

Discordance among creatinine- and cystatin C-based eGFR equations and its impact on chronic kidney disease staging in older adults: a cross-sectional study

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Abstract

Background

Serum creatinine is routinely used to estimate the glomerular filtration rate (eGFR) but is strongly influenced by non-GFR determinants. Current guidelines therefore recommend incorporating cystatin C, alone or in combination with creatinine, to improve the accuracy of eGFR and chronic kidney disease (CKD) staging.

Method

We conducted a cross-sectional study of 721 adults aged 65 years and older with concurrent serum creatinine and cystatin C measurements at University Malaya Medical Centre, Kuala Lumpur, Malaysia. eGFR was calculated using the CKD-EPI 2009 creatinine, CKD-EPI 2021 creatinine, CKD-EPI 2012 cystatin C, CKD-EPI 2012 creatinine–cystatin C, and CKD-EPI 2021 creatinine-cystatin C equations. As no measured GFR was available, the analysis evaluated equation-to-equation agreement rather than accuracy against a criterion standard.

Results

The mean age was 74.6 ± 6.2 years, and 53.5% had diabetes. Relative to the CKD-EPI 2009 creatinine equation, the CKD-EPI 2012 cystatin C equation systematically returned lower eGFR (mean bias 16.7 mL/min/1.73 m²; ICC 0.669; 95% limits of agreement – 6.9 to 40.3) and up-staged 459 participants (63.7%) to more advanced CKD categories. Combined equations attenuated this effect (CKD-EPI 2021 creatinine-cystatin C: mean bias 5.6 mL/min/1.73 m²; ICC 0.923) while still up-staging 25.9%. Large negative discordance affected 244 participants (33.8%) and was independently associated with older age (odds ratio 1.060 per year), higher body mass index (odds ratio 1.075 per kg/m²), and diabetes mellitus (odds ratio 1.620).

Conclusions

In older Malaysian adults, the choice of filtration marker substantially alters CKD staging: cystatin C-based eGFR often reclassifies patients into more advanced stages, whereas combined equations provide more consistent, intermediate estimates.

Introduction

Rapid population ageing and the increasing burden of age-related conditions have become major global challenges. By 2030, one in six individuals worldwide is projected to be aged 60 years or older, with the population forecast to rise from 1 billion in 2020 to 1.4 billion in 2030 and to double to 2.1 billion by 2050. This demographic shift imposes considerable pressure on healthcare systems and social support structures worldwide [1]. Health risks among older Malaysians remain a major concern, given the rising prevalence of non-communicable diseases. The proportion of elderly individuals has increased from

6.2% in 2000 to 11.3% in 2023. The National Health and Morbidity Survey 2023 reported a high burden of non-communicable diseases among Malaysian adults, with prevalences of 29.2% for hypertension, 15.6% for diabetes and 33.3% for hypercholesterolaemia. Prevalences among adults aged 60 years and above were 53.2% for hypertension, 29.3% for diabetes and 45.7% for hypercholesterolaemia [2, 3]. The World Health Organisation notes that healthy ageing includes not only extending life expectancy but also ensuring additional years are lived in good health, with independence and a sense of purpose [1, 3]. Chronic kidney disease (CKD) represents a major and expanding public health burden in Malaysia. Successive National Health and Morbidity Surveys documented a rise in adult CKD prevalence from 9.07% in 2011 to 15.48% in 2018, meaning roughly one in seven Malaysian adults now lives with some stage of CKD [4]. According to the 32nd Report of the Malaysian Dialysis and Transplant Registry, over 56% of patients with newly diagnosed end-stage kidney disease are pre-elderly (55–64 years) or elderly (65 years and older) [5]. The economic consequences are substantial, and the number of patients requiring kidney replacement therapy is projected to rise steeply over the coming two decades [6].

Precise staging of CKD is fundamental to optimal clinical management. The glomerular filtration rate (GFR) category assigned to a patient by the Kidney Disease: Improving Global Outcomes (KDIGO) framework guides the monitoring schedule, nephrology referral thresholds, eligibility criteria for transplantation and clinical trials, and safety considerations regarding iodinated contrast and nephrotoxic agents. Importantly, it influences dosing adjustments of renally cleared medications, where inaccurate classification may lead to inadequate treatment or adverse drug reactions. CKD staging additionally influences prognosis: the stage of CKD serves as a significant and independent predictor of cardiovascular incidents, renal failure, and mortality. Consequently, staging errors directly affect risk assessment and treatment intensity, not just administrative processes [7].

Estimated GFR (eGFR) is mainly derived from serum creatinine in most settings. Creatinine is a cost-effective, widely accessible marker; however, it is an imperfect indicator of filtration because its concentration is influenced by non-GFR determinants such as muscle mass, dietary protein intake, tubular secretion, and medication use. Furthermore, serum creatinine levels do not increase significantly until GFR declines substantially [8, 9]. These challenges are more noticeable in older adults, as sarcopenia and lower dietary protein intake can reduce creatinine production. This may cause creatinine-based eGFR to overestimate actual kidney function, highlighting the importance of considering these factors in assessments. Cystatin C is a low molecular weight protein produced by all nucleated cells and eliminated almost entirely by glomerular filtration. It is largely independent of muscle mass and has been proposed as a more reliable marker in these patients [8–10].

Switching or combining markers often results in eGFR discordance. This eGFR discordance is more than a laboratory anomaly. A cystatin C-based eGFR significantly lower than the creatinine-based value has been repeatedly associated with sarcopenia, frailty, and higher mortality rates, leading to renewed scrutiny of whether creatinine-based estimates cause underdiagnosis or overdiagnosis of CKD in older adults. In a large cohort, patients who moved to a lower eGFR category when cystatin C was used had a 44–76% higher adjusted risk of cardiovascular death than patients who were not reclassified [8].

We therefore examined a cohort of older adults at University Malaya Medical Centre (UMMC), a tertiary referral centre, who had contemporaneous serum creatinine and cystatin C measurements. Our main aim was to evaluate the degree of discordance between creatinine-based and cystatin C-based eGFR equations among older adults. We also aimed to (1) compare CKD staging based on creatinine-derived, cystatin C-derived, and combined creatinine-cystatin C eGFR equations; (2) determine the proportion of older adults reclassified into different CKD stages following incorporation of cystatin C; (3) assess the agreement between creatinine-based, cystatin C-based, and combined creatinine-cystatin C eGFR equations; and (4) identify clinical and demographic factors associated with discordance between creatinine-based and cystatin C-based eGFR.

Importantly, this study was conducted using routinely available biochemistry and did not include a measured GFR (mGFR) reference standard. We address this design feature explicitly and discuss its limitations, as well as the clinically meaningful questions that between-equation comparison can still answer.

Materials and methods

Study design and participants

We conducted a cross-sectional study at the blood-taking centre of University Malaya Medical Centre (UMMC), Kuala Lumpur, Malaysia. Participants were adults aged 65 years or older who had concurrent measurements of serum creatinine and cystatin C as part of routine clinical care. We excluded patients receiving renal replacement therapy and those with missing anthropometric data required for eGFR calculation.

eGFR estimation and definitions

eGFR was calculated for each participant using the following equations: (1) CKD-EPI 2009 creatinine equation (the current clinical reference equation at our centre) [11], (2) CKD-EPI 2021 creatinine (race-free) [12], (3) CKD-EPI 2012 cystatin C [13], (4) CKD-EPI 2012 creatinine–cystatin C [13], and (5) CKD-EPI 2021 creatinine–cystatin C (race-free) [12]. CKD staging was assigned using KDIGO eGFR categories: G1 (≥ 90 mL/min/1.73 m²), G2 (60–89), G3a (45–59), G3b (30–44), G4 (15–29), and G5 (< 15 mL/min/1.73 m²). Clinically significant CKD was defined as G3a or greater (eGFR < 60 mL/min/1.73 m²). Staging was based on the GFR category (G) only; albuminuria (A) categories were unavailable and were therefore not incorporated. Large negative discordance was defined as an eGFR based on the CKD-EPI 2012 cystatin C equation at least 30% lower than the eGFR based on the CKD-EPI 2009 creatinine equation, following the threshold used by the CKD Prognosis Consortium meta-analysis [14]:

$$[(\text{eGFR}_{2012\text{CysC}} - \text{eGFR}_{2009\text{Cr}}) / \text{eGFR}_{2009\text{Cr}}] \times 100 < -30\%$$

Creatinine and cystatin C assay platforms and calibration

Serum creatinine and cystatin C concentrations were measured on the Atellica Solution automated biochemistry platform (Siemens Healthineers, Erlangen, Germany) at the Department of Pathology, University Malaya Medical Centre. Serum creatinine was determined using an enzymatic assay calibrated against an Isotope Dilution Mass Spectrometry (IDMS)-traceable reference material (National Institute of Standards and Technology [NIST] SRM 967) [15]. Serum cystatin C was measured using a particle-enhanced immunoturbidimetric assay (PETIA), standardised against the international certified reference material ERM-DA471/IFCC [16].

Statistical analysis

Continuous variables are reported as mean $\pm$ standard deviation (SD) or median [interquartile range (IQR)]. Categorical variables are reported as frequencies and percentages. Pairwise comparisons of eGFR between equations used the Wilcoxon signed-rank test. Agreement between eGFR_{2009Cr} and each alternative equation was assessed by (i) the Pearson correlation coefficient, (ii) the two-way mixed-effects absolute agreement intraclass correlation coefficient (ICC), and (iii) Bland–Altman analysis (mean bias and 95% limits of agreement).

CKD reclassification was quantified as the number and proportion of patients up-staged (to more advanced CKD) or down-staged (to less severe CKD) compared with eGFR_{2009Cr}. Predictors of large negative discordance (eGFR_{2012CysC} at least 30% below eGFR_{2009Cr}) were examined using univariate analyses (independent t-test or chi-square test as appropriate) followed by multivariable binary logistic regression. Covariates included age, sex, body mass index (BMI), presence of diabetes mellitus, hypertension, dyslipidemia, and ischaemic heart disease. Two-sided p-values < 0.05 were considered statistically significant. No adjustment was made for multiple comparisons, so the pairwise analyses should be interpreted as descriptive and exploratory. For the CKD-EPI 2009 and CKD-EPI 2012 equations, which include a coefficient for Black race, all participants were treated as non-Black; the CKD-EPI 2021 equations do not include race. Analyses were conducted using IBM SPSS version 31.0 (IBM Corp., Armonk, NY, USA).

Results

Cohort characteristics

We included 721 older adults. The mean age was 74.6 ± 6.2 years (median 74, IQR 69–79), with a near-equal sex distribution (353 men, 49.0%; 368 women, 51.0%). The cohort was predominantly Chinese (50.3%), followed by Malay (30.0%), Indian (17.1%), and other ethnicities (2.6%). Mean BMI was 24.8 ± 4.6 kg/m². Comorbidity burden was high: hypertension was present in 604 patients (83.8%), dyslipidaemia in 624 (86.5%), diabetes mellitus in 386 (53.5%), and ischaemic heart disease in 217 (30.1%) (Table 1).

Table 1

Baseline demographic and clinical characteristics stratified by eGFR discordance between CKD-EPI 2009 creatinine and CKD-EPI 2012 cystatin C equations (n = 721).

Baseline characteristic	Overall	eGFR _{cys} > 30% lower (n = 244)	Concordant within 30% (n = 469)	eGFR _{cys} > 30% higher (n = 8)	p
Age, mean ± SD (years)	74.6 ± 6.2	75.6 ± 6.3	74.1 ± 6.2	74.4 ± 6.7	0.011
Sex					0.411
Male, n (%)	353 (49.0)	111 (45.5)	238 (50.7)	4 (50.0)	
Female, n (%)	368 (51.0)	133 (54.5)	231 (49.3)	4 (50.0)	
Race					< 0.001
Malay, n (%)	216 (30.0)	88 (36.1)	126 (26.9)	2 (25.0)	
Chinese, n (%)	363 (50.3)	98 (40.2)	263 (56.1)	2 (25.0)	
Indian, n (%)	123 (17.1)	47 (19.3)	73 (15.6)	3 (37.5)	
Others, n (%)	19 (2.6)	11 (4.5)	7 (1.5)	1 (12.5)	
BMI, mean ± SD (kg/m ²)	24.8 ± 4.6	25.9 ± 5.5	24.3 ± 4.0	24.0 ± 2.7	< 0.001
Diabetes mellitus, n (%)	386 (53.5)	155 (63.5)	225 (48.0)	6 (75.0)	< 0.001
Hypertension, n (%)	604 (83.8)	217 (88.9)	381 (81.2)	6 (75.0)	0.024
Dyslipidaemia, n (%)	624 (86.5)	213 (87.3)	405 (86.4)	6 (75.0)	0.592
Ischaemic heart disease, n (%)	217 (30.1)	78 (32.0)	138 (29.4)	1 (12.5)	0.431
Serum creatinine (µmol/L)	103.0 ± 76.1	87.7 ± 39.7	105.3 ± 76.1	431.4 ± 146.7	< 0.001
Serum cystatin C (mg/L)	1.51 ± 0.74	1.6 ± 0.6	1.4 ± 0.8	3.4 ± 0.8	< 0.001
CKD-EPI 2009 Cr (mL/min/1.73 m ²)	67.6 ± 24.2	70.1 ± 21.0	67.3 ± 24.8	11.1 ± 6.6	< 0.001

Baseline characteristic	Overall	eGFR _{cys} > 30% lower (n = 244)	Concordant within 30% (n = 469)	eGFR _{cys} > 30% higher (n = 8)	p
CKD-EPI 2021 Cr (mL/min/1.73 m ²)	71.5 ± 25.1	74.2 ± 21.6	71.1 ± 25.7	13.8 ± 12.7	< 0.001
CKD-EPI 2012 CysC (mL/min/1.73 m ²)	50.9 ± 20.4	42.5 ± 13.4	55.8 ± 21.5	17.0 ± 10.4	< 0.001
CKD-EPI 2012 Cr–CysC (mL/min/1.73 m ²)	58.4 ± 22.1	54.1 ± 16.8	61.4 ± 23.5	13.0 ± 8.0	< 0.001
CKD-EPI 2021 Cr–CysC (mL/min/1.73 m ²)	62.0 ± 23.5	57.0 ± 17.7	65.5 ± 25.0	14.1 ± 8.4	< 0.001

Data are mean ± SD or n (%). Discordance is defined relative to the CKD-EPI 2009 creatinine equation. BMI, body mass index; Cr, creatinine; CysC, cystatin C; eGFR, estimated glomerular filtration rate; eGFR_{cys}, cystatin C-based estimated glomerular filtration rate; SD, standard deviation.

Participants with cystatin C-based eGFR more than 30% below the creatinine-based value (large negative discordance; n = 244, 33.8%) were significantly older and had higher BMI than those with concordant estimates (p = 0.011 and p < 0.001, respectively). Ethnic distribution differed across groups (p < 0.001), with a higher proportion of Malay and a lower proportion of Chinese participants in the discordant group. Diabetes was markedly more frequent in the discordant group (63.5% versus 48.0% in the concordant group; p < 0.001). Biochemically, the discordant group had lower cystatin C-based and combined eGFR values than their creatinine-based estimates, consistent with a more advanced CKD classification when using cystatin C (all p < 0.001).

CKD stage distribution across equations

CKD stage distribution varied substantially by equation (Table 2). Using the CKD-EPI 2009 creatinine equation, most participants fell into G1-G2 (140 [19.4%] and 347 [48.1%], respectively). In contrast, the CKD-EPI 2012 cystatin C equation shifted the distribution markedly toward more advanced categories, with only 20 participants (2.8%) in G1 and substantially larger proportions in G3a and G3b (30.4% and 18.9%, respectively). The combined equations produced distributions intermediate between the creatinine-only and cystatin C-only equations.

Table 2
CKD stage distribution by eGFR equation (n = 721).

CKD stage	CKD-EPI 2009 Cr	CKD-EPI 2021 Cr	CKD-EPI 2012 CysC	CKD-EPI 2012 Cr–CysC	CKD-EPI 2021 Cr–CysC
G1 (≥ 90)	140 (19.4)	233 (32.3)	20 (2.8)	41 (5.7)	69 (9.6)
G2 (60–89)	347 (48.1)	292 (40.5)	228 (31.6)	352 (48.8)	362 (50.2)
G3a (45–59)	105 (14.6)	78 (10.8)	219 (30.4)	143 (19.8)	131 (18.2)
G3b (30–44)	51 (7.1)	49 (6.8)	136 (18.9)	91 (12.6)	72 (10.0)
G4 (15–29)	49 (6.8)	43 (6.0)	82 (11.4)	61 (8.5)	56 (7.8)
G5 (< 15)	29 (4.0)	26 (3.6)	36 (5.0)	33 (4.6)	31 (4.3)

Values are n (%). GFR categories are given in mL/min/1.73 m² and follow the KDIGO classification. CKD, chronic kidney disease; Cr, creatinine; CysC, cystatin C; eGFR, estimated glomerular filtration rate.

Reclassification of CKD stages

Compared with the CKD-EPI 2009 creatinine equation, the CKD-EPI 2012 cystatin C equation reclassified most older adults into more advanced CKD stages. Overall, 459 participants (63.7%) were up-staged, 250 (34.7%) remained in the same stage, and only 12 (1.7%) were down-staged (Fig. 1).

Fig. 1. CKD stage reclassification: CKD-EPI 2009 creatinine (rows) versus CKD-EPI 2012 cystatin C (columns).

Figure 1: eGFR categories are expressed in mL/min/1.73 m². Vertical axis represents baseline staging using the CKD-EPI 2009 creatinine equation; horizontal axis represents reclassification using the CKD-EPI 2012 cystatin C equation.

When staging was recalculated using the CKD-EPI 2021 creatinine equation, agreement with the 2009 equation was high: 569 participants (78.9%) remained in the same stage, 152 (21.1%) were down-staged, and none were up-staged, reflecting the modestly higher eGFR values returned by the 2021 creatinine equation (Fig. 2).

Fig. 2. CKD stage reclassification: CKD-EPI 2009 creatinine (rows) versus CKD-EPI 2021 creatinine (columns).

Figure 2: eGFR categories are expressed in mL/min/1.73 m². Vertical axis represents baseline staging using the CKD-EPI 2009 creatinine equation; horizontal axis represents reclassification using the CKD-EPI 2021 creatinine equation.

The combined equations produced more modest reclassification than the cystatin C-only equation. Relative to the CKD-EPI 2009 creatinine equation, the CKD-EPI 2012 creatinine-cystatin C equation up-staged 270 participants (37.4%), left 445 (61.7%) unchanged, and down-staged 6 (0.8%) (Fig. 3). The CKD-EPI 2021 creatinine-cystatin C equation up-staged 187 participants (25.9%), left 512 (71.0%) unchanged, and down-staged 22 (3.1%) (Fig. 4).

Fig. 3. CKD stage reclassification: CKD-EPI 2009 creatinine (rows) versus CKD-EPI 2012 creatinine-cystatin C (columns).

Figure 3: eGFR categories are expressed in mL/min/1.73 m². Vertical axis represents baseline staging using the CKD-EPI 2009 creatinine equation; horizontal axis represents reclassification using the CKD-EPI 2012 Creatinine-Cystatin C equation.

Fig. 4. CKD stage reclassification: CKD-EPI 2009 creatinine (rows) versus CKD-EPI 2021 creatinine-cystatin C (columns).

Figure 4: eGFR categories are expressed in mL/min/1.73 m². Vertical axis represents baseline staging using the CKD-EPI 2009 creatinine equation; horizontal axis represents reclassification using the CKD-EPI 2021 Creatinine-Cystatin C equation.

Table 3 summarises the overall reclassification pattern relative to the clinical reference equation. The most striking contrast was between the CKD-EPI 2009 creatinine and CKD-EPI 2012 cystatin C equations, with 63.7% of participants up-staged. Introducing creatinine into the combined equations attenuated but did not abolish this up-staging, still moving a quarter to a third of participants into more advanced CKD categories.

Table 3

Summary of CKD stage reclassification compared with the CKD-EPI 2009 creatinine equation (n = 721).

Comparison (versus CKD-EPI 2009 Cr)	Unchanged, n (%)	Up-staged, n (%)	Down-staged, n (%)
CKD-EPI 2021 Cr	569 (78.9)	0 (0.0)	152 (21.1)
CKD-EPI 2012 CysC	250 (34.7)	459 (63.7)	12 (1.7)
CKD-EPI 2012 Cr–CysC	445 (61.7)	270 (37.4)	6 (0.8)
CKD-EPI 2021 Cr–CysC	512 (71.0)	187 (25.9)	22 (3.1)

Values are n (%). CKD, chronic kidney disease; Cr, creatinine; CysC, cystatin C.

Agreement between eGFR equations

Table 4 shows agreement with the CKD-EPI 2009 creatinine equation. The CKD-EPI 2021 creatinine equation showed near-perfect agreement (Pearson r = 0.986; ICC = 0.973), with a small negative bias

(-3.9 mL/min/1.73 m²) and narrow limits of agreement (-12.3 to 4.5 mL/min/1.73 m²). In contrast, the CKD-EPI 2012 cystatin C equation showed the weakest agreement. Although the correlation remained strong (r = 0.868), the ICC was only moderate (0.669), and the mean bias was large (16.7 mL/min/1.73 m²), with wide limits of agreement (-6.9 to 40.3 mL/min/1.73 m²). The positive bias indicates that the CKD-EPI 2009 creatinine equation systematically returned higher eGFR values than the CKD-EPI 2012 cystatin C equation. The combined equations improved agreement: the CKD-EPI 2012 creatinine-cystatin C equation achieved r = 0.955, ICC = 0.882, and a mean bias of 9.2 mL/min/1.73 m², while the CKD-EPI 2021 creatinine-cystatin C equation achieved r = 0.949, ICC = 0.923, and the smallest bias (5.6 mL/min/1.73 m²).

Table 4
Agreement between the CKD-EPI 2009 creatinine equation and alternative eGFR equations.

Comparison (versus CKD-EPI 2009 Cr)	Pearson r	ICC	Mean bias (mL/min/1.73 m ²)	95% LoA (mL/min/1.73 m ²)
CKD-EPI 2021 Cr	0.986	0.973	-3.9	-12.3 to 4.5
CKD-EPI 2012 CysC	0.868	0.669	16.7	-6.9 to 40.3
CKD-EPI 2012 Cr-CysC	0.955	0.882	9.2	-5.0 to 23.4
CKD-EPI 2021 Cr-CysC	0.949	0.923	5.6	-9.5 to 20.7

A positive mean bias indicates that the CKD-EPI 2009 creatinine equation returns higher eGFR values than the comparator equation. Cr, creatinine; CysC, cystatin C; eGFR, estimated glomerular filtration rate; ICC, intraclass correlation coefficient; LoA, limits of agreement.

Predictors of large negative discordance

In a multivariable logistic regression model, older age, higher BMI, and diabetes mellitus were each independently associated with large negative discordance (cystatin C-based eGFR more than 30% lower than creatinine-based eGFR). The odds of discordance increased by 6.0% per additional year of age (odds ratio [OR] 1.060, 95% confidence interval [CI] 1.031–1.089; p < 0.001) and by 7.5% per 1 kg/m² increase in BMI (OR 1.075, 95% CI 1.036–1.117; p < 0.001). Diabetes mellitus was associated with 62% higher odds of discordance (OR 1.620, 95% CI 1.138–2.306; p = 0.007). Sex, hypertension, dyslipidaemia, and ischaemic heart disease were not independent predictors (Table 5).

Table 5
Multivariable logistic regression: independent predictors of large negative discordance (n = 721).

Predictor	Adjusted OR	95% CI	p-value
Age (per year)	1.060	1.031–1.089	< 0.001
Male sex	0.757	0.542–1.058	0.103
BMI (per kg/m ²)	1.075	1.036–1.117	< 0.001
Diabetes mellitus	1.620	1.138–2.306	0.007
Hypertension	1.148	0.691–1.909	0.595
Dyslipidaemia	0.827	0.499–1.370	0.461
Ischaemic heart disease	1.054	0.732–1.517	0.777

BMI, body mass index; CI, confidence interval; OR, odds ratio.

Discussion

In this cross-sectional study of 721 older Malaysian adults, the choice of filtration marker substantially influenced CKD staging. Switching from the creatinine-based CKD-EPI 2009 equation to the cystatin C-based 2012 equation upstaged nearly 64% of participants to a more severe CKD category and introduced a systematic bias of 16.7 mL/min/1.73 m². Using combined creatinine-cystatin C equations provided a middle ground, offering more consistent estimates and up-staging about 25–37% of participants. Notably, one-third of the participants showed a large negative discordance, with cystatin C indicating considerably worse kidney function than creatinine, mainly among older, higher-BMI, diabetic individuals.

The key finding of this study is the significant disagreement between creatinine- and cystatin C-based estimates. Although the correlation between the markers appeared strong (Pearson $r = 0.868$), correlation assesses covariation, not true agreement. The ICC, which accounts for systematic differences, was only moderate at 0.669. The mean bias was substantial at 16.7 mL/min/1.73 m², and the 95% limits of agreement spanned a wide range of 47 mL/min/1.73 m² (–6.9 to 40.3). For an older individual, selecting one marker over the other could alter the estimated eGFR enough to shift a patient across an entire CKD stage or more. This variation is not a minor laboratory detail but a difference significant enough to impact the diagnosis.

Clinically, reclassification was substantial: 459 of 721 participants (63.7%) were moved to a higher CKD stage when cystatin C replaced creatinine. The reclassification mainly resulted in up-staging rather than down-staging. Since more advanced CKD stages necessitate closer monitoring, earlier referrals, and stricter drug dosing, and help identify patients at higher cardiovascular risk, this change in staging directly affects the management of many older patients [14].

The combined creatinine-cystatin C equation was designed to fix this problem. In our study, it worked as expected: results fell between the two single-marker equations and matched the clinical comparator equation (CKD-EPI 2009 Cr) much more closely (ICC rose to 0.882 for the 2012 version and 0.923 for the 2021 version, with the average error dropping to 9.2 and 5.6 mL/min/1.73 m², respectively). It also caught 25.9–37.4% of patients whose kidney problems creatinine alone would have missed. This makes sense because creatinine and cystatin C are affected by different factors: serum creatinine by muscle mass, while cystatin C by inflammation [17]. These errors tend to push eGFR in opposite directions. Because higher adiposity, diabetes and chronic inflammation raise cystatin C independently of GFR, the association of large negative discordance with higher BMI and diabetes may partly reflect cystatin C overestimating dysfunction rather than creatinine alone overestimating function [17]. Because the two markers are largely independent, combining them reduces error and provides a more stable, reliable estimate, especially when the single-marker results disagree [7, 10, 18, 19].

These findings match current guidelines and other published research. The KDIGO 2024 guideline recommends using the combined equation to estimate the GFR category whenever cystatin C is available, and states that combining creatinine and cystatin C is more accurate than using either marker alone when the two disagree [7]. Other validation studies support a similar rule: when creatinine- and cystatin C-based estimates differ by more than about 30–40%, neither marker alone can be trusted. In these cases, use the combined equation or, if possible, measured GFR to guide clinical decisions [20]. Our data illustrate that, in this cohort of older Malaysian adults attending a tertiary hospital, one-third of patients with more than 30% negative discordance are precisely the group for whom relying solely on a single creatinine-based eGFR is unwise.

Our results align closely with the international literature. The tendency for creatinine-based eGFR to be higher than cystatin C-based eGFR in older adults reflects reports that creatinine tends to overestimate kidney function when muscle mass is reduced. Pooled cohort studies have demonstrated that cystatin C-based eGFR reclassifies a significant number of individuals into lower eGFR categories, with important implications for risk stratification of cardiovascular disease and end-stage kidney disease [21].

Recognition that discordance, particularly a cystatin C-based eGFR lower than a creatinine-based eGFR, indicates a phenotype characterised by sarcopenia, frailty, adiposity, and higher mortality has increased rapidly. Our identification of age, BMI, and diabetes as independent predictors closely aligns with these mechanistic and epidemiological insights. Recent reviews highlighted concerns that creatinine-based staging might underdiagnose CKD in older adults, whereas cystatin C could reclassify them more accurately [8, 18, 22, 23].

Our data advise caution against the uncritical use of cystatin C alone. The cystatin C equation shows a wide range of agreement (−6.9 to 40.3 mL/min/1.73 m²), indicating that, for individual patients, the two markers can differ significantly in either direction. The combined equations, endorsed by the KDIGO 2024 guideline as the preferred method when cystatin C is available, yielded the best overall agreement in our cohort, significantly enhancing agreement (ICC up to 0.923) while still capturing additional CKD cases

that creatinine alone may miss. This suggests that a confirmatory approach using a combined equation is preferable to replacing one single-marker equation with another [7, 19].

The clinical message is practical. A single creatinine-based eGFR is least reliable in the specific groups our analysis identified, namely older patients with higher BMI and diabetes. In these cases, confirming with a cystatin C test and using the combined equation is most likely to change the stage, affecting drug dosing, nephrology referrals, and prognosis discussions. Considering the high and rising burden of CKD in Malaysia, targeted cystatin C testing, rather than universal testing, could be a cost-effective way to reduce misclassification where it matters most. Our findings offer locally relevant, ethnically diverse South-East Asian data to guide such policies.

Strength and Limitations

The study has notable strengths: a relatively large, real-world cohort with simultaneous measurements of creatinine and cystatin C in an under-represented, multi-ethnic South-East Asian population.

The defining limitation of this study is the absence of a measured GFR (mGFR) reference. Without exogenous clearance measurement, we cannot determine which equation best approximates true kidney function, and our statistics quantify concordance between estimates rather than accuracy against a criterion standard. Keep this distinction in mind when interpreting the large cystatin C bias: it reflects differences from creatinine, not proof of error in either marker.

However, this limitation reflects real-world practice and does not diminish the clinical relevance of our findings. First, the clinical scenario we depict closely reflects routine practice: in Malaysian clinical settings, mGFR measurement is rarely available, and decisions rely on estimating equations. Therefore, quantifying the extent of staging variation among these equations used by clinicians is directly applicable, regardless of which equation is considered most accurate [8]. Second, the direction and magnitude of our findings are well supported by cohorts that included mGFR, as well as by the equation-development studies. These studies showed that creatinine tends to overestimate GFR in individuals with low muscle mass and that combined equations provide the most accurate estimates when compared with mGFR [12, 13, 18]. Third, the prognostic literature shows that discordance provides prognostic information independent of true GFR, so identifying discordant patients is clinically useful [8, 14, 21]. Rather than invalidating the study, the lack of mGFR clarifies its contribution: it provides a real-world depiction of clinicians' decision-making challenges and highlights how marker selection influences outcomes.

Beyond the absence of measured GFR, several additional limitations are recognised. The study was performed at a single tertiary hospital, which may limit the generalizability of the results to community settings, and referral patterns could bias the sample towards more comorbidities. Its cross-sectional design also prevents assessment of outcomes such as disease progression or mortality, which would add prognostic value. Additionally, the study did not account for factors such as albuminuria, acute illness, thyroid disorders, corticosteroid use, or inflammation, all of which can independently influence

cystatin C levels. The subgroup whose cystatin C-based eGFR exceeded the creatinine-based estimate by more than 30% was small (n = 8), limiting the stability of comparisons involving that group.

Conclusions

Among older adults at a Malaysian tertiary hospital, the choice of filtration marker changed CKD stage in up to two-thirds of patients. Cystatin C-based eGFR systematically reclassified patients into more advanced CKD stages than creatinine-based eGFR, whereas combined creatinine-cystatin C equations yielded intermediate and more stable estimates, consistent with the KDIGO 2024 recommendations. In the absence of measured GFR, we cannot identify a single correct estimate; however, the magnitude of discordance and its clinical predictors, namely older age, higher BMI, and diabetes, define a high-risk group in whom creatinine-based eGFR is least reliable and confirmatory cystatin C testing is most likely to alter management. These findings support targeted use of combined equations in older, high-risk patients and motivate future mGFR-based validation studies in this population.

Abbreviations

BMI

Body mass index

CI

Confidence interval

CKD

Chronic kidney disease

CKD-EPI

Chronic Kidney Disease Epidemiology Collaboration

Cr

Creatinine

CysC

Cystatin C

eGFR

Estimated glomerular filtration rate

ERM

European Reference Material

GFR

Glomerular filtration rate

ICC

Intraclass correlation coefficient

IDMS

Isotope dilution mass spectrometry

IFCC

International Federation of Clinical Chemistry and Laboratory Medicine

IQR

Interquartile range

KDIGO

Kidney Disease:Improving Global Outcomes

LoA

Limits of agreement

mGFR

Measured glomerular filtration rate

NIST

National Institute of Standards and Technology

OR

Odds ratio

PETIA

Particle-enhanced immunoturbidimetric assay

SD

Standard deviation

UMMC

University Malaya Medical Centre

Declarations

Participant Consent Statement: Informed consent was obtained from all individual participants or their legally authorised representatives prior to their inclusion in the study.

Ethics statement and consent to participate

This retrospective study was approved by the Medical Research Ethics Committee of University Malaya Medical Centre (UMMC-MREC; MREC ID 202512-14551; National Medical Research Register ID RSCH ID-25-05230-NYR) under expedited review on 13 July 2025. The MREC approval letter specified an approved study timeframe from 1 May 2025 to 30 April 2026. The study was conducted in accordance with the Declaration of Helsinki and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Guidelines for Good Clinical Practice. Data were accessed retrospectively from 1 May 2025 to 30 April 2026 within the timeframe specified in the MREC approval.

Consent for publication

Not applicable

Availability of data and materials:

The datasets generated and analysed during the current study are not publicly available because they contain routinely collected clinical and laboratory information from patients at University Malaya Medical

Centre and the ethics approval does not cover public data deposition, but they are available from the corresponding author on reasonable request and with the permission of the UMMC Medical Research Ethics Committee.

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Competing interests

The authors have declared that no competing interests exist.

Authors' contributions

ELA and MJ conceived and designed the study. LYW, ACWX, YZQ and CYZ collected the clinical data and compiled the study database. AHAH, NZ and FAJ supervised and performed the serum creatinine and cystatin C measurements and advised on assay calibration and traceability. ELA performed the statistical analysis and drafted the manuscript. MJ supervised the study and critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

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Figures

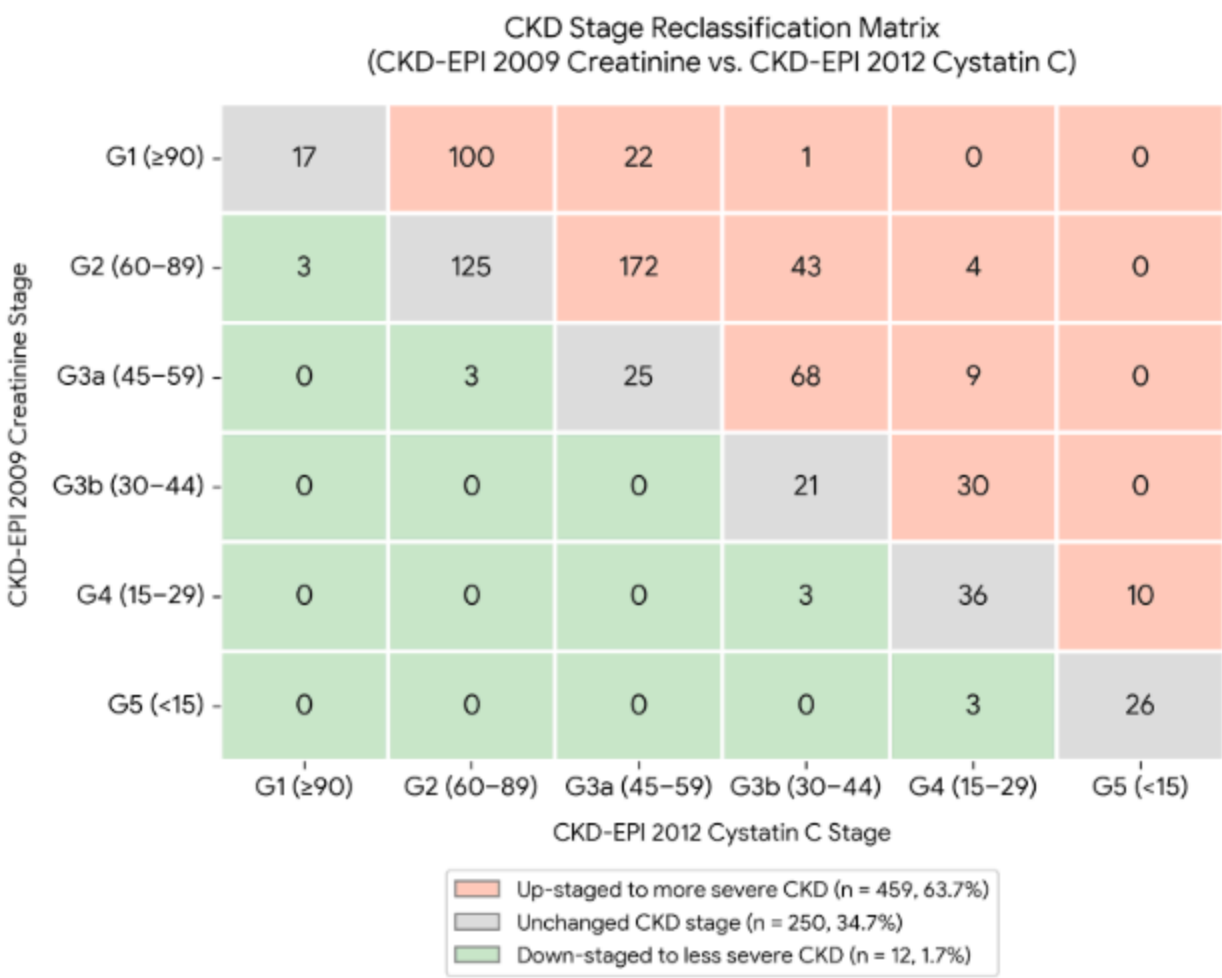


Figure 1

CKD stage reclassification: CKD-EPI 2009 creatinine (rows) versus CKD-EPI 2012 cystatin C (columns).

eGFR categories are expressed in mL/min/1.73 m². Vertical axis represents baseline staging using the CKD-EPI 2009 creatinine equation; horizontal axis represents reclassification using the CKD-EPI 2012 cystatin C equation.

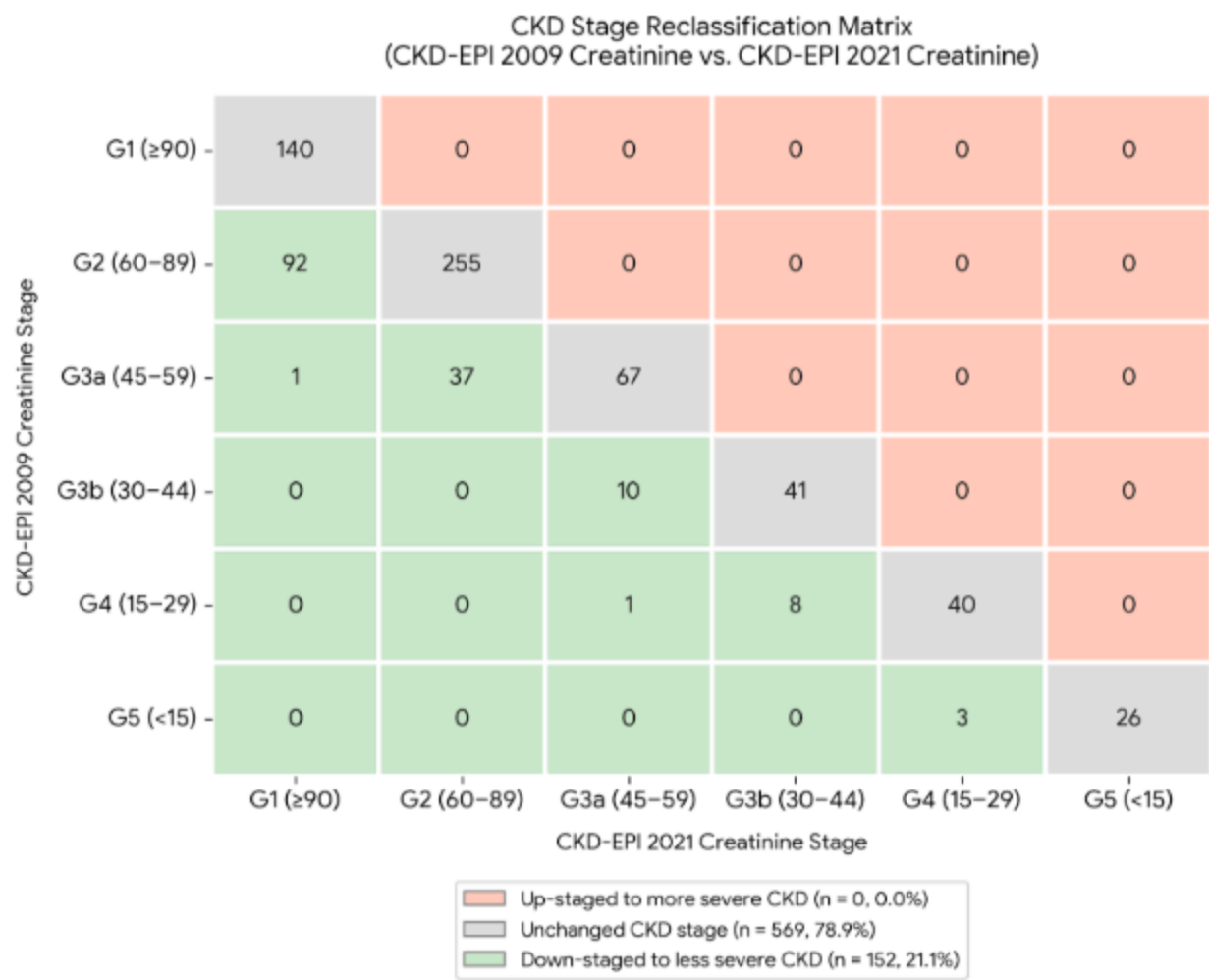


Figure 2

CKD stage reclassification: CKD-EPI 2009 creatinine (rows) versus CKD-EPI 2021 creatinine (columns).

eGFR categories are expressed in mL/min/1.73 m². Vertical axis represents baseline staging using the CKD-EPI 2009 creatinine equation; horizontal axis represents reclassification using the CKD-EPI 2021 creatinine equation.

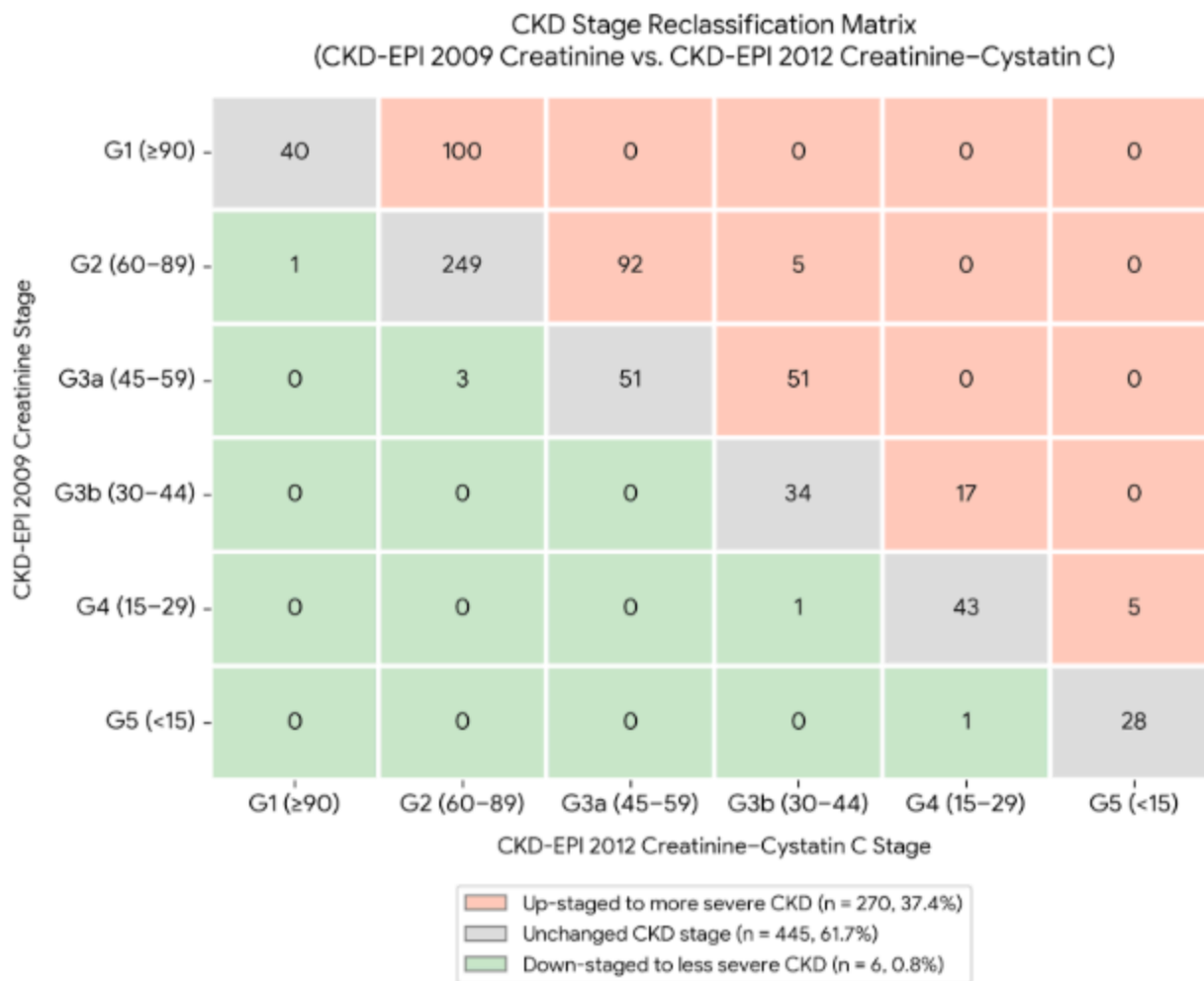


Figure 3

CKD stage reclassification: CKD-EPI 2009 creatinine (rows) versus CKD-EPI 2012 creatinine-cystatin C (columns).

eGFR categories are expressed in mL/min/1.73 m². Vertical axis represents baseline staging using the CKD-EPI 2009 creatinine equation; horizontal axis represents reclassification using the CKD-EPI 2012 Creatinine-Cystatin C equation.

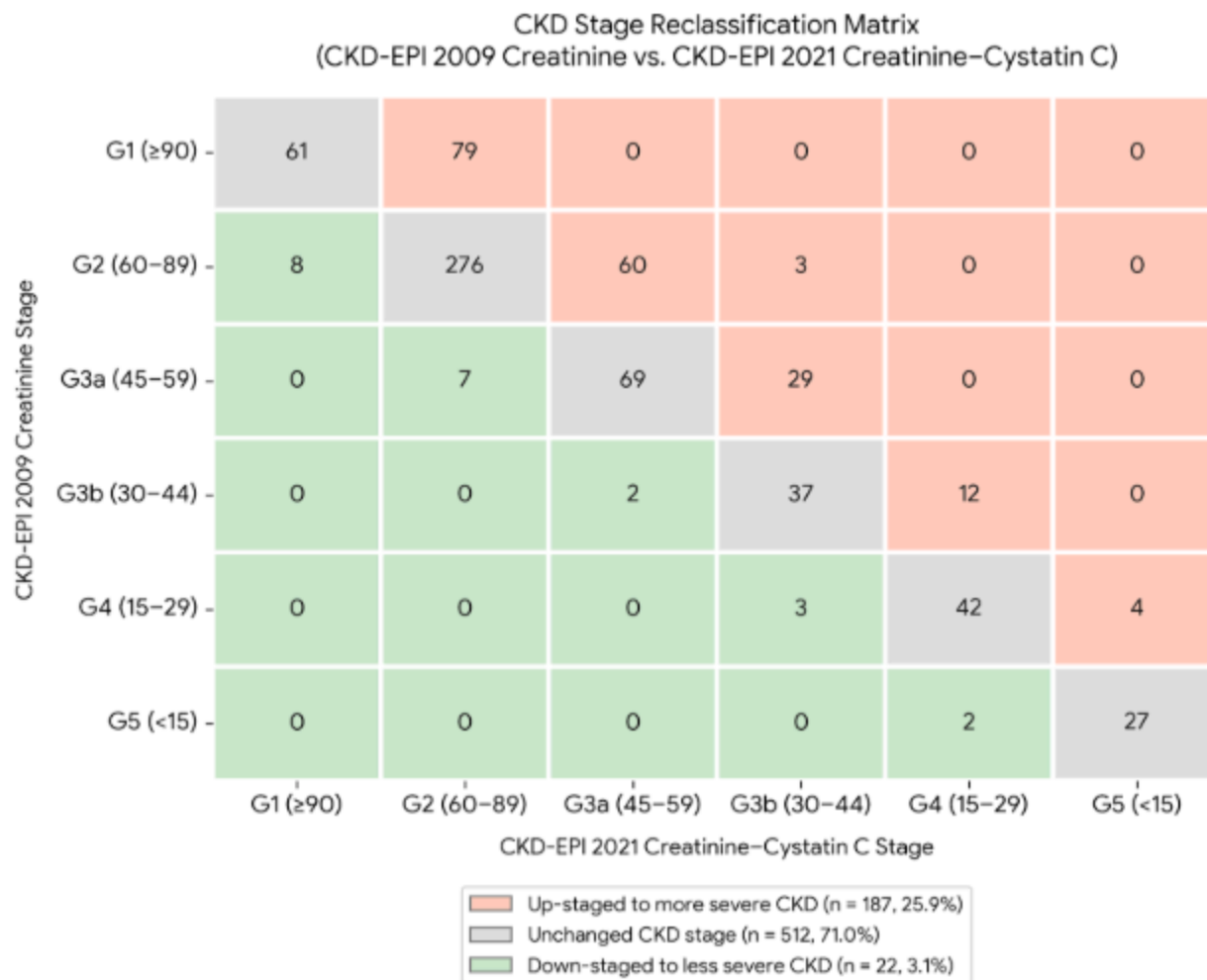


Figure 4

CKD stage reclassification: CKD-EPI 2009 creatinine (rows) versus CKD-EPI 2021 creatinine-cystatin C (columns).

eGFR categories are expressed in mL/min/1.73 m². Vertical axis represents baseline staging using the CKD-EPI 2009 creatinine equation; horizontal axis represents reclassification using the CKD-EPI 2021 Creatinine-Cystatin C equation.