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# HIDDEN RENAL DISFUNCTION IN TYPE 2 DIABETES MELLITUS: DIAGNOSTIC UTILITY OF SERUM CYSTATIN C IN NORMOALBUMINURIC AND MICROALBUMINURIC PATIENTS FROM MYSORE DISTRICT, KARNATAKA – AN OBSERVATIONAL STUDY

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**ABSTRACT**
Diabetic nephropathy (DN) is among the most serious microvascular difficulties of Diabetes Mellitus and a leading reason for chronic kidney disease worldwide, is conventionally identified using microalbuminuria; however, renal dysfunction often begins prior to the appearance of overt albuminuria, resulting in delayed diagnosis and intervention. Early detection of subclinical renal impairment is therefore critical, particularly in high-risk South Asian populations with rapidly increasing diabetes prevalence. Serum cystatin C, a low–molecular-weight protein freely filtered by the glomerulus, has emerged as a promising biomarker capable of detecting early decline in renal function before conventional indicators become abnormal. The present cross-sectional study represents one of the first regional epidemiological validations from Mysuru, Karnataka, evaluating the analytical usefulness of serum cystatin C for timely detection of diabetic nephropathy in patients with Type 2 Diabetes Mellitus (T2DM). A total of 200 T2DM patients aged 35–70 years were enrolled and categorized into normoalbuminuric (ACR <30 mg/g; n=100) and microalbuminuric groups (ACR 30–300 mg/g; n=100). Serum cystatin C, creatinine, fasting blood glucose, and HbA1c levels were measured, while glomerular filtration rate (eGFR) was estimated using the CKD-EPI equation. Statistical significance was considered at $p < 0.05$. The higher correlation value of 0.89 suggests that serum cystatin C have a better and accurate diagnostic potential for identifying early renal impairment. Meanwhile serum creatinine and eGFR exhibited comparatively lower accuracies with AUC values of 0.72 and 0.75, respectively. Moreover, cystatin C showed better sensitivity among multiple specificity limits and maintained higher performance at lower false-positive rates, allowing effective identification of early renal dysfunction even among normoalbuminuric diabetic patients without noticeable clinical indication of nephropathy.
In conclusion, the study reports significant regional epidemiological evidence from Mysuru, Karnataka, supporting cystatin C in serum as a sensitive and dependable biomarker for a timely detection of subclinical diabetic nephropathy.

**KEYWORDS:** Diabetes Mellitus, Normoalbuminuric, Microalbuminuric, Chronic kidney disease, Mysore,

## INTRODUCTION

Diabetes mellitus is one of the rising chronic illnesses globally and is identified as one of the primary reasons for chronic kidney disease (CKD). CKD is of a significant global medical concern, leading to reduced life expectancy due to its related increased dialysis requirement and cardiovascular complications (1). Diabetic nephropathy (DN), which develops in approximately 30–40% of persons with type 2 diabetes, is one of the major reasons leading to morbidity and mortality. The DN patients are also exposed to an increased risk of faster progression to end-stage renal disease (ESRD) and are also found to develop cardiovascular diseases and premature death (2). According to the World Health Organization (WHO), the average occurrence of diabetes across all age groups was found to be 2.8% in 2000 and is expected to significantly increase to 4.4% by 2030. (3).
Chronic kidney disease (CKD) is often markedly underrecognized, specifically during its early stages in individuals with diabetes. Traditionally renal function has been assessed using serum creatinine levels and calculated glomerular filtration rate (eGFR). However, these markers have limitations. Serum creatinine, the conventional marker of renal function, lacks sensitivity in early stages because its levels rise only after significant nephron loss. They are also influenced by factors such as age, sex, and muscle mass, which reduces their relevancy in identifying renal impairment at early stage (4). Early detection of renal damage in diabetic individuals helps for prompt intervention which can delay progression in disease and helps to maintain healthy lifestyle.
Cystatin C a 13-kDa non-glycosylated cysteine proteases inhibitor first identified in cerebrospinal fluid in 1961, is produced by nucleated cells. It passes freely through the glomerular membrane and gets completely reabsorbed and broken down in the proximal tubules, making it a potential and dependable kidney function biomarker. Cystatin C is encoded by

the CST3 gene which belongs to the type 2 cystatin gene family and having the major function of regulating the activity of endogenous proteinases released from lysosomes of injured or apoptotic cells (5) The amount of cystatin C in the serum is the same in adults and children older than a year. (6). Age, gender, and muscle mass have less of an impact on its levels since glomerulus filters it with ease and is fully metabolized in the proximal tubule and resorbed. (7). Because it is largely unaffected by age, body composition, or dietary factors, cystatin C is measured as a reliable endogenous indicator for the timely detection of kidney dysfunction. In diabetes, advanced glycation end products, hyperglycemia and oxidative stress accelerate tubular and glomerular damage. The increased levels of cystatin C may therefore not only indicate reduced filtration but also reflect early tubular dysfunction, providing a broader picture of renal injury. (8)

Numerous findings indicate that serum Cystatin C may detect mild reductions in GFR earlier than creatinine, making it a more sensitive and reliable indicator of renal dysfunction.

Given the high burden of diabetic nephropathy and the necessity for specific diagnostic markers, this study was undertaken to evaluate the correlation of Cystatin C levels in serum with diabetic nephropathic patients showing decline in renal function.

The present study targets to explore the diagnostic importance of serum cystatin C in detecting hidden renal function impairment in normoalbuminuric and microalbuminuric diabetic patients.

The study was also aimed at estimating cystatin C concentrations in normoalbuminuric and microalbuminuric type 2 diabetic patients, and assessed its correlation with key renal markers, including urinary albumin elimination, serum creatinine, and assessed glomerular filtration rate (eGFR). Additionally, evaluated the potential role of cystatin C to identify hidden or early renal dysfunction among normoalbuminuric diabetic individuals, who may otherwise appear to have normal kidney function through conventional markers.

## MATERIALS AND METHODS

Study Design and Setting

A hospital-based cross-sectional observational study was conducted in the Departments of General Medicine and Biochemistry at Cauvery Heart and Multispeciality Hospital, Mysore, over an 18-month period (January 2024 to September 2025), involving patients identified having Type 2 Diabetes Mellitus aged 35–70 years with a minimum disease duration of five years. Individuals with Type 1 Diabetes Mellitus, pre-existing Chronic Kidney imapirment, nephrotic syndrome, other renal disorders, urinary tract infection or hematuria at the time of sampling, hypertensive emergencies or poorly controlled hypertension (>160/100 mmHg), as well as those with liver disease, thyroid dysfunction, acute infections, malignancy, systemic inflammatory conditions, or those receiving nephrotoxic medications such as Nonsteroidal Anti-Inflammatory Drugs were excluded to minimize confounding factors. Ethical clearance for this research was received from the Institutional Ethics Committee of Cauvery Heart and Multispeciality Hospital, Mysore (Approval No: CHMH/IEC/01/01/CS/2024-25/002), and all participants were registered after getting written informed consent; strict confidentiality was maintained, and participation was entirely voluntary.

Sample size:

Altogether 200 patients with Type 2 Diabetes Mellitus attending the outpatient and inpatient departments were enrolled using purposive sampling based on defined inclusion and exclusion criteria.

The sample size (n=200) was determined by the formula for comparing two means:

$$n = \frac{(Z1-\alpha/2+Z1-\beta)2(\sigma12+\sigma22)}{(\mu1-\mu2)}$$

Assuming a power of 80%, significance level of 5%, and expected mean difference in cystatin C levels between groups (0.3 mg/L based on pilot data), a minimum of 90 subjects per group was required; hence, 100 per group were enrolled to justify for dropouts. Using the formula, the minimum necessary sample size was 200 participants, adjusted to 220 to describe for incomplete data and non-Diabetic CKD. Participants were recruited using systematic random sampling from clinic registers and screening lists

Urinary albumin-to-creatinine ratio (ACR) was assessed using an early morning spot urine sample. Levels of Urinary albumin was estimated by the immunoturbidimetric method, wherein albumin present in the sample reacts with specific anti-human albumin antibodies to form antigen–antibody complexes, and the resulting turbidity was measured spectrophotometrically. Urinary creatinine was quantified by the kinetic Jaffe's method based on the reaction between creatinine and alkaline picrate. The ACR was calculated by dividing urinary albumin concentration by urinary creatinine concentration and expressed as mg/g creatinine

### Grouping of Subjects

Based on the urinary albumin-to-creatinine ratio (ACR), patients with Type 2 Diabetes Mellitus were stratified into normoalbuminuric (ACR < 30 mg/g; n=100) and microalbuminuric groups (ACR 30–300 mg/g; n=100), with exclusion of macroalbuminuria (ACR > 300 mg/g) to focus on early Diabetic Nephropathy, and comprehensive clinical evaluation—including structured history, anthropometry, and blood pressure measurement—was performed alongside standardized collection of fasting venous blood (5 mL after 10–12 hours fasting) and morning spot urine samples for estimation of urinary albumin, creatinine, fasting blood glucose, serum creatinine, HbA1c and eGFR, with all specimens processed promptly and stored at –20°C to ensure analytical integrity.

### Statistical Analysis

Data were compiled in Microsoft Excel and statistically examined using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Detailed statistics were expressed as mean ± standard deviation (SD), and inferential analyses were

conducted using independent sample t-test and one-way ANOVA for assessment of normally distributed continuous variables between groups, while non-parametric tests such as the Mann–Whitney U test and Chi-square test were applied for variables that did not follow normal distribution. Pearson's correlation coefficient assessed relationships between continuous variables. A *p*-value < 0.05 was considered statistically significant.

**RESULTS**

Clinical and Biochemical Characteristics

| Parameter | Normoalbuminuria | Microalbuminuria | p-value |
|---|---|---|---|
| Age (years) | 54.1 ± 8.2 | 56.5 ± 9.0 | 0.08 |
| Duration of DM (years) | 7.4 ± 3.1 | 10.3 ± 4.2 | <0.001 |
| HbA1c (%) | 7.6 ± 1.0 | 8.7 ± 1.5 | <0.01 |

**Table 1. Comparison of clinical and biochemical parameters between normoalbuminuric and microalbuminuric type 2 diabetic patients**

The average age of patients in the normoalbuminuria group was 54.1 ± 8.2 years, while that of the microalbuminuria group was 56.5 ± 9.0 years. Although the microalbuminuric patients were slightly older on average, the difference was not statistically significant (p = 0.08). This observation suggests that age alone did not notably influence the presence of early diabetic nephropathy in the present study population.

The mean duration of diabetes was notably longer in patients with microalbuminuria (10.3 ± 4.2 years) in comparison to those with normoalbuminuria (7.4 ± 3.1 years). This difference was highly significant (p < 0.001). Duration of diabetes is a well-established risk factor for diabetic kidney disease. The markedly longer disease duration in the microalbuminuric group indicates progressive cumulative exposure to hyperglycemia, oxidative stress, and microvascular damage over time.

The mean glycated hemoglobin (HbA1c) level was 7.6 ± 1.0% in the normoalbuminuria group and 8.7 ± 1.5% in the microalbuminuria group which was statistically significant (p < 0.01). Higher HbA1c levels in the microalbuminuric group indicate poorer long-term glycemic control.

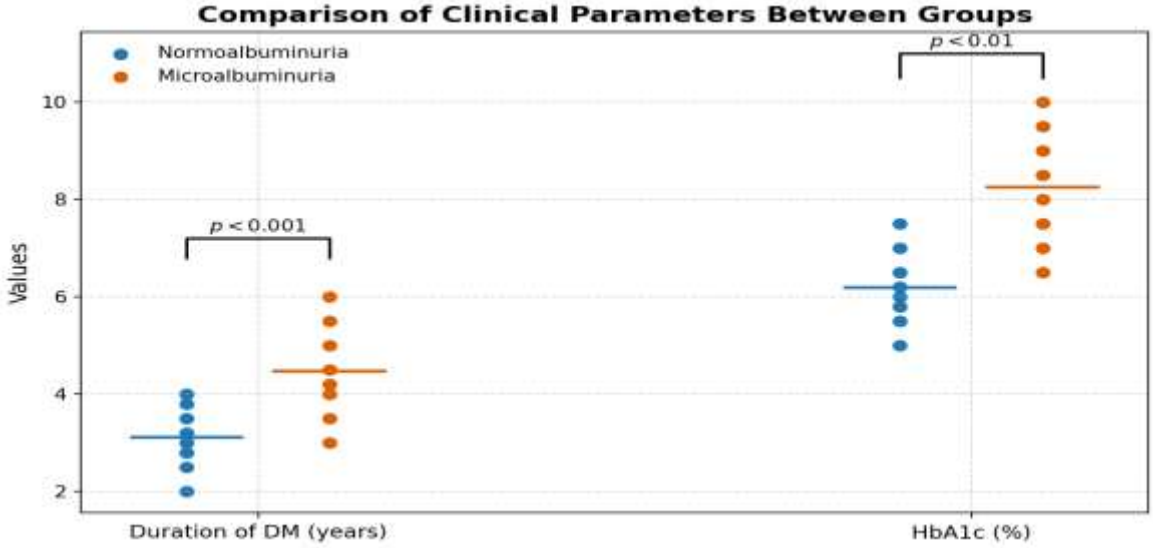


**Figure 1: Comparison of Clinical Parameters Between Groups**

The dot graph illustrates the comparison of duration of diabetes mellitus (DM) and HbA1c levels between the normoalbuminuria and microalbuminuria groups. The findings indicates that patients with microalbuminuria exhibited a prolonged period of diabetes along with higher HbA1c concentrations when compared to the normoalbuminuria group. The significantly increased duration of DM in the microalbuminuria group (p < 0.001) indicates that prolonged diabetes may contribute to the progression of renal damage.

| Parameter | Normoalbuminuria | Microalbuminuria | p-value |
|---|---|---|---|
| Serum Creatinine (mg/dL) | 0.92 ± 0.21 | 1.48 ± 0.42 | <0.001 |
| Blood Urea (mg/dL) | 27.6 ± 5.8 | 39.2 ± 10.4 | <0.001 |
| eGFR (mL/min/1.73 m²) | 94 ± 17 | 69 ± 21 | <0.001 |
| ACR (mg/g) | 18 ± 7 | 112 ± 65 | <0.001 |

**Table 2. Comparison of conventional biomarkers between normoalbuminuric and microalbuminuric type 2 diabetic patients**

The comparison of conventional renal parameters between normoalbuminuria and microalbuminuria groups demonstrated statistically significant differences across all variables ($p < 0.001$). The average serum creatinine level was higher in the microalbuminuria group (1.48 ± 0.42 mg/dL) in comparison to the normoalbuminuria group (0.92 ± 0.21 mg/dL). Similarly, blood urea levels were elevated in the microalbuminuric patients (39.2 ± 10.4 mg/dL) compared to those with normoalbuminuria (27.6 ± 5.8 mg/dL), The mean eGFR was lower in the macroalbuminuric patients (69 ± 21 mL/min/1.73 m²) than in the normoalbuminuria ones (94 ± 17 mL/min/1.73 m²). Additionally, the albumin–creatinine ratio (ACR) was markedly higher in the microalbuminuric group (112 ± 65 mg/g) compared to the normoalbuminuric group (18 ± 7 mg/g).

| Parameter | Normoalbuminuria | Microalbuminuria | p-value |
|---|---|---|---|
| Serum Cystatin C (mg/L) | 0.86 ± 0.19 | 1.47 ± 0.36 | <0.001 |

**Table 3 Comparison of Cystatin C levels among normoalbuminuric and microalbuminuric type 2 diabetic patients**

The average serum cystatin C concentrations was significantly higher in the microalbuminuria patient group (1.47 ± 0.36 mg/L) in relation to the normoalbuminuria ones (0.86 ± 0.19 mg/L), with the difference being significant statistically ($p < 0.001$).

| Variable | Correlation (r) | P-value |
|---|---|---|
| eGFR | −0.74 | <0.001 |
| Serum Creatinine | +0.63 | <0.001 |
| ACR | +0.61 | <0.001 |
| Duration of DM | +0.48 | <0.01 |
| HbA1c | +0.39 | <0.05 |

**Table 4 Correlation of Serum Cystatin C with Renal Function Parameters and Clinical Variables**

Pearson's correlation analysis confirmed that serum cystatin C had a robust indirect correlation with eGFR ($r = −0.74$, $p < 0.001$) and significant positive correlations with serum creatinine ($r = +0.63$, $p < 0.001$), albumin–creatinine ratio (ACR) ($r = +0.61$, $p < 0.001$), duration of diabetes mellitus ($r = +0.48$, $p < 0.01$), and HbA1c ($r = +0.39$, $p < 0.05$)..
Although age was equivalent between groups, a longer duration of diabetes and higher HbA1c levels showed a important association with microalbuminuria, highlighting their pivotal role in the early development of renal involvement in patients with Type 2 Diabetes Mellitus.

**Receiver Operating Characteristic (ROC) Curve Analysis**

| Marker | AUC | Sensitivity | Specificity |
|---|---|---|---|
| Cystatin C | 0.89 | 86% | 82% |
| Creatinine | 0.72 | 64% | 70% |
| eGFR | 0.75 | 68% | 72% |

**Table 5: Receiver Operating Characteristic (ROC) Curve Analysis of Serum Cystatin C and Conventional Renal Markers**

Receiver operating characteristic (ROC) curve analysis demonstrated clear superiority of Cystatin C over conventional renal markers in discriminating early Diabetic Kidney Disease. Serum cystatin C achieved the highest diagnostic accuracy with an AUC of 0.89, accompanied by high sensitivity (86%) and specificity (82%), indicating excellent discriminatory power. In contrast, serum creatinine exhibited comparatively lower performance (AUC 0.72, sensitivity 64%, specificity 70%), reflecting its limited utility in detecting early renal dysfunction, while calculated glomerular filtration rate (eGFR) showed only modest improvement (AUC 0.75, sensitivity 68%, specificity 72%) but remained inferior to cystatin C. Notably, cystatin C maintained robust performance even in normoalbuminuric individuals, where traditional markers often remain within normal limits, underscoring its value as a highly sensitive and reliable biomarker for the early identification of subclinical nephropathy in patients with Type2 DM.

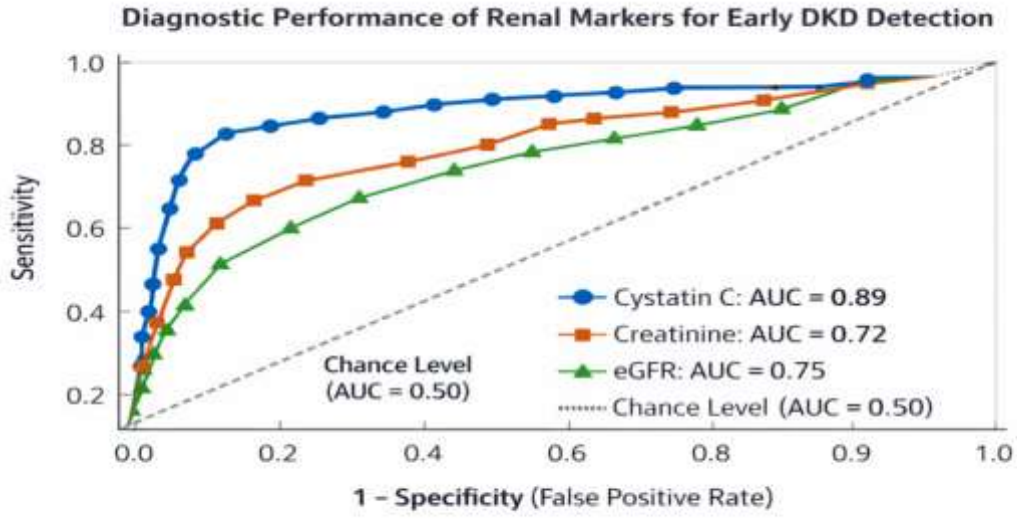


**Figure 2: ROC curve showing the diagnostic performance of Cystatin C**

## DISCUSSION

The present observational study conducted in the Mysore population provides important insights into the clinical and biochemical determinants of early diabetic kidney disease (DKD), particularly highlighting the role of cystatin C in serum as a sensitive biomarker of renal dysfunction. The study also is one of the first regional epidemiological study from Mysuru, Karnataka, in which the potential of serum cystatin C to detect early renal dysfunction in Type 2 diabetic patients was evaluated. Considering the increasing burden of diabetes and diabetic kidney disease in Karnataka and South India, evaluation and understanding of the population for promising and sensitive renal biomarkers holds significance. The study demonstrates that levels of serum cystatin C are significantly elevated in microalbuminuric and even in a subgroup of normoalbuminuric patients with normal renal function. Similar increase in serum cystatin C levels with increasing severity of albuminuria have been reported in several studies on diabetic kidney disease. Increased cystatin C concentrations have been observed in patients with early renal damage including the one with microalbuminuria suggesting its correlation with deteriorating renal function. Cystatin C thus proves to be effective in detecting renal dysfunction even before the onset of microalbuminuria and therefore in earliest possible diagnosis of subclinical nephropathy during the preliminary stages of diabetic kidney disease development. The results therefore suggests that cystatin C could serve as an early marker of dysfunctions in glomerular and tubular segments even before the onset of microalbuminuria. This finding is consistent with the observations of Jeon YK(9), who reported that urinary and serum cystatin C measurements are effective and non-invasive markers for assessing diabetic related renal complications, particularly among normoalbuminuric patients. Similar observations were reported by Mussap et al. (2002) (10), who found cystatin C to be a more sensitive early marker compared to creatinine. The inverse relation between cystatin C and eGFR further reconfirms its importance in early stage detection of renal diseases which is further established by its non-dependency on muscle mass and diet. Meanwhile its established correlation with HbA1c suggests a potential association between glycemic control and minor renal injury.

The result of this observational study clearly underlines the differences in the clinical observations such as glycemic control, disease duration, and renal biomarkers. Patients with microalbuminuria showed significantly higher HbA1c levels (8.7% vs 7.6%) and longer duration of diabetes (10.3 vs 7.4 years), which demonstrates the contribution of chronic hyperglycemia and prolonged disease exposure as the crucial factors leading to Diabetic Kidney Disease.

### Cystatin C, an Early Diabetic Nephropathy Biomarker

In our study, serum cystatin C concentrations were elevated even among normoalbuminuric diabetic patients, suggesting that cystatin C may indicate early glomerular filtration impairment before evident albuminuria develops. This observation is significant from an epidemiological point of view, as typical microalbuminuria based screening strategies may fail to identify a subgroup of patients with early renal dysfunction in the Mysore diabetic population. This finding is persistent with previous studies by Finney et al. (2000) (11.) and Shilpak et al. (12), who showed that cystatin C is an accurate predictor of early renal dysfunction compared to creatinine, specifically in diabetic populations. The independence of cystatin C levels from age, sex, as well as muscle mass makes it a reliable biomarker for renal function in diverse patient groups.A key strength of the present study is the evaluation of Cystatin C, which was significantly elevated in the microalbuminuric group (1.47 vs 0.86 mg/L). This finding agrees with the Karnataka based study by **Shetty S** etal (13**)**, which reported that the median serum Cystatin C level (1.34 mg/l) was much above the upper reference limit and demonstrated a strong negative correlation with eGFR. Unlike creatinine, cystatin C is less affected by non-renal factors and even predicts minor changes in glomerular filtration, making it a more sensitive biomarker for early renal impairment. Moreover, the present study highlights that cystatin C elevation occurs even in early stages of kidney dysfunction, possibly before significant changes in creatinine or eGFR are observed. This is particularly significant in normoalbuminuric

patients, where traditional markers may fail to detect early renal damage. Thus, cystatin C may assist in early detection of high-risk individuals and timely intervention.

**Correlation with Renal and Glycemic Parameters**

With respect to markers of renal function, serum creatinine and eGFR in the current study (0.92 vs 1.48 mg/dL and 94 vs 69 mL/min, respectively) showed expected trends of declining renal function in microalbuminuric patients. Similar values have been reported in other Indian studies, where creatinine ranged from 1.0–1.6 mg/dL and eGFR declined to 60–70 mL/min in patients with DKD. However, creatinine has limitations as an early marker, as it is affected by muscle mass, age, and gender, and often increases only after significant renal damage.

The strong negative correlation between cystatin C and eGFR ($r = –0.74$) observed in our study supports its role as a sensitive indicator of declining filtration function. The positive association between cystatin C and ACR ($r = 0.63$) further strengthens its utility in detecting glomerular injury. Moreover, its moderate correlation with HbA1c ($r = 0.39$) suggests that poor glycemic control leads to early renal impairment, probably due to increased oxidative stress and endothelial dysfunction. Similar correlations were reported by Lee et al. (2011) (14) who noted that cystatin C levels rise even before microalbuminuria becomes evident, indicating early tubular involvement in diabetic kidneys. Sajid et al. (15) confirmed that cystatin C is capable of identifying early reductions in eGFR even among patients who have normal serum creatinine levels and normoalbuminuria, highlighting its value as a sensitive marker for the early detection of diabetic kidney disease.

The direct link between cystatin C and urinary albumin-to-creatinine ratio (ACR) ($r = 0.61$, $p < 0.001$) further supports its role as an early indicator of glomerular injury. As microalbuminuria develops due to glomerular basement membrane thickening and podocyte damage, cystatin C levels rise concurrently, suggesting that both biomarkers represent complementary aspects of diabetic nephropathy pathophysiology. In a study by Arceo et al., in 2019, where a positive correlation was found between cystatin C serum levels and albuminuria. (16). Similar significant positive associations between Cystatin C and ACR was demonstrated in a study conducted by Yahya A (17).

A moderate positive relation with HbA1c ($r = 0.39$, $p < 0.01$) was also observed, demonstrating the link relating poor glycemic control and rising cystatin C levels. Studies by Nilsson C have reported similar trends, suggesting that Cystatin C may prove useful as an adjunct to HbA1c in predicting eventual advancement to diabetic complications (18). The consistency and strength of these associations confirm the clinical effectiveness of cystatin C as a sensitive, early-rising biomarker for identifying patients at risk of diabetic nephropathy, particularly those still classified as normoalbuminuric. (19)

Overall, the findings from this Mysore population-based observational study are in strong agreement with both national and international literature. However, the present study carries importance as one of the first Mysuru-based regional validation demonstrating the effectiveness of serum cystatin C for detecting early diabetic kidney dysfunction prior to evident microalbuminuria in a South Indian diabetic population. In addition, this study adds regional significance by demonstrating that cystatin C performs reliably in an Indian clinical setting, where early detection of DKD remains a major challenge. The findings support the growing need for incorporation of more sensitive biomarkers into regional diabetic screening programs to facilitate earlier diagnosis and intervention before irreversible nephron damage occurs. The results support the inclusion of cystatin C in routine evaluation for early renal dysfunction, particularly in patients with extended duration of diabetes and poor glycemic control.

## CONCLUSION

Serum cystatin C is a sensitive and early indicator of renal impairment in type 2 diabetes mellitus. Elevated cystatin C levels in normoalbuminuric patients highlight the presence of *hidden renal dysfunction* that microalbuminuria alone may not detect.

Routine inclusion of cystatin C estimation could improve early identification and management of diabetic nephropathy, reducing progression to chronic kidney disease.

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