

Discordance Between Creatinine- and Cystatin-C-Based EGFR As A Predictor Of Frailty, Cardiovascular Events and Mortality in Patients With Diabetes

Dr. Vraj Rajeshkumar Shah¹, Dr. Anis Preethi Aruldas², Dr. Viknesh Prabu Anbalagan³

¹Junior Resident, Department of General Medicine, Sree Balaji Medical College and Hospital Chennai, Tamil Nadu

²Assistant Professor, Department of General Medicine, Sree Balaji Medical College and Hospital Chennai, Tamil Nadu

³Associate Professor, Department of General Medicine, Sree Balaji Medical College and Hospital Chennai, Tamil Nadu

Corresponding Author:

Dr. Vraj Rajeshkumar Shah, Email Id: vraj.shah2311@gmail.com

Abstract

Background: Estimated glomerular filtration rate (eGFR) is central to the assessment of kidney disease in diabetes, but creatinine- and cystatin-C-based equations do not always classify an individual similarly. This discordance may contain clinical information beyond the absolute eGFR value. Creatinine is influenced by muscle mass and creatinine generation, whereas cystatin C is influenced by several non-GFR determinants including inflammation, adiposity, thyroid status and corticosteroid exposure. Consequently, a markedly lower cystatin-C-based eGFR than creatinine-based eGFR may identify a phenotype of reduced physiologic reserve that is not fully captured by conventional creatinine-based kidney staging.

Objective: To determine whether discordance between creatinine-based eGFR (eGFR_{cr}) and cystatin-C-based eGFR (eGFR_{cys}) is associated with frailty, incident cardiovascular events and all-cause mortality among adults with diabetes, and to determine whether discordance provides incremental prognostic information beyond conventional kidney-function measures and established cardiovascular risk factors.

Methods: This proposed prospective cohort study will enroll adults with diabetes with contemporaneous serum creatinine and cystatin C measurements. eGFR will be calculated using validated contemporary equations, preferably the 2021 CKD-EPI creatinine and cystatin-C equations and the combined creatinine-cystatin-C equation where applicable. The principal exposure will be negative discordance, defined a priori as eGFR_{cys} at least 30% lower than eGFR_{cr}; absolute and alternative relative thresholds will be examined in sensitivity analyses. Frailty will be assessed using a validated instrument, and participants will be followed for cardiovascular events and mortality. Multivariable Cox and logistic regression models will evaluate associations after adjustment for age, sex, diabetes duration, albuminuria, kidney function, cardiovascular risk factors and relevant non-GFR determinants.

Conclusion: The study is designed to test whether eGFR discordance is a clinically meaningful phenotype in diabetes. Current evidence supports an association between lower eGFR_{cys} relative to eGFR_{cr} and adverse outcomes, but the optimal discordance threshold and the mechanisms linking discordance to frailty remain incompletely established. The proposed study therefore treats discordance as a prognostic exposure rather than assuming that it represents a direct measurement of measured GFR.

Keywords: diabetes mellitus; creatinine; cystatin C; estimated glomerular filtration rate; eGFR discordance; frailty; cardiovascular disease; mortality; chronic kidney disease; diabetic kidney disease.

Introduction

Diabetes is a major risk factor for chronic kidney disease (CKD), cardiovascular disease and premature mortality. Kidney function is therefore a core component of cardiovascular risk assessment in people with diabetes. Serum creatinine remains the conventional filtration marker, but creatinine concentration depends partly on muscle mass, dietary intake and creatinine generation. These determinants become especially relevant in older adults and people with sarcopenia, frailty, altered body composition or chronic illness [1–3].

Cystatin C provides an alternative filtration marker because its concentration is less dependent on muscle mass than creatinine. However, cystatin C is not biologically specific for GFR: inflammation, obesity, thyroid dysfunction, smoking and corticosteroid exposure may affect its concentration. KDIGO 2024 therefore recommends creatinine-based eGFR for initial assessment and recommends combined creatinine-cystatin-C eGFR when cystatin C is available, particularly when creatinine-based eGFR may be less accurate and GFR affects clinical decisions [1].

The difference between eGFR_{cr} and eGFR_{cys} is increasingly recognized as more than a technical discrepancy. A recent systematic review and meta-analysis found that discordance characterized by a substantially lower eGFR_{cys} was consistently associated with higher mortality and cardiovascular risk. Across the included literature, lower

eGFR_{cys} relative to eGFR_{cr} was associated with approximately 58% higher mortality and 32% higher cardiovascular-event risk, although definitions of discordance varied between studies [4].

More recently, an individual-participant meta-analysis involving more than 860,000 participants reported that an eGFR_{cys} at least 30% lower than eGFR_{cr} was associated with higher all-cause mortality, cardiovascular mortality, atherosclerotic cardiovascular disease, heart failure and kidney-failure outcomes. The association was present across outpatient cohorts, while substantial negative discordance was also common among inpatients [5].

The phenomenon may be particularly relevant to diabetes. In a prospective cohort of 1,153 people with diabetes, cystatin-C-based CKD classification was independently associated with cardiovascular events after adjustment for established cardiovascular risk factors, whereas creatinine-based CKD definitions were substantially attenuated [6]. Contemporary diabetes literature has consequently begun to consider eGFR discordance as a potential marker of broader health status rather than simply an alternative method of estimating filtration [7].

Frailty provides a clinically important bridge between kidney-function measurement and outcomes. Reduced muscle mass can make creatinine-based eGFR appear relatively preserved, while a lower cystatin-C-based eGFR may identify a patient whose biological reserve is lower than creatinine alone suggests. At the same time, cystatin C itself may rise because of inflammatory and metabolic processes. Thus, discordance may represent the interaction of kidney dysfunction, altered body composition and systemic vulnerability rather than a single pathophysiological mechanism. In older adults, large negative eGFR discordance has been associated with falls, hospitalization and death independent of kidney function [8].

Rationale and Research Gap

The key clinical problem is not simply whether eGFR_{cr} or eGFR_{cys} is 'better.' Rather, disagreement between the two estimates may identify patients in whom either creatinine-based assessment or cystatin-C-based assessment alone fails to represent the complete clinical picture. In diabetes, where obesity, sarcopenia, inflammation, cardiovascular disease and CKD commonly coexist, this discrepancy may have particular prognostic significance.

Existing evidence establishes an association between negative eGFR discordance and adverse outcomes in general populations, older adults and mixed clinical cohorts [4,5,8]. However, diabetes-specific evidence connecting discordance simultaneously with frailty, cardiovascular events and mortality remains comparatively limited. There is also no universally accepted definition of clinically important discordance. The proposed study addresses these gaps by prospectively evaluating a diabetes cohort using both relative and absolute discordance measures and by formally incorporating frailty into the outcome framework.

Aim and Objectives

Primary Aim

To evaluate whether discordance between eGFR_{cr} and eGFR_{cys} predicts frailty, cardiovascular events and all-cause mortality in adults with diabetes.

Primary Objectives

1. To determine the prevalence and magnitude of eGFR discordance in adults with diabetes.
2. To assess the association between negative eGFR discordance and frailty at baseline.
3. To determine whether negative eGFR discordance predicts incident major cardiovascular events.
4. To determine whether negative eGFR discordance predicts all-cause mortality.
5. To determine whether discordance provides incremental prognostic information beyond eGFR_{cr}, albuminuria and established cardiovascular risk factors.

Secondary Objectives

6. To compare outcomes across concordant, negative-discordant and positive-discordant eGFR groups.
7. To compare relative discordance definitions with absolute eGFR differences.
8. To examine whether the relationship between discordance and outcomes differs by age, sex, diabetes type, diabetes duration, albuminuria and baseline eGFR.
9. To determine whether frailty mediates or modifies the association between negative discordance and adverse outcomes.

10. To evaluate whether the combined eGFRcr-cys equation improves risk classification compared with eGFRcr or eGFRcys alone.

Research Questions and Hypotheses

- Negative eGFR discordance will be more prevalent among older adults and individuals with greater comorbidity, frailty and altered body composition.
- Participants whose eGFRcys is substantially lower than eGFRcr will have a higher prevalence of frailty after adjustment for age, sex, diabetes duration and kidney-function measures.
- Negative discordance will be independently associated with major cardiovascular events and all-cause mortality.
- The association between discordance and mortality will persist after adjustment for albuminuria and conventional cardiovascular risk factors.
- The combined interpretation of eGFRcr and eGFRcys will provide additional prognostic information beyond either marker alone.

Materials and Methods

Study Design

Prospective observational cohort study of adults with diabetes recruited from diabetes, nephrology, internal-medicine and/or cardiovascular outpatient services. The study should be registered prospectively and conducted according to the Declaration of Helsinki and applicable institutional ethics requirements.

Study Population

Adults with established diabetes who have contemporaneous creatinine and cystatin C measurements and sufficient clinical information to calculate validated eGFR values and ascertain frailty and follow-up outcomes.

Inclusion Criteria

- Age ≥ 18 years.
- Established type 1 or type 2 diabetes according to accepted diagnostic criteria.
- Available serum creatinine and cystatin C obtained within the same prespecified assessment window, ideally the same blood draw.
- Ability to complete baseline frailty assessment or availability of sufficient information for a validated frailty measure.
- Consent for longitudinal outcome follow-up.

Exclusion Criteria

- Acute kidney injury at the time of biomarker assessment, unless the protocol specifically intends to study acute illness.
- Kidney replacement therapy at baseline, unless included as a predefined subgroup.
- Conditions or treatments expected to produce major non-GFR effects on either marker when these cannot be adequately measured or adjusted for.
- Recent major cardiovascular event if the study objective is incident cardiovascular events from a stable baseline.
- Insufficient information to classify eGFR discordance or ascertain the primary outcomes.

Exposure Definition: eGFR Discordance

The primary exposure will be the relative difference between eGFRcys and eGFRcr. A prespecified primary definition will classify negative discordance as $\text{eGFRcys/eGFRcr} \leq 0.70$, equivalent to eGFRcys being at least 30% lower than eGFRcr. This threshold is supported by recent large-scale outcome literature [5], but it should not be interpreted as a universally validated clinical cutoff.

Participants will initially be classified into: (1) concordant eGFR, eGFR_{cys} >70% to <130% of eGFR_{cr}; (2) negative discordance, eGFR_{cys} ≤70% of eGFR_{cr}; and (3) positive discordance, eGFR_{cys} ≥130% of eGFR_{cr}. Sensitivity analyses will examine an absolute difference of ≤-15 mL/min/1.73 m² and other thresholds reported in systematic reviews [4].

Variable	Definition	Purpose
eGFR _{cr}	Creatinine-based eGFR using a validated contemporary equation	Primary renal comparator
eGFR _{cys}	Cystatin-C-based eGFR using a validated contemporary equation	Primary renal comparator
eGFR _{cr-cys}	Combined creatinine-cystatin-C eGFR	Reference/secondary renal estimate
Relative eGFR _{diff}	eGFR _{cys} /eGFR _{cr}	Primary discordance exposure
Absolute eGFR _{diff}	eGFR _{cys} – eGFR _{cr} , mL/min/1.73 m ²	Sensitivity exposure
Negative discordance	eGFR _{cys} ≤70% of eGFR _{cr}	Primary high-risk category
Concordance	eGFR _{cys} within 70–130% of eGFR _{cr}	Reference category
Positive discordance	eGFR _{cys} ≥130% of eGFR _{cr}	Secondary comparison group

Frailty Assessment

Frailty should be measured using a validated instrument selected before recruitment. Preferred options include the Fried frailty phenotype, Clinical Frailty Scale, Edmonton Frail Scale or a validated deficit-accumulation frailty index. The selected instrument should be applied consistently across participants and should include objective or standardized assessment of physical performance, weakness, exhaustion, weight loss and/or functional impairment as appropriate.

The primary frailty endpoint may be defined as frailty versus non-frailty using the selected validated instrument. Secondary analyses should retain frailty as an ordinal or continuous measure when statistically appropriate. Because low muscle mass can simultaneously affect creatinine and frailty, muscle mass, BMI, weight loss and physical performance should be collected whenever feasible.

Cardiovascular Outcomes

The primary cardiovascular endpoint will be a composite major adverse cardiovascular event (MACE), preferably defined prospectively as cardiovascular death, nonfatal myocardial infarction, nonfatal ischemic stroke and hospitalization for heart failure. Secondary endpoints may include each component separately, peripheral arterial events and coronary revascularization.

Events should be adjudicated using prespecified definitions and blinded to baseline discordance status where feasible. Hospital records, physician documentation, ECG/imaging reports and death certificates or validated national registries may be used for ascertainment.

Mortality Outcome

The primary mortality endpoint will be all-cause mortality. Cardiovascular mortality will be a secondary endpoint. Time-to-event should be calculated from the date of biomarker/eGFR assessment to death, last confirmed follow-up, or study end.

Covariates and Potential Confounders

- Age, sex and ethnicity where permitted and relevant to the chosen equation and local reporting requirements.
- Diabetes type, duration and treatment regimen.
- HbA1c and glucose control.
- Systolic and diastolic blood pressure.
- Urinary albumin-to-creatinine ratio and proteinuria.
- Serum creatinine, cystatin C, eGFR_{cr}, eGFR_{cys} and eGFR_{cr-cys}.
- BMI, waist circumference, recent weight loss and measures of muscle mass or physical performance where feasible.
- History of coronary artery disease, heart failure, stroke/TIA, peripheral arterial disease and hypertension.

- Smoking, lipid profile and lipid-lowering therapy.
- CRP or another inflammatory marker where available.
- Thyroid function, corticosteroid exposure and other major non-GFR determinants of cystatin C.
- Frailty and functional status.

Laboratory Methods

Creatinine and cystatin C should ideally be measured from the same blood draw. The laboratory should document assay platform, calibration/traceability, analytical range, lower limit of detection, coefficient of variation and sample handling procedures. eGFR should be calculated using prespecified validated equations, and the same equation should be used consistently within the primary analysis. KDIGO 2024 emphasizes the importance of understanding non-GFR determinants of creatinine and cystatin C and specifically notes that differences between eGFR_{cr} and eGFR_{cys} can themselves be informative [1].

Potential non-GFR determinants should be recorded rather than ignored. KDIGO identifies situations such as severe inflammation, high cell turnover, advanced heart failure, high-dose steroids and very frail states as circumstances in which creatinine and/or cystatin-C-based estimates may be less reliable [1]. These factors should therefore be addressed through exclusion, adjustment or sensitivity analyses according to the prespecified protocol.

Sample Size Consideration

A target sample of approximately 1,000 participants is proposed for an initial prospective diabetes cohort, subject to formal power calculation using local event rates. If the anticipated prevalence of primary negative discordance is approximately 15–30%, the study should be sized to ensure adequate numbers in the discordant group and sufficient cardiovascular and mortality events for multivariable survival analysis. The final sample size should be calculated from the anticipated MACE and mortality rates, effect size, alpha, power, number of prespecified model parameters and expected loss to follow-up.

The final statistical analysis plan should be finalized before outcome-driven subgroup selection or model optimization.

Statistical Analysis

- Baseline characteristics will be compared across concordant, negative-discordant and positive-discordant groups using appropriate parametric/non-parametric and categorical tests.
- Continuous eGFR discordance will be evaluated alongside categorical definitions to avoid dependence on a single arbitrary threshold.
- Frailty will be analysed using multivariable logistic/ordinal regression and, where appropriate, a continuous frailty index.
- Time-to-event cardiovascular and mortality outcomes will be evaluated using Kaplan–Meier methods and Cox proportional-hazards models.
- The primary model will adjust for age, sex, diabetes duration, albuminuria, eGFR_{cr} and established cardiovascular risk factors. Additional models will assess whether the association persists after adding BMI, muscle-related variables, inflammation and relevant medication exposures.
- Because discordance mathematically depends on both eGFR_{cr} and eGFR_{cys}, collinearity will be assessed and model specifications will avoid simultaneously including highly redundant variables without justification.
- Restricted cubic splines will explore non-linear associations between continuous relative discordance and outcomes.
- Incremental predictive value will be assessed using change in discrimination, likelihood-based measures, calibration and decision-curve analysis where appropriate.
- Interactions will be prespecified for age, sex, baseline eGFR, albuminuria, diabetes duration and frailty.
- Multiple imputation will be considered for missing covariates when missingness and assumptions support its use.
- Sensitivity analyses will repeat the main models using alternative discordance definitions, excluding acute illness, excluding advanced CKD, and restricting to participants with stable kidney function.

Proposed Data Collection Framework

Domain	Variables
Demographics	Age, sex, ethnicity where relevant, BMI, waist circumference
Diabetes	Type, duration, HbA1c, treatment, hypoglycaemia history
Kidney	Creatinine, cystatin C, eGFRcr, eGFRcys, eGFRcr-cys, UACR, CKD stage
Body composition	Weight, recent weight loss, muscle mass/strength where feasible
Frailty	Validated frailty score, gait speed, grip strength, exhaustion, activities of daily living
Cardiovascular	CAD, MI, HF, stroke/TIA, PAD, BP, lipids
Inflammation / modifiers	CRP, thyroid status, corticosteroid exposure, smoking
Outcomes	MACE, individual CV events, cardiovascular death, all-cause death
Follow-up	Date of event, hospitalization, last contact, cause of death

Expected Findings and Interpretation

Based on existing literature, the most plausible hypothesis is that a substantially lower eGFRcys than eGFRcr will identify a subgroup with greater frailty and higher cardiovascular and mortality risk. This does not necessarily mean that cystatin C is always a more accurate measure of measured GFR. Rather, the discordance may capture a combination of lower filtration and non-GFR biological characteristics that correlate with vulnerability.

The distinction is important. If negative discordance remains associated with outcomes after adjustment for measured eGFRcr, albuminuria, age and cardiovascular risk factors, this would support the hypothesis that discordance contains information beyond conventional kidney staging. If the association disappears after adjustment for frailty or muscle-related variables, discordance may primarily act as a marker of altered body composition and reduced physiologic reserve.

Positive discordance should also be studied rather than treated as a neutral category. A higher eGFRcys relative to eGFRcr may arise when creatinine is disproportionately elevated because of greater muscle mass, dietary intake or other non-GFR determinants. Its relationship with outcomes may therefore differ from negative discordance and should be interpreted separately.

Discussion

The proposed study addresses an increasingly relevant issue in diabetes care: two accepted filtration markers can produce materially different estimates of kidney function in the same patient. KDIGO 2024 explicitly recognizes that differences between eGFRcr and eGFRcys may be informative and recommends combined eGFRcr-cys when creatinine-based estimation is less accurate and GFR affects clinical decisions [1].

Recent outcome evidence strengthens the rationale for studying discordance itself. A systematic review and meta-analysis reported consistent associations between lower eGFRcys relative to eGFRcr and mortality and cardiovascular outcomes [4]. A subsequent individual-participant meta-analysis of more than 821,000 outpatient participants found that eGFRcys at least 30% lower than eGFRcr was associated with higher all-cause mortality, cardiovascular mortality, atherosclerotic cardiovascular disease and heart failure [5]. These findings provide a strong external basis for the proposed exposure definition, while also demonstrating that the threshold should remain a research construct until further validated.

Diabetes provides a particularly important clinical context. A Diabetes Care cohort study found that cystatin-C-defined CKD was more strongly associated with cardiovascular events than creatinine-based CKD definitions after adjustment for established cardiovascular risk factors [6]. This suggests that cystatin C may capture clinically relevant risk that creatinine-based assessment can miss. However, cystatin C is also influenced by obesity and inflammation, both common in diabetes, so a lower eGFRcys should not automatically be interpreted as pure renal impairment [6].

Frailty may be one mechanism linking discordance with outcomes. Creatinine generation falls with reduced muscle mass; therefore, a person with low muscle mass can have a deceptively reassuring creatinine concentration despite impaired filtration. A substantially lower eGFR_{cys} may reveal this mismatch. Evidence from older adults shows that large negative discordance is associated with falls, hospitalizations and death, supporting the possibility that discordance reflects a broader phenotype of reduced physiologic reserve [8].

The principal scientific contribution of the proposed study would be to integrate these domains in a diabetes-specific population. Rather than asking whether creatinine or cystatin C is superior in isolation, the analysis asks whether disagreement between the two markers identifies a clinically meaningful subgroup. Such a framework may be more useful for risk stratification because it preserves information contained in the relationship between biomarkers.

Clinical implementation would nevertheless require external validation and evidence of utility. Even a statistically significant hazard ratio does not demonstrate that measuring cystatin C changes management or improves outcomes. Before routine adoption, future studies should determine whether discordance-guided assessment improves identification of frailty, medication safety, cardiovascular prevention or other clinically actionable decisions.

Strengths

- Prospective design with contemporaneous creatinine and cystatin C measurements.
- Diabetes-specific cohort directly addresses a high-risk population.
- Frailty is incorporated as a clinically meaningful phenotype rather than treating mortality as the only endpoint.
- Both relative and absolute discordance definitions are evaluated.
- The study distinguishes biomarker prognostication from direct measurement of GFR.
- Potential non-GFR determinants of both biomarkers are explicitly incorporated into the analysis plan.

Limitations and Potential Bias

- Observational associations cannot establish causality.
- Cystatin C is influenced by non-GFR determinants, so discordance may not represent true GFR measurement error alone.
- Creatinine-based eGFR may be biased by low muscle mass, high muscle mass, diet and other factors.
- The selected discordance threshold may influence prevalence and effect estimates; no single threshold is universally accepted.
- Frailty measurement varies by instrument and may introduce classification differences.
- Residual confounding by inflammation, nutrition, socioeconomic status and functional status may remain.
- Loss to follow-up may bias long-term mortality estimates.
- Single-centre recruitment may limit generalizability.

Conclusion

Discordance between creatinine- and cystatin-C-based eGFR may represent a clinically informative phenotype in people with diabetes. Existing evidence indicates that substantially lower eGFR_{cys} relative to eGFR_{cr} is associated with mortality and cardiovascular outcomes, while evidence in older adults suggests associations with falls and hospitalization. Diabetes-specific studies also suggest that cystatin-C-based kidney assessment may identify cardiovascular risk not fully captured by creatinine-based definitions. The proposed prospective study therefore evaluates whether negative eGFR discordance is associated with frailty, cardiovascular events and mortality and whether it adds prognostic information beyond conventional kidney and cardiovascular risk measures. The study should ultimately determine whether eGFR discordance is merely a laboratory discrepancy or a reproducible marker of reduced physiologic reserve and adverse prognosis.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney International*. 2024;105(4S):S117–S314.

2. Levey AS, Inker LA. Assessment of glomerular filtration rate in health and disease: a state of the art review. *Clinical Pharmacology & Therapeutics*. 2017;102:405–419.
3. Delanghe JR, Speeckaert MM. Cystatin C: a novel biomarker for cardiovascular disease. *Clinical Biochemistry*. 2015;48:168–176.
4. Zhu Y, et al. Discordance between cystatin C-based and creatinine-based estimated glomerular filtration rate and health outcomes in adults: a systematic review and meta-analysis. *Clinical Kidney Journal*. 2025.
5. CKD Prognosis Consortium. Discordance in Creatinine- and Cystatin C-Based eGFR and Clinical Outcomes: A Meta-Analysis. *JAMA*. 2025.
6. Shlipak MG, et al. Cystatin C– and Creatinine-Based Estimated Glomerular Filtration Rate, Vascular Disease, and Mortality in Persons With Diabetes in the U.S. *Diabetes Care*. 2014;37:1002–1008.
7. Harjutsalo V, et al. Comparison of Serum Creatinine– and Cystatin C–Based eGFR at Baseline and Their Prediction of Incident Moderate Albuminuria in Individuals With Type 1 Diabetes. *Diabetes Care*. 2025.
8. Rifkin DE, et al. Large Discordance between Creatinine-Based and Cystatin C–Based eGFRs is Associated with Falls, Hospitalizations, and Death in Older Adults. *American Journal of Kidney Diseases*. 2024.
9. Inker LA, et al. New Creatinine- and Cystatin C–Based Equations to Estimate GFR without Race. *New England Journal of Medicine*. 2021;385:1737–1749.
10. Grubb A, et al. Cystatin C—a new marker for glomerular filtration rate independent of age and gender. *Scandinavian Journal of Clinical and Laboratory Investigation*. 1995;55:221–228.
11. American Diabetes Association Professional Practice Committee. Chronic Kidney Disease and Risk Management: Standards of Care in Diabetes—2026. *Diabetes Care*. 2026.
12. Tietz Textbook of Laboratory Medicine. 7th ed. Elsevier; 2022.
13. Harrison's Principles of Internal Medicine. 22nd ed. McGraw Hill; 2025.