

ORIGINAL ARTICLE

Efficacy of cystatin C for the detection of chronic kidney disease in patients with type 2 diabetes mellitus

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Keywords:

cystatin C; chronic kidney disease; diabetes mellitus, type 2; glomerular filtration rate; creatinine (source: MeSH-NLM).

ABSTRACT

Objective. To evaluate the diagnostic performance of cystatin C for detecting chronic kidney disease in patients with type 2 diabetes mellitus (T2DM), comparing it with serum creatinine, estimated glomerular filtration rate (eGFR), and microalbuminuria. **Methods.** An observational, cross-sectional, analytical study was conducted in 243 patients with T2DM. Renal function was assessed by measuring serum creatinine, cystatin C, eGFR using the CKD-EPI equation, and urinary albumin-to-creatinine ratio in a first-morning urine sample. Chronic kidney disease was defined according to KDIGO criteria, considering eGFR <60 mL/min/1.73 m² or albumin-to-creatinine ratio ≥ 30 mg/g. The diagnostic performance of the biomarkers was evaluated using ROC curves, calculating the area under the curve, sensitivity, specificity, and optimal cutoff point using the Youden index. **Results.** Cystatin C showed the highest diagnostic performance, with an AUC of 0.89, sensitivity of 86%, and specificity of 82%. Microalbuminuria (AUC 0.87) and eGFR (AUC 0.85) showed good performance, whereas creatinine showed moderate performance (AUC 0.78). **Conclusions.** Cystatin C outperformed traditional biomarkers in detecting chronic kidney disease in patients with T2DM, supporting its usefulness as a more sensitive tool for early diagnosis in clinical practice.

Eficacia de la cistatina C para la detección de la enfermedad renal crónica en pacientes con diabetes mellitus tipo 2

Palabras clave:

cistatina C; enfermedad renal crónica; diabetes tipo 2; tasa de filtración glomerular; creatinina (fuente: DeCs-BIREME).

RESUMEN

Objetivo. Evaluar la capacidad diagnóstica de la cistatina C para la detección de enfermedad renal crónica en pacientes con diabetes mellitus tipo 2 (DM2), comparándola con creatinina sérica, tasa de filtración glomerular estimada (TFGe) y microalbuminuria. **Métodos.** Se realizó un estudio observacional, transversal y analítico en 243 pacientes con DM2. La función renal fue evaluada mediante la medición de creatinina sérica, cistatina C, TFGe mediante ecuación CKD-EPI y relación albúmina/creatinina urinaria en muestra de la primera orina de la mañana. La enfermedad renal crónica fue definida de acuerdo con los criterios KDIGO, considerando TFGe <60 mL/min/1.73 m² o relación albúmina/creatinina ≥ 30 mg/g. La capacidad diagnóstica de los biomarcadores fue evaluada mediante curvas ROC, calculando área bajo la curva, sensibilidad, especificidad y punto de corte óptimo mediante índice de Youden. **Resultados.** La cistatina C mostró el mayor rendimiento diagnóstico, con un AUC de 0,89, sensibilidad del 86 % y especificidad del 82 %. La microalbuminuria (AUC 0,87) y la TFGe (AUC 0,85) presentaron buen desempeño, mientras que la creatinina evidenció un rendimiento moderado (AUC 0,78). **Conclusiones.** La cistatina C superó a los biomarcadores tradicionales en la detección de enfermedad renal crónica en pacientes con DM2, lo que respalda su utilidad como herramienta más sensible para el diagnóstico temprano en la práctica clínica.

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INTRODUCTION

Chronic kidney disease (CKD) is one of the most frequent and serious complications of type 2 diabetes mellitus (T2DM) and represents a major cause of morbidity, mortality, and progression to kidney replacement therapy worldwide ⁽¹⁾. Early detection of impaired kidney function in patients with diabetes is essential for implementing therapeutic strategies aimed at delaying disease progression and reducing the associated cardiovascular risk ⁽²⁾.

Traditionally, kidney function has been assessed using serum creatinine, estimated glomerular filtration rate (eGFR), and quantification of albuminuria. However, these markers have important limitations ⁽³⁾. In particular, serum creatinine is influenced by factors such as muscle mass, age, sex, and nutritional status, which reduces its sensitivity for detecting mild reductions in glomerular filtration ⁽⁴⁾. Likewise, albuminuria may be absent in the early stages of kidney damage in type 2 diabetes mellitus (T2DM), and a nonalbuminuric phenotype of diabetic kidney disease has even been described ⁽⁵⁾.

Cystatin C has been proposed as a more sensitive alternative biomarker for assessing kidney function. It is a low-molecular-weight protein produced at a constant rate by all nucleated cells, freely filtered by the glomerulus, and almost completely reabsorbed and catabolized in the proximal tubule, with no significant tubular secretion ⁽⁶⁾. Unlike creatinine, its production is not dependent on muscle mass, diet, or sex, resulting in lower biological variability and greater independence from extrarenal factors ⁽⁷⁾. This characteristic is particularly relevant in patients with T2DM, in whom sarcopenia, protein malnutrition, and alterations in body composition may distort creatinine levels and underestimate the true degree of kidney dysfunction. Similarly, in the nonalbuminuric kidney disease phenotype, which is present in 30%–40% of patients with T2DM, microalbuminuria loses its usefulness as a screening marker; in this setting, cystatin C emerges as a complementary tool with greater diagnostic accuracy ^(8,9).

In this regard, several studies have evaluated the diagnostic performance of cystatin C in patients with T2DM. Sagar et al. ⁽¹⁰⁾ reported that cystatin C showed greater diagnostic accuracy than creatinine for detecting CKD in a cross-sectional study of patients with diabetes, with a higher AUC for cystatin C. Similarly, Pottel et al. ⁽⁹⁾ highlighted the usefulness

of cystatin C for estimating glomerular filtration in populations with specific metabolic characteristics. However, evidence from Latin American populations remains limited, given that factors such as body composition, ethnicity, and socioeconomic and healthcare conditions may influence the behavior of kidney biomarkers, thereby supporting the need for studies in these settings.

Although cystatin C testing is more costly than serum creatinine measurement, its greater ability to detect kidney impairment at early stages could translate into long-term clinical and economic benefits. Within the Ecuadorian healthcare system, late detection of CKD results in high costs associated with hospitalizations, management of cardiovascular complications, and kidney replacement therapy or transplantation, whose economic burden substantially exceeds the cost of a more sensitive biomarker when used strategically in high-risk populations such as patients with T2DM. Therefore, evaluating the diagnostic performance of cystatin C in this population provides not only scientific evidence but also a basis for informed decisions regarding its incorporation into primary care protocols.

The objective of this study was to evaluate the diagnostic performance of cystatin C for detecting chronic kidney disease in patients with T2DM, compared with serum creatinine, estimated glomerular filtration rate, and microalbuminuria.

METHODS

Study design and area

An observational, cross-sectional, analytical study was conducted at the “Dr. Efrén Jurado López” Day Hospital in Guayaquil, Ecuador. This facility provides care to an affiliated urban population, predominantly of middle socioeconomic status, with a high prevalence of chronic noncommunicable diseases, including type 2 diabetes mellitus (T2DM). The patients included represented the usual caseload of endocrinologic and metabolic follow-up at the center during the study period, in whom biochemical assessment of kidney function was performed as part of routine clinical monitoring.

The study was conducted within an ongoing process of clinical and biochemical data collection in patients with T2DM. Accordingly, the period from October 2022 to January 2024 was considered, during

which complete and standardized information was available for all variables of interest. The study was conducted and reported in accordance with the STARD (Standards for Reporting Diagnostic Accuracy Studies) guidelines.

Population and sample

The study population consisted of patients diagnosed with T2DM. Sample size was calculated using a 95% confidence level, an expected prevalence of chronic kidney disease among patients with T2DM of 30%, and a maximum allowable error of 5%. The formula for infinite populations was used ($Z = 1.96$, $p = 0.30$, and $d = 0.05$). The minimum required sample size was 203 participants. However, all patients who met the eligibility criteria during the study period were ultimately included, for a total of 243 participants, exceeding the minimum required sample size and thereby increasing statistical power and the precision of the estimates.

Patients of both sexes, aged >18 years, with a confirmed clinical diagnosis of T2DM according to American Diabetes Association (ADA) criteria ⁽¹¹⁾, and with a complete biochemical assessment of kidney function, including serum cystatin C, creatinine, microalbuminuria, and metabolic parameters allowing calculation of eGFR using the CKD-EPI equation, were included. Patients with acute kidney injury, severe infectious diseases, active autoimmune disorders, neoplasms, pregnancy, immunosuppressive treatment, or any condition that could alter cystatin C levels or kidney function independently of T2DM were excluded, as were patients with incomplete clinical or biochemical information.

Variables and data collection instruments

Demographic, clinical, anthropometric, and biochemical variables were recorded. Demographic variables included age and sex. Clinical variables included duration of T2DM, body mass index (BMI), and blood pressure.

Biochemical variables included fasting glucose, glycated hemoglobin (HbA1c), serum creatinine, cystatin C, and urinary albumin-to-creatinine ratio (UACR) measured in a first-morning urine sample. Serum creatinine was used to estimate glomerular filtration rate (eGFR) using the CKD-EPI equation.

Kidney function was assessed using eGFR, serum cystatin C levels, and the presence of albuminuria. Chronic kidney disease was defined according to the

Kidney Disease: Improving Global Outcomes (KDIGO) guideline criteria, considering kidney damage to be present when eGFR was <60 mL/min/1.73 m² or the albumin-to-creatinine ratio was ≥30 mg/g.

For the analysis of diagnostic performance, cystatin C, serum creatinine, eGFR, and microalbuminuria were evaluated using receiver operating characteristic (ROC) curves, with calculation of the area under the curve, sensitivity, specificity, and optimal cutoff value.

Data collection techniques and procedures

Data were collected using a form specifically designed for the study, in which the demographic, clinical, and biochemical variables of the included patients were recorded. The collected data were organized in an electronic database for subsequent processing and statistical analysis.

Sample collection and determination of biochemical parameters

Venous blood samples were obtained after an 8- to 12-hour fasting period by antecubital venipuncture using standard biosafety procedures. Serum was obtained by centrifugation and stored at -20 °C until processing in automated analyzers calibrated with validated commercial reagents and internal quality controls.

Serum cystatin C was measured using an automated immunoturbidimetric method. Serum creatinine was measured using a kinetic enzymatic method traceable to international reference standards. Plasma glucose was quantified using the glucose oxidase enzymatic method, and HbA1c was measured by turbidimetric inhibition immunoassay (Tina-quant® Gen. 3, Cobas C501, Roche), certified by IFCC/NGSP.

Microalbuminuria was assessed using the urinary albumin-to-creatinine ratio (UACR) in a first-morning urine sample, with urinary albumin quantified by immunoturbidimetry and urinary creatinine by a standardized enzymatic method. Results were expressed in mg/g and classified according to KDIGO criteria ⁽¹²⁾.

For the analysis of the diagnostic performance of the biomarkers, the presence of chronic kidney disease was defined according to KDIGO guideline criteria, considering kidney damage to be present when the estimated glomerular filtration rate (eGFR) was <60 mL/min/1.73 m² or the urinary albumin-to-creatinine ratio was ≥30 mg/g. This combined

definition allowed the diagnostic performance of the biomarkers analyzed to be assessed independently, avoiding bias derived from the use of a single parameter as the reference standard, particularly when comparing markers related to the estimation of glomerular filtration rate ⁽¹³⁾.

Based on serum creatinine, age, and sex, the estimated glomerular filtration rate (eGFR) was calculated using the 2021 CKD-EPI equation ⁽¹³⁾, which estimates glomerular filtration from serum creatinine, age, and sex without incorporating a race correction factor, thereby promoting greater diagnostic equity. Values were expressed in mL/min/1.73 m² and categorized according to KDIGO guidelines into six stages of kidney function: G1 (normal or high, ≥90), G2 (mildly decreased, 60–89), G3a (mildly to moderately decreased, 45–59), G3b (moderately to severely decreased, 30–44), G4 (severely decreased, 15–29), and G5 (kidney failure, <15).

$$eGFR = 142 \times \min(SCr/\kappa, 1)^{\alpha} \times \max(SCr/\kappa, 1)^{-1.200} \times 0.9938^{\text{age}} \times [1.012 \text{ if female}].$$

Where: SCr = serum creatinine (mg/dL); κ (kappa) = 0.7 for women and 0.9 for men; α (alpha) = −0.329 for women and −0.411 for men; min/max = the minimum or maximum value of SCr/ κ and 1.

All analytical procedures were performed in accordance with the internal and external quality control standards of the institutional laboratory, thereby ensuring the reliability and reproducibility of the results used for the statistical analysis of the study.

Data analysis

Data were processed using SPSS version 25.0. The normality of quantitative variables was assessed using the Kolmogorov–Smirnov test. Continuous variables were expressed as mean ± standard deviation, whereas categorical variables were presented as absolute frequencies and percentages.

For comparisons of means between two independent groups, Student's t test was used, whereas one-way analysis of variance (ANOVA) was applied for comparisons involving more than two groups. Categorical variables were compared using Pearson's chi-square test.

The diagnostic performance of cystatin C, serum creatinine, eGFR, and microalbuminuria for detecting chronic kidney disease was evaluated using receiver

operating characteristic (ROC) curves. The area under the curve (AUC), sensitivity, specificity, and optimal cutoff value based on the Youden index were calculated. A p value < 0.05 was considered statistically significant.

Ethical considerations

The study protocol was approved by the Research Ethics Committee of the "Dr. Efrén Jurado López" Day Hospital (Minutes No. 020-2021) and by the Bioethics Committee of the Doctoral Program in Health Sciences of the Faculty of Medicine, University of Zulia.



RESULTS

A total of 243 patients diagnosed with T2DM were studied and classified into two groups according to the presence of kidney damage. The group without kidney damage consisted of 145 patients, whereas 98 patients had impaired kidney function.

Patients with kidney damage were older, had a longer duration of diabetes, higher BMI, higher serum glucose and glycated hemoglobin levels, significantly higher concentrations of creatinine, cystatin C, and microalbuminuria, and significantly lower eGFR values ($p < 0.05$ for all comparisons), as assessed using Student's t test.

Regarding categorical variables, male sex, arterial hypertension, and obesity were significantly more frequent in the group with kidney damage than in the group without kidney damage. These comparisons were performed using the chi-square test. The results are shown in Table 1.

Kidney function parameters according to chronic kidney disease stage

Patients were subsequently classified according to kidney function stages based on eGFR. One-way ANOVA showed significant differences across stages in cystatin C, creatinine, microalbuminuria, glycated hemoglobin, and duration of diabetes ($p < 0.05$).

A progressive increase in cystatin C and creatinine levels was observed as eGFR decreased, accompanied by increases in microalbuminuria and duration of disease. These findings demonstrate a direct relationship between worsening kidney function and

Table 1. General characteristics of patients with type 2 diabetes mellitus according to the presence of kidney damage

Variable	Without kidney damage (n = 145)	With kidney damage (n = 98)	p
Age (years)	56.2 ± 8.7	62.9 ± 9.4	< 0.001
Male sex, n (%)	58 (40.0 %)	60 (61.22 %)	< 0.001
Arterial hypertension, n (%)	54 (37.2 %)	82 (83.7 %)	< 0.001
Duration of DM (years)	7.1 ± 3.5	11.4 ± 4.2	< 0.001
BMI (kg/m²)	29.4 ± 3.8	31.1 ± 4.1	0.002
Serum glucose (mg/dL)	148 ± 32	176 ± 40	< 0.001
HbA1c (%)	7.4 ± 1.1	8.6 ± 1.3	< 0.001
Creatinine (mg/dL)	0.89 ± 0.18	1.42 ± 0.36	< 0.001
Cystatin C (mg/L)	0.92 ± 0.21	1.68 ± 0.39	< 0.001
eGFR (mL/min/1.73 m²)	88.5 ± 14.2	54.3 ± 12.6	< 0.001
Microalbuminuria (mg/g)	18 ± 9	146 ± 82	< 0.001
Obesity, n (%)	49 (33.8 %)	61 (62.2 %)	< 0.001

* Data are presented as mean ± standard deviation or absolute frequencies and percentages. BMI: body mass index; DM: diabetes mellitus; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate. Student's *t* test was used for continuous variables and the chi-square test for categorical variables. Clinical variables such as obesity, arterial hypertension, and other comorbidities represent the proportion of patients with each condition within each group; therefore, their frequencies are not additive to the total sample size.

increases in the biochemical markers evaluated. The data are presented in Table 2.

(95% CI: 0.82–0.95), sensitivity of 86%, and specificity of 82%, indicating high diagnostic performance.

Diagnostic performance of cystatin C for detecting kidney damage

To evaluate the diagnostic performance of the biomarkers for detecting CKD in patients with T2DM, ROC curves were constructed using the KDIGO definition of CKD as the reference criterion, considering the presence of eGFR <60 mL/min/1.73 m² or an albumin-to-creatinine ratio ≥30 mg/g.

The analysis showed that cystatin C had the greatest discriminatory ability for detecting chronic kidney disease, with an area under the curve (AUC) of 0.89

Microalbuminuria also showed good diagnostic performance, with an AUC of 0.87 (95% CI: 0.79–0.93), followed by estimated glomerular filtration rate, with an AUC of 0.85 (95% CI: 0.77–0.92).

Serum creatinine showed lower discriminatory ability, with an AUC of 0.78 (95% CI: 0.69–0.86), suggesting moderate diagnostic performance compared with the other biomarkers.

These results indicate that cystatin C has greater accuracy for detecting chronic kidney disease in

Table 2. Kidney function parameters according to chronic kidney disease stage

Variable	Stage 1 (n = 80)	Stage 2 (n = 65)	Stage 3 (n = 70)	Stage 4 (n = 28)	p*
Creatinine (mg/dL)	0.82 ± 0.12	1.01 ± 0.18	1.62 ± 0.34	2.41 ± 0.48	0.010
Cystatin C (mg/L)	0.88 ± 0.10	1.05 ± 0.14	1.78 ± 0.32	2.74 ± 0.41	0.001
eGFR (mL/min/1.73 m²)	98.4 ± 8.6	71.2 ± 7.4	44.6 ± 8.1	22.3 ± 4.9	0.001
Microalbuminuria (mg/g)	14.6 ± 5.2	26.8 ± 9.4	118.5 ± 64.3	286.7 ± 95.2	0.001
HbA1c (%)	7.2 ± 0.7	7.8 ± 0.9	8.7 ± 1.1	9.4 ± 1.3	0.02
Duration of DM (years)	5.1 ± 3.2	7.4 ± 3.8	11.8 ± 4.6	16.2 ± 5.1	0.001
Hypertension (%)	32 %	48 %	71 %	86 %	0.001

** Data are presented as mean ± standard deviation. DM: diabetes mellitus; HbA1c: glycated hemoglobin; eGFR: estimated glomerular filtration rate.
* Analysis of variance (ANOVA). Serum creatinine values at each stage should be interpreted in the context of patients' sex, age, and body composition, variables incorporated into the 2021 CKD-EPI equation. In patients with long-standing diabetes and low muscle mass, serum creatinine may underestimate the degree of kidney impairment. The mean eGFR in stage G4 (22.3 ± 4.9 mL/min/1.73 m²) confirms the appropriate classification of patients in this stage.

Table 3. ROC curve analysis of biomarkers for detecting chronic kidney disease in patients with T2DM

Variable	AUC (95% CI)	Cutoff value	Sensitivity (%)	Specificity (%)	Youden index
Cystatin C	0.89 (0.82-0.95)	≥ 1.15 mg/L	86	82	0.68
Serum creatinine	0.78 (0.69-0.86)	≥ 1.20 mg/dL	72	75	0.47
eGFR (CKD-EPI)	0.85 (0.77-0.92)	≤ 62 mL/min/1.73 m ²	80	78	0.58
Microalbuminuria (UACR)	0.87 (0.79-0.93)	≥ 30 mg/g	83	80	0.63

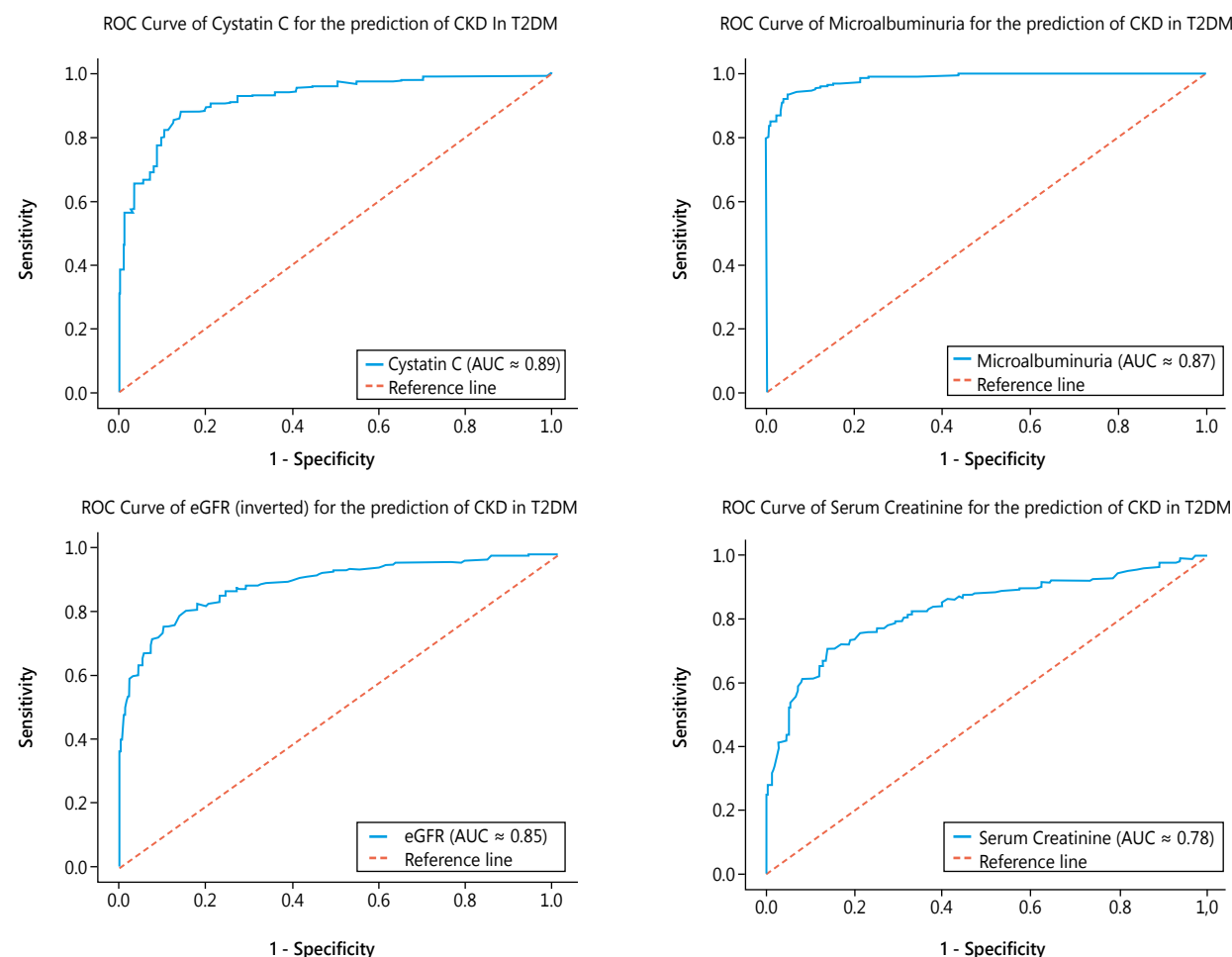
* Chronic kidney disease was defined according to KDIGO criteria (eGFR <60 mL/min/1.73 m² and/or UACR ≥ 30 mg/g).

patients with T2DM, particularly in the early stages of kidney function impairment (Table 3).

ROC curve analysis

ROC curves were constructed to evaluate the diagnostic performance of cystatin C, serum creatinine, eGFR, and microalbuminuria for detecting CKD, using the combined KDIGO criteria as the reference standard.

The curve corresponding to cystatin C was located closest to the upper-left corner, reflecting greater diagnostic accuracy. Microalbuminuria showed a similar pattern, whereas eGFR demonstrated adequate discriminatory ability. The serum creatinine curve was closer to the diagonal reference line, indicating lower ability to discriminate the presence of kidney damage (Figure 1).



* Chronic kidney disease was defined according to KDIGO criteria, using eGFR <60 mL/min/1.73 m² and/or UACR ≥ 30 mg/g as the reference standard.

Figure 1. ROC curve analysis of cystatin C (A), urinary albumin-to-creatinine ratio (B), estimated glomerular filtration rate calculated using CKD-EPI (C), and serum creatinine (D) for detecting chronic kidney disease in patients with type 2 diabetes mellitus.

DISCUSSION

The results of the present study demonstrate that cystatin C has greater discriminatory ability for detecting CKD in patients with T2DM compared with traditional biomarkers such as serum creatinine, eGFR, and microalbuminuria. These findings highlight the usefulness of cystatin C as a more sensitive marker for the early identification of kidney function impairment in populations at high metabolic risk, particularly in patients with long-standing diabetes and suboptimal glycemic control ⁽¹⁰⁾.

In the comparison between patients with and without kidney damage, significant differences were observed in clinical and metabolic variables, including age, duration of diabetes, body mass index, glycemic control, and levels of kidney biomarkers. Likewise, male sex was significantly more frequent in the group with kidney damage than in the group without kidney damage, a finding consistent with the available evidence on sexual dimorphism in diabetic kidney disease. Previous studies have indicated that male sex is associated with greater susceptibility to the progression of kidney damage in patients with T2DM, partly attributed to differences in sex hormone profiles and inflammatory or metabolic mechanisms at the renal level. In particular, loss of glomerular filtration has been reported to occur more rapidly in men, and albuminuria appears to have greater predictive value for kidney disease progression in men than in women with diabetic kidney disease ⁽¹⁴⁾.

Although the cross-sectional design of the present study does not allow causal relationships to be established, this finding may reflect the pathophysiological patterns described in the literature and warrants further investigation in longitudinal studies in the Ecuadorian population. Overall, these results are consistent with the known pathophysiology of diabetic kidney disease, in which prolonged exposure to hyperglycemia, insulin resistance, arterial hypertension, and obesity contribute to progressive glomerular and renal interstitial damage. The significantly higher cystatin C levels observed in the group with impaired kidney function suggest that this biomarker may detect functional changes at earlier stages than serum creatinine, as previously described in recent clinical studies ^(15–17).

Analysis according to kidney disease stage showed a progressive increase in cystatin C levels as glomerular filtration rate decreased, accompanied by increases

in serum creatinine and albuminuria. This pattern confirms the close relationship between serum cystatin C concentration and reduced glomerular filtration and is consistent with reports indicating that this biomarker has lower biological variability and is less influenced by nonrenal factors than creatinine, thereby improving the accuracy of kidney function assessment, particularly in patients with T2DM, in whom muscle mass may be altered ⁽¹⁸⁾.

In the ROC curve analysis, cystatin C showed the highest area under the curve, with adequate sensitivity and specificity for detecting chronic kidney disease, outperforming serum creatinine and showing diagnostic performance comparable to or slightly better than that of microalbuminuria and eGFR. For this analysis, kidney disease was defined using combined KDIGO criteria, considering the presence of reduced glomerular filtration or albuminuria. This approach allowed the diagnostic performance of each biomarker to be assessed independently and reduced bias arising from the use of a single parameter as the reference standard. This methodological approach is particularly relevant when comparing markers closely related to the estimation of glomerular filtration rate.

The optimal cystatin C cutoff identified in this study was ≥ 1.15 mg/L, which falls within the range reported in international studies of patients with T2DM, where thresholds between 1.10 and 1.22 mg/L have been described depending on the population evaluated ⁽¹⁰⁾. This agreement suggests that the cutoff obtained may not be exclusive to the population of Guayaquil and could have broader applicability in Latin American settings with similar clinical characteristics. Nevertheless, because cystatin C levels may be influenced by factors such as age, sex, body weight, and thyroid status, prospective validation in other populations in the region is recommended before definitive diagnostic thresholds are established.

The lower discriminatory ability observed for serum creatinine is consistent with current evidence describing it as a late marker of kidney dysfunction because of its dependence on muscle mass, age, sex, and nutritional status. In patients with T2DM, these factors may vary considerably, limiting the sensitivity of creatinine for detecting mild reductions in glomerular filtration ⁽¹⁹⁾. In contrast, cystatin C is produced at a constant rate by all nucleated cells and is eliminated almost exclusively through glomerular filtration, without significant tubular secretion, making it a more stable and potentially more accurate marker for assessing kidney function ^(6,7).

Regarding microalbuminuria, although it showed good diagnostic performance, its discriminatory ability was slightly lower than that of cystatin C. This finding may be explained by the phenotypic heterogeneity of kidney disease in T2DM, in which nonalbuminuric forms of kidney dysfunction have been described^(20,21). In this regard, recent studies have shown that a considerable proportion of patients with reduced glomerular filtration do not have elevated albuminuria, limiting its usefulness as a standalone marker for the early detection of chronic kidney disease^(22,23).

From a clinical perspective, early identification of kidney dysfunction in patients with T2DM has important implications because it enables the initiation of interventions aimed at optimizing glycemic control, blood pressure management, and kidney protection, with the goal of delaying progression to advanced stages of kidney disease and reducing the associated cardiovascular risk. In this context, incorporating cystatin C as a complementary biomarker could improve risk stratification and contribute to a more accurate assessment of kidney function in clinical practice⁽²⁴⁾.

From the standpoint of clinical applicability, cystatin C also offers relevant diagnostic advantages in specific settings in which traditional markers have known limitations. First, in patients with apparently normal serum creatinine but early kidney dysfunction, a common situation in individuals with low muscle mass, older adults, women, or patients with malnutrition associated with long-standing T2DM, cystatin C may detect reductions in glomerular filtration that are not identified by creatinine, a phenomenon known as the "creatinine-blind range"^(25,26). Second, in the nonalbuminuric CKD phenotype, which has been described in an increasing proportion of patients with T2DM⁽²⁷⁾, microalbuminuria loses sensitivity as a screening marker, and cystatin C emerges as an alternative with greater diagnostic utility in this setting.

Regarding its implementation in Latin American healthcare systems, although cystatin C testing is more costly than serum creatinine measurement, its greater accuracy in the early stages of CKD could translate into long-term economic benefits through reductions in cardiovascular complications and hospitalizations, as well as delayed initiation of kidney replacement therapy⁽²⁸⁾. However, formal evidence regarding the cost-effectiveness of cystatin C in the

region remains limited and represents a priority for future research to support its incorporation into local clinical practice guidelines.

Nevertheless, the present study has several limitations that should be considered. Nonprobability convenience sampling represents a limitation because it may introduce selection bias and restrict the generalizability of the findings to populations with clinical and sociodemographic characteristics similar to those of the study population. These findings should be replicated in studies using probability sampling and conducted at other healthcare centers in the region. In addition, the cross-sectional design does not allow causal relationships to be established or kidney disease progression to be assessed over time. Furthermore, kidney function was estimated using creatinine-based equations rather than direct measurement of glomerular filtration rate, which may have introduced some degree of misclassification. Likewise, the study population consisted of patients treated at a single center, which may limit the generalizability of the results. Therefore, prospective multicenter studies are needed to evaluate the predictive value of cystatin C for the progression of diabetic kidney disease and its usefulness in models combining it with other emerging biomarkers.

From a methodological perspective, the use of CKD-EPI eGFR as a component of the reference standard for defining CKD, while simultaneously evaluating it as a diagnostic test, introduces incorporation bias that may artificially overestimate the diagnostic performance of creatinine and eGFR. This limitation is inherent to the study design and the clinical setting in which it was conducted, where direct measurement of glomerular filtration rate was not available. The diagnostic performance estimates for cystatin C and microalbuminuria are not affected by this bias because these biomarkers are independent of the reference standard used.

Conclusions

Cystatin C showed greater diagnostic performance than serum creatinine for detecting chronic kidney disease in patients with T2DM, with high sensitivity and specificity in ROC curve analysis based on KDIGO criteria. Microalbuminuria and estimated glomerular filtration rate also showed good diagnostic performance; however, cystatin C identified kidney function impairment with greater accuracy, particularly at earlier stages.

These findings suggest that incorporating cystatin C as a complementary biomarker could improve the early detection of kidney disease in patients with diabetes and thereby contribute to better kidney risk stratification. Nevertheless, prospective multicenter studies are needed to evaluate its usefulness in predicting the progression of diabetic kidney disease.

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Authorship contribution

EGP-P: results analysis, discussion, final review of the manuscript, supervision, funding acquisition, investigation, project administration, resources, software, conceptualization, methodology, data curation, and writing – original draft.

SB-A: results analysis, discussion, final review of the manuscript, supervision, funding acquisition, investigation, project administration, resources, software, conceptualization, methodology, data curation, and writing – original draft.

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Conflict of interest statement

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