UNIVERSITY OF
EASTERN FINLAND

Recent Creatinine and Cystatin C eGFR Equations as Predictors of All-Cause Mortality in Finnish Elderly

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May 2024

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Amenu, Robel A: Recent Creatinine and Cystatin C eGFR Equations as Predictors of All-Cause Mortality in Finnish Elderly

Master's thesis, 76 pages

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May 2024

Keywords: glomerular filtration rate, chronic kidney disease, creatinine, cystatin C, mortality

Abstract

Chronic kidney disease (CKD) is a major global health problem. In CKD management, estimated glomerular filtration rate (eGFR) is the most used method to determine renal function. Novel European Kidney Function Consortium (EKFC) eGFR equations, although found to be more accurate in GFR estimation over the classic CKD-Epidemiology Collaboration (CKD-EPI) equations, have not yet been investigated as mortality risk predictors, especially in the elderly. This study compared the mortality prediction performance of these equations and evaluated equations involving cystatin C as compared to those involving creatinine in the Kuopio Ischemic Heart Disease Risk Factor study (KIHD), a continuous cohort study involving Eastern Finnish population.

An elderly Finnish cohort of 1241 males and 634 females, with a median age of 73.6 years, was prospectively followed for a median period of 11.9 years. Unadjusted and multivariable-adjusted Cox proportional hazard models were employed to evaluate the association of CKD-EPI and EKFC eGFR equations with all-cause mortality, with data obtained from the Cause of Death Registry.

Over the follow-up period, 711 (37.9%) deaths occurred. Lower eGFR associated with mortality by all equations (p <0.001). EKFC cystatin C (EKFC Cys) appeared to have the strongest association, with a 28.7% increased hazard of mortality per 10-unit decrease in eGFR in the fully-adjusted model (HR [95% CI] 1.29 [1.20, 1.39]) and 2.76 times increased risk of mortality in the lower eGFR category compared to the higher one (<60 against >=90 ml/min/1.76 m^2) (HR [95% CI] 2.76 [1.62, 4.69]). It demonstrated the highest area under the curve of 0.700 in the unadjusted models, while an improvement of only 0.001 over CKD-EPI Cys in the adjusted models. EKFC Cys again had the highest discrimination improvement while CKD-EPI Cys had the highest reclassification improvement to the multivariate model. The creatinine equations showed weaker associations.

The EKFC Cys equation demonstrated the strongest association with all-cause mortality in Finnish elderly. Equations involving cystatin C had better predictive performance over creatinine equations in the KIHD. EKFC Cys showed the only significant association with mortality in both males and females, and it was the least sensitive to changes by diabetes and hypertension status. This study affirms the importance of using accurate eGFR equations, like EKFC Cys, for better mortality risk stratification in clinical settings, particularly in the elderly.

Acknowledgments

First and foremost, I thank the Almighty God for helping me reach this far. I thank my parents and brother for their unwavering patience and support in my long educational journey. I always strive to make them proud. I also thank and appreciate my wonderful thesis supervisors Prof. Tomi-Pekka Tuomainen and Dr. Mounir Ould Setti for their constant guidance, mentorship, and patience in developing this master's thesis.

Abbreviations

ACR	Albumin to Creatinine Ratio
BMI	Body Mass Index
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CKD-EPI Cr	CKD-EPI Creatinine Equation
CKD-EPI Cys	CKD-EPI Cystatin C Equation
CKD-EPI CrCys	CKD-EPI Creatinine-Cystatin C Equation
CVD	Cardiovascular Disease
eGFR	Estimated Glomerular Filtration Rate
EKFC	European Kidney Function Consortium
EKFC Cr	EKFC Creatinine Equation
EKFC Cys	EKFC Cystatin C Equation
EKFC CrCys	EKFC Creatinine-Cystatin C Equation
ESRD	End-Stage Renal Disease
GFR	Glomerular Filtration Rate
KDIGO	Kidney Disease: Improving Global Outcomes
KIHD	Kuopio Ischemic Heart Disease Risk Factor Study
MDRD	Modification of Diet in Renal Disease
mGFR	Measured Glomerular Filtration Rate
NCD	Non-Communicable Disease

Contents

1 Introduction

Globally, chronic kidney disease (CKD) is an emerging public health problem. The aging global population and increasing sedentary lifestyle lead to a rise in the prevalence of non-communicable diseases (NCDs). These NCDs in turn lead to an increase in the development of CKD. According to a study by Kovesdy in 2022, more than 10% of the global population is affected. The most alarming fact is the trend of increase, where there has been an increase in death rate due to CKD by more than 40% in the past 3 decades. From 1990 to 2017, the global number of cases of CKD increased by 29.3% (Cockwell & Fisher 2020).

Estimated glomerular filtration rate (eGFR) is the most commonly used method to estimate renal function in the management of CKD. eGFR is calculated using equations that include endogenous biomarkers in the blood, which currently include creatinine and cystatin C. Despite the development of newer eGFR equations intended to improve the accuracy of CKD diagnosis and staging, significant questions remain. These include how these equations compare with each other, particularly in different populations and clinical settings, and how they perform in predicting critical clinical outcomes. The problems with these equations include over- or under-estimation of the actual GFR that causes misdiagnosis and lack of timely management, inconsistencies among different population characteristics, and inaccurate prediction of outcomes (Kasozi et al. 2023). Three eGFR equations, which include the 2009 Chronic Kidney Disease Epidemiology Collaboration Creatinine (CKD-EPI Cr), the 2012 CKD-EPI Cystatin C (CKD-EPI Cys), and the 2012 CKD-EPI Combined Creatinine-Cystatin C (CKD-EPI CrCys), are currently the standard equations that are in clinical use and are recommended by the Kidney Disease: Improving Global Outcomes (KDIGO) international guideline (KDIGO 2024). Recently, 3 novel equations were developed, which include the 2021 European kidney function consortium Creatinine (EKFC Cr), the 2023 EKFC Cystatin C (EKFC Cys), and the 2023 EKFC Combined Creatinine-Cystatin C (EKFC CrCys) equations. These are very promising in their accuracy and are expected to be better than the previous ones in predicting kidney outcomes (Pottel et al. 2021, Pottel et al. 2023). However, there still remains a need for a better and more accurate eGFR equation that can accurately

diagnose and stage kidney disease, and equally, a need for studies to identify which of the existing equations is the best in predicting major clinical outcomes like all-cause mortality.

Previous studies have shown results suggesting lower eGFR levels as independent predictors of the risk of all-cause mortality. Specifically, eGFR <60 ml/min/1.73 m^2, which is defined as one criterion to diagnose CKD in routine clinical setups and by the KDIGO guidelines, has been shown to associate with future risk of all-cause mortality. A meta-analysis of general population cohorts by Chronic Kidney Disease Prognosis Consortium in the USA in 2010 established that such low levels of eGFR are independent predictors of all-cause mortality in the general population. Subsequent studies have tried to compare which of the available eGFR equations associates the most with the risk of all-cause mortality. A study comparing creatinine-based eGFR (CKD-EPI Cr), cystatin C-based eGFR (CKD-EPI Cys), and eGFR combining the 2 markers (CKD-EPI CrCys) showed that the cystatin C-based eGFR was superior in its association with mortality compared with the other 2 (Helmersson-Karlqvist et al. 2016).

Previous studies about renal function in the Kuopio Ischemic Heart Disease Risk Factor Study (KIHD), which is a continuous cohort study developed to investigate risks related to cardiovascular diseases (CVDs) and their outcomes in middle-aged population in Eastern Finland, have used creatinine as a renal marker in estimating GFR (Ould Setti et al. 2023, Kunutsor et al. 2023). Studies from other cohorts comparing the relative accuracies of creatinine and cystatin C as markers of renal function have found that eGFR equations involving cystatin C are better than creatinine-based equations in their association with major clinical outcomes, including mortality (Zhu et al. 2022, Helmersson-Karlqvist et al. 2016). Therefore, it is important to evaluate the latest developed formulae which use relatively superior markers, modified coefficients, and attempt to avoid non-GFR related factors. Moreover, up to now, no study has compared the mortality predictive performance of these novel equations with the standard equations, especially in elderly populations.

In this study, 6 eGFR equations were compared for their predictive performance of the risk of all-cause mortality among elderly Finnish population in the KIHD. These include the standard equations which are CKD-EPI Cr, CKD-EPI Cys, and CKD-EPI CrCys against the recent novel equations which are EKFC Cr, EKFC Cys, and EKFC CrCys. Thus, the objective of this study was to analyze the comparative performances of the 6 eGFR equations in their prediction of all-cause mortality among older Finnish population, investigate how cystatin C-based eGFRs perform as compared to creatinine-based eGFRs in the KIHD cohort, and assess how these performances vary in different subgroups.

2 Literature review

In the context of an aging global population and increasing prevalence of chronic diseases, CKD emerges as a critical public health concern. A fundamental aspect of CKD management is the accurate assessment of renal function, which is most commonly estimated using eGFR. Various equations have been developed to estimate GFR, each with its own set of variables, strengths, and limitations.

2.1 Chronic kidney disease

CKD represents a significant global health challenge, affecting approximately 10% of the global population and leading to serious health consequences (Kovesdy 2022). It is projected to be among the top five conditions contributing to years of life lost by 2040, yet it remains under-recognized by both patients and providers (Kovesdy 2022).

CKD is defined as the presence of an eGFR measurement <60 ml/min/1.73 m^2 together with evidence of kidney structural damage, which includes albuminuria, all persisting for more than 3 months (KDIGO 2024). CKD's progression is often silent, with early stages typically showing no symptoms. This lack of awareness contributes to its underdiagnosis and undertreatment (Evans et al. 2022). The disease is multifaceted, involving both non-modifiable factors like age, family history, and ethnicity, and modifiable risk factors such as type 2 diabetes, hypertension, and dyslipidemia. These factors can trigger renal function impairment, leading to glomerular/interstitial damage, decreased GFR, and increased albuminuria (Evans et al. 2022).

As CKD progresses, it imposes a significant clinical and economic burden. Patients with advanced stages of CKD face an array of complications, including mineral bone disorder, anemia, hypertension, and hyperkalemia, which contribute to the acceleration of CKD progression and risk of CVD-related morbidities (Evans et al. 2022). The economic burden is also substantial, with

management costs increasing with disease progression and end-stage renal disease (ESRD) accounting for the largest proportion of these costs (Evans et al. 2022).

Managing CKD involves a multifaceted approach, including lifestyle interventions, blood pressure and glucose control, renin-angiotensin-aldosterone system blockade, and statin therapy. Despite these strategies, a residual risk of adverse events and CKD progression remains, highlighting an unmet need for effective treatments (Chen et al. 2023).

2.2 Evaluation of renal function

Evaluating renal function is crucial for the diagnosis and management of kidney diseases. One key parameter for this evaluation is the GFR, which is considered the best overall index of renal function (Gama et al. 2023). GFR can be measured directly using exogenous filtration markers like inulin, iohexol, ^{51}Cr-EDTA, and ^{99m}Tc-DTPA. However, these methods, while accurate, are cumbersome and not always practical for routine clinical use (Gama et al. 2023). Thus, eGFR using serum creatinine-based equations became more common in clinical practice.

The Modification of Diet in Renal Disease (MDRD) study provided an equation to estimate GFR, which was later improved by the CKD-EPI equation for better accuracy across different levels of GFR (Alaini et al. 2017). The MDRD equation, developed from data involving participants with measured GFR (mGFR) using urinary clearance of ^{125}I-iothalamate, included creatinine and demographic variables. Despite its widespread use, it showed limitations, particularly at higher GFR levels (Gama et al. 2023).

The CKD-EPI equations were introduced to address these limitations, providing less biased estimates across a broader range of GFR values. It utilized data from various cohorts, enhancing its applicability to a more diverse population (Aklilu 2023). Additionally, advancements in eGFR have

seen a shift towards standardizing creatinine assays and broadening the diversity of derivation cohorts to improve the generalizability of estimating equations (Aklilu 2023).

It is essential to acknowledge that while eGFR provides a convenient method for assessing renal function, it is not without its drawbacks, particularly concerning the overestimation of GFR due to tubular secretion of creatinine (Tio et al. 2023). This is especially significant in individuals with GFR values just above the threshold of 60 mL/min/1.73 m^2. Therefore, in certain clinical situations, particularly when accurate GFR measurement is crucial for therapeutic decisions, direct measurement methods may still be preferred despite their complexity (Tio et al. 2023).

2.3 Creatinine as a marker of renal function

Serum creatinine measurement is a pivotal element in assessing renal function, particularly in estimating GFR. However, creatinine's reliability as a GFR indicator diminishes in advanced CKD, where estimations like eGFR become less precise (Methven et al. 2017). A study using the Swedish CKD Registry compared plasma-iohexol mGFR against creatinine-based eGFR in predicting mortality among advanced CKD patients. It was observed that mGFR, as opposed to creatinine-based eGFR, presented a superior correlation with patient outcomes, emphasizing the importance of GFR itself over non-GFR determinants of prognosis (Methven et al. 2017).

The standardization of creatinine measurement is essential for accurate GFR estimation. In a comparative study across three cohorts, which included Chronic Renal Insufficiency Cohort (CRIC), Minnesota cohort, and EKFC cohort, creatinine was measured using standardized methods, although its calibration was not assured in the CRIC (Pottel et al. 2022). The findings suggested that the associations between creatinine and mGFR differed notably between the cohorts, indicating variations in creatinine calibration could lead to discrepancies in the performance of creatinine-based equations (Pottel et al. 2022).

Several non-GFR factors affect serum creatinine levels. It is influenced by factors affecting muscle mass, making it a marker of health status beyond renal function (Levey et al. 2000). Conditions like liver cirrhosis, which affect muscle mass, can lead to GFR overestimation. Medications that inhibit tubular secretion of creatinine, like cimetidine and trimethoprim, can increase creatinine levels, falsely indicating reduced renal function (Levey et al. 2000).

While it remains a valuable biomarker for renal function assessment, its limitations, particularly in advanced CKD stages, necessitate the use of more accurate measures like mGFR or other eGFR alternatives (Björk et al. 2020). Additionally, the standardization of creatinine measurement is important for the reliable application of eGFR equations, and understanding non-GFR factors can enhance the interpretation of renal function assessments (Björk et al. 2020).

2.4 Cystatin C as a marker of renal function

Cystatin C is a low-molecular-weight protein that has been identified as a more reliable biomarker for estimating GFR compared to traditional creatinine-based measurements (Spencer et al. 2023). It is produced at a constant rate by all nucleated cells of the human body, filtered in the glomeruli, and then reabsorbed and metabolized by tubular epithelial cells, making it a suitable indicator of renal function. Unlike creatinine, cystatin C levels are not affected by muscle mass, diet, or other non-renal factors, thus providing a more accurate reflection of the kidneys' filtering capacity (Spencer et al. 2023).

Cystatin C offers several advantages over creatinine. This attribute makes cystatin C a more sensitive marker for detecting mild reductions in GFR, particularly in individuals with GFR between 60 and 90 ml/min/1.73 m^2, where creatinine-based estimations may not be reliable (Ferguson et al. 2015). Moreover, cystatin C has demonstrated stronger associations with all-cause mortality and CVD events, suggesting its potential as a superior prognostic marker in clinical settings (Ferguson et al. 2015).

Studies have highlighted the effectiveness of cystatin C-based eGFR in predicting clinical outcomes, particularly in elderly populations and various ethnic groups (Spencer et al. 2023). For instance, in a large UK Biobank study focusing on South Asian individuals, cystatin C identified a significantly higher number of participants with reduced eGFR compared to creatinine, revealing individuals at increased risk for mortality and CVD events not identified by creatinine-based eGFR (Chen et al. 2023).

Lower cystatin C eGFR values have been associated with higher risks of mortality due to any cause and CVD, enhancing the prediction accuracy for such adverse outcomes when compared to creatinine-based eGFR (Chen et al. 2022a). This suggests that cystatin C can identify individuals at risk of CVD issues earlier than creatinine, even when their renal function is considered within normal ranges based on creatinine measurements (Chen et al. 2022a).

Cystatin C levels can be measured using various methods, including particle-enhanced immunonephelometry (PENIA) and particle-enhanced turbidimetry assays (Ferguson et al. 2015). The accuracy and standardization of these assays are critical for ensuring reliable cystatin C measurements, which can subsequently improve the precision of GFR estimation and CKD diagnosis when incorporated into eGFR equations (Ferguson et al. 2015).

Cystatin C emerged as a promising alternative to creatinine for assessing renal function, offering enhanced sensitivity, specificity, and better predictive value for CVD outcomes and mortality in CKD patients. Its adoption in clinical practice could refine the accuracy of renal function assessments, aiding in the early detection and management of kidney diseases and associated comorbidities.

2.5 CKD-EPI and EKFC eGFR equations

2.5.1 The 2009 CKD-EPI Creatinine (CKD-EPI Cr) equation

$$eGFR = 141 \times \min(Cr/\kappa,1)^{\alpha} \times \max(Scr/\kappa, 1)^{-1.209} \times 0.993^{Age} \times 1.018 \text{ (if female)}$$

Where $\kappa = 0.7$ if female or 0.9 if male

Where $\alpha = -0.329$ if female or -0.411 if male

The CKD-EPI Cr equation for estimating GFR marked a significant advancement in the evaluation of renal function. This equation leverages creatinine, age, sex, and ethnicity to provide an estimation of renal function across diverse populations (Levey et al. 2009). The inception of the CKD-EPI Cr equation stemmed from the need for an accurate tool in clinical settings to assist in detecting, evaluating, and managing kidney diseases and to guide drug dosing and other therapeutic interventions based on renal function (Levey et al. 2009).

Since its publication in 2009, it has been greatly adopted and validated in different populations and clinical settings. Several studies have shown that it has better accuracy and precision than the previous MDRD Study and Cockroft-Gault equations. It is the most used and first-line measurement in routine clinical setups to estimate GFR up to now. This has been the case since its recommendation by the KDIGO guideline in 2012. However, some challenges remain, such as the need for further validation in diverse ethnic groups and regions and the lack of consensus on the optimal indications and reporting of eGFR in clinical practice (Inker et al. 2018). Specifically, its limitations include that it is inconsistent among different age groups and creatinine can be confounded by different factors, the most common one being muscle mass.

Furthermore, the ethnicity factor has been an issue of great debate for many years because of the finding that, at the same levels of creatinine, there are higher eGFR values in Black Americans than in the non-Black population, which may lead to an unfair delay in the kidney transplant

waiting list (Eneanya et al. 2022). Nevertheless, the ethnicity factor of this equation was not applied in European clinical setups since its introduction, therefore is not a subject of debate (Delanaye et al. 2023). This is also true in Finland, where there is no need for considering equations that take into consideration ethnicity because it is a relatively ethnically homogenous country.

A meta-analysis by Zou et al. (2020) compared the CKD-EPI Cr equation with its cystatin C counterpart and found that while CKD-EPI equations incorporating cystatin C exhibited less bias and greater accuracy in estimating GFR, the CKD-EPI Cr equation remained a fundamental tool in clinical practice due to its widespread applicability and ease of use. Despite the introduction of cystatin C-based equations, the CKD-EPI Cr equation continues to be the preferred method for GFR estimation in many clinical scenarios, highlighting the balance between accessibility, cost, and accuracy in the choice of GFR estimation tools (Zou et al. 2020).

The validation of the CKD-EPI Cr equation underscored its improved performance over the MDRD equation, especially in people with GFR ≥60 mL/min/1.73 m^2, enhancing the precision in diagnosing and staging CKD as well as influencing the public health perception of CKD prevalence (Zou et al. 2020).

Despite its advantages, the ongoing evaluation of the CKD-EPI Cr emphasizes the need for continuous refinement. The dynamic nature of clinical research and the diverse needs of patient populations necessitate the evolution of eGFR equations to encompass a broader array of biomarkers and clinical variables, ensuring their relevance and applicability in an ever-changing healthcare landscape (Zou et al. 2020).

2.5.2 The 2012 CKD-EPI Cystatin C (CKD-EPI Cys) equation

$$eGFR = 133 \times \min(Cys / 0.8,1)^{-0.499} \times \max(Cys / 0.8,1)^{-1.328} \times 0.996^{Age} [\times 0.932 \text{ (if female)}]$$

The CKD-EPI Cys equation was developed in an effort to address the limitations of the creatinine-based equation (Inker et al. 2012). Recognizing the necessity for a more precise and less biased measure, especially in patients with near-normal GFR, the CKD-EPI collaboration developed an equation incorporating cystatin C, a protein less influenced by muscle mass, diet, and other non-GFR related factors (Inker et al. 2012). This equation which uses cystatin C alone does not require information on ethnicity, which makes it more applicable and convenient for clinical practice.

A meta-analysis highlighted the CKD-EPI Cys equation's superior performance compared to its creatinine counterpart (Zou et al. 2020). This equation demonstrated lesser bias and higher accuracy, notably in populations with a lower GFR. Particularly, it showed improved performance in Asian populations, indicating its broader applicability across diverse demographic groups. This emphasized the equation's utility in enhancing the precision of CKD classification and reducing the need for ethnic adjustments in GFR estimation (Zou et al. 2020).

Inker et al. (2012) illustrated the clinical relevance of integrating cystatin C into the CKD-EPI equation. While the CKD-EPI Cys equation marked a leap forward, ongoing research and refinement are vital. Limitations of this eGFR equation include confounding factors affecting serum levels of cystatin C such as obesity and CVDs, its measurement being cumbersome, as well as its expensiveness to apply in routine clinical setup. Consequently, KDIGO recommended that it only be used as a confirmatory test. The need for standardized calibration of cystatin C measurements and the integration of additional biomarkers are areas of active investigation (Spencer et al. 2023). Such enhancements aim to further reduce bias, increase accuracy, and ensure the equation's cost-effectiveness and adaptability to various clinical settings and patient populations (Spencer et al. 2023).

2.5.3 The 2012 CKD-EPI Combined Creatinine–Cystatin C (CKD-EPI CrCys) equation

$$eGFR = 135 \times \min(Cr/\kappa,1)^{\alpha} \times \max(Cr/\kappa,1)^{-0.601} \times \min(Cys/0.8,1)^{-0.375} \times \max(Cys/0.8,1)^{-0.711} \times 0.995^{Age} \times 0.969 \text{ (if female)}$$

Where $\kappa = 0.7$ if female or 0.9 if male

Where $\alpha = -0.248$ if female or -0.209 if male

Inker et al. (2012) introduced this combined equation, highlighting its superior performance in diverse populations. The development involved cross-sectional analyses with over 5,000 participants, leading to an equation that outperformed single-marker equations with regard to bias, precision, and accuracy. This combined approach was particularly effective in patients with near-normal GFR, where traditional creatinine-based estimates were less reliable (Inker et al. 2012). By combining cystatin C with creatinine, the equation enhanced precision and accuracy in GFR estimation. This combined approach significantly improved the classification of patients with borderline GFR values, aiding in the more accurate identification of individuals with CKD (Inker et al. 2012). Such advancements are pivotal for guiding treatment decisions and assessing the prognosis of kidney-related and cardiovascular diseases (Inker et al. 2012).

It was demonstrated that the CKD-EPI CrCys equation had a similar bias to the creatinine and cystatin C equations but showed improved precision and accuracy (Inker et al. 2012). This equation was notably beneficial in classifying GFR accurately, especially in the critical range of 45 to 74 ml/min/1.73 m², enhancing the identification of CKD (Inker et al. 2012). Such precision in eGFR is crucial for appropriate clinical decision-making and resource allocation in CKD management.

The CKD-EPI CrCys equation's development signifies a major step toward refining eGFR, aiding in the early detection and classification of CKD. Its ability to provide more precise eGFR supports its use as a confirmatory test for CKD diagnosis, especially in cases where creatinine-based estimates fall short (Fan et al. 2014).

2.5.4 The 2021 EKFC Creatinine (EKFC Cr) equation

EKFC Cr	Age 2–40	Cr/Q < 1.0	$107.3 \times (Cr/Q)^{-0.322}$
		Cr/Q ≥ 1.0	$107.3 \times (Cr/Q)^{-1.132}$
	Age >40	Cr/Q < 1.0	$107.3 \times (Cr/Q)^{-0.322} \times 0.990^{(Age-40)}$
		Cr/Q ≥ 1.0	$107.3 \times (Cr/Q)^{-1.132} \times 0.990^{(Age-40)}$

Q Values

For ages 2-25 y:

Males:

$$\ln(Q) = 3.200 + 0.259 \times Age - 0.543 \times \ln(Age) - 0.00763 \times Age^2 + 0.0000790 \times Age^3$$

Females:

$$\ln(Q) = 3.080 + 0.177 \times Age - 0.223 \times \ln(Age) - 0.00596 \times Age^2 + 0.0000686 \times Age^3$$

For ages >25 y:

Males:

Q = 80 µmol/L (0.90 mg/dl)

Females:

Q = 62 µmol/L (0.70 mg/dl)

(Modified from: Pottel et al. 2021)

The EKFC Cr equation, designed to estimate GFR, incorporates median normal values of creatinine from healthy populations. It aims to provide a more accurate assessment by addressing the limitations of previous equations like CKD-EPI Cr, particularly in terms of age and racial biases (Pottel et al. 2021). Notably, it shows improved accuracy in estimating GFR in adults and children, with a particular focus on the 18-30 age group, where previous equations showed significant overestimation (Delanaye et al. 2023).

A systematic comparison between EKFC and CKD-EPI equations highlighted the practical implications of adopting EKFC over CKD-EPI (Buchkremer & Segerer 2021). This analysis focused on the differences in GFR estimation across age ranges and CKD-EPI values, demonstrating the enhanced reliability and applicability of the EKFC Cr equation in clinical settings.

The EKFC Cr equation was validated for a broad age range (2 to 90 years), showing low bias and fewer estimation errors compared to CKD-EPI equations, in the measurement of eGFR (Buchkremer & Segerer 2021). This makes it a versatile tool for assessing renal function across a wide demographic (Buchkremer & Segerer 2021).

The adoption of the EKFC equation can lead to better clinical decision-making, given its improved accuracy and reduced bias. It is particularly significant in the context of diagnosing and managing kidney-related disorders, where precise eGFR is crucial (Pottel et al. 2021). However, the EKFC equation still has some limitations, such as the influence of muscle mass and proteinuria on creatinine levels, possible under/overestimation at specific eGFR levels, and the need for further comparison with cystatin C-based equations (Buchkremer & Segerer 2020). It may be a useful tool for estimating GFR across the full age spectrum, but it may not be applicable to all situations and may require further refinement (Delanaye et al. 2023, Pottel et al. 2021).

Research should focus on further validating the EKFC Cr equation in diverse populations, including studies on its predictive value for kidney disease progression and major outcomes like mortality in various clinical scenarios (Buchkremer & Segerer 2021).

2.5.5 The 2023 EKFC Cystatin C (EKFC Cys) equation

EKFC Cys	18–40	Cys/Q < 1.0	$107.3 \times (Cys/Q)^{-0.322}$
		Cys/Q ≥ 1.0	$107.3 \times (Cys/Q)^{-1.132}$
	>40	Cys/Q < 1.0	$107.3 \times (Cys/Q)^{-0.322} \times 0.990^{(Age-40)}$
		Cys/Q ≥ 1.0	$107.3 \times (Cys/Q)^{-1.132} \times 0.990^{(Age-40)}$

Q = 0.83 until 50 years and Q = 0.83 + 0.005x(Age−50) after 50 years

The study by Pottel et al. (2023) presented a comprehensive analysis of various eGFR equations, emphasizing the EKFC's integration of cystatin C measurements. It highlighted the equation's design to offer a more accurate eGFR, particularly valuable in clinical scenarios where traditional creatinine-based equations may falter due to their reliance on muscle mass, potentially misleading in conditions like malnutrition or paralysis. The EKFC Cys equation does not need sex or ethnicity variables, unlike EKFC Cr, and had similar or better accuracy than the existing equations recommended by KDIGO (Pottel et al. 2023).

The study by Delanaye et al. (2023) underscored the EKFC Cys equation’s effectiveness in estimating GFR across the full age spectrum and renal function range. It demonstrated the equation's low bias and fewer estimation errors exceeding 30% compared to CKD-EPI equations.

These studies reinforced the EKFC Cys equation's potential to enhance eGFR accuracy, particularly in diverse clinical settings. They suggest a paradigm shift towards more inclusive and adaptable eGFR models, although acknowledging the necessity for continued validation across varied demographic groups.

2.5.6 The 2023 EKFC Combined Creatinine-Cystatin C (EKFC CrCys) equation

Mean value of EKFC Cr and EKFC Cys

Pottel et al. (2023) again introduced the EKFC CrCys equation to estimate renal function using cystatin C combined with creatinine. Similar to EKFC Cys, this equation also does not need sex or ethnicity variables and has the same or superior accuracy than the standard equations. EKFC CrCys is simply an average of the EKFC Cr and EKFC Cys, and the study shows that this combined equation can further improve the accuracy of GFR estimation. It suggests that the equation could simplify and standardize the assessment of renal function across different populations and settings, and potentially improve the diagnosis and management of CKD (Pottel et al. 2023).

The EKFC equations are new methods to estimate GFR. They have been evaluated in studies that compared them with other existing equations in different populations and settings (Delanaye et al. 2023). They have shown improved accuracy, precision, and bias than the CKD-EPI equations in estimating GFR, including in women and non-White patients. These equations have also been applied to estimate GFR in children, pregnant women, and patients with liver cirrhosis, with promising results. Consequently, they have been endorsed by some international guidelines and societies as alternative methods to estimate GFR (Delanaye et al. 2023).

2.6 Renal function and mortality

The intricate relationship between renal function, as measured by eGFR, and mortality has garnered significant attention across various patient populations, emphasizing the critical need for precise and reliable eGFR estimation methods. Studies spanning diverse cohorts, including the general population, intensive care patients, those with CKD, and elderly individuals have explored the prognostic value of different eGFR equations, predominantly those based on creatinine, cystatin C, and combined markers. These studies aim to elucidate the most accurate and

clinically relevant markers for assessing renal function and predicting mortality, thereby shaping the understanding and management of patients at risk.

A study conducted by the Chronic Kidney Disease Prognosis Consortium (2010) examined how eGFR, albuminuria, and mortality are linked in various general population cohorts. The meta-analysis examined data from 14 studies involving 105,872 participants for albumin-to-creatinine ratio (ACR) and seven studies with 1,128,310 participants for urine protein dipstick measurements. The findings indicated that eGFR values below 60 mL/min/1.73 m^2 and ACR above 1.1 mg/mmol are both independent predictors of increased mortality risk in the general population.

In a prospective cohort study involving 13,054 unselected adult patients from Uppsala University Hospital, mortality risk predictions using different eGFR equations were compared (Helmersson-Karlqvist et al. 2016). The research divided the participants into risk categories based on eGFR values calculated using creatinine-based, cystatin C-based, and combined equations. Over a median follow-up period of 4.6 years, the study observed that cystatin C-based eGFR is more closely associated with all-cause and CVD mortality than the other equations. This finding suggested the potential superiority of cystatin C as a biomarker in mortality risk prediction, highlighting its clinical relevance over creatinine-based or combined eGFR equations in routine care (Helmersson-Karlqvist et al. 2016). Yet another study by Helmersson-Karlqvist et al. (2021) explored the efficacy of the same eGFR equations in predicting long-term mortality among 22,488 intensive-care patients, findings revealing that cystatin C-based eGFR is more accurately associated with risk of mortality. This superiority in prediction was demonstrated through various statistical measures, including net reclassification improvement and C-statistics, underscoring the potential of cystatin C as a more reliable biomarker in critical care settings.

A nationwide research initiative, conducted in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) cohort and encompassing 26,643 U.S. adults, evaluated the efficacy of a triple-marker approach—including creatinine, cystatin C, and urine ACR—in detecting CKD and predicting the progression to ESRD and mortality (Peralta et al. 2011). Findings revealed that

individuals with CKD identified by all three markers exhibited significantly elevated risks for mortality and ESRD compared to those identified by creatinine alone. Specifically, the hazard ratios for mortality intensified when CKD was defined using additional markers—cystatin C and ACR—beyond creatinine, underscoring the potential of a multi-marker strategy in enhancing the prognostic accuracy for individuals with CKD.

In another nationwide study, Liu et al. (2023) examined the associations between eGFR by different biomarkers and all-cause mortality among Chinese individuals, with a particular focus on the impact of diabetes status. This study found that eGFR's predictive value for mortality varied significantly based on the biomarkers used and the presence of diabetes. Among individuals without diabetes, only CKD as defined by eGFR using cystatin C and the combined creatinine and cystatin C showed significant associations with mortality. In contrast, among diabetic individuals, all eGFR categories and measures were strongly linked to increased mortality risk, emphasizing the enhanced predictive value of eGFR in this group. The study demonstrated the need for a meticulous application of eGFR measures in clinical practice, considering the individual's diabetic status to improve mortality risk prediction.

In a study by Sundin et al. (2017), a detailed investigation was conducted on 1,157 Swedish adults to assess whether cystatin C and creatinine levels, independent of mGFR, can predict mortality. Utilizing Cox regression analysis, the study found that higher concentrations of cystatin C and lower concentrations of creatinine, adjusted for mGFR, were independently linked with increased mortality rates. Notably, the study demonstrated that adding mGFR to the predictive model did not enhance mortality risk assessment, suggesting that cystatin C and creatinine alone provide significant prognostic value.

On the contrary, a prospective cohort study utilizing data from the Swedish CKD Registry and encompassing 2,705 participants with CKD stages 4 and 5, found that an increase in mGFR was associated with significant reduction in all-cause mortality, demonstrating a superior performance of mGFR over eGFR in both etiological and prognostic models for predicting mortality (Methven

et al. 2017). This contrast from Sundin et al.'s (2017) study suggests the crucial role of accurate mGFR, beyond eGFR estimations, in assessing mortality risk in patients with advanced CKD.

A study by Foster et al. (2013) investigated the predictive value of novel filtration markers—β-trace protein (BTP), β2-microglobulin (B2M), and cystatin C—compared to CKD-EPI Cr for all-cause and CVD mortality in a cohort of 6,445 US adults. They found that higher levels of BTP, B2M, and cystatin C were significantly associated with increased mortality risk after adjusting for demographic variables. Whereas, CKD-EPI Cr showed a weaker association. This suggested that these markers may offer more robust predictive value for mortality risk than CKD-EPI Cr, supporting their potential utility as alternative markers for renal function assessment.

Another prospective cohort study involving 6942 adult participants from NHANES III, focused on how different methods of estimating GFR affect the prediction of mortality risk (Astor et al. 2009). The study found that lower eGFR values with the cystatin C-based equations were strongly associated with a higher risk of mortality across the spectrum of normal to moderately decreased eGFR. Conversely, creatinine-based estimates yielded weaker associations, with the relationship between eGFR and mortality reversing at higher eGFR levels. The equation based on cystatin C alone offered better mortality prediction than those using both creatinine and cystatin C, emphasizing the superiority of cystatin C in risk stratification for mortality (Astor et al. 2009).

A study exploring the implications of creatinine versus cystatin C-based eGFRs on the prognosis of ESRD and mortality among 4,956 individuals with CKD discovered that individuals with a cystatin C-based eGFR substantially lower than the creatinine-based eGFR demonstrated increased mortality risks (Chen et al. 2022b). Conversely, those with higher eGFR cys compared to eGFR cr exhibited reduced risks for ESRD and mortality. These findings suggested that discrepancies in eGFR measurements can serve as critical indicators for risk stratification in CKD patients, advocating for the dual monitoring of creatinine and cystatin C in this population (Chen et al. 2022b).

Yet another study by Chen et al. (2023) examined the effectiveness of cystatin C versus creatinine-based eGFR in predicting mortality among 7,738 South Asian individuals in the UK Biobank. They found that cystatin C-based eGFR identified significantly more individuals at risk for CKD than the creatinine-based eGFR. Particularly, the eGFR Cys categories of 45 to 59 mL/min/1.73 m^2 were associated with increased risks of mortality compared to the eGFR Cys ≥90 mL/min/1.73 m^2 category, a connection not observed with creatinine-based eGFR. This highlights cystatin C's potential in refining CKD-associated risk stratification, suggesting a physiological mechanism where cystatin C might better reflect the intrinsic renal function, thus improving the prediction of adverse outcomes among South Asian populations (Chen et al. 2023).

Collectively, the reviewed studies underscore the superior predictive ability of cystatin C-based eGFR equations over creatinine-based and combined markers in various settings, including intensive care patients, populations with diabetes, and diverse ethnicities. They reveal the nuanced role that renal function plays in mortality risk, highlighting the limitations of traditional creatinine-based measurements, especially in the elderly and those with CKD. The researches advocate for a more refined approach in evaluating renal function, considering factors such as diabetes status and utilizing multi-marker strategies to enhance prognostic accuracy.

Longitudinal studies, which illustrate the relationship between renal function, as estimated by different eGFR equations, and all-cause mortality, are summarized in Table 1.

Table 1. Reviewed longitudinal studies that illustrate the association of renal function measured by different eGFR equations and all-cause mortality

Study		Methodology/Study Design	Results/Conclusion
Chronic Kidney Disease Prognosis Consortium 2010	Association of estimated glomerular filtration rate and albuminuria with all-cause and CVD mortality in general population cohorts	Collaborative meta-analysis of general population cohorts; 105,872 participants with Urine ACR and 1,128,310 participants with urine protein dipstick; Median age 61 years; Median f/up time 7.9 years; different regions and diverse population; Cox proportional hazard models used.	• Compared with an eGFR of 95, HR (95% CI) for all-cause mortality were 1.18 (1.05, 1.32) at 60, 1.57 (1.39, 1.78) at 45, and 3.14 (2.39, 4.13) at 15. • eGFR below 60 and ACR of 1.1 mg/mmol or higher found to be independent predictors of mortality risk.
Helmerssson-Karlqvist et al. 2016	Cystatin C-based glomerular filtration rate associates more closely with mortality than creatinine-based or combined glomerular filtration rate equations in unselected patients	Prospective cohort study of unselected adults in Uppsala County, Sweden; 13,054 participants; adults ≥18 years old; Median f/up time 4.6 years; Cox proportional hazard regression models and NRI used.	• Reduced eGFR was significantly associated with death across all eGFR equations. • NRI of 0.1 for all-cause mortality when CKD-EPI CrCys replaced CKD-EPI Cr • NRI of -0.06 when CKD-EPI CrCys replaced CKD-EPI Cys

Study		Methodology/Study Design	Results/Conclusion
			• CKD-EPI Cys was more closely associated with mortality
Helmerssson-Karlqvist et al. 2021	Cystatin C predicts long term mortality better than creatinine in a nationwide study of intensive care patients	Retrospective observational study of ICU patients at 3 Swedish University Hospitals; 22,488 participants; Median age 65 years; Median f/up time 5.1 years; Cox proportional hazard regression models, NRI, and IDI used.	• C-statistic for CAPA cystatin C, CKD-EPI Cr, and CKD-EPI CrCys were 0.667, 0.640, and 0.664 respectively. • Cystatin C-alone eGFR equation was better in predicting mortality than the combined or the creatinine-alone equation.
Peralta et al. 2011	Detection of Chronic Kidney Disease With Creatinine, Cystatin C, and Urine Albumin-to-Creatinine Ratio and Association With Progression to ESRD and Mortality	Prospective cohort study from REGARDS study in USA; 26,643 participants; Mean age 65 years; Median f/up time 4.6 years; Cox proportional hazard models, NRI, and IDI used.	• HR (95% CI) for CKD defined by Cr and ACR, CKD defined by Cr and CysC, and CKD defined by all 3 were 3.3 (2.0, 5.6), 3.2 (2.2, 4.7), and 5.6 (3.9, 8.2) respectively. • A combined marker approach with serum creatinine, cystatin C, and albuminuria enhances the ability to discriminate the risk of death.

Study		Methodology/Study Design	Results/Conclusion
Chen et al. 2023	Differential Associations of Cystatin C Versus Creatinine-Based Kidney Function With Risks of CVD Event and Mortality Among South Asian Individuals in the UK Biobank	Prospective cohort study from UK Biobank study in UK; 7,738 South Asian participants; Mean age 53 years; Median f/up time 11 years; Cox proportional hazard models used.	• CKD-EPI Cys 45 to 59 was associated with higher risks of mortality (HR, 2.38) compared to ≥90; no significant associations were found with CKD-EPI Cr in these ranges. • Cystatin C revealed a high-risk CKD population not identified by creatinine, enhancing eGFR-based risk stratification for mortality
Liu et al. 2023	Glomerular filtration rate estimated by differing measures and risk of all-cause mortality among Chinese individuals without or with diabetes	Prospective cohort study from CHARLS study in China; 6,995 participants without diabetes and 1,543 participants with diabetes; Mean age 60.4 years; F/up time 7 years; Cox proportional hazard models used.	• In non-diabetics, eGFR <60 with CKD-EPI Cys and CKD-EPI CrCys was associated with higher mortality risks (HR, 1.71 and 1.55, respectively), unlike CKD-EPI Cr. • Among diabetics, all eGFR categories below 90 were linked with increased mortality risks, with the highest HRs observed in the eGFR <60 category.

Study		Methodology/Study Design	Results/Conclusion
			• CKD-EPI Cys and CKD-EPI CrCys are better associated with all-cause mortality risk than CKD-EPI Cr, regardless of diabetes status.
Sundin et al. 2017	Measured glomerular filtration rate does not improve prediction of mortality by cystatin C and creatinine	Prospective observational study of Swedish residents from Örebro University Hospital; 1157 participants; Adults ≥18 years old; Mean f/up time 4.71 years; Cox regression analysis used.	• Combination of cystatin C and creatinine provides a mortality risk assessment comparable to that of mGFR. • Serum creatinine and cystatin C have independent associations with mortality not totally related to mGFR. • mGFR does not confer more precise mortality risk assessment than combined cystatin C and creatinine.
Astor et al. 2009	Method of Glomerular Filtration Rate Estimation Affects Prediction of Mortality Risk	Prospective cohort study from NHANES III in USA; 6,942 participants; Adults ≥18 years old; Median f/up 8 years; Multivariable	• CKD-EPI Cys was more strongly associated with higher risks for overall mortality than MDRD and CKD-EPI CrCys.

Study		Methodology/Study Design	Results/Conclusion
		Poisson regression models and ROC curves used.	• CKD-EPI CrCys did not predict mortality as effectively as CKD-EPI Cys, despite better performance in estimating GFR.
Foster et al. 2013	Novel Filtration Markers as Predictors of All-Cause and CVD Mortality in US Adults	Prospective cohort study from NHANES III in USA; 6,445 participants; Adults 20 years or older; Median f/up time 14.4 years; Cox proportional hazard models used.	• The highest sub-quintiles for cystatin C (HR 1.94), BTP (HR 2.14), and B2M (HR 2.58) were associated with increased risk of mortality compared to the middle quintile, whereas CKD-EPI Cr showed a weaker association (HR 1.31). • Cystatin C levels had a strong association with mortality, with decreased eGFR showing improved risk prediction than CKD-EPI Cr.
Methven et al. 2017	Routinely measured iohexol glomerular filtration rate versus creatinine-based estimated glomerular filtration rate as predictors of mortality in	Prospective cohort study from SRR-CKD registry in Sweden; 2,705 participants with advanced CKD; Adults 18 years and older;	• A 1 unit increase in mGFR was associated with a 5.3% decrease in all-cause mortality, whereas a similar increase in CKD-EPI Cr was associated with a 1.7% decrease.

Study		Methodology/Study Design	Results/Conclusion
	patients with advanced chronic kidney disease	Median f/up time 45 months; Cox proportional hazard models and IDI used.	• mGFR was better than eGFR in predicting mortality in individuals with advanced CKD.
Chen et al. 2022	Association of Intraindividual Difference in Estimated Glomerular Filtration Rate by Creatinine vs Cystatin C and ESRD and Mortality	Prospective cohort study from the CRIC Study in USA; 4,956 participants with mild to moderate CKD; Mean age 59.5 years; F/up time 15 years; Fine and Gray proportional sub-hazards regression and Cox proportional hazard regression analyses used.	• When CKD-EPI Cys was substantially lower than CKD-EPI Cr (eGFRdiffcys-cr < −15), there was a higher risk of mortality (HR, 1.86; 95% CI, 1.40, 2.48). • In cases where eGFRdiffcys-cr was 15 or greater, there were lower mortality risks (HR, 0.68; 95% CI, 0.58, 0.81). • Big differences between eGFR Cys and eGFR Cr are common in individuals with CKD and are associated with significant risks for ESRD and mortality.

2.7 Renal function and mortality in the elderly

Understanding the nuanced interplay between renal function and mortality, particularly in the elderly, is vital. Recent studies have explored various methods of eGFR measurement, utilizing creatinine and cystatin C-based equations to predict mortality risk in this demographic. These investigations, encompassing diverse cohorts and methodologies, aim to discern the most accurate and clinically relevant eGFR equations. By examining the predictive validity and discriminative ability of these equations, these studies try to inform more tailored and effective clinical decision-making for the elderly population.

Wang et al. (2020) conducted a study involving 278 participants with an average age of 97 years, drawn from the Rugao Longevity cohort. Their research focused on evaluating the effectiveness of different creatinine-based eGFR equations in predicting mortality among elderly individuals with exceptional longevity (over 95 years). The objective was to determine the most accurate eGFR equation for this demographic by comparing the predictive validity and discriminative capacity of four equations: CKD-EPI Cr, MDRD, Berlin Initiative Study 1 (BIS-1), and modified MDRD, over two-year and six-year mortality periods. The findings revealed that the CKD-EPI Cr equation offered superior estimation of renal function and exhibited a stronger correlation with mortality risk. Specifically, higher eGFR values derived from the CKD-EPI Cr equation were associated with decreased mortality, suggesting its potential as a dependable tool for assessing renal function and predicting mortality risk in the elderly (Wang et al. 2020).

In a study involving 805 elderly individuals from the community-based Age, Gene/Environment Susceptibility (AGES) Study, the effectiveness of various estimated glomerular filtration rate (eGFR) equations was comprehensively assessed. The focus was on comparing CKD-EPI equations, mGFR, and equations developed by Japanese, BIS, and Caucasian and Asian pediatric and adult subjects (CAPA) (Fan et al. 2015). The CKD-EPI equations were found to outperform the Japanese, BIS, and CAPA equations across the cohort. Notably, the combined creatinine and cystatin C equation (CKD-EPI CrCys) exhibited superior performance compared to equations based on

individual markers, suggesting that utilizing multiple markers may improve predictive accuracy for mortality and end-stage renal disease (ESRD) in the elderly (Fan et al. 2015).

Salminen et al. (2016) investigated the predictive value of cystatin C, creatinine, and different eGFRs for CVD and non-CVD mortality among 1260 elderly Finnish individuals. Over a 9-year follow-up period, the study found that cystatin C was a significant predictor of both CVD and non-CVD deaths for both genders, even after adjusting for confounding factors. In contrast, creatinine and creatinine-based eGFRs (MDRD and CKD-EPI Cr) showed limited predictive value, particularly after multivariable adjustments. The CKD-EPI CrCys equation did predict CVD mortality for both men and women and non-CVD mortality for women in age-adjusted models, with its predictive value for non-CVD deaths in women remaining significant even after additional adjustments. This research suggested that cystatin C, a biomarker less influenced by muscle mass and dietary factors compared to creatinine, provides superior mortality risk prediction among the elderly. It emphasized the clinical relevance of considering cystatin C in assessing renal function and associated mortality risks in older populations, offering a more accurate tool for clinical decision-making than creatinine-based estimates or even the combined CKD-EPI CrCys equation in individuals over 64 years old (Salminen et al. 2016).

Another study assessed the association between reduced eGFR, as estimated by the BIS1 and MDRD equations, with CVDs and all-cause mortality in elderly patients (Losito et al. 2017). Involving 2998 patients who are 70 or older, the study found significant associations between reduced eGFR (<60 mL/min/1.73 m^2) and mortality, regardless of the equation used. However, the BIS1 equation, specifically designed for older populations, did not show a superior predictive value for mortality compared to the MDRD equation. This suggested that while reduced eGFR is a significant predictor of CVD events and mortality in the elderly, the choice of eGFR estimation equation (BIS1 vs. MDRD) may not significantly alter the predictive association (Losito et al. 2017).

In a diverse elderly cohort of 2,988 participants from the Northern Manhattan Study (NOMAS), Willey et al. (2020) examined the predictive value of eGFR derived from creatinine (CKD-EPI Cr)

and cystatin C (CKD-EPI Cys) for all-cause mortality. With a median follow-up period of 18 years, the study found that CKD-EPI Cys had a better mortality risk prediction than CKD-EPI Cr. This highlighted the superiority of cystatin C over creatinine in predicting mortality in elderly populations, which might be due to cystatin C's lesser dependence on muscle mass and other factors that can affect creatinine levels (Willey et al. 2020).

A more demographically focused study by Malmgren et al. (2020) examined age-related changes in renal function among elderly women and the association of these changes with mortality, using cystatin C-based eGFR. Involving 981 women aged 75 years at baseline, the study tracked changes in eGFR over a decade, utilizing the CKD-EPI and CAPA cystatin C equations. The findings indicate a significant decline in eGFR with age, with about 80% of participants at age 85 showing eGFR levels indicative of CKD stages 3–5. The study also found that lower eGFR levels were associated with increased mortality risk, particularly for those in CKD stages 3b–5. These results highlight the high prevalence of reduced eGFR in this population and suggest that current CKD staging might not adequately reflect the risk in older adults. The study argues for the potential need for age-adapted CKD definitions to prevent overdiagnosis and more accurately predict risks, contributing to a nuanced understanding of renal function's impact on elderly mortality.

The analyzed studies illuminate the critical relationship between eGFR and mortality among the elderly, underscoring the necessity of selecting the most appropriate equations. The findings indicate a trend toward the superior predictive power of cystatin C-based equations over creatinine-based ones, especially in contexts of exceptional longevity and diverse elderly populations. The research suggests that integrating multi-marker approaches could refine mortality risk predictions, advocating for a shift towards more refined renal function assessments in elderly care.

Studies that evaluated the association between eGFR measurements and all-cause mortality among elderly populations are summarized in Table 2.

Table 2. Reviewed studies that evaluated the association of eGFR measurements and all-cause mortality among elderly populations

Study		Methodology/Study design	Results/Conclusion
Wang et al. 2020	Comparative Performance of Creatinine-Based GFR Estimation Equations in Exceptional Longevity	Prospective cohort study from Rugao Longevity Cohort in China; 278 participants; Mean age 97 years; Median f/up time 2.6 years; Cox proportional hazards and NRI used.	• Improved NRI of 0.14 when replacing BIS with CKD-EPI Cr • CKD-EPI Cr had more accurate estimation of renal function and prediction of mortality risk compared to the other equations
Fan et al. 2015	Comparing GFR Estimating Equations Using Cystatin C and Creatinine in Elderly Individuals	Cross-sectional study from AGES-Reykjavik Study in Iceland; 805 participants; Mean age 80.3 years; performances compared based on bias, precision, and accuracy.	• CKD-EPI CrCys was less biased, more precise, and more accurate than CKD-EPI Cr and CKD-EPI Cys.
Salminen et al. 2016	Biomarkers of kidney function and prediction of death from CVD and other causes in the elderly	Prospective cohort study from Lieto, Finland; 1260 participants; Mean age 74 years; F/up 9 years; Cox regression analysis used.	• Cystatin C accurately predicted the risk of mortality whereas creatinine, MDRD, and CKD-EPI Cr lost predictive value after multivariate adjustment.

Study		Methodology/Study design	Results/Conclusion
			• Cystatin C identified as best predictor of deaths, surpassing creatinine, MDRD, CKD-EPI Cr, and CKD-EPI CrCys.
Losito et al. 2017	Association of reduced kidney function with CVD and mortality in elderly patients	Retrospective cohort study from Perugia, Italy; 2998 Caucasian admitted patients; Elderly with minimum age 70 years; Median f/up 27.8 months; Logistic regression and Cox proportional hazard regression models used.	• Significant association of eGFR <60 with all-cause mortality for MDRD (HR, 1.27, 95%CI 1.11, 1.45) and BIS1 (HR, 1.17, 95%CI 1.03, 1.34).
Willey et al. 2020	Creatinine versus cystatin C for renal function based mortality prediction in an elderly cohort	Prospective cohort study from NOMAS cohort; 2988 participants; Mean age 69 years; Median f/up 18 years; Cox proportional hazards models, ROC curves, and NRI used.	• AUC of CKD-EPI Cys (0.73) was greater than that of CKD-EPI Cr (0.67, $p < 0.0001$), indicating better mortality risk prediction. • NRI when replacing CKD-EPI Cr with CKD-EPI Cys was 4.2%, indicating improved risk classification. • CKD-EPI Cys predicted all-cause mortality better than CKD-EPI Cr.

Study		Methodology/Study design	Results/Conclusion
Malmgren et al. 2020	Longitudinal Changes in Kidney Function Estimated from Cystatin C and Its Association with Mortality in Elderly Women	Prospective cohort study from OPRA cohort in Malmö, Sweden; 981 women participants; All 75 years old; F/up 10 years; Cox proportional hazard analysis used.	• Mortality risk increased for women in CKD stages 3b–5 compared to those in stages 1 and 2. For ages 75–80, the adjusted HR was 3.9 (95% CI: 2.3, 6.5), and for ages 80–85, it was 1.7 (95% CI: 1.0, 2.7). • A significant proportion of these women had eGFR levels indicating CKD, which doubled by the end of follow-up. By age 85, 4 out of 5 women had eGFR in the CKD range.

2.8 Summary of literature

The CKD-EPI and EKFC eGFR equations are designed to offer a precise and reliable estimation of renal function, which is crucial for the diagnosis, staging, and management of CKD, as well as for the risk assessment of major clinical outcomes, including mortality. The literature review highlights the theoretical basis of the association between renal function and mortality as well as the development and performance of the different eGFR equations. This study provides an extensive comparison of these six key eGFR equations, focusing on their predictive accuracies, strengths, and limitations in determining risk of all-cause mortality among the elderly population.

3 Aims

This study compares the predictive performances of recent creatinine and cystatin C eGFR equations regarding all-cause mortality among elderly Finnish population in the KIHD study cohort.

The specific aims are:

- To compare the performances of recent creatinine and cystatin C eGFR equations in predicting the risk of all-cause mortality in elderly Finnish population in the KIHD cohort.

- To evaluate if cystatin C-based eGFR equations have a better prediction of all-cause mortality than creatinine-based ones in the KIHD cohort.

- To investigate how these predictive performances differ by gender, diabetes status, and hypertension status of participants in the KIHD cohort.

4 Subjects and methods

4.1 Study setting and design

This was a prospective cohort study from the KIHD. The KIHD is a continuous cohort study established to explore the risk elements associated with CVDs and their outcomes in 2,682 middle-aged males and 920 females from Eastern Finland, predominantly residing in Kuopio and the surrounding rural areas. It has comprehensive data on demographic characteristics, health behaviors, laboratory measurements, and clinical outcome variables for each participant, which were collected at baseline between March 1984 and December 1989, then at specific follow-up rounds, which took place at 4 years, 11 years, and 20 years from the baseline (Kauhanen 2013). The female participants were included in the cohort at the 11th-year follow-up round, making the total study population 3602 at that time.

Kuopio is a municipality located in the region of North Savo, Finland. It has a population of 124,011, which makes it the 8th most populous municipality in Finland. 14.5% of the population is aged 0 to 14, 63.8% is 15 to 64, and 21.7% is 65 or older (Statistics Finland 2024).

A total of 1875 participants were involved in this study including 1241 males and 634 females having a median age of 73.6 years. This population comprised all subjects who participated in the 20-year follow-up round, which was taken as the baseline in this study, and had creatinine and cystatin C levels measured. They were followed from the 20-year follow-up round, that took place from 2005-2008, to 2019, and the mortality outcome of each participant was assessed.

4.2 Data collection

This study was conducted using the existing KIHD database, which contains data collected from multiple examination cycles conducted over several years and ongoing until now. The dataset includes detailed information on demographic features and baseline investigations from 1984 to 1989, as well as on the 20-year follow-up round that took place from 2005 to 2008. These demographic information and investigations include age, gender, body mass index (BMI) measurements, waist circumference, smoking status, alcohol consumption, renal function markers such as serum creatinine, cystatin C, urinary albumin, urinary creatinine, medical history, lifestyle factors, use of medications, and other relevant parameters. Venous blood samples were drawn without a tourniquet after participants abstained from alcohol for 3 days, fasted for 12 hours, and after they rested supine for 30 minutes. The KIHD study has been monitoring the health of participants through yearly evaluations of their electronic health records. Data for all-cause mortality and follow-up time of participants were acquired from the Cause of Death Registry of Statistics Finland.

4.3 Estimation of GFR

eGFR calculated using 6 different measurement methods:

- CKD-EPI Creatinine (CKD-EPI Cr)
- CKD-EPI Cystatin C (CKD-EPI Cys)
- CKD-EPI Creatinine-Cystatin C (CKD-EPI CrCys)
- EKFC Creatinine (EKFC Cr)
- EKFC Cystatin C (EKFC Cys)
- EKFC Creatinine-Cystatin C (EKFC CrCys)

Serum levels of creatinine were measured from venous blood samples with the modified Jaffe method (Levey et al. 2009). The eGFR measurements were calculated with the designated formulae for each using either serum creatinine, cystatin C, or both together with age and gender (Equations presented in Section 2.5). eGFR value was used as a continuous exposure evaluating the association with risk of all-cause mortality per 10-unit decrement in eGFR, as well as in 3 categories including higher (>= 90 ml/min/1.73 m^2), moderate (60 – 89.99 ml/min/1.73 m^2), and lower (<60 ml/min/1.73 m^2) eGFR categories. The higher category was used as a reference so that the risk of mortality with the lower eGFR categories could be analyzed.

4.4 Outcome assessment

The latest report of the mortality status of participants, which was in 2019, was used for this study. Therefore, participants were followed from the 20-year follow-up round to 2019, making a total follow-up time of 11-14 years (Figure 1). No loss to follow-up was reported in this period.

4.5 Covariates

Demographic factors like age and gender, lifestyle factors including BMI, smoking, and alcohol consumption, as well as comorbid conditions and surrogates such as diabetes, hypertension, CVD history, dyslipidemia, and urinary albumin-to-creatinine ratio, were included as covariates. Participants taking anti-diabetic medications and having a fasting blood glucose measurement of >= 7 mmol/L were assigned as diabetic. Hypertension was defined as the use of anti-hypertensive agents and BP measurement of >=140/90 mmHg. Dyslipidemia included participants taking cholesterol medications, total cholesterol >= 5.2 mmol/l, triglyceride >= 1.7 mmol/l, LDL cholesterol >= 3.4 mmol/l, and HDL cholesterol <1 mmol/l for males and <1.3 mmol/l for females. Urine albumin and creatinine levels were determined using spot urine samples. These included clinical and demographic factors that were identified based on prior literature and clinical considerations. These variables were collected at baseline which is the 20-year follow-up, using

standardized protocols including questionnaires, physical examinations, and laboratory tests.

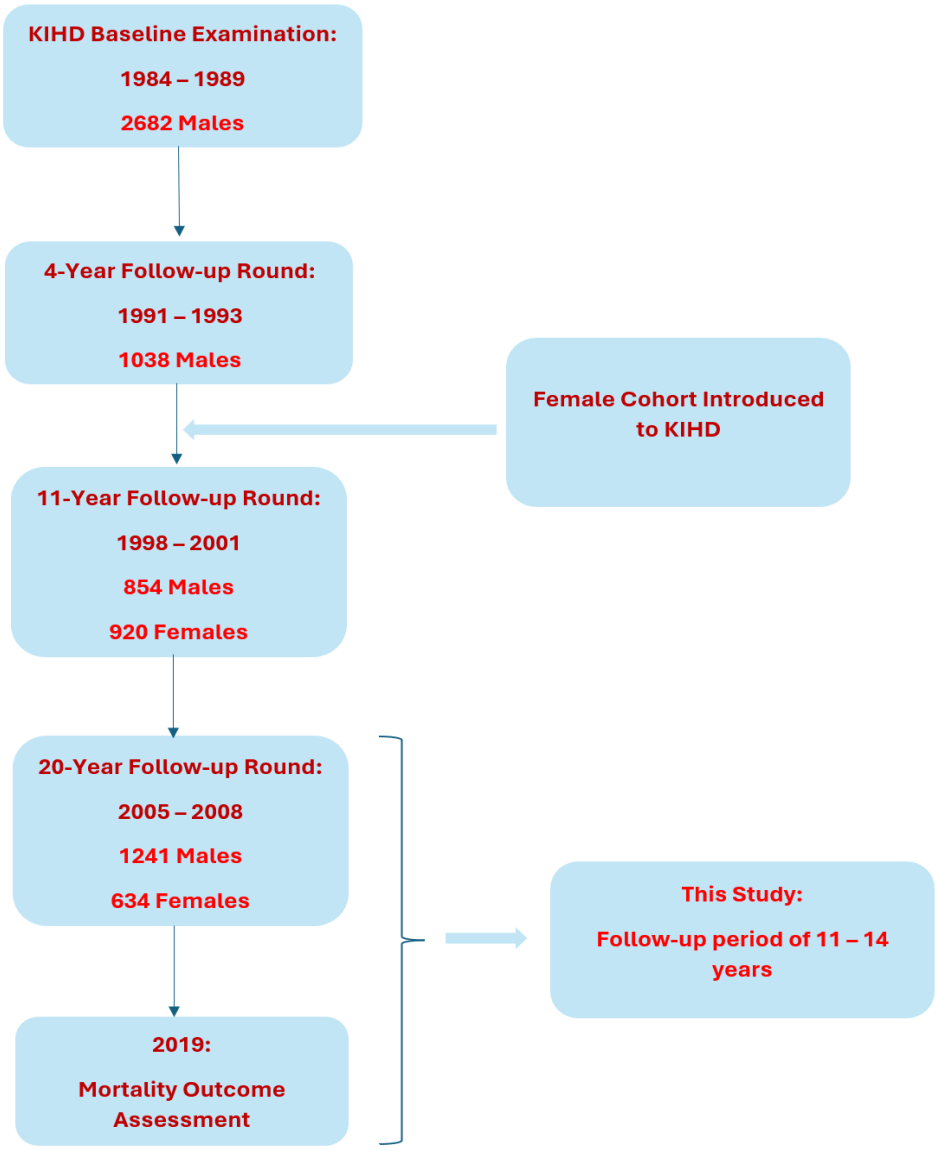


Figure 1. *Follow-up process of this study within the KIHD*

4.6 Statistical analysis

Baseline characteristics of participants are presented as median and interquartile range [IQR] for continuous variables and as counts and percentages for categorical variables. Chi-square and Kruskal-Wallis tests were used to present the baseline characteristics with respect to eGFR measurements using CKD-EPI Cys (best mortality predictor in previous studies) in 3 categories, i.e., >=

90 ml/min/1.73 m^2, 60-89.99 ml/min/1.73 m^2, and <60 ml/min/1.73 m^2. Fisher's exact and Mann-Whitney U tests were used to show the association of the baseline characteristics with the mortality status of participants.

The 6 eGFR measurement methods, consisting of CKD-EPI Cr, CKD-EPI Cys, CKD-EPI CrCys, EKFC Cr, EKFC Cys, and EKFC CrCys, were compared in their association with the risk of all-cause mortality. For each eGFR measurement method separately, the participants were divided into 3 categories based on their level of eGFR using the reference ranges recommended by KDIGO. These included higher (>= 90 ml/min/1.73 m^2), moderate (60 – 89.99 ml/min/1.73 m^2), and lower (<60 ml/min/1.73 m^2) eGFR categories.

The association of each eGFR measurement and risk of all-cause mortality was assessed using eGFR as continuous exposure by investigating the risk of mortality per 10-unit decrement in eGFR as well as using eGFR as categorical exposure by evaluating the risk of mortality in the moderate and lower categories of eGFR as compared to the higher one. Cox proportional hazard models were used to estimate the hazard ratios (HR) and 95% confidence intervals (95% CI) of these associations. Proportional hazard assumption was met and variance inflation factor as well as correlation coefficients were used to check for multicollinearity. After initially analyzing the association of each eGFR measurement alone, 3 models were introduced subsequently to adjust for covariables. Model 1 included age, gender, and examination year. In model 2, BMI, smoking status, and alcohol consumption were added. Subsequently, model 3 was additionally adjusted for diabetes, hypertension, CVD history, dyslipidemia, and urinary albumin-to-creatinine ratio (ACR). To visualize the linearity and trends of these associations clearly, unadjusted and fully-adjusted cubic spline curves were constructed.

The performances of each 6 models in predicting the risk of all-cause mortality were compared using receiver operating characteristics (ROC) curves and evaluating the area under the curve

(AUC) of each. To further discern the predictive performance of these eGFR measurements, continuous net reclassification improvement (NRI) and integrated discrimination improvement (IDI) were used. Pairwise comparisons of the relative performances were made between eGFR measurements which were found to perform the highest in the ROC analyses. Furthermore, it was analyzed how much of an added predictive value each eGFR measure had when introduced to the multivariable model.

Subgroup analyses were done to investigate the interactions of gender, diabetes status, and hypertension status with each of the eGFR measures on the association with the risk of all-cause mortality.

There were missing values in 6 variables which included serum creatinine (3 missing values), serum cystatin C (34 missing values), smoking status (4 missing values), alcohol consumption (13 missing values), spot urine albumin (8 missing values), and spot urine creatinine (8 missing values). These summed up to 70 missing values (0.18%) and were handled using multiple imputations with five datasets. Statistical analyses were conducted using SPSS (version 29, IBM Corp.) and R version 4.3.3. A p-value of <0.05 was considered statistically significant.

4.7 Ethical considerations

The University of Kuopio and Kuopio University Hospital Research Ethics Committee approved the baseline examinations of the KIHD study on December 01, 1983. The Northern Savo Hospital District Ethics Board approved the 20-year follow-up round on December 14, 2004 (approval number 103/2002). Mortality data from the Cause of Death Registry was retrieved with the diary number TK/782/07.03.00/2021 from Statistics Finland. KIHD participants were adult volunteers who gave consent in written form. The ethical principles stated in the Declaration of Helsinki were strictly followed.

5 Results

5.1 Baseline characteristics

A total of 1875 participants were included in this study, with a median age of 73.6 years and 634 (33.8%) females. With lower eGFR measurements, participants were older, had higher BMI, urinary ACR, serum creatinine levels, serum cystatin C levels, and higher likelihood of having hypertension and CVD history (p <0.001). Furthermore, lower eGFR was associated with diabetes status (p = 0.043). On the other hand, lower eGFR was associated with lower alcohol consumption but no significant difference across genders, by smoking status, and dyslipidemia (Table 3).

Table 3. Baseline characteristics by CKD-EPI cystatin C eGFR categories

		CKD-EPI Cystatin C eGFR Categories (ml/min/1.73 m^2)			
Characteristics	**Total**	**>=90**	**60-89.99**	**<60**	**P-value**
N	1875	973 (51.9)	777 (41.4)	125 (6.7)	
Age (Years)	73.6 [67.3, 74.8]	68.2 [62.5, 74.4]	74.3 [68.4, 75.3]	75.3 [74.1, 79.5]	<0.001
Gender					0.063
Male	1241 (66.2)	668 (68.7)	493 (63.4)	80 (64.0)	
Female	634 (33.8)	305 (31.3)	284 (36.6)	45 (36.0)	
BMI (Kg/m^2)	26.7 [24.5, 29.9]	26.1 [24.1, 29.1]	27.4 [24.7, 30.6]	27.7 [25.1, 31.5]	<0.001
Smoking					0.455
Non-smoker	1056 (56.3)	549 (56.4)	443 (57.0)	64 (51.2)	
Previous smoker	681 (36.3)	359 (36.9)	270 (34.7)	52 (41.6)	
Current smoker	138 (7.4)	65 (6.7)	64 (8.2)	9 (7.2)	
Alcohol consumption (g/week)	10.5 [0.0, 47.6]	16.0 [1.5, 60.8]	7.0 [0.0, 39.0]	3.8 [0.0, 21.0]	<0.001
Diabetes (yes)	192 (10.2)	88 (9.0)	84 (10.8)	20 (16.0)	0.043
Hypertension (yes)	1209 (64.5)	550 (56.5)	550 (70.8)	109 (87.2)	<0.001
CVD History (yes)	642 (34.2)	272 (28.0)	312 (40.2)	58 (46.4)	<0.001
Dyslipidemia (yes)	1373 (73.2)	699 (71.8)	572 (73.6)	102 (81.6)	0.064
Urinary ACR (mg/mmol)	1.1 [0.7, 2.2]	1.0 [0.6, 1.9]	1.1 [0.7, 2.4]	2.4 [1.0, 8.3]	<0.001
Serum Cr (µmol/l)	81.0 [71.0, 91.0]	76.0 [68.0, 84.5]	84.0 [75.0, 93.0]	107 [94.0, 120.0]	<0.001
Serum Cc (mg/l)	0.8 [0.8, 1.0]	0.8 [0.7, 0.8]	0.9 [0.9, 1.0]	1.3 [1.2, 1.5]	<0.001

Note: *Chi-square test and Kruskal-Wallis test were used. Values are presented as n (%) and median [IQR]. Column percentages are presented.* ***Abbreviations:*** *ACR – Albumin to Creatinine Ratio; BMI – Body Mass Index; CVD – Cardiovascular Disease; Cr – Creatinine; Cc – Cystatin C; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration;*

Over a median follow-up period of 11.9 years (maximum 14.9 years), 711 (37.9%) deaths occurred. Mortality was associated with older age, being male, and smoking (p <0.001 each), as well as higher BMI (p = 0.04) (Table 4).

Table 4. Baseline characteristics by mortality status

Characteristics	Total	Survivor	Non-Survivor	P-value
		1164	711	
N	1875			
Age (Years)	73.6 [67.3, 74.8]	68.4 [62.7, 74.4]	74.5 [73.5, 75.3]	<0.001
Gender				<0.001
Male	1241 (66.2)	690 (59.3)	551 (77.5)	
Female	634 (33.8)	474 (40.7)	160 (22.5)	
BMI (Kg/m^2)	26.7 [24.5, 29.9]	26.6 [24.4, 29.6]	27.0 [24.6, 30.1]	0.040
Smoking status				<0.001
Non-smoker	1056 (56.3)	709 (60.9)	347 (48.8)	
Previous smoker	681 (36.3)	380 (32.6)	301 (42.3)	
Current smoker	138 (7.4)	75 (6.4)	63 (8.9)	
Alcohol consumption (g/week)	10.5 [0.0, 47.6]	12.0 [0.3, 51.0]	8.0 [0.0, 48.0]	0.022
Diabetes (yes)	192 (10.2)	88 (7.6)	104 (14.6)	<0.001
Hypertension (yes)	1209 (64.5)	705 (60.6)	504 (70.9)	<0.001
CVD history (yes)	642 (34.2)	342 (29.4)	300 (42.2)	<0.001
Dyslipidemia (yes)	1373 (73.2)	862 (74.1)	511 (71.9)	0.307
Urinary ACR (mg/mmol)	1.10 [0.70, 2.20]	1.00 [0.60, 1.80]	1.40 [0.70, 3.20]	<0.001
S-Creatinine (µmol/L)	81.0 [71.0, 91.0]	80.0 [70.3, 89.0]	82.0 [72.0, 94.0]	<0.001
S-Cystatin C (mg/L)	0.80 [0.80, 1.00]	0.80 [0.70, 0.90]	0.90 [0.80, 1.00]	<0.001
CKD-EPI Cr	77.5 [67.6, 86.2]	77.9 [68.6, 86.6]	76.1 [65.1, 85.6]	0.001
CKD-EPI Cys	91.3 [77.3, 101]	95.0 [81.7, 103]	85.4 [71.0, 98.4]	<0.001
CKD-EPI CrCys	84.7 [74.6, 94.2]	86.7 [77.3, 95.0]	81.6 [69.9, 91.6]	<0.001
EKFC Cr	71.8 [62.4, 78.6]	72.2 [63.4, 79.5]	69.7 [60.0, 77.5]	<0.001
EKFC Cys	80.5 [75.2, 85.9]	82.8 [77.5, 88.2]	77.3 [70.5, 81.9]	<0.001
EKFC CrCys	76.1 [69.6, 81.2]	77.6 [71.6, 82.9]	73.4 [66.1, 79.1]	<0.001
Follow-up time (Days)	4356 [3601, 4828]	4649 [4335, 4956]	3037 [1882, 3970]	<0.001

Note: *Chi-square, Fisher's exact, and Mann-Whitney U tests were used. Values are shown as n (%) and median [IQR]. Column percentages are presented. The unit for eGFR values is in ml/min/1.73 m^2.* ***Abbreviations:*** *ACR – Albumin to Creatinine Ratio; BMI – Body Mass Index; CVD – Cardiovascular Disease; Cr – Creatinine; Cc – Cystatin C; CrCc – Combined Creatinine and Cystatin C; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; EKFC – European Kidney Function Consortium.*

There were higher percentages of diabetes, hypertension, and CVD history among non-survivors than survivors (p <0.001). Mortality was further associated with higher levels of urinary ACR, serum creatinine, and serum cystatin C. All eGFR measurements had significantly lower values among non-survivors than survivors (p <0.001). There was also a significant association between lower eGFR categories and mortality. On the contrary, mortality was associated with lower alcohol consumption (p = 0.022), and no significant relation with dyslipidemia (Table 4).

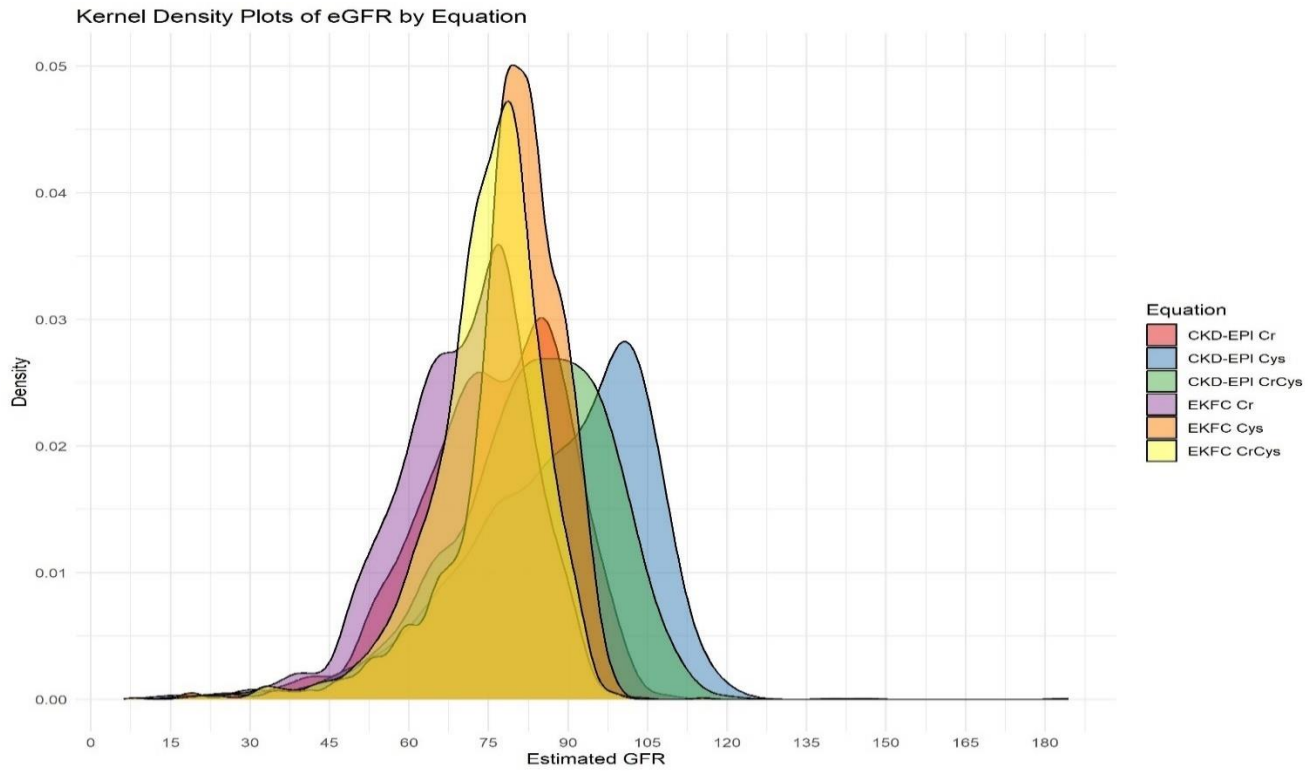


Figure 2. *Density plots of the eGFR equations*

Kernel density plots of the eGFR equations illustrate significant variations in their distributions (Figure 2). Using EKFC Cys, a great majority of the participants were categorized in the 60-89.99 ml/min/1.73 m^2 eGFR group, whereas the majority were placed in the >=90 ml/min/1.73 m^2 group when CKD-EPI Cys was used. EKFC Cr and EKFC CrCys tend to classify more participants to the lower category over the higher category.

5.2 Association of the different eGFR measurements with all-cause mortality

CKD-EPI Cys, CKD-EPI CrCys, EKFC Cys, and EKFC CrCys showed significant associations with risk of mortality, having significantly increased hazard ratios in all the models per 10-unit decrease in eGFR. Creatinine-alone eGFR measures (CKD-EPI Cr and EKFC Cr) showed an association with risk of mortality in the unadjusted models but had no relation with risk of mortality per 10-unit decrement after adjusting with covariates.

EKFC Cys had the strongest association, showing a 53.3% and a 28.7% increased hazard of mortality per 10-unit decrease in eGFR, with no adjustment and after fully adjusted for covariates respectively (HR [95% CI] 1.53 [1.46, 1.61] and 1.29 [1.20, 1.39] respectively). Comparatively, CKD-EPI Cys showed a 28% increase (1.28 [1.23, 1.33]) and a 15.6% increase (1.16 [1.10, 1.21]) in hazard of mortality per 10-unit decrement, with unadjusted and fully adjusted models respectively.

In the unadjusted models, all eGFR measurements except for CKD-EPI Cr had statistically significant increases in HR in the moderate (60-89.99 ml/min/1.73 m^2) and lower (<60 ml/min/1.73 m^2) eGFR categories as compared to the higher eGFR category (>=90 ml/min/1.73 m^2). CKD-EPI Cr showed statistically significant increases in the lower eGFR category, but not in the moderate eGFR category (Table 5).

Table 5. Cox proportional hazard models for all-cause mortality by different eGFR measurements

			Unadjusted	Model 1	Model 2	Model 3
eGFR Measures	**N**	**Event**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**	**HR (95% CI)**
CKD-EPI Cr						
Per 10-unit dec.			1.15 (1.09, 1.21)	1.03 (0.97, 1.10)	1.03 (0.97, 1.10)	1.01 (0.95, 1.07)
>=90	273	89	Ref	Ref	Ref	Ref
60-89.99	1377	514	1.16 (0.92, 1.45)	0.68 (0.53, 0.86)	0.68 (0.54, 0.87)	0.69 (0.54, 0.87)
<60	225	108	1.74 (1.31, 2.30)	0.83 (0.61, 1.12)	0.81 (0.59, 1.10)	0.76 (0.56, 1.04)
P for trend			<0.001	0.448	0.363	0.170
CKD-EPI Cys						
Per 10-unit dec.			1.28 (1.23, 1.33)	1.20 (1.14, 1.25)	1.18 (1.12, 1.23)	1.16 (1.10, 1.21)
>=90	973	286	Ref	Ref	Ref	Ref
60-89.99	777	335	1.66 (1.42, 1.94)	1.31 (1.11, 1.54)	1.26 (1.07, 1.49)	1.23 (1.04, 1.45)
<60	125	90	3.94 (3.11, 5.00)	2.61 (2.03, 3.36)	2.40 (1.86, 3.11)	2.19 (1.68, 2.86)
P for trend			<0.001	<0.001	<0.001	<0.001
CKD-EPI CrCys						
Per 10-unit dec.			1.25 (1.19, 1.31)	1.15 (1.09, 1.21)	1.14 (1.08, 1.20)	1.11 (1.05, 1.17)
>=90	678	206	Ref	Ref	Ref	Ref
60-89.99	1066	424	1.43 (1.21, 1.69)	1.15 (0.97, 1.37)	1.15 (0.96, 1.37)	1.11 (0.93, 1.33)
<60	131	81	2.92 (2.26, 3.78)	2.01 (1.52, 2.65)	1.87 (1.41, 2.47)	1.70 (1.27, 2.27)
P for trend			<0.001	<0.001	<0.001	0.003
EKFC Cr						
Per 10-unit dec.			1.21 (1.14, 1.28)	1.05 (0.97, 1.12)	1.04 (0.97, 1.12)	1.02 (0.95, 1.09)
>=90	55	10	Ref	Ref	Ref	Ref
60-89.99	1452	524	2.19 (1.17, 4.10)	0.83 (0.44, 1.60)	0.92 (0.48, 1.78)	0.92 (0.48, 1.77)
<60	368	177	3.41 (1.80, 6.44)	1.02 (0.52, 2.01)	1.11 (0.56, 2.20)	1.06 (0.54, 2.10)
P for trend			<0.001	0.050	0.067	0.171
EKFC Cys						
Per 10-unit dec.			1.53 (1.46, 1.61)	1.35 (1.26, 1.44)	1.32 (1.23, 1.41)	1.29 (1.20, 1.39)
>=90	217	23	Ref	Ref	Ref	Ref
60-89.99	1545	605	4.24 (2.79, 6.43)	1.56 (0.98, 2.47)	1.47 (0.92, 2.33)	1.45 (0.91, 2.30)
<60	113	83	12.1 (7.61, 19.2)	3.45 (2.05, 5.82)	3.05 (1.81, 5.17)	2.76 (1.62, 4.69)
P for trend			<0.001	<0.001	<0.001	<0.001
EKFC CrCys						
Per 10-unit dec.			1.44 (1.35, 1.52)	1.22 (1.13, 1.32)	1.20 (1.11, 1.30)	1.16 (1.07, 1.26)
>=90	71	11	Ref	Ref	Ref	Ref
60-89.99	1646	606	2.68 (1.48, 4.86)	0.96 (0.51, 1.79)	1.04 (0.55, 1.95)	1.05 (0.56, 1.97)
<60	158	94	5.64 (3.02, 10.5)	1.49 (0.76, 2.92)	1.51 (0.76, 2.96)	1.40 (0.71, 2.77)
P for trend			<0.001	<0.001	0.003	0.023

Note: *Model 1 – adjusted for age, gender, examination year; Model 2 – additionally for BMI, smoking status, alcohol consumption; Model 3 – additionally for diabetes, hypertension, CVD history, dyslipidemia, urinary ACR. The unit for eGFR values is in ml/min/1.73 m^2.* ***Abbreviations:*** *Cr – Creatinine; Cc – Cystatin C; CrCc – Combined Creatinine and Cystatin C; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; EKFC – European Kidney Function Consortium; HR – Hazard Ratio.*

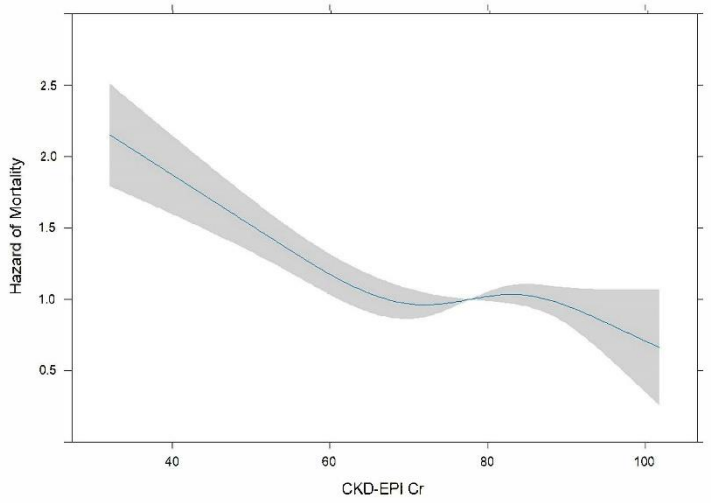
Similar to the continuous models, after fully adjusting with covariates, EKFC Cys had the best association, having a 2.76 times increased risk of mortality in the lower eGFR category compared to the higher eGFR category (HR [95% CI] 2.76 [1.62, 4.69]). Comparatively, CKD-EPI Cys uniquely showed a consistently significant association in both moderate and lower eGFR categories across all the models, which EKFC Cys failed to achieve in the fully adjusted model (p = 0.118 for moderate category). CKD-EPI Cys showed a statistically significant increased risk in both the moderate and lower eGFR categories in the fully adjusted model, with a 22.6% increased risk in the moderate category (HR [95% CI] 1.23 [1.04, 1.45]) and a 2.19 times increased risk in the lower eGFR category (HR [95% CI] 2.19 [1.68, 2.86]) compared to the higher eGFR category.

Creatinine-alone eGFRs (CKD-EPI Cr and EKFC Cr) had no significant association with risk of mortality in both the moderate and lower eGFR categories after adjusting with covariates.

P-value for trend in the 3 eGFR categories of CKD-EPI Cys and EKFC Cys showed significance (<0.001) in all 4 models, indicating a consistent and strong increasing trend in the risk of mortality moving down the eGFR categories. This trend is also seen with lower magnitude in CKD-EPI CrCys and EKFC CrCys. The trends in creatinine-alone eGFRs lose significance in the adjusted models.

These trends of association were also clearly visualized in the spline curves of each of the eGFR equations (Figure 3). CKD-EPI Cys and EKFC Cys maintained consistent downward linear curves with increasing eGFR after fully adjusting for covariates, whereas CKD-EPI Cr and EKFC Cr turned into U-shaped curves, signifying increased hazards of mortality with increasing eGFR after the curve reaches around the higher eGFR category.

A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1.0
0.5
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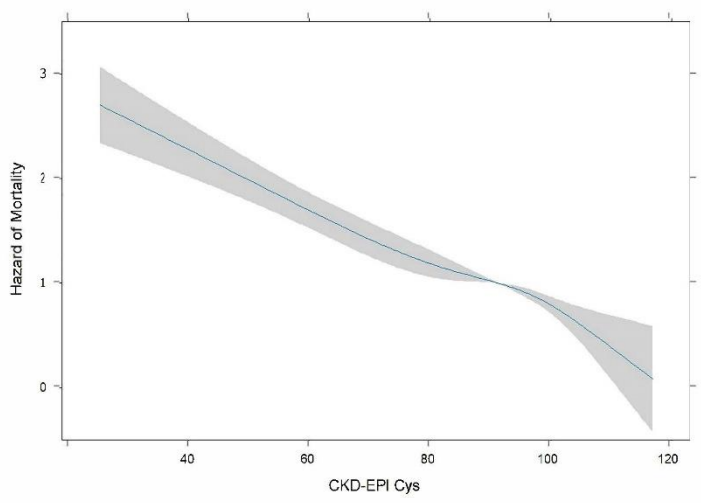
60
80
100
CKD-EPI Cr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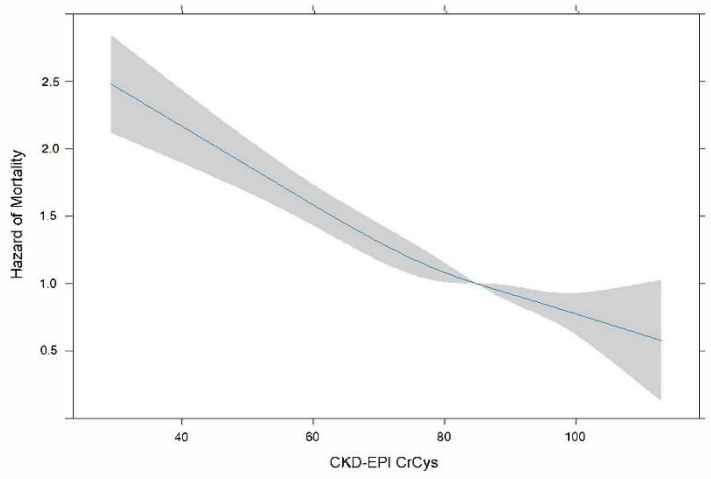
CKD-EPI Cys


Hazard of Mortality
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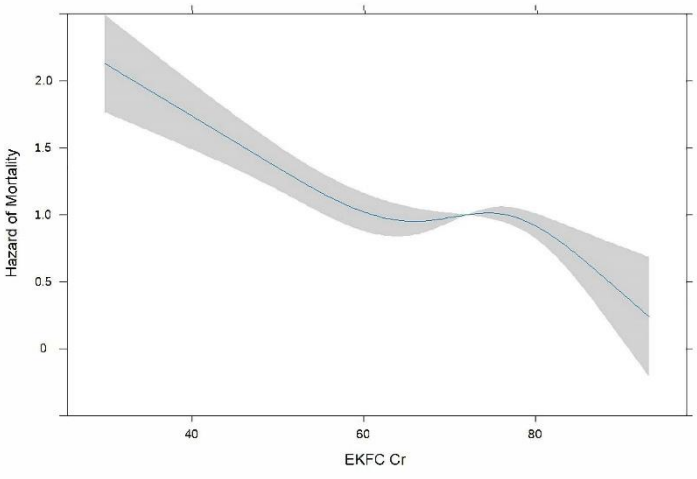
CKD-EPI CrCys


Hazard of Mortality
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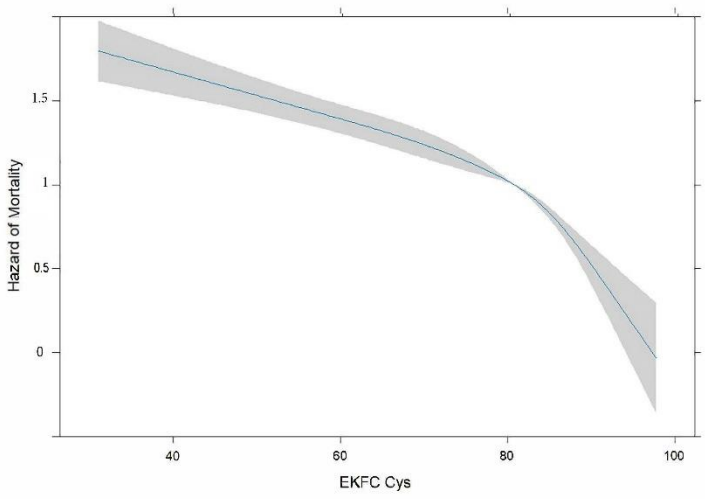
EKFC Cr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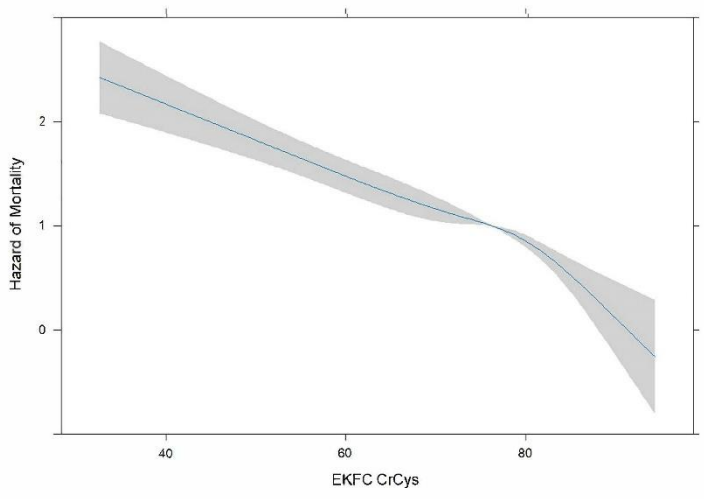
0.5
0
40
60
80
100
EKFC Cys


Hazard of Mortality
2
1
0
40
60
80
EKFC CrCys

B

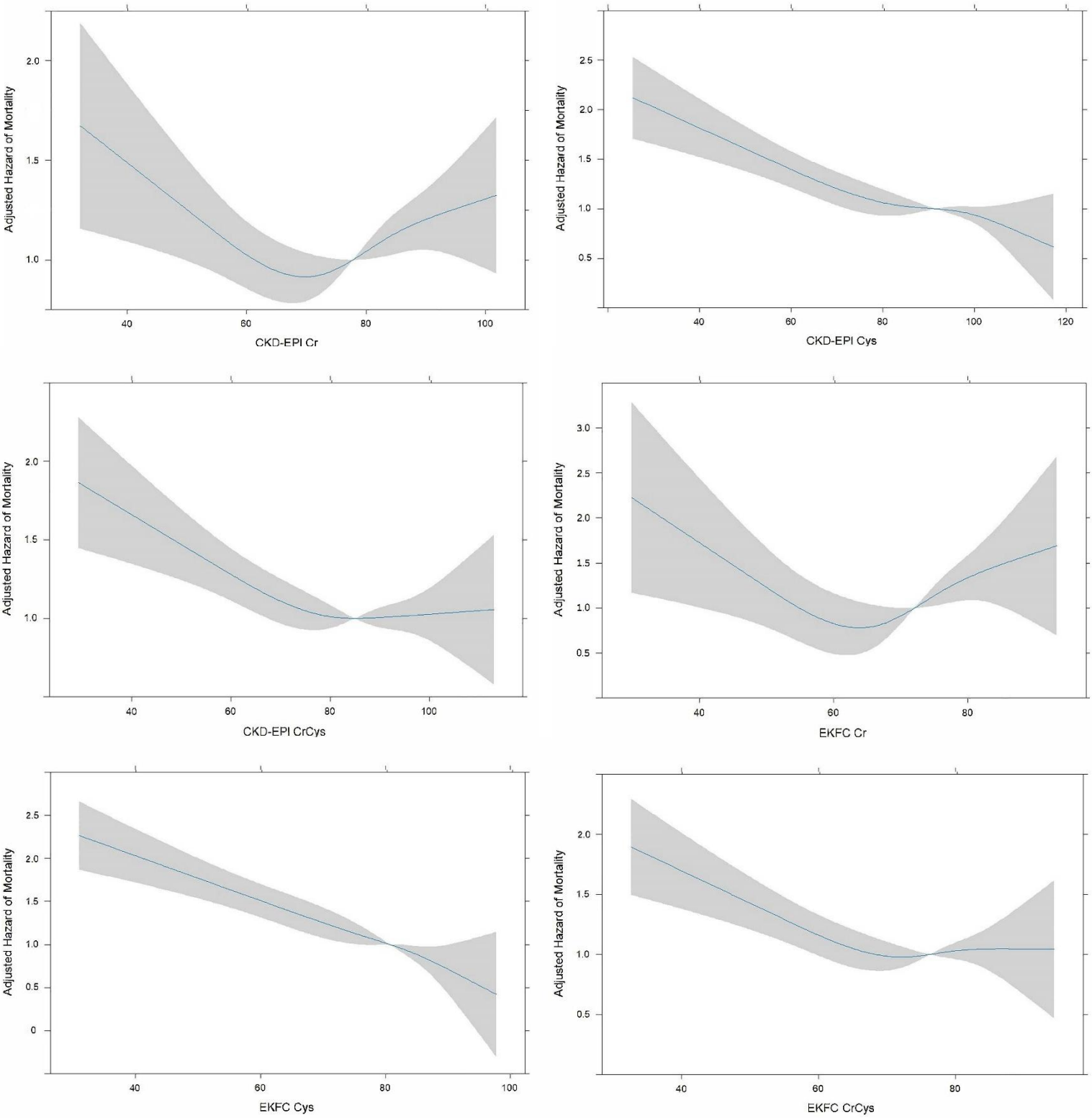


Figure 3. *Unadjusted (**A**) and fully adjusted (**B**) regression cubic splines for CKD-EPI Cr, CKD-EPI Cys, CKD-EPI CrCys, EKFC Cr, EKFC Cys, and EKFC CrCys. Models in B were adjusted for age, gender, examination year, BMI, smoking status, alcohol consumption, diabetes, hypertension, CVD history, dyslipidemia, and urinary ACR.*

5.3 Comparison of the added predictive values of each model

5.3.1 Receiver operating characteristics (ROC) and area under the curve (AUC)

In the unadjusted models, the receiver operating characteristic (ROC) curve of EKFC Cys showed the highest area under the curve (AUC 0.7) (Figure 4). CKD-EPI Cr and EKFC Cr showed much lower AUCs, with CKD-EPI Cr having the lowest value of all the other eGFR measures (0.54). AUC of EKFC Cys was significantly higher than AUC of CKD-EPI Cys (p = 0.0004). The same was seen in comparison to AUC of the other equations, with even higher significance in difference (P <0.0001).

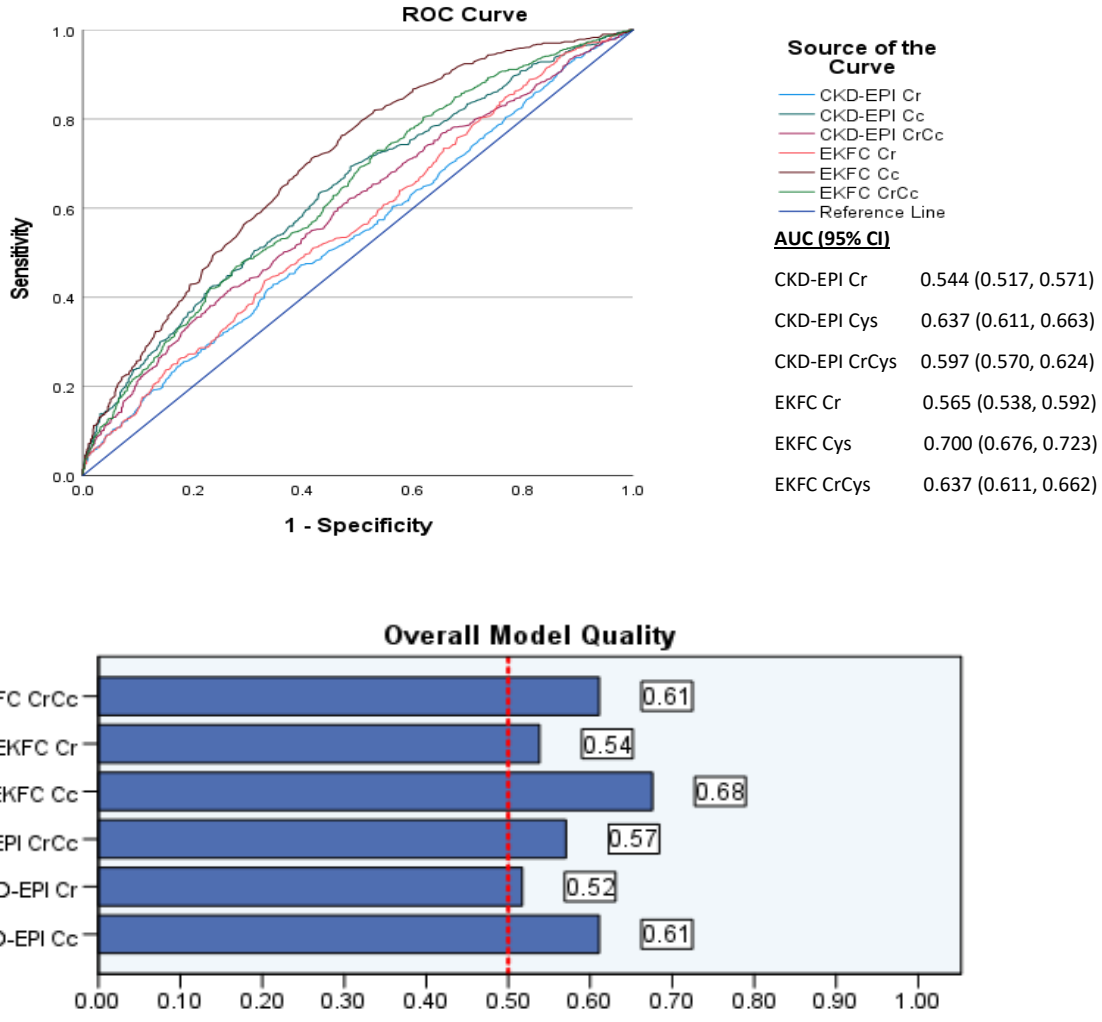


Figure 4. *Unadjusted eGFR models*

ROC curves and AUC were further used to analyze the added predictive values of each eGFR model to the multivariable model (model 3), by depicting the ROC curves of the fully adjusted models (Figure 5). EKFC Cys again showed the best performance (AUCs = 0.763), only slightly higher than CKD-EPI Cys (AUC = 0.762). CKD-EPI Cr and EKFC Cr again showed the lowest performance, with no added values to the multivariable model (0.757 for both). However, in this fully adjusted comparison of the models, the differences were not statistically significant (P-for difference >0.05 for all).

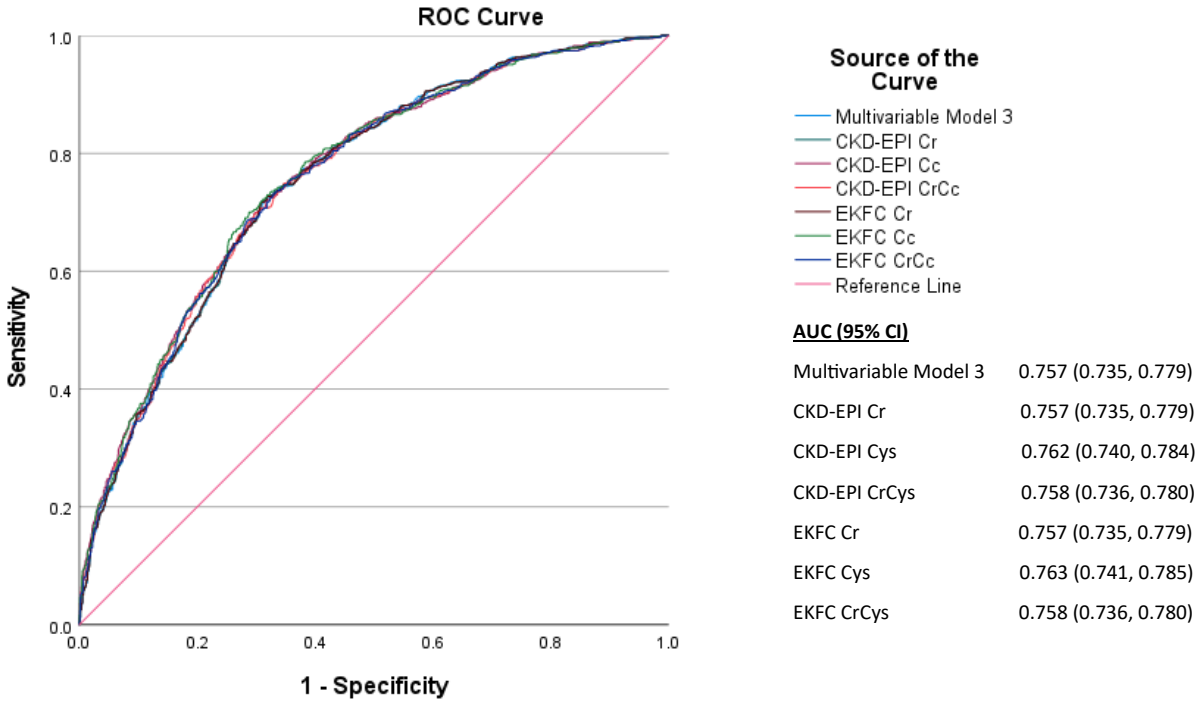


Figure 5. *Models adjusted for age, gender, examination year, BMI, smoking status, alcohol consumption, diabetes, hypertension, CVD history, dyslipidemia, and urinary ACR.*

5.3.2 Net reclassification improvement and integrated discrimination improvement

Additional comparison of the predictive performance of the 2 best ROC-AUC eGFR measurements (CKD-EPI Cys and EKFC Cys) using continuous net reclassification improvement and integrated discrimination improvement showed that CKD-EPI Cys had a slightly better reclassification improvement while EKFC Cys had a slightly better discrimination ability. When replacing

CKD-EPI Cys with EKFC Cys, there was a slight improvement in the correct classification of mortality (Event NRI = 0.024), a decrease in correct classification of survival (Non-Event NRI = −0.022), a slight non-statistically significant improvement in overall classification performance (Overall NRI [95%CI] 0.002 [−0.089, 0.093]), and a slight non-statistically significant improvement in discrimination ability (IDI [95%CI] 0.006 [−0.001, 0.013]). The exact inverse of this is seen when replacing EKFC Cys with CKD-EPI Cys, suggesting a slight improvement when using EKFC Cys in place of CKD-EPI Cys (Table 6).

Comparing CKD-EPI Cr with CKD-EPI Cys as well as with EKFC Cys showed that there is a significant improvement in both overall classification and discrimination ability when either of the latter 2 measurements replaced it (Table 6).

Table 6. Continuous net reclassification and integrated discrimination improvements

Comparator	New Model	Event NRI	Non-Event NRI	Overall NRI (95% CI)	IDI (95% CI)
CKD-EPI Cr	**CKD-EPI Cys**	−0.05	0.18	0.136 (0.045, 0.226)	0.050 (0.030, 0.070)
CKD-EPI Cr	**EKFC Cys**	−0.21	0.35	0.145 (0.052, 0.234)	0.056 (0.035, 0.077)
CKD-EPI Cys	**EKFC Cys**	0.02	−0.02	0.002 (−0.089, 0.093)	0.006 (−0.001, 0.013)
EKFC Cys	**CKD-EPI Cys**	−0.02	0.02	−0.002 (−0.093, 0.089)	−0.006 (−0.013, 0.001)
Multiv. Model	**CKD-EPI Cr**	−0.08	0.00	−0.075 (−0.179, 0.021)	−0.000 (−0.001, 0.001)
Multiv. Model	**CKD-EPI Cys**	−0.04	0.17	0.130 (0.035, 0.218)	0.050 (0.029, 0.070)
Multiv. Model	**CKD-EPI CrCys**	−0.05	0.09	0.037 (−0.056, 0.128)	0.019 (0.005, 0.032)
Multiv. Model	**EKFC Cr**	−0.08	0.03	−0.054 (−0.156, 0.040)	0.000 (−0.002, 0.002)
Multiv. Model	**EKFC Cys**	−0.22	0.33	0.116 (0.024, 0.206)	0.056 (0.034, 0.077)
Multiv. Model	**EKFC CrCys**	−0.17	0.15	−0.016 (−0.111, 0.071)	0.017 (0.004, 0.030)

Note: *The multivariable model included age, gender, examination year, BMI, smoking status, alcohol consumption, diabetes, hypertension, CVD history, dyslipidemia, and urinary ACR.* ***Abbreviations:*** *Cr – Creatinine; Cc – Cystatin C; CrCc – Combined Creatinine and Cystatin C; CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration; EKFC – European Kidney Function Consortium; IDI – Integrated Discrimination Improvement; NRI – Net Reclassification Improvement.*

Furthermore, investigation of the added predictive ability of each eGFR measurement to the multivariable model suggested that CKD-EPI Cys adds the most improvement in overall classification ability (Overall NRI [95%CI] 0.130 [0.035, 0.218]) while EKFC Cys adds the most improvement in discrimination ability (IDI (95%CI) 0.056 (0.034, 0.077)).

5.4 Sub-group analyses

5.4.1 Analysis by gender

Although there were no significant interactions between eGFR measurements and gender on risk of all-cause mortality (p-values for interaction in Table 7), EKFC Cys was the only measurement that had significant associations in both female and male participants (19.2% and 30.8% increased risk of mortality per 10-unit decrease respectively). CKD-EPI Cys, CKD-EPI CrCys, and EKFC CrCys showed significant associations with risk of mortality among male participants but failed to show significant results in the female participants. Creatinine-alone eGFR equations had no statistically significant associations in both genders.

Table 7. Association of eGFR equations with mortality by gender

	Female	Male	
Per 10-unit Decrease	**HR (95% CI)**	**HR (95% CI)**	**P-value for Interaction**
CKD-EPI Cr	0.96 (0.85, 1.09)	1.02 (0.95, 1.10)	0.210
CKD-EPI Cys	1.07 (0.96, 1.20)	1.17 (1.12, 1.24)	0.080
CKD-EPI CrCys	1.01 (0.89, 1.15)	1.13 (1.07, 1.21)	0.060
EKFC Cr	0.95 (0.82, 1.10)	1.03 (0.95, 1.12)	0.190
EKFC Cys	1.19 (1.00, 1.42)	1.31 (1.21, 1.42)	0.110
EKFC CrCys	1.05 (0.88, 1.26)	1.19 (1.09, 1.31)	0.100

Note: *Models adjusted for age, examination year, BMI, smoking status, alcohol consumption, diabetes, hypertension, CVD history, dyslipidemia, and urinary ACR.*

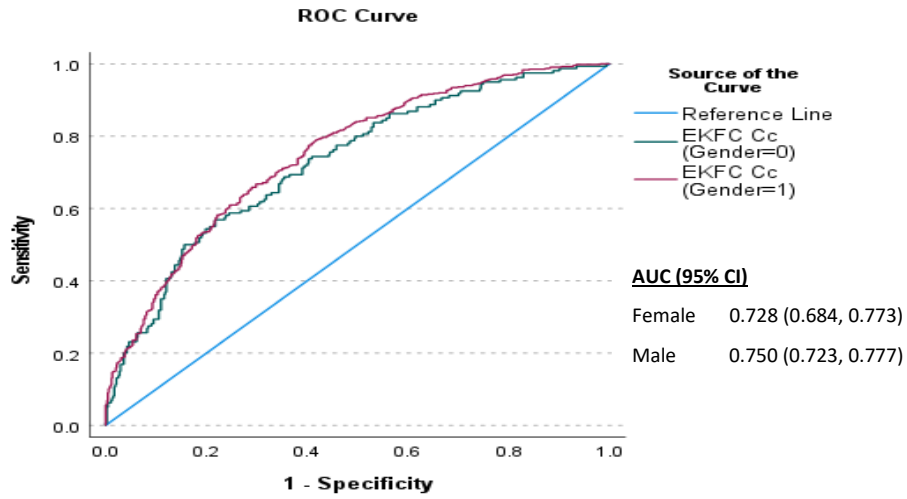


Figure 6. *Fully adjusted EKFC Cys eGFR models for male and female participants. Models were adjusted for age, examination year, BMI, smoking status, alcohol consumption, diabetes, hypertension, CVD history, dyslipidemia, and urinary ACR.*

Using EKFC Cys as a representative of the eGFR measurements in the ROC curves illustrated that there was higher predictive performance of the model among males compared to females (AUC 0.750 > 0.728) but is not statistically significant (p = 0.412) (Figure 6).

5.4.2 Analysis by diabetes status

The interactions between each of the different eGFR measures and diabetes status on the association with risk of all-cause mortality were not statistically significant, with EKFC Cr being an exception (p = 0.038). EKFC Cys, CKD-EPI Cys, CKD-EPI CrCys, and EKFC CrCys showed significant associations with risk of all-cause mortality among both non-diabetic and diabetic participants (Table 8). The point estimates and p-value for interaction for EKFC Cys indicated that it was the most resistant to and least affected by diabetes status.

Table 8. Association of eGFR equations with mortality by diabetes status

	Non-Diabetic	Diabetic	
Per 10-unit Decrease	**HR (95% CI)**	**HR (95% CI)**	**P-value for Interaction**
CKD-EPI Cr	0.99 (0.92, 1.05)	1.11 (0.95, 1.29)	0.210
CKD-EPI Cys	1.15 (1.09, 1.21)	1.19 (1.06, 1.33)	0.260
CKD-EPI CrCys	1.09 (1.03, 1.16)	1.17 (1.03, 1.34)	0.100
EKFC Cr	0.99 (0.91, 1.07)	1.13 (0.95, 1.35)	0.040
EKFC Cys	1.27 (1.17, 1.38)	1.35 (1.12, 1.62)	0.340
EKFC CrCys	1.13 (1.03, 1.24)	1.26 (1.04, 1.53)	0.110

Note: *Models adjusted for age, gender, examination year, BMI, smoking status, alcohol consumption, hypertension, CVD history, dyslipidemia, and urinary ACR.*

5.4.3 Analysis by hypertension status

Hypertension showed significant interactions with the creatinine-alone measurements (CKD-EPI Cr and EKFC Cr), results suggesting decreased hazards of mortality per 10-unit decrease in these eGFR measurements among non-hypertensive participants while showing no significant associations in the hypertensive group. EKFC Cys again was found to have the most resistance and least variation by hypertension status (Table 9).

Table 9. Association of eGFR equations with mortality by hypertension status

	Non-Hypertensive	Hypertensive	
Per 10-unit Decrease	**HR (95% CI)**	**HR (95% CI)**	**P-value for Interaction**
CKD-EPI Cr	0.84 (0.73, 0.97)	1.06 (0.99, 1.14)	0.010
CKD-EPI Cys	1.08 (0.97, 1.20)	1.18 (1.12, 1.24)	0.270
CKD-EPI CrCys	0.97 (0.86, 1.02)	1.15 (1.08, 1.22)	0.040
EKFC Cr	0.82 (0.69, 0.97)	1.08 (0.99, 1.17)	0.010
EKFC Cys	1.23 (0.99, 1.52)	1.30 (1.20, 1.40)	0.930
EKFC CrCys	0.92 (0.74, 1.15)	1.21 (1.11, 1.33)	0.080

Note: *Models adjusted for age, gender, examination year, BMI, smoking status, alcohol consumption, diabetes, CVD history, dyslipidemia, and urinary ACR.*

6 Discussion

This study revealed that EKFC Cys has the strongest association with the risk of all-cause mortality as compared to the other EKFC and CKD-EPI eGFR equations. It showed the highest hazard of mortality of all the eGFR equations in the survival analysis testing the association of eGFR, as both a continuous and categorical variable, with all-cause mortality. This was true for the unadjusted as well as all the multivariable-adjusted models. Furthermore, in both unadjusted and fully-adjusted models, it performed as the best predictor of the risk of all-cause mortality, as showcased by its highest AUC in the ROC analysis and highest discriminative ability in the IDI analysis. CKD-EPI Cys closely followed, but still showed some findings which appeared superior to EKFC Cys. The results suggesting this include that, in all the models, CKD-EPI Cys showed the only persistently significant increment in hazard ratio in the moderate (60-89.99 ml/min/1.73 m^2) eGFR category as compared to the higher (>=90 ml/min/1.73 m^2) eGFR category, although the HRs were weaker than that of EKFC Cys. Moreover, it had a slightly higher added reclassification improvement to the multivariable model than EKFC Cys. Overall, a decrement in eGFR values of all the 6 eGFR equations showed an association with risk of all-cause mortality. This association is lost in the creatinine-based equations - CKD-EPI Cr and EKFC Cr – at the minimum adjustment of the model for confounders, signifying a weak association affected by basic demographics. Cystatin C and combined equations were found to be better than creatinine equations in their association and prediction of all-cause mortality, indicating the high contribution cystatin C has to the association with mortality in this specific cohort.

In its initial validation study, the EKFC Cys equation showed improved GFR estimation accuracy compared to the commonly used equations, including the CKD-EPI Cys equation (Pottel et al. 2023). However, the study did not investigate its performance in predicting the risk of mortality. To our knowledge, no study has yet compared this equation’s risk prediction performance among elderly population, which this study provides. This present study found that the performance of EKFC Cys as a risk prediction tool equates to its previous status as having one of the best GFR estimation accuracy. Yet, Pottel et al. (2023), in the same study found that the EKFC

CrCys equation, which is the arithmetic mean of its creatinine and cystatin C counterparts, further enhanced the accuracy of GFR estimates beyond using either biomarker equation alone. But this does not reflect to its mortality risk prediction ability, because it is inferior to EKFC Cys in both its association and prediction of the risk of all-cause mortality. Several previous studies have shown a similar relation between the cystatin C-alone CKD-EPI equation (CKD-EPI Cys) and the combined creatinine-cystatin C CKD-EPI equation (CKD-EPI CrCys), in which CKD-EPI CrCys had the better accuracy in GFR estimation while CKD-EPI Cys had the better accuracy in mortality risk prediction (Helmersson-Karlqvist et al. 2016, Helmersson-Karlqvist et al. 2021). This indicates that cystatin C, when used as a sole GFR estimator, performs as the best mortality risk predictor, whereas when used together with creatinine, performs as the most accurate GFR estimator. This is exactly consistent with the findings of Astor et al. (2009), who concluded that despite better performance in estimating GFR, equations using both creatinine and cystatin C did not predict mortality as effectively as those using cystatin C alone. Thus, in this present study, it was confirmed that this holds true for the EKFC equations and among elderly populations.

Furthermore, prior studies have demonstrated the superiority of eGFR equations using either cystatin C alone or in combination with creatinine over eGFR equations using creatinine alone in their use as risk-predicting tools (Peralta et al. 2011, Chen et al. 2023). It is important to note that the same findings were reached in studies involving elderly participants (Willey et al. 2020). Similarly, in this present study, which involved elderly Finnish men and women, eGFR equations using cystatin C and combined creatinine-cystatin C (EKFC Cys, EKFC CrCys, CKD-EPI Cys, CKD-EPI CrCys) had better performances in both their association as well as prediction of the risk of all-cause mortality, compared to the creatinine-alone equations. A similar Finnish study was conducted by Salminen et al. (2016), which was a longitudinal cohort study that investigated the associations of serum cystatin C, serum creatinine, CKD-EPI Cr equation, and CKD-EPI CrCys equation with CVD and non-CVD mortality, among 1260 elderly Finnish individuals in Lieto, Finland. They found that serum cystatin C remained a significant predictor whereas serum creatinine and the creatinine-based eGFR equations lost their predictive value after multivariate adjustment. The results of this present study highlight these findings of previous literature, confirming that

lower eGFR values by cystatin C-based equations have better association with all-cause mortality as compared to creatinine-based equations in the KIHD cohort of elderly Eastern Finnish population.

There was a great variation in the distribution of GFR by the six equations, with participants being categorized in the 3 eGFR groups differently. Based on this, when comparing the performance of these eGFR equations in predicting all-cause mortality using this fixed categorization for all, significant differences are generally expected. Taking this into account, it may be required to identify ideal threshold values for each eGFR equation to form separate risk categories for each. However, the practicality of this approach is highly questionable in routine clinical setups, where the common risk categories set by the KDIGO are utilized for risk stratification (KDIGO 2024). This is also the case in Finnish clinical setups (HUSLAB 2020). Despite this, comparison using continuous eGFR values gives a common ground on which we can identify the eGFR equation that can more accurately predict all-cause mortality, as in this study.

The general findings of this study agree with the current evidence of the underlying physiological mechanisms relating cystatin C and creatinine with renal function and risk of all-cause mortality. Cystatin C, a low molecular weight protein produced by all nucleated cells, undergoes free filtration at the glomerulus and subsequent metabolism in the proximal tubule, making it a dependable indicator for estimating GFR (Ferguson et al. 2015). Unlike serum creatinine, which is influenced by various non-GFR factors like muscle mass and diet, cystatin C is less affected by such factors, making it a more reliable indicator of renal function (Chen et al. 2022a). In the context of CKD, accurate detection and staging are crucial because CKD elevates risks for adverse outcomes such as ESRD and mortality (Spencer et al. 2023). Cystatin C-based eGFR reclassification can change the risk categorization for patients, providing a more accurate risk stratification (Chen et al. 2022a). In line with this present study, previous literature show that cystatin C and cystatin C-based eGFRs have stronger and more linear associations with mortality risk compared to serum creatinine and creatinine-based eGFRs (Menon et al. 2007, Shlipak et al. 2013, Lees et

al. 2019). The same findings were demonstrated among elderly cohorts (Shlipak et al. 2005, Shlipak et al. 2006, Shlipak et al. 2006). The mere inclusion of cystatin C in GFR estimation provides a more accurate prognostic tool (Tolomeo et al. 2023). This was also evidenced by this present study which showed that the combined creatinine-cystatin C equations (CKD-EPI CrCys and EKFC CrCys) had higher prediction of mortality as compared to their creatinine-alone counterparts.

A subgroup analysis by gender illustrated that EKFC Cys was the only equation that had significant associations with all-cause mortality in both males and females, with a higher HR and AUC seen in males. The others, including CKD-EPI Cys, showed non-significant associations among female participants but significant associations among male participants. This is with the exception of the creatinine-alone equations, which showed no associations for both genders. This result contrasts with the findings of the study by Malmgren et al. (2020), that followed the association between CKD-EPI Cys and mortality among elderly women for 10 years. They found that among women in CKD categories 3b to 5 (based on KDIGO <45 ml/min/1.73 m^2), the hazard of mortality increased compared to those in categories 1 and 2 (>60 ml/min/1.73 m^2). For ages 75–80 years, the adjusted HR was 3.9 (95% CI: 2.3, 6.5), and for ages 80–85 years, it was 1.7 (95% CI: 1.0, 2.7), indicating a significant association of lower eGFR values by CKD-EPI Cys with risk of mortality. However, in this present study, CKD-EPI Cys was not found to have significant association with mortality in female participants after fully adjusting for confounders. The relatively lower number of confounders accounted for in the Malmgren et al. (2020) study and the lower sample size for females in this present study might serve as the most likely explanations for these contrasting findings. Overall, this indicates that EKFC Cys is the best predictor of risk of all-cause mortality for both males and females, even though it shows a relatively lower HR and AUC in females as compared to males.

There was a slightly higher hazard of mortality among diabetic participants as compared to non-diabetic participants seen in all eGFR equations. This goes in line with the findings of a recent

study from China which compared the association of different eGFRs with risk of all-cause mortality by diabetes status of participants (Liu et al. 2023). They found that per 10-unit decline in eGFR, non-diabetic participants had HR of 1.14 using CKD-EPI Cys, 1.13 using CKD-EPI CrCys, and 1.04 using CKD-EPI Cr, whereas diabetic participants had HR of 1.30 using CKD-EPI Cys, 1.31 using CKD-EPI CrCys, and 1.16 using CKD-EPI Cr. Thus, the relationship between eGFR and mortality risk varies by the presence of diabetes, showing enhancement among diabetic individuals (Liu et al. 2023). Furthermore, in this present study, the results in the analysis by diabetes status indicate that EKFC Cys has relatively higher resistance to changes based on diabetes and could be used among diabetic and non-diabetic individuals more reliably as compared to the other equations.

Similarly, in an analysis based on hypertension status, the eGFR equations showed a more increased HR in hypertensive participants. The creatinine-alone eGFRs (CKD-EPI Cr and EKFC Cr) had decreased hazards of mortality per 10-unit decrease among non-hypertensive participants while having weak and non-significant rises in hazards of mortality among hypertensive participants. Despite the lack of studies evaluating the effect of hypertension on the association of eGFR with risk of mortality, a prospective cohort study by Chowdhury et al. (2015) investigated risk prediction of mortality using the CKD-EPI Cr equation among elderly hypertensive population. They divided participants into 4 categories by this eGFR equation as >60, 45-59, 30-44, and <30 ml/min/1.73 m^2, and used the >60 category as the reference to investigate the relative hazards of mortality in the lower eGFR categories. The study found that all 3 lower eGFR categories had significantly larger hazards of mortality as compared to the higher category, with consistent increment seen in the HR going down the categories (Chowdhury et al. 2015). Again, in this present study, it was found that EKFC Cys had the least variation among hypertensive and non-hypertensive participants, having very low sensitivity to hypertension status.

With lower categories of eGFR (using CKD-EPI Cys) and among non-survivors, alcohol consumption was found to be lower. This association with alcohol consumption was peculiar, with,

perhaps, abstinence among individuals with risks or previous excess alcohol use serving as a potential explanation. Similarly, a study by Agahi et al. (2016) found that among 863 elderly Institutionalized Swedish individuals, light-to-moderate drinkers lived longer than those who did not drink or who drank heavily. Agahi et al. (2016) further found that participants who did not drink alcohol had more health problems than those who drank light to moderate amounts.

This study had certain limitations worthy of discussion. It included only single initial measurements of serum creatinine and cystatin C. Although there were prior measurements of serum creatinine in the KIHD cohort, measurement of serum cystatin C was made only at the 20-year follow-up round, which this study considered as baseline. Repeated measures of these markers at regular intervals would have given a better understanding of the trend of renal function through time, clearly differentiating participants with a lower but more stable GFR from those with a dramatic decline in their renal function. In addition, there was no mGFR using exogenous filtration markers, which hindered us from investigating for and validating the most accurate equation in estimating true GFR values. Another limitation was that the study cohort was ethnically and socio-culturally homogenous including Caucasian population in Kuopio, Finland. Thus, it may lack reliability to extend the findings to other groups. Furthermore, data for defining diagnosis of diabetes, hypertension, and dyslipidemia was attained from single measurements of fasting blood glucose levels, blood pressure, and lipid profiles. However, the definitions for these conditions were adequately supported by data on medication use for each comorbidity.

7 Conclusion

The EKFC Cys eGFR equation demonstrated the strongest association as well as prediction of the risk of all-cause mortality among elderly Finnish population. The CKD-EPI Cys equation, which was regarded as the best mortality risk predictor in prior studies, had a weaker association with the risk of all-cause mortality compared to EKFC Cys. Higher predictive performance of cystatin C and combined creatinine-cystatin C equations over creatinine-alone equations was noted, highlighting prior findings that cystatin C is generally a better mortality risk predictor than creatinine. EKFC Cys significantly associated with mortality risk in both men and women, which the other eGFR equations failed to achieve. All in all, EKFC Cys appears the best-performing eGFR equation in both predicting all-cause mortality and being least sensitive to changes by gender and comorbidities in this population. This study affirms the importance of using more accurate eGFR equations, like EKFC Cys, for better risk stratification in clinical settings, particularly in the elderly, and potentially for guiding clinical decision-making in these groups.

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