Section: Biochemistry

Original Research Article

COMPARATIVE DIAGNOSTIC PERFORMANCE OF SERUM CYSTATIN C– AND CREATININE-BASED ESTIMATED GLOMERULAR FILTRATION RATE FOR EARLY DETECTION OF DIABETIC KIDNEY DISEASE IN ADULTS WITH TYPE 2 DIABETES MELLITUS

Tirpti Verma[1], *Alka Meena*[2], *Renu Meena*[3]

[1]*Associate Professor, Department, Biochemistry, SMS Medical College, Jaipur, India.*
[2]*Associate Professor Department, Biochemistry, SMS Medical College, Jaipur, India.*
[3]*Assistant Professor Department, Biochemistry, SMS Medical College, Jaipur, India.*

Received *: 13/09/2026*
Received in revised form *: 12/10/2026*
Accepted *: 26/10/2026*

Corresponding Author:
Dr. Tirpti Verma,
Associate Professor, Department, Biochemistry, SMS Medical College, Jaipur, India.
Email: tripti.verma31@gmail.com

DOI: 10.70034/ijmedph.2026.4.285

Source of Support: Nil,
Conflict of Interest: None declared

Int J Med Pub Health
2026; 16 (4); 1880-1887

ABSTRACT

Background: Diabetic kidney disease (DKD) is a leading cause of chronic kidney disease and end-stage renal disease worldwide. Serum creatinine-based estimated glomerular filtration rate (eGFRcr) may remain deceptively normal during early kidney injury because creatinine is influenced by age, sex, muscle mass, and non-glomerular determinants. Cystatin C is freely filtered by the glomerulus and is less dependent on muscle mass, suggesting potential value for earlier detection of diabetic kidney dysfunction. **Objectives:** To compare the diagnostic performance of cystatin C-based eGFR (eGFRcys) and creatinine-based eGFR (eGFRcr) for detecting early diabetic kidney injury, using urine albumin-to-creatinine ratio (UACR) of 30 mg/g or higher as the clinical reference standard, and to quantify discordance between the two eGFR estimates in adults with type 2 diabetes mellitus (T2DM).

Materials and Methods: This hospital-based cross-sectional analytical study included 50 adults with T2DM and 30 age-matched healthy controls. Fasting plasma glucose, glycated haemoglobin, serum creatinine, serum cystatin C, and early-morning urinary albumin-to-creatinine ratio were measured. eGFR was calculated using the 2021 race-free CKD-EPI creatinine and cystatin C equations. Group differences were analysed using independent-samples t-tests, associations using Pearson correlation, and diagnostic performance using receiver operating characteristic analysis. Agreement was assessed by paired comparison and Bland-Altman analysis.

Results: Cases had significantly higher cystatin C (1.29 ± 0.22 vs 0.73 ± 0.09 mg/L; $p < 0.001$) and lower eGFRcys (59.55 ± 14.04 vs 113.04 ± 11.57 mL/min/1.73 m²; $p < 0.001$) than controls. Mean eGFRcr in cases was 85.13 ± 17.55 mL/min/1.73 m², significantly higher than eGFRcys by 25.58 mL/min/1.73 m² ($p < 0.001$). At an eGFR threshold of 90 mL/min/1.73 m², eGFRcys showed sensitivity of 100%, specificity of 96.8%, accuracy of 98.8%, positive predictive value of 98.0%, and negative predictive value of 100%; corresponding values for eGFRcr were 55.1%, 80.6%, 65.0%, 81.8%, and 53.2%, respectively. The area under the ROC curve was 0.986 for eGFRcys and 0.772 for eGFRcr. Twenty-two cases (44.0%) had eGFRcr ≥90 mL/min/1.73 m² despite eGFRcys <90 mL/min/1.73 m².

Conclusion: In this cohort, cystatin C-based eGFR identified substantially more early renal functional impairment than creatinine-based eGFR. eGFRcys demonstrated markedly superior sensitivity and overall discriminative ability for albuminuria-defined early DKD. Incorporating cystatin C into renal risk

assessment among adults with T2DM may reduce missed early DKD, although external validation in larger longitudinal cohorts is required.
Keywords: Diabetic kidney disease; cystatin C; creatinine; estimated glomerular filtration rate; albuminuria; type 2 diabetes mellitus.

INTRODUCTION

Diabetes mellitus has become one of the most important non-communicable diseases globally, and its microvascular complications account for a major proportion of long-term morbidity and mortality. Diabetic kidney disease (DKD), formerly termed diabetic nephropathy, is the most frequent cause of chronic kidney disease (CKD) and end-stage renal disease (ESRD) in many countries, including India.[1,2] The disease is characterised initially by glomerular hyperfiltration, thickening of the glomerular basement membrane, mesangial expansion, and increasing urinary albumin excretion. If glycaemic control, blood pressure, and renin-angiotensin system blockade are not optimised, albuminuria may progress and glomerular filtration rate (GFR) may decline irreversibly.[3,4]

The clinical concept of early DKD is crucial because interventions initiated before substantial nephron loss can slow progression. Intensified glycaemic control, blood-pressure lowering, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, SGLT2 inhibitors, and newer non-steroidal mineralocorticoid receptor antagonists have all demonstrated renal benefit when used appropriately in at-risk patients.[5-7] However, the effectiveness of these strategies depends on timely identification of patients with early kidney involvement. A marker that remains normal until considerable nephron damage has occurred cannot support truly early intervention.

For decades, serum creatinine has been the most widely used endogenous marker of kidney function. Creatinine is produced from creatine and phosphocreatine in muscle and is released at a relatively constant rate. It is freely filtered at the glomerulus, but it is also secreted by the proximal tubule and its serum concentration is affected by muscle mass, sex, age, ethnicity-related body-composition differences, protein intake, and certain drugs.[8,9] Consequently, a serum creatinine value within the conventional laboratory reference interval does not necessarily indicate normal kidney function, particularly in older adults, women, and individuals with low muscle mass.

Estimated GFR equations were developed to overcome some limitations of raw creatinine values by incorporating age and sex. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations are widely used and were refit in 2021 without a race coefficient.10 Nevertheless, eGFR based on creatinine alone (eGFRcr) continues to inherit the non-GFR determinants of creatinine. In early DKD, creatinine may remain near normal despite a meaningful decline in measured GFR, because increased tubular secretion and reduced creatinine generation can partially compensate for reduced filtration. This phenomenon may delay diagnosis and understate renal risk.[11,12]

Cystatin C is a low-molecular-weight (13.3 kDa) basic protein belonging to the cystatin superfamily of cysteine protease inhibitors. It is produced at a relatively constant rate by all nucleated cells, freely filtered by the glomerulus, and almost completely reabsorbed and catabolised by proximal tubular cells. Because it is not returned to the circulation in appreciable amounts and is minimally affected by muscle mass, cystatin C has been proposed as a sensitive marker of early GFR decline.[13,14] Its concentration can, however, be influenced by thyroid dysfunction, glucocorticoids, inflammation, obesity, smoking, and malignancy; these conditions therefore require consideration during interpretation.[15,16]

Cystatin C-based eGFR (eGFRcys) has shown promise in diabetes. Several studies have reported that eGFRcys detects renal impairment earlier than eGFRcr, particularly in patients with preserved or near-normal creatinine-based function.[17-19] Cystatin C may also improve cardiovascular and mortality risk prediction beyond creatinine-based eGFR, suggesting that it reflects not only filtration function but also broader vascular and metabolic risk.[20,21] In DKD, however, the relative usefulness of eGFRcys versus eGFRcr must be interpreted alongside albuminuria, because albuminuria and GFR decline are complementary but not identical manifestations of diabetic kidney injury.[22]

Urine albumin-to-creatinine ratio (UACR) is recommended by contemporary clinical guidelines for initial and longitudinal assessment of DKD. An UACR of 30–300 mg/g defines moderately increased albuminuria, previously called microalbuminuria, whereas values above 300 mg/g define severely increased albuminuria.[23] Persistent albuminuria indicates glomerular barrier injury and is a strong predictor of progression to advanced CKD. Nevertheless, some patients with diabetes develop reduced GFR without significant albuminuria, and albuminuria may fluctuate with acute illness, exercise, fever, poor glycaemic control, and urinary tract infection. Therefore, a combined assessment of albuminuria and filtration markers remains desirable.[23,24]

In routine hospital practice, especially in resource-constrained settings, serum creatinine remains the predominant renal function test. Cystatin C assays are increasingly available on automated analysers but are not yet universally used because of cost and limited awareness of their clinical advantage. There is a need for local evidence comparing cystatin C-based and creatinine-based eGFR in Indian adults with T2DM, where variation in body composition, dietary

patterns, and late presentation of diabetes may influence biomarker performance. The present study was therefore designed to compare the diagnostic performance of eGFRcys and eGFRcr for early diabetic kidney injury and to determine the frequency of clinically important discordance between the two estimates.

MATERIALS AND METHODS

2.1 Study design and setting

This was a hospital-based, cross-sectional, analytical study conducted in the Department of Biochemistry at S.M.S. Medical College and Attached Hospitals, Jaipur, India. Consecutive eligible adults with T2DM attending the outpatient or inpatient services were recruited as cases. Age-matched healthy volunteers accompanying patients or recruited from hospital staff and community contacts served as controls. The study was conducted in accordance with the Declaration of Helsinki and applicable national ethical guidelines. Institutional Ethics Committee approval was obtained before commencement, and written informed consent was obtained from every participant.

2.2 Study participants

A total of 80 participants were included: 50 adults with T2DM (cases) and 30 healthy controls. Cases were adults aged 35–65 years with physician-diagnosed T2DM. Controls were healthy adults without diabetes, with fasting plasma glucose below 100 mg/dL or HbA1c below 5.7%, normoalbuminuria (UACR <30 mg/g), and no known kidney disease.

Participants were excluded if they had eGFR below 60 mL/min/1.73 m², gross proteinuria or macroalbuminuria, known non-diabetic kidney disease, acute kidney injury, active systemic infection, malignancy, pregnancy, thyroid dysfunction, or current systemic glucocorticoid therapy. These exclusions were applied because advanced renal impairment would reduce the ability to evaluate early disease and because several excluded conditions can independently alter cystatin C production or metabolism.

2.3 Clinical and anthropometric assessment

A structured proforma recorded age, sex, duration of T2DM, antidiabetic treatment, blood pressure, and relevant medical history. Height and weight were measured using standardised equipment. Fasting venous blood samples were collected after an overnight fast of at least 8 hours. An early-morning spot urine sample was collected for albumin and creatinine measurement. Samples were processed on the same day, and serum was separated and stored at 2–8°C until analysis when immediate processing was not possible.

2.4 Laboratory methods

Fasting plasma glucose was measured by the hexokinase method on a fully automated chemistry analyser. Glycated haemoglobin (HbA1c) was measured by high-performance liquid chromatography using an NGSP-certified method. Serum creatinine was estimated by an IDMS-traceable enzymatic or kinetic Jaffe method, according to the laboratory protocol. Serum cystatin C was measured by particle-enhanced immunoturbidimetric assay (PETIA). Urinary albumin was measured by immunoturbidimetry and urinary creatinine by the Jaffe or enzymatic method; UACR was expressed in mg/g.

All assays were performed according to manufacturer instructions, with daily internal quality-control procedures. Calibration was verified using manufacturer-provided calibrators, and results outside acceptable quality-control limits were repeated after corrective action.

2.5 Calculation of eGFR

Creatinine-based eGFR was calculated using the 2021 CKD-EPI creatinine equation, which does not include a race coefficient. Cystatin C-based eGFR was calculated using the 2021 CKD-EPI cystatin C equation. Both values were expressed in mL/min/1.73 m². The same laboratory values were used for all participants, and calculations were performed using standardised formulas without manual adjustment.

2.6 Outcome definitions

Early diabetic kidney injury was operationally defined as UACR ≥30 mg/g, consistent with the category of moderately increased albuminuria. This definition was selected because UACR is a guideline-endorsed marker of early DKD and was available for all participants. Renal functional reduction was classified as eGFR below 90 mL/min/1.73 m². Discordance was defined as eGFRcr ≥90 mL/min/1.73 m² while eGFRcys was below 90 mL/min/1.73 m², representing cases in which creatinine-based assessment would not have flagged reduced filtration despite cystatin C-based evidence of impairment.

2.7 Statistical analysis

Data were entered and analysed using standard statistical software. Continuous variables were summarised as mean ± standard deviation, and categorical variables as frequencies and percentages. The Shapiro-Wilk test was used to assess normality. Differences between cases and controls were compared using the independent-samples t-test for normally distributed continuous variables. Paired eGFR values within the T2DM group were compared using the paired-samples t-test.

Pearson correlation coefficients were calculated to examine associations between UACR and serum creatinine, serum cystatin C, eGFRcr, eGFRcys, age, diabetes duration, and HbA1c. Diagnostic performance was evaluated using receiver operating characteristic (ROC) analysis. For eGFR variables, the direction of association was reversed so that lower eGFR indicated higher probability of early DKD. The optimal cut-off was selected using the maximum Youden index. Sensitivity, specificity, accuracy, positive predictive value, negative predictive value,

and area under the ROC curve (AUC) were calculated at the prespecified eGFR threshold of 90 mL/min/1.73 m². Agreement between eGFRcr and eGFRcys was displayed using a Bland-Altman plot. A two-sided p value below 0.05 was considered statistically significant.

RESULTS

3.1 Baseline characteristics

The study included 50 T2DM cases and 30 controls. Cases comprised 29 men and 21 women; controls comprised 16 men and 14 women. The mean age was 52.40 ± 9.15 years in cases and 47.30 ± 9.88 years in controls, a small but statistically significant difference (p = 0.025). Mean diabetes duration was 8.78 ± 3.41 years. Cases had markedly higher fasting glucose, HbA1c, UACR, serum creatinine, and cystatin C than controls (all p < 0.001).

Table 1: Baseline clinical and biochemical characteristics of study participants. Values are mean ± SD or n (%)

Variable	T2DM cases (n=50)	Controls (n=30)	p value
Age, years	52.40 ± 9.15	47.30 ± 9.88	0.025
Male sex, n (%)	29 (58.0)	16 (53.3)	0.682
T2DM duration, years	8.78 ± 3.41	—	—
Fasting glucose, mg/dL	177.71 ± 28.74	89.90 ± 8.20	<0.001
HbA1c, %	9.11 ± 0.97	5.22 ± 0.19	<0.001
UACR, mg/g	154.27 ± 72.72	14.71 ± 6.29	<0.001
Serum creatinine, mg/dL	0.96 ± 0.17	0.78 ± 0.11	<0.001
Serum cystatin C, mg/L	1.29 ± 0.22	0.73 ± 0.09	<0.001
eGFR creatinine, mL/min/1.73 m²	85.13 ± 17.55	103.29 ± 14.26	<0.001
eGFR cystatin C, mL/min/1.73 m²	59.55 ± 14.04	113.04 ± 11.57	<0.001

3.2 Renal markers and eGFR estimates

Mean eGFRcr in cases was 85.13 ± 17.55 mL/min/1.73 m², whereas mean eGFRcys was 59.55 ± 14.04 mL/min/1.73 m². The mean within-person difference was 25.58 ± 20.07 mL/min/1.73 m², with eGFRcr significantly higher than eGFRcys (p < 0.001). In controls, the two estimates were closer, with eGFRcr of 103.29 ± 14.26 and eGFRcys of 113.04 ± 11.57 mL/min/1.73 m². Thus, the discrepancy between the two eGFR estimates was much greater in the diabetic group than in healthy controls.

Table 2: Comparison of creatinine- and cystatin C-based eGFR between groups. eGFR values are in mL/min/1.73 m²

Parameter	T2DM cases (n=50)	Controls (n=30)	Mean difference / p value
eGFR creatinine	85.13 ± 17.55	103.29 ± 14.26	−18.16; p < 0.001
eGFR cystatin C	59.55 ± 14.04	113.04 ± 11.57	−53.49; p < 0.001
eGFRcr − eGFRcys	25.58 ± 20.07	−9.75 ± 14.03	35.33; p < 0.001
eGFRcr <90, n (%)	23 (46.0)	3 (10.0)	—
eGFRcys <90, n (%)	49 (98.0)	0 (0.0)	—

Among cases, 23 participants (46.0%) were classified as having eGFR below 90 mL/min/1.73 m² by the creatinine-based equation, compared with 49 participants (98.0%) by the cystatin C-based equation. In contrast, no control had eGFRcys below 90 mL/min/1.73 m². These findings indicate that cystatin C-based estimation identified a substantially larger proportion of diabetic participants with reduced filtration function.

3.3 Diagnostic performance

Using UACR ≥30 mg/g as the reference definition of early DKD, eGFRcys below 90 mL/min/1.73 m² correctly identified 49 of 49 participants with early DKD, yielding sensitivity of 100.0%. It misclassified one control as positive, giving specificity of 96.8%. Accuracy was 98.8%, positive predictive value was 98.0%, and negative predictive value was 100.0%. eGFRcr below 90 mL/min/1.73 m² identified only 27 of 49 early-DKD participants, producing sensitivity of 55.1%, specificity of 80.6%, accuracy of 65.0%, positive predictive value of 81.8%, and negative predictive value of 53.2%.

Table 3: Diagnostic performance of eGFR estimates for early diabetic kidney disease defined by UACR ≥30 mg/g

Diagnostic measure	eGFR cystatin C <90	eGFR creatinine <90
True positive	49	27
False positive	1	6
False negative	0	22
True negative	30	25
Sensitivity, %	100.0	55.1
Specificity, %	96.8	80.6
Accuracy, %	98.8	65.0
Positive predictive value, %	98.0	81.8
Negative predictive value, %	100.0	53.2

AUC	0.986	0.772

ROC analysis confirmed the superiority of cystatin C-based assessment. The AUC was 0.986 for serum cystatin C and 0.986 for eGFRcys, compared with 0.793 for serum creatinine and 0.772 for eGFRcr. The optimal cystatin C threshold was 0.96 mg/L, with sensitivity of 100.0% and specificity of 96.8%. For eGFRcys, the optimal threshold was 84.3 mL/min/1.73 m², with sensitivity of 100.0% and specificity of 96.8%. These results demonstrate that cystatin C-based measures had near-perfect discrimination in this cohort, whereas creatinine-based measures had moderate discrimination.

3.4 Correlation and agreement analyses

In the T2DM group, UACR did not correlate significantly with serum creatinine ($r = -0.059$; $p = 0.686$), serum cystatin C ($r = -0.153$; $p = 0.289$), eGFRcr ($r = 0.121$; $p = 0.401$), or eGFRcys ($r = 0.148$; $p = 0.306$). UACR also did not correlate significantly with age, diabetes duration, or HbA1c. This lack of correlation likely reflects the restricted case-mix: nearly all cases had albuminuria, while filtration-marker values varied widely. It also supports the view that albuminuria and GFR decline represent related but partially independent pathways of diabetic kidney injury.

Table 4: Pearson correlations between UACR and clinical or biochemical variables among T2DM cases (n=50)

Variable correlated with UACR	Pearson r	p value	Interpretation
Serum creatinine	−0.059	0.686	No significant correlation
Serum cystatin C	−0.153	0.289	No significant correlation
eGFR creatinine	0.121	0.401	No significant correlation
eGFR cystatin C	0.148	0.306	No significant correlation
Age	0.079	0.587	No significant correlation
T2DM duration	−0.050	0.728	No significant correlation
HbA1c	0.082	0.573	No significant correlation

Bland-Altman analysis showed a mean bias of 25.58 mL/min/1.73 m², with eGFRcr systematically exceeding eGFRcys in diabetic participants. The limits of agreement were wide, indicating that the two equations cannot be used interchangeably in this population. The scatter plot demonstrated that many participants with eGFRcr above 90 mL/min/1.73 m² had eGFRcys values far below this threshold.

3.5 Discordance between eGFR estimates

Discordance, defined as eGFRcr ≥90 mL/min/1.73 m² with eGFRcys <90 mL/min/1.73 m², was observed in 22 of 50 T2DM cases (44.0%). Thus, nearly half of the diabetic cohort would have been considered to have preserved filtration function if assessed by creatinine alone, despite cystatin C-based evidence of reduced eGFR. This discordance was clinically important because these participants also had elevated UACR, with a group mean of 154.27 mg/g.

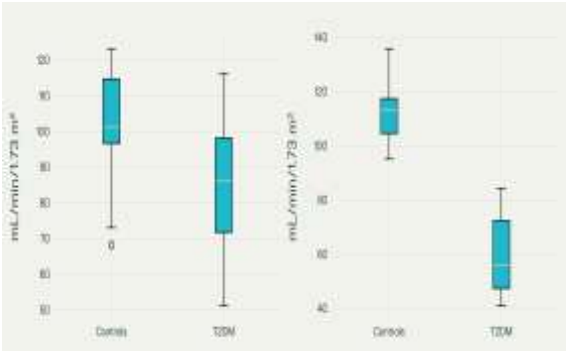


Figure 1: Boxplots showing eGFR creatinine and eGFR cystatin C in healthy controls and adults with type 2 diabetes mellitus

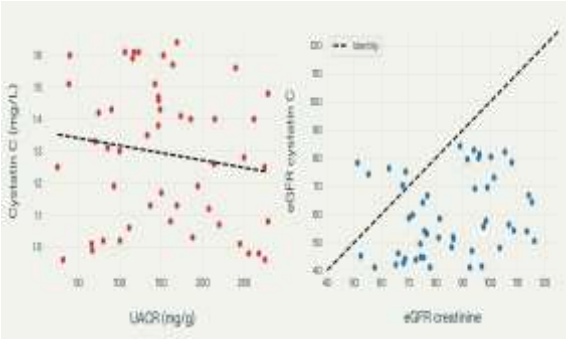


Figure 2: Left panel: relationship between UACR and serum cystatin C in T2DM cases. Right panel: agreement between creatinine- and cystatin C-based eGFR in T2DM cases; the dashed line represents identity

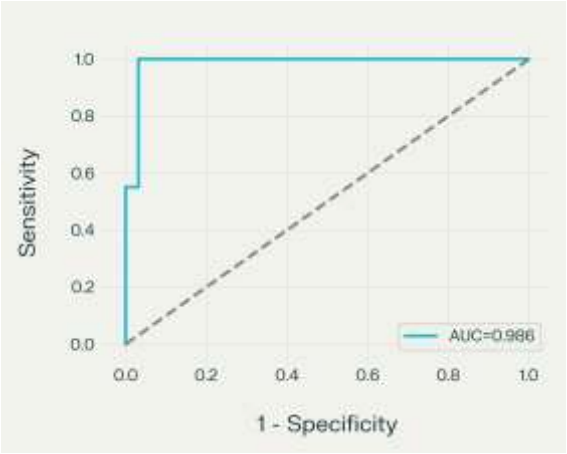


Figure 3: Receiver operating characteristic curves for eGFR cystatin C and eGFR creatinine for detecting early diabetic kidney disease, defined as UACR ≥30 mg/g

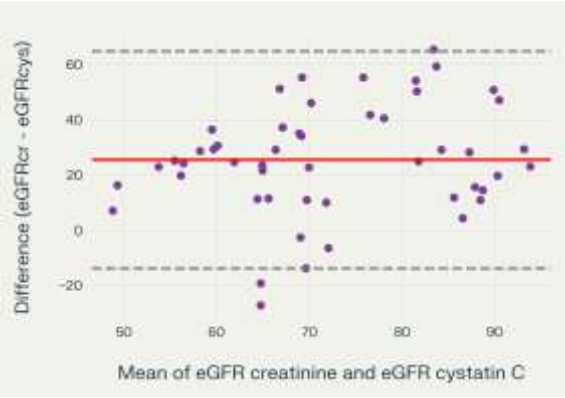


Figure 4: Bland-Altman plot of the difference between eGFR creatinine and eGFR cystatin C against their mean in T2DM cases

DISCUSSION

This cross-sectional study compared cystatin C-based and creatinine-based eGFR for the detection of early diabetic kidney injury in adults with T2DM. The principal finding was that eGFRcys identified renal functional reduction far more frequently than eGFRcr. At the conventional threshold of 90 mL/min/1.73 m², eGFRcys detected 49 of 50 diabetic participants, whereas eGFRcr detected only 23. Furthermore, 22 participants (44.0%) had normal creatinine-based eGFR but reduced cystatin C-based eGFR. These results support the hypothesis that cystatin C provides earlier and more sensitive detection of diabetic kidney dysfunction than creatinine.

The markedly higher cystatin C concentration in cases is consistent with its biology. Cystatin C is produced by nucleated cells at a relatively stable rate, freely filtered by the glomerulus, and catabolised after proximal tubular uptake. Therefore, even modest reductions in GFR produce a measurable rise in serum concentration.[13,14] In contrast, creatinine is affected by muscle mass and tubular secretion, and its serum level may remain within the laboratory reference interval despite early GFR loss.[8,9] The present findings mirror this physiological distinction: cases had only a modest elevation in creatinine but a much larger relative increase in cystatin C.

The large difference between eGFRcr and eGFRcys in cases deserves careful interpretation. Mean eGFRcr was 85.13 mL/min/1.73 m², whereas mean eGFRcys was 59.55 mL/min/1.73 m², a difference of 25.58 mL/min/1.73 m². This magnitude is larger than that typically reported in some general-population studies, suggesting that the study cohort was enriched for early kidney injury, as reflected by the high mean UACR of 154.27 mg/g. It may also reflect the known tendency of creatinine-based equations to overestimate GFR in individuals with reduced muscle mass or increased tubular creatinine secretion.[11,12] Because the study did not measure muscle mass, body composition, or measured GFR, these mechanisms cannot be definitively separated in the present analysis.

The diagnostic performance results were striking. eGFRcys below 90 mL/min/1.73 m² had 100% sensitivity and 96.8% specificity for UACR-defined early DKD, with an AUC of 0.986. eGFRcr had substantially lower sensitivity (55.1%) and only moderate AUC (0.772). The near-perfect performance of eGFRcys should be interpreted with caution. First, the reference standard was albuminuria rather than measured GFR; therefore, the analysis evaluates concordance with an albuminuria-based clinical definition, not true filtration accuracy. Second, the cohort was selected to include diabetic patients with early albuminuric kidney injury, which increases the separation between cases and controls. Third, the sample size was modest, particularly the control group, and confidence intervals around sensitivity and specificity estimates are therefore wide. Nevertheless, the direction and magnitude of the difference are biologically plausible and consistent with prior literature.[17-19]

The weak correlations between UACR and both eGFR estimates in cases are noteworthy. Albuminuria reflects glomerular endothelial and podocyte injury, whereas GFR decline reflects loss of filtering nephron mass and haemodynamic adaptation. These processes may diverge, especially early in disease. Some patients have prominent albuminuria with relatively preserved GFR, whereas others show GFR decline with lesser albuminuria.[22,24] The absence of significant correlation in this dataset therefore does not invalidate either marker; rather, it reinforces guidelines recommending assessment of both albuminuria and eGFR rather than reliance on a single parameter.[23]

The 44.0% discordance rate has direct clinical implications. If clinicians rely only on eGFRcr, a substantial proportion of diabetic patients with albuminuria and cystatin C-based evidence of reduced filtration may be misclassified as having preserved kidney function. Such misclassification can delay intensification of glycaemic management, blood-pressure control, renin-angiotensin system blockade, SGLT2 inhibitor therapy, and nephrology referral.[5-7] Conversely, cystatin C-based assessment may support earlier risk stratification and more appropriate monitoring. However, cystatin C can be elevated by hypothyroidism, glucocorticoid exposure, inflammation, obesity, and smoking; these factors should be excluded or interpreted before assigning a new diagnosis of CKD solely on the basis of eGFRcys.[15,16]

Our findings are broadly consistent with previous studies showing that cystatin C detects GFR decline earlier than creatinine in diabetes. Studies in diabetic cohorts have reported that cystatin C-based equations reclassify a meaningful proportion of patients from apparent normal renal function to reduced eGFR.[17-19] Other investigations have found that cystatin C improves prediction of DKD progression, cardiovascular events, and mortality beyond creatinine-based eGFR.[20,21] The present study adds

context-specific evidence from an Indian hospital population, where early detection is particularly important because diabetes often presents late and renal risk factors may coexist with variable nutritional and muscle-mass profiles.

Several limitations should be acknowledged. The cross-sectional design prevents inference about whether eGFRcys predicts future decline in kidney function. The reference standard, UACR ≥30 mg/g, is a marker of albuminuria rather than a direct measure of GFR; measured GFR using iohexol, iothalamate, or EDTA clearance would provide a stronger criterion standard. The sample comprised 80 participants from a single centre, limiting generalisability and statistical precision. Potential confounders such as body mass index, waist circumference, smoking, thyroid function, inflammatory markers, medication use, and muscle mass were not fully characterised. Finally, the cystatin C assay, although automated and widely used, may vary across platforms; threshold values should therefore be validated locally before clinical implementation.

Despite these limitations, the study has several strengths. It used a clearly defined clinical cohort, measured both albuminuria and two contemporary eGFR estimates, applied the race-free 2021 CKD-EPI equations, and evaluated clinically meaningful diagnostic indices rather than relying only on group-mean differences. The inclusion of healthy controls allowed assessment of specificity, and the discordance analysis directly addressed the practical question of how many patients would be missed by creatinine-based assessment alone.

Future studies should prospectively follow patients with discordant eGFR values to determine whether eGFRcys predicts subsequent eGFR decline, albuminuria progression, or cardiovascular events. Studies should also compare cystatin C-based eGFR with measured GFR and evaluate combined creatinine-cystatin C equations, which may provide the most accurate estimation across diverse body-composition profiles.[10,20] Cost-effectiveness analysis is needed to determine whether routine cystatin C testing is justified in all patients with T2DM or only in high-risk subgroups, such as those with long diabetes duration, hypertension, retinopathy, obesity, or borderline creatinine.

CONCLUSION

In adults with type 2 diabetes, cystatin C-based eGFR detected early renal functional impairment substantially more often than creatinine-based eGFR. eGFRcys demonstrated excellent discrimination for albuminuria-defined early diabetic kidney disease, whereas eGFRcr missed nearly half of affected participants. The high rate of discordance suggests that creatinine-based assessment alone may underestimate early diabetic kidney injury. Cystatin C-based eGFR, used alongside UACR, may improve early detection and risk stratification, but its routine implementation should be supported by larger, longitudinal, measured-GFR validation studies.

Declarations

Ethics approval and consent to participate: The study protocol was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants.

Consent for publication: Not applicable.

Availability of data and materials: The de-identified dataset supporting the findings is available from the corresponding author on reasonable request.

Conflicts of interest: The authors declare no conflicts of interest.

Funding: This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' contributions: All authors contributed to study conception, data collection, analysis, interpretation, manuscript preparation, and final approval.

REFERENCES

1. Koye DN, Magliano DJ, Nelson RG, Pavkov ME. The global epidemiology of diabetes and kidney disease. Adv Chronic Kidney Dis. 2018;25(2):121-32.
2. Indian Council of Medical Research. ICMR guidelines for management of type 2 diabetes mellitus. New Delhi: ICMR; 2020.
3. American Diabetes Association Professional Practice Committee. 11. Chronic kidney disease and risk management: Standards of Care in Diabetes—2024. Diabetes Care. 2024;47(Suppl 1):S219-31.
4. Kanwar YS, Sun L, Xie P, Liu FY, Chen S. A glimpse of various pathogenetic mechanisms of diabetic nephropathy. Annu Rev Pathol. 2011;6:395-423.
5. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med. 2019;380(24):2295-306.
6. Heerspink HJL, Stefánsson BV, Correa-Rotter R, et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med. 2020;383(15):1436-46.
7. Bakris GL, Agarwal R, Anker SD, et al. Effect of finerenone on chronic kidney disease outcomes in type 2 diabetes. N Engl J Med. 2020;383(23):2219-29.
8. Perrone RD, Madias NE, Levey AS. Serum creatinine as an index of renal function: new insights into old concepts. Clin Chem. 1992;38(10):1933-53.
9. Delanghe JR, Speeckaert MM. Creatinine determination according to Jaffe—what does it stand for? NDT Plus. 2011;4(2):83-6.
10. Inker LA, Eneanya ND, Coresh J, et al. New creatinine- and cystatin C–based equations to estimate GFR without race. N Engl J Med. 2021;385(19):1737-49.
11. Stevens LA, Coresh J, Greene T, Levey AS. Assessing kidney function—measured and estimated glomerular filtration rate. N Engl J Med. 2006;354(23):2473-83.
12. MacIsaac RJ, Ekinci EI, Jerums G. Markers of glycemic control and complications of diabetes. Diabetes Metab. 2014;40(5):331-43.
13. Grubb A, Simonsen O, Sturfelt G, Truedsson L, Thysell H. Serum concentration of cystatin C, factor D and beta 2-microglobulin as a marker of glomerular filtration rate. Acta Med Scand. 1985;218(5):499-503.
14. Newman DJ, Thakkar H, Edwards RG, et al. Serum cystatin C measured by automated immunoassay: a more sensitive marker of changes in GFR than serum creatinine. Kidney Int. 1995;47(1):312-8.

15. Stevens LA, Schmid CH, Greene T, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. Kidney Int. 2009;75(6):652-60.
16. Knight EL, Verhave JC, Spiegelman D, et al. Factors influencing serum cystatin C levels other than renal function and the impact on renal function measurement. Kidney Int. 2004;65(4):1416-21.
17. Perkins BA, Nelson RG, Ostrander BE, et al. Detection of renal function decline in patients with diabetes and normal or elevated GFR by serial measurements of serum cystatin C concentration: results of a 4-year follow-up study. J Am Soc Nephrol. 2005;16(5):1404-12.
18. Jeon YK, Kim MR, Huh JE, et al. Cystatin C as an early marker of diabetic nephropathy in patients with type 2 diabetes mellitus. Diabetes Res Clin Pract. 2011;93(3):321-7.
19. Sharma K, Premaratne E, MacIsaac RJ, Jerums G. Cystatin C and diabetic kidney disease. Clin Biochem. 2014;47(16-17):1-8.
20. Shlipak MG, Matsushita K, Ärnlöv J, et al. Cystatin C versus creatinine in determining risk based on kidney function. N Engl J Med. 2013;369(10):932-43.
21. Astor BC, Levey AS, Stevens LA, et al. Association of serum cystatin C with mortality and cardiovascular events. Ann Intern Med. 2008;149(1):23-31.
22. MacIsaac RJ, Panagiotopoulos S, McNeil KJ, et al. Correlation between glomerular filtration rate and albuminuria in type 2 diabetes. Am J Kidney Dis. 2002;40(4):792-801.
23. Kidney Disease: Improving Global Outcomes Diabetes Work Group. KDIGO 2022 clinical practice guideline for diabetes management in chronic kidney disease. Kidney Int. 2022;102(5S):S1-127.
24. Ekinci EI, Jerums G, Skene A, et al. Renal hyperfiltration and albuminuria in type 2 diabetes. Diabetes Care. 2013;36(10):3212-8.