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Phenotypic Determinants and Clinical Implications of Creatinine-Cystatin C eGFR Discordance in Nigerian Adults

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Abstract

Background: Discordance between creatinine-based estimated glomerular filtration rate (eGFRcr) and cystatin C-based estimated glomerular filtration rate (eGFRcys) is increasingly recognised, but remains poorly characterised in African populations. We evaluated the magnitude, determinants, and clinical consequences of eGFR discordance among Nigerian adults with and without chronic kidney disease (CKD).

Methods: In this cross-sectional study, 303 Nigerian adults were recruited at the University of Abuja Teaching Hospital, Nigeria, between February, 2020, and February, 2022. Serum creatinine and cystatin C were measured, and eGFR was calculated using the 2021 CKD-EPI equations. Agreement was assessed using Bland-Altman analysis and intraclass correlation coefficients (ICC). Multivariable regression identified determinants of biomarker variability and CKD stage reclassification.

Results: Overall agreement between eGFRcr and eGFRcys was moderate (ICC 0.515), but differed markedly by CKD status (ICC 0.088 without CKD vs 0.804 with CKD). Among participants without CKD, 198 (81.8%) had absolute eGFR discordance of at least 15 mL/min per 1.73 m² and 145 (59.9%) had discordance of at least 30 mL/min per 1.73 m². Male sex was associated with lower odds of substantial discordance (OR 0.40, 95% CI 0.20–0.80). Overall, 153 (50.5%) participants were reclassified to a different KDIGO stage using eGFRcys, with upward reclassification predominating in those without CKD and downward reclassification in those with CKD. In participants without CKD, sex was the principal determinant of biomarker variability, whereas mean arterial pressure and age predominated in CKD. Each 1 mmHg increase in mean arterial pressure increased the odds of stage reclassification by 4% (aOR 1.04, 95% CI 1.02–1.07).

Interpretation: eGFR discordance is common in Nigerian adults and reflects distinct biological processes according to CKD status. These findings support contextual interpretation of eGFR and selective use of cystatin C to improve CKD classification and clinical decision making in African populations.

Highlights

• Creatinine-cystatin C eGFR discordance is highly prevalent among healthy Nigerian adults.

• Biological determinants of eGFR discordance differ fundamentally by CKD status.

• Sex drives biomarker discordance in non-CKD, whereas mean arterial pressure predominates in CKD.

• Cystatin C reclassified 50.5% of participants into different KDIGO CKD stages.

• Selective cystatin C testing may improve CKD classification and clinical decision-making in African populations.

1. Introduction

Chronic kidney disease (CKD) has emerged as one of the fastest-growing non-communicable diseases worldwide, imposing an expanding burden of premature mortality, cardiovascular disease, and healthcare expenditure. The Global Burden of Disease Study 2023 estimated that approximately 788 million adults are living with CKD globally, with an age-standardised prevalence of 14.2% and a continuing rise over the past three decades [1]. The burden is particularly severe in sub-Saharan Africa, where late presentation, limited access to kidney replacement therapy, and constrained diagnostic capacity amplify the consequences of delayed disease recognition [2]. Nigeria is among the countries with the highest CKD burden globally, emphasizing the need for accurate and equitable approaches to kidney function assessment in populations that remain underrepresented in nephrology research [3].

Estimated glomerular filtration rate (eGFR) is central to the diagnosis, staging, prognosis, and management of CKD. Current Kidney Disease: Improving Global Outcomes (KDIGO) guidelines recommend creatinine-based eGFR (eGFRcr) for routine evaluation, while advocating cystatin C-based eGFR (eGFRcys), or combined creatinine–cystatin C equations, when greater diagnostic precision is required or when non-glomerular determinants may compromise creatinine-based estimates [4]. The adoption of the 2021 CKD Epidemiology Collaboration (CKD-EPI) race-free equations represented a major advance towards more equitable kidney function assessment, particularly for Black populations previously affected by race-adjusted estimation strategies [5, 6]. Nevertheless, replacing race coefficients does not eliminate the biological variability inherent in endogenous filtration markers.

Creatinine and cystatin C each reflect glomerular filtration but are influenced by distinct non-GFR determinants. Creatinine is strongly affected by skeletal muscle mass, dietary protein intake, and tubular secretion, whereas cystatin C is comparatively independent of muscle mass but may vary with inflammation, adiposity, thyroid dysfunction, smoking, and corticosteroid exposure [7, 8]. Consequently, the two biomarkers frequently generate discordant eGFR estimates in the same individual. Increasing evidence suggests that this discordance is not simply analytical variability but a clinically meaningful phenotype associated with adverse kidney, cardiovascular, and mortality outcomes independent of estimated kidney function itself [9].

Emerging studies have further shown that disagreement between eGFRcr and eGFRcys follows predictable biological patterns rather than occurring at random. Large population-based analyses have demonstrated that approximately one-quarter of adults exhibit clinically important discrepancies between creatinine- and cystatin C-derived eGFR, with the magnitude and direction of discordance influenced by characteristics such as age, sex, body composition, and comorbidity [10]. However, an important unanswered question is whether the biological determinants of discordance remain constant across the spectrum of kidney disease. Progressive nephron loss may fundamentally alter the relative influence of muscle mass, haemodynamic factors, and other non-GFR determinants on each biomarker, yet studies explicitly examining the architecture of discordance according to CKD status remain scarce [8, 10].

This knowledge gap is particularly relevant in sub-Saharan Africa, where CKD develops within a markedly different clinical and epidemiological context from that of Europe and North America. Hypertension and chronic glomerular disease remain leading causes of CKD, patients frequently present at younger ages and with more advanced disease, and differences in body composition, nutritional status, and cardiovascular risk profiles may modify the biological behaviour of endogenous filtration markers [2, 11]. Yet evidence describing eGFR discordance in African populations remains extremely limited, despite the potential implications for CKD classification, medication dosing, specialist referral, and implementation of current KDIGO recommendations regarding selective cystatin C testing [4].

We therefore evaluated the magnitude, phenotypic determinants, and clinical consequences of discordance between creatinine- and cystatin C-based eGFR among Nigerian adults with and without CKD. We hypothesised that eGFR discordance represents a biologically structured phenomenon whose determinants differ fundamentally according to CKD status, leading to distinct patterns of biomarker agreement and clinically relevant CKD stage reclassification.

2. Materials and Methods

2.1 Study Design and Setting

This study employed a cross-sectional analytical design to evaluate the clinical, anthropometric, and metabolic determinants of renal biomarker variability and the resulting phenotypic discordance between creatinine- and cystatin C-based estimated glomerular filtration rate (eGFR) equations. Participants were recruited between February 2020 and February 2022 in Abuja, Federal Capital Territory (FCT), Nigeria. Enrolment and clinical assessments were conducted through the Department of Chemical Pathology, University of Abuja Teaching Hospital (UATH), Gwagwalada, Abuja.

2.2 Ethical Consideration

Ethical approval was obtained from the Health Research Ethics Committee of the University of Abuja Teaching Hospital, Abuja, Nigeria (Ref No: UATH/HREC/PR/2020/002/089; approved on 6 February 2020). The study adhered to the ethical principles outlined in the Declaration of Helsinki. Detailed verbal and written information regarding study objectives, procedures, risks, and benefits was provided, and written informed consent was obtained from all participants prior to evaluation. Confidentiality was strictly maintained using anonymized identification numbers.

2.3 Study Population

The study population comprised 303 Nigerian adults aged 18 years and above, categorized into two distinct cohorts: individuals with established chronic kidney disease (CKD cohort, n = 61) and individuals without evidence of CKD (Non-CKD cohort, n = 242). Non-CKD participants were recruited from voluntary blood donor clinics, occupational screening programmes, and community volunteers. CKD participants were recruited from the nephrology outpatient clinics of UATH and consisted of patients receiving

routine specialist care. Clinical classification was based on comprehensive medical history, clinical evaluation, and laboratory assessment.

2.4 Eligibility Criteria

Non-CKD Cohort: Eligible participants were clinically healthy adults aged 18–65 years with no history of chronic kidney disease or major chronic medical disorders. Participants were excluded if they had diabetes mellitus, chronic liver disease, cardiovascular disease, autoimmune disorders, active urinary tract infection, HIV, Hepatitis B or C, pregnancy, lactation, or current use of medications known to influence protein metabolism. Participants were required to avoid strenuous physical activity for 24 hours preceding specimen collection.

CKD Cohort: Eligible participants were adults with established CKD attending nephrology services. Exclusions included acute kidney injury, active systemic infection, severe dehydration, recent hospitalization for acute illness, pregnancy, or incomplete clinical records.

For both cohorts, samples exhibiting significant haemolysis, lipaemia, or icterus were excluded.

2.5 Clinical Evaluation and Data Collection

Data collection utilized a structured, interviewer-administered proforma capturing age, sex, medication history, alcohol intake, and herbal supplement use. Anthropometric measurements were obtained using a calibrated SECA 700 mechanical column scale with an integrated stadiometer (SECA GmbH & Co. KG, Hamburg, Germany). Body mass index (BMI) was calculated as weight (kg) divided by height squared (m2). Blood pressure was measured using a validated automated oscillometric sphygmomanometer (Omron HEM-705CP) after a 10-minute seated rest; the average of two readings taken 5 minutes apart was recorded. Mean arterial pressure (MAP) was calculated from systolic and diastolic values.

2.6 Specimen Collection and Biochemical Analysis

Venous blood samples (5 mL) were collected between 08:00 and 10:00 hours following an overnight fast of 8–12 hours to minimize metabolic variability and determine fasting/random blood sugar (RBS) alongside renal biomarkers. Serum was separated via centrifugation at 3,000 rpm for 10 minutes.

Serum cystatin C was measured using the ST AIA-PACK CYSTATIN C immunoenzymometric assay on the TOSOH AIA-360 automated analyser (Tosoh Bioscience Inc., USA). Serum creatinine was determined using the alkaline picrate (Jaffe) method (AGAPPE Diagnostics Switzerland GmbH) and quantified spectrophotometrically at 492 nm.

Estimated GFR was calculated using the CKD-EPI 2021 equations for creatinine (eGFRcr) and cystatin C (eGFRcys). Kidney function was categorized according to KDIGO G-stages: G1 (>= 90), G2 (60–89), G3a (45–59), G3b (30–44), G4 (15–29), and G5 (< 15 mL/min/1.73m2).

2.7 Quality Assurance Procedures

Internal quality control was performed daily using two-level control materials. Analytical performance was monitored using Levey-Jennings charts and Westgard multi-rule criteria. The analytical performance target required intra-assay and inter-assay coefficients of variation to remain below 5% for all analytes. All analyses were performed by laboratory scientists blinded to participants' clinical classifications.

2.8 Statistical Analysis

Data were reviewed for completeness, and variables were assessed for normal distribution using the Shapiro-Wilk test and density plots. As continuous variables deviated from a normal distribution, non-parametric approaches and appropriate standardization were utilized. Baseline characteristics were compared using Mann-Whitney U tests for continuous data and Chi-square tests for categorical variables. The magnitude of phenotypic divergence between cohorts was quantified using standardized effect sizes (Cohen's d) with 95% confidence intervals (CIs). Monotonic relationships between biomarkers and demographic variables were evaluated using Spearman's rank correlation (rho).

To evaluate comparative drivers of biomarker variability, multiple linear regression models were constructed for creatinine and cystatin C. Prior to modelling, all continuous predictors and outcomes were standardized (mean = 0, standard deviation = 1) to generate Standardized beta coefficients, enabling direct comparison of effect magnitudes across variables measured on different scales. To determine if biomarker associations are modified by underlying renal health, these models were strictly stratified by CKD status. Multicollinearity was rigorously assessed; variables with a Variance Inflation Factor (VIF) ≥ 5 were iteratively removed, ensuring all final models maintained a VIF < 2.0.

Equation agreement was evaluated using Bland-Altman analysis (mean bias and 95% Limits of Agreement [LOA]) and two-way mixed Intraclass Correlation Coefficients (ICC). Because the mathematical constraints of the CKD-EPI equations at lower GFRs artificially force convergence, analyses of absolute discordance (|Delta eGFR|) were stratified. Binary logistic regression was applied exclusively to the non-CKD cohort to identify independent predictors of substantial (|Delta eGFR| >= 15) and major (|Delta eGFR| >= 30) clinical discordance.

Clinical consequences were assessed via stage reclassification cross-tabulations. Overall and subgroup-specific staging agreement was quantified using quadratic weighted Cohen's Kappa with 95% CIs. Binary logistic regression was utilized to identify variables independently associated with the likelihood of experiencing any KDIGO stage shift, reporting adjusted Odds Ratios (aOR) and 95% CIs. All analyses were conducted using R software, with two-tailed statistical significance established at $p < 0.05$.

3. Results

3.1 Baseline Phenotypic Divergence and Effect Sizes

The study included 303 Nigerian adults (242 non-CKD controls; 61 CKD patients). As anticipated by the case-control design, phenotypic separation was substantial. The CKD cohort was significantly older (p <

0.001), exhibited a lower BMI (p = 0.001), and had markedly elevated blood pressure compared to healthy controls. Standardized effect size calculations revealed that the magnitude of functional difference between the cohorts was greater when measured by creatinine (Cohen's d = 3.64, 95% CI: 3.24 to 4.05) than by cystatin C (Cohen's d = 3.16, 95% CI: 2.79 to 3.54). Consequently, eGFRcr exhibited a wider separation between the groups (Cohen's d = -4.90) compared to eGFRcys (Cohen's d = -1.65) (Table 1).

Table 1
Baseline Characteristics and Standardized Effect Sizes (CKD vs. Non-CKD)

Variable	Non-CKD (n = 242) Mean (SD) or n (%)	CKD (n = 61) Mean (SD) or n (%)	p-value	Cohen's d (95% CI)
Age (years)	28.57 (9.71)	44.69 (14.16)	< 0.001	1.49 (1.20 to 1.77)
Sex (Female)	122 (50.4%)	25 (41.0%)	0.241	-
BMI (kg/m2)	27.53 (6.31)	24.68 (4.13)	0.001	-0.49 (-0.77 to -0.21)
Systolic BP (mmHg)	118.05 (11.78)	143.90 (18.56)	< 0.001	1.88 (1.58 to 2.18)
Diastolic BP (mmHg)	79.27 (7.91)	88.15 (14.85)	< 0.001	0.86 (0.58 to 1.14)
Creatinine (umol/L)	78.52 (16.21)	480.05 (234.12)	< 0.001	3.64 (3.24 to 4.05)
Cystatin C (mg/L)	0.95 (0.18)	2.64 (1.05)	< 0.001	3.16 (2.79 to 3.54)

Spearman rank correlations confirmed that while creatinine had a strong inverse correlation with its derived eGFR (rho = -0.86, p < 0.001), cystatin C demonstrated an almost perfect inverse correlation with eGFRcys (rho = -0.99, p < 0.001). Cross-biomarker correlation was only moderate (rho = 0.57, p < 0.001), previewing significant disagreement.

3.2 Stratified Determinants of Biomarker Associations

To provide explanatory context for the varying biomarker levels, standardized multiple linear regression models directly compared the relative determinants of each biomarker. Stratified analyses demonstrated that clinical associations differ profoundly according to CKD status.

Among healthy non-CKD adults, age, MAP, and random blood sugar (RBS) were not statistically significant predictors of either biomarker in adjusted models. In the absence of disease, biological sex was the primary driver of variation, exerting a large effect on creatinine (Standardized beta = 0.47, p < 0.001) but a substantially weaker effect on cystatin C (Standardized beta = 0.14, p = 0.036).

However, CKD status heavily modified these relationships. In the presence of established kidney disease, sex was no longer a statistically significant determinant (p > 0.10). Instead, MAP and age emerged as the

dominant predictors. Elevated MAP was independently associated with higher concentrations of both creatinine (Standardized beta = 0.51, p < 0.001) and cystatin C (Standardized beta = 0.46, p < 0.001) among CKD patients (Table 2).

Table 2
Stratified Determinants of Renal Biomarkers in Non-CKD vs. CKD Patients

Predictor	Non-CKD Creatinine Std beta	p-value	Non-CKD Cystatin C Std beta	p-value	CKD Creatinine Std beta	p-value	CKD Cystatin C Std beta	p-value
Age	-0.030	0.615	0.050	0.451	-0.300	0.005	-0.351	0.001
Sex (Male)	0.471	< 0.001	0.137	0.036	0.146	0.164	0.156	0.136
BMI	0.033	0.577	0.033	0.613	0.195	0.065	0.021	0.837
MAP	-0.012	0.837	-0.042	0.519	0.515	< 0.001	0.464	< 0.001

3.3 eGFR Agreement and Predictors of Discordance

The differential behaviour of the biomarkers resulted in highly variable equation agreement. Across the overall cohort, systematic mean bias was minimal (+ 2.17 mL/min/1.73m2), but individual-level agreement varied drastically by subgroup.

In the non-CKD group, absolute agreement was poor (ICC = 0.088), and Bland-Altman Limits of Agreement (LOA) spanned 212.5 units (-105.18 to 107.31). Conversely, the CKD group demonstrated excellent absolute agreement (ICC = 0.804) with exceptionally narrow LOA (-5.20 to 18.31). This tight agreement in the CKD cohort likely reflects the restricted eGFR range and non-linear mathematical constraints of the CKD-EPI equations at lower levels of estimated kidney function, rather than biological harmony (Table 3; Fig. 1).

Table 3
Agreement Metrics and Bland-Altman Limits of Agreement (eGFRcys vs eGFRcr)

Cohort	Intraclass Correlation (ICC)	Mean Bias (mL/min/1.73m2)	Lower 95% LOA	Upper 95% LOA
Overall (n = 303)	0.515	+ 2.17	-92.98	+ 97.33
Non-CKD (n = 242)	0.088	+ 1.07	-105.18	+ 107.31
CKD (n = 61)	0.804	+ 6.55	-5.20	+ 18.31

Clinical discordance was evaluated exclusively in the Non-CKD cohort because mathematical constraints prevented any CKD patient from exhibiting an absolute difference > = 15 mL/min/1.73m2. At

a standard threshold (|Delta eGFR| >= 15), 81.8% of healthy individuals exhibited disagreement. Male sex was independently associated with a lower likelihood of substantial discordance (OR = 0.40, 95% CI: 0.20 to 0.80, p = 0.010). Even at a stricter threshold representing major discordance (|Delta eGFR| >= 30), 59.9% of the healthy cohort met the criteria, with male sex remaining the sole protective factor (OR = 0.55, 95% CI: 0.32 to 0.93, p = 0.027).

3.4 KDIGO Stage Reclassification and Its Predictors

To evaluate the clinical implications of this discordance, a reclassification analysis mapped standard eGFRcr KDIGO stages against eGFRcys stages. The use of cystatin C resulted in substantial reclassification; exactly 50.5% (153/303) of the population experienced a stage shift (Table 4).

Overall staging agreement was moderate (weighted Kappa = 0.72, 95% CI: 0.65 to 0.78). However, agreement within the non-CKD cohort was extremely poor (weighted Kappa = 0.06, 95% CI: -0.01 to 0.13), compared to substantial agreement in the CKD cohort (weighted Kappa = 0.68, 95% CI: 0.54 to 0.77). Of those reclassified, 30.4% (n = 92) shifted to a higher (more severe) CKD stage, while 20.1% (n = 61) shifted to a lower (less severe) stage (Fig. 2).

Table 4
Net Reclassification Matrix (eGFRcr vs. eGFRcys)

eGFRcr Stage	eGFRcys Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Stage 1	119	26	23	25	0
Stage 2	24	6	8	8	2
Stage 3	0	1	5	0	0
Stage 4	0	0	1	11	0
Stage 5	0	0	0	0	44

Stratifying the reclassification patterns revealed asymmetric shifts. Among apparently healthy non-CKD controls, 38.0% were reclassified to a higher disease stage, suggesting cystatin C identified individuals who appeared normal by creatinine but exhibited lower estimated function. Conversely, among patients with established CKD, 59.0% were reclassified to a lower, less severe disease stage (Table 5).

Table 5
Stratified Reclassification Directionality

Cohort	Reclassified to Higher Stage (%)	Reclassified to Lower Stage (%)	No Change (%)
Non-CKD (n = 242)	38.0%	10.3%	51.7%
CKD (n = 61)	0.0%	59.0%	41.0%

To identify clinical characteristics associated with stage reclassification instability (shifting stages in any direction), a binary logistic regression was conducted. Higher mean arterial pressure (MAP) was a small but statistically significant driver of reclassification; every 1 mmHg increase in MAP increased the odds of a patient experiencing a stage shift by 4.3% (aOR = 1.04, 95% CI: 1.02 to 1.07, p = 0.001), linking the hemodynamic variability of the biomarkers directly to clinical staging outcomes.

4. Discussion

4.1 Summary of Key Findings

This study demonstrates that discordance between creatinine- and cystatin C-based estimates of glomerular filtration is not simply an analytical discrepancy but a biologically structured phenomenon whose determinants differ according to the presence of CKD. Four principal observations emerged. First, agreement between eGFR derived from creatinine and cystatin C was poor among adults without CKD but substantially higher among those with established disease. Second, the factors associated with each biomarker differed fundamentally across disease states: sex predominated in individuals without CKD, whereas mean arterial pressure (MAP) and age became the principal correlates in established CKD. Third, substitution of cystatin C for creatinine resulted in clinically important CKD stage reclassification in half of the study population. Finally, the direction of reclassification differed systematically by disease status, with apparently healthy individuals tending towards more advanced CKD stages and patients with established CKD more frequently moving towards less severe stages. These findings suggest that eGFR discordance reflects a context-dependent biological phenotype rather than random measurement variability.

4.2 Biological interpretation

The transition from sex-associated discordance in healthy adults to haemodynamic-associated discordance in CKD provides a biological framework for understanding why endogenous filtration markers behave differently across the spectrum of kidney disease. In individuals with preserved renal function, variation in creatinine production arising from differences in skeletal muscle mass remains an important source of between-person variability despite incorporation of sex into the CKD-EPI equation, whereas cystatin C is comparatively less influenced by body composition [7, 12]. Under these circumstances, discordance between eGFRcr and eGFRcys largely reflects differences in biomarker generation rather than filtration itself.

By contrast, in established CKD, the influence of declining nephron function appears to outweigh much of the physiological variation associated with creatinine generation. The emergence of MAP as the strongest correlate of both biomarkers is consistent with the central role of haemodynamic injury in CKD progression, particularly in populations where hypertension remains a leading cause of kidney disease [2, 13]. Rather than representing distinct biological processes, creatinine and cystatin C increasingly converge on the common signal of impaired filtration as disease advances. The relatively high agreement observed in the CKD cohort should nevertheless be interpreted cautiously because

convergence of the CKD-EPI equations at lower GFR ranges may contribute to reduced apparent discordance [8]. These findings support the concept that the biological architecture of eGFR discordance evolves with progressive kidney dysfunction, shifting from variation in biomarker production towards variation driven predominantly by disease severity.

4.3 Clinical implications

The clinical importance of eGFR discordance extends beyond differences between laboratory measurements because discordant estimates frequently alter CKD staging and, consequently, clinical decision-making. In this study, one in two participants experienced KDIGO stage reclassification when cystatin C-based eGFR was substituted for creatinine-based estimation, indicating that biomarker selection has the potential to influence eligibility for nephrology referral, medication dosing, monitoring intensity, and implementation of kidney-protective therapies.

These findings support a selective rather than universal approach to cystatin C testing, consistent with current KDIGO recommendations [4]. Individuals in whom creatinine may be an unreliable surrogate for filtration including those with discordant clinical features, altered body composition, or circumstances in which accurate GFR estimation would alter management, are likely to derive the greatest benefit from adjunctive cystatin C measurement. Our data further suggest that patients with elevated blood pressure may represent an additional subgroup in whom cystatin C is particularly informative, given the consistent association between MAP and both biomarker behaviour and stage reclassification.

The implications may be especially important in sub-Saharan Africa. CKD is frequently diagnosed late, access to kidney replacement therapy remains limited, and opportunities for early intervention are often constrained. In such settings, improving the precision of CKD staging among patients whose management depends on estimated kidney function may offer greater clinical value than indiscriminate cystatin C testing. Population-specific evidence is therefore essential for adapting international recommendations to healthcare systems where both disease epidemiology and resource availability differ substantially from those in high-income countries.

4.4 Comparison with previous studies

Our findings extend a growing body of evidence demonstrating that discordance between creatinine- and cystatin C-based eGFR is both common and clinically meaningful. A recent systematic review and meta-analysis showed that eGFR discordance is consistently associated with adverse kidney, cardiovascular, and mortality outcomes, highlighting that disagreement between biomarkers conveys prognostic information beyond estimated GFR alone [9]. Large observational studies from the United Kingdom and Sweden similarly demonstrated that discordance follows predictable biological patterns and is associated with clinically important differences in patient outcomes [10, 14].

Our study both confirms and extends these observations in several important respects. First, the prevalence of clinically significant discordance in our Nigerian cohort exceeded that reported in most European populations. Differences in body composition, CKD aetiology, cardiovascular risk profiles, and

the younger age structure of African populations may contribute to these observations, although direct comparisons require confirmation in studies incorporating measured GFR and objective assessment of muscle mass [11]. Second, whereas previous studies primarily identified demographic and anthropometric correlates of discordance, our stratified analyses indicate that these relationships are fundamentally modified by CKD status. This finding suggests that disease progression itself reshapes the biological determinants of endogenous filtration markers, providing a conceptual framework that may help explain the heterogeneous patterns of discordance reported across previous cohorts. Finally, our observations complement current KDIGO recommendations advocating selective cystatin C use by identifying clinical contexts in which biomarker disagreement is particularly likely to influence CKD classification and management [4, 15].

4.5 Strengths and limitations

This study provides one of the first detailed evaluations of creatinine–cystatin C discordance in a West African population using the 2021 CKD-EPI race-free equations. Inclusion of adults with and without established CKD enabled direct comparison of biomarker behaviour across distinct stages of kidney health, while stratified regression analyses permitted evaluation of disease-specific determinants rather than assuming uniform biomarker biology across the CKD spectrum.

Certain limitations should be considered when interpreting the findings. The cross-sectional design precludes assessment of temporal changes in biomarker discordance or its association with long-term clinical outcomes. Measured GFR was unavailable, preventing determination of which biomarker more closely approximated true filtration, and direct measures of muscle mass or inflammatory status were not obtained. Finally, recruitment from a single tertiary centre may limit generalisability to other African populations. These findings therefore warrant confirmation in prospective multicentre studies incorporating measured GFR, body composition, and longitudinal outcome assessment.

5. Conclusion

Discordance between creatinine- and cystatin C-based estimates of glomerular filtration should be regarded not as an analytical inconsistency but as a biologically meaningful phenotype whose determinants evolve across the continuum of chronic kidney disease. In this Nigerian cohort, the biological basis of discordance shifted from predominantly demographic influences in individuals with preserved kidney function to haemodynamic correlates in established CKD, resulting in frequent and clinically important CKD stage reclassification. These findings support a context-specific approach to kidney function assessment in which cystatin C is used selectively when creatinine-based estimates are likely to influence major clinical decisions or may be susceptible to non-GFR determinants. More broadly, our results underscore the importance of generating population-specific evidence to inform implementation of international CKD guidelines in African populations, where disease epidemiology, patient phenotypes, and healthcare resources differ substantially from those in the populations from which current estimating equations were derived. Prospective studies incorporating measured GFR and

longitudinal clinical outcomes are now needed to determine whether integrating biomarker discordance into routine clinical assessment improves risk stratification and patient care.

Abbreviations

CKD; chronic kidney disease, eGFR; estimated glomerular filtration rate, eGFRcr; creatinine-based estimated glomerular filtration rate, eGFRcys; cystatin C-based estimated glomerular filtration rate, eGFRcr-cys; combined creatinine–cystatin C-based estimated glomerular filtration rate, CKD-EPI; Chronic Kidney Disease Epidemiology Collaboration, GFR; glomerular filtration rate, KDIGO; Kidney Disease: Improving Global Outcomes, sCr; serum creatinine, sCysC; serum cystatin C, UACR; urine albumin-to-creatinine ratio, ACR; albumin-to-creatinine ratio, T2DM; type 2 diabetes mellitus, HTN; hypertension, CVD; cardiovascular disease, BMI; body mass index, SBP; systolic blood pressure, DBP; diastolic blood pressure, HbA1c; glycated haemoglobin, TC; total cholesterol, TG; triglycerides, HDL-C; high-density lipoprotein cholesterol, LDL-C; low-density lipoprotein cholesterol, EDTA; ethylenediaminetetraacetic acid, ROC; receiver operating characteristic, AUC; area under the curve, OR; odds ratio, aOR; adjusted odds ratio, CI; confidence interval, SD; standard deviation, IQR; interquartile range, SPSS; Statistical Package for the Social Sciences.

Declarations

Clinical trial number

Not applicable.

Ethics approval and consent to participate:

Ethical approval number: UATH/HREC/PR/2020/002/089 (6 February 2020). Conducted in compliance with the Declaration of Helsinki. All participants provided written informed consent.

Availability of data:

Available upon reasonable request to the corresponding author. This is because the dataset includes additional data that are not relevant to this study and may require exclusion.

Competing interests:

The authors declare no conflict of interest.

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Authors' contributions:

INM and II conceived and designed the study, performed analysis, and contributed to interpretation. BB and JAM participated in data collection and manuscript drafting. NDA and EBJ contributed to interpretation, critical revision, and final approval. All authors read and approved the final manuscript.

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Figures

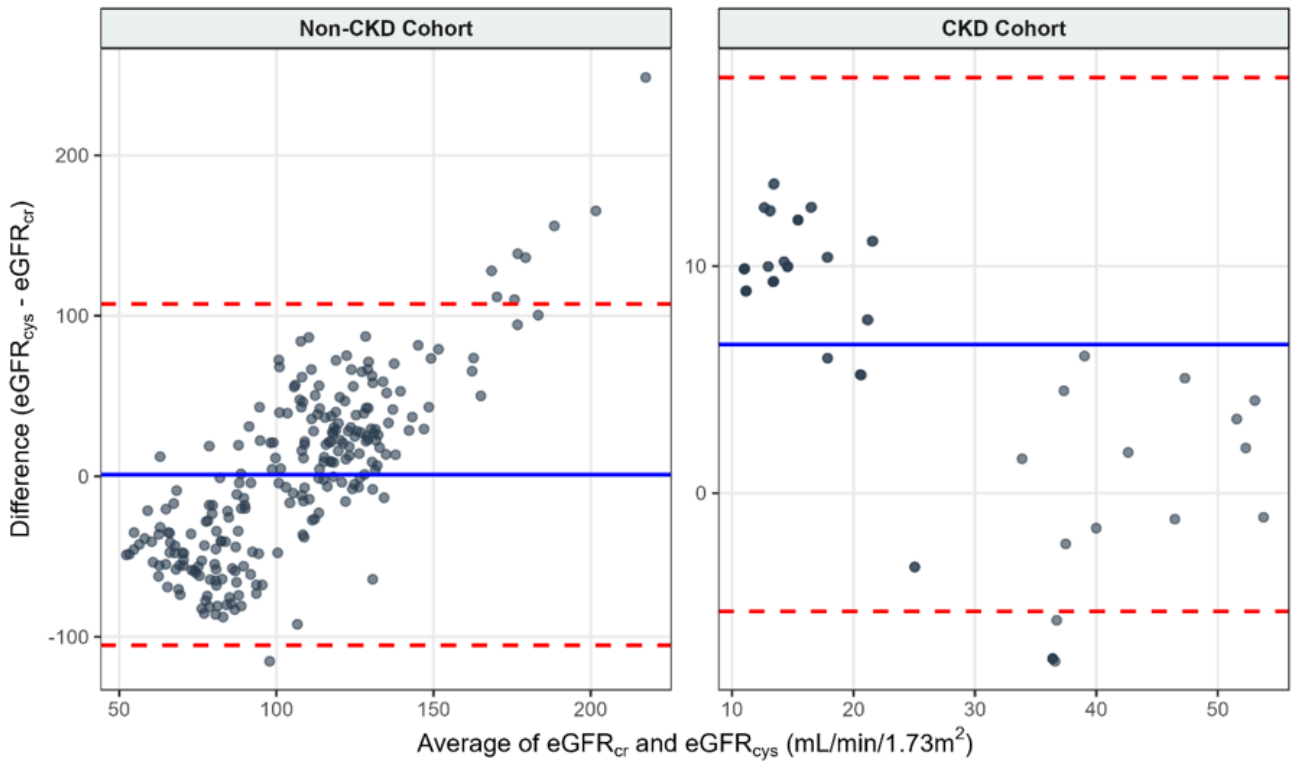


Figure 1

Bland-Altman plots comparing eGFRcr and eGFRcys stratified by clinical cohort. Agreement analysis demonstrates wide measurement variability in non-CKD participants and mathematically restricted clustering of estimates in CKD participants.

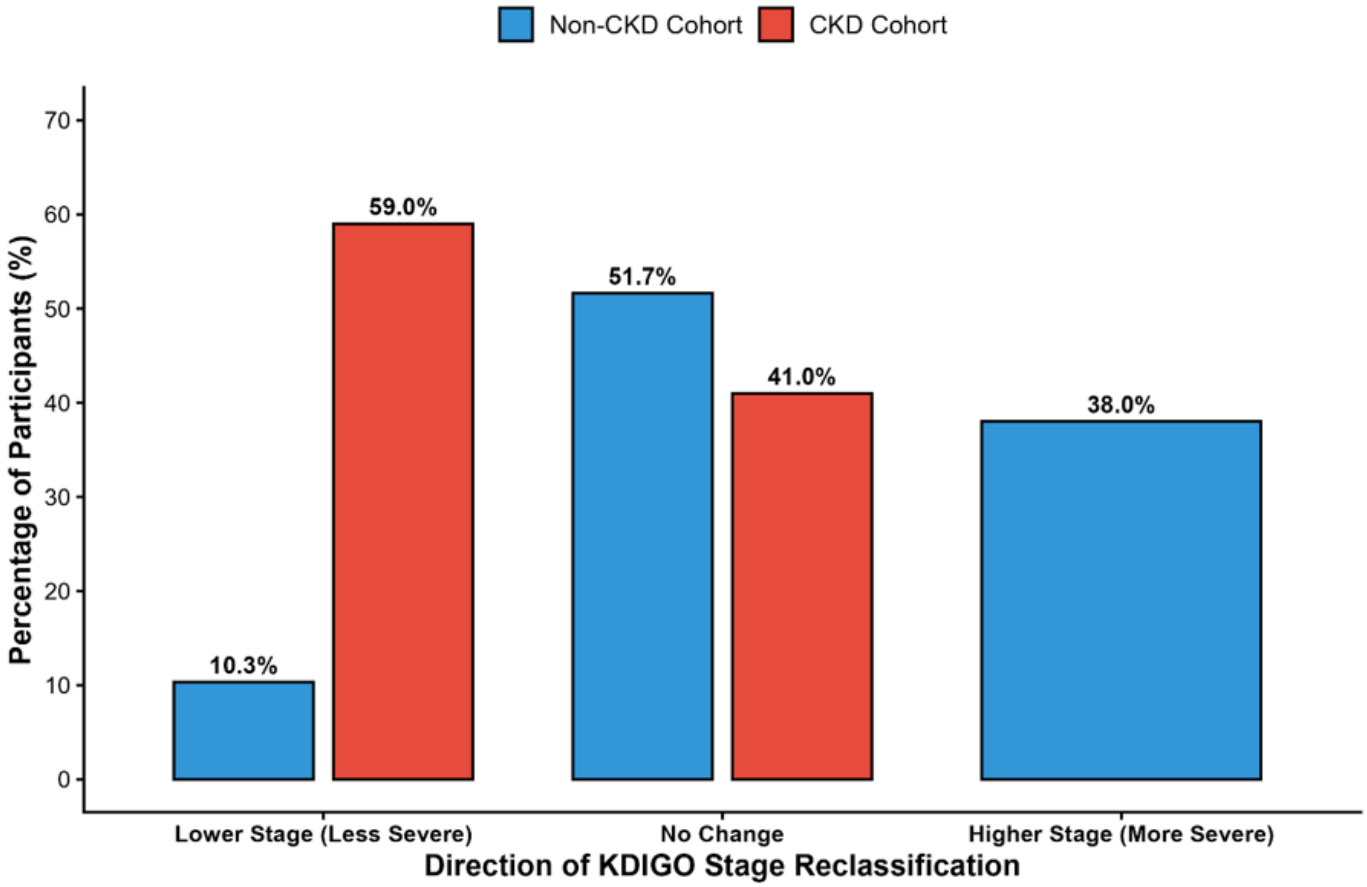


Figure 2

Distribution of KDIGO stage reclassification directionality between creatinine- and cystatin C-based equations, demonstrating asymmetric shifting patterns between CKD and Non-CKD cohorts.

Supplementary Files

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- GraphicalAbstract.docx