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CONTENTS OF THE JOURNAL

CYSTATIN C AS AN EARLY MARKER OF RENAL DYSFUNCTION IN PATIENTS WITH CHRONIC KIDNEY DISEASE STAGES 1–2

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Abstract. *Chronic kidney disease (CKD) is a prevalent condition characterized by an asymptomatic early course and a high risk of cardiovascular complications. Early detection remains challenging, as traditional markers such as serum creatinine have limited sensitivity in the initial stages.*

This study aimed to evaluate the clinical and laboratory characteristics of patients with CKD stages 1–2 and to assess the diagnostic value of cystatin C as an early biomarker of renal dysfunction. A total of 88 patients were divided into stage 1 (n = 53) and stage 2 (n = 35) groups. Comprehensive clinical and laboratory assessments were performed.

Patients with CKD stage 2 were older and had a longer disease duration. While creatinine levels were moderately elevated, the most significant differences were observed in cystatin C levels ($p < 0.001$). ROC analysis demonstrated high diagnostic accuracy of cystatin C (AUC = 0.89), with a cut-off value of ≥18.0 mg/L providing 84.6% sensitivity and 81.1% specificity.

Cystatin C is a sensitive and specific marker for early renal dysfunction and may improve early diagnosis and management of CKD.

Keywords: *Chronic kidney disease; cystatin C.*

Introduction. Diabetes mellitus type 2 is a prevalent metabolic disorder characterized by chronic hyperglycemia, resulting from either inadequate insulin secretion or insulin resistance [28].This condition significantly increases the risk of developing microvascular complications, including diabetic kidney disease, which is a leading cause of chronic kidney disease and end-stage renal failure [14].Traditional markers such as serum creatinine often fail to detect early renal dysfunction, as their levels only rise significantly after a substantial loss of renal function [41]. Consequently, identifying more sensitive and early biomarkers for renal impairment in diabetic patients is crucial for timely intervention and improved patient outcomes [39]. In this context, cystatin C has emerged as a promising candidate due to its consistent production rate, independence from muscle mass and age, and its effective filtration by the glomeruli with subsequent reabsorption and catabolism by the proximal tubules, making its serum levels a reliable indicator of glomerular filtration rate [2]. Unlike creatinine, cystatin C levels are unaffected by inflammatory processes, nutritional status, or dietary factors, further enhancing its reliability as a marker for subtle changes in renal function [30]. Prompt identification of renal damage in diabetic patients is paramount for mitigating adverse outcomes, thus necessitating potent markers for staging and monitoring the progression of diabetic nephropathy [35]. This clinical imperative underscores the utility of cystatin C as an early screening tool for assessing incipient renal failure in individuals with Type 2 Diabetes Mellitus [7]. Specifically, elevated serum cystatin C levels have been correlated with an increased risk of both cardiovascular disease and chronic kidney disease, often indicating preclinical renal impairment associated with adverse outcomes [29]. Moreover, studies have indicated that urinary cystatin C can serve as an early predictor of tubular damage even before the onset of albuminuria, highlighting its potential utility in detecting subclinical renal injury [11]. In patients with Type 2 Diabetes Mellitus, increased serum cystatin C concentrations have been observed even in the absence of microalbuminuria, indicating its superior diagnostic accuracy for early nephropathy compared to serum creatinine [15]. This enhanced sensitivity underscores cystatin C's potential as a superior

biomarker for detecting subtle declines in renal function, even before conventional markers like microalbuminuria become evident [16]. Its consistent production and independence from muscle mass make it an ideal marker for endogenous glomerular filtration rate, providing a more sensitive parameter than serum creatinine for assessing renal function [41]. This enhanced accuracy is particularly beneficial in populations with varying muscle mass, such as those with sarcopenia or diabetes, where creatinine-based estimations may be less reliable [4]. The consistent expression of cystatin C across most bodily tissues and its complete reabsorption and catabolism within proximal tubules further support its role as a more precise indicator of glomerular filtration rate, especially in the initial stages of kidney dysfunction [35]. Moreover, its low molecular weight of 13 kDa allows for free filtration by the renal glomeruli, making it a sensitive indicator of subtle changes in glomerular function [5].

This makes it a valuable tool for early diagnosis and prognostication of renal impairment, particularly in conditions like diabetic nephropathy where early detection is critical for effective management [5]. Indeed, the superior predictive capacity of cystatin C-based estimated glomerular filtration rate (eGFR) equations over creatinine-based equations for identifying individuals at risk of end-stage renal disease further supports its clinical utility [19]. The utility of cystatin C in discerning early renal dysfunction is rooted in its inherent physiological characteristics, distinguishing it from traditional markers like creatinine [8]. Specifically, cystatin C's concentration is unaffected by factors such as age, gender, muscle mass, diet, liver diseases, or inflammation, which can significantly influence serum creatinine levels [10]. This makes cystatin C a more reliable biomarker for assessing kidney function in diverse patient populations, particularly in those with early-stage chronic kidney disease, where creatinine-based estimations may still fall within the normal range [24]. Therefore, cystatin C provides a more accurate and consistent measure of glomerular filtration rate in comparison to serum creatinine, especially in detecting early impairments in renal function [7]. This advantage is crucial for identifying subtle reductions in glomerular filtration levels that creatinine often misses [3]. Several studies corroborate cystatin C's superior correlation with estimated glomerular filtration rate (eGFR) compared to creatinine, particularly in the early stages of CKD and in high-risk groups such as diabetic patients [34]. This enhanced accuracy positions cystatin C as a valuable biomarker for improved risk stratification and monitoring of renal function, particularly in susceptible populations where early intervention can significantly alter disease progression [13]. The stable generation of cystatin C in the body, coupled with its unhindered filtration and subsequent reabsorption in the proximal tubules, positions it as an acceptable endogenous measure of GFR, uninfluenced by factors that confound creatinine assessments [36]. Consequently, integrating cystatin C into clinical practice could lead to earlier detection of compromised renal function, thereby facilitating timely therapeutic interventions and potentially slowing the progression of chronic kidney disease [28]. This enhanced diagnostic capability extends to scenarios where creatinine values may be misleading due to sarcopenia, malnutrition, or acute fluctuations in muscle mass, providing a more robust assessment of renal health [12]. The Kidney Disease: Improving Global Outcomes guidelines also endorse the use of cystatin C-based equations for a more precise estimation of GFR, especially when accurate GFR is crucial for confirming a diagnosis of CKD or adjusting drug dosages [20]. This is further supported by research demonstrating that incorporating cystatin C alongside serum creatinine in GFR estimation equations significantly improves accuracy, particularly in identifying individuals at risk for adverse renal outcomes [17]. In fact, the CKD-EPI creatinine-cystatin C equation has demonstrated superior reliability in estimating GFR compared to equations utilizing creatinine alone [42]. This combined approach offers a more robust assessment of kidney function, particularly in cases where isolated creatinine measurements may not fully capture the extent of renal impairment [26]. Indeed, combining cystatin C with traditional CKD markers, such as eGFRcreatinine and urinary albumin/creatinine ratio, has been shown to improve risk classification and provide a more comprehensive assessment of kidney function [43]. Moreover, the assessment of cystatin C levels has

been shown to improve risk stratification for future cardiovascular disease and mortality, particularly in individuals with estimated GFR (eGFR) greater than or equal to 45 mL/min/1.73 m2 [23]. This underscores the multifaceted utility of cystatin C not only for identifying renal dysfunction but also for refining prognostic assessments across various clinical outcomes [40]. The superior diagnostic and prognostic capabilities of cystatin C-based glomerular filtration rate estimation over creatinine-based methods have been consistently demonstrated across diverse patient cohorts [33]. This has led to calls for expanding the Kidney Disease: Improving Global Outcomes guidelines to incorporate cystatin C measurements alongside creatinine, at least for initial and follow-up patient evaluations, to improve early detection and management of kidney diseases [1]. This expanded application is especially pertinent given cystatin C's demonstrated independence from variables like age, sex, and muscle mass, making it a universally applicable biomarker for renal function [32]. Studies have shown that combining cystatin C with creatinine in eGFR equations, such as the CKD-EPI equation, significantly enhances the accuracy of GFR estimation, outperforming equations based solely on either biomarker [18]. This superior accuracy extends to detecting rapid decline in renal function, where cystatin C-based eGFR proves more sensitive than creatinine eGFR [26]. This heightened sensitivity allows for earlier detection of subtle changes in kidney function, which is critical for timely intervention strategies in progressive renal diseases. Furthermore, cystatin C-based eGFR is increasingly recognized for its utility in cardiovascular risk assessment, demonstrating a stronger association with cardiovascular disease and mortality than creatinine-based measures [23].

Aim of the study. To evaluate the clinical and laboratory characteristics of patients with chronic kidney disease stages 1–2, with a focus on the diagnostic significance of cystatin C as an early marker of renal dysfunction.

Materials and Methods. The study included 88 patients with chronic kidney disease (CKD), who were divided into two groups according to disease stage: CKD stage 1 (n = 53) and CKD stage 2 (n = 35). All patients underwent a comprehensive clinical and laboratory examination.

Parameters of nitrogen metabolism (urea, creatinine, cystatin C), carbohydrate and lipid metabolism, hemodynamic parameters, and hemostatic system indicators were assessed. The results are presented as mean ± standard error of the mean (M ± m). Statistical significance of differences between groups was evaluated at a level of $p < 0.05$.

Results.

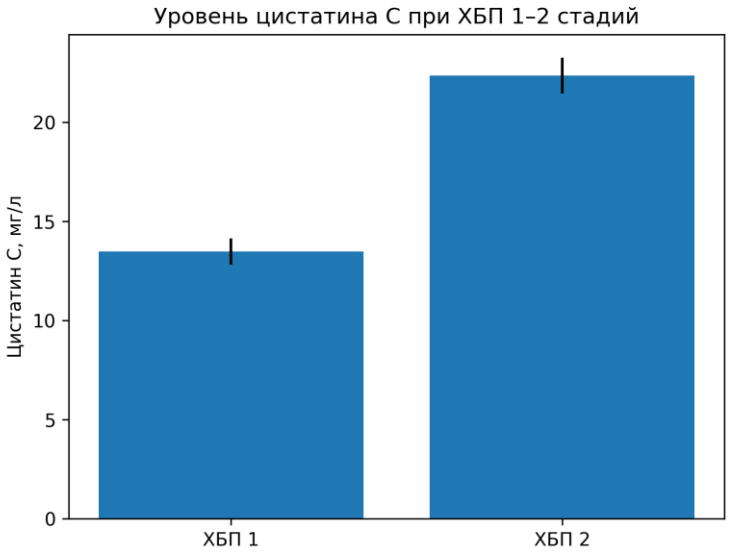
Table 1.

Clinical and Laboratory Characteristics of Patients with Stage 1 and Stage 2 Chronic Kidney Disease

Parameter	CHKD 1 (n=53)	CHKD 2 (n=35)	p
Age, years	49,76 ± 1,76	59,7 ± 2,04	0,001
Disease duration, years	3,18 ± 0,51	5,47 ± 0,64	0,004
Creatinine, mmol/L	64,6 ± 2,18	80,8 ± 2,57	<0,001
Urea, mmol/L	5,37 ± 0,22	6,06 ± 0,22	0,06
Cystatin C, ng/ml	**13,47 ± 0,66**	**22,35 ± 0,91**	**<0,001**
HbA1c, %	8,9 ± 0,42	8,17 ± 0,44	0,24
Total cholesterol, mmol/L	4,89 ± 0,29	6,15 ± 0,31	0,002
Triglycerides, mmol/L	1,84 ± 0,10	1,99 ± 0,12	0,31
Systolic blood pressure (SBP), mmHg	126,7 ± 2,12	128,0 ± 4,17	0,74
Diastolic blood pressure (DBP), mmHg	82,16 ± 0,92	81,0 ± 1,77	0,59
Heart rate (HR), beats/min	82,1 ± 1,38	76,6 ± 2,1	0,08

ROC analysis demonstrating the diagnostic performance of cystatin C for distinguishing CKD stage 2 from stage 1.

Parameter	Value
AUC (95% CI)	0,89 (0,82–0,96)
Optimal cut-off, mg/L	≥ 18,0
Sensitivity, %	84,6
Specificity, %	81,1
p	< 0,001



Discussion. The present study demonstrates that clinically significant alterations in laboratory parameters reflecting early renal dysfunction are already detectable in the initial stages of CKD [40,41]. The most prominent differences between CKD stages 1 and 2 were observed in cystatin C levels, confirming its high sensitivity in detecting subclinical impairment of renal function [3,10,35].

ROC analysis revealed excellent diagnostic performance of cystatin C (AUC = 0.89), indicating its strong ability to discriminate between early stages of CKD. The identified cut-off value (≥18.0 mg/L) provided high sensitivity and specificity, which is consistent with previous studies highlighting the superior diagnostic accuracy of cystatin C in early renal impairment [12,13,32].

In contrast, serum creatinine showed only moderate changes between groups, despite statistically significant differences. This observation reflects the well-known limitations of creatinine as an early biomarker, since its concentration is influenced by multiple extrarenal factors and does not adequately reflect early reductions in GFR [9,32,41]. As a result, creatinine levels may remain within normal limits even in the presence of early renal dysfunction.

Importantly, increased cystatin C levels in CKD stage 2 were observed despite minimal changes in urea and only moderate increases in creatinine, further supporting its role as an early indicator of glomerular dysfunction [5,7,24]. This finding highlights the clinical importance of cystatin C for early detection, allowing timely initiation of nephroprotective interventions.

The association between elevated cystatin C levels, older age, and longer disease duration suggests that this biomarker may also reflect disease progression. These findings are consistent with previous studies demonstrating that cystatin C is an independent predictor of CKD progression, cardiovascular complications, and mortality [22,23,33].

Although metabolic parameters such as HbA1c and triglycerides did not differ significantly between groups, total cholesterol levels were higher in CKD stage 2, indicating a potential role of

dyslipidemia in disease progression [21,22]. However, these parameters did not demonstrate comparable diagnostic value to cystatin C.

From a clinical standpoint, incorporating cystatin C into routine diagnostic practice may significantly improve early detection and risk stratification of CKD, particularly in patients with type 2 diabetes mellitus [1,17,40]. This may facilitate earlier initiation of targeted therapeutic strategies and improve long-term outcomes.

Furthermore, the use of cystatin C in combination with creatinine in GFR estimation equations enhances diagnostic precision and supports more accurate clinical decision-making [12,18,42]. This combined approach is especially valuable in patients with conditions affecting muscle mass or metabolic status.

Despite these findings, certain limitations should be acknowledged. The relatively small sample size and cross-sectional design limit the ability to establish causal relationships. Further large-scale prospective studies are required to confirm these results and to evaluate the prognostic value of cystatin C in CKD progression.

Conclusions:

1. Patients with CKD stage 2 demonstrated a significantly higher level of cystatin C compared to those with CKD stage 1.
2. Measurement of cystatin C is advisable for the early diagnosis and monitoring of CKD progression in stages 1–2.
3. Incorporation of cystatin C into standard diagnostic algorithms may facilitate earlier initiation of nephroprotective therapy.

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