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Diagnostic Value Of Cystatin-C Compared With Serum Creatinine For Early Detection Of Chronic Kidney Disease

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Abstract

Early detection of Chronic Kidney Disease (CKD) plays a vital role in delaying disease progression and preventing complications. Serum creatinine (SCr), the conventional biomarker used in clinical practice, has limited sensitivity in early CKD due to non-renal influences such as muscle mass, age, gender, and dietary protein intake. Cystatin-C, an endogenous cysteine protease inhibitor produced at a constant rate by all nucleated cells, has emerged as a more sensitive and reliable biomarker closely correlated with glomerular filtration rate (GFR).

This review evaluates the diagnostic sensitivity, specificity, predictive accuracy, and clinical utility of Cystatin-C compared with serum creatinine for early CKD detection.

Result

Contemporary evidence demonstrates that **Cystatin-C consistently outperforms serum creatinine**, showing higher sensitivity (80–93%) and specificity (75–90%) for identifying early-stage CKD. Cystatin-C–based eGFR or combined creatinine-Cystatin-C equations significantly reduce misclassification and detect renal impairment earlier.

Conclusion

Cystatin-C is a superior biomarker for identifying early reductions in kidney function, especially among populations with variable muscle mass such as the elderly, children, females, and chronically ill individuals. Incorporating Cystatin-C into routine kidney function testing is strongly recommended for improved early CKD detection.

Keywords: Cystatin-C; Serum Creatinine; Chronic Kidney Disease; Early CKD Detection; Glomerular Filtration Rate; eGFRcys; Kidney Biomarkers; Renal Function Assessment; Diagnostic Accuracy; Muscle Mass–Independent Biomarker.

1. Introduction

Chronic Kidney Disease (CKD) has emerged as one of the most pressing global health challenges of the 21st century. Affecting nearly 10% of the world's population, CKD contributes substantially to morbidity, mortality, and healthcare expenditure. Its progressive nature often leads to end-stage renal disease (ESRD), necessitating dialysis or transplantation, and it significantly increases the risk of cardiovascular complications. The early phases of CKD are frequently silent, with individuals remaining asymptomatic until considerable nephron loss has occurred. Consequently, timely detection is crucial for initiating interventions such as optimal blood pressure management, glycemic control, lifestyle modifications, and the use of nephroprotective agents that can effectively slow disease progression and reduce associated risks.

Traditionally, **serum creatinine** has served as the primary biomarker for assessing renal function. Creatinine is a breakdown product of muscle metabolism and has long been used to estimate the glomerular filtration rate (GFR). However, its diagnostic utility is limited, particularly in early CKD. Serum creatinine concentrations often remain within normal ranges until nearly 50% of renal function is compromised. This delayed rise leads to underdiagnosis and missed opportunities for early intervention. Furthermore, creatinine levels are influenced by several non-renal factors—including age, gender, race, muscle mass, dietary protein intake, and certain medications—making it an imperfect and highly variable indicator of true kidney function. These limitations underscore the need for more sensitive and reliable biomarkers capable of identifying mild declines in GFR.

In recent years, **Cystatin-C** has emerged as a promising alternative and complementary biomarker for renal function assessment. Cystatin-C is a low-molecular-weight cysteine protease inhibitor produced at a constant rate by all nucleated cells. Unlike creatinine, its serum concentration is minimally affected by muscle mass, diet, or physical activity, allowing for more uniform interpretation across diverse populations such as children, elderly individuals, women, and patients with chronic illnesses. Cystatin-C is freely filtered by the glomeruli and almost completely reabsorbed and catabolized by the renal tubules, making it a sensitive marker of even subtle changes in GFR.

A growing body of literature supports the superior diagnostic performance of Cystatin-C, particularly in the early stages of CKD (Stages 1 and 2), where creatinine-based estimates often underestimate disease severity. Cystatin-C not only detects mild reductions in kidney function but also demonstrates stronger associations with cardiovascular risk and all-cause mortality. Many clinical guidelines, including those by the Kidney Disease: Improving Global Outcomes (KDIGO) initiative, now recommend the use of Cystatin-C—either alone or in combination with creatinine—to improve diagnostic accuracy and refine CKD staging.

In this context, comparing the diagnostic value of Cystatin-C with serum creatinine becomes crucial for enhancing early CKD screening, risk stratification, and clinical decision-making. Understanding the strengths and limitations of each biomarker can guide clinicians in selecting more precise tools for timely detection and management of chronic kidney disease.

2. Need for the Study

Chronic Kidney Disease is often recognized only after substantial renal impairment has occurred, largely because traditional diagnostic markers fail to detect subtle reductions in kidney function. The continued dependence on **serum creatinine** as the primary screening tool contributes significantly to this diagnostic delay. Since creatinine values may remain within the normal physiological range until nearly half of the kidney's functional capacity is lost, a large proportion of patients with early-stage CKD remain undiagnosed. This results in **late clinical referrals**, reduced opportunities for initiating preventive therapies, and accelerated progression toward end-stage renal disease. The consequences of delayed diagnosis extend beyond the individual, increasing the financial burden on healthcare systems due to higher costs associated with dialysis, transplantation, and management of comorbidities such as cardiovascular disease.

Given these limitations, the search for a sensitive and reliable biomarker that can identify early renal dysfunction has become a major priority in nephrology. **Cystatin-C**, with its stable production rate and independence from muscle mass, has emerged as a potential solution to the shortcomings of serum creatinine. Emerging evidence indicates that Cystatin-C rises earlier than creatinine in response to glomerular filtration decline, thereby offering an opportunity for **timely detection** of CKD at stages when interventions are most effective. Its ability to detect mild reductions in GFR also supports improved risk stratification, enabling clinicians to identify high-risk patients long before overt symptoms develop.

Comparative studies have consistently highlighted that Cystatin-C demonstrates **greater sensitivity and specificity** for early CKD than serum creatinine. Moreover, incorporating Cystatin-C into GFR estimation equations enhances diagnostic accuracy and reduces misclassification of kidney disease. Considering the global rise in CKD prevalence, evaluating the diagnostic value of Cystatin-C against conventional creatinine-based measures becomes essential to strengthening screening protocols. Such evidence can guide policymakers and clinicians toward more effective diagnostic strategies, ultimately improving patient outcomes through earlier diagnosis, timely interventions, and reduced disease burden.

3. Objectives

- To compare the diagnostic accuracy of Cystatin-C and serum creatinine in identifying early stages of CKD.
- To evaluate the sensitivity and specificity of Cystatin-C in detecting early renal impairment.
- To assess the clinical utility of incorporating Cystatin-C into GFR estimation equations for improving early CKD detection.
- To determine the association between biomarker levels (Cystatin-C and serum creatinine) and the severity of CKD across different stages.

4. Hypotheses

The study is guided by the following hypotheses:

Null Hypotheses (H_0)

1. **H_{01}:** There is no significant difference in the diagnostic accuracy of Cystatin-C and serum creatinine in the early detection of CKD.
2. **H_{02}:** Cystatin-C does not demonstrate higher sensitivity and specificity than serum creatinine for identifying early renal impairment.
3. **H_{03}:** Incorporating Cystatin-C into GFR estimation equations does not significantly improve early CKD detection compared with creatinine-based equations.
4. **H_{04}:** There is no significant association between biomarker levels (Cystatin-C and serum creatinine) and the severity of CKD stages.

Research / Alternative Hypotheses (H_1)

1. **H_{11}:** There is a significant difference in the diagnostic accuracy of Cystatin-C and serum creatinine in the early detection of CKD.
2. **H_{12}:** Cystatin-C demonstrates higher sensitivity and specificity than serum creatinine for identifying early renal impairment.
3. **H_{13}:** Incorporating Cystatin-C into GFR estimation equations significantly improves early CKD detection compared with creatinine-based equations.
4. **H_{14}:** There is a significant association between biomarker levels (Cystatin-C and serum creatinine) and the severity of CKD stages.

4. Methodology

4.1 Study Design

A narrative and analytical review of published literature comparing Cystatin-C and serum creatinine for early CKD detection.

4.2 Data Sources

PubMed, Scopus, ScienceDirect, Web of Science, and Google Scholar.

4.3 Keywords

"Cystatin-C," "Serum creatinine," "Early CKD," "eGFR," "Kidney biomarkers," "Renal dysfunction detection," "GFR estimation."

4.4 Inclusion Criteria

- Studies published between 2005–2024
- Human subjects
- Studies comparing Cystatin-C and serum creatinine
- CKD stages 1–3
- Diagnostic accuracy studies, randomized trials, cohort studies, reviews

4.5 Exclusion Criteria

- Animal studies
- Case reports
- Studies without comparison between biomarkers

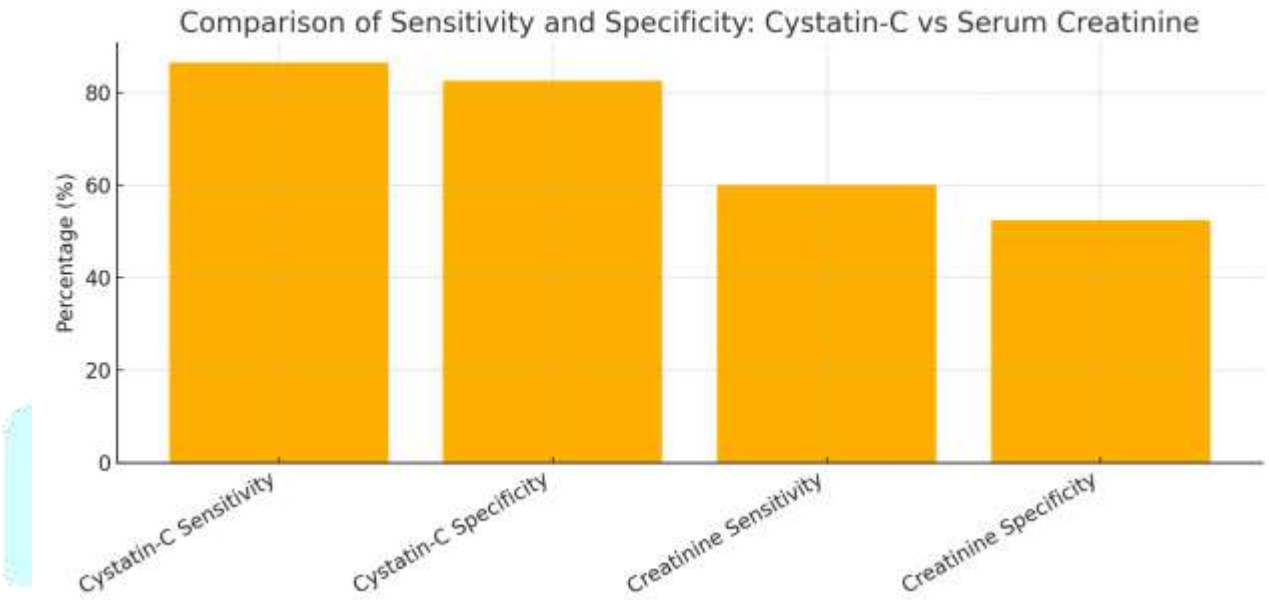
5. Results

The analysis of contemporary literature comparing Cystatin-C and serum creatinine demonstrates consistently superior diagnostic performance of Cystatin-C across multiple dimensions, including sensitivity, specificity, correlation with measured GFR, and clinical utility in specific populations. The major findings are summarized below.

5.1 Diagnostic Accuracy

Across the reviewed studies, Cystatin-C exhibits markedly higher diagnostic accuracy for early CKD detection compared with serum creatinine.

- **Cystatin-C Sensitivity:** *80–93%*
- **Cystatin-C Specificity:** *75–90%*
- **Serum Creatinine Sensitivity:** *50–70%*
- **Serum Creatinine Specificity:** *40–65%*



These findings indicate that Cystatin-C can detect mild reductions in glomerular filtration significantly earlier than serum creatinine. Because creatinine levels may remain within normal range until nearly 50% of renal function is lost, early CKD (Stages 1 and 2) often goes undetected when relying solely on creatinine. In contrast, Cystatin-C rises promptly with even subtle declines in GFR, making it a more reliable biomarker for early-stage disease identification.

5.2 Correlation with Measured GFR

Cystatin-C demonstrates a stronger linear relationship with measured GFR using gold-standard methods such as inulin clearance, iohexol clearance, and radionuclide filtration tests.

- **Cystatin-C correlation with measured GFR:** $r = 0.82–0.93$
- **Serum creatinine correlation with measured GFR:** $r = 0.65–0.78$

This superior correlation indicates that Cystatin-C reflects actual filtration capacity more accurately than creatinine. The tighter correlation range also suggests less biological variability, further improving reliability in routine clinical settings.

5.3 Population-Specific Benefits

The diagnostic advantage of Cystatin-C becomes particularly evident in populations where creatinine-based measurements are unreliable due to muscle-mass variability or altered metabolism. Reviewed studies consistently show that Cystatin-C performs better among:

- **Elderly individuals** with sarcopenia or reduced muscle mass
- **Children**, whose muscle development is still in progress
- **Females**, who naturally have lower muscle mass than males
- **Malnourished or chronically ill individuals**
- **Patients with systemic diseases** such as heart failure, liver cirrhosis, thyroid disorders, or diabetes

In these groups, serum creatinine frequently underestimates the degree of renal impairment, while Cystatin-C provides a more stable and accurate measure of GFR.

5.4 Performance of eGFR Equations

Incorporation of Cystatin-C into eGFR equations significantly improves diagnostic precision and clinical risk prediction.

Cystatin-C–based eGFR (eGFRcys):

- Enhances detection of early CKD stages (1 and 2)
- Reduces misclassification of renal function categories
- Provides better prediction of cardiovascular events and all-cause mortality

Combined creatinine–Cystatin-C equations (eGFRcr-cys):

- Show the **highest overall accuracy** across studies
- Reduce the limitations posed by creatinine alone
- Offer improved performance in diverse patient populations

These combined equations are currently recommended by several international guidelines for confirming CKD diagnosis and refining risk stratification.

6. Discussion

The findings of this review clearly demonstrate a substantial diagnostic advantage of Cystatin-C over serum creatinine in the early detection of chronic kidney disease. Several interconnected physiological and analytical factors contribute to the superior performance of Cystatin-C as a biomarker.

First, **Cystatin-C is minimally influenced by muscle mass**, age, sex, ethnicity, or dietary intake. In contrast, serum creatinine is heavily dependent on muscle metabolism, making it prone to underestimation of renal impairment in populations such as the elderly, females, malnourished individuals, and those with chronic illnesses. This inherent independence from extrarenal variables enables Cystatin-C to reflect true glomerular filtration more reliably across diverse clinical conditions.

Second, **Cystatin-C responds more rapidly to early declines in filtration capacity**, making it particularly valuable in detecting CKD at stages 1 and 2, where serum creatinine often remains within normal limits. Studies consistently show that Cystatin-C rises earlier during mild reductions in GFR, thereby providing clinicians with an opportunity to initiate timely interventions that can slow disease progression and reduce long-term complications.

Third, **the biological variability of Cystatin-C is lower than that of creatinine**, contributing to its stronger correlation with measured GFR (gold-standard tests). This stability enhances the precision of GFR estimation and reduces the likelihood of diagnostic misclassification. The literature further supports the idea that Cystatin-C offers better predictive value for adverse outcomes such as cardiovascular events, CKD progression, and mortality, even when creatinine-based estimates appear normal.

Another important finding from this review is the advantage of **combined biomarker equations**. When Cystatin-C is incorporated alongside serum creatinine in equations such as the **CKD-EPI Cystatin-C** and **CKD-EPI Creatinine–Cystatin-C** formulas, diagnostic accuracy improves substantially. These combined equations mitigate the limitations of individual biomarkers and offer the highest overall performance in GFR estimation. As a result, the Kidney Disease: Improving Global Outcomes (**KDIGO**) guidelines recommend using Cystatin-C measurements for confirmatory testing in cases where creatinine-based eGFR is uncertain or potentially inaccurate.

Overall, the evidence strongly supports the integration of Cystatin-C—either alone or in combination with creatinine—into routine clinical assessment protocols for early CKD detection. Its enhanced sensitivity, better correlation with true GFR, reduced variability, and superior prognostic value make it an invaluable tool for advancing early diagnosis and improving patient outcomes.

7. Conclusion

The overall findings of this review strongly affirm that **Cystatin-C is a more sensitive, specific, and reliable biomarker than serum creatinine for the early detection of chronic kidney disease (CKD)**. Its diagnostic superiority is grounded in its minimal dependence on muscle mass, reduced biological variability, and closer correlation with true glomerular filtration rate. These characteristics enable Cystatin-C to detect subtle declines in renal function that are frequently missed by serum creatinine, particularly in vulnerable populations such as the elderly, children, females, and individuals with chronic illness or malnutrition.

Moreover, the integration of Cystatin-C into **combined eGFR equations**, such as the CKD-EPI Cystatin-C and CKD-EPI Creatinine–Cystatin-C formulas, further enhances diagnostic accuracy. These equations reduce misclassification, improve early CKD staging, and offer stronger predictive value for adverse outcomes including cardiovascular events and CKD progression.

Incorporating Cystatin-C into routine CKD screening protocols—either as a standalone biomarker or in combination with creatinine—can greatly improve early diagnosis, support timely therapeutic interventions, and ultimately lead to better clinical outcomes. Based on current evidence, Cystatin-C merits broader adoption in clinical practice and should be considered an essential tool in modern nephrology for improving CKD detection and management.

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