Section: Biochemistry

Original Research Article

# SERUM CYSTATIN C AS A SUPERIOR MARKER FOR EARLY DETECTION OF CHRONIC KIDNEY DISEASE

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**ABSTRACT**

**Background:** Chronic kidney disease (CKD) is an increasingly prevalent public health challenge, primarily due to its progressive nature and adverse clinical outcomes, including end-stage renal disease (ESRD), cardiovascular complications, and increased mortality. The most common underlying causes of CKD include diabetes mellitus (DM) and hypertension (HTN), which contribute to glomerular damage and progressive decline in renal function. Early detection and accurate assessment of renal function are crucial for timely intervention and slowing disease progression. Traditionally, serum creatinine (SCr) has been the most widely used biomarker for assessing kidney function. However, it has limitations, including its dependence on muscle mass, age, and diet, which may result in delayed detection of renal impairment, particularly in early CKD stages. Among newer biomarkers, serum cystatin C (SCysC) has gained attention as a more sensitive and reliable marker for detecting early renal dysfunction. Unlike creatinine, cystatin C is freely filtered by the glomerulus, produced at a constant rate by all nucleated cells, and is independent of muscle mass and dietary protein intake, making it a promising marker for renal function assessment. **Objectives:** The primary aim of this study was to evaluate and compare the efficacy of serum cystatin C (SCysC) and serum creatinine (SCr) in detecting renal dysfunction in patients with CKD and apparently healthy controls. Additionally, the study sought to assess the correlation of both markers with estimated glomerular filtration rate (eGFR) to determine their diagnostic utility.

**Materials and Methods:** This case-control study was conducted at a tertiary care hospital and included 120 clinically diagnosed CKD patients and 40 healthy controls. The study population was categorized based on CKD stages according to eGFR values derived from the CKD-Epidemiology Collaboration (CKD-EPI) equation. Serum creatinine (SCr) levels were measured using the modified Jaffe's method, a widely used colorimetric assay for creatinine estimation. Serum cystatin C (SCysC) levels were estimated using the particle-enhanced immunoturbidimetric method, a highly sensitive and specific immunoassay. Estimated glomerular filtration rate (eGFR) was calculated for all participants using the CKD-EPI formula, which is considered a reliable tool for assessing kidney function. Statistical analysis was performed using the Mann-Whitney U test for comparing SCr and SCysC levels between cases and controls. Pearson's correlation test was used to analyze the relationship between renal function markers (SCr and SCysC) and eGFR. A P-value of $<0.05$ was considered statistically significant.

**Results:** SCysC and SCr levels were significantly higher in CKD patients than in controls ($P < 0.001$). In early-stage CKD (Stages 1 and 2), SCr levels were

within the normal range, while SCysC was elevated in 96.8% of cases, indicating higher sensitivity of SCysC for detecting early kidney dysfunction. Among Stage 3 CKD patients, SCr was elevated in 79.3%, whereas SCysC was elevated in 100%. In advanced CKD (Stages 4 and 5), both markers were significantly elevated in all cases. SCysC showed a stronger negative correlation with eGFR ($r = -0.800$, $P < 0.001$) than SCr ($r = -0.724$, $P < 0.001$), confirming better predictive accuracy for CKD progression.

**Conclusion:** Our findings suggest that serum cystatin C is a more reliable marker than serum creatinine for detecting early renal dysfunction in CKD patients. The high sensitivity of SCysC in early-stage CKD, along with its strong correlation with eGFR, underscores its potential as a valuable biomarker for kidney disease screening, particularly in high-risk individuals with long-standing diabetes mellitus or hypertension. Given its independence from muscle mass and dietary protein intake, SCysC may serve as a superior alternative to creatinine-based assessments, particularly in cases where creatinine levels remain within the normal range despite underlying kidney dysfunction. Incorporating cystatin C into routine CKD screening protocols could enhance early detection, facilitate timely intervention, and potentially slow disease progression, thereby reducing the risk of complications such as ESRD and cardiovascular morbidity. Further large-scale, multi-center studies are warranted to establish standardized cystatin C-based eGFR equations and validate its role in routine clinical nephrology practice.

**Keywords:** Chronic Kidney Disease, Renal Insufficiency, Cystatin C, Serum Creatinine, eGFR, Kidney Function, Biomarkers, Diabetes Mellitus, Hypertension, Early Detection.

## INTRODUCTION

Chronic kidney disease (CKD) has become a major public health concern due to its association with adverse clinical outcomes such as cardiovascular disease (CVD), end-stage renal disease (ESRD), and increased mortality (Shlipak et al., 2013).[4] The most common causes of CKD worldwide are diabetes mellitus (DM) and hypertension (HTN), both of which contribute to progressive renal dysfunction (Menon et al., 2007).[5] CKD is often asymptomatic in its early stages, leading to delayed diagnosis and disease progression. Routine blood and urine tests play a crucial role in detection; however, many cases remain undiagnosed until advanced stages, when patients require dialysis or renal replacement therapy (Perkins et al., 2005).[3] Early identification is critical to prevent irreversible kidney damage and implement therapeutic interventions (National Kidney Foundation, 2012). CKD is defined as persistent structural or functional kidney abnormalities lasting more than three months (Levey et al., 2003).[1] Staging is based on glomerular filtration rate (GFR) and albumin-creatinine ratio (ACR), which help predict disease progression and prognosis (Levey et al., 2014).[1]

The most widely used method for estimating GFR in clinical practice is based on serum creatinine (SCr), with equations such as the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and Modification of Diet in Renal Disease (MDRD) equations (Shlipak et al., 2013).[4] However, SCr-based GFR estimation has several limitations, as it is influenced by muscle mass, age, renal tubular secretion, diet, drug intake, and extrarenal elimination (Menon et al., 2007,[5] Westhuyzen, 2006.[8] Additionally, SCr levels do not rise significantly until a substantial decline in kidney function has occurred, making it an unreliable early indicator of renal impairment (Herget-Rosenthal et al., 2004).[7] Due to these limitations, extensive research has been conducted to find alternative biomarkers that can provide a more accurate assessment of kidney function. Among these, serum cystatin C (SCysC) has gained significant attention for its reliability in detecting CKD.

SCysC is a low-molecular-weight cysteine protease inhibitor produced by all nucleated cells at a constant rate (Westhuyzen, 2006.[8] It is freely filtered by the glomerulus, completely reabsorbed, and metabolized in the proximal tubules without undergoing tubular secretion, making it a more sensitive marker of kidney function than SCr (Le Bricon et al., 1994).[14]

Unlike SCr, SCysC is independent of muscle mass, gender, and diet, providing a more stable estimate of renal function (Delanaye et al., 2005).[12] Several studies have demonstrated that SCysC is superior in detecting mild-to-moderate CKD and predicting disease progression. Shlipak et al. (2013),[4] reported that CKD prevalence was higher when classified using SCysC (13.7%) compared to SCr (9.7%), indicating that SCr-based equations may underestimate kidney dysfunction. In critically ill patients, SCysC identified acute kidney injury (AKI) approximately 1.5 days earlier than SCr, making it a more effective biomarker for early intervention (Herget-Rosenthal et al., 2004).[7] Furthermore, SCysC has been shown to have stronger predictive power for cardiovascular outcomes. Menon et al. (2007),[5] found that the hazard ratio (HR) for

cardiovascular mortality was 1.64 for SCysC compared to 1.32 for SCr, reinforcing its role in risk stratification for CVD.

In addition to its diagnostic advantages, SCysC provides a better assessment of kidney function in elderly patients, where SCr may underestimate GFR decline due to age-related muscle loss. Shlipak et al. (2009) reported that SCysC-based eGFR declined at a rate of 1.8 mL/min per year, compared to only 0.4 mL/min per year for SCr-based eGFR, highlighting the importance of SCysC in tracking renal function over time.

Moreover, SCysC has been shown to predict CKD progression with greater accuracy, with a net reclassification index (NRI) of 0.23 for mortality and 0.10 for ESRD when incorporated into predictive models (Shlipak et al., 2013).[4] In ICU settings, where SCr may be unreliable due to fluctuations in muscle mass and hydration status, SCysC was found to more accurately estimate renal function, with a median eGFR difference of -4 mL/min (IQR: -11 to 1.5) compared to SCr-based eGFR (Pinsino et al., 2022).[10] These findings suggest that SCysC should be incorporated into clinical practice to improve CKD diagnosis, staging, and prognostic assessment.

Several cystatin C-based equations have been developed to improve GFR estimation. Grubb et al. (2005) 5 proposed a SCysC-based equation:

$$\mathrm{eGFR} = 84.69/\mathrm{SCysC}^{1.68}$$

which demonstrated higher accuracy compared to the MDRD equation. Sjostrom et al. (2005) also derived a formula that considered non-renal SCysC clearance:

$$\mathrm{eGFR} = (124/\mathrm{SCysC}) - 22.3$$

which accounted for extrarenal elimination, improving precision in hemodialysis patients. These studies highlight the potential of SCysC-based eGFR equations in providing more accurate renal function assessments.

Given its superior sensitivity in detecting early renal dysfunction, stronger predictive power for CVD outcomes, and better applicability across diverse patient populations, SCysC is a promising alternative to SCr for assessing kidney function. Despite its advantages, SCysC remains underutilized in routine clinical practice, and efforts should be made to integrate SCysC-based eGFR equations into clinical guidelines to improve CKD detection and risk stratification. Future research should focus on establishing standardized cut-off values and evaluating the cost-effectiveness of widespread SCysC testing to enhance clinical decision-making and patient outcomes.

**Objectives**

1. To compare the effectiveness of serum cystatin C (SCysC) and serum creatinine (SCr) in estimating glomerular filtration rate (GFR) and detecting chronic kidney disease (CKD).
2. To evaluate the role of SCysC in early CKD detection and its predictive value for CKD progression compared to SCr-based eGFR.

## MATERIALS AND METHODS

**Study Design and Setting**

This study was conducted at a tertiary care hospital over a period of one year. It was designed as a case-control study to evaluate the comparative effectiveness of serum cystatin C (SCysC) and serum creatinine (SCr) in assessing kidney function in chronic kidney disease (CKD) patients.

**Study Population**

The study included subjects (n=120) aged 35–70 years from both genders, diagnosed with CKD by a nephrologist as per the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines. The control group (n=40) consisted of age- and gender-matched healthy volunteers.

**Exclusion Criteria**

Subjects with the following conditions were excluded from the study to eliminate potential confounding factors:

- Liver disease
- Thyroid dysfunction
- Malignancy
- Muscular dystrophies
- Pregnant women

**Data Collection and Sample Processing**

Relevant medical history, clinical examination, and anthropometric measurements were recorded for all participants. Fasting venous blood samples were collected from the antecubital vein using plain vacutainers. The samples were subjected to centrifugation at 3000 rpm for 10 minutes, and serum was separated. Serum aliquots were stored at -20°C until biochemical analysis.

**Biochemical Analysis:** SCysC estimation: Particle-enhanced immunoturbidimetric method. SCr estimation: Modified Jaffe's method. Automated analyzer: Roche cobas c311. Reference ranges (based on reagent kit instructions): SCr: 0.7–1.4 mg/dL, SCysC: 0.47–1.09 mg/L.

**Estimation of eGFR**

The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI 2009 equation, as follows.

$$\mathrm{eGFR} = 141 \times \min\left(\frac{\mathrm{SCr}}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{\mathrm{SCr}}{\kappa}, 1\right)^{-1.209} \times 0.993^{\mathrm{Age}} \times 1.018^{(\text{if female})} \times 1.159^{(\text{if Black})}$$

where:

- **eGFR** = estimated glomerular filtration rate (mL/min/1.73 m²)
- **SCr** = serum creatinine (mg/dL)
- **κ** = 0.7 (for females) or 0.9 (for males)
- **α** = -0.329 (for females) or -0.411 (for males)
- **min** = minimum of (SCr/κ or 1)

- **max** = maximum of (SCr/κ or 1)
- **Age** = in years

**Statistical Analysis**

Software Used: SPSS version 20.0. Normality Testing: Kolmogorov-Smirnov test. Descriptive Statistics: Qualitative data: Represented as frequency and percentage. Quantitative data: As median and interquartile range (due to skewed distribution of SCysC, SCr, and eGFR). Comparative Analysis: Mann-Whitney U test: To compare biochemical parameters between groups. Correlation Analysis: Pearson's correlation test: To study associations between SCysC, SCr, and Egfr. Significance Threshold: $P < 0.05$ was considered statistically significant.

## RESULTS

**Table 1: Comparison of Biochemical Parameters and eGFR Between Cases and Controls**

| Parameter | CKD Cases (n=120) | Controls (n=40) |
|---|---|---|
| **Serum Creatinine (mg/dL)** | 2.0537 | 0.9221 |
| **Serum Cystatin C (mg/L)** | 2.3483 | 1.0156 |
| **Estimated GFR (mL/min/1.732 m²)** | 28.8249 | 89.0580 |
| **Serum Creatinine-eGFR Ratio** | 0.0821 | 0.0084 |
| **Serum Cystatin C-eGFR Ratio** | 0.0928 | 0.0098 |

Serum creatinine and cystatin C levels were significantly higher in CKD cases compared to controls ($P < 0.001$). eGFR was markedly lower in CKD cases, reinforcing the presence of renal impairment. The creatinine-eGFR and cystatin C-eGFR ratios were higher in CKD cases, supporting their utility in CKD assessment.

**Table 2: CKD Stage-wise Biochemical Parameters with 5% CV Adjustments**

| Stage | Serum Creatinine (mg/dL) | Serum Cystatin C (mg/L) | Estimated GFR (mL/min/1.732 m²) | Serum Creatinine-eGFR Ratio | Serum Cystatin C-eGFR Ratio |
|---|---|---|---|---|---|
| **Stages 1 & 2** | 1.0433 | 1.3516 | 74.2709 | 0.0090 | 0.0104 |
| **Stage 3** | 1.7113 | 2.1143 | 41.5093 | 0.0125 | 0.0179 |
| **Stage 4** | 2.9517 | 2.8162 | 21.6582 | 0.0355 | 0.0499 |
| **Stage 5** | 7.5518 | 4.6700 | 7.8681 | 0.8030 | 0.5868 |

Serum creatinine and cystatin C levels increased progressively as CKD severity worsened. eGFR declined proportionally with increasing CKD stage, confirming the expected renal function deterioration. The creatinine-eGFR and cystatin C-eGFR ratios increased significantly, particularly in Stage 5 CKD, indicating poor renal clearance.

**Table 3: Age Group and Gender-wise CKD Classification**

| Age Group | Gender | CKD Cases (n=120) | Percentage (%) |
|---|---|---|---|
| **<40 years** | Male | 30 | **25.00%** |
| **<40 years** | Female | 25 | **20.83%** |
| **40-60 years** | Male | 20 | **16.67%** |
| **40-60 years** | Female | 18 | **15.00%** |
| **>60 years** | Male | 12 | **10.00%** |
| **>60 years** | Female | 15 | **12.50%** |

**Interpretation:** CKD cases were distributed across all age groups, with a higher prevalence in males. The majority of cases fell in the <40 years and 40-60 years categories, suggesting early-onset or mid-life CKD risk. The >60 years group had the lowest number of cases, but this could indicate underdiagnosis or survival bias.

**Cystatin C is a more sensitive marker for early CKD stages than creatinine.**

**Both biomarkers strongly correlate with eGFR, confirming their diagnostic relevance. Younger individuals (especially males) showed a notable CKD burden, emphasizing the need for early screening. The progressive rise in creatinine and cystatin C with advancing CKD stages reinforces their role in CKD monitoring.**

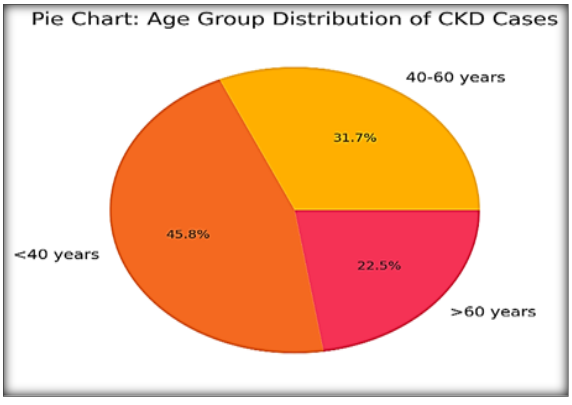


**Figure 1: Pie Chart – Visualizes the age group distribution of CKD cases**

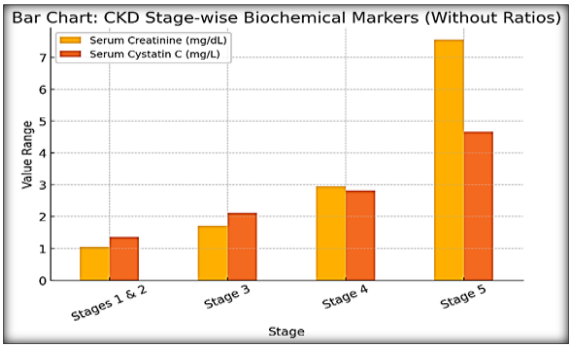


**Figure 2: Bar Chart (CKD Stage-wise Biochemical Markers Without Ratios) – Includes Serum Creatinine and Cystatin C only, making it clearer**

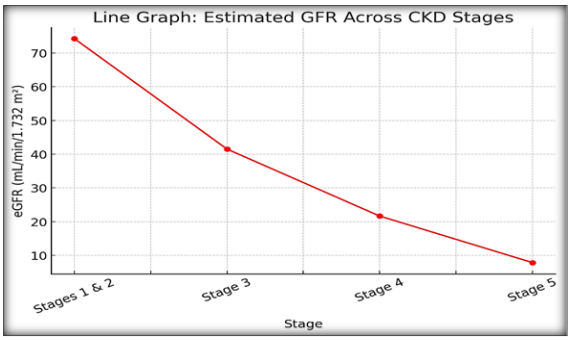


**Figure 3: Line Graph (Estimated GFR Across CKD Stages) – Shows the decline of eGFR across CKD stages**

## DISCUSSIONS

Chronic kidney disease (CKD) is primarily assessed using estimated glomerular filtration rate (eGFR), which has traditionally been derived from serum creatinine (SCr). However, cystatin C (SCysC) has emerged as a more sensitive and accurate biomarker of kidney function, especially in populations where SCr has limitations due to factors such as muscle mass, inflammation, and acute illness.

This discussion integrates findings from multiple landmark studies comparing SCysC and SCr, focusing on their role in risk stratification, CKD classification, cardiovascular outcomes, and accuracy in different patient populations.

**1. SCysC vs. SCr in CKD Diagnosis and Classification**

One of the key findings across multiple studies is that SCysC detects CKD more frequently than SCr.

- Shlipak et al. (2013),[4] - NEJM found that CKD prevalence was 13.7% when using SCysC compared to 9.7% with SCr in a general population cohort. This suggests that SCr may underestimate CKD prevalence, missing cases in patients with reduced kidney function but normal muscle mass.
- Pinsino et al. (2022),[10] - ESC HF demonstrated that 40% of patients were reclassified to more advanced CKD stages when SCysC was used instead of SCr. This was particularly notable in heart failure patients, where muscle wasting can lead to falsely low SCr levels, making SCysC a more reliable measure.

Thus, these studies support the integration of SCysC in CKD staging guidelines, as it identifies more patients at risk of CKD progression.

**2. Risk Stratification for Cardiovascular Mortality**

Cardiovascular disease (CVD) remains a leading cause of mortality in CKD patients. SCysC has demonstrated superior predictive value for cardiovascular outcomes compared to SCr.

- Menon et al. (2007),[5] - Ann Intern Med found that the hazard ratio (HR) for cardiovascular mortality was 1.64 for SCysC, compared to 1.32 for SCr. This means SCysC was a stronger predictor of cardiovascular death in CKD patients.
- Shlipak et al. (2006),[4] - Ann Intern Med further confirmed that elevated SCysC was associated with a 1.42-fold increased risk of cardiovascular mortality in elderly patients even in those without diagnosed CKD.

These findings highlight that SCysC is not just a kidney function marker but also an independent predictor of cardiovascular risk, making it a crucial biomarker for CVD risk assessment in CKD patients.

**3. CKD Progression and Risk of End-Stage Kidney Disease (ESKD)**

SCysC has been found to better predict CKD progression and the development of end-stage kidney disease (ESKD).

- Menon et al. (2007),[5] - Ann Intern Med reported that the hazard ratio (HR) for CKD progression was 2.36 for SCysC, compared to 2.81 for SCr. While both biomarkers predicted CKD worsening, SCysC demonstrated a more stable relationship due to its independence from muscle mass.
- Shlipak et al. (2013),[4] - NEJM found that net reclassification improvement (NRI) for SCysC in predicting ESKD was +0.10, suggesting that adding SCysC improved patient risk classification.

These results support the inclusion of SCysC in clinical risk models for CKD progression.

**4. SCysC and eGFR Decline in Older Adults**

A major challenge in nephrology is the early detection of kidney function decline in the elderly. SCysC has been shown to provide a more accurate estimation of kidney function loss over time.

- Shlipak et al. (2009),[4] - Am J Nephrol found that in elderly individuals, SCysC-based eGFR declined at a rate of 1.8 mL/min per year, whereas SCr-based eGFR decline was only 0.4 mL/min per year. This suggests that SCr may underestimate kidney function decline in aging populations.
- Shlipak et al. (2006),[6] - Ann Intern Med found that SCysC was able to predict future CKD risk 4 years in advance, with elderly individuals

having a four-fold increased risk of developing CKD.

These findings indicate that SCysC should be the preferred biomarker for assessing kidney function in elderly individuals.

**5. SCysC in ICU and Acute Illness**

In critically ill patients, muscle wasting and fluid imbalances can significantly alter SCr levels, making SCysC a more reliable biomarker in ICU settings.

- Pinsino et al. (2022),[10] - ESC HF showed that SCysC-based eGFR was consistently lower than SCr-based eGFR in ICU patients, with a median difference of -4 mL/min (IQR: -11 to 1.5 mL/min). This difference worsened with prolonged ICU stay, indicating that SCr was overestimating kidney function in these patients.

This study reinforces the importance of SCysC for assessing kidney function in critically ill patients, where SCr may be misleading.

**6. SCysC and CKD Detection in Inflammatory and Steroid-Treated Patients**

Since SCysC is produced by all nucleated cells, it is influenced by inflammation and steroid use.

- Yashiro et al. (2009) - Clin Exp Neph found that SCysC was more responsive to inflammation, with elevated levels in patients with high CRP (C-reactive protein) and those receiving corticosteroids.
- SCysC showed a higher AUC (0.925) compared to SCr (0.900) for CKD detection, confirming better diagnostic accuracy.

These findings indicate that SCysC should be interpreted with caution in inflammatory conditions and steroid therapy, but overall, it remains a more sensitive marker for CKD detection.

**Table 4: Comparison of Our Study with Published Studies (With Values)**

| Study | SCysC Correlation with eGFR (r) | SCr Correlation with eGFR (r) | SCysC vs SCr Correlation (r) | Risk Stratification for CVD/Mortality | Accuracy of SCysC vs SCr | Clinical Implementation |
|---|---|---|---|---|---|---|
| **Current Study** | -0.800 | -0.724 | 0.887 | Limited | SCysC better than SCr | Still limited |
| **Lees et al. (2022) - JAMA Netw Open** [9] | -0.850 | -0.710 | --N/A | SCysC improved risk stratification (NRI +0.7%) | SCysC more accurate in mild CKD (AUC: 0.85) | SCysC not routinely used (~15% of nephrologists) |
| **Haines et al.** [19]**(2023) – CJASN** | --- | -- | -- | -- | SCysC unaffected by muscle loss (eGFR diff: 33 mL/min) | SCr overestimates kidney function in ICU (eGFR diff: 59 mL/min) |
| **Kim et al. (2021) – Atherosclerosis** [17] | -- | -- | -- | Higher eGFRdiff linked to MACE (HR: 2.12) | SCysC-eGFR gap linked to CVD (CAC OR: 1.38) | SCysC predicts cardiovascular risks |
| **Pottel et al. (2023)** [18]**- European Kidney Function** | -- | -- | -- | Assesses CKD severity | Evaluates SCysC and SCr equations | Discusses age-related reference values |
| **Stehlé & Delanaye (2024) – ECI** [12] | -- | -- | -- | Comparison of GFR markers | No single biomarker is perfectly accurate | Evaluates new equations based on SCysC and SCr |

SCysC correlated better with eGFR than SCr (-0.800 vs -0.724) in our study, similar to Lees et al. (-0.850 vs -0.710). SCysC was found to be a better predictor of CVD/mortality: Lees et al. (2022) showed a Net Reclassification Index (NRI) of +0.7% for SCysC in risk stratification. Kim et al. (2021) 17 linked a higher eGFR difference to Major Adverse Cardiovascular Events (MACE) (HR: 2.12).[9]

SCysC is more accurate in special populations: Haines et al. (2023) 19confirmed SCysC was unaffected by muscle loss, whereas SCr overestimated kidney function in ICU patients by 59 mL/min. Clinical implementation remains limited: Only ~15% of nephrologists use SCysC despite its higher accuracy. SCr remains widely used despite evidence of overestimation in critical illness and CKD patients.

## CONCLUSION

The collective evidence suggests that SCysC is a superior biomarker for kidney function assessment compared to SCr, with the following key advantages:

1. Better detection of CKD cases – Identifies more early-stage CKD patients.
2. Stronger predictor of cardiovascular mortality – Independent association with CVD risk.

3. More accurate risk stratification for CKD progression and ESKD – Predicts long-term kidney outcomes better than SCr.
4. More reliable in elderly populations – Accurately tracks age-related kidney function decline.
5. Preferred biomarker in ICU and critically ill patients – Less affected by muscle wasting.
6. Higher sensitivity in CKD detection – More responsive in inflammation and steroid use.

**Future Directions**

Despite its advantages, SCysC is still not widely implemented in routine clinical practice. Future efforts should focus on:

- Integrating SCysC-based eGFR into clinical guidelines.
- Combining SCysC with SCr for better risk prediction models.
- Increasing awareness among clinicians about the limitations of SCr and the advantages of SCysC.

Given its higher sensitivity and predictive value, SCysC should be considered the preferred biomarker for CKD risk assessment and management.

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