

Diagnostic Discrepancy and Staging Reclassification Between Cystatin C and Creatinine-Based eGFR in Sarcopenic Adults: A Cross-Sectional Study.

Abstract:

Background: Sarcopenia leads to reduced skeletal muscle mass, causing lower endogenously generated serum creatinine and subsequent overestimation of renal clearance when using creatinine-based estimated glomerular filtration rate ($eGFR_{cr}$). Serum cystatin C, produced at a constant rate by nucleated cells, is largely independent of muscle mass. This study aimed to evaluate the extent of diagnostic discordance and stage reclassification between $eGFR_{cr}$ and cystatin C-based eGFR ($eGFR_{cys}$) in sarcopenic older adults.

Methods: An analytical cross-sectional study was conducted among 260 sarcopenic patients aged ≥ 60 years recruited from a tertiary-care hospital. Sarcopenia was defined using standard criteria combining reduced handgrip strength and low appendicular skeletal muscle mass index. Serum creatinine and cystatin C were determined. $eGFR_{cr}$, $eGFR_{cys}$, and the combined $eGFR_{cr-cys}$ were calculated using the 2021 CKD-EPI equations. Categorical staging concordance was evaluated using weighted kappa (κ_w) and reclassification proportions. Continuous differences were evaluated with Bland-Altman analysis and multivariable regression.

Results: The mean age was 68.4 ± 7.1 years. Mean $eGFR_{cr}$ was significantly higher than $eGFR_{cys}$ (78.6 ± 18.4 vs. 56.2 ± 19.8 mL/min/1.73 m², $p < 0.001$), with a mean overestimation bias of 22.4 mL/min/1.73 m². Overall, 38.5% ($n = 100$) of participants were reclassified to a more severe KDIGO CKD stage when assessed by $eGFR_{cys}$, with the greatest discordance around the threshold of 60 mL/min/1.73 m². Among individuals categorized as non-CKD (≥ 60 mL/min/1.73 m²) by $eGFR_{cr}$, 34.6% had covert Stage ≥ 3 CKD on

eGFR_{cys}. Lower ASMI ($\beta = -0.42$, $p < 0.001$) and lower handgrip strength ($\beta = -0.31$, $p = 0.002$) were independently associated with wider divergence ($eGFR_{cr} - eGFR_{cys}$).

Conclusion: Creatinine-based equations markedly overestimate kidney function in sarcopenic adults, obscuring clinically significant chronic kidney disease. Incorporating cystatin C prevents missed CKD diagnoses and allows accurate risk stratification and drug dosing in muscle-depleted populations.

Keywords: Chronic Kidney Disease, Creatinine, Cystatin C, Glomerular Filtration Rate, Reclassification, Sarcopenia.

Introduction

Chronic kidney disease (CKD) and sarcopenia frequently coexist, mutually accelerating functional decline, hospitalization, and mortality in aging populations. (1, 2) Sarcopenia characterized by progressive loss of skeletal muscle quantity, quality, and strength, poses a major physiological challenge to routine biochemical monitoring. (3, 4) The most widespread clinical tool for screening renal clearance, serum creatinine-derived estimated glomerular filtration rate ($eGFR_{cr}$), relies fundamentally on the assumption that endogenous creatinine generation is steady and proportional to standard demographic averages. (5)

Creatinine is an endogenous waste product formed by non-enzymatic conversion of creatine and phosphocreatine in skeletal muscle. (6) In the presence of substantial muscle wasting, daily production of creatinine drops sharply. (7) Consequently, circulating serum creatinine levels remain deceptively low even in the face of progressive nephron loss. (8) This creates a systematic "creatinine blind spot," wherein sarcopenic individuals exhibit falsely elevated $eGFR_{cr}$ values, leading to under detection of CKD stage 3 or worse, delayed nephrology referral, and improper clearance-based dosing of narrow-therapeutic-index medications. (9, 10)

Cystatin C, a 13-kDa non-glycosylated basic protein synthesized by all nucleated cells, is freely filtered by the glomerulus, completely reabsorbed, and catabolized by proximal tubular epithelial cells without tubular secretion. (11) Because its generation is independent of muscle bulk, physical exertion, and dietary meat consumption, cystatin C-based estimated glomerular filtration rate (eGFR_{cys}) provides a more objective measure of renal clearance in frail or malnourished populations. (12, 13) Furthermore, the mathematical discrepancy between eGFR_{cr} and eGFR_{cys} has emerged as a potential physiological index reflecting the severity of muscle loss itself. (14, 15)

Despite increasing international consensus emphasizing cystatin C in muscle-wasted cohorts, direct comparative data evaluating the scale of diagnostic discordance and categorical stage shifts within South Asian sarcopenic cohorts remain limited. (16, 17) Therefore, this study was designed to assess the degree of CKD stage reclassification between eGFR_{cr} and eGFR_{cys} and investigate its correlation with physical markers of sarcopenia.

Materials & Methods

Study Design and Setting: This observational, analytical cross-sectional study was carried out at a tertiary care teaching hospital from January 2025 to February 2026.

Sample Size Calculation: The required sample size was determined using Cochran's formula: (18)

$$n = \frac{Z_{1-\alpha/2}^2 \cdot p(1-p)}{d^2}$$

Assuming a reclassification proportion (**p**) of 32% based on prior literature examining altered clearance markers in muscle-wasting states, a two-sided type I error (**α**) of 0.05 ($Z = 1.96$), and an absolute precision margin (**d**) of 6% (0.06) (19)

$$n = \frac{(1.96)^2 \times 0.32 \times (1 - 0.32)}{(0.06)^2} \approx 232$$

Accounting for an anticipated 10% rate of non-evaluable tests (e.g., sample hemolysis, incomplete physical assessment), the final target sample size was set at 260 participants. Consecutive systematic sampling from outpatient clinics was utilized.

Study Population: Adults aged ≥ 60 years meeting standard diagnostic criteria for confirmed sarcopenia (assessed by low grip strength and reduced appendicular skeletal muscle mass as per Asian Working Group for Sarcopenia - AWGS criteria). (4)

Individuals with acute kidney injury within the past 30 days, on current maintenance dialysis, getting active systemic corticosteroid therapy (≥ 20 mg/day prednisone equivalent), uncontrolled thyroid disorders (overt hyper- or hypothyroidism), active malignancy, and severe localized or generalized oedema precluding were excluded from the study. (20, 21)

Clinical & Anthropometric Assessment: Sarcopenia was staged according to regional consensus guidelines:

- **Muscle Strength:** Evaluated using a calibrated Jamar hydraulic hand dynamometer. Three trials were performed on each hand, and the maximal reading was recorded (< 28 kg for men, < 18 kg for women). (4)
- **Muscle Mass:** Assessed by multi-frequency bioelectrical impedance analysis (BIA) performed under fasting conditions with an empty bladder. Appendicular Skeletal Muscle Mass Index ($ASMI = ASM/height^2$) was determined, with cut-offs set at $< 7.0 \text{ kg/m}^2$ in men and $< 5.7 \text{ kg/m}^2$ in women. (4)

Laboratory Procedures & Calculations: Venous blood samples were collected between 08:00 and 10:00 AM after an overnight fast.

- Serum creatinine was quantified using an enzymatic method traceable to isotope dilution mass spectrometry (IDMS)(22)
- Serum cystatin C was measured using particle-enhanced immunoturbidimetry calibrated against ERM-DA471/IFCC reference materials. (23)

GFR calculations utilized the 2021 CKD-EPI equations without race adjustment: (24)

- $eGFR_{cr}$ (2021 CKD-EPI Creatinine) (24)
- $eGFR_{cys}$ (2012 CKD-EPI Cystatin C) (12)
- $eGFR_{cr-cys}$ (2021 CKD-EPI Creatinine–Cystatin C) (24)

CKD stages were designated following KDIGO definitions: Stage 1 (≥ 90), Stage 2 (60--89), Stage 3a (45--59), Stage 3b (30--44), Stage 4 (15--29), and Stage 5 ($< 15 \text{ mL/min/1.73 m}^2$). (25)

Statistical Analysis: Analyses were completed using IBM SPSS Statistics version 26.0 and R version 4.3. Continuous variables were expressed as mean $\pm$ standard deviation (SD) or median (interquartile range, IQR) according to distribution normality assessed via the Shapiro-Wilk test. Differences between paired eGFR values were analyzed using the Wilcoxon signed-rank test or paired t -test. Categorical agreement across CKD stages was evaluated using quadratic weighted kappa (κ_w). (26) Concordance and discordant shifts were evaluated via the McNemar-Bowker test of symmetry. Multivariable linear regression was performed to evaluate predictors of the eGFR discrepancy ($\Delta eGFR = eGFR_{cr} - eGFR_{cys}$). A two-tailed p -value < 0.05 was considered statistically significant.

Ethical Considerations: The study protocol received institutional review board approval. All participants or their legal representatives provided written informed consent in accordance with the Declaration of Helsinki.

Results

A total of 260 sarcopenic older adults were evaluated, and the mean age of the participants was 68.4 ± 7.1 years; 158 (60.8%) were men and 102 (39.2%) were women. Hypertension was present in 164 (63.1%) and type 2 diabetes mellitus in 118 (45.4%).

Baseline Parameters and Renal Metrics: The mean serum creatinine was 0.98 ± 0.31 mg/dL, while mean serum cystatin C was 1.34 ± 0.44 mg/L. Mean $eGFR_{cr}$ was significantly higher than $eGFR_{cys}$ (78.6 ± 18.4 vs. 56.2 ± 19.8 mL/min/1.73 m², paired difference 22.4 ± 11.2 mL/min/1.73 m², $p < 0.001$).

Bold diagonal values indicate exact agreement ($n = 134, 51.5\%$). Weighted kappa_w = 0.44 (95% CI: 0.37--0.51), indicating moderate agreement. (Figure 1) Downward reclassification (worse stage by $eGFR_{cys}$) occurred in 118 patients (45.4%). McNemar-Bowker test $p < 0.001$.

Staging Discrepancy Around the 60 mL/min/1.73 m² Threshold (Table 1& Figure 1)

When evaluating the standard clinical threshold for CKD (< 60 mL/min/1.73 m²):

- Based on $eGFR_{cr}$, only 74 patients (28.5%) were identified as having CKD Stage ≥ 3 .
- Based on $eGFR_{cys}$, 139 patients (53.5%) had an $eGFR < 60$ mL/min/1.73 m².
- Among 186 participants classified as non-CKD (Stages 1 and 2) by creatinine, 65 (34.9%) were reclassified to Stage ≥ 3 CKD upon measuring cystatin C.

The primary driver of the eGFR discrepancy was skeletal muscle quantity, as reflected by the Appendicular Skeletal Muscle Mass Index (ASMI). ASMI exhibited the strongest independent inverse association with the eGFR gap (unstandardized $\beta = -3.45$, standardized

$\beta = -0.42$, $t = -5.94$, $p < 0.001$). This indicates that for every 1 kg/m^2 reduction in appendicular muscle mass, the creatinine-based overestimation of kidney function widened by $3.45 \text{ mL/min/1.73 m}^2$. Muscle quality and function showed a congruent pattern: handgrip strength was also an independent negative predictor ($\beta = -0.38$, standardized $\beta = -0.31$, $t = -3.16$, $p = 0.002$), demonstrating that progressive physical weakness independently amplifies the gap between creatinine- and cystatin C-based clearance estimates. (Table 2)

Among demographic and biochemical covariates, advancing age displayed a modest, statistically significant positive association with the discrepancy gap ($\beta = 0.18$, standardized $\beta = 0.12$, $t = 2.25$, $p = 0.025$), indicating greater overestimation of renal clearance in older individuals even after controlling for body composition. In contrast, male sex ($\beta = 2.14$, $p = 0.071$) and baseline serum albumin ($\beta = -1.82$, $p = 0.084$) trended toward wider and narrower discrepancies respectively, but neither reached statistical significance in the fully adjusted model. Collectively, these results confirm that the discordance between the two equations is directly proportional to the anatomical and functional severity of sarcopenia. Lastly, the overall model was statistically significant ($F = 31.4$, $p < 0.001$) and demonstrated robust explanatory power, accounting for 38.2% of the total variance in the divergence between the two filtration markers ($R^2 = 0.382$, Adjusted $R^2 = 0.369$).

Discussion

In this cross-sectional study of sarcopenic older adults, reliance on creatinine-based equations introduced a substantial overestimation bias in renal clearance, resulting in misclassification of over one-third of the study cohort. When evaluated with cystatin C, more than half of the participants had GFR values consistent with Stage 3 to 5 CKD, compared to fewer than thirty percent by creatinine alone.

The observed mean overestimation bias of $22.4 \text{ mL/min/1.73 m}^2$ directly reflects the pathophysiological reduction of muscle-derived creatinine synthesis. Because the 2021 CKD-EPI creatinine equation assumes standard muscle mass for a given age and sex (24), low circulating creatinine is interpreted as hyper-efficient renal clearance. This physiological bias is consistent with findings reported by Inker et al. (24) and Levey et al. (12), who noted that non-GFR determinants of serum creatinine led to systematic overestimation of GFR in individuals with low body mass index and muscle wasting. Similar magnitude differences were observed by Baxmann et al. (6), who demonstrated that muscle mass explains up to 50% of the variance in serum creatinine concentrations, whereas serum cystatin C concentrations remain unaffected by muscle cross-sectional area.

When compared with prior investigations in geriatric cohorts, our findings closely parallel the work of Purde et al. (27) and Kilbride et al. (28), who demonstrated that eGFR_{cr} routinely overestimates measured GFR in frail, community-dwelling octogenarians. Kilbride et al. (28) reported that creatinine-based formulas overestimated measured clearance by an average of 15 to $20 \text{ mL/min/1.73 m}^2$ when compared against iohexol clearance. However, while Kilbride et al. (28) studied an unselected elderly population, our study specifically enrolled individuals with confirmed sarcopenia diagnosed via bioimpedance and dynamometry, which explains the even larger mean overestimation ($22.4 \text{ mL/min/1.73 m}^2$) observed in our cohort. In contrast, in healthy adult populations with preserved muscle mass evaluated by Rule et al. (29), creatinine-based formulas show minimal bias relative to cystatin C, highlighting that the marked divergence between the two markers is specific to states of reduced muscularity.

The categorical reclassification observed in our study (38.5% to a more severe stage, and 34.9% covert CKD unmasked among those with $\text{eGFR}_{\text{cr}} \geq 60 \text{ mL/min/1.73 m}^2$) is substantially higher than the reclassification rates documented in general CKD screening

cohorts. For instance, Shlipak et al. (30) evaluated large population-based cohorts and observed that measuring cystatin C reclassified approximately 13% of participants across the 60 mL/min/1.73 m² threshold. The markedly higher rate of downward reclassification in our study underscores that general population estimates cannot be extrapolated to sarcopenic individuals, where the "creatinine blind spot" is far more pronounced. Our findings also corroborate studies in end-stage liver disease by Mindikoglu et al. (31) and cirrhotic cohorts by Piano et al. (32), who noted that profound muscle sarcopenia masked renal impairment in over 40% of patients when relying on standard creatinine-based formulas, whereas cystatin C accurately identified true renal clearance verified by measured isotopic GFR.

The distortion identified around the critical threshold of 60 mL/min/1.73 m² carries profound clinical ramifications. In geriatric medicine, dosing for narrow-therapeutic-index drugs cleared primarily by the kidneys, such as direct oral anticoagulants (DOACs), gabapentin, SGLT2 inhibitors, and hydrophilic antibiotics, is determined by renal clearance cut-offs at 60, 45, or 30 mL/min/1.73 m² (33, 34). As emphasized by Corsonello et al. (35), overestimating GFR in frail older patients leads directly to inappropriate drug dosing, increased adverse drug reactions, and preventable hospital admissions. Relying on eGFR_{cr} in sarcopenic individuals risks drug accumulation toxicity while simultaneously delaying nephrology interventions, dietary protein modifications, and cardiovascular risk factor optimization (36).

Multivariable linear regression confirmed that lower ASMI and lower handgrip strength were independent drivers of the divergence between the two markers (Δ eGFR). This inverse association aligns directly with the conceptual framework proposed by Kashani et al. (14) and validated by Kim et al. (37), who established the creatinine-to-cystatin C ratio as the "Sarcopenia Index." While those investigators used the ratio to estimate muscle mass, our findings demonstrate the reverse clinical reality: physical muscle wasting directly drives

mathematical divergence between the two eGFR equations ($\beta = -3.45$ for ASMI and $\beta = -0.38$ for grip strength). This confirms that the discrepancy gap itself acts as an objective physiological biomarker of muscular depletion.

Strengths & Limitations: Key strengths of this study include the standardized, simultaneous evaluation of muscle quality and mass using validated diagnostic criteria (multi-frequency BIA and calibrated Jamar dynamometry) combined with IDMS-traceable creatinine and IFCC-standardized cystatin C assays. However, several limitations must be acknowledged. First, measured GFR (mGFR) using exogenous clearance markers such as iohexol or inulin was not performed due to institutional resource constraints. Nonetheless, extensive multicenter validation by Inker et al. (24) and Stevens et al. (38) has robustly validated the superior accuracy of eGFR_{cys} against mGFR in patients with altered body habitus. Second, the single-center cross-sectional design precludes assessment of longitudinal renal progression, cardiovascular events, or mortality. Third, non-GFR determinants of cystatin C, such as subclinical inflammation or adiposity, could introduce minor confounding (39); however, strict protocol exclusion of patients with active systemic infections, thyroid dysfunction, and systemic corticosteroid therapy minimized these confounders.

Conclusion

Serum creatinine systematically overestimates glomerular filtration in sarcopenic older adults, masking Stage ≥ 3 chronic kidney disease in over one-third of affected individuals. Incorporating cystatin C provides a more accurate reflection of renal status in patients with documented muscle wasting. In geriatric and cachectic populations, clinical guidelines should prioritize eGFR_{cys} or the combined eGFR_{cr-cys} equation to ensure accurate staging, safe pharmacotherapy, and timely clinical intervention.

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Table 1: Cross-Classification Matrix of CKD Staging by $eGFR_{cr}$ vs. $eGFR_{cys}$ ($N = 260$)

CKD Stage by $eGFR_{cr}$	CKD Stage by $eGFR_{cys}$						Total by $eGFR_{cr}$
	Stage 1	Stage 2	Stage 3a	Stage 3b	Stage 4	Stage 5	
	(≥ 90)	(60–89)	(45–59)	(30–44)	(15–29)	(<15)	
Stage 1 (≥ 90)	22	31	5	0	0	0	58
Stage 2 (60--89)	0	68	46	14	0	0	128
Stage 3a (45--59)	0	0	23	18	2	0	43
Stage 3b (30--44)	0	0	0	14	8	0	22
Stage 4 (15--29)	0	0	0	0	6	2	8
Stage 5 (< 15)	0	0	0	0	0	1	1
Total by $eGFR_{cys}$	22	99	74	46	16	3	260

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Table 2: Multivariable Linear Regression Predicting the Discrepancy Gap ($\Delta eGFR = eGFR_{cr} - eGFR_{cys}$) ($N = 260$)

Independent Predictor	Unstandardized β	Standard Error	Standardized β	t- statistic	p-value
Constant	44.82	6.12	—	7.32	< 0.001
Age (Years)	0.18	0.08	0.12	2.25	0.025
Sex (Male = 1, Female = 0)	2.14	1.18	0.09	1.81	0.071
ASMI (kg/m^2)	-3.45	0.58	-0.42	-5.94	< 0.001
Handgrip Strength (kg)	-0.38	0.12	-0.31	-3.16	0.002
Serum Albumin (g/dL)	-1.82	1.05	-0.08	-1.73	0.084

Dependent variable: $\text{eGFR}_{\text{diff}}$ (mL/min/1.73 m^2). Model statistics: $R^2 = 0.382$, *Adjusted* $R^2 = 0.369$, $F = 31.4$, $p < 0.001$.

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Figure 1: Bland–Altman Plot Illustrating the Disagreement Between Creatinine- and Cystatin C–Based eGFR in Sarcopenic Adults (N = 260)

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