RESEARCH PAPER

Assessing Renal Function In Sickle Cell Disease: A Comparative Analysis Of Cystatin-C, Beta-2 Microglobulin, And NAG

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ABSTRACT

Introduction:

Renal dysfunction is a well-recognized but often underdiagnosed complication of sickle cell disease (SCD). Conventional renal function markers such as serum creatinine and urea may underestimate early kidney injury, necessitating the evaluation of novel biomarkers. So, estimation of serum Cystatin-C and β-2 microglobulin (β2M) and NAG has been proposed as a sensitive alternative in SCD patients

AIM: This study aimed to assess the prevalence of renal dysfunction in SCD and evaluate the diagnostic performance of Cystatin-C and β2M compared to conventional markers.

Materials and Methods:

A cross-sectional study was conducted at Smt. Bhikhiben kanjibhai shah medical institute and research centre, Piparia, Vadodara. Over a period of one year (January 2024 to December 2024) on 200 SCD patients aged 18–35 years. Participants were stratified into two groups: Group 1 (n=177) without renal dysfunction and Group 2 (n=23) with renal dysfunction, based on serum creatinine and Demographic distribution. Biochemical parameters (blood urea, creatinine, uric acid, total protein, albumin, and electrolytes), and novel biomarkers (Cystatin-C and β2M) were analyzed. $P<0.05$ is significant. Correlations between novel and conventional renal markers were assessed using Pearson's correlation coefficient.

Results:

Renal dysfunction was identified in 23 (11.5%) of the cohort, with higher prevalence in males 13 (17.1%) compared to females 10 (8.1%), and greater frequency in the 23–27 years age group (19.4%). Patients with renal impairment exhibited significantly higher levels of blood urea (72.5 ± 51.9 vs. 24.7 ± 8.02 mg/dL, $p<0.001$), serum creatinine (2.13 ± 1.5 vs. 0.67 ± 0.12 mg/dL, $p<0.001$), and uric acid (6.6 ± 1.7 vs. 5.17 ± 0.86 mg/dL, $p<0.001$), along with reduced serum albumin and total protein. Electrolyte disturbances (Na^+, K^+, Cl^-) were also more pronounced in the renal dysfunction group. Cystatin-C levels were markedly elevated in Group 2 (4.40 ± 2.1 vs. 0.78 ± 0.25 mg/L, $p<0.001$) and showed significant correlations with urea ($r=0.416$, $p=0.048$) and creatinine ($r=0.520$, $p=0.011$). In contrast, β2M levels did not differ significantly between groups ($p=0.502$) and showed weak, non-significant correlations with conventional markers, $p< 0.05$ is significant.

Conclusion:

Serum Cystatin-C demonstrated superior sensitivity and significant correlation with conventional renal markers. As per results finding β2M, although biologically relevant, and show less significant predictive value compare to others in this cohort. Incorporating Cystatin-C into routine monitoring of SCD patients may enable earlier intervention, potentially reducing progression to chronic kidney disease.

Keywords: Sickle cell, renal dysfunction, biomarkers, kidney disease, creatinine.

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Introduction

Sickle cell disease (SCD) is one of the most prevalent inherited hemoglobinopathies worldwide, affecting approximately 20–25 million people, with the highest burden in sub-Saharan Africa, India, and the Middle East [1]. It is caused by a single point mutation in the β-globin gene, resulting in the substitution of valine for glutamic acid at the sixth position of the β-globin chain. This alteration produces hemoglobin S (HbS), which polymerizes under hypoxic conditions, leading to red cell sickling, hemolysis, and recurrent vaso-occlusive episodes [2,3]. Over time, chronic hemolysis and vascular dysfunction result in progressive multi-organ complications, including renal involvement, which significantly contributes to morbidity and mortality [4].

The kidney is particularly vulnerable in SCD due to repeated ischemia-reperfusion injury, oxidative stress, and deposition of sickled erythrocytes within the renal microvasculature [5]. Renal abnormalities range from hyposthenuria, hematuria, and tubular dysfunction in childhood to progressive glomerulopathy, proteinuria, and chronic kidney disease (CKD) in adulthood [6,7]. One Studie suggest that up to 30% of adult SCD patients develop CKD, and a significant proportion may progress to end-stage renal disease (ESRD) [8]. Early detection of renal dysfunction is therefore critical for timely intervention and long-term renal preservation.

Traditionally, renal function assessment has relied on serum urea, creatinine. However, these markers have major limitations in SCD. Serum creatinine is influenced by muscle mass, diet, and tubular secretion, making it unreliable in young patients with low muscle bulk and hyperfiltration [9]. Furthermore, renal damage in SCD may begin at the tubular level before glomerular impairment becomes apparent, resulting in delayed recognition if creatinine is used as the sole marker [10]. This has created an urgent need for more sensitive biomarkers capable of detecting subtle and early renal dysfunction in SCD.

Beta-2 microglobulin (β2M) has gained attention in this context. β2M is a low-molecular-weight protein (11.8 kDa) that forms the light chain of class I major histocompatibility complex (MHC-I) molecules expressed on nearly all nucleated cells [11]. It is continuously shed into the bloodstream, freely filtered by the glomerulus, and almost completely reabsorbed and metabolized by proximal tubular cells [12]. Consequently, serum β2M levels reflect both glomerular filtration and tubular reabsorptive function. Elevated levels may therefore indicate impaired GFR, increased cellular turnover, or proximal tubular dysfunction, all of which are highly relevant in the pathophysiology of SCD [13].

In SCD, chronic hemolysis, endothelial activation, and recurrent vaso-occlusion result in heightened inflammatory states and increased β2M release into the circulation [14]. Simultaneously, ischemic tubular injury and microinfarctions impair reabsorption, further elevating β2M levels [15]. Thus, β2M serves not only as a marker of renal dysfunction but also as a reflection of systemic disease activity. Several studies have demonstrated elevated serum β2M in SCD patients with proteinuria, reduced eGFR, or histological evidence of nephropathy, often preceding abnormalities in serum creatinine [16,17].

Cystatin C, a 13-kDa cysteine protease inhibitor produced by all nucleated cells, has emerged as a sensitive endogenous marker of glomerular filtration rate (GFR). Unlike creatinine, serum cystatin C is less affected by age, sex, or muscle mass, making it a potentially more reliable biomarker in populations with altered body composition such as SCD patients

This positions β2M as a potential early warning biomarker capable of unmasking hidden renal dysfunction in SCD patients. Its incorporation into routine renal monitoring could provide clinicians with a more sensitive tool for early detection, risk stratification, and timely intervention, ultimately improving long-term outcomes.

This article explores the emerging role of β2M in SCD-related nephropathy, highlights the limitations of conventional renal function tests, and emphasizes the need for integrating novel biomarkers into clinical practice. By unmasking subtle renal impairment at an earlier stage, β2M may help reshape the management of SCD patients and reduce the burden of CKD and ESRD in this vulnerable population.

Materials and Methods

This cross-sectional study was conducted at Dhiraj General Hospital and SBKS Medical Institute & Research Centre (SBKSMI&RC), Piparia, Vadodara**,** Gujarat, India. Over a period of one year (January 2024 to December 2024). Prior to commencement, ethical clearance was obtained from the Sumandeep Vidyapeeth Institutional Ethics Committee, (approval number: SVIEC/ON/MED1/Ph.D./18014) SBKSMI&RC, and Dhiraj Hospital, Piparia. A total of 200 adult patients (both male and female) with confirmed sickle cell disease (SCD) attending the Medicine Outpatient Department (OPD) were enrolled in the study after obtaining written informed consent**.**

Inclusion and Exclusion Criteria

- **Inclusion:** Newly diagnosed Adult male and female patients with SCD, conformed with Hb electrophoresis, who attended Medicine OPD during the study period.
- **Exclusion:** Patients with pre-existing renal dysfunction or renal failure, history of renal surgery, current

use of nephrotoxic or renal-specific medications, and those with known endocrinopathies.

Sample size: This formula is commonly used for calculating sample size in prevalence studies.

The formula for sample size is: n=4pq/L2

n:The required sample size.

p:The estimated prevalence or proportion of the characteristic in the population.

q; Calculated as $1-p$

L: The allowable error

$n = 4\times15\times85/5^2$

n =5100/25

n =204

Hence, the sample size for cases round figure of 200

So, a total of 200 human subjects were taken in the study.

Sampling Method: Purposive sampling methods & questionnaire.

Data Collection

For all participants, A detailed medical history including demographic details like Age, Sex (male/female), Sickle cell and renal disease history, and clinical features was obtained at Dhiraj General Hospital and SBKSMI&RC, Piparia, Vadodara. A detailed medical history was obtained, and findings of a comprehensive physical examination were documented in a predesigned proforma.

Sample Collection and Laboratory Analysis

Blood Collection: From each participant, 3 mL of fasting venous blood was drawn under strict aseptic precautions.

Biomarker Estimation:

- Serum Cystatin-C (reference range: 0.5-1.6 ugm/ml), Beta-2 Microglobulin (0-2.0 ug/ml) and NAG (0.4-1.7 U/L) were analyzed using enzyme-linked immunosorbent assay (ELISA) immunoassay technique**.** [24].
- Routine renal function tests – including tests and reference range serum urea (15-45mg/dl), creatinine(0.6-1.3mg/dl), uric acid(M:3.6-8.2 mg/dl.F:36.-6.1 mg/dl), and electrolytes Na+(135-145meq/l), K+(3.5-5.0meq/l),Cl-(90-110meq/l) were measured using a fully automated biochemistry analyzer (EM-200, Transasia), and Nulyte smart analyzer. [25].
- **eGFR –** calculation using the CKD-EPI 2021 equation (race-free) for each patient

(Normal: eGFR ≥ 90 mL/min/1.73 m². **Abnormal:** eGFR < 90 mL/min/1.73 m²) [23].

Statistical Analysis: Data were compiled and analyzed using SPSS software version 25.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics were applied for baseline characteristics. Pearson correlation coefficients were performed to evaluate the correlation between biomarkers and conventional renal function parameters; $p< 0.05$ was determined to be statistically significant.

RESUTS

A total of 200 patients with sickle cell disease (SCD) were enrolled in the study. Of these, 177 patients (88.5%) had no evidence of renal dysfunction (Group 1). while 23 patients (11.5%) were diagnosed with renal dysfunction (Group 2). As shown in Table 1, the majority of the study populations were females 120 (60%), with a male-to-female ratio of 1:1.6. Renal dysfunction was slightly more prevalent among males 13 (16.2%) compared to females 10 (8.3%). With respect to age distribution, the majority of subjects belonged to the 18–22 years category (62.5%), followed by 23–27 years (31%). The prevalence of renal dysfunction was higher in the 23–27 years age group (19.4%), indicating an age-related increase in risk.

Table-1. Renal dysfunction found in sickle cell disease patients

Characteristics	Overall Cohort (N=200)	No Renal dysfunction Group 1(N=177)	Renal dysfunction Group 2(N=23)
Gender			
Male	80	67	13
Female	120	110	10
Age categories			
18-22 years	125	115	10
23-27 years	62	50	12
28-35 years	13	12	01

Table 2: Comparison of mean values of biochemical parameters between SCD subjects with and without renal insufficiency.

Variable	No Renal dysfunction (N=177) (Mean±SD)	Renal dysfunction (N=23) (Mean±SD)	p-value
RBS	95.83±16.2	119.3±34.4	<0.001
Blood Urea	24.7±8.02	72.5±51.9	<0.001

Creatinine, mg/dL	0.67±0.12	2.13±1.5	<0.001
Uric acid	5.17±0.86	6.6±1.7	<0.001
Albumin	3.39±0.56	2.98±0.6	<0.001
Na^+	135.0±3.78	138.4±9.1	<0.001
K^+	3.68±0.45	4.34±0.8	<0.001
Cl^-	99.9±3.68	103.6±8.9	<0.001
Total Protein	6.59±0.68	5.60±1.1	<0.001
eGFR	127.33±15.31	66.44±47.38	<0.001

p< 0.05 is significant

Table 2 demonstrates a significant difference in the biochemical parameters between SCD subjects with and without renal dysfunction.

- **Renal function markers** such as blood urea, serum creatinine, and uric acid were markedly elevated in Group 2 compared to Group 1 ($p < 0.001$).
- **Serum albumin and total protein** were significantly reduced in patients with renal dysfunction, reflecting impaired renal synthetic and filtration capacity.
- **Electrolyte imbalances** were also observed: serum sodium (Na^+), potassium (K^+), and chloride (Cl^-) levels were significantly higher in Group 2, suggesting tubular dysfunction and impaired electrolyte handling.
- **Random blood sugar (RBS)** was significantly higher in Group 2, though none of the patients had known diabetes, suggesting a possible stress-related metabolic alteration.
- **eGFR** was significantly reduced in patients with renal dysfunction in Group 2, ($p < 0.001$).

Table 3: Showing Cystatin and β-2 microglobulin and NAG status in SCD subjects with and without renal insufficiency.

Variable	No Renal dysfunction (N=177) (Mean±SD)	Renal dysfunction (N=23) (Mean±SD)	p-value
Cys- C	0.78±0.25	4.40±2.1	<0.001
β-2 M	5.09±5.52	5.88±2.3	0.502
NAG	4.17±1.8	1.13±5.46	<0.001

p< 0.05 is significant

Renal Biomarkers (Cystatin-C , β2M and NAG)

As presented in Table 3**,** serum Cystatin-C levels were significantly elevated in the renal dysfunction group (4.40 ± 2.1) compared to the no dysfunction group (0.78 ± 0.25; $p < 0.001$). This highlights its superior sensitivity in detecting renal impairment compared to conventional markers.

Serum N-acetyl-β-D-glucosaminidase (NAG), a marker of tubular damage, was also significantly higher in Group 2 (4.17 ± 1.8 vs. 1.13 ± 5.46; $p < 0.001$). In contrast, serum β-2 microglobulin (β2M) levels showed no statistically significant difference between groups ($p = 0.502$). This suggests that, although β2M may reflect disease activity, it might be less sensitive for detecting renal dysfunction compared to Cystatin-C and NAG in SCD patients.

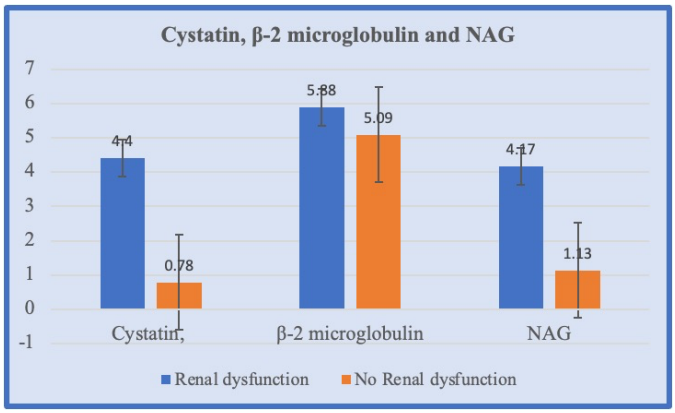


Table 4: Correlations of Urea, uric acid and creatinine with markers of renal insufficiency.

Sr. No.	Variables		Urea	Uric Acid	Creatinine
1	Cystatin-C	*r*	.416*	.272	.520*
		p	.048	.210	.011
2	β-2 microglobulin	*r*	.287	.177	.379
		p	.184	.419	.075
3	NAG	*r*	.649*	.367	.744**
		p	<.001	.085	<.0001

p< 0.05 is significant

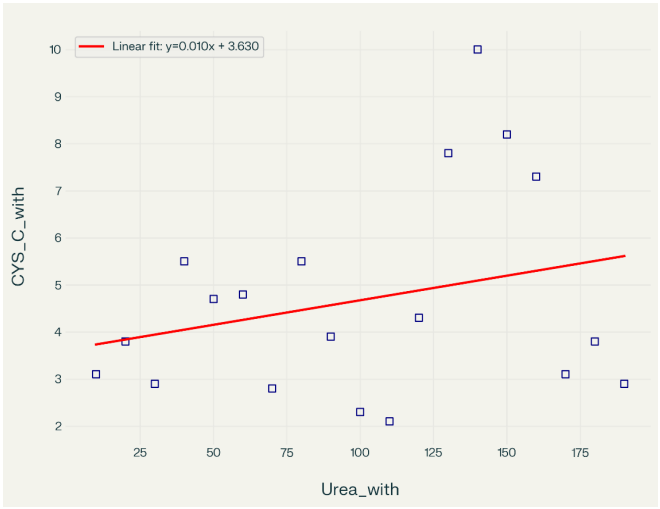
Correlation Analysis

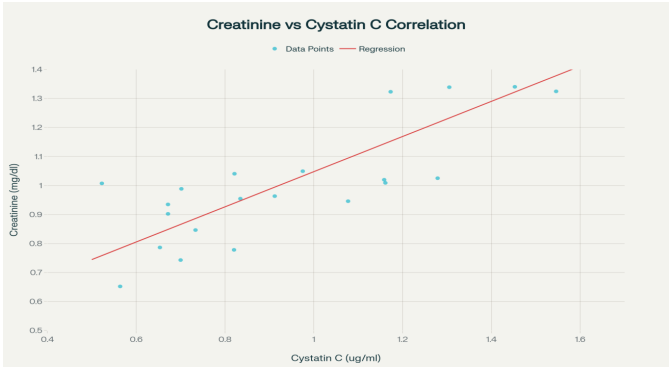
The relationship between conventional renal function parameters and novel biomarkers is summarized in Table 4**.**

- **Cystatin-C** showed significant positive correlations with serum urea ($r = 0.416$, $p = 0.048$) and creatinine ($r = 0.520$, $p =< 0.011$).

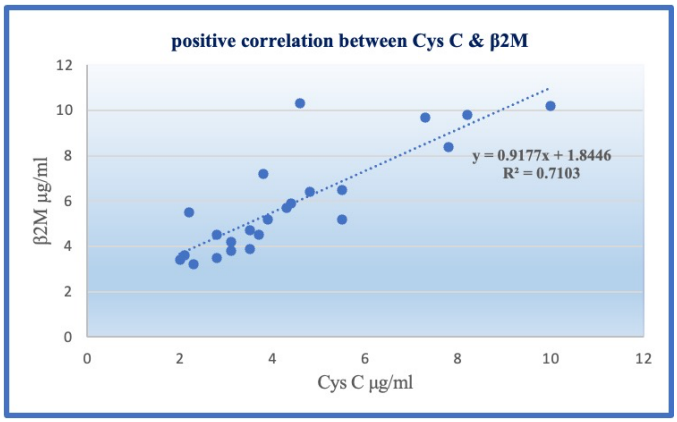
- **β2M**, however, did not show statistically significant correlations with conventional renal function tests.
- **NAG** demonstrated strong correlations with urea (r = 0.649, p = <0.001) and creatinine (r = 0.744, p= <0.001), confirming its role as a sensitive tubular injury marker.

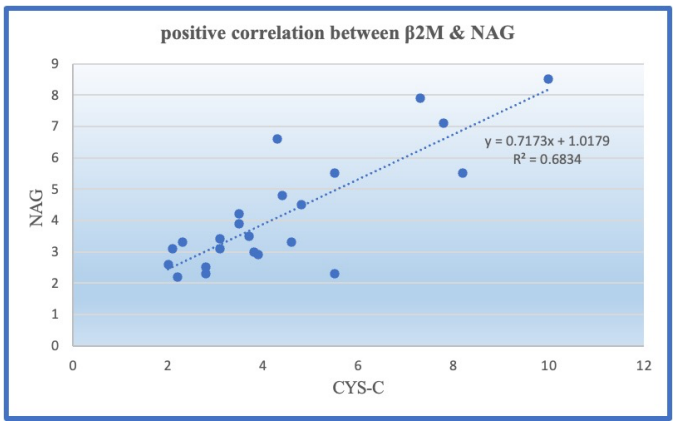
Graph 3: Correlation of serum Cystatin-C with Urea and Creatinine in Sickle cell disease with renal dysfunction





Graph 4: Correlation of serum Cystatin-C with Beta 2 Microglobulin(B2M) and NAG in Sickle cell disease with renal dysfunction





Graph 4: indicates a strong positive linear correlation: as B_2M_with increases, CYS_C_with increases at a consistent rate. The data points closely follow the fitted line, suggesting a nearly perfect linear relationship.

Discussion

The present study evaluated the correlation of novel biomarkers—Cystatin-C, Beta-2 Microglobulin (β2M), and NAG with conventional renal function tests in 200 sickle cell disease (SCD) patients, of whom 11.5% had renal dysfunction, a prevalence consistent with previous reports that 10–30% of adult SCD patients develop nephropathy [1,2]. The analysis of serum urea and creatinine levels in relation to renal dysfunction status revealed significant insights into the biochemical markers associated with renal impairment in sickle cell disease. Specifically, elevated creatinine levels were strongly associated with renal dysfunction, with 61% of individuals with renal dysfunction exhibiting high creatinine levels, thereby underscoring the clinical utility of creatinine as an indicator of renal damage [18]. Renal dysfunction was more common among males (17.1%) compared to females (8.1%), supporting earlier findings that gender differences influence susceptibility to kidney injury in SCD [3,4]. And was most frequent in the 23–27 years age group (19.4%), reflecting the age-related progression of nephropathy [5]. Current methods for assessing kidney function, such as serum creatinine and estimated glomerular filtration rate (eGFR), have limitations in early detection of kidney damage [19]. Patients with renal dysfunction showed significant derangements in conventional biochemical markers, including elevated blood urea, creatinine, and uric acid with reduced albumin and total protein, confirming the glomerular and tubular pathology of SCD nephropathy, as described in previous studies [6,7]. Electrolyte abnormalities (higher sodium, potassium, chloride) indicated impaired tubular handling, while elevated random blood sugar may represent stress-related metabolic alteration rather than diabetes. Among

novel biomarkers, Cystatin-C was markedly elevated in patients with renal dysfunction (4.40 ± 2.1 vs. 0.78 ± 0.25; $p < 0.001$) and strongly correlated with serum urea and creatinine, supporting its superiority over creatinine for early GFR assessment, as reported in prior studies [9,12]. In contrast, β2M levels did not differ significantly between groups and showed no meaningful correlation with conventional renal parameters, suggesting its limited sensitivity for renal dysfunction in SCD, possibly due to confounding influences of hemolysis and inflammation that independently raise β2M [15,16]. Although a linear association with Cystatin-C suggests potential value as a supportive marker when used in combination. The prevalence and biochemical profile of renal dysfunction in this cohort align with prior reports of early-onset nephropathy in SCD [17]. and our findings reinforce that Cystatin-C and are more reliable markers for detecting early renal dysfunction compared to β2M and conventional tests. Urinary NAG was found to correlate positively with albuminuria and proteinuria, as well as with ribonuclease and lysozyme in patients with persistent proteinuria [20]. The excretion of NAG was a useful test for detecting tubular damage [21]. Urinary N-acetyl-β-D-glucosaminidase is excreted in abnormally high amounts in many renal diseases [22].The clinical implications are significant: incorporating Cystatin-C into routine monitoring could enable earlier intervention, slowing progression to chronic kidney disease and end-stage renal disease, which remain major causes of morbidity and mortality in SCD [2,6]. While β2M may not serve as a standalone renal biomarker in SCD, it could still reflect systemic disease activity. The strengths of this study include its relatively large cohort and comprehensive biomarker evaluation; however, Overall, this study underscores the need for integrating novel biomarkers, particularly Cystatin-C into clinical practice for unmasking early renal impairment in SCD and improving long-term renal outcomes.

Limitations: This was a cross-sectional study of 200 adults, with only 23 meeting our criteria for renal insufficiency. The small number of affected patients limits statistical power and may underrepresent the full spectrum of sickle nephropathy, by design we compared biomarker levels at one time point, so we cannot assess how cystatin C might change over time. These constraints mean our findings should be validated prospectively in larger, diverse cohorts.

Conclusion

The present study demonstrates that renal dysfunction is a significant complication among sickle cell disease (SCD) patients, with a prevalence of 11.5% in the studied cohort. The risk of renal impairment was higher in males and increased with age, underscoring the progressive nature of sickle cell nephropathy. Conventional biochemical markers such as elevated serum urea, creatinine, and uric acid, along with reduced albumin and total protein, reliably reflected established renal impairment, whereas electrolyte abnormalities suggested concomitant tubular dysfunction. Importantly, serum Cystatin-C emerged as a superior and sensitive biomarker for early detection of renal dysfunction, showing strong correlations with conventional renal parameters, while β-2 microglobulin did not demonstrate significant diagnostic utility in this cohort. These findings highlight the limitations of relying solely on conventional renal tests for screening and emphasize the clinical value of incorporating Cystatin-C into the routine evaluation of SCD patients. Early detection and monitoring using sensitive biomarkers may allow timely intervention, potentially delaying progression to chronic kidney disease and improving long-term outcomes in this high-risk population.

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