presented higher levels of cystatin C (2.44 mg/L vs. 3.04 mg/L), EKFCcre (16.2 ml/min/1.73 $m^2$ vs. 35.9 mL/min/1.73 $m^2$), Cys/Cre ratio (0.74 vs. 1.62) and higher proportion of CKD stage 3 (17.9% vs. 39.0%). In addition, the lowest tertile had lower creatinine levels (0.30 mmol/L vs. 0.17 mmol/L), EKFCcys (24.6 ml/min/1.73 $m^2$ vs. 19.8 mL/min/1.73 $m^2$) and lesser proportion of male (59.3% vs. 26.8%), whereas the incidence of mortality and dialysis were higher in the lowest tertile (0.9 vs. 4.2 per 1000 patient-month, 6.1 vs. 7.0 per 1000 patient-months). The GFRdiff was minimal in 2nd tertile group (-2.2 mL/min/1.73 $m^2$) ($p < 0.01$), and the GFRdiff was minimal in the second tertile (GFRdiff: -13.9 mL/min/1.73 $m^2$ vs. 7.3 mL/min/1.73 $m^2$) (ps < 0.01). There were no differences among the three

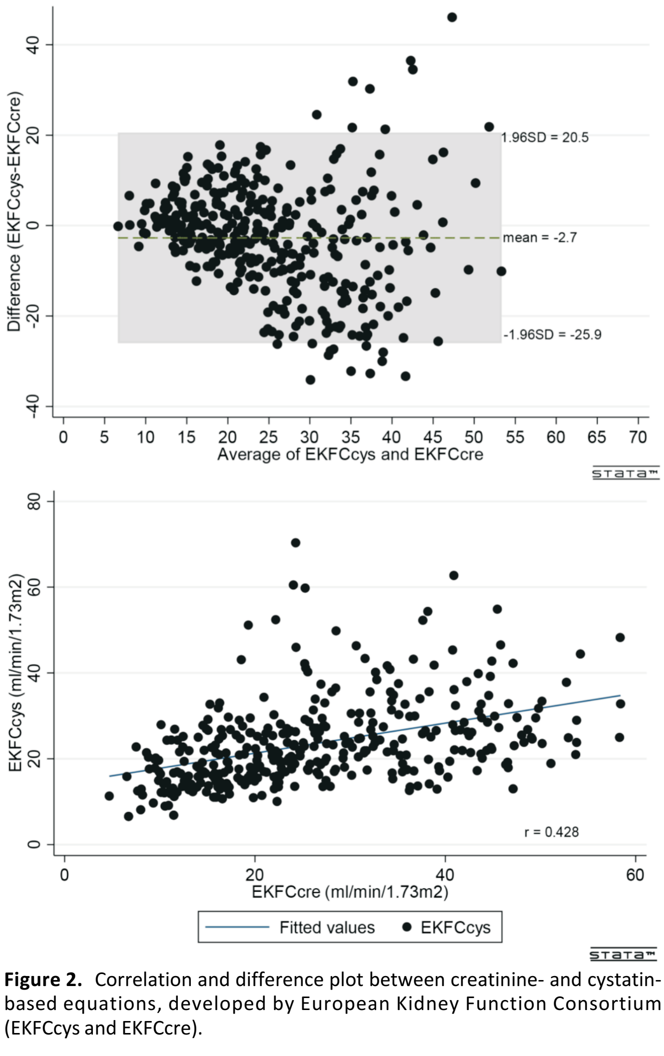


**Figure 2.** Correlation and difference plot between creatinine- and cystatin-based equations, developed by European Kidney Function Consortium (EKFCcys and EKFCcre).

groups in terms of age, BMI, length of follow-up, laboratory data such as albumin, UPCR, hemoglobin, cholesterol, the proportion of DM and HTN, and the use of diuretics, RASb, and steroids (Table 1).

### *3.3. The predictors of mortality and dialysis as well as time to outcome*

In the competing risk regression model, old age, male sex, and the lowest tertile were predictors of mortality (sHR [95% CI] = 1.08 [1.01–1.15], 4.01 [1.21–13.25], and 6.78 [2.34–19.68]), whereas high creatinine and UPCR were predictors of dialysis (sHR [95% CI] = 2.11 [1.67–2.63 and 1.39 [1.15–1.68], respectively) (Table 2). In CS-AFT model for mortality and dialysis, the lowest tertile group compared to the highest tertile group changed median survival time by 0.27 (0.11–0.68) and 0.36 (0.20–0.67), approximately 73% and 64% decrease in median survival time to mortality and dialysis (Table 3). The cumulative incidence functions for mortality and dialysis among the three groups using competing risk regression are shown in Figure 3. In the sensitivity test, the lowest tertile remained a significant predictor of mortality even after adjusting for EKFCcre (sHR [95% CI]

**Table 1**
Baseline characteristics of study population.

| Parameters | $1^{st}$ tertile<br>Ratio < 0.77<br>N = 123 | $2^{nd}$ tertile<br>Ratio: 0.77–1.11<br>N = 123 | $3^{rd}$ tertile<br>Ratio > 1.11<br>N = 123 | *p* value |
|---|---|---|---|---|
| Age (year) | 76.1 ± 8.7 | 77.5 ± 9.0 | 76.4 ± 8.7 | 0.441 |
| Male (%) | 33 (26.8) | 62 (50.4) | 73 (59.3) | < 0.001* |
| BMI (Kg/$m^2$) | 24.9 ± 4.4 | 24.7 ± 3.8 | 24.2 ± 3.4 | 0.335 |
| CKD stage 3/4/5 | 48/42/33 | 27/44/52 | 22/40/61 | < 0.001* |
| Length of follow-up (months) | 19.5 (7.5–26.7) | 23.9 (13.6–27.4) | 19.6 (12.2–26.5) | 0.148 |
| DM (n) | 75 | 73 | 58 | 0.058 |
| Hypertension (n) | 80 | 91 | 95 | 0.087 |
| Use of diuretics (n) | 24 | 35 | 41 | 0.051 |
| Use of steroid (n) | 19 | 21 | 14 | 0.429 |
| Use of RASb | 71 | 75 | 61 | 0.180 |
| Laboratory data | | | | |
| Albumin (g/L) | 41.0 ± 4.0 | 40.8 ± 4.3 | 40.6 ± 3.9 | 0.708 |
| Creatinine (mmol/L) | 0.17 ± 0.06 | 0.20 ± 0.10 | 0.30 ± 0.13 | < 0.001* |
| Cystatin C (mg/L) | 3.04 ± 0.95 | 2.83 ± 1.55 | 2.44 ± 0.94 | < 0.001* |
| Hemoglobin (g/L) | 108.3 ± 17.7 | 111.7 ± 22.5 | 107.1 ± 19.5 | 0.182 |
| Cholesterol (mmol/L) | 5.16 ± 1.20 | 5.01 ± 1.05 | 4.80 ± 1.17 | 0.050 |
| UPCR (mg/mg) | 1.58 ± 1.80 | 1.74 ± 1.79 | 1.62 ± 1.64 | 0.759 |
| GFR estimation | | | | |
| EKFCcre (ml/min/1.73 $m^2$) | 35.9 (26.9, 43.8) | 23.5 (17.2, 31.1) | 16.2 (11.8, 22.6) | < 0.001* |
| EKFCcys (ml/min/1.73 $m^2$) | 19.8 (16.0, 24.6) | 21.3 (15.6, 28.4) | 24.6 (18.2, 31.8) | 0.002* |
| EKFCcys/EKFCcre (%) | 60.9 (49.4, 69.0) | 91.2 (83.5, 99.5) | 142.0 (122.6, 181.2) | < 0.001* |
| GFRdiff (ml/min/1.73 $m^2$) | -13.9 (-9.0, -21.8) | -2.2 (-3.9, -0.1) | 7.3 (3.9, 12.1) | < 0.001* |
| Cys/Cre | 1.62 (1.33, 1.87) | 1.14 (1.05, 1.23) | 0.74 (0.61, 0.87) | 0.001* |
| Outcome | | | | |
| Death (n) | 9 | 8 | 2 | 0.130 |
| Dialysis commencement (n) | 15 | 21 | 14 | |

Data were percentage, mean ± standard deviation, median (interquartile range (IQR)).
* $p < 0.05$, Ratio = EKFCcys/EKFCcre.
Abbreviations: BMI, body-mass index; Cys/Cre, cystatin-to-creatinine ratio; DM, diabetes mellitus; EKFCcre & EKFCcys: creatinine- and cystatin-based equations, developed by European Kidney Function Consortium; GFR, glomerular filtration rate; RASb, renin-angiotensin-aldosterone blocker; UPCR, urine protein-to-creatinine ratio.
GFRdiff = EKFCcys – EKFCcre.

**Table 2**
Multivariate analysis among risk factors and mortality and dialysis using competing risk regression.

| Parameters | Mortality | | Dialysis | |
|---|---|---|---|---|
| | SHR (95% CI) | p value | SHR (95% CI) | p value |
| Age (per year) | 1.08 (1.01–1.15) | 0.020* | 1.01 (0.97–1.05) | 0.576 |
| Male (vs. Female) | 4.01 (1.21–13.25) | 0.023* | 1.52 (0.73–3.18) | 0.262 |
| BMI (per Kg/$m^2$) | 0.95 (0.82–1.19) | 0.568 | 0.98 (0.89–1.07) | 0.614 |
| DM (vs. Non-DM) | 1.93 (0.67–5.55) | 0.221 | 1.36 (0.65–2.85) | 0.416 |
| HTN (vs. non-HTN) | 0.40 (0.12–1.33) | 0.136 | 1.49 (0.44–5.11) | 0.519 |
| Tertile 1 vs. 3 | 6.78 (2.34–19.68) | 0.006* | 4.26 (0.81–22.50) | 0.068 |
| Tertile 2 vs. 3 | 3.06 (1.34–6.96) | 0.023* | 2.86 (0.70–11.97) | 0.096 |
| Albumin (per g/L) | 0.99 (0.84–1.18) | 0.932 | 1.01 (0.91–1.11) | 0.900 |
| Hemoglobin (per g/L) | 0.99 (0.97–1.03) | 0.949 | 1.01 (0.99–1.03) | 0.348 |
| Creatinine (per 0.1 mmol/L) | 1.58 (0.91–2.76) | 0.104 | 2.11 (1.67–2.63) | < 0.001* |
| Cholesterol (per mmol/L) | 1.03 (0.61–1.75) | 0.890 | 0.89 (0.67–1.18) | 0.420 |
| UPCR (per mg/mg) | 1.16 (0.79–1.70) | 0.436 | 1.39 (1.15–1.68) | < 0.001* |

* $p < 0.05$.
Abbreviations: BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; sHR, subhazard ratio; UPCR, urine protein-to-creatinine ratio.

**Table 3**
Multivariate analysis using cause-specific accelerated failure time with Weibull distribution for clinical outcome.

| Parameters | Mortality | | Dialysis | |
|---|---|---|---|---|
| | Time ratio (95% CI) | p value | Time ratio (95% CI) | p value |
| Age (per year) | 0.97 (0.95–0.99) | 0.033* | 0.99 (0.97–1.01) | 0.497 |
| Male (vs. Female) | 1.78 (1.08–2.93) | 0.024* | 1.22 (0.85–1.76) | 0.280 |
| BMI (per Kg/m$^2$) | 1.01 (0.97–1.03) | 0.628 | 1.01 (0.96–1.05) | 0.628 |
| DM (vs. non-DM) | 0.82 (0.60–1.24) | 0.324 | 0.88 (0.61–1.27) | 0.501 |
| HTN (vs. non-HTN) | 1.27 (0.82–1.98) | 0.278 | 0.79 (0.43–1.46) | 0.459 |
| Tertile 1 vs. 3 | 0.27 (0.11–0.68) | 0.005* | 0.36 (0.20–0.67) | 0.001* |
| Tertile 2 vs. 3 | 0.43 (0.20–0.94) | 0.034* | 0.45 (0.28–0.73) | 0.001* |
| Albumin (per g/L) | 0.99 (0.94–1.06) | 0.966 | 0.99 (0.95–1.04) | 0.918 |
| Hemoglobin (per g/L) | 1.00 (0.99–1.01) | 0.875 | 0.99 (0.98–1.00) | 0.343 |
| Creatinine (per 0.1 mmol/L) | 0.81 (0.66–0.99) | 0.047* | 0.69 (0.61–0.78) | < 0.001* |
| Cholesterol (per mmol/L) | 1.00 (0.82–1.22) | 0.998 | 1.06 (0.92–1.22) | 0.382 |
| UPCR (per mg/mg) | 0.95 (0.82–1.09) | 0.462 | 0.84 (0.76–0.92) | < 0.001* |

* p < 0.05.
BMI, body mass index; DM, diabetes mellitus; HTN, hypertension; UPCR, urine protein-to-creatinine ratio.

= 4.71 [2.08–10.70], p = 0.006). The Cys/Cre ratio was also included in this model. The Cys/Cre ratio was negatively associated with mortality, whereas the highest tertile of Cre/Cys was a significant predictor of mortality and dialysis (sHR [95%CI] = 5.59 [2.20–14.20] and 7.84 [2.64–23.30], p < 0.01) (Supplementary data). The discriminative power of EKFCcys/EKFCcre and Cre/Cys for mortality was also investigated.

The AUROC for EKFCcys/EKFCcre and Cre/Cys were 0.622 and 0.677, respectively (p < 0.05). EKFCcys/EKFCcre was not inferior to Cre/Cys in predicting mortality (chi-square = 0.285, p = 0.593) (Figure 4).

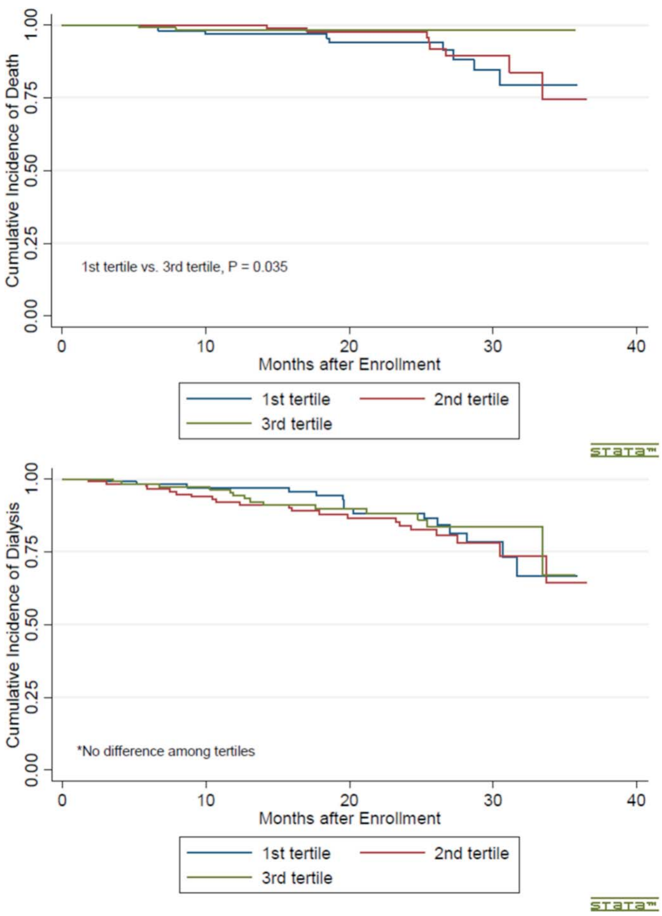


Figure 3. Cumulative survival curve for (A) Mortality and (B) Dialysis among 3 groups using competing risk regression.

## 4. Discussion

This observational cohort study demonstrated that the cystatin C- to creatinine-based eGFR ratio could predict mortality and dialysis risk in older patients with CKD. The correlation between creatinine- and cystatin C-based eGFR, according to EKFC equations, were fair (r = 0.428) with mean difference up to -2.7 (20.5 to -25.9) mL/min/1.73 m$^2$. The lowest tertile of the EKFCcy/EKFCcre ratio was a risk factor for mortality. Patients with a lower ratio were also prone to commence dialysis earlier.

A significantly low cystatin C-to-creatinine-based eGFR ratio, defined as SPS, has been reported as a predictor of mortality, dialysis, and heart failure.[7,8,10–12] The accumulation of atherosclerosis-promoting proteins may explain this phenomenon.[20] Heme oxygenase-I, hydroxyacid oxidase-1, and osteoprotegerin are common CVD-related proteins upregulated during SPS.[20–22] Inflammatory cytokines, such as CXCL-9, CXCL-10, IL-10, and IL-6, are also elevated in SPS.[23] In addition, adrenomedullin and tumor necrosis factor receptor superfamily 9 and 11 (TNFRSF 9 and 11) levels are relatively high in patients with SPS, whereas T-cell immunoglobulin and mucin domain protein 1 and 4 (TIM-1 and 4) levels are relatively low.[21] TNFRSF is considered a checkpoint regulator that promotes atherosclerosis and vascular inflammation,[20] whereas TIM-1 & 4 mediated

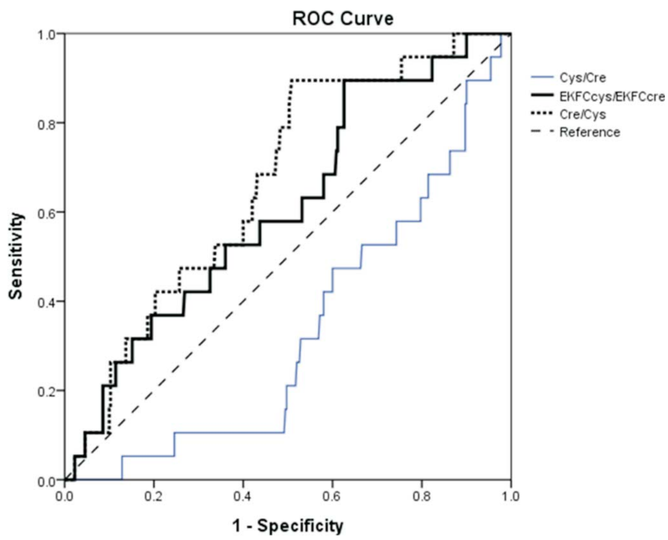


Figure 4. The discriminative power among creatinine- to cystatin-based equations (EKFCcys /EKFCcre), creatinine-to-cystatin C (Cre/Cys), and cystatin C-to-creatinine (Cys/Cre) ratio in predicting mortality.

ASCVD by balancing Th1 and Th2 cells.[19] Adrenomedullin, a peptide hormone secreted in response to cell ischemia, is produced in association with carotid plaques and intimal media thickness.[24] This might explain why SPS was associated with a higher risk of mortality than CKD as defined by creatinine levels. Factors affecting cystatin levels include age, sex, eGFR, muscle mass, and nutritional and inflammatory statuses. Adjustment for these factors has been suggested to have a greater effect on their association with creatinine than cystatin C[6]. Cystatin C measurement is recommended when the creatinine levels are considered inaccurate. In this study, a large discordance between EKFCcys and EKFCcre was observed in older individuals. A lower EKFCcys/EKFCcre ratio is associated with a higher risk of mortality.

The prevalence of SPS varies according to the cutoff ratio of the cystatin C-to-creatinine based equation, methods of GFR estimation, and CKD stage, ranging from 0.2% to 36%.[25] The most common cutoff ratio ranges from 0.6 to 0.7.[6,20] As creatinine may underestimate the GFR in the older patients, we estimated the GFR using a more reliable and well-validated equation after dividing creatinine and cystatin C by unique normalization factors (Qcre and Qcys).[17,26,27] Although the CKD-EPI equations were more common than the EKFC equations, there were still several differences. The EKFC equation has less bias in older individuals than the CKD-EPI equations; therefore, classification of the cystatin C- to creatinine-based GFR ratio is more reliable.[26] The EKFC equations display higher sensitivity and a larger AUROC for mortality than the CKD-EPI equations.[17] It also provided better reclassification than the CKD-EPI equations for the risk of mortality in the general non-Black and Chinese populations.[17,28] In addition, the EKFC equation was developed by combining the advantages of the CKD-EPI and the full-age spectrum equation (FAS). The FAS provided relatively more accurate estimates of GFR than the CKD-EPI in older adults. The EKFC equation may be a better option than the CKD-EPI equation in older adults.[29]

In this study, the proportion of male was lower in the lowest tertile group. The sex difference in vascular endothelial cell response may be explanatory.[30] Estrogen promoted endothelium healing and protected the integrity of endothelial barrier than androgen did;[30] thus, the retention of medium- to large-sized molecules was more common in female and the proportion of female was higher in the low EKFCcys/EKFCcre group. We also compared the Cys/Cre and EKFCcys/EKFCcre levels to predict mortality. As the Cys/Cre ratio is a surrogate for sarcopenia, it can undoubtedly predict mortality.[9] Muscle mass confounds the association between biomarkers and clinical outcome were confounded by muscle mass.[3] Although we lacked muscle mass data, we adjusted for BMI using an acceptable surrogate. It is an early manifestation or compensatory change in kidney injury, with swelling of glomerular endothelial cells, followed by shrinkage of the glomerular filtration pores.[25] The filtration of medium- to large-sized molecules, but not creatinine, was reduced in SPS. Although reversible, early identification of patients with normal creatinine levels and elevated cystatin C levels is crucial. In addition, more than 20 larger molecules were retained in SPS, leading to high protein-to-creatinine ratios. These unrelated proteins have different functions and are encoded on different chromosomes. It is less likely that elevated protein levels are co-regulated by non-renal mechanisms.[12,20] Furthermore, SPS disrupts nitro oxide metabolism, which is associated with decompensated heart failure.[9] It is associated with risk factors for CKD progression such as deterioration of heart failure, cardiovascular disease, and possibly the occurrence of glomerulosclerosis with nephron loss, suggesting its predictive power for rapid kidney function deterioration.[11,31]

The loss of charge selectivity in the glomerular filtration barrier results in albuminuria,[32] whereas pore size reduction in the barrier results in SPS. This may be a more powerful phenotype of kidney dysfunction in predicting catastrophic outcomes. The strength of this study is that it analyzed the median survival time to outcome using the CS-AFT model rather than a proportional hazard model. We also compared the performance of EKFCcys/EKFCcre and Cre/Cys. In addition, we conducted a sensitivity analysis for several scenarios. However, the present study has several limitations. First, this was a retrospective observational study; therefore, causal inferences were not possible. Second, generalizability is limited because of the specific and selected populations. Third, because both creatinine and cystatin C levels are affected by muscle mass, anthropometric parameters should be measured. Moreover, other comorbidities and use of diuretics and steroids should be adjusted. Diuretics may increase the thickness of the glomerular basement membrane and the incidence of SPS, whereas steroids may distort cystatin C levels.[6,33,34] Additionally, the study lacked inflammatory markers, and sampling of subjects requiring both creatinine and cystatin C testing may have introduced bias towards individuals with severe conditions. Finally, information regarding the reasons for undergoing a kidney function test is unknown.

In conclusion, a low EKFCcy/EKFCcre ratio predicts mortality and the need for dialysis in older patients, suggesting that it could be a strong biomarker for predicting clinical outcomes. This study was limited by the small sample size. Further basic research is warranted to elucidate the mechanisms underlying SPS and its clinical outcomes in different settings.

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## Data availability statement

Data available on request due to privacy/ethical restrictions.

## Declaration of interest

The authors report no conflicts of interest.

## Supplementary materials

Supplementary materials for this article can be found at http://www.sgecm.org.tw/ijge/journal/view.asp?id=35.

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