Nigerian Medical Journal
NIGERIA MEDICAL ASSOCIATION
Print ISSN 0300-1652, E-ISSN 2229-774X

Original Article

Exploring the Relationship Between Angiogenesis Inhibition of sFLT-1 and Sickle Cell Nephropathy

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Abstract

Background: Sickle cell anaemia (SCA) is a chronic haemoglobinopathy associated with multi-organ complications, among which nephropathy remains a significant cause of morbidity and mortality. Early detection of sickle cell nephropathy (SCN) is crucial, yet conventional markers such as serum creatinine and estimated glomerular filtration rate (eGFR) often fail to detect early renal impairment. Emerging biomarkers like soluble fms-like tyrosine kinase-1 (sFLT-1) have shown potential in identifying early endothelial and glomerular injury in SCA. This study explores the role of angiogenesis inhibition via sFLT-1 in the pathogenesis of renal injury in SCD, aiming to identify correlations between elevated sFLT-1 levels, proteinuria, and declining renal function.

Methodology: A cross-sectional analytical study was conducted involving confirmed SCD patients and age- and sex-matched controls. Serum sFLT-1 levels were measured using enzyme-linked immunosorbent assay (ELISA). At the same time, renal function was assessed through estimated glomerular filtration rate (eGFR), serum creatinine, and urinary microalbumin and microalbumin: creatinine ratio quantification. Statistical analyses included correlation studies and group comparisons to determine the association between sFLT-1 concentrations and renal impairment indicators.

Results: SCD patients demonstrated significantly elevated sFLT-1 levels compared to controls ($p < 0.001$). Higher sFLT-1 levels were strongly associated with increased albuminuria and reduced eGFR, indicating early renal damage. These findings suggest that elevated sFLT-1 contributes to glomerular endothelial dysfunction, possibly via inhibition of vascular endothelial growth factor (VEGF)-mediated repair mechanisms.

Conclusion: The study reveals a significant relationship between angiogenesis inhibition by sFLT-1 and renal dysfunction in individuals with SCD. sFLT-1 may serve as a promising early biomarker for SCD nephropathy and a potential therapeutic target to preserve renal function in this vulnerable population. Furthermulticentred and longitudinal studies are recommended to establish causality and explore interventional strategies.

Keywords: Sickle Cell Disease, sFLT-1, angiogenesis, renal damage, VEGF, microalbuminuria, endothelial dysfunction

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How to Cite: Ogunkunle AK, Abubakar MG, Mahmud FA, Dogara AB, Suleiman HM, Awwalu S, Aliyu IS. Exploring the Relationship Between Angiogenesis Inhibition of sFLT-1 and Sickle Cell Nephropathy. Niger Med J 2025; 66 (6): 2240-2252 https://doi.org/10.71480/nmj.v66i6.857

Quick Response Code:

Introduction

Sickle Cell Disease (SCD) is an inherited haemoglobinopathy characterized by chronic haemolysis, vaso-occlusion, and widespread endothelial dysfunction, leading to various organ complications, including nephropathy[1]. Sickle Cell Nephropathy (SCN) could manifest as haematuria, proteinuria, hyposthenuria, renal papillary necrosis, renal tubular disorders, acute and chronic kidney injury, sickle cell glomerulopathy, and even renal medullary carcinoma[2]. These significantly contribute to morbidity and mortality in SCD patients[2]. Despite the clinical importance of SCN, the underlying mechanisms remain incompletely understood, necessitating further investigation into potential pathogenic factors.[3]

Angiogenesis, the formation of new blood vessels from thepre-existing vasculature, is crucial for maintaining renal microvascular integrity and functions.[4] Vascular Endothelial Growth Factor A (VEGF-A) is a key pro-angiogenic cytokine that binds to its receptors on endothelial cells, promoting their survival, proliferation, and nitric oxide (NO) production[4,5], thereby ensuring adequate blood flow and organ perfusion. Disruption in VEGF-A signaling can impair endothelial function, leading to vascular complications [5]

Soluble FMS-like tyrosine kinase-1 (sFLT-1) is an endogenous inhibitor of VEGF-A, acting as a decoy receptor that binds VEGF-A, preventing its interaction with cell surface receptors. Elevated levels of sFLT-1 have been implicated in endothelial dysfunction and are associated with conditions such as preeclampsia and chronic kidney disease[6,7]. In the context of SCD, increased sFLT-1 levels have been observed and correlated with markers of haemolysis and endothelial activation, suggesting a potential role in the disease's vascular complications[8].

Emerging evidence indicates that sFLT-1 may contribute to the pathogenesis of SCN by promoting endothelial dysfunction and impairing angiogenic balance[6,7]. Studies have demonstrated that elevated sFLT-1 levels are associated with increased urinary albumin excretion and pulmonary hypertension in SCD patients, highlighting a link between angiogenesis inhibition and renal damage. Furthermore, research in diabetic nephropathy models has shown that modulation of sFLT-1 levels can influence renal function and inflammation, underscoring the significance of angiogenic factors in kidney disease[9].

sFlt-1 is influenced by several confounding factors in Sickle Cell Disease (SCD), including inflammation, haemolysis, and oxidative stress. Intravascular haemolysis releases free haemoglobin and heme, generating reactive oxygen species and chronic inflammation, which can independently affect endothelial function and potentially alter sFlt-1 levels without reflecting renal injury[10]. In chronic kidney disease, sFlt-1 levels may poorly correlate with production due to loss of matrix-bound sFlt-1 and oxidative stress[6]. Experimental data also show that sFlt-1 effects on endothelial permeability are modulated by inflammatory and oxidative environments[11]. Thus, in SCD, circulating sFlt-1 may reflect haemolytic, inflammatory, and oxidative processes rather than nephropathy alone, limiting its specificity as a biomarker.

Given the potential involvement of sFLT-1 in SCN, exploring the relationship between angiogenesis inhibition by sFLT-1 and renal damage in SCD is imperative. Understanding this relationship could provide insights into novel therapeutic targets aimed at preserving renal function and improving outcomes for SCD patients. This study aims to elucidate the role of sFLT-1 in SCN pathogenesis, contributing to the broader understanding of this SCDcomplicationand informing future clinical interventions.

Material And Method

This was a cross-sectional comparative study involving 240 participants. Using a power-based formula for continuous variables (90% power, 5% significance, SD = 5.1, mean difference = 3.9, and a 10% non-

response adjustment)[12], the minimum sample size was calculated as 60 SCA participants with nephropathy, 60 without nephropathy, and 120 healthy HbAA controls, giving a total of 240 participants.Steady state in SCA was defined as the absence of acute painful episodes requiring hospitalization in the preceding 4 weeks, no blood transfusion in the past 3 months, no intercurrent illness such as infection within the last 4 weeks, and no use of medications (e.g., antibiotics) that could affect blood counts in the preceding 3 weeks[13].Nephropathy was defined as a urinary microalbuminuria creatinine ratio of >2.5mg/mmol for male subjects and >3.0mg/mmol for female subjects[14].

SCA patients were recruited from the sickle cell clinic between August 2023and February 2024. While apparently healthy HbAAadults were also enrolled. Informed consent was obtained from all participants after the study had been fully explained to them in the language they understood best.Ethical approval for this study was obtained from the Health Research Ethics Committee of Ahmadu Bello University Teaching Hospital, Zaria (ABUTH/HREC/H41/2023) on 27 January 2023.

The study utilized interviewer-administered questionnaires to obtain both qualitative and quantitative data.Anthropometric and blood pressure measurements were taken, after which 5 mL of venous blood was collected into plain tubes. Serum was separated by centrifugation and stored at –80 °C, and urine samples were similarly collected and stored at –80 °C. Serum creatinine was analyzed in batches using the Selectra automated clinical chemistry analyzer, while urinary creatinine was measured manually using the Jaffe kinetic method. Urinary microalbumin was determined by the immunonephelometric method, and serum sFLT-1 was analyzed using ELISA. eGFR was calculated using the CKD-EPI 2021 equation, and the urinary albumin–creatinine ratio (UACR) was subsequently derived. Ethical approval for the study was obtained from the institutional Health Research Ethics Committee.

Data obtained from the study were analysed using Statistical Package for the Social Sciences 25.0 (SPSS 25.0) for Windows (SPSS Inc., Chicago, IL, USA) and Microsoft Excel 2016. Qualitative values were summarised as percentages, frequencies, and tables. The distributions of quantitative variables were assessed using the Kolmogorov-Smirnov test. The concentration of sFLT-1 and calculated eGFR for the three study groups were compared using the One-Way ANOVA test, while Kruskal-Wallis was used to compare the concentrations of urinary creatinine, microalbumin, and the calculated UACR. Receiver Operator Curve was generated using MedCalc to determine the sFLT-1 diagnostic cut-off for nephropathy. The level of statistical significance was set at a p-value of ≤ 0.05.

Results

The participants were stratified by age and sex, with no statistically significant differences observed across the groups ($p = 0.991$ and $p = 0.752$, respectively). However, there were significant differences in the participants' level of education and occupation ($p < 0.001$ for both), with more HbAA controls having attained higher levels of education and being employed, whereas a larger proportion of SCD participants were students or unemployed. Table 1.

Table 1: Sociodemographic characteristics

Variable	SCA in Steady State with Nephropathy (n-60)	SCA in Steady State without Nephropathy (n-60)	HbAA Control (n-120)	*p-value*
Age (mean±SD)	27.7±8.4	24.2±8.4	24.9±4.5	0.991
Sex				
Male	30 (50.0%)	27 (45.0%)	53 (44.2%)	0.752
Female	30 (50.0%)	33 (55.0%)	67 (55.8%)	0.752
Marital status				
Married	15 (15.0%)	14 (23.3%)	30 (25.0%)	0.967
Single	45 (75.0%)	46 (76.7%)	90 (75.0%)	0.967
Highest level of education				
Primary	6 (10.0%)	3 (5.0%)	0 (0.0%)	**0.001**
Secondary	27 (45.0%)	40 (66.7%)	87 (72.5%)	**0.001**
Tertiary	27 (45.0%)	17 (28.3%)	33 (27.5%)	**0.001**
Occupation				
Artisan	4 (10.0%)	6 (10.0%)	0 (0.0%)	**<0.001**
Business	20 (16.7%)	10 (16.7%)	2 (1.7%)	**<0.001**
Civil servant	5 (10.0%)	6 (10.0%)	29 (24.2%)	**<0.001**
Housewife	6 (5.0%)	3 (5.0%)	0 (0.0%)	**<0.001**
Student	21 (51.7%)	31 (51.7%)	97 (80.8%)	**<0.001**
Unemployed	4 (6.6%)	4 (6.7%)	0 (0.0%)	**<0.001**

Biochemical analysis revealed significant differences in key renal function markers across the groups. Urine microalbumin and urine albumin-to-creatinine ratio (UACR) were significantly elevated in SCD patients with nephropathy compared to both those without nephropathy and the HbAA controls ($p < 0.001$). Although serum creatinine was highest among the HbAA group, its elevation in the nephropathy group compared to the non-nephropathy group supports the diagnosis of renal impairment. Estimated glomerular filtration rate (eGFR) was significantly lower in the nephropathy group (mean 86.00 mL/min/1.73m²) compared to the non-nephropathy group (109.23 mL/min/1.73m²). ($p = 0.002$). Urinary creatinine levels were highest in the control group and lowest in the nephropathy group. Table 2.

Table 2: Biochemical parameters of study population

Variable Median (IQR)	SCA with nephropathy (n-60)	SCA without nephropathy (n-60)	HbAA Control (n-120)	p-value
Urine microalbumin (mg/dl)	7.59 (12.37)	0.02 (0.79)	0.0 (0.00)	**<0.001**
Urine creatinine (mmol/L)	5.50 (7.52)	9.00 (7.96)	17.35 (9.68)	**<0.001**
UACR (mg/mol)	12.05 (17.15)	0.00 (0.00)	0.00 (0.00)	**<0.001**

Serum creatinine (µmol/L)	82.08 (97.07)	59.01 (34.96)	90.74 (22.17)	**<0.001**
s-FLT 1 (pg/ml)**	248.58±99.55*	235.51±75.56*	138.6 2± 48.46*	**<0.001**
eGFR (mL/min/1.73m^2)**	86.00 ± 26.75*	109.23 ± 35.59*	90.39 ± 20.46*	**0.002**

N.B. Kruskal-Wallis non-parametric test was used except for s-FLT-1 and eGFR that are normally distributed.

* Mean (SD) was used for this data because it is normally distributed ** One Way ANOVA

eGFR: Estimated Glomerular Filtration Rate n: Number of participants

UACR: Urinary Abumin Creatinine Ratio SD: Standard deviation

s-FLT1: soluble fms-like tyrosine kinase-1 IQR: Interquartile Range

Serum sFLT-1 levels were markedly elevated among individuals with SCD compared to HbAA controls ($p < 0.001$). The highest mean levels were recorded in the nephropathy group (248.58 ± 99.55 pg/ml), followed by the non-nephropathy SCD group (235.51 ± 75.56 pg/ml), and the lowest in the control group (138.62 ± 48.46 pg/ml). Table II. The post hoc analysis revealed statistically significant differences in eGFR and UACR across all study group comparisons, indicating progressive renal impairment and albuminuria from HbAA controls to HbSS patients with nephropathy. However, sFLT-1 levels were significantly higher in both HbSS groups compared to HbAA controls, but the difference between HbSS patients with and without nephropathy was not statistically significant ($p = 0.697$). Table 3.

Table 3: Post hoc analysis between the biochemical parameters and the different study populations

	p-value for Post Hoc		
Study groups	eGFR	UACR	sFLT-1
SCA with nephropathy vs SCA without nephropathy	**<0.001***	**<0.001***	0.697**
SCA with nephropathy vs SCA controls	**0.002***	**<0.001***	**<0.001****
SCA without nephropathy vs HbAA controls	**<0.001***	**<0.001***	**<0.001****

*Mann–Whitney U test was used because the data were not normally distributed.

**t-test was used because the data were normally distributed

Table 4a and b revealed that across both education and occupation categories, there were no statistically significant differences in UACR or serum sFLT-1, and only eGFR showed a significant variation across education levels. Overall, the findings suggest that although socioeconomic differences exist across groups, their unadjusted influence on the biochemical parameters appears minimal, except for eGFR.

Table 4a: Group Differences in Education and its Potential Unadjusted Socioeconomic Confounding on eGFR, UACR and serum sFLT-1

Variable	Occupation						*t*	*p* value
	Artisan (n=4)	Business (n=20)	Civil Servant (n=5)	Housewife (n=6)	Student (n=21)	Unemp-loyed (n=4)		
eGFR (mL/min/1.73^2) mean (±SD)	85.74 ± 40.73	85.11 ± 43.61	83.87± 39.83	79.82± 37.43	86.21 ± 43.23	83.63± 31.58	0.163	0.928
UACR (mmol/mol) median (IQR)	11.60 (8.40)	12.05 (21.03)	8.86 (18.20)	16.21 (20.56)	10.32 (20.56)	15.80 (7.73)	NA	0.204
Serum sFLT-1 (pg/mL) mean ± SD	218.52 ± 53.60	251.53 ± 63.32	229.54± 91.65	247.24± 93.48	239.54± 93.45	272.44± 105.29	0.892	0.479

eGFR: Estimated Glomerular Filtration Rate
UACR: Urinary Abumin Creatinine Ratio
s-FLT1: soluble fms-like tyrosine kinase-1
n= Number of participants
NA: Not applicable
SD: Standard deviation
IQR: Interquartile Range

Table IVb: Group Differences in Occupation and its Potential Unadjusted Socioeconomic Confounding on eGFR, UACR and serum sFLT-1

Variable	Primary (n=6)	Secondary (n=27)	Tertiary (n=27)	*t*	*p* value
eGFR (mL/min/1.73^2) mean (±SD)	100.33 ± 34.17	95.54 ± 38.88	68.50± 35.66	3.757	**0.029**
UACR (mmol/mol) median (IQR)	13.50 (18.35)	10.65 (9.40)	12.35 (16.47)	NA	0.697
Serum s-FLT 1 (pg/mL) mean ± SD	281.12 ± 70.01	229.50 ± 78.30	242.14 ±73.46	1.217	0.304

eGFR: Estimated Glomerular Filtration Rate
UACR: Urinary Abumin Creatinine Ratio
s-FLT1: soluble fms-like tyrosine kinase-1
n= Number of participants
NA: Not applicable
SD: Standard deviation
IQR: Interquartile Range

Further analysis using Receiver Operating Characteristic (ROC) curves showed that serum sFLT-1 had strong discriminatory power in differentiating SCD nephropathy from non-nephropathy cases. When UACR was used as the reference standard, sFLT-1 yielded an Area Under the Curve (AUC) of 0.779 (95% CI: 0.721–0.830; p < 0.0001).Compared with eGFR-based nephropathy, the AUC for sFLT-1 was 0.606 (p = 0.0046). Interestingly, eGFR itself had a lower discriminative ability against UACR (AUC = 0.586; p = 0.0832).Figures I and II and Table 5.

Table 5:Summary of different AUC with correspondent 95%CI and p-value from ROC curves of different analytes studied

Criteria for the definition of nephropathy	Analyte	AUC	95% CI	*p*-value
UACR	s-FLT-1	0.779	0.721 - 0.830	**<0.0001**
UACR	eGFR	0.586	0.521 - 0.649	0.0832
eGFR	sFLT-1	0.606	0.540 - 0.700	**0.0046**
eGFR	UACR	0.536	0.476 - 0.607	0.3372

eGFR: Estimated Glomerular Filtration Rate
UACR: Urinary Abumin Creatinine Ratio
s-FLT1: soluble fms-like tyrosine kinase-1
AUC: Area under the curve
CI: Confidence interval

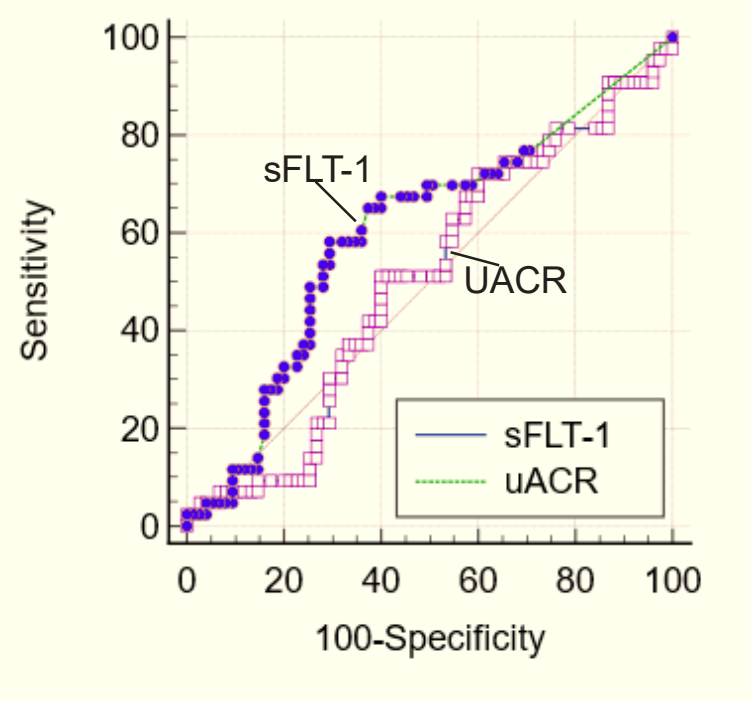

Fig. 1: A comparison of ROC curves of UACR and sFLT-1 (using eGFR of **<90 ml/min/1.73m^{2}to define nephropathy)**

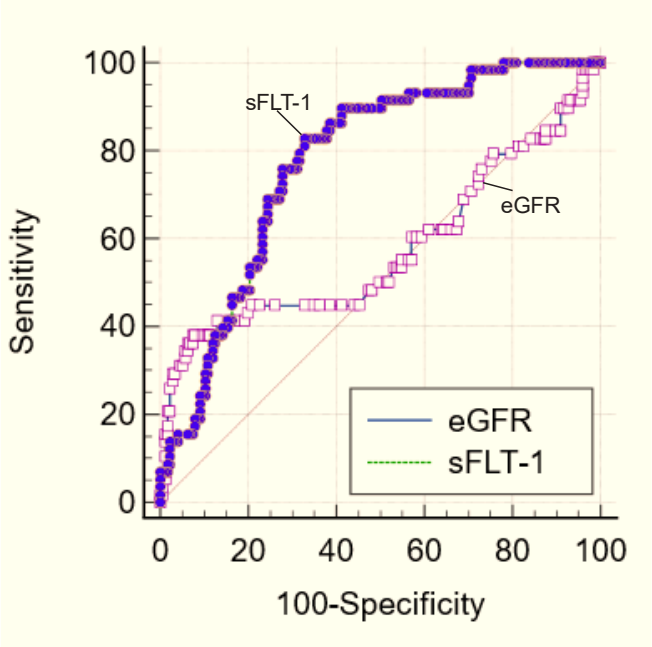

Fig. 2. Comparing ROC and AUC of sFLT-1 and eGFR (using UACR of >2.5mg/mmol for males and >3.0mg/mmol for females to define nephropathy)

Discussion

The mean age of participants in this study (27.7 ± 8.4 years) aligns with findings from Zaria by Manu et al[15] who reported mean ages of 24 and 25 years, respectively, among sickle cell anaemia (SCA) patients. In contrast, studies from Southern Nigeria by Asafa et al.[16]reported lower mean ages, possibly due to increased awareness and early healthcare-seeking behaviours. In Western settings, higher mean ages have been documented—such as 39 years by Ataga et al. [17] in the USA and 33 years by Laurentino et al. [18] in Brazil—likely due to improved survival rates and reduced disease prevalence.The study observed an equal distribution of male and female SCA patients with nephropathy, indicating no sex predilection. This finding is consistent with Manu et al. [15] and Niss et al. [19] but differs from Youssry et al. [20] in Egypt, who reported male predominance. Differences in sex distribution across studies may reflect varying demographic compositions and health-seeking behaviours.

Although the study observed differences in education and occupation across groups, these socioeconomic factors were not adjusted for in the analysis of biochemical parameters, raising the possibility of confounding. Evidence from recent nephrology research[19, 21] indicates that lower socioeconomic status, including lower education and disadvantaged occupation, is associated with poorer renal outcomes and faster declines in eGFR, even after controlling for clinical risk factors. Therefore, some of the variation (or lack thereof) in biochemical markers in our study may reflect underlying socioeconomic or lifestyle influences rather than purely biological differences. Future studies should incorporate structured socioeconomic variables to better isolate biological effects.

Urinary microalbumin:creatinine ratio (UACR) was significantly elevated in SCA patients with nephropathy, consistent with findings from Bolarinwa et al.[21], Ranque et al.[22] and Vazquez et al.[23]. Microalbuminuria in SCA is attributed to glomerular injury from haemoglobinuria, oxidative stress, haemodynamic changes, endothelial dysfunction, and chronic inflammation[24-26]. The progressive

decline in renal function contributes to creatinine retention and reduced urinary creatinine levels, explaining the significant differences observed among study groups.

SCA patients with nephropathy demonstrated significantly lower urinary creatinine levels than other groups, likely due to lower muscle mass, increased fluid intake, or impaired creatine synthesis linked to mild hepatic dysfunction[27]. Impaired renal function further reduces creatinine secretion and clearance[28].Serum creatinine levels varied significantly among the groups, with the lowest values observed in SCA patients without nephropathy. Although within normal ranges, these findings support earlier reports from Manu et al.[15], Nnaji et al.[29],Youssry et al.[20] and Niss et al.[19]. They emphasize the limitations of serum creatinine as a renal marker, as significant nephron loss (40–50%) must occur before elevations become evident[30,31,32].

sFLT-1 concentrations were highest in SCA patients with nephropathy and lowest in HbAA controls, with statistically significant differences observed between the control group and both SCA groups. Although SCA patients with nephropathy exhibited higher mean sFLT-1 levels than those without nephropathy, this difference did not reach statistical significance. This pattern aligns with findings from Youssry et al.[20] in Egypt, Ataga et al.[17, 33, 34] in the USA, and Landburg et al. [35] in the Netherlands, who reported significantly elevated sFLT-1 levels in SCA patients with nephropathy compared to both SCA patients without nephropathy and healthy controls. Variations in study populations, including age group (paediatric versus adult), sample size, and disease severity, may explain the differences in statistical outcomes. For instance, Youssry et al.[20] focused on paediatric patients with a smaller sample size, potentially exaggerating the observed differences. Despite the lack of statistical significance between the two SCA groups in the present study, the observed upward trend in sFLT-1 concentrations supports its potential role as a biomarker in the pathophysiology and progression of sickle cell nephropathy.

Although circulating sFLT-1 is elevated in patients with Sickle Cell Anaemia (SCA) compared with healthy controls, supporting its role in endothelial dysfunction, the lack of a statistically significant difference between SCA patients with and without nephropathy suggests that circulating sFLT-1 alone may not be sufficiently sensitive or specific as a biomarker for renal involvement in SCA. This finding may be influenced by the cross-sectional design of the study, which captures only a single time point and may miss temporal fluctuations in sFLT-1 that occur with disease progression or acute vaso-occlusive events. Biologically, sFLT-1 exists in both free circulating and matrix-bound forms, and standard assays may not reflect total sFLT-1 availability, while modest or context-dependent elevations may not correlate directly with structural renal damage[6, 11]. Therefore, while elevated sFLT-1 as seen in this study supports its involvement in SCA vascular pathology, its utility as a standalone biomarker for nephropathy is limited, highlighting the need for longitudinal studies and multimarker approaches to better assess renal risk in this population.

Furthermore, the Receiver Operating Characteristic (ROC) curve analysis revealed that serum sFLT-1 exhibited the highest diagnostic performance among the evaluated biomarkers for sickle cell nephropathy, surpassing both UACR and eGFR. The area under the curve (AUC) for sFLT-1 was 0.779, indicating good diagnostic utility. The marker demonstrated a sensitivity of 47.46%, specificity of 82.49%, positive predictive value (PPV) of 53.98%, and negative predictive value (NPV) of 78.40%. These findings underscore the potential of sFLT-1 as a reliable screening and diagnostic biomarker for early renal impairment in SCA patients. Comparable diagnostic performance was reported by Youssry et al.[20] in Egypt, who similarly observed higher sensitivity and specificity values in a paediatric population.

The relatively lower sensitivity in this study could be attributed to age-related differences in biomarker expression and variability in disease manifestations among adult SCA patients. Nevertheless, the high specificity and negative predictive value observed indicate that sFLT-1 could be particularly useful for ruling out nephropathy in SCA populations. Mechanistically, the increased levels of sFLT-1 may also reflect the overexpression of peripheral blood monocytes (PBM), a known source of sFLT-1 in SCA patients[36]. This supports the hypothesis that the pathogenesis of sickle cell nephropathy involves not only traditional haemodynamic and inflammatory pathways but also a complex interplay of angiogenic dysregulation.

Conclusion

Based on current findings and recent literature, sFLT-1 shows strong promise as a better, earlier marker of sickle cell nephropathy, especially in detecting early glomerular endothelial damage. Its link with albuminuria and its role in angiogenic regulation give it biological plausibility and clinical potential.However, its lack of specificity, dependence on broader systemic factors, and the need for prospective validation mean it should not yet replace standard markers like eGFR and albuminuria. Instead, it could serve as a complementary biomarker, especially useful in identifying high-risk patients or in research settings.Furthermore, while sFLT-1 levels were assessed, VEGF (its primary target) was not measured. Since sFLT-1 exerts its anti-angiogenic effects by neutralizing VEGF, evaluating both factors would offer a clearer understanding of the angiogenic balance. Additionally, the study did not account for potential confounding variables that may influence renal function or sFLT-1 levels, such as inflammatory markers (e.g., CRP, IL-6), VEGF, the primary target of sFLT-1, and oxidative stress indicators. Future studies should aim to validate sFLT-1 in larger, multi-center, longitudinal SCD cohorts, investigate its potential as a biomarker for sickle cell nephropathy, evaluate its predictive utility, and determine whether modulating sFLT-1 could have therapeutic benefits. These studies should also account for confounding factors that may influence renal function or sFLT-1 levels, including inflammatory markers, VEGF, and indicators of oxidative stress.

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