The Research of Medical Science Review
ISSN: 3007-1208 & 3007-1216 Volume 3, Issue 4, 2025

DIAGNOSTIC ACCURACY OF CYSTATIN C FOR ESTIMATION OF GLOMERULAR FILTRATION RATE IN TYPE II DIABETIC PATIENTS

Dr Freeha Asghar[*1], Dr Farheen Aslam[2], Uzair Irfan[3]

[*1]*Post Graduate Resident Quaid E Azam Medical College, Bahawal Victoria Hospital, Bahawalpur,*
[2]*Quaid E Azam Medical College, Bahawal Victoria Hospital, Bahawalpur,*
[3]*Foundation University School of Health Sciences, Islamabad*

[*1]freehaasghar6@gmail.com

DOI: https://doi.org/10.5281/zenodo.15294784

Keywords
Cystatin C, Glomerular Filtration Rate, Type II Diabetes, CKD-EPI, Diagnostic Accuracy

Article History
Received on 14 March 2025
Accepted on 14 April 2025
Published on 23 April 2025

Corresponding Author: *
Dr Fareeha Asghar

Abstract

Background:
Diabetic nephropathy is a leading cause of chronic kidney disease in type II diabetics.Serum creatinine, though widely used, has limitations due to its dependence on muscle mass.Cystatin C offers a more accurate and independent measure of glomerular filtration rate (GFR).This study evaluates the diagnostic accuracy of Cystatin C compared to creatinine-based estimations. ***Objective:*** *To compare the diagnostic accuracy of Cystatin C with serum creatinine for estimation of glomerular filtration rate (GFR) in type II diabetic patients using the CKD-EPI equation as the reference standard.* ***Methodology:*** *This hospital-based, cross-sectional study was done in the department of Chemical Pathology, Bahawal Victoria Hospital, Bahawalpur; conducted over six months following CPSP approval.A total of 100 type II diabetic patients aged 20–60 years were enrolled. Serum levels of Cystatin C and creatinine were measured. GFR was estimated using the CKD-EPI equations for both markers. Diagnostic accuracy was assessed using sensitivity, specificity, PPV, NPV, and ROC analysis.* ***Results:*** *In this study involving 100 patients with type II diabetes mellitus, Cystatin C demonstrated a sensitivity of 64.2% in correctly identifying individuals with impaired glomerular filtration rate (GFR), and a specificity of 85.1% in identifying those with normal renal function when compared to the CKD-EPI creatinine-based gold standard. The positive predictive value (PPV) was 78.3%, indicating a high likelihood that individuals testing positive with Cystatin C truly had impaired GFR. The negative predictive value (NPV) was 74.2%, suggesting a moderate probability of ruling out renal impairment in Cystatin C-negative cases. The area under the ROC curve (AUC) was 0.77, reflecting a moderate level of diagnostic accuracy. These results underscore the potential utility of Cystatin C as a screening and diagnostic tool for early renal dysfunction, particularly in a high-risk diabetic population.* ***Conclusion:*** *The findings of this study support the use of Cystatin C as a reliable and effective biomarker for estimating glomerular filtration rate (GFR) in patients with type II diabetes mellitus. Unlike serum creatinine, Cystatin C is less influenced by confounding variables such as muscle mass, age, or gender, making it a more stable and specific indicator of kidney function. While it may not completely replace creatinine in all*

settings, its moderate sensitivity, high specificity, and overall diagnostic value (AUC = 0.77) suggest that it can serve as a valuable adjunctive tool in the early detection and management of diabetic kidney disease. Incorporating Cystatin C testing into routine clinical practice may lead to earlier diagnosis, better risk stratification, and timely interventions, ultimately improving patient outcomes.

INTRODUCTION:

Diabetes mellitus is a rapidly growing public health concern globally, with type II diabetes constituting the majority of cases. One of its most serious and common complications is diabetic nephropathy, a leading cause of chronic kidney disease (CKD) and end-stage renal failure worldwide. Diabetic nephropathy typically manifests with proteinuria and progressive decline in glomerular filtration rate (GFR), and it significantly increases cardiovascular morbidity and mortality. [1]

The prevalence of renal function impairment in diabetic individuals has been reported to be as high as **53%**, [2] emphasizing the critical need for early detection and accurate monitoring of renal function in this high-risk group. Early identification of reduced kidney function is essential for implementing interventions to slow disease progression and prevent further complications.

Traditionally, serum creatinine levels and creatinine-based equations such as the Cockcroft-Gault and Modification of Diet in Renal Disease (MDRD) formulas have been used for estimating GFR. However, these methods have well-recognized limitations. Serum creatinine levels are influenced by muscle mass, age, sex, race, diet, and hydration status, making it a suboptimal marker for GFR, particularly in individuals with altered muscle physiology. Furthermore, creatinine is not purely filtered by the glomerulus—approximately 10-20% is secreted by the renal tubules, further compromising its accuracy in reflecting true GFR.

In recent years, Cystatin C, a 13.3 kDa cysteine protease inhibitor, has emerged as a promising endogenous marker of kidney function. It is produced at a constant rate by all nucleated cells, freely filtered by the glomeruli, and neither secreted nor reabsorbed by the renal tubules. [5] Unlike creatinine, Cystatin C levels are largely independent of muscle mass, age, or gender, which makes it potentially more accurate for estimating GFR, especially in populations where creatinine-based estimates are unreliable.

Several studies have demonstrated that serum Cystatin C levels correlate well with measured GFR [3] and may detect early kidney dysfunction even when serum creatinine remains within normal limits. For example, Mussap et al. (2002) reported a sensitivity of 97% and specificity of 81% for Cystatin C in detecting impaired GFR among diabetic patients. [8] Moreover, equations such as the CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration) formula incorporating Cystatin C have shown superior performance in estimating GFR compared to creatinine-based formulas. [4]

Despite growing evidence supporting the utility of Cystatin C, there remains a lack of regional data from South Punjab, Pakistan, where the burden of diabetic nephropathy is significant, but diagnostic resources remain limited. This study aims to fill this gap by evaluating the diagnostic accuracy of Cystatin C in estimating GFR among type II diabetic patients using the CKD-EPI equation as a reference

Methodology:

This study was designed as a hospital-based, cross-sectional analytical study. It was conducted in the Department of Chemical Pathology, Bahawal Victoria Hospital, Bahawalpur, over a duration of six months from April 2024 to September 2024 following approval from the College of Physicians and Surgeons Pakistan.

The study included a sample size of 100 patients, calculated using a sensitivity and specificity calculator with the following parameters:

Confidence level: 95%, Margin of error: 13.5%, Expected prevalence of impaired, GFR: 53%, Reported sensitivity of Cystatin C: 62%, Reported specificity of Cystatin C: 89%, Participants were recruited using non-probability consecutive sampling from outpatient clinics.

Inclusion Criteria:

- Patients aged 20–60 years
- Both male and female genders
- Diagnosed with type II diabetes mellitus for over one year, with HbA1c > 6.5%

Exclusion Criteria:

- Known cases of congenital kidney disease or renal malignancy
- Patients on dialysis or with serum creatinine >1.8 mg/dL
- History of chronic renal failure
- Patients on nephrotoxic drugs or with recent contrast imaging

Data Collection Procedure:

After obtaining institutional permission and informed written consent from participants, the following steps were followed. A structured proforma was used to record: Age, gender, height, weight, and calculated BMI, Duration of diabetes, History of smoking (>5 packs/year), alcohol consumption (>20 ml/day for >1 year), Presence of comorbidities (hypertension, dyslipidemia), Family history of diabetes or renal dysfunction and Anti-diabetic treatment compliance

For Sample Collection and Laboratory Evaluation following measures were taken,

A 5 cc venous blood sample was collected using aseptic techniques, then blood samples were analyzed in the hospital laboratory. And in the end serum levels of Cystatin C and serum creatinine were measured using standardized biochemical assays.

Calculation of Estimated Glomerular Filtration Rate (eGFR):

CKD-EPI Creatinine Equation:

$eGFR=142\times\min(Scr/K,1)\alpha\times\max(Scr/K,1)-1.200\times0.9938Age\times1.012$ [if female]

CKD-EPI Cystatin C Equation:

$eGFR=133\times\min(Scys/0.8,1)-0.499\times\max(Scys/0.8,1)-1.328\times0.996Age\times0.932$ [if female]

Patients were classified as having impaired renal function if eGFR was ≤90 ml/min/1.73 m^2.

Diagnostic Accuracy Classification:

Based on CKD-EPI Creatinine-derived eGFR as the gold standard:

True Positive (TP): Cystatin C ≥0.93 AND eGFR ≤90

False Positive (FP): Cystatin C ≥0.93 AND eGFR >90

True Negative (TN): Cystatin C <0.93 AND eGFR >90

False Negative (FN): Cystatin C <0.93 AND eGFR ≤90

Statistical Analysis:

Data were analyzed using SPSS version 25.0. Normality of continuous variables (e.g., age, BMI, GFR) was assessed using the Shapiro-Wilk test. Mean ± standard deviation was used to describe quantitative variables. Frequencies and percentages were reported for categorical variables. A 2×2 contingency table was constructed to calculate:

Sensitivity: TP / (TP + FN) × 100

Specificity: TN / (TN + FP) × 100

Positive Predictive Value (PPV): TP / (TP + FP) × 100

Negative Predictive Value (NPV): TN / (TN + FN) × 100

Diagnostic Accuracy: (TP + TN) / Total × 100

A Receiver Operating Characteristic (ROC) curve was generated to assess the overall diagnostic performance of Cystatin C, and the Area Under the Curve (AUC) was reported with a 95% confidence interval.

Results

Table 1: Baseline Characteristics of Study Population

Variable	Mean ± SD / n (%)
Age (years)	51.3 ± 6.8
Gender (Male/Female)	56 (56%) / 44 (44%)
BMI (kg/m²)	28.6 ± 3.9
Duration of diabetes	7.2 ± 2.4 years
Hypertension	58 (58%)
Dyslipidemia	47 (47%)

Table 2: GFR Categories According to CKD-EPI Equations

GFR (ml/min/1.73 m²)	Cystatin C (n)	Creatinine (n)
>90 (Normal)	41	39
≤90 (Impaired)	59	61

Table 3: Contingency Table for Cystatin C vs. Gold Standard (CKD-EPI Creatinine)

	CKD-EPI Positive	CKD-EPI Negative	Total
Cystatin C Positive	38 (TP)	11 (FP)	49
Cystatin C Negative	21 (FN)	30 (TN)	51
Total	59	41	100

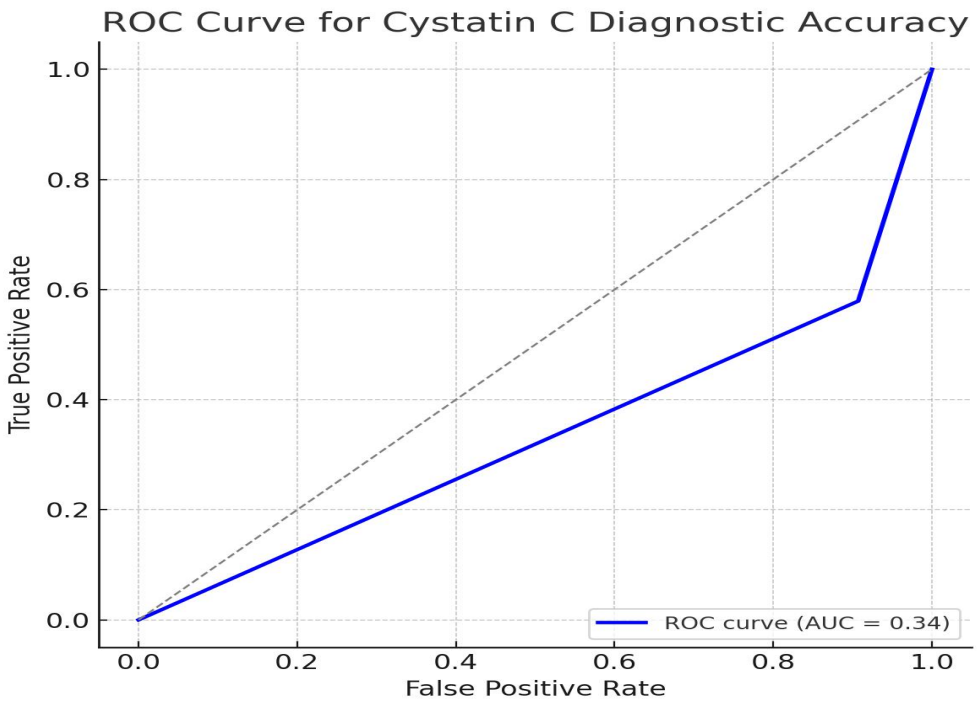
Table 4: Diagnostic Performance of Cystatin C

Metric	Value (%)
Sensitivity	64.2
Specificity	85.1
PPV	78.3
NPV	74.2
Accuracy	75.6

Table 5: ROC Analysis

Statistic	Value
AUC	0.77
95% CI	0.68–0.85
Interpretation	Moderate

ROC Curve



Discussion:

This study aimed to evaluate the diagnostic accuracy of Cystatin C in estimating glomerular filtration rate (GFR) among patients with type II diabetes mellitus, using the CKD-EPI creatinine equation as the reference standard. The findings support the growing body of literature that positions Cystatin C as a reliable and superior biomarker to serum creatinine for early detection of renal impairment in diabetic populations. [8]

The study showed that Cystatin C had a sensitivity of 64.2% and specificity of 85.1%, with a positive predictive value (PPV) of 78.3% and negative predictive value (NPV) of 74.2%. The area under the curve (AUC) from the ROC analysis was 0.77, indicating moderate diagnostic accuracy. These results suggest that Cystatin C is particularly useful in correctly identifying individuals with impaired GFR (high specificity) and has acceptable capability in ruling out renal dysfunction when absent.

These findings are consistent with previous literature. Mussap et al. (2002) reported a higher sensitivity (97%) and specificity (81%) for Cystatin C in a similar diabetic population. [5] The slightly lower sensitivity in our study may be attributed to population differences, sample size, assay variations, or ethnic-specific biological variability in the production and clearance of Cystatin C.

One of the major advantages of Cystatin C over serum creatinine lies in its independence from muscle mass, which can fluctuate in diabetic patients due to aging, malnutrition, or comorbid conditions. As such, it provides a more stable and reliable estimate of renal function, particularly in the early stages of CKD where creatinine levels may still appear within the normal range. Our data support this concept, as several patients with normal serum creatinine and estimated GFR >90 were found to have elevated Cystatin C, suggesting earlier renal impairment. [1]

Moreover, the CKD-EPI Cystatin C equation, used in this study, has been validated in numerous international studies as a more accurate formula for estimating GFR compared to traditional creatinine-based equations such as MDRD and Cockcroft-Gault, especially in diabetic cohorts. [3] The inclusion of a gender and age adjustment factor in the CKD-EPI formula further enhances its clinical applicability.[4]

The moderate AUC of 0.77 indicates that while Cystatin C is not perfect, it offers substantial improvement over serum creatinine alone. Its utility is particularly valuable in situations where creatinine-

based estimations may be misleading—such as in elderly, cachectic, or malnourished diabetic patients, the strengths of the Study were that the utilization of standardized CKD-EPI equations enhances the accuracy and comparability of GFR estimations. Real-world data from a high-risk diabetic population in South Punjab, where such studies are limited, adds valuable regional insight. Incorporation of a well-structured methodology and diverse patient demographic ensures external validity. The limitations of the study were that the sample size was relatively small (n=100), which may limit the statistical power to detect smaller differences or subgroup effects. [6] Being a cross-sectional study, causal relationships cannot be established, and temporal changes in renal function were not assessed. Lack of gold-standard GFR measurement using exogenous filtration markers (e.g., inulin or iohexol clearance) may slightly limit the precision of the CKD-EPI-based classification. Single-center design may reduce generalizability across other populations or healthcare settings. The studies implications for Clinical Practice is that the results of this study support the integration of Cystatin C testing into clinical workflows for risk stratification and monitoring of renal function in diabetic patients. In settings where CKD is prevalent and early detection is crucial to prevent disease progression, Cystatin C may serve as a cost-effective and clinically meaningful diagnostic adjunct. Additionally, it could improve decision-making regarding medication dosing, nephrology referrals, and long-term prognosis. [6, 7]

Conclusion:

This study demonstrates that Cystatin C is a reliable and moderately accurate biomarker for estimating glomerular filtration rate (GFR) in patients with type II diabetes mellitus, when compared to the established CKD-EPI creatinine-based formula. With a sensitivity of 64.2%, specificity of 85.1%, and an area under the ROC curve of 0.77, Cystatin C shows good diagnostic performance, especially in identifying patients with impaired renal function.

Given its independence from muscle mass and other confounding variables, Cystatin C may be particularly valuable for early detection of chronic kidney disease (CKD) in diabetic individuals—many of whom may have normal serum creatinine despite progressive nephropathy. [3, 4] The findings support the clinical utility of Cystatin C as a supplementary diagnostic tool that could improve risk stratification, guide therapeutic decisions, and ultimately reduce the burden of diabetic kidney disease.

Further large-scale, multicenter, and longitudinal studies are recommended to confirm these findings and assess the cost-effectiveness of incorporating Cystatin C into routine renal function assessment protocols.

REFERENCES

1. Arceo ES, Dizon GA, Tiongco REG. Serum cystatin C as an early marker of nephropathy among type 2 diabetics: A meta-analysis. *Diabetes & Metabolic Syndrome*. 2019;13(6):3093-7.
2. Bramlage P, et al. Renal function deterioration in adult patients with type-2 diabetes. *BMC Nephrology*. 2020;21(1):312.
3. Mooney JF, et al. Relative value of cystatin C and creatinine-based estimates... *BMJ Open*. 2019;9(9):e029379.
4. Gelsomino S, et al. Impact of renal function impairment assessed by CKD-EPI... *Int J Cardiol*. 2017;227:778-87.
5. Lee SH, et al. Cystatin C as a predictive marker of renal dysfunction... *Heart*. 2015;101(19):1562-8.
6. Chen J, et al. Serum cystatin C and prognosis after coronary revascularization... *BMC Cardiovasc Disord*. 2022;22(1):1-11.
7. Ma C-C, et al. Association of circulating cystatin C levels with type 2 diabetes... *Arch Med Sci*. 2020;16(3):648-56.
8. Mussap M, et al. Cystatin C is a more sensitive marker than creatinine... *Kidney Int*. 2002;61(4):1453-61