

Factors influencing blood pressure fluctuation in pediatric patients with sickle cell disease in Saudi Arabia

A retrospective single-center cohort study

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ABSTRACT

الأهداف: هدفت هذه الدراسة البحثية إلى دراسة تأثير مرض فقر الدم المنجلي على ضغط الدم لدى الأطفال وتحديد العوامل التي قد تؤثر فيه.

المنهجية: وقد شملت الدراسة مئة طفل ممن يعانون من هذا المرض، وقد تم جمع البيانات السريرية وقياسات ضغط الدم ومستوى الهيموجلوبين الكلي والهيموجلوبين المنجلي والكرياتينين في الدم.

النتائج: أظهرت النتائج أن 68% من المرضى كان لديهم ضغط دم انقباضي طبيعي، 13% كان لديهم ضغط دم انقباضي مرتفع، 17% كانوا يعانون من ارتفاع ضغط الدم مرحلة 1، في حين أن 2% فقط كان لديهم ارتفاع ضغط الدم مرحلة 2 وفقاً لتصنيف ضغط الدم من قبل الأكاديمية الأمريكية لطب الأطفال (AAP، 2017). وجد أيضاً في هذه الدراسة أن الأطفال المصابين بزيادة في الوزن يعانون من ضغط دم أعلى مقارنة بالأطفال النحيفين أو ذوي الوزن الطبيعي. كما تبين أن متوسط ضغط الدم يرتبط بشكل كبير مع مؤشر كتلة الجسم ومستوى الكرياتينين في الدم.

الخلاصة: بناءً على ذلك، يمكن الاستنتاج أن الوزن الزائد ومستوى الكرياتينين في الدم قد يؤثران بشكل كبير على ضغط الدم لدى الأطفال المصابين بفقر الدم المنجلي. ومن الممكن لهذه الدراسة أن تساهم في فهم أفضل للعلاقة بين مرض فقر الدم المنجلي والتغيرات المصاحبة لهذا المرض في قياسات ضغط الدم، مما يساعد على التشخيص المبكر والعلاج لهذه الفئة العمرية.

Objectives: To investigate changes in blood pressure (BP) among pediatric patients with sickle cell disease (SCD) and determine the variables that might influence these changes.

Methods: A total of 100 pediatric patients with SCD who followed up in the pediatric outpatient clinic were recruited for this retrospective cohort study. Clinical data included anthropometric measures, average systolic and diastolic BP recorded during multiple follow-up visits, hemoglobin (Hb) level, serum creatinine, and hemoglobin S percentage. Blood pressure measurements were categorized according to the guidelines of the American Academy of Pediatrics (AAP, 2017).

Results: In this cohort, 68% of the patients had normal systolic BP, 13% had elevated systolic BP, 17% had stage 1 hypertension (HTN), while only 2% reported stage 2 HTN. Patients who were overweight had relatively high systolic BP compared to patients who were underweight ($p=0.034$) or had normal weight ($p=0.023$). The average systolic BP significantly correlates with body mass index ($r=0.377$, $p<0.001$) and serum creatinine ($r=0.369$, $p<0.001$).

Conclusion: Pediatric overweight SCD patients exhibited higher average systolic BP than those underweight or normal weight. Body mass index and serum creatinine significantly influenced the average systolic BP more than the Hb level or Hb S percentage.

Keywords: blood pressure, body mass index, sickle cell disease, hypertension, overweight

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Sickle cell disease (SCD) is a chronic form of hemolytic anemia with an autosomal recessive inheritance. It is caused by a mutation in the beta-globin chain of the hemoglobin molecule with the substitution of glutamic

acid with valine, explaining the aberrant development of erythrocytes into a distinctive sickle cell shape. The clinical manifestations of SCD vary according to the mutation type, which includes hemoglobin (Hb) SA disease (sickle cell trait), hemoglobin SS disease, and hemoglobin SC disease. Patients with SCD may present with typical hemolytic anemia and severe symptoms such as vaso-occlusive crisis (painful crisis), splenic sequestration crisis, and end-organ dysfunction.^{1,2}

The interaction between increased blood viscosity due to sickle hemoglobin polymerization, increased stroke volume, and decreased peripheral resistance can significantly determine blood pressure (BP) status in pediatric SCD patients. Blood pressure status is a crucial physiological measure because hypertension and hypotension can negatively affect the health of individuals. In addition to influencing long-term health outcomes, growth, and development, high BP can affect short-term health outcomes.^{3,4}

Despite abundant studies on the adverse effects and treatment of SCD, the association between BP and SCD in pediatric populations needs to be better understood. Several studies have shown that SCD patients have lower BP than the general population.⁵ Other studies have found no differences in BP between patients with SCD and healthy controls.⁴ However, some studies reported hypertension in a significant proportion of patients with SCD.^{6,7} In Saudi Arabia, the prevalence of SCD is significant, with 4.2% of the general population carrying the sickle cell trait while 0.26% carrying SCD.⁸

Notably, BP fluctuations in pediatric patients with SCD have yet to be studied in Saudi Arabia. This research aimed to investigate changes in BP among pediatric patients with SCD in Saudi Arabia and to determine the variables that might influence these changes.

Methods. The present investigation is a retrospective cohort study carried out at King Abdulaziz University Hospital, Jeddah, Saudi Arabia. The cohort comprised 100 individuals diagnosed with SCD, <18 years and were followed up in the outpatient clinics between January 2015 and December 2022. Patients with cardiovascular or renal structural abnormalities were excluded. The parents provided informed consent, and

the ethical board approved the study (Reference No 347-22).

Age, weight, height, body mass index (BMI), pulse rate, systolic, and diastolic BP were collected. The BP measurements were performed with the digital non-invasive automatic monitor for arterial BP during routine follow-up in the pediatric outpatient clinic and not during hospitalization for vaso-occlusive crisis. The systolic and diastolic BP was measured. An average of 2 to 3 readings were taken during outpatient visits within 3 months. Only one reading is recorded for each patient on the medical record system during each visit. The average systolic and diastolic BP were measured, and BP was graded according to the AAP 2017 guidelines.⁹ Blood pressure measurements were graded as normal, elevated, or stage 1 or 2 hypertension (HTN). The BMI percentiles of patients were then classified as underweight, normal weight, overweight, and obese based on the classification by the Center for Disease Control and Prevention (CDC) of BMI categories for children and teens.¹⁰ The most recent results regarding serum creatinine, Hb level, and Hb S percentage (HbS%) were collected. The estimated glomerular filtration rate (eGFR) was computed utilizing the bedside Schwartz formula [$eGFR=0.413*\text{height}/\text{serum creatinine}$]. In this formula, height is entered in cm, and creatinine is entered as mg/dl after conversion of the unit of serum creatinine measurement from $\mu\text{mol/L}$ to mg/dl by dividing the creatinine values by 88.4.¹¹

Statistical analysis. Jamovi software (The jamovi project [2022]. jamovi, version 2.3) was used for statistical analysis. The Shapiro-Wilk test tested the normality of numerical variables. Numerical data were presented as mean, standard deviation, median, interquartile range (25th-75th percentile), minimum, and maximum. Numbers and percentages were used to represent nominal variables. To compare 2 unrelated groups, we employed the parametric Student's t-test for quantitative variables that exhibited normal distribution and the non-parametric Mann-Whitney U test for those that did not. In contrast, we used a one-way ANOVA followed by post hoc tests to compare multiple unrelated groups. Pearson and Spearman correlation coefficients were used to examine the correlation between variables, and a p -value of <0.05 was considered statistically significant.

Results. One hundred patients with sickle cell anemia were enrolled in this retrospective cohort study. The minimum age was 7 years, the maximum was 17 years, and the average was 14.75 years. The average weight was 41.93 kg, the average BMI was 18.5, and

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Table 1 - Numeric clinical data of all patients (N=100).

Characteristics	Mean±SD	Min	Max	Percentiles		
				25th	50th	75th
Age (years)	14.75±2.60	7.00	17.0	13.00	16.00	17.00
Weight (kg)	41.93±12.78	14.95	81.7	31.88	41.00	50.20
Height (cm)	149.04±12.38	101.00	172.0	141.38	150.00	158.00
BMI	18.52±4.07	11.97	30.4	15.37	17.75	20.70
BMI percentile	33.08±33.84	1.00	97.0	2.75	20.00	63.25
Pulse rate (BPM)	93.25±12.88	64.00	131.0	85.75	94.00	101.00
Hb level (gm/dl)	8.51±1.52	5.30	13.1	7.70	8.45	9.10
Hb S%	69.40±20.41	11.20	94.9	54.55	78.40	85.85
Creatinine (µmol/L)	36.1±10.6	16.0	74.0	29.0	34.0	41.5
eGFR (ml/min/1.73m ²)	161.1±45.6	82.0	357.0	128.8	155.0	185.0
Average systolic BP (mmHg)	115.06±10.46	95.33	151.5	107.00	114.25	121.00
Average diastolic BP (mmHg)	65.94±9.30	43.50	110.0	60.92	65.50	70.00

BMI: body mass index, BP: blood pressure, BPM: beat per minute, Hb: hemoglobin, eGFR: estimated glomerular filtration rate, Min: minimum, Max: maximum

Table 2 - Categorical clinical data of all patients.

Characteristics	n (%)
Gender	
Male	55 (55)
Female	45 (45)
BMI	
Underweight	30 (30)
Normal weight	54 (54)
Overweight	14 (14)
Obese	2 (2)
Systolic BP	
Normal	68 (68)
Elevated	13 (13)
Stage 1 HTN	17 (17)
Stage 2 HTN	2 (2)
Diastolic BP	
Normal	89 (89)
Elevated	4 (4)
Stage 1 HTN	6 (6)
Stage 2 HTN	1 (1)
BP category	
Normal	68 (68)
Abnormally elevated	32 (32)

BP: blood pressure, BMI: body mass index, HTN: hypertension

the average recent Hb level at the time of BP recording was 8.5 g/dl. The mean Hb S level was 69.4%, the mean serum creatinine level was 36.1 µmol/L, and the mean eGFR was 161. **Table 1** shows the patients' clinical data.

Table 3 - Comparison between groups regarding body mass index (BMI) categories.

BMI Category	n	Mean±SD	SE	P-value
Age (years)				
Underweight	30	14.93±2.333	0.426	0.920
Normal weight	54	14.57±2.744	0.373	
Overweight	14	15.07±2.731	0.730	
Obese	2	14.50±3.536	2.500	
Average systolic BP (mmHg)				
Underweight [§]	30	113.64±10.151	1.853	0.019*
Normal weight [§]	54	113.65±10.024	1.364	
Overweight [§]	14	123.36±10.282	2.748	
Obese	2	116.67±0.943	0.667	
Average diastolic BP (mmHg)				
Underweight	30	64.60±9.216	1.683	0.739
Normal weight	54	66.01±8.831	1.202	
Overweight	14	68.63±11.776	3.147	
Obese	2	65.42±1.532	1.083	
Pulse rate (BPM)				
Underweight	30	95.33±12.767	2.331	0.298
Normal weight	54	90.50±12.589	1.713	
Overweight	14	98.86±12.532	3.349	
Obese	2	97.00±15.556	11.000	
Hemoglobin level (gm/dl)				
Underweight	30	8.43±1.443	0.263	0.481
Normal weight	54	8.44±1.447	0.197	
Overweight	14	8.64±1.652	0.442	
Obese	2	10.70±3.394	2.400	

SD: standard deviation, SE: standard error, BP: blood pressure, BPM: beat per minute *: Statistically significant, §: post-Hoc test (underweight-overweight, $p=0.034$), (normal weight-overweight, $p=0.023$).

Male patients constituted 55% of all cases. Regarding BMI, 54% of the patients had an average BMI, 30% were underweight, 14% were overweight, and only 2% were obese. Considering average systolic BP and based on the 2017 AAP grading of HTN, most patients (68%) had normal systolic BP, 13% had elevated systolic BP, 17% had stage 1 HTN, 2% had stage 2 HTN. **Table 2** presents the categorical clinical information of the study participants.

The BMI percentiles categorized the patients into 4 distinct ordinal groups (underweight, average, overweight, and obese). These groups did not differ significantly regarding recent Hb levels or average diastolic BP. The overweight group had substantially higher average systolic BP (123 mmHg) than the underweight and normal weight groups (113.6 mmHg; $p=0.019$). A comparison between the patient groups based on BMI categories is shown in **Table 3**.

Patients were separated into 2 groups based on their average systolic BP: i) normotensive group, which had a normal average systolic BP, and ii) hypertensive group,

Table 4 - Comparison between normotensive and hypertensive groups.

High BP (yes/no)	n	Mean±SD	Percentiles			P-value
			25th	50th	75th	
<i>Age (years)</i>						
Normotensive	68	14.91±2.45	14.00	16.00	17.00	0.552
Hypertensive	32	14.41±2.92	12.75	16.00	17.00	
<i>Weight (kg)</i>						
Normotensive	68	39.93±11.96	30.00	39.25	45.75	0.017
Hypertensive	32	46.18±13.61	37.92	48.05	56.50	
<i>Height (cm)</i>						
Normotensive	68	148.27±11.42	140.75	150.00	156.00	0.191
Hypertensive	32	150.67±14.28	144.38	152.25	160.88	
<i>Body mass index</i>						
Normotensive	68	17.84±3.74	15.32	17.26	19.28	0.022
Hypertensive	32	19.95±4.43	16.92	19.16	23.39	
<i>Pulse rate (BPM)</i>						
Normotensive	68	89.93±11.36	83.75	91.00	98.00	<.001
Hypertensive	32	100.31±13.22	93.50	98.00	108.50	
<i>Serum creatinine (µmol/L)</i>						
Normotensive	66	35±10.2	29.0	33.0	40.0	0.142
Hypertensive	29	38.7±11.2	32.0	38.0	47.0	
<i>eGFR (ml/min/1.73m²)</i>						
Normotensive	66	165.8±48.4	134.1	155.1	193.3	0.213
Hypertensive	29	150.6±37.1	119.9	151.0	175.1	
<i>Hb level (gm/dl)</i>						
Normotensive	68	8.62±1.60	7.77	8.50	9.15	0.311
Hypertensive	32	8.28±1.32	7.52	8.15	9.03	
Normotensive	50	68.75±20.70	52.82	76.55	86.10	0.825
<i>Hb S %</i>						
Hypertensive	21	70.96±20.11	65.60	79.50	85.70	

BP: blood pressure, Hb: hemoglobin, eGFR: estimated glomerular filtration rate, BPM: beat per minute

Table 5 - Correlation between weight, height, BMI, and average systolic blood pressure.

Correlated parameters	Correlation coefficient (r)	P-value
<i>Average Systolic blood pressure</i>		
BMI	0.377	<0.001
Weight	0.525	<0.001
Height	0.498	<0.001
Pulse rate	0.264	0.008
Hb level	0.122	0.226
Serum creatinine	0.369	<0.001
eGFR	-0.270	0.008
Hb S%	-0.011	0.927

BMI: body mass index, Hb: hemoglobin, eGFR: estimated glomerular filtration rate

which comprised patients with elevated BP, stage 1 HTN, and stage 2 HTN. Age, Hb level, and HbS% did not differ significantly between the normotensive and hypertensive groups. The hypertensive group had

considerably greater body weight, BMI, and pulse rate than the normotensive group, as seen in [Table 4](#). The average systolic BP showed a statistically significant positive correlation with weight, height, BMI, heart rate, and creatinine. In contrast, the average systolic BP correlates negatively to the eGFR, as shown in [Table 5](#) and [Figure 1](#).

Discussion. Changes in BP among patients with SCD have varied in previous studies. In this cohort, 13% of the study population had elevated BP. In comparison, 17% had stage 1 HTN, and 2% had stage 2 HTN. This contrasts with earlier studies that reported lower BP readings in individuals with SCD.^{5,12}

Prehypertension is characterized by BP readings that exceed the 90th percentile but fall below the 95th percentile. Our study revealed a prehypertension prevalence of 13%, consistent with several other studies' findings. For instance, Shatat et al¹³ reported a

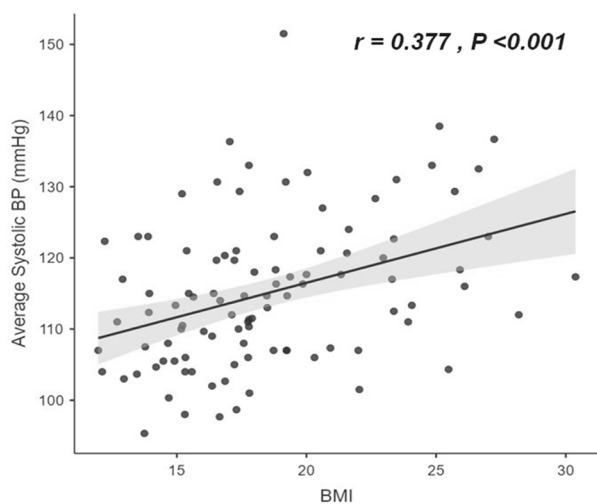


Figure 1 - Correlation between body mass index (BMI) and average systolic blood pressure. BP: blood pressure

prehypertension prevalence of 10% among adolescent patients with SCA, whereas Becker et al¹⁴ found a prevalence of 17% in a similar population.

Previous research has described the prevalence of hypertension among patients with SCD owing to a substantially faster decline in renal function. Because the kidney is a highly vascular organ, it is vulnerable to vaso-occlusive events. Hematuria, proteinuria, concentrating defects, renal insufficiency, and hypertension are symptoms of hemodynamic changes caused by chronic anemia, renal hypoxia from recurrent vaso-occlusion, and hemolysis-related endothelial dysfunction that can progress to chronic kidney disease (CKD).¹⁵⁻¹⁷

Although our patients had normal renal function test results, subtle renal dysfunction could not be excluded. In this study, the average systolic BP was positively correlated with serum creatinine while negatively correlated to the eGFR. This finding may be related to the close link between renal function reflected by serum creatinine/eGFR and BP.^{18,19} Usually, serum creatinine levels do not increase except after a significant loss of renal function. Early dysfunction can be detected by measuring unique markers, namely cystatin C, kidney injury molecule 1 (KIM1), and neutrophil-associated gelatinase lipocalin (NGAL), which were not performed in our cohort. Moreover, unlike our study, previous studies were conducted mainly on adult patients whose kidneys were exposed to the previously mentioned risk factors for a prolonged duration compared to pediatric patients.

Hypertension prevalence was 19% among SCD patients in our study; this aligns with the results of a prior investigation in Ghana.⁷ Other studies have reported SCD prevalence rates ranging from 3.2% to 10% for hypertension.^{20,21} Bodas et al²² found that 16.7% of children with SCD had abnormal BP (elevated BP or hypertension). Based on clinical BP measurements, Shatat et al¹³ reported a lower prevalence of HTN (10.3%) among children with SCD during BP measurement in clinic visits. However, ambulatory BP measurements revealed an elevated prevalence of HTN (43.6% in their study population). This implies that our cohort's actual hypertension prevalence may have been higher than the 19% observed in our study.

Although most previous reports have demonstrated hypertension in SCD patients, few studies have documented normal BP despite abnormally calculated glomerular filtration rates.^{23,24}

According to our data, age, Hb levels, and HbS% did not differ considerably between the normotensive and hypertension groups. In contrast, the hypertensive group had a substantially higher BMI and pulse rate than the normotensive group, and the average systolic BP was positively correlated with BMI and serum creatinine while negatively correlated to the eGFR. Similar to the results reported by and Pegelow et al⁵ and Oguanobi et al²⁵ who reported a positive correlation between BMI and systolic and diastolic BP, we found a positive correlation between BMI and systolic BP.

Study limitations. The present study exhibits certain limitations. The study design was retrospective, and the sample size was limited. Furthermore, only one Saudi Arabian center was used for the research, which might determine how broadly the findings could be applied. Additionally, ambulatory BP monitoring, urine analysis, albumin-to-creatinine ratio, renal ultrasound, and markers of renal injuries, such as NGAL, cystatin C, and KIM1, were not performed in all patients to determine the effect of functional renal abnormalities on BP. Future research in Saudi Arabia should use larger sample sizes and prospective study designs to validate these results.

In conclusion, patients with SCD who were overweight or obese had a higher average systolic BP than those underweight or normal. In addition, the patients' BMI affected the average systolic BP substantially more than the Hb level or HbS percentage.

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