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Evaluation of Glomerular Hyperfiltration and Albuminuria in Sickle Cell Disease Adolescents: Cross-Sectional Retrospective Study

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Abstract

Background: Sickle Cell Disease (SCD) renal abnormalities commence early in childhood. The glomerular abnormalities, glomerular hyperfiltration and albuminuria are the most prevalent. However, these SCD glomerulopathies have not been considered exclusively in the adolescent age group. **Objective:** To determine the prevalence of glomerular hyperfiltration and albuminuria as well as identify the determinants for glomerular hyperfiltration in adolescents with SCD. **Patients and Methods:** The electronic patient records of 153 adolescents with SCD aged 10 - <19 years, attending the Paediatrics Haematology Clinic at Evelina London Children's Hospital, United Kingdom, were reviewed from the 10th to 23rd June 2019. Clinical information and laboratory parameters were obtained. The glomerular filtration rate was derived using the Bedside Schwartz's method. Grouping of the adolescents was based on the presence and absence of glomerular hyperfiltration, which was defined as glomerular filtration rate > 140 ml/min/m^2. The presence of albuminuria was defined as urine albumin-to-creatinine ratio > 3 mg/mmol or protein-to-creatinine ratio of >15 mg/mmol. The clinical and laboratory determinants of glomerular hyperfiltration in the total study population were investigated. **Result:** Prevalence of glomerular hyperfiltration was 33.3% in the adolescents studied, and that of albuminuria was 15.7% amongst the SCD adolescents studied, of which 13.7% of those with glomerular hyperfiltration also had albuminuria. On univariable analysis, the SCD adolescents with glomerular hyperfiltration had significantly lower weight (48.0 ± 18.0 versus 54.8 ± 17.0 kg; p = 0.02), height (155.1 ± 13.1 versus 160.6 ± 13.1 cm; p = 0.01), body

mass index (19.4 ± 5.0 versus 21.0 ± 4.3; $p = 0.04$), haemoglobin level (88.7 ± 13.3 versus 98.1 ± 21.7 g/L; $p = 0.001$), and serum creatinine level (0.4 ± 0.1 versus 0.6 ± 0.2 mg/dl; $p = 0.0001$) as compared to those with no glomerular hyperfiltration. The SCD adolescents with glomerular hyperfiltration also had significantly higher lactate dehydrogenase levels (525.9 ± 180.3 versus 449.6 ± 170.3 IU/L; $p = 0.01$) than those with no glomerular hyperfiltration. But, multivariable analysis revealed no associations. **Conclusion:** This study revealed that the prevalence of glomerular hyperfiltration in SCD children in the adolescent age group is high, and the high glomerular filtration rates begin to decline toward normal values in middle adolescence.

Keywords

Glomerular Hyperfiltration, Albuminuria, Sickle Cell Disease, Adolescent

1. Introduction

Sickle Cell Disease (SCD) is the most common inherited red blood cell disorder [1]. The global incidence is estimated at 300,000 new-borns annually [2]. This figure is predicted to rise by 30% due to improved life expectancy, with more children surviving into adulthood by 2050 [3]. Identified reasons for improvements in survival are the availability of comprehensive care programmes, including neonatal screening, which facilitates early access to penicillin prophylaxis, pneumococcal and influenza vaccination, growth and development monitoring, dietary advice and parental education, which enhances prompt consultation [1]. Although advances in children's care with SCD have improved, these children's long-term survival implies that chronic morbidities from the disease such as chronic heart disease, pulmonary hypertension, chronic leg ulcers, and chronic kidney disease will be more prevalent.

The renal complications of SCD are a spectrum of renal abnormalities collectively referred to as Sickle Cell Nephropathy (SCN) [4]. SCN manifests early in childhood as glomerular hyperfiltration, microalbuminuria and hyposthenuria. In late childhood, the microalbuminuria progressively increases with the development of albuminuria which may be associated with regression of the glomerular filtration rate, which can subsequently develop in Chronic Kidney Disease (CKD) in late adolescence and, in the extreme case, End-Stage Renal Disease (ESRD) develops in early adulthood [5].

Glomerular hyperfiltration and its accompanying glomerular hypertrophy are the earliest glomerular abnormalities in SCD [6]. It manifests clinically as markedly elevated GFR. Its aetiology in SCD is not clearly understood but, its development and progression are believed to be driven by increased glomerular perfusion and increased effective glomerular filtration surface area, but not by increased glomerular capillary hydrostatic pressure [7]. The reported prevalence of glomerular hyperfiltration in SCD, mainly in children with SCA, ranges from

40% to 98% [8] [9] [10]. These prevalence rates differ from study to study because there is no uniform definition of glomerular hyperfiltration. Brewin *et al.* noted that the threshold used from most paediatric studies was between 130 - 140 ml/min/m^2 [9]. Utilizing a single criterion for all ages of children may be inaccurate; this may be responsible for the high prevalence rate of glomerular hyperfiltration in the literature. Hence in this study, the standard clinical definition of glomerular hyperfiltration, which is >140 ml/min/m^2 [9] was restricted to only the adolescent age group. Besides, there are no studies on the prevalence of glomerular hyperfiltration exclusively in the adolescent age group of children with SCD, implying that the proportion of children with SCD that may develop CKD in later life is unknown.

Glomerular Hyperfiltration in children with SCD has been documented to be present throughout childhood [8] [9] [11]. However, conflicting reports exist on the rates in adolescents. Wigfall *et al.* and Aygun *et al.* reported that GFR declines towards normal range in the second decade of life [8] [11], while Brewin *et al.* observed that the elevated GFR did not vary with age [9]. These contradicting reports may have arisen because a small number of adolescents were represented in the adolescent group of these studies. These varying reports further buttress the need for glomerular hyperfiltration to be studied exclusively in the adolescents' population.

Proteinuria is the most frequent clinical evidence of SCD glomerulopathy [12]. Children with SCD present with proteinuria of varying degrees which are: microalbuminuria, macroalbuminuria, and rarely nephrotic range proteinuria. The development of albuminuria in SCD is believed to be due to several factors: glomerular hyperfiltration, glomerular hypertension, ischemia-reperfusion injury, oxidative stress, and decreased Nitric Oxide (NO) bioavailability, and endothelial dysfunction [12]. The prevalence of microalbuminuria in children with SCA ranges from 16% - 27% from several studies [8] [13] [14] [15] [16] [17]. From several research works, the prevalence of macroalbuminuria in children with SCA is 6% - 23% [6] [11]. It has been reported to increase with increasing age in children [11] as well as in adults [18]. Although some authors [13] reported that the prevalence of albuminuria is higher when considering purely adolescent populations, their criteria for albuminuria is not the standard definition; therefore, the prevalence of albuminuria amongst the adolescent SCD population is also not known. Thus, the purpose of this study was to determine the prevalence of glomerular hyperfiltration and albuminuria, as well as the determinants of glomerular hyperfiltration in adolescents with SCD.

2. Methods

2.1. Patients

In this cross-sectional study, a review of the electronic patient records of the children attending the Paediatrics Haematology Clinic at Evelina London Children's Hospital, United Kingdom, was carried out between 10th to 23rd June 2019.

The adolescents recruited from the database were 10 - <19 years with the diagnosis of SCD. The adolescents excluded were those with associated comorbidities that may affect their renal function, such as chronic lung disease, chronic heart disease, endocrine dysfunction, diabetes mellitus, human immunodeficiency virus (HIV), Hepatitis B virus or Hepatitis C virus infection, including those with pre-existing kidney disease. This was to ensure that SCD alone clearly explains the development of glomerular abnormalities.

2.2. Data Collection

Clinical data obtained from the most recent outpatient visit included age, gender, sickle cell type. The clinical history details included were: acute events —Vaso-Occlusive Crisis (VOC), Acute Chest Syndrome (ACS), Cerebrovascular Accident (CVA), acute sequestration crisis; the history of chronic blood transfusion; duration on chronic blood transfusion; the age of onset of chronic blood transfusion; the history of hydroxyurea use; duration on hydroxyurea use. The physical examination parameters obtained were: weight, height, body mass index, systolic blood pressure and diastolic blood pressure. The laboratory parameters obtained were urine albumin-creatinine ratio or protein-creatinine ratio, haemoglobin level, white blood cell count, red blood cell count, platelet count, reticulocyte count, foetal haemoglobin level, lactate dehydrogenase level, serum creatinine and serum ferritin level. The Bedside Schwartz method [19] was used to determine the GFR, recommended by the Kidney Disease: Improving Global Outcomes [20] to evaluate renal function in children. The formula is the constant 0.413 × height in cm / serum creatinine in mg/dl.

2.3. Definition of Terms

Glomerular hyperfiltration was defined as GFR > 140 ml/min/m^2. While albuminuria was defined as urine Albumin Creatinine Ratio (ACR) > 3 mg/mmol or urine Protein Creatinine Ratio (PCR) of >15 mg/mmol, depending on which was available for the patient. Albuminuria was further classified into microalbuminuria defined as urine ACR 3 - 30 mg/mmol or urine PCR of 15 - 50 mg/mmol and macroalbuminuria as urine ACR > 30 mg/mmol or urine PCR > 50 mg/mmol [20]. The adolescents were categorised into two groups, hyperfiltration present and hyperfiltration absent. The adolescence was categorised into three age groups early adolescence 10 - 13 years, mid-adolescence 14 - 16 years, and late adolescence 17 - <19 years [21].

2.4. Ethical Approval

Ethical approval, with project number 9949, issued by the Clinical Governance Committee for Service Improvement, Evelina London Children's Hospital, Guy's and St Thomas NHS Foundation Trust, dated 19-August 2019.

2.5. Data Analysis

The data collected were analysed using International Business Machines, Statis-

tical Package for the Scientific Solutions (SPSS) version 24 (SPSS for Window Inc.; Chicago, IL, USA) Statistical software. Continuous variables; age, the physical clinical parameters such as weight, height and laboratory parameters and the GFR were summarised as mean ± Standard Deviation (SD), while categorised variables; age group, clinical histories, and presence of albuminuria represented as proportions. Pearson's chi-square or Fishers Exact tests were used in comparing the categorised variable of the two groups (age group, gender, history of acute event, history of blood transfusion, and hydroxyurea therapy). The continuous parametric data (age, weight, height, BMI, systolic blood pressure, diastolic blood pressure, haemoglobin level, red blood cell count, white blood cell count, reticulocyte count, platelet count, lactate dehydrogenase level and serum creatinine level) of the two groups of children were compared by Student t-test. While the Mann Whitney U test was used in analysing the non-parametric variable (foetal haemoglobin level and serum ferritin level). Multivariable logistic regression analysis was used to identify the factors associated with glomerular hyperfiltration. The level of significance of each test was set at a *P*-value of < 0.05.

3. Results

Following the review of the electronic database of the Paediatric Haematology Clinic, 217 patients with SCD aged 10 - <19 years were identified. Of these, 153 were recruited, and 64 were excluded. Nine of the adolescents were excluded because they had chronic comorbidities (four chronic heart disease, three chronic lung diseases, and two chronic kidney diseases). Also excluded were four of the adolescents who had undergone stem cell transplantation and were on immunotherapy, while the remaining 51 excluded were because of incomplete results. The flow chat shows the details of the recruitment process (Figure 1).

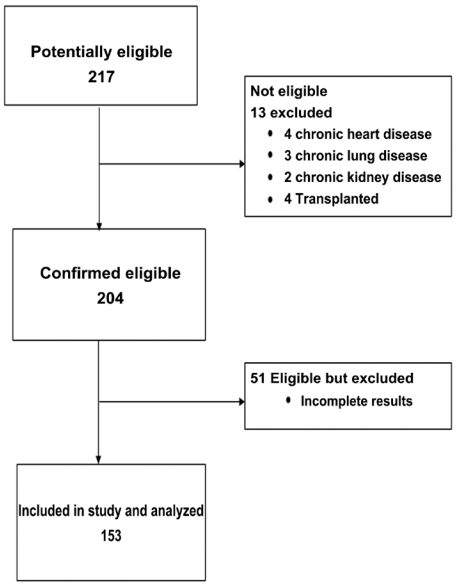

Figure 1. Flow diagram showing the exclusion process.

3.1. Demographic and Clinical Details of the Adolescents Studied

The mean (SD) ages of the adolescents were 13.73 ± 2.5 years. Most were in the 10 - 13 years old age group, 70 (45.8%) and were females 79 (51.6%). Most of the adolescents had Hb SS disease 115 (75.2%), 31 (20.3%) had Hb SC, and 5 (3.3%) had Hb S/beta$^+$ thalassemia. Demographic characteristics and distribution of the types of SCD of all the adolescents studied are shown in Table 1. Of the 153 adolescents studied, 94 (61.4%) had a history of an acute event (Forty-nine (52.1%) of these adolescents had experienced severe, frequent vaso-occlusive crisis (VOC), 28 (29.8%) had a history of ACS, 12 (12.7%) CVA, 3 (3.2%) acute sequestration crisis and 2 (2.1%) had a history of both ACS and CVA. Ninety-two (60.1%) of the adolescents studied were on sickle cell modifying therapy. Seventy (76.1%) were on hydroxyurea therapy, and 22 (23.9%) were on chronic blood transfusion, while the remaining 61 (39.9%) adolescents were not on any sickle cell modifying therapy. The most frequent reasons for treatment among the 92 adolescents on sickle cell modifying therapy were severe frequent VOC 57 (62%), abnormal transcranial scan indicative of impending CVA 19 (20.6%) and CVA 10 (10.8%). Figure 2 shows the reasons for sickle cell modifying therapy. The glomerular filtration rate of the studies population shows a decrease with increasing age, see Figure 3. The median (interquartile range) GFR for those in the age 10 - 13 years was 132.5 (114.7 - 151.3) ml/min/min^2, it was 122.0 (105.0 - 143.5) ml/min/min^2; for those in the 14 - 16 years age group and 107 (83.6 - 130) ml/min/min^2; for those in the 17 - <19 years.

3.2. Glomerular Hyperfiltration

Of the 153 adolescents with SCD, 51 (33.3%) had glomerular hyperfiltration but absent in 102 (66.7%). The mean estimated glomerular filtration rate of the SCD

Table 1. Demographic characteristics of the study population.

Characteristics	n (%) n = 153
Age. Mean ± SD in years	13.7 ± 2.5
Age Group	
10 - 13 years	70 (45.8)
14 - 16 years	57 (37.3)
17 - <19 years	26 (17.0)
Gender	
Female	79 (51.6)
Male	74 (48.4)
Haemoglobin S distribution	
Hb SS	115 (75.2)
Hb SC	31 (20.3)
Hb S/Sickle B$^+$ thal	5 (3.3)
Other	2 (1.3)

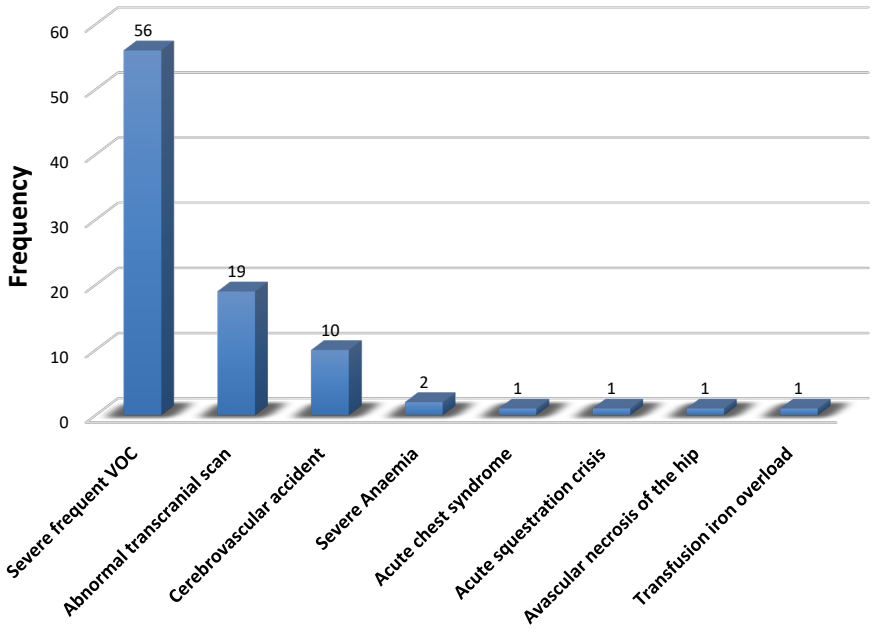

Figure 2. Reasons for being on sickle cell modifying therapy.

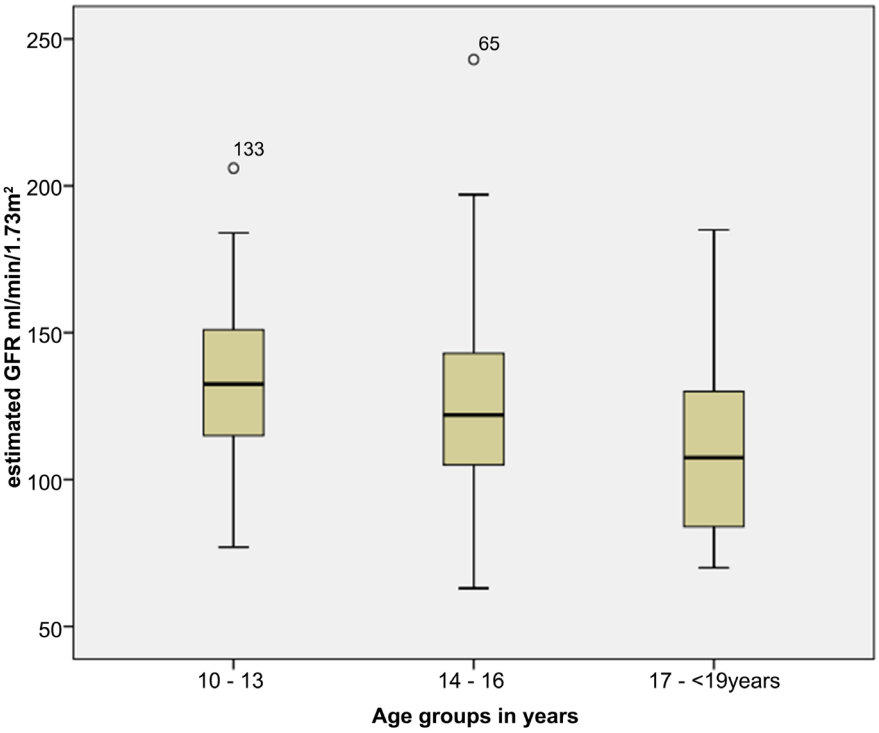

Figure 3. Box plot of the estimated glomerular filtration rate categorised into age groups.

adolescents who had hyperfiltration was 160.2 ± 20.0 ml/min/1.73m^2, and that of those with no hyperfiltration was 109.9 ± 19.3 ml/min/min^2.

The SCD adolescents with hyperfiltration were significantly younger than those without it. The mean age of those with hyperfiltration was 13.0 ± 2.4 years, while it was 14.1 ± 2.6 years for those with no hyperfiltration $P = 0.01$ CI: −1.904

- −0.213. There was no statistically significant difference in gender; however, they were more females amongst the SCD adolescents with hyperfiltration 28 (54.9%) versus 23 (45.1%), while the proportion of the males and females in the group of adolescents with no hyperfiltration were similar (See Table 2). A significantly higher percentage of adolescents with SCD who had hyperfiltration had the HbSS disease (47 (92.2%) versus 68 (66.7%); $P = 0.007$). However, among those with the HbSC disease variant, those with no hyperfiltration were more than those with hyperfiltration (27 (26.5%) versus 4 (7.8%)). Also, a higher proportion of SCD adolescents with hyperfiltration were on hydroxyurea therapy than those with no hyperfiltration 31 (60.8%) versus 39 (38.2%); $p = 0.01$. However, there was no significant difference between adolescents with hyperfiltration and those without hyperfiltration regarding the type of acute events they had experienced or their blood transfusion history. The demographic and clinical history of those with hyperfiltration and those with no hyperfiltration depicted in Table 2.

Table 3 shows the physical examination measurements and laboratory variables of the SCD adolescent with hyperfiltration and those with no hyperfiltration.

Table 2. Demographic and clinical history of those with hyperfiltration and those with no hyperfiltration

Characteristics	Hyperfiltration present n (%) n = 51 (33.3)	Hyperfiltration absent n (%) n = 102 (66.7)	*P*-value
Age group			
10 - 13 years	29 (56.9)	41 (40.2)	0.05
14 - 16 years	18 (35.3)	39 (38.2)	
17 - <19 years	4 (7.8)	22 (21.6)	
Gender			
Female	28 (54.9)	51 (50)	0.609
Male	23 (45.1)	51 (50)	
Haemoglobin Variants			
Hb SS	47 (92.2)	68 (66.7)	**0.007**
HB SC	4 (7.8)	27 (26.5)	
Sickle B^+ thal	0 (0.0)	5 (4.9)	
Other	0 (0.0)	2 (2.0)	
History of Acute events			
Severe recurrent VOC	21 (41.2)	28 (27.5)	0.405
Acute chest syndrome	9 (17.6)	19 (18.6)	
Cerebrovascular accident	5 (9.8)	7 (6.9)	
Acute sequestration crisis	1 (2.0)	2 (2.0)	
Combination of ACS/CVA	1 (2.0)	1 (1.0)	
None	14 (27.5)	45 (44.1)	
History of Chronic Blood Transfusion			
Yes	5 (9.8)	17 (16.7)	0.331
No	46 (90.2)	85 (83.3)	
History of Hydroxyurea therapy			
Yes	31 (60.8)	39 (38.2)	**0.01**
No	20 (39.2)	63 (61.8)	

Table 3. Physical examination measurements and laboratory variables of the SCD adolescent with hyperfiltration and those with no hyperfiltration.

Variables	Hyperfiltration Present n = 51 mean ± SD	Hyperfiltration Absent n = 102 mean ± SD	*P*-value	Confidence interval
Weight in Kg*	48.0 ± 18.0	54.8 ± 17.0	**0.026**	−12.807 - −0.843
Height in cm*	155.1 ± 13.1	160.6 ± 13.1	**0.016**	−10.003 - −1.026
BMI*	19.4 ± 5.0	21.0 ± 4.3	**0.043**	−3.172 - −0.048
SDP in mmHg	110.0 ± 10.8	112.9 ± 10.2	0.107	−6.435 - 0.631
DBP in mmHg	63.6 ± 8.9	65.5 ± 8.6	0.201	−4.856 - 1.033
Haemoglobin levels g/L	88.7 ± 13.3	98.1 ± 21.7	**0.001**	−14.988 - 3.744
Red blood cell count × 10^{12}/L	3.4 ± 2.7	3.6 ± 0.9	0.686	−0.946 - 0.627
White blood cell count × 10^{9}/L	9.7 ± 4.1	8.7 ± 3.6	0.160	−0.384 - 2.294
Reticulocyte count × 10^{9}/L	222.5 ± 104.3	190.9 ± 93.6	0.071	−2.784 - 65.941
Platelet count × 10^{9}/L	326.5 ± 141.6	280.2 ± 124.2	0.050	−0.019 - 92.688
Haemoglobin F levels %	8.1 ± 6.3	8.3 ± 9.0	0.376[+]	
Lactate dehydrogenase level IU/L	525.9 ± 180.3	449.6 ± 170.3	**0.014**	16.111 - 136.653
Serum ferritin levels µg/L	852.0 ± 1606.1	744.2 ± 1541.6	0.211[+]	
Serum creatinine levels mg/dl	0.4 ± 0.1	0.6 ± 0.2	**0.0001**	−0.261 - −0.193

**Missing data weight 5 Height 4 BMI 5 BMI Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; [+]Statistic test was Mann-Whitney U.

The adolescents with hyperfiltration had significantly lower weight (48.0 ± 18.0 versus 54.8 ± 17.0 kg; $p = 0.02$), height (155.1 ± 13.1 versus 160.6 ± 13.1 cm; $p = 0.01$), BMI (19.4 ± 5.0 versus 21.0 ± 4.3; $p = 0.04$) haemoglobin level (88.7 ± 13.3 versus 98.1 ± 21.7 g/L; $p = 0.001$), and serum creatinine level (0.4 ± 0.1 versus 0.6 ± 0.2 mg/dl; $p = 0.0001$) as compared to those with no hyperfiltration. The adolescents with hyperfiltration also had significantly higher lactate dehydrogenase levels (525.9 ± 180.3 versus 449.6 ± 170.3 IU/L; $p = 0.01$) compared to those with no hyperfiltration. Other parameters, namely their systolic blood pressures, diastolic blood pressure, red blood cell count, white blood cell count, reticulocyte count, platelet count, haemoglobin F levels, and serum ferritin levels, not significantly different in the two groups of adolescents with SCD. No factor was associated with glomerular hyperfiltration on multivariable analysis; **Table 4** shows the factors analysed using multivariable logistics regression.

3.3. Albuminuria

Twenty-four (15.7%) of the total normal of the adolescents with SCD studies had albuminuria, of which 22 (91.7%) had microalbuminuria, and 2 (8.3) had macroalbuminuria, thus in this study, the prevalence of microalbuminuria was 14.4%, and 1.3% was the prevalence of overt proteinuria. In this study, the proportion of albuminuria did not vary with increasing age. The age group-specific

Table 4. Logistic regression models showing the factors associated with glomerular hyperfiltration.

Factors	β Coefficient	Odds ratio	95% Confidence interval	*p*-value
Age in years	−0.129	0.879	0.760 - 1.016	0.082
Hemoglobin level g/L	−0.017	0.983	0.964 - 1.004	0.108
Lactate dehydrogenase level IU/L	0.001	1.001	0.999 - 1.004	0.194

prevalence was 6.5% for both the age groups 10 - 13 years and 14 - 16 years respectively, while 2.6% for the age group 17 - <19 years. Most of the children with albuminuria had Haemoglobin SS disease 18 (75.0%), 4 (16.7%) had haemoglobin SC, while 1 (4.2%) each had the Sickle cell β^+ thalassemia and HBS/HPFH variant, respectively.

4. Discussion

Glomerular hyperfiltration and albuminuria are the earliest evidence of renal impairment in SCD. This study is one of the first studies evaluating renal glomerular abnormalities exclusively in the adolescent SCD population. In this observational study, the prevalence of glomerular hyperfiltration and albuminuria were determined. The adolescents with SCD who had glomerular hyperfiltration were compared to those with no hyperfiltration.

From this study, a high proportion of adolescents with SCD had glomerular hyperfiltration, but the unavailability of similar studies in the adolescent age group of children with SCD precludes comparison. Nevertheless, since glomerular hyperfiltration is believed to be one of the drivers of renal glomerulopathy in SCD, this high prevalence of glomerular hyperfiltration observed in this study provides further evidence that a large proportion of children with SCD enter adult life already experiencing early asymptomatic glomerular abnormalities, which may subsequently develop into CKD. This highlights the importance of regular determination of glomerular filtration rate in children to ensure early identification and follow-up of the children that may develop chronic kidney disease in the future.

This study's finding that none of the factors examined was associated with glomerular hyperfiltration is at variance with previous studies. In the paediatric age group, the only available research on the determinants of glomerular hyperfiltration [10], reported that older age and reduced body mass index were factors associated with glomerular hyperfiltration. However, this study cannot be compared to the previous study because their definition of glomerular hyperfiltration differs. While this study defined glomerular hyperfiltration as GFR > 140 min/ml/1.73m^2 according to the standard clinical definition, the previous study's definition was GFR less than 140 min/ml/1.73m^2. Furthermore, this study's finding of no factor associated with glomerular hyperfiltration is also at variance with studies in the adult population. Haymann *et al.* reported that hyperfiltration was

associated with young age, a lower haemoglobin level and lower fetal haemoglobin level, of note this adult study included adolescents as young as 16 years [22].

Other studies by Aygun *et al.* and Wigfall *et al.* [8] [11] report that GFR decline toward normal during the adolescent years in children with SCD. In this study examining the adolescent age group alone, a progressive decline in GFR is observed. However, the onset age for the decline in GFR in this study is earlier than that reported by Aygun *et al.* In this current study GFR declined from the age group 14 years, but it was stated to decline from 16 years in the previous study [8]. Glomerular filtration rate differs depending on the method used in its determination. In this study, it was the creatinine-based Bedside Schwarz formula which is known to overestimate glomerular filtration rate, while in the study by Aygun *et al.*, measured glomerular filtration rate by plasma clearance of 99-technetium diethylenetriamine pentaacetate (99Tc-DTPA) was used, which correlated well with the gold standard inulin clearance [8]. This difference in methods used in the two studies may be responsible for the age difference regarding when the glomerular filtration rate decline in adolescents with SCD.

In this study, the adolescents with HbSS were more in the glomerular hyperfiltration group. Those with HbSC disease were predominantly in the group with no glomerular hyperfiltration, and those with all other types of sickle cell haemoglobin variant were also in the group with no glomerular hyperfiltration. This finding suggests that glomerular involvement in SCD is dependent on disease severity. Haemoglobin SC disease and sickle cell β^+ thalassemia are known to run a milder course with less frequent vaso-occlusive crises and other acute complications than SCA disease. In the study by Platt *et al.* on pain in sickle cell disease, they reported that the average rate of pain episode per patient-years in their SCA patient was 0.8, and this rate was twice that observed in their haemoglobin SC disease patient and those with sickle cell β^+ thalassemia [23]. Also. Castro *et al.* demonstrated that the incidence of acute chest syndrome was more amongst patients with sickle cell anaemia than those with Haemoglobin SC disease [24]. These studies support the notion that less vaso-occlusion results in reduced frequency of acute events, resulting in less chronic organ involvement; hence the kidney may be protected from glomerulopathy in milder SCD variants.

The prevalence of albuminuria in this study is inconsonant with the studies by Becton *et al.*, Aygun *et al.*, Brewin *et al.*, who reported a proteinuria prevalence of 15.1%, 15.5% and 15.9%, respectively [8] [9] [17]. Of note, in these studies, albuminuria was predominately observed after the age of 10years supporting the observation by other authors that glomerular damage possibly commences from the second decade of life. In this study, albuminuria was predominately microalbuminuria, and its prevalence amongst the adolescents with SCD was similar to a previous report by Alvarez *et al.*, who reported a microalbuminuria prevalence of 19% in their children ten years and older [16]. It was, however, in contrast with the report of Dharnidharka *et al.* that observed a microalbuminuria prevalence of 46% amongst their adolescent studied [13]. In the study by Dhar-

nidharka *et al.* the definition of microalbuminuria was urine albumin/creatinine ratio > 20 mg/g, which is 1.77 mg/μmol. This may have been responsible for the higher prevalence observed in that study.

The strength of this study is that it is the first study examining the characteristics and association of glomerular hyperfiltration in an exclusively adolescent population with a large sample size. One of the limitations of this study is its retrospective design. Since the data were obtained from a secondary source not intentionally recorded for research, missing data were observed for some variables; however, these were few. Another possible limitation that the study design may confer is the issue of measurement error. In particular, a potential limitation of this study is the serum creatinine-based formula used in deriving the estimated GFR. The Bedside Schwartz formula [19] can overestimate GFR because creatinine is secreted in the proximal tubules in healthy individuals. This physiological process may hyperfunction in individuals with SCD, resulting in increased creatinine secretion [25]. Aygun *et al.* compared measured GFR by plasma clearance with 99Tc-DTPA, which has been shown to correlate with the inulin clearance, the gold standard with and creatinine-based formulas [8]. They reported that the estimates of GFR by the modified Schwartz formula [26] positively correlated with the measured glomerular filtration rate by the plasma 99Tc-DTPA clearance [8]. This modified Schwartz formula was not used in this study as it requires estimates of serum cystatin C to compute the GFR estimates, which were unavailable as it was not routinely measured. Despite these limitations, the Bedside Schwartz formula [19] used in this study is currently the best non-invasive clinically approach in estimating GFR in children and adolescents. Finally, in this study on SCD, the comparison was mainly made to other studies on SCA alone. These studies are the available literature on glomerular hyperfiltration and albuminuria in children; nevertheless, most of the adolescents investigated in this current study had SCA.

In conclusion, this is the first adolescent SCD study demonstrating the prevalence of glomerular hyperfiltration, its associated factors and its relationship with albuminuria in a single cohort. This finding would be strengthened by prospectively monitoring renal function in a multicenter study.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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