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ARTICLE

A new method of determining factors affecting arterial blood pressure indices among young adults with Sickle Cell Anaemia and Haemoglobin AA in Nigeria

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Abstract

Sickle Cell Anaemia (SCA) is a genetic blood disorder caused by a mutation in the haemoglobin gene, leading to the production of abnormal haemoglobin known as haemoglobin S. This abnormal haemoglobin causes red blood cells to become rigid, sticky, and shaped like a crescent or sickle, which obstructs blood flow and leads to various complications such as pain, infections, and potential damage to nerves and organs (kidneys, liver and spleen). This research utilizes a two-level factorial experiment to evaluate the impact of four major factors (Age, Sex, Genotype, and Rhythm) on six distinct blood pressure (BP) indices: Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Pulse Rate (PR), Pulse Pressure (PP), Mean Arterial Pressure (MAP), and Rate Pressure Product (RPP). The experimental units consist of young adults with Sickle Cell Anaemia (SCA) and Haemoglobin AA (HbAA). The results indicate that Age and Genotype are the major factors affecting blood pressure (BP) indices. Meanwhile, Pulse Pressure (PP) appears to be more sensitive to the aforementioned factors when compared to SBP or DPB in terms of sensitivity. Also, the interaction effects between Age and Genotype, and between Age and Sex demonstrate clinical relevance. Importantly, these results highlight the importance of early detection of

abnormal cardiovascular symptoms and open ways for further heart disease diagnostic tests and treatments in young adults. It is also worthwhile to note that Pulse Pressure (PP) provides a more comprehensive measure for abnormal cardiovascular detection among young adults.

Keywords: Sickle Cell Anaemia, Blood Pressure Indices, Factorial Experiment, and Treatment Effects.

1. Introduction

Sickle Cell Anaemia (SCA) is a genetic blood disorder caused by a mutation in the haemoglobin gene, leading to the production of abnormal haemoglobin known as haemoglobin S (Kumar *et al.,* 2021). This abnormal haemoglobin causes red blood cells to become rigid, sticky, and shaped like a crescent or sickle, which can obstruct blood flow and lead to various complications such as pain, infections, and organ damage (Rees *et al.,* 2010). Sickle cell anaemia (SCA) is highly prevalent in sub-Saharan Africa, with Nigeria carrying a substantial share of the disease burden (Grosse, *et al.* 2018). According to the World Health Organization (2020), Nigeria has the highest number of individuals with SCA, with approximately 150,000 births affected each year. It is the most common genetic disorder in humans, particularly among individuals of African descent, though it is also observed in other ethnic groups (Mengnjo *et al., 2016*). A systematic review of randomized controlled trials (RCTs) was conducted by (Gyamfi *et al., 2021*) and implemented evidence-based interventions (EBIs) for managing sickle cell disease (SCD) in low and middle-income countries (LMICs). The review synthesized data on various therapies and highlighted key implementation research outcomes reported in these trials. The study emphasized the need for rigorous evaluation methods and identified significant barriers to effective SCD management in LMICs, including limited access to therapies, lack of provider knowledge, and high treatment costs.

Arterial blood pressure (BP) is a critical physiological parameter that reflects the force exerted by circulating blood on the walls of blood vessels. Proper regulation of BP is essential for maintaining cardiovascular health (Hall, 2021). Recent research has underscored the critical need for comprehensive health assessments in individuals with SCA, particularly in young adults, transitioning from pediatric to adult healthcare services (Blinder, *et al.* 2013). Sickle red cells differ in physical shape from normal red cells with a curved sickle-shape rather than flat-disc-shaped cells. As such, the cells are more likely to hemolyze, cause blockages in the blood vessels and disrupts the flow of blood (Smith and Yolanda, 2021). Blood Pressure (BP) indices provide important measures of cardiovascular function and are critical for assessing the health status of individuals with SCA(Liem *et al.,* 2017). The key BP indices include Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP), Pulse Pressure (PP), Pulse Rate (PR) and Rate Pressure Product (RPP). (Adewoyin, *2*015) noted that traditional approaches to evaluating blood pressure (BP) indices in individuals with SCA often fall short in capturing the complex interactions of various factors influencing BP. These methods typically focus on standard measurements such as systolic and diastolic BP, which may not fully account for the unique pathological aspects of SCA. It is also worthwhile to know that a significant remark was made by (Montgomery, *2*017) on the extensive application of factorial designs in experiments that involve multiple factors. Such designs are practically valuable when it becomes necessary to investigate the joint (interaction) effects of various factors on a response. He then outlined the general methods for analyzing factorial designs, with special attention to the k factors in which each factor operates at two levels and is able to estimate the main and interaction effects.

A study reviewed ten distinct research journals and concluded that dominant factors influencing the incidence of hypertension with respect to attitude include smoking and excessive consumption

of salt and coffee, (Sauma, *et al*., 2022). The (Lugo-Mata *et al.,* 2017) study revealed that there is an association between age, family history and hypertension but no association was found with gender, educational level, body mass index and hypertension. A study conducted by (Asafa, *et al.,* 2023) showed that SCA is associated with lower SBP, DBP, and MAP and higher PP when compared with age and sex in young adults with normal haemoglobin type. In 2003 the Asia Pacific Cohort Studies Collaboration suggested in their study that SBP is statistically more important than DBP as a measure for determining the cardiovascular disease in Asia Pacific populations and that serious emphasis on PP should be avoided since there was no evidence that it has a stronger association than SBP.

In previous researches, it was observed that comparisons were majorly made on ranking degree of blood pressure (BP) indices such as SBP, DBP and MAP see (Asafa *et al.,* 2023) and (Asia Pacific Cohort Studies Collaboration, 2003). However, attention was not given to the real factors that influence the BP indices which is of course important. As such, this study aims to determine the factors affecting or influencing blood pressure (BP) indices among Age, Sex, Genotype, and Rhythm with respect to the physical development in young adults with SCA and normal haemoglobin AA. Also, to determine whether these main effects or interaction effects are associated.

2. Methodology

In this section, the source and structure of the experimental data used in this research is explained with simplicity in the design construction.

2.1 Data Source and Structure

This study involved two groups of young adults, the first group comprises 69 patients with the Sickle Cell Anaemia (SCA) gene but in a steady state while the second group comprises 63 patients with the haemoglobin (AA) gene also in a steady state. The experimental units are within the age of 18-35 years without any acute crisis or illness in the last two weeks prior to the time this data were obtained. This experiment was carried out by the Department of Physiological Sciences, Obafemi Awolowo University, Ile-Ife, Nigeria. Information on Age (Factor A), Sex (Factor B), Genotype (Factor C) and Rhythm (Factor D) were obtained with respect to the following blood pressure indices: Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Pulse Rate (PR), Pulse Pressure (PP), Mean Arterial Pressure (MAP).

Table 1. Structural Representation of Factors and Levels

S/N	Factors	Low	High
1	Age (A)	-1 ($\leq$ 20)	+1 (> 20)
2	Sex (B)	-1 (Male)	+1 (Female)
3	Genotype (C)	-1 (AA)	+1 (SCA)
4	Rhythm (D)	-1 (Sinus rhythm)	+1 (Bradycardia)

It is noted that each factor was considered at two levels, coded as (-1, +1) which correspond to low and high levels, respectively (Table 1). Therefore, the design model is a linear additive presented as:

$$\begin{aligned} \gamma_{ijklm} = \mu + \tau_i + \alpha_j + \beta_k + \gamma_l + (\tau\alpha)_{ij} + (\tau\beta)_{ik} + (\tau\gamma)_{il} + (\alpha\beta)_{jk} + (\alpha\gamma)_{jl} + (\beta\gamma)_{kl} \\ +(\tau\alpha\beta)_{ijk} + (\tau\alpha\gamma)_{ijl} + (\tau\beta\gamma)_{ikl} + (\alpha\beta\gamma)_{jkl} + (\tau\alpha\beta\gamma)_{ijkl} + \epsilon_{ijklm}, \end{aligned} \tag{1}$$

where:

- μ is the overall mean effect.
- τ_i is the effect of the ith level of factor A, $i = 1, 2$.
- α_j is the effect of the jth level of factor B, $j = 1, 2$.
- β_k is the effect of the kth level of factor C, $k = 1, 2$.
- γ_l is the effect of the lth level of factor D, $l = 1, 2$.
- ϵ_{ijklm} is a random error component, $i, j, k, l, m = 1, 2$.

Thus, i, j, k, l represent the number of levels of the individual factors with respect to Age, Sex, Genotype, and Rhythm.

2.2 Design Structure

In this experiment, a 2^k factorial design, with $k = 4$ factors and 2 levels each is considered with all possible combinations of levels across the four factors. This results into $2^4 = 16$ experimental runs with 3 distinct replications. Meanwhile, to obtain the main and interaction effects the contrasts are calculated by summing the product of the coded levels (+1 and -1) for each factor with respect to their response values.

Table 2. Yates Order Structure of (- and +) Signs for the 2^4 Factorial Design

Run Label	(I)	A	B	AB	C	AC	BC	ABC	D	AD	BD	ABD	CD	ACD	BCD	ABCD
(I)	+	-	-	+	-	+	+	-	-	+	+	-	+	-	-	+
a	+	+	-	-	-	-	+	+	-	-	+	+	+	+	-	-
b	+	-	+	-	-	+	-	+	-	+	-	+	+	-	+	-
ab	+	+	+	+	-	-	-	-	-	-	-	-	+	+	+	+
c	+	-	-	+	+	-	-	+	-	+	+	-	-	+	+	-
ac	+	+	-	-	+	+	-	-	-	-	+	+	-	-	+	+
bc	+	-	+	-	+	-	+	-	-	+	-	+	-	+	-	+
abc	+	+	+	+	+	+	+	+	-	-	-	-	-	-	-	-
d	+	-	-	+	-	+	+	-	+	-	-	+	-	+	+	-
ad	+	+	-	-	-	-	+	+	+	+	-	-	-	-	+	+
bd	+	-	+	-	-	+	-	+	+	-	+	-	-	+	-	+
abd	+	+	+	+	-	-	-	-	+	+	+	+	-	-	-	-
cd	+	-	-	+	+	-	-	+	+	-	-	+	+	-	-	+
acd	+	+	-	-	+	+	-	-	+	+	-	-	+	+	-	-
bcd	+	-	+	-	+	-	+	-	+	-	+	-	+	-	+	-
abcd	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

3. Analysis and Results

Here, the data obtained from the clinical experiment would be analyzed, and the Analysis of Variance (ANOVA) is obtained and discussed in Section 4. Also, the predictive models for the blood pressure (BP) indices: SBP, DBP, PR, PP and MAP are developed and presented in Equation 2 through 5.

Table 3. The Probability Effect of Design Factors on SBP, DBP, PR, PP and MAP

Design Factors	Pr(> |t|): SBP	DBP	PR	PP	MAP
Age	0.014	0.0700	0.7960	0.52300	0.0295
Sex	0.119	0.6407	0.0462	0.00784	0.8397
Genotype	0.0066	0.0002	0.0138	0.04268	0.0003
Rhythm	0.101	0.0748	0.7291	0.68801	0.0601
Age:Sex	0.686	0.9729	0.1411	0.87535	0.8743
Age:Genotype	0.433	0.1873	0.8811	0.02628	0.4553
Age:Rhythm	0.142	0.5029	0.2926	0.16515	0.3114
Sex:Genotype	0.595	0.6083	0.2706	0.22569	0.8852
Sex:Rhythm	0.276	0.8734	0.7832	0.26334	0.5853
Genotype:Rhythm	0.898	0.8097	0.6211	0.63006	0.8664

The regression model for predicting SBP, DBP, PR, PP and MAP with the average responses as 112.656, 71.46, 74.8, 41.71875 and 85.0563 are presented via Equation 2, 3, 4, 5 and 6 respectively, where the coded variables x_1, x_2, x_3, x_4 take on values between -1 and +1. :

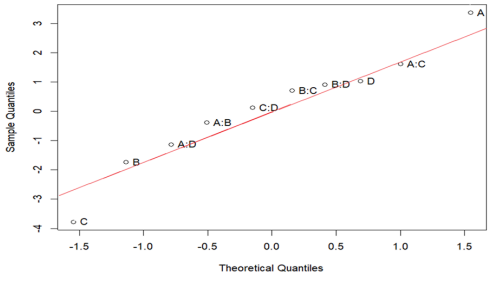
$$\hat{y} = 112.656 + 3.35625x_1 - 1.98125x_2 - 3.76875x_3 + 1.59375x_4 - 1.10625x_1x_2 - 1.60625x_1x_3 - 1.85625x_1x_4 + 1.26875x_2x_3 + 1.48125x_2x_4 - 0.23125x_3x_4. \quad (2)$$

$$\hat{y} = 71.4625 + 2.99x_1 + 1.1125x_2 - 6x_3 + 1.5375x_4 - 1.0125x_1x_2 - 0.875x_1x_3 - 0.4125x_1x_4 + 0.25x_2x_3 + 0.7125x_2x_4 - 0.17x_3x_4, \quad (3)$$

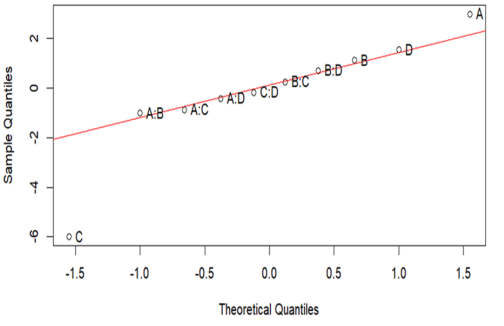
$$\hat{y} = 74.8 + 0.8125x_1 + 3.2x_2 + 2.9375x_3 + 0.8x_4 + 2.3625x_1x_2 - 0.15x_1x_3 - 0.9375x_1x_4 + 1.1375x_2x_3 + 0.1x_2x_4 - 0.1875x_3x_4. \quad (4)$$

$$\hat{y} = 41.71875 + 0.49375x_1 - 3.08125x_2 + 1.94375x_3 + 0.30625x_4 + 0.11875x_1x_2 - 2.24375x_1x_3 - 1.16875x_1x_4 + 0.99375x_2x_3 + 0.90625x_2x_4 - 0.36875x_3x_4, \quad (5)$$

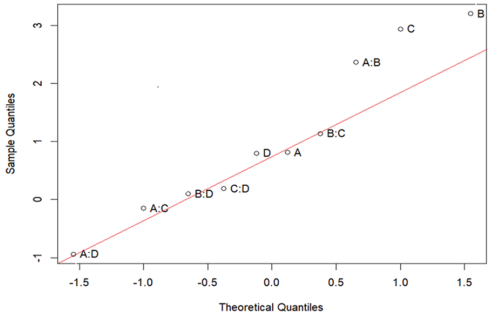
$$\hat{y} = 85.0563 + 3.1063x_1 + 0.1063x_2 - 5.2313x_3 + 1.5688x_4 - 1.0188x_1x_2 - 0.1063x_1x_3 - 0.9063x_1x_4 + 0.6435x_2x_3 + 1.0188x_2x_4 - 0.1438x_3x_4 \quad (6)$$



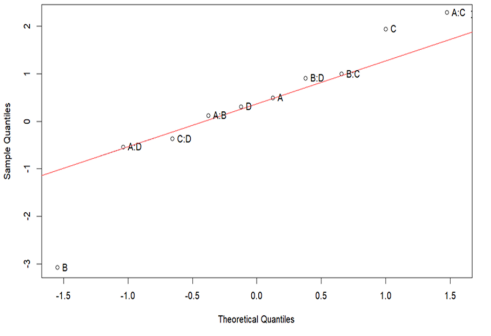
(a) Normal Probability plot of the effect for the 2^4 Factorial design for Average SBP



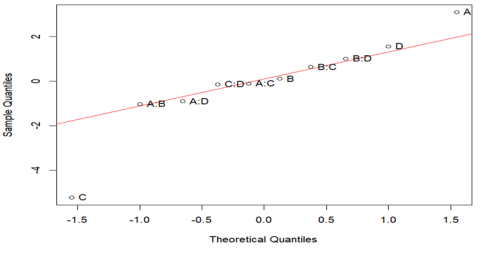
(b) Normal Probability plot of the Effects for DBP



(c) Normal Probability plot of effects for PR



(d) Normal Probability Plot of Effect for PP



(e) Normal Probability Plot for Effects of MAP

Figure 1. Collection of Normal Probability Plots for Different Blood Pressure Indices

4. Results and Discussion

This study examined the influence of four categorical factors: Age, Sex, Genotype, and Rhythm on five key blood pressure (BP) indices: Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Pulse Rate (PR), Pulse Pressure (PP), and Mean Arterial Pressure (MAP), using a two-level factorial experimental design. The primary objective was to identify the main and interaction effects of these variables and their contributions to variations in BP indices among young adults with sickle cell anaemia (SCA) and normal haemoglobin (AA).

The results revealed that Genotype was the most significant determinant across all BP indices considered. In particular, it exhibited highly significant effects on DBP ($p = 0.0002$) and MAP ($p = 0.0003$), underscoring the profound influence of sickle cell pathology on cardiovascular function. These findings are consistent with prior research indicating that individuals with the HbSS genotype often experience chronic cardiovascular complications due to hemolysis, increased vascular resistance, and endothelial dysfunction (Piel et al., 2017; Rees et al., 2010).

The improvement in the quality of life in patients with sickle cell disease has been closely linked to advances in early diagnosis and implementation of specific comprehensive therapies (e.g., hydroxyurea) (Rees et al., 2010). Age significantly influenced SBP ($p = 0.014$) and MAP ($p = 0.0295$), highlighting the role of physiological development in shaping BP outcomes. As arterial stiffness and systemic vascular resistance tend to increase with age, these findings reflect known age-related trends in cardiovascular physiology. However, the low effect of age on other BP indices (PR ($p = 0.7960$) and PP ($p = 0.52300$)) could be attributed to the relatively narrow age range in the study sample, and a low effect of age was also observed** in similar studies involving young adult populations (Platt et al., 1994; Rees et al., 2010). Sex also showed significant associations with specific BP indices, particularly PP ($p = 0.00784$) and PR ($p = 0.0462$). These results may be related to sex-based differences in hormonal profiles, autonomic regulation, or cardiovascular responsiveness. Previous studies have suggested that females may exhibit more favorable BP patterns and heart rate variability, though this may vary depending on age, genotype, and other contextual factors (Platt et al., 1994; Yawn et al., 2014; Rees et al., 2010).

Rhythm showed marginal significance on DBP ($p = 0.0748$) and MAP ($p = 0.0601$). While not statistically significant at the 5% level of significance, these results suggest a potential influence of rhythm on BP regulation that merits further investigation, particularly in the context of autonomic dysfunction in SCA, where abnormal heart rate variability and dysrhythmias have been observed (Kolo et al., 2013).

Notably, interaction effects were mostly non-significant, suggesting that the main effects of Age, Sex, Genotype, and Rhythm act independently on BP indices. However, an exception was observed in the Age × Genotype interaction, which was significant and implied a synergistic effect between developmental stage and genetic status on certain BP outcomes. This finding aligns with prior research indicating that genetic effects on blood pressure can be modulated by age, suggesting that the influence of genotype may vary across different stages of physiological development (Winkler et al., 2024; Simino et al., 2014; Shi et al., 2009). Figures 1a through 1e provide visual evidence supporting these.

5. Conclusion

In this real-world study, we have shown that Genotype has played a significant role by distinguishing itself as a major factor influencing the blood pressure (BP) among the young adults in Nigeria. It has also been identified as one of the major factors influencing patients with sickle cell

disease (SCD). This study also showed that Age and Sex had a significant effect, suggesting their potential influence in complementing Genotype to achieve a more comprehensive assessment and the detection of BP variations. It is also worthwhile to note that the significant interaction effect of Age and Genotype was observed, indicating the importance of genetic effects on BP are modulated by age. This underscores the complexity of BP dynamics in SCD and supports a more nuanced, multi-factorial approach to its clinical management.

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Conflicts of Interest

The authors declare no conflict of interest.

Author Contributions

Conceptualization: SAKA,A.J.; AKINTUNDE,M.A.; ADELEKE,K.A. **Data curation:** SAKA, A.J.; AKINTUNDE, M.A.; ADELEKE, K.A.; ASAFA, M.A. **Formal analysis:** SAKA, A.J.; AKINTUNDE, M.A.; ADELEKE, K.A. **Investigation:** SAKA, A.J.; AKINTUNDE, M.A.; ADELEKE, K.A.; ASAFA,M.A.; OSUOLALE,K.A. **Methodology:** SAKA,A.J.; AKINTUNDE,M.A.; ADELEKE, K.A.; OSUOLALE, K.A.; BUENO FILHO, J.S.S. **Software:** SAKA, A.J.; AKINTUNDE, M.A.; ADELEKE, K.A. **Resources:** SAKA, A.J.; AKINTUNDE, M.A.; ADELEKE, K.A. **Supervision:** SAKA, A.J.; AKINTUNDE, M.A.; ADELEKE, K.A. **Validation:** SAKA, A.J.; AKINTUNDE, M.A.; ADELEKE,K.A. **Visualization:** SAKA,A.J.; AKINTUNDE,M.A.; ADELEKE,K.A. **Writing original draft:** SAKA, A.J.; AKINTUNDE, M.A.; ADELEKE, K.A.; BUENO FILHO, J.S.S. **Writing-review and editing:** SAKA, A.J.; ; OSUOLALE,K.A.; ADELEKE, K.A

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