

**POTENTIAL PREDICTORS OF MUSCULOSKELETAL MANIFESTATIONS IN
PAEDIATRIC PATIENTS WITH SICKLE CELL DISEASE AT THE UNIVERSITY
TEACHING HOSPITAL, LUSAKA**

By

RAYMOND MPANJILWA MUSOWOYA

**A dissertation submitted to the University Of Zambia in partial fulfilment of the
requirements for the Master of Medicine in Orthopaedic and Trauma Surgery**

THE UNIVERSITY OF ZAMBIA

LUSAKA

2019

COPYRIGHT

All rights reserved, no part of the dissertation may be reproduced, stored in a retrieval system or transmitted in any form by any other means, electronic, mechanical, photocopying or recording without prior consent from the author.

By Dr Raymond Mpanjilwa Musowoya

2019

DECLARATION

I, **Raymond Mpanjilwa Musowoya**, hereby declare that this dissertation herein presented for the Degree of Master of Medicine (Orthopaedic and Trauma Surgery) has not been previously submitted wholly or in part for any other degree at this or any other university nor is it being currently submitted for any other degree.

Signed.....(Candidate)

by.....(Supervisor 1)

by.....(Supervisor 2)

APPROVAL

This dissertation of **Dr Raymond Mpanjilwa Musowoya** is approved as fulfilling part of the requirements for the award of the Degree of Master of Medicine in Orthopaedic and Trauma Surgery by the University of Zambia, subject to the examiner's report

Examiner 1.....

Signature Date

Examiner 2.....

Signature Date.....

Examiner 3.....

Signature Date.....

Board of Examiners' Chairperson.....

Signatures..... Date.....

Supervisor.....

Signature..... Date.....

ABSTRACT

Sickle Cell Disease (SCD) is an autosomal recessive inherited condition characterized by the inheritance of two abnormal genes coding for the formation of Haemoglobin and one of them is Haemoglobin s. Musculoskeletal manifestations are the commonest clinical presentations of both acute and chronic cases of vaso-occlusive crisis (VOC). According to the Surgical department (of the University Teaching Hospital, Lusaka) audits done in the last 3 years, patients with SCD have been presenting very late with advanced musculoskeletal manifestations.

The objective of this study was to explore the potential predictors of Musculoskeletal Manifestations in Paediatric patients presenting with Sickle Cell Disease seen at the University Teaching Hospital, Lusaka. The specific objectives were: To determine the commonest musculoskeletal manifestations in paediatric patients presenting with Sickle Cell Disease seen at University Teaching Hospital; then to determine the socio-demographic factors associated with these musculoskeletal manifestations of Sickle Cell Disease; and finally, was to establish if there was any relationship between the musculoskeletal manifestations and the potential predictors.

This was an unmatched case-control study conducted at the University Teaching Hospital in Lusaka, Zambia. This study was conducted between January and April 2019. A total of 171 patients all with SCD of 16 years or below were recruited. The ‘cases’ had Musculoskeletal Manifestations, while the ‘controls’ did not have. A full assessment of these patients was done to establish these musculoskeletal manifestations and their potential predictors.

The commonest musculoskeletal manifestations were found to be Chronic Osteomyelitis (29.82%), Acute Osteomyelitis (21.05%) and Avascular necrosis of the femoral head (14.04%). The median age for the cases was 9.5 years (Interquartile range (IQR), 7 – 12) while for the controls was 7 (IQR, 4 – 11). Increase in age ($p=0.003$), age at diagnosis ($p<0.001$), monthly income ($p=0.03$), percentage of Haemoglobin s (<0.001), frequency of vaso-occlusive crisis ($p<0.001$) and Aspartate transaminase ($p=0.01$) had a significant association with the development of musculoskeletal manifestations. However, using multivariable logistic regressions: Increase in age, frequency of vaso-occlusive crisis and the percentage of Haemoglobin s were the only variables with significant association.

Musculoskeletal manifestations are common and their main predictors are: Increase in age, frequency of vaso-occlusive crisis and percentage of Haemoglobin s. Chronic Osteomyelitis is the commonest musculoskeletal manifestation in the paediatric population with SCD seen at the University Teaching Hospital, Lusaka.

Keywords: Sickle Cell Disease, Sickle Cell Anaemia, Musculoskeletal Manifestation, Vaso-Occlusive Crisis

DEDICATION

I would like to dedicate this research work to my wife, Tendai Musowoya and my parents, Hatchwell and Hildah Musowoya. Thank you so much for your encouragement.

ACKNOWLEDGEMENT

I would like to sincerely thank my supervisors Dr James Munthali and Dr Catherine Chuunda-Lyoka for their input in this research paper. I have learnt a lot from my supervisors during this whole process.

I would also like to thank Prof Yakub Mullah, Prof Belington Vwalika and my late grandfather, Prof Chifumbe Chintu for their advice during the research proposal stage.

In a special way, I would like to thank Dr Patrick Kaonga for his drive, mentorship and support through this whole research.

I would like also thank Joshua Kapoma and Bizwell Mwaba for the assistance they rendered.

I would like to recognise Metropolis Laboratories- Zambia for the support they rendered to me when processing the laboratory samples.

I also thank my senior colleagues: Dr James Mulenga, Dr Jonathan Sitali, Dr Collin West, Dr Penelope Machona and Dr Victor Mapulanga for taking time and interest in looking at this work and advising accordingly.

Finally, I would also like to thank the University Teaching Hospital, for permission to carry out my research.

TABLE OF CONTENTS

COPYRIGHT	i
DECLARATION	ii
APPROVAL	iii
ABSTRACT.....	iv
DEDICATION	v
ACKNOWLEDGEMENT.....	vi
TABLE OF CONTENTS	vii
LIST OF TABLES	ix
LIST OF FIGURES	x
LIST OF APPENDICES	xi
ABBREVIATIONS AND ACRONYMS.....	xii
DEFINITIONS OF TERMS	xiii
CHAPTER ONE: INTRODUCTION.....	1
1.1 Background.....	1
1.2 Statement of the Problem.....	4
1.3 Study Justification.....	5
1.4 Conceptual Framework.....	5
1.5 Research Question	6
1.6 General objective	6
1.7 Specific objectives	7
1.8 Organization of the Dissertation	7
CHAPTER TWO: LITERATURE REVIEW.....	8
CHAPTER THREE: METHODOLOGY	12
3.1 Study design.....	12
3.2 Study Site	12
3.3 Target Population.....	12
3.4 Study Population.....	12
3.5 Study duration.....	13

3.6.1 Inclusion criteria	13
3.6.2 Exclusion criteria	13
3.7 Sample size	13
3.8 Sampling strategy.....	14
3.9 Study Process	14
3.10 Variables	15
3.11 Data Analysis	16
3.12 Ethical issues.....	17
3.13 Study Limitations.....	18
CHAPTER FOUR: RESULTS	19
4.1 Social demographic characteristics of the study participants	19
4.2 The commonest musculoskeletal manifestations.....	19
4.3 Association of baseline demographic data.....	22
4.4 Association of Clinical Parameters.....	25
4.4.1 Frequency of Vaso-occlusive Crisis.....	25
4.4.2 Use of Hydroxyurea	26
4.4.3 Frequency of blood transfusion.....	27
4.5 Association of Laboratory Parameters.....	28
4.5.1 Genotype	28
4.5.2 Percentage of ‘Haemoglobin s’	28
4.5.3 Haemoglobin Concentration	29
4.5.4 White Blood Cell Count (WBC)	30
4.5.5 Neutrophil count.....	31
4.5.6 Lymphocyte Count.....	32
4.5.7 Alkaline Phosphatase (ALP)	33
4.5.8 Alanine Aminotransferase (ALT)	33
4.5.9 Aspartate Transaminase (AST).....	34
4.5.10 Direct Bilirubin	35
4.5.11 Lactate Dehydrogenase (LDH)	36
4.6 Multivariable Logistic Regression Analysis.....	38
4.7 Predictive Margins of the Main Predictors of Musculoskeletal Manifestations.....	40
CHAPTER FIVE: DISCUSSION.....	43
CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS	47
6.1 Conclusion	47
6.2 Recommendations.....	47
REFERENCES.....	49

LIST OF TABLES

Table 3.1: The Beit Cure Classification for Chronic Osteomyelitis.....	15
Table 3.2: Variables for Musculoskeletal Manifestations	16
Table 4.1: Baseline demographic characteristic of study participants.....	20
Table 4.2: The commonest Musculoskeletal Manifestations.....	21
Table 4.3: Commonest sites for Musculoskeletal Manifestations	21
Table 4.4: Beit Cure Classification of Chronic Osteomyelitis (COM).....	22
Table 4.5: Culture results of Chronic Osteomyelitis (COM).....	22
Table 4.6: Association of baseline demographic data between cases and control.....	24
Table 4.7: Use of Hydroxyurea.....	27
Table 4.8: Association of Genotype between cases and controls	29
Table 4.9: Multivariable logistic regression for determination of Predictors of Musculoskeletal Manifestations of Sickle Cell Disease	39

LIST OF FIGURES

Figure: 1.1: Conceptual framework for potential predictors of Musculoskeletal Manifestations of Sickle Cell Disease	6
Figure 4.1: Comparison of age between cases and control.....	23
Figure 4.2: Comparison of age at diagnosis between cases and control.....	24
Figures 4.3: Frequency of VOCs	26
Figure: 4.4: Frequency of blood transfusion per year.....	27
Figure 4.5: Percentage of Haemoglobin s between cases and control.....	28
Figure 4.6: Haemoglobin concentration for cases and controls.....	29
Figure 4.7: Association of White Blood Cell Count (WBC) between cases and controls.....	30
Figure 4.8: Neutrophil Count between cases and controls	31
Figure 4.9: Lymphocyte Count between cases and controls.....	32
Figure 4.10: ALP between cases and controls	33
Figure 4.11: ALT between cases and controls.....	34
Figure 4.12: AST between cases and controls	35
Figure 4.13: Direct Bilirubin between cases and controls	36
Figure 4.14: Lactate Dehydrogenase (LDH) between cases and controls	37
Figure 4.15: Predictive margins of Musculoskeletal Manifestations with age.....	40
Figure 4.16: Predictive margins of Musculoskeletal Manifestations with the frequency of VOCs.....	41
Figure 4.17: Predictive margins of Musculoskeletal Manifestations with the percentage of Haemoglobin s	42

LIST OF APPENDICES

Appendix 1: Participant Information Sheet	53
Appendix 2: Participant Information Sheet (Bemba)	58
Appendix 3: Parent/Guardian Consent Form.....	64
Appendix 4: Child Assent Form	65
Appendix 5: Participant Evaluation Form	67

ABBREVIATIONS AND ACRONYMS

ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Transaminase
AVN	Avascular Necrosis
COM	Chronic Osteomyelitis
CT Scan	Computed Tomography
DC	Differential Count
FBC	Full Blood Count
Hb F	Foetal Haemoglobin
HIV	Human Immunodeficiency Virus
Hbs	Sickle Cell Gene
Hbss	Homozygous ss Haemoglobin
LFT	Liver Function Test
MRI	Magnetic Resonance Imaging
PLTs	Platelets
UTH	University Teaching Hospital (Lusaka- Zambia)
SCA	Sickle Cell Anaemia
SCD	Sickle Cell Disease
VOC	Vaso-Occlusive Crises
WHO	World Health Organisation

DEFINITIONS OF TERMS

Sickle Cell Disease: Is an autosomal recessive inherited condition characterized by the inheritance of two abnormal genes coding for the formation of haemoglobin and one of them is haemoglobin s.

Sickle Cell Anaemia: Is an autosomal recessive inherited condition characterized by the inheritance of two abnormal genes coding for the formation of haemoglobin and both of them are haemoglobin s (Homozygous Hb ss).

Controls: Paediatric patients (16 years or below) with Sickle Cell Disease who were recruited into the study.

Cases: Paediatric patients (16 years or below) with Sickle Cell Disease who presented with Musculoskeletal manifestations and were recruited into the study.

CHAPTER ONE: INTRODUCTION

1.1 Background

Sickle Cell Disease is an autosomal recessive inherited condition characterized by the inheritance of two abnormal genes coding for the formation of haemoglobin and one of them is haemoglobin s (Bender, 2017). It results from a single amino acid substitution (valine for glutamic acid at position 6) in the β globin gene (Piel, Steinberg and Rees, 2017). This disease results when both β globin genes are abnormal—either homozygous (Sickle Cell Anaemia) or heterozygous (Ejindu et al., 2007).

Acute vasoocclusive crisis is the hallmark of Sickle Cell Disease and is the most common acute presentation (Maakaron and Besa, 2018). Musculoskeletal manifestations are the commonest clinical presentations of both acute and chronic cases of vasoocclusive crisis (Maakaron and Besa, 2018). According to Vaishya *et al*, (2015), the commonest musculoskeletal manifestations that present in Sickle Cell Disease are Avascular necrosis of the hip, Osteomyelitis, Septic arthritis, Leg ulcers, Growth retardation and skeletal immaturity, Dactylitis, Osteoporosis and vertebral collapse and Arthritis.

Many of the studies that have been done have shown a high prevalence rate of these Musculoskeletal Manifestations of Sickle Cell Disease in children especially in West Africa. For example, Chinawa *et al*. (2013), found the prevalence of 32.1% of these Musculoskeletal Manifestations in a study done at the University of Nigeria Teaching Hospital (UNTH) Ituku Ozalla in Nigeria. However, the gap in most of these studies that had been done was that they

had not established the predictors or associated factors that are likely to contribute to the development of these Musculoskeletal Manifestations. The problem that was identified in our setting, was that, according to monthly clinical audits done at the University Teaching Hospital (Lusaka), in the past 3 years, paediatric patients with musculoskeletal manifestations of Sickle Cell Disease were presenting very late with advanced Musculoskeletal Manifestations of the disease. Therefore, this study aimed to explore the potential predictors of these Musculoskeletal Manifestations in Paediatric Patients presenting with Sickle Cell Disease seen at the University Teaching Hospital, Lusaka.

It was estimated that 5% of the global population carries genes responsible for haemoglobinopathies and each year, about 300,000 infants are born with major haemoglobin disorders (WHO, 2006). In Guadeloupe (Caribbean Islands), Mukisi-Mukaza *et al.* (2011) observed that Sickle Cell Anaemia patients with higher haemoglobin levels had an increased risk of avascular necrosis of the femoral head (One of the Musculoskeletal Manifestations of Sickle Cell Disease). In another study (done in the United State), Hernigou *et al.* (2010), noted that Sickle Cell Disease patients who presented with Septic arthritis (another common Musculoskeletal Manifestation of Sickle Cell Disease) also had associated co-morbidities such as Diabetes, Rheumatoid arthritis, glucocorticoids, and the use of hydroxyurea. According to Makani *et al.* (2013), Sub-Saharan Africa accounts for 75% of all Sickle Cell Disease patients. This distribution of the Sickle Cell gene is predominantly in areas where malaria is endemic: This because the Sickle Cell trait confers a survival advantage against malaria and the presence of Haemoglobin s lessens the severity of infection with falciparum malaria (Alli *et al.*, 2014). According to a study done in Nigeria, Eyichukwu *et al.* (2009), they reported that before the age

of 10, approximately 90% of Sickle Cell Anaemia patients developed Osteomyelitis of one or more bones. They noted that the factors that predispose these patients to musculoskeletal infections, include: hyposplenism, impaired complement activity, and the presence of infarcted and necrotic bone. The Mulago study (done in Uganda) revealed that increase in age, highly demanding physical activity status and the annual frequency of painful crises were associated factors of musculoskeletal Manifestations in Sickle Cell Disease patients (Akaro et al., 2016). Zambia has a carrier rate of about 17.5% of Sickle Cell Disease (Barclay *et al.*, 1970), and the University Teaching Hospital currently follows up over 1050 children with Sickle Cell Disease (Nchimba, 2015). However, no studies had been done on the potential predictors or factors associated with Musculoskeletal Manifestations of Sickle Cell Disease patients in our setting.

With early diagnosis, early referral and prompt treatment, the quality of life would improve in these patients and the cost on the healthcare system would significantly be reduced. Currently, the paucity of information on these musculoskeletal manifestations of Sickle Cell Disease made it very difficult in making an early diagnosis, early referrals and treatment protocols. Therefore, this study tried and identified the potential predictors of these musculoskeletal manifestations of Sickle Cell Disease in the paediatric population presenting to the University Teaching Hospital. It also helped in identifying the commonest musculoskeletal manifestations of Sickle Cell Disease. It is hoped that this study would be one of the studies that would help decision-makers in formulating a treatment protocol for these patients in the future.

1.2 Statement of the Problem

In 2013 alone, over one thousand Sickle cell anaemia patients were seen at the University Teaching Hospital (Lusaka) - Department of Paediatrics and Child Health in-patient facility with various complications of the disease (Machila, 2016). According to clinical audits done in the Department of Surgery in the past 3 years, patients with Sickle Cell Disease had been presenting very late with advanced musculoskeletal manifestations. The commonest musculoskeletal manifestations included Chronic Osteomyelitis, Avascular Necrosis of the Femoral Head, Septic Arthritis and leg ulcer. Despite many patients presenting with these conditions, the predictors of these manifestations were not known in our setting. Many studies that have been done have shown the prevalence of these Musculoskeletal Manifestations of Sickle Cell Disease to be high in the Sub-Saharan region but most of these studies had not given us information on the factors that are likely to contribute to the development of these conditions.

These late presentations also led to challenges in the treatment of these conditions. For example, in the case of Avascular Necrosis of Femoral Head, the only treatment available is that of total hip replacement (Tsukanaka *et al.*, 2016). However, it is usually not recommended in children due to high revision rates: This is because children are still skeletally immature (Van de Velde, Loh, & Donnan, 2017). Total hip replacements are also very costly (Clarke *et al.*, 2015).

Indeed, if these musculoskeletal manifestations were not identified and managed early, the affected patients would end up with complications such as abnormal gait, chronic pain, growth disturbances, amputations and would usually have prolonged hospitalisation.

1.3 Study Justification

The osteoarticular complications must be hunted in children with sickle cell disease to diagnose them early. A quick and efficient treatment would help to avoid serious orthopaedic sequela (Clarke *et al.*, 2015).

The paucity of information in our country on the musculoskeletal manifestations of Sickle Cell Disease made it very difficult in making an early diagnosis and also posed a great challenge in the choice of treatment. This, in turn, became a great cost to the health care system, as many surgical and medical interventions had to be done for these patients with these late manifestations.

This study helped understand the predictors of musculoskeletal manifestations of children presenting with Sickle Cell Disease at the University Teaching Hospital in Lusaka. If the predictors were known, this would help in the management of the patients and the prevention of these complications.

1.4 Conceptual Framework

The Figure 1.1 illustrates the conceptual framework for the potential predictors of Musculoskeletal Manifestations.

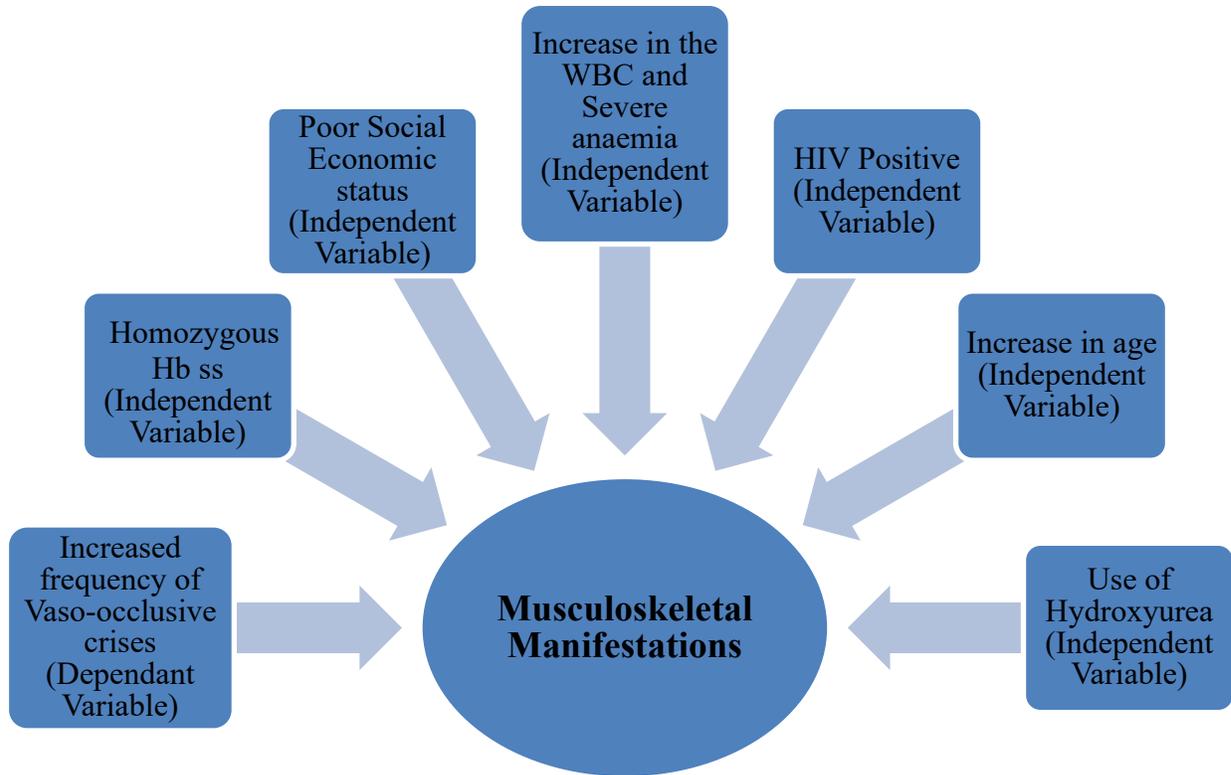


Figure: 1.1: Conceptual framework for potential predictors of Musculoskeletal Manifestations of Sickle Cell Disease

1.5 Research Question

What are the Potential Predictors of Musculoskeletal Manifestations in Paediatric Patients presenting with Sickle Cell Disease seen at the University Teaching Hospital, Lusaka?

1.6 General objective

To explore the Potential Predictors of Musculoskeletal Manifestations in Paediatric Patients presenting with Sickle Cell Disease seen at the University Teaching Hospital, Lusaka

1.7 Specific objectives

1. To determine the commonest Musculoskeletal Manifestations in Paediatric Patients presenting with Sickle Cell Disease seen at University Teaching Hospital.
2. To determine the socio-demographic factors associated with these Musculoskeletal Manifestations of Sickle Cell Disease.
3. To establish if there is any relationship between the Musculoskeletal Manifestations and the potential predictors.

1.8 Organization of the Dissertation

This study is divided into Chapters which are included as follows:

Chapter 1: Describes the background, statement of the problem, study justification objectives and specific objectives.

Chapter 2: Deals with the literature review: Explains the different findings from different studies that have been done.

Chapter 3: Provides the research methodology and ethical considerations.

Chapter 4: States the results of the study with figures and tables to interpret the data collected.

Chapter 5: Discusses the study findings comparing them with other studies that have been done

Chapter 6: Summarises the study findings and the recommendations

CHAPTER TWO: LITERATURE REVIEW

In a retrospective study done in Belgium by DeGheldere *et al.* (2006), patients records were reviewed from 1975 to 2004. Out of 325 patients' records looked at, 84% had homozygous ss. In this study, musculoskeletal manifestations were only encountered in those patients who were homozygous ss. The commonest manifestation was that of diaphyseal necrosis (16%). Clinical evaluation and imaging were done which revealed that the Tibia was the most frequently affected bone at 29% of the cases with diaphyseal necrosis and the proximal Tibia accounted for 77% of these cases. Other site included: The femur at 24% (distal femur in 82% of the femur cases) and the spine at 13%. The other cases showed a random distribution. They also observed that only 5% of these 325 patients had infections. The type of infection being Osteomyelitis and Septic Arthritis. Of these cases infections, 80% had Osteomyelitis. The commonest causative organism was Salmonella species (42%), followed by Escherichia coli (17%) and Pneumococci (8%). The commonest site of infection was the Tibia (33%), femur (17%) and the Spine (17%). Avascular necrosis of the femoral head was 4%. In another retrospective study by Hernigou *et al.* (2010), about 2000 patients' records were looked at. This study was done in the United States. They noted that the incidence of Septic Arthritis only accounted for 3% amongst adult patients with Sickle Cell Disease. In this study, 95% of patients were homozygous ss. The hip was the commonest site for Septic Arthritis (61%). The clinical presentation was mostly: Pain, swelling and fever of greater than 38.2°C. Leucocytosis of greater than 15,000/mm³ (range: 7900–32,300/mm³), Erythrocyte sedimentation rate more than 24 mm/hour, and C-reactive protein greater than 20 mg/L. Unlike the previous study, Staphylococcus and Gram-negative infection were the most common causative organisms. These patients who presented with Septic arthritis also had other Orthopaedic manifestations, such as, Osteomyelitis and avascular necrosis. Risk

factors to the development of Septic Arthritis included Osteonecrosis (49% of the patients) and Osteomyelitis (63% of the cases) in childhood, Diabetes, Rheumatoid arthritis, glucocorticoids, and the use of hydroxyurea were associated co-morbidities. In Guadeloupe, a prospective study was done by Mukisi-Mukaza *et al.* (2011) on the prevalence, clinical features, and risk factors of Osteonecrosis revealed that out of 113 patients with Sickle Cell Disease, 59% were homozygous ss and 41% were heterozygous. Approximately, 37.2% of the patients had Osteonecrosis of one or both hips (29.6%) without association to a particular genotype, although bilateral involvement was more frequent among ss patients. While the prevalence of femoral head Osteonecrosis increased with age, patients of all ages were affected, particularly young adults. Osteonecrosis of the femoral head was diagnosed at pre-radiographic stages in 30% of hips and was frequently asymptomatic (60% of all cases; 95% and 90% of stages I and II, respectively). Avascular necrosis of the femoral head was strongly associated with a history of leg ulcer. Sickle cell anaemia patients with higher haemoglobin levels had an increased risk of Osteonecrosis of the femoral head.

A review of children less than 15 years of age was done in Togo: In this review, Akakpo-Numado *et al.* (2013) noted that Acute Osteomyelitis was the most frequent musculoskeletal manifestation in children with Sickle Cell Disease. It was classically due mainly to *Salmonella* species. However, recent studies have found other micro-organisms such as *Staphylococcus aureus*, *Streptococcus Pneumonia*, *Klebsiella* (Lepage *et al.*, 2004). Akakpo-Numado *et al.* (2013) argued that *Salmonella* is more common in underdeveloped countries due to poor hygiene. They also found out that multiple sites could be affected at the same time. Long bones were the most affected and according to the study, the most frequent being the humerus, the tibia

or the femur. They noted that Acute Osteomyelitis, if not diagnosed early, would lead to Chronic Osteomyelitis which in turn would lead to a risk of long term Orthopaedic sequela; Arthritis would affect any joint. The hip and knee were the favoured sites. If not adequately treated, destruction of joints would occur. Avascular osteonecrosis of the femoral head was noted to be a late manifestation, usually occurs after the age of 10 years. In a retrospective study done by Chinawa *et al.* (2013), to determine the pattern of musculoskeletal complications among children with Sickle Cell Anaemia admitted to the University of Nigeria Teaching Hospital (UNTH) Ituku Ozalla over 58-months, a total of 78 patients were enrolled. Out of these admitted, 67% were males and 33% were females. The median age of the patients was 10 years and the range were 9 months to 17 years. In this study, the prevalence rate of musculoskeletal complications was 32.1%. The common musculoskeletal complications were: Acute Osteomyelitis (12.8%), Chronic Osteomyelitis (6.4%), avascular necrosis of head of the femur (6.4%), Septic Arthritis (2.6%), while 1.3% each had chronic leg ulcers, pathological fractures, and vertebral collapse. Another retrospective study to determine the various musculoskeletal disorders associated with Sickle cell anaemia, types of treatments given including physiotherapy and the mortality rate in Sickle cell anaemia patients admitted in two Nigerian hospitals was done. Here, Aliyu *et al.* (2017) reviewed the case notes of Sickle Cell Anaemia patients in two hospitals in Kano, North-Western Nigeria. A total of 248 patients (in 10 years) were admitted with Sickle Cell Anaemia. Results revealed that 53.6% were males and 46.4% females. Prevalence of musculoskeletal disorders was found to be 54.1%. Painful bone crisis (35.5%) were the commonest musculoskeletal manifestation and Osteomyelitis accounted for 11.6%. The majority (61.7%) presenting with musculoskeletal disorders were between the age of 3 months and 10 years. The mortality rate was 8.9% and only 8.9% of these cases received physiotherapy.

In the Mulago study which was done at Mulago National Referral Hospital, Uganda, a total of 365 Sickle Cell Anaemia patients who attended the clinic between 1st August 2014 and 31st October 2014 were enrolled into the study (Akaro et al., 2016). In this descriptive cross-sectional study, Akaro *et al.* (2016) noted that the prevalence of musculoskeletal disorders among Sickle Cell Anaemia patients was found to be 11.5%. In this study, the commonest manifestations included: Avascular necrosis of the Femoral Head and the Spine, Chronic Osteomyelitis and leg ulcers. The ages affected was 11-20 years, highly demanding physical activity status and the annual frequency of painful crises were associated with musculoskeletal disorders (Akaro et al., 2016).

Only one study related to this subject has been done at the University Teaching Hospital in Lusaka. This study looked at factors influencing the outcome of Acute Haematogenous Osteomyelitis at the University Teaching Hospital, Lusaka (Chowa, 2013). About, 13% of the children (112 patients) who had presented with acute haematogenous Osteomyelitis had Sickle Cell Disease (Chowa, 2013). In the studies above, there is a difference in the prevalence of these musculoskeletal manifestations depending on the geographic location. Also, most studies on this subject focus only on the patterns of these musculoskeletal manifestations but the predictors of these musculoskeletal manifestations remain unclear. It is hoped that this study would establish the predictors of these musculoskeletal manifestations.

CHAPTER THREE: METHODOLOGY

3.1 Study design

This was an unmatched case-control study. In this study, two groups of patients were recruited to compare the potential predictors of musculoskeletal manifestations: The first group comprised the 'cases'. The 'cases' by definition were paediatric patients of the age of 16 or below who had Sickle Cell Disease and presented with Musculoskeletal Manifestations. The second group were the 'controls': The 'controls' comprised of paediatric patients of the age of 16 or below who had Sickle Cell Disease but did not present with any Musculoskeletal manifestations.

3.2 Study Site

The study was conducted at The University Teaching Hospital in Lusaka. Recruitment of patients was done from Paediatric admission ward, Sickle cell Clinic and Surgical Admission ward.

3.3 Target Population

Paediatric patients who had Sickle Cell Disease and were 16 years or below in Lusaka

3.4 Study Population

Paediatric patients who had Sickle Cell Disease and were 16 years or below, presenting to the University Teaching Hospital in Lusaka, Zambia.

3.5 Study duration

The study was conducted in three months (between January and April 2019)

3.6.1 Inclusion criteria

1. All Sickle Cell Disease patients were 16 or below (16 years as the maximum age had been picked because this is the average age of skeletal maturity in both male and females)

3.6.2 Exclusion criteria

1. Sickle Cell Disease patients who had presented with other co-morbidities that have musculoskeletal manifestation such as Rheumatoid Arthritis

3.7 Sample size

$N = (Z_a + Z_b)^2 * (P_1(1-P_1) + P_2(1-P_2)) / (P_1-P_2)^2$ where:

N= Sample size

Z_a= Z static (usually 1.96)- When using 95% confidence interval

Z_b=20% beta error; 80% power desired (one-tailed test); Z_b=0.84

P₁= Patients with musculoskeletal manifestations (60% VOC)

P₂= Patient without musculoskeletal manifestations (35% VOC)

d= accepted accuracy range (+/- 10%)

The sample size calculated was 58 patients (that is, patients with Musculoskeletal manifestations). A ratio of 1:2 between Sickle Cell Disease patients with Musculoskeletal Manifestations and those without was applied. Therefore, a total of 174 patients with and without Musculoskeletal Manifestations was to be recruited. However, this study managed to recruit a total of 171 patients.

3.8 Sampling strategy

All patients meeting the inclusion criteria were systematically sampled.

3.9 Study Process

The patients that were enrolled in the study were assessed according to routine clinical practice. These patients were assessed for the musculoskeletal manifestations. A standard form/tool (check Appendix) was used during the assessment.

The different musculoskeletal manifestations were identified, staged and classified according to the standard Orthopaedic classification systems. Radiography i.e Digital X-Rays were used in staging and classifying of these musculoskeletal manifestations. In the case of infection such as Osteomyelitis and Septic Arthritis, deep tissue cultures were collected during operative procedures as planned by the managing Orthopaedic Units. These samples were taken to the laboratory for microscopy, sensitivity and culture. Blood samples were also be taken for laboratory investigations. The researcher ensured that the patients remained comfortable during the procedures and that minimal pain was caused by the needle during blood collection.

The Beit Cure Classification used to stage the severity of the Chronic Osteomyelitis, as shown in Table 3.1:

Table 3.1: The Beit Cure Classification for Chronic Osteomyelitis

Classification type	Radiological appearance of bone segment
A	Abscess type, osteolytic area(s), no sequestrum, no involucrum
B1	Peripheral, localised cortical sequestrum; minimal/no involucrum
B2	Sequestrum present; stable, normal-looking cortical involucrum
B3	Sequestrum present; stable, sclerotic involucrum
B4	Sequestrum present; unstable, inadequate involucrum
C	No sequestrum visible on plain X-ray; densely, diffusely sclerotic bone segment; abscess may be present.
Unclassifiable	Inadequate X-ray/disease onset >6-months/previous surgery.

Physal involvement is indicated by adding a suffix of P for proximal involvement, D for distal involvement and PD for dual physal involvement

(Stevenson et al.,2015)

In both of these groups (the cases and controls), a detailed clinical assessment was done. The genotypes, laboratory parameters, that is, Haematological parameters (Hb, WBC, DC, PLTS), blood chemistry (LFTs) and HIV status were done. This was done to compare between the two groups.

3.10 Variables

The following variables were used, as shown in Table 3.2:

Table 3.2: Variables for Musculoskeletal Manifestations

Independent Variables	Scale of Measurement	Dependent Variable
Age	Continuous	Outcome: Development of Musculoskeletal Manifestations
sex	Nominal	
Referring Hospital/Province/ District	Categorical	
Caregiver	Categorical	
Social Economic status (Income)	Continuous	
Age of Diagnosis of Sickle Cell Disease	Continuous	
Current Musculoskeletal diagnosis	Categorical	
Site of Pathology	Categorical	
Stage or Classification of Pathology	Categorical	
Genotype	Categorical	
HIV status	Nominal	
Frequency of Vaso-occlusive Crisis (VOC)	Continuous	
Number of blood transfusions	Continuous	
Haematological parameters (HB, WBC, PLTs)	Continuous	
Blood Chemistry (LFTs)	Continuous	
Use of Hydroxyurea	Categorical	
Microscopy/Culture/ Sensitivity	Categorical	

3.11 Data Analysis

All data collected was entered into excel spreadsheets which was password protected. Data analysis was done using Strata version 13. All continuous variables such as age and haematological parameters were as reported median and interquartile ranges because the data was not normally distributed. To check for Normality of data Shapiro-Wilk Test was used. To compare, a continuous variable between patients with musculoskeletal manifestations and those without, Mann-Whitney (Wilcoxon Rank-Sum) Test was applied. Spearman's correlation was applied.

Categorical variables were reported as proportions. Chi-Square Test was used to determine the association between two categorical variables if all the cells are five and above. However, if the number of cells is less than five, Fisher's Exact Test was used.

To determine predictors Odds ratios at 95% confidence intervals in Multivariable logistic analysis was used.

3.12 Ethical issues

The study was carried out following the Good Clinical Practice guidelines (GCP). Permission was obtained from the University Teaching Hospital Department of Surgery to carry out the study. Ethical approval was obtained from a local private ethics committee, **ERES Converge**. Participation in this study was strictly voluntary. All eligible patients were explained to (or their parents/guardians) and informed consent was obtained. Patients were not remunerated. All data collected has been kept confidential, as this was an observational study, there will be no interference with the management of the patients. Any information gathered that had a bearing on patient management was made available to the units responsible for the management concerned patient.

Collection of blood samples (such as the HIV test) and cultures (in cases of infection) was done for laboratory investigations. The results of the HIV test and other results were kept confidential and if the patient wished to know the results, the patient would first be counselled before and after the testing. The blood that was collected was all used for the tests and after testing, the blood samples were discarded according to the hospital guidelines of medical waste disposal.

Meaning that the samples were incinerated or burnt just like any other blood samples collected during normal clinical practice.

Minimal discomfort was caused when drawing blood with a needle from the patient's arm and some physical examination would have been a little bit uncomfortable. In the event that the patient got injured during the course of the research study, for example, an injury to the arm caused by the needle prick when drawing blood, immediately the patient's caregiver was advised to notify the Principal Investigator or the Chairperson of **ERES Converge IRB office** at the following physical address: 33 Joseph Mwilwa Road, Rhodes Park, Lusaka, Zambia. If they (care-giver) believed that their child's injury directly resulted from the research procedures of this study, they were advised to file a complaint against the Principal Investigator. For a further description of this process, the contact address for the Chairperson of Research Biomedical Ethics Committee, **ERES Converge IRB** was given as shown in the Appendix 1.

3.13 Study Limitations

1. A limited number of patients with Chronic Osteomyelitis who underwent sequestrectomy during the study. Therefore, only 6 deep tissues cultures were obtained. Sequestrectomy is an elective procedure and usually is dependent on the stage of the disease.
2. Unavailability of imaging modalities such as MRI. This would have been important in further characterisation of the different Musculoskeletal Manifestations such avascular necrosis of the femoral head.

CHAPTER FOUR: RESULTS

This chapter describes the data that was obtained. In this study, the first objective was to determine the commonest Musculoskeletal Manifestations in Paediatric Patients presenting with Sickle Cell Disease seen at University Teaching Hospital. The second was to determine the socio-demographic factors associated with these Musculoskeletal Manifestations. The third was to establish if there is any relationship between the Musculoskeletal Manifestations and the potential predictors.

4.1 Social demographic characteristics of the study participants

Out of 174 patients, 171 (98.2%) were recruited into the study. The median age in years of the study participants was 8 (IQR, 5 -11). The majority (69%) of the study participants were more than 5 years of age. Males were 50.4% and females were 49.1%. About 98% of the participant were follow up patients. The majority (68.4%) of the participants had both parents (as caregivers). Only 4.1% of the study participants were HIV positive. This is as shown in Table 4.1.

4.2 The commonest musculoskeletal manifestations

The commonest Musculoskeletal Manifestations were: Chronic Osteomyelitis (29.82%), Acute Osteomyelitis (21.05%), Avascular necrosis of the femoral head (14.04) and Septic Arthritis (10.53%).

Other manifestations included: Leg ulcer, Pathological fractures, Vertebral collapse and Dactylitis. Of note is that all the children that presented with avascular necrosis of the femoral head (AVN) were above the age of 11 years, while 83% of the children that presented with Septic Arthritis were below the age of 5 years. This is as shown Table 4.2.

For both Acute and Chronic Osteomyelitis, the lower limbs were more affected (62.07%) than the upper limbs (37.93). The commonest site was the Tibia (41.38%). This is as shown in Table 4.3.

Table 4.1: Baseline demographic characteristic of study participants

Variable	Category	Proportion (%)
Age (years)	< 2	14 (8.2)
	2 - 5	39 (22.8)
	>5	118 (69.0)
Sex	Female	84 (49.1)
	Male	87 (50.4)
Patient Category	New patient	11 (6.4)
	Follow up patient	160 (93.6)
Care-giver	Both parents	117 (68.4)
	Mother only	39 (22.8)
	Father only	2 (1.2)
	Other	13 (7.6)
Monthly income (of the caregiver)	< K1000	65 (38.0)
	K1001-K5000	75 (43.9)
	K5001-K10,000	15 (8.8)
	>K10,000	16 (9.4)
HIV status	Positive	7 (4.1)
	Negative	164 (96.9)

Table 4.2: The commonest Musculoskeletal Manifestations

Musculoskeletal Manifestations	Number of Patients	Proportion (%)
Chronic Osteomyelitis (COM)	17	29.82
Acute Osteomyelitis	12	21.05
Avascular necrosis of femoral head (AVN)	8	14.04
Septic Arthritis	6	10.53
Leg ulcer	5	8.77
Pathological Fracture	3	5.26
Vertebra collapse	3	5.26
Dactylitis	3	5.26

Table 4.3: Commonest sites for Musculoskeletal Manifestations

Site	Frequency	Proportion (%)
Tibia	12	41.38
Femur	6	20.69
Humerus	6	20.69
Radius	5	17.24

The cases of Chronic Osteomyelitis were further staged using the Beit Cure classification. The results showed that the commonest stage of the disease was stage B₃ (41.18%) as shown in Table 4.4.

Table 4.4: Beit Cure Classification of Chronic Osteomyelitis (COM)

Stage	Frequency	Proportion (%)
B₂	1	5.88
B₃	7	41.18
B₄	6	35.29
C	3	17.65

Staphylococcus aureus was the commonest (66.67%) micro-organism that was cultured in the Chronic Osteomyelitis cases where sequestrectomy had been done. This as shown in Table 4.5 below:

Table 4.5: Culture results of Chronic Osteomyelitis (COM)

Micro-Organism	Frequency	Proportion (%)
Staphylococcus aureus	4	66.67
Salmonella	1	16.67
No growth	1	16.67

4.3 Association of baseline demographic data

In terms of age: The median age for the controls was found to be 7 (IQR, 4 – 11), while that of the cases was 9.5 (IQR, 7 – 12). There was a significant association in age between the two groups ($p=0.003$). This as shown in Figure 4.1.

The Median age at diagnosis of the Sickle Cell Disease was found to be 1.1 (IQR, 0.6 – 2.3) for the controls, while 3 (IQR, 1.2 – 4) for the cases. This also showed a significant association ($p < 0.001$) as shown in Figure 4.2.

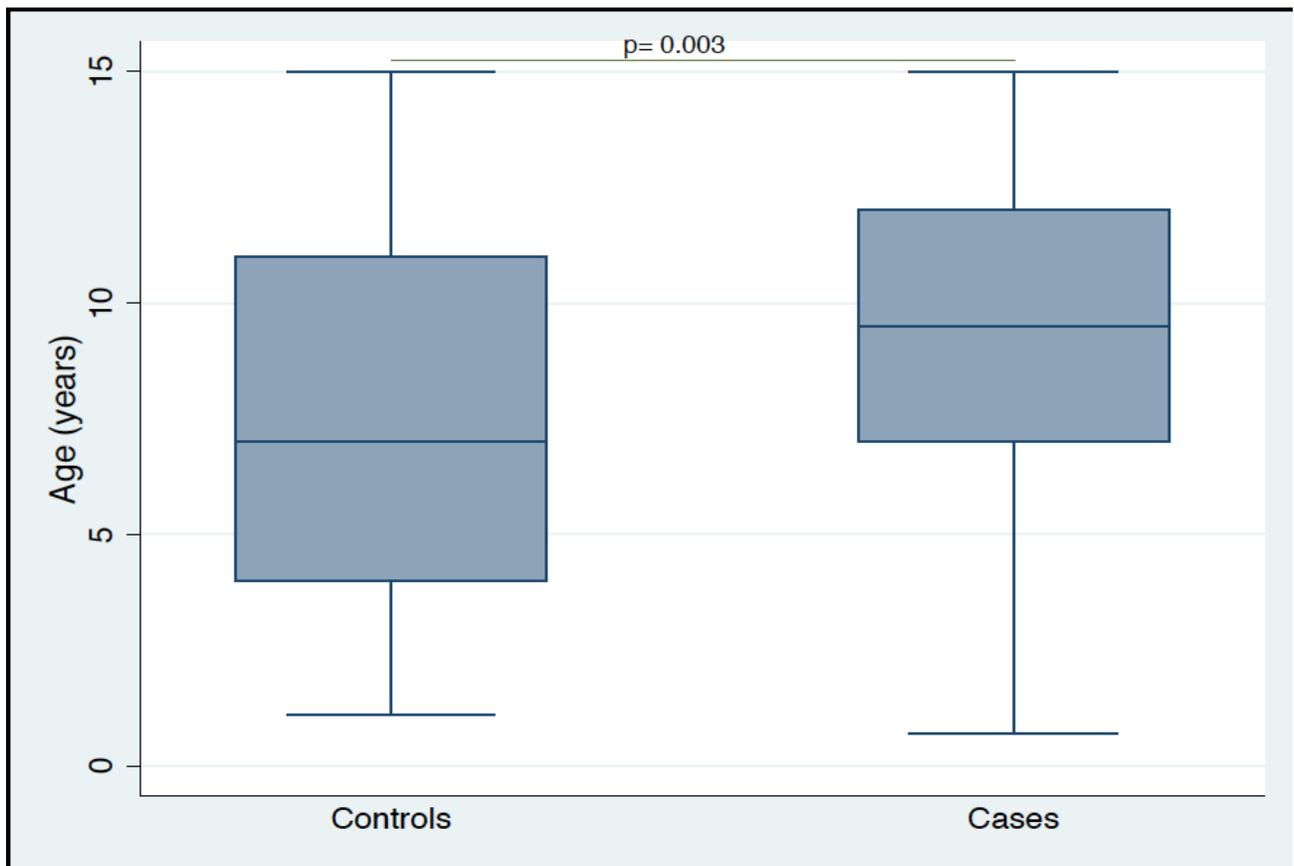


Figure 4.1: Comparison of age between cases and control

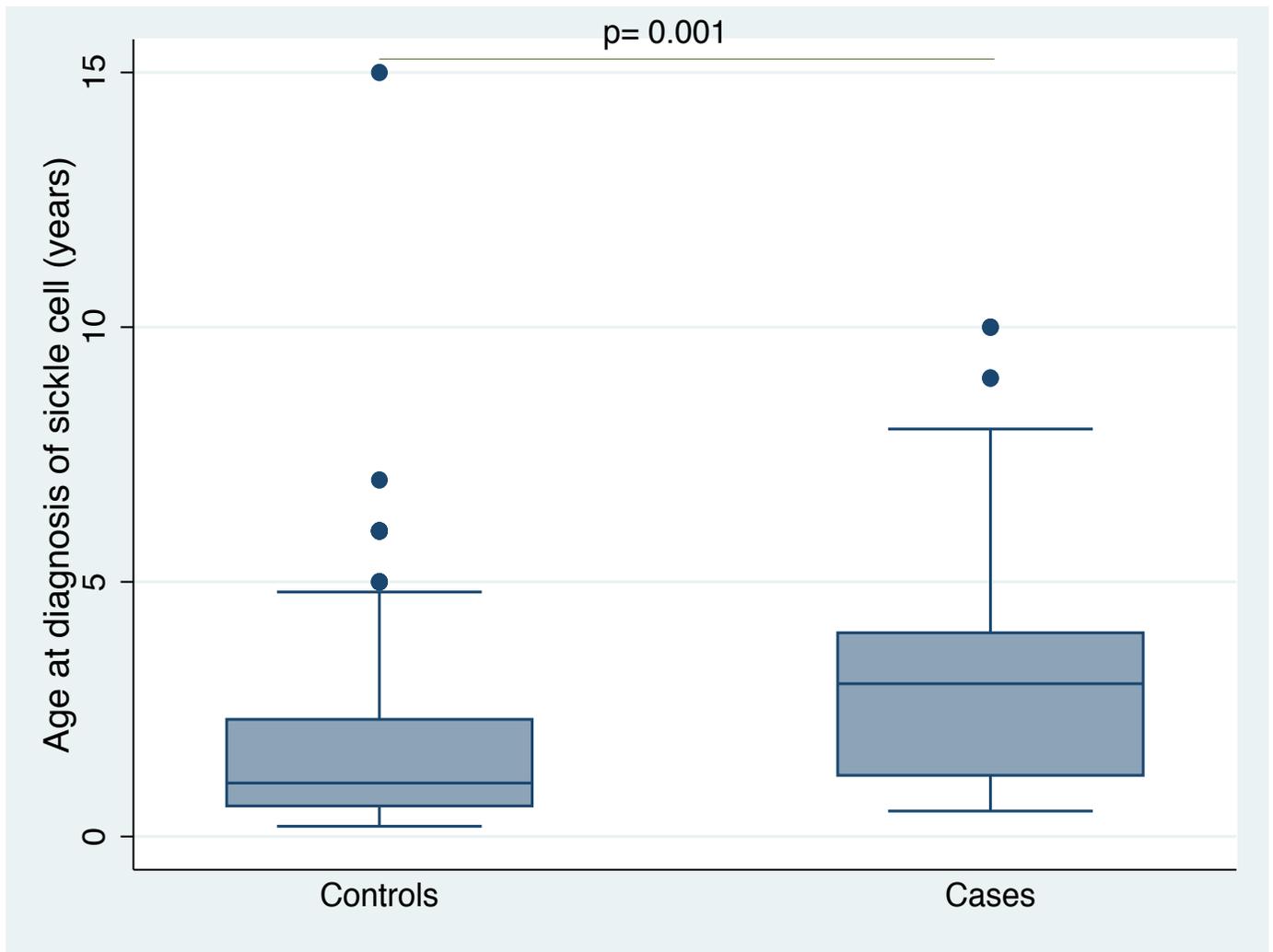


Figure 4.2: Comparison of age at diagnosis between cases and control

Other associations of the baseline demographic data revealed that there was a significant association in the monthly income between the cases and controls ($p=0.03$). However, was no significant association with sex, patient category and care-giver as shown in Table 4.6.

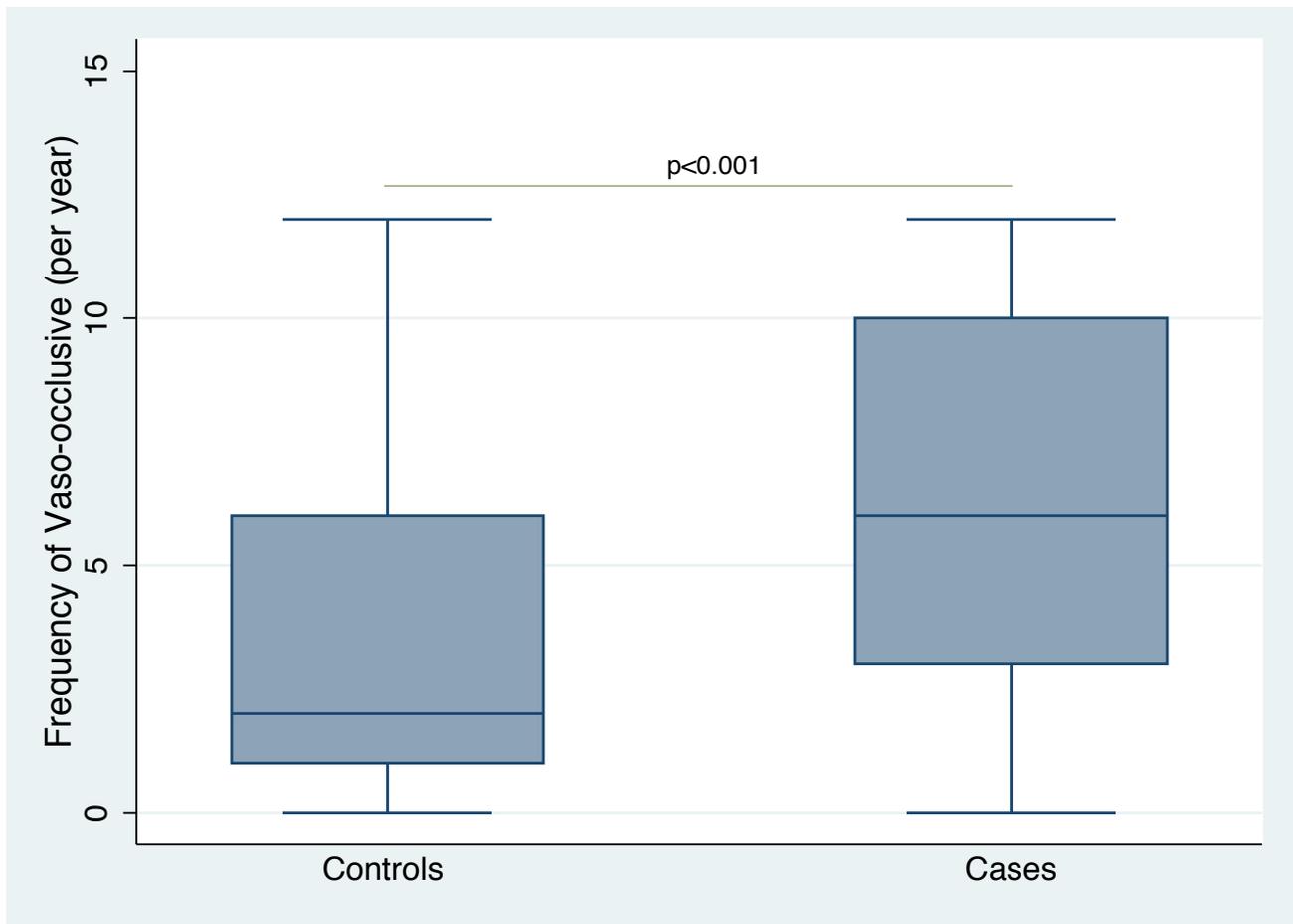
Table 4.6: Association of baseline demographic data between cases and control

Variable	Cases (n= 57)	Control (n=114)	p-value
Sex:			
Female	33	54	0.19
Male	24	60	
Patient Category:			
New patient	5	6	0.38
Follow up patient	52	108	
Care-giver:			
Both parents	33	84	0.06
Mother only	17	22	
Father only	2	0	
Other	5	8	
Monthly income			
< K1000	24	41	0.03
K1001-K5000	28	47	
K5001-K10,000	5	10	
>K10,000	0	16	
HIV Status			
Positive	4	3	0.17
Negative	53	111	

4.4 Association of Clinical Parameters

4.4.1 Frequency of Vaso-occlusive Crisis

The median frequency of vaso-occlusive crisis per year was 2 (IQR, 1 – 6) for the controls and 6 (IQR, 3 – 10) for the cases. This showed a significant association between the two groups ($p < 0.001$) as shown in Figure 4.3.



Figures 4.3: Frequency of VOCs

4.4.2 Use of Hydroxyurea

The association between use of Hydroxyurea and overall musculoskeletal manifestations showed no significant association ($p=0.43$) as shown in Table 4.7. However, it must be noted that 10% of children that presented with avascular necrosis of the femoral head (AVN) were on hydroxyurea.

4.5 Association of Laboratory Parameters

4.5.1 Genotype

Out of 171 participants, the majority (98%) had homozygous Haemoglobin s (Hb ss). Only 2 patients had other variants of the genotype of the Sickle Cell Disease spectrum. Both patients were heterozygous (Hb sc and Hb As). There was no significant association ($p=0.31$) between the two groups in terms of genotype. This is as shown in Table 4.8.

4.5.2 Percentage of 'Haemoglobin s'

The percentage of 'Haemoglobin s' that each Sickle Cell Disease patient had, showed a significant association between the cases and the controls (<0.001) as illustrated in Figure 4.5.

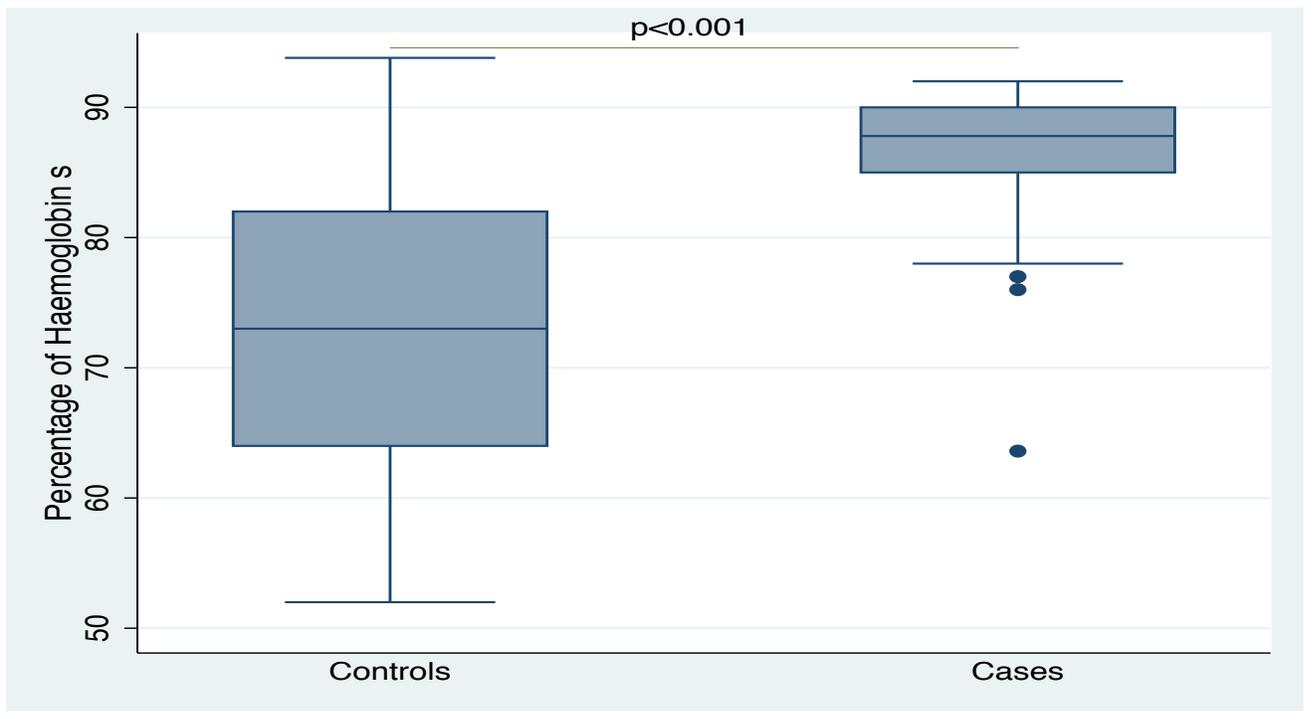


Figure 4.5: Percentage of 'Haemoglobin s' between cases and control

Table 4.8: Association of Genotype between cases and controls

Variable	Cases (n= 57)	Control (n=114)	p-value
Genotype:			
Hbss	57	112	
Other	0	2	0.31

4.5.3 Haemoglobin Concentration

The median Haemoglobin for the controls was 7.3 (IQR, 6.7 – 8.1) and for the cases was 7.0 (IQR, 6.2 – 7.7). The association between Haemoglobin and Musculoskeletal Manifestations revealed that it was not significant ($p=0.08$) as shown in Figures 4.6:

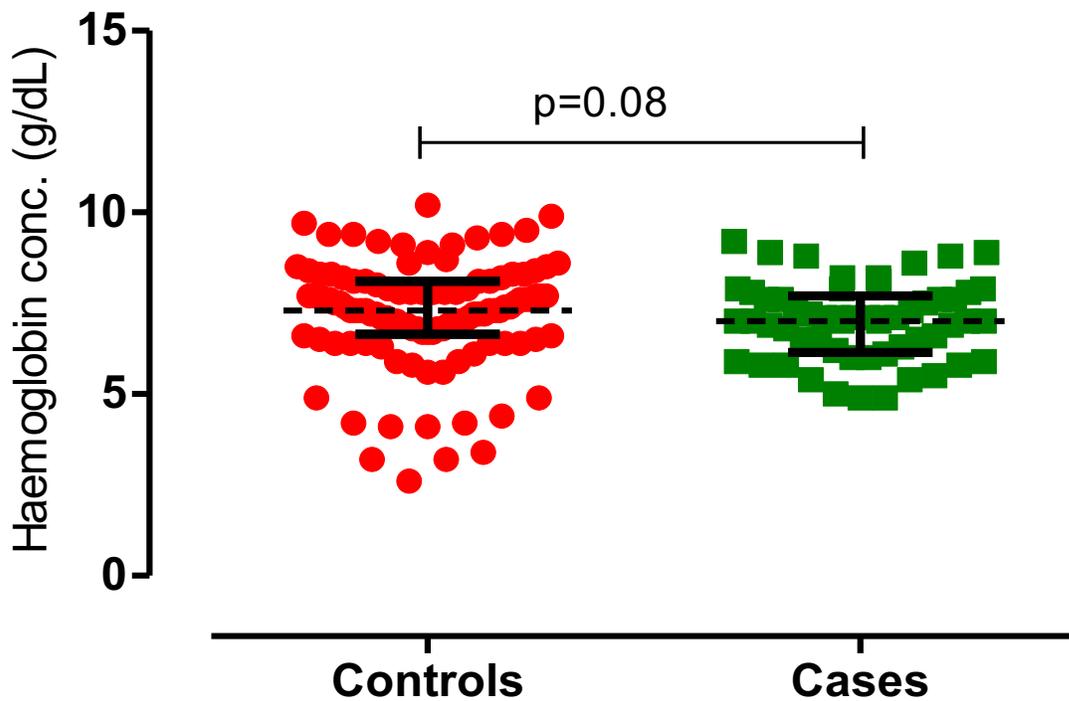


Figure 4.6: Haemoglobin concentration for cases and controls

4.5.4 White Blood Cell Count (WBC)

In terms of White Blood Cells, the median for the control 13.7 (IQR, 11.3 – 18.4) and the case 12.5 (IQR, 9.1 – 17.1), ($p=0.057$). Therefore, was no significant association as shown in Figure 4.7:

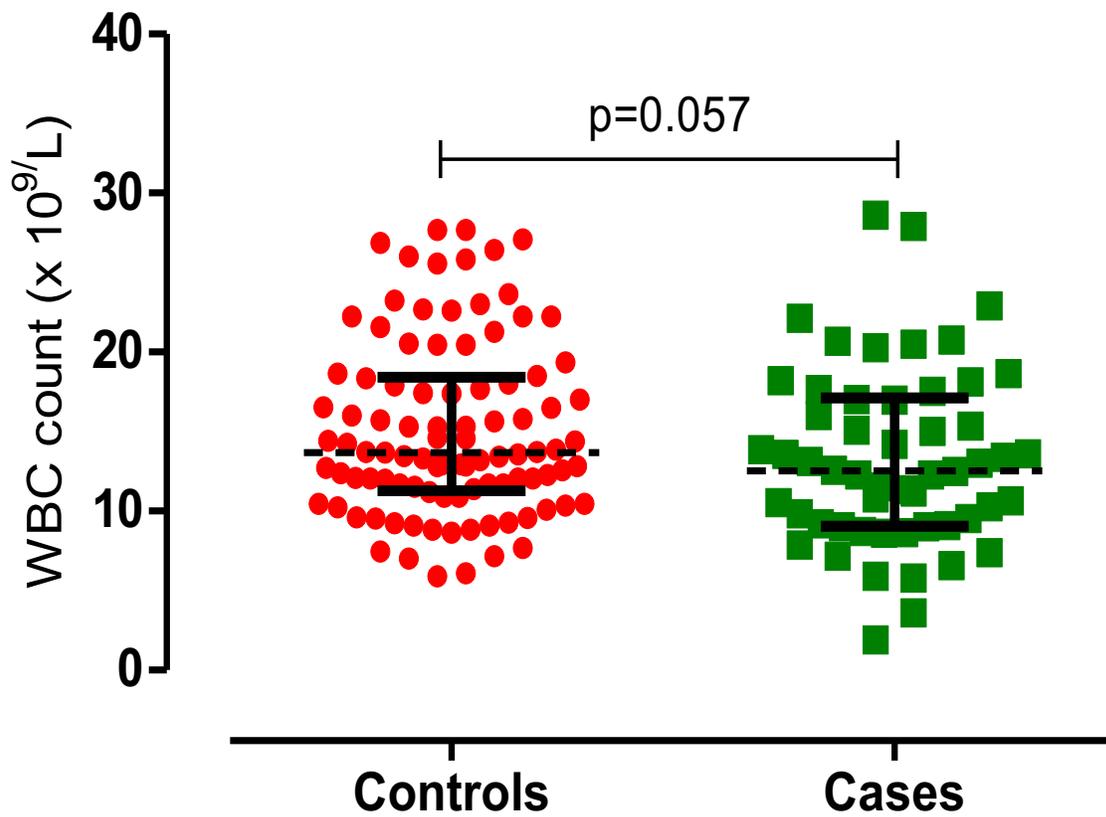


Figure 4.7: Association of White Blood Cell Count (WBC) between cases and controls

4.5.5 Neutrophil Count

In the association between Neutrophil count and musculoskeletal manifestations, the median for the control was 6.4 (IQR, 4.7 – 10.2) and that of the case was 5.2 (IQR, 4.2 – 8.3), ($p=0.08$).

Therefore, was no significant association as shown in Figure 4.8:

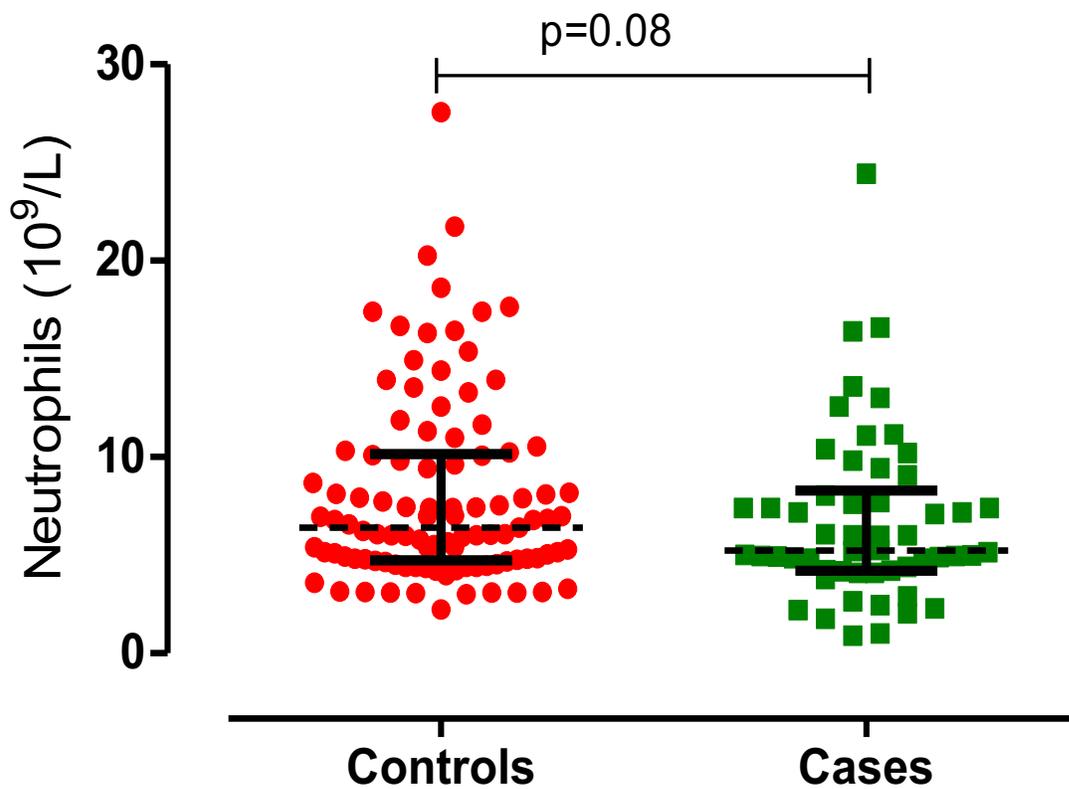


Figure 4.8: Neutrophil Count between cases and controls

4.5.6 Lymphocyte Count

The Lymphocyte count had a median of 11.2 (IQR, 7.6 – 22.6) for the controls, and 16 (IQR, 9.1 – 23.9) for the cases, ($p=0.09$). There was no significant association as shown in Figure 4.9:

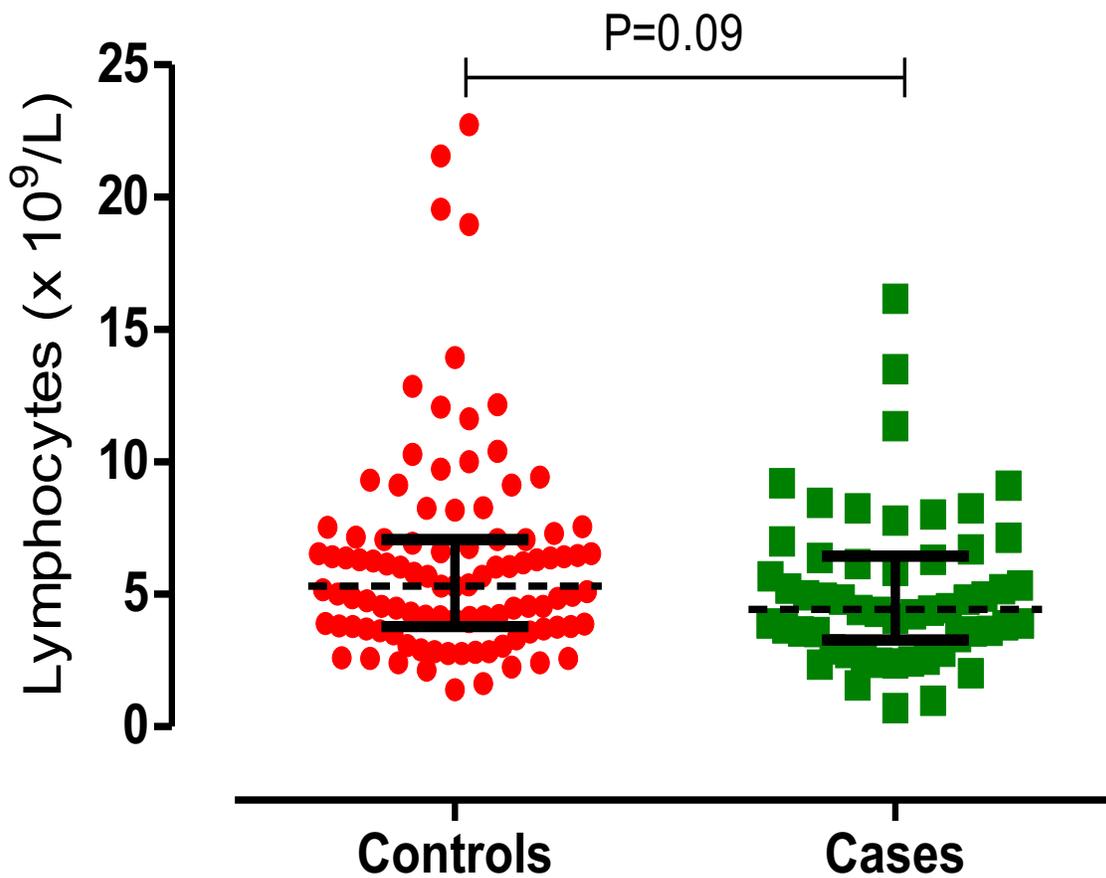


Figure 4.9: Lymphocyte Count between cases and controls

4.5.7 Alkaline Phosphatase (ALP)

The median for the control was 180.4 (IQR, 143.6 – 231.9) and that of the case was 180.4 (IQR, 140 – 224.9). There was no significant association ($p=0.62$) as shown in Figure 4.10:

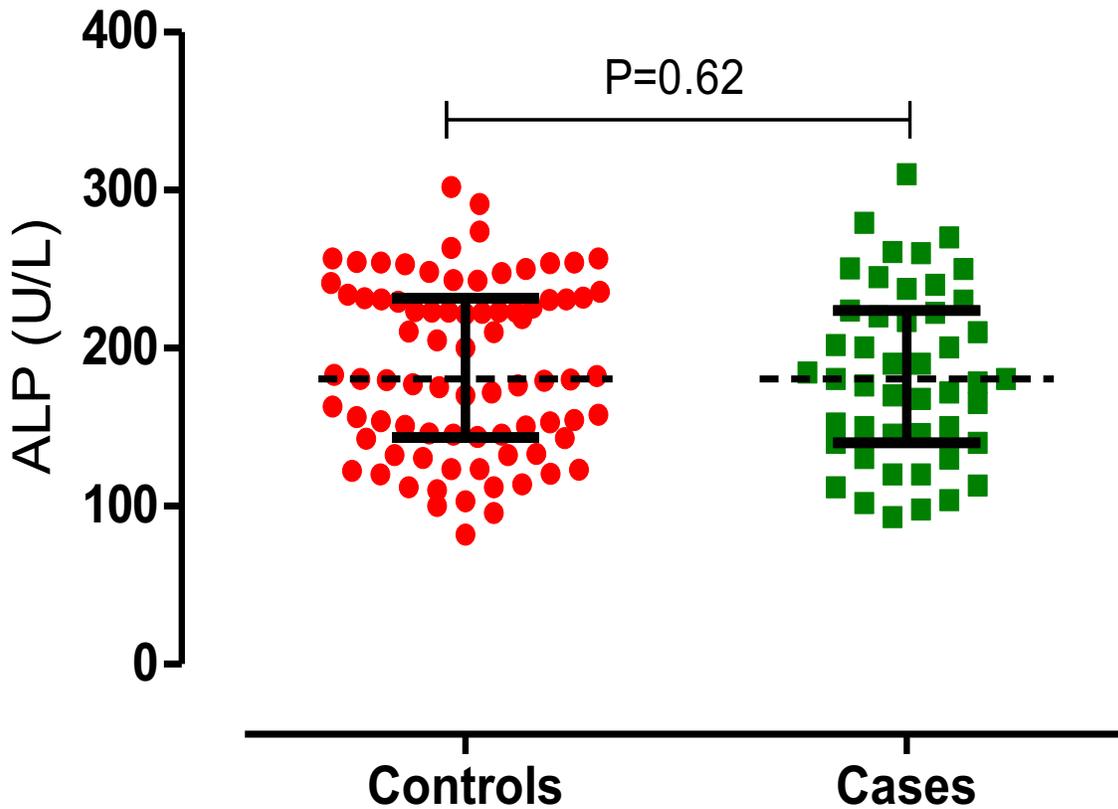


Figure 4.10: ALP between cases and controls

4.5.8 Alanine Aminotransferase (ALT)

The median for the controls was 23 (IQR, 17 -28.9) and that of cases was 27.1 (IQR, 17.6 – 32.2). This showed no significant association ($p=0.23$) as illustrated by Figure 4.11:

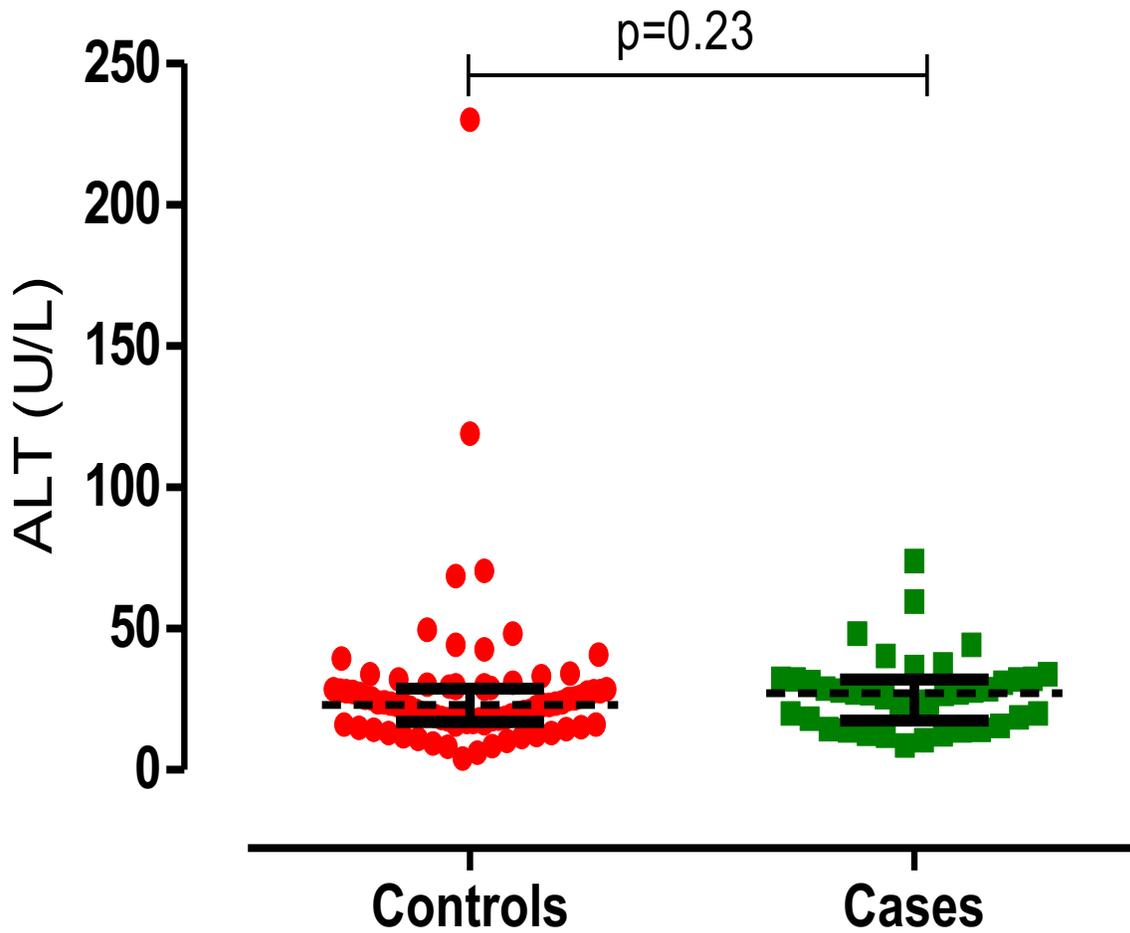


Figure 4.11: ALT between cases and controls

4.5.9 Aspartate Transaminase (AST)

Unlike, the ALP and ALT, the median for the controls was 57 (IQR, 30 - 74.1) and the cases was 67 (IQR, 54 – 84.6), ($p=0.01$). There was significant association as shown in Figure 4.12:

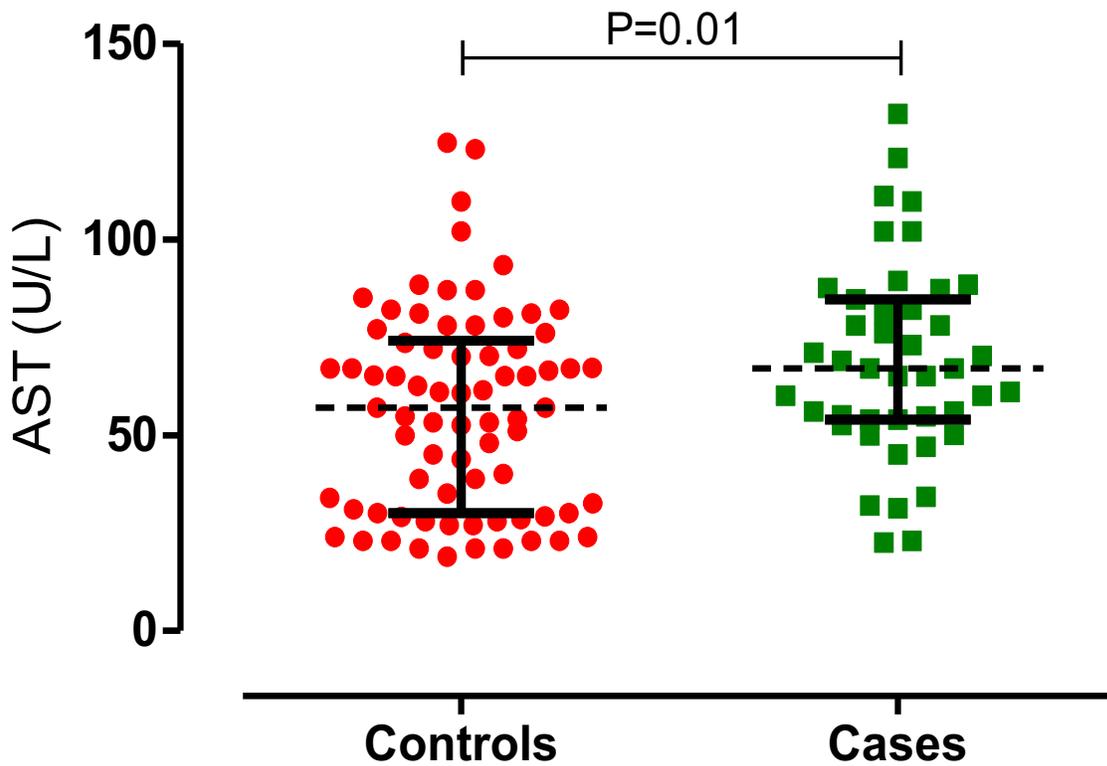


Figure 4.12: AST between cases and controls

4.5.10 Direct Bilirubin

In the association between direct bilirubin and musculoskeletal manifestations (cases and control), the median for the controls was 11.2 (IQR, 7.6 - 23) and that of the case was 16 (IQR, 9.1 - 23.7). There was no significant association ($p=0.17$) as shown in Figure 4.13:

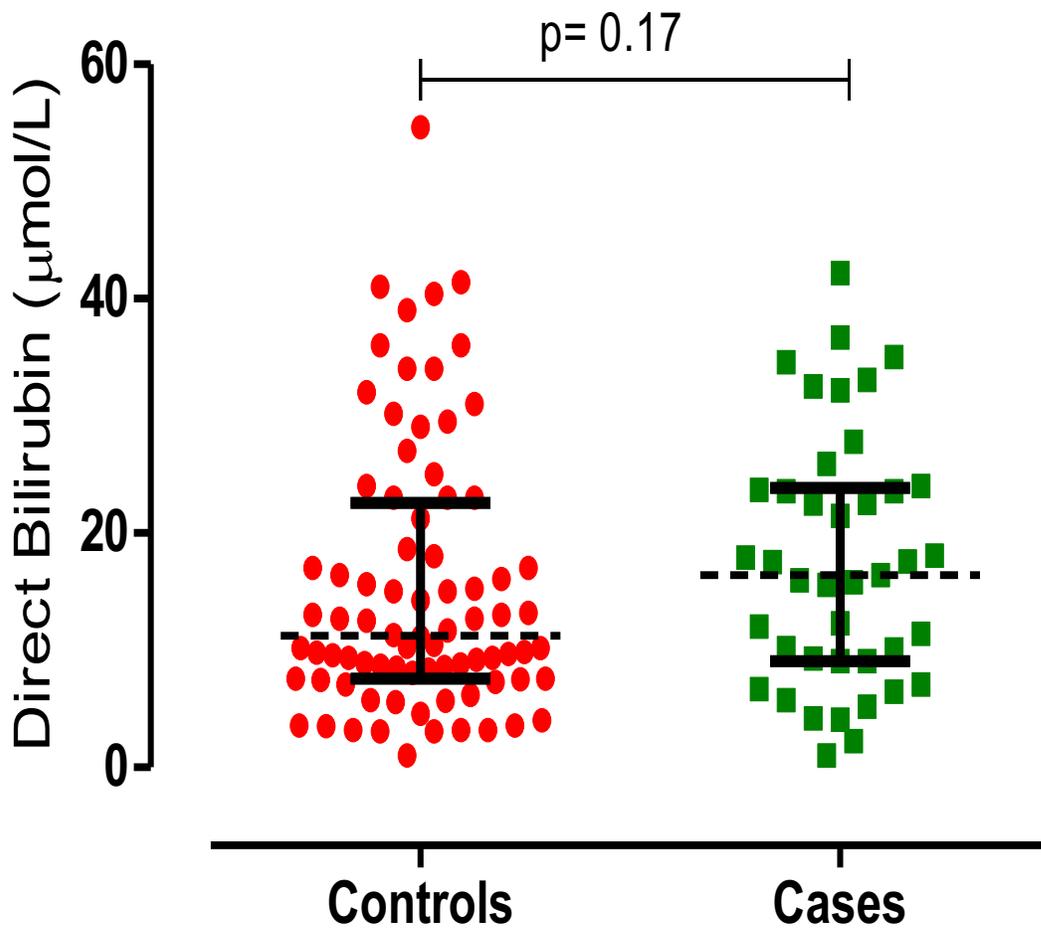


Figure 4.13: Direct Bilirubin between cases and controls

4.5.11 Lactate Dehydrogenase (LDH)

The study also explored the association between Lactate Dehydrogenase (LDH) and musculoskeletal manifestations. The Median for the control was 822 (IQR, 560 - 906.5) and that for the case was 749 (IQR, 640 – 801). There was no significant association ($p=0.25$) as shown in Figure 4.14:

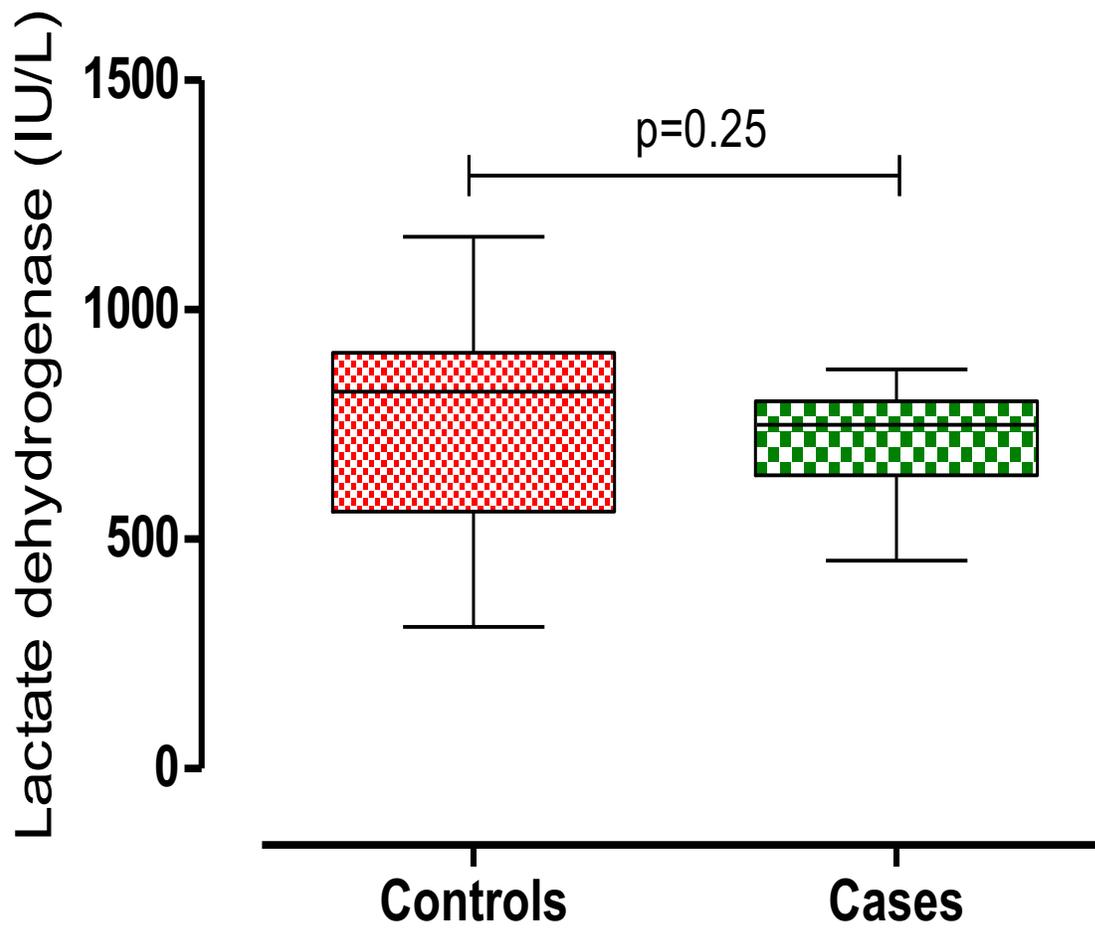


Figure 4.14: Lactate Dehydrogenase (LDH) between cases and controls

4.6 Multivariable Logistic Regression Analysis

Some independent variables were selected, and Multivariate logistic regressions was used to determine the association, odds ratio (OR) with 95% confidence interval (CI) of having Musculoskeletal Manifestations among patients with Sickle Cell Disease.

For every unit increase in age (per year), there is 13% increase in the possibility of developing Musculoskeletal Manifestations (aOR = 1.23, 95% CI: 1.10 – 1.50, p-value = 0.04). While there is a 27% increase in the possibility of developing Musculoskeletal Manifestations for every year that passes before the diagnosis of Sickle Cell Disease is made (aOR = 1.15, 95% CI: 0.83 – 1.59, p-value = 0.39). There is a 23% increase in the possibility of developing Musculoskeletal Manifestations for every increase in the frequency of vaso-occlusive crisis (aOR = 1.38, 95% CI: 1.10 – 1.72, p = 0.005). For every increase in the percentage of Haemoglobin s there is a 21% increase in the development of the Musculoskeletal Manifestations (aOR = 1.21, 95% CI: 1.10 – 1.34, p-value = 0.001). In the case of AST, the odds ratio is 1.0. Surprisingly, there is an 8% less likelihood of developing Musculoskeletal Manifestations for every unit increase in the White Blood Cell Count (aOR = 0.59, 95% CI: 0.17 – 1.98, p-value = 0.39). However, this finding is not significant.

In this Multivariate logistic regressions, age, frequency of vaso-occlusive crisis and the percentage of Haemoglobin s were the main predictors of Musculoskeletal Manifestations in this study. This as shown in Table 4.9:

Table 4.9: Multivariable logistic regression for determination of Predictors of Musculoskeletal Manifestations of Sickle Cell Disease

Variable	Univariable			Adjusted variable		
	cOR	95% C.I	p-value	aOR	95% C.I	p-value
Age	1.13	1.04 – 1.23	0.004	1.23	1.10 – 1.50	0.04
Age at diagnosis	1.27	1.10 – 1.48	0.002	1.15	0.83 – 1.59	0.39
VOC	1.23	1.12 – 1.35	<0.001	1.38	1.10 – 1.72	0.005
Percentage of Haemoglobin s	1.19	1.09 – 1.29	<0.001	1.21	1.10 – 1.34	0.001
AST	1.00	0.99 – 1.02	0.99	-	-	-
Hb	0.89	0.69 – 1.13	0.33	-	-	-
WBC	0.92	0.87 – 0.97	0.005	0.59	0.17 – 1.98	0.39
Neutrophil Count	0.93	0.86 – 1.01	0.07	1.75	0.47 – 6.59	0.41
Lymphocyte Count	0.91	0.82 – 1.00	0.062	2.10	0.51 – 8.75	0.31

cOR= Crude Odds ratio, C.I= Confidence Interval, aOR= adjusted Odds ratio, VOC= Frequency of Vaso-occlusive crisis per year, Hb= Haemoglobin, AST=Aspartate transaminase, WBC= White Cell Count

AST and Haemoglobin were excluded because, in the univariable analysis, their p-values were above 10%

4.7 Predictive Margins of the Main Predictors of Musculoskeletal Manifestations

As shown by Figure 4.15 and Figure 4.16, as the age and frequency of vaso-occlusive crisis per year increase the likelihood of developing Musculoskeletal Manifestations also increased in both sexes.

Predictive Margins of sex with 95% Confidence Interval

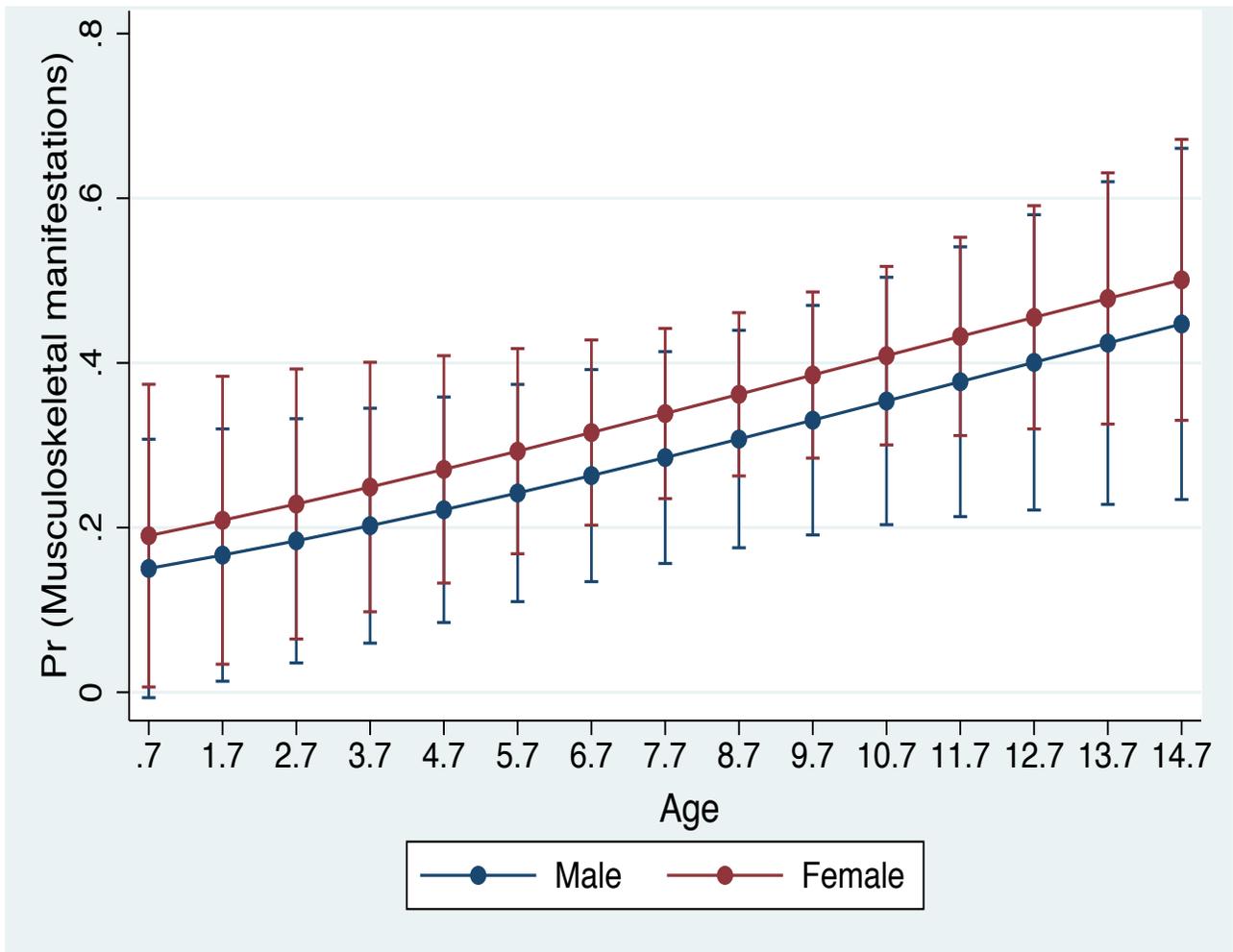


Figure 4.15: Predictive margins of Musculoskeletal Manifestations with age

Predictive Margins of sex with 95% Confidence Interval

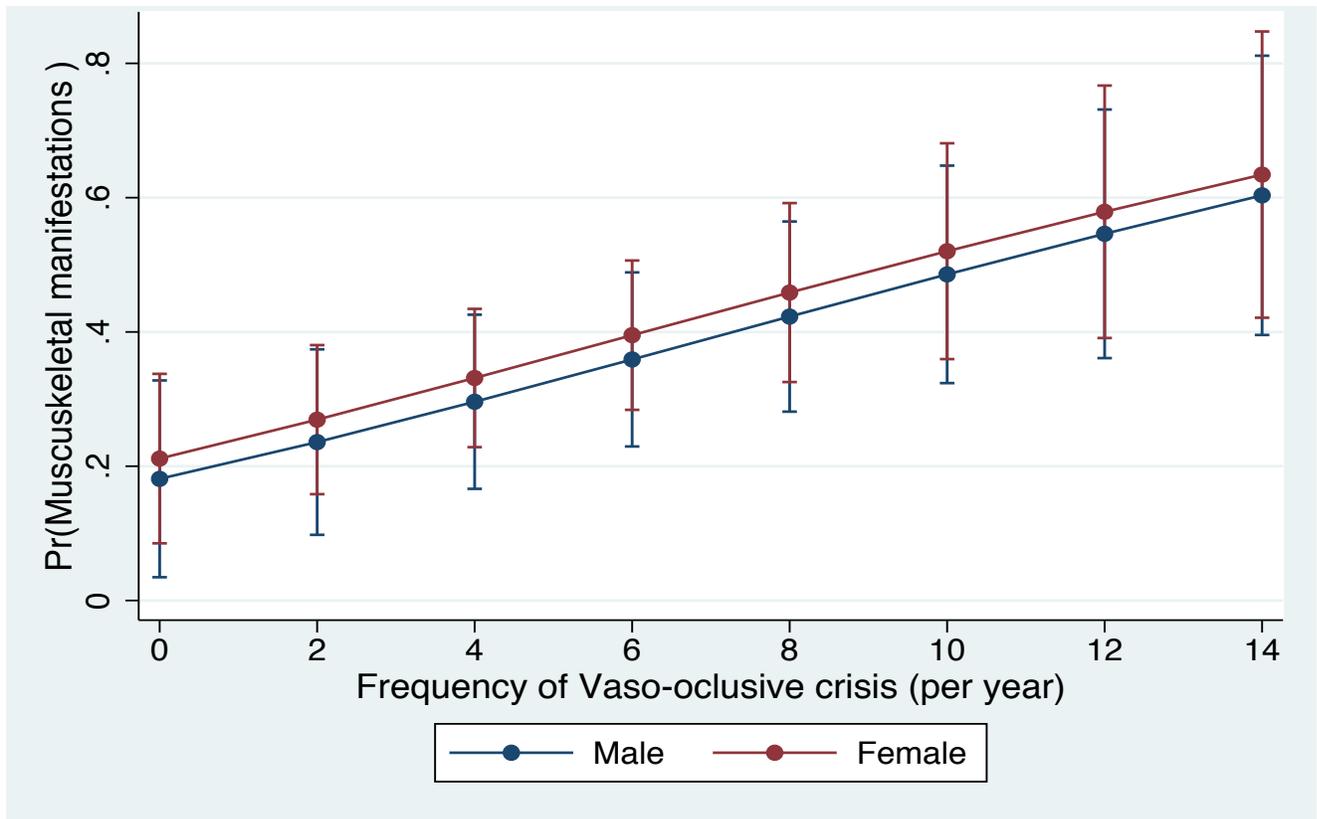


Figure 4.16: Predictive margins of Musculoskeletal Manifestations with the frequency of VOCs

It can be noted that, when the percentage of ‘Haemoglobin s’ is less than 50, the risk of developing Musculoskeletal Manifestations is very low as shown in Figure 4.17. However, above 50% of ‘Haemoglobin s’, the risk sharply increases going beyond 80% risk, as the percentage of ‘Haemoglobin s’ approaches 100. This trend is seen in both sexes.

Predictive Margins of sex with 95% Confidence Interval

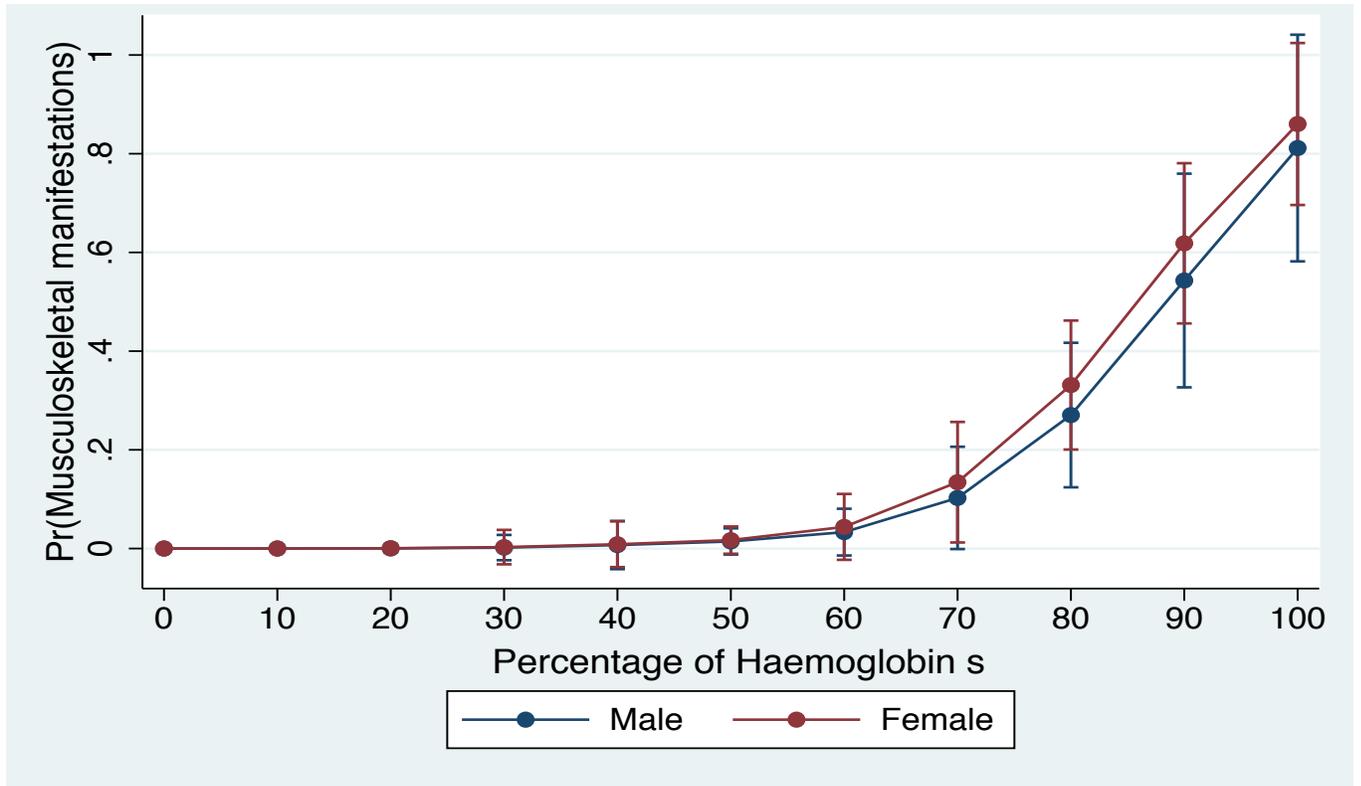


Figure 4.17: Predictive margins of Musculoskeletal Manifestations with the percentage of Haemoglobin s

CHAPTER FIVE: DISCUSSION

In this study, the commonest musculoskeletal manifestation in our environment was found to be Chronic Osteomyelitis. This accounted for 29.82% of all musculoskeletal manifestations and followed by Acute Osteomyelitis with a prevalence of 21.05%. Chinawa *et al.* (2013), reported that the commonest musculoskeletal manifestation they found was Acute Osteomyelitis at a study done at the University of Nigeria Teaching Hospital (UNTH) Ituku Ozalla in Nigeria. This difference could be attributed to the late referrals, delayed or missed diagnosis of the acute phase of the Osteomyelitis especially for patients who are referred from rural settings. This could explain why there is an increased number of paediatric patients with Sickle cell Disease presenting with Chronic Osteomyelitis to the University Teach Hospital, Lusaka. The Mulago study in Uganda revealed that the commonest musculoskeletal manifestation was avascular necrosis of the femoral head (AVN). The difference here is that, in the Mulago study, the focus was on both paediatric and adult populations, whereas this study only focused on the paediatric population. Nevertheless, similar results were noted in this study as in all the children who presented with avascular necrosis of the femoral head (AVN) were above the age of 11 years. As evident by these findings, it's clear to note that, avascular necrosis of the femoral head (AVN), presents late in the paediatric patients with Sickle Cell Disease. The possible reasons for this are outlined below under the age factor.

The commonest site of Osteomyelitis was the lower limbs, especially the Tibia at (41.38%). This is similar to findings in the Mulago study. In this study, the commonest stage of the Chronic Osteomyelitis was Beit Cure Classification type B3. It was also noted that the majority of cases were B-type (82.35%). This is similar to what Stevenson *et al.* (2015) found in the general

population (88%). *Staphylococcus aureus* was commonest micro-organism (66.67%) cultured from the deep tissues samples taken during sequestrectomy. This was different from the expected outcome, as *Salmonella* is reported to be the commonest micro-organism (Akakpo-Numado, 2013). However, Nwadiaro et al. (2000) also reported that *Staphylococcus aureus* was the commonest (58.8%) in a retrospective study done at Jos University Teaching Hospital in Jos, Nigeria. In this study, only 6 sequestrectomies out of the 17 patients who had Chronic Osteomyelitis were done during the study period. This could have affected the outcome. Of note is that only one (16.67%) case of *Salmonella* was cultured.

To find out the potential predictors of these Musculoskeletal manifestations, this case-control study looked at the demographic characteristics of the patients, some clinical parameters and laboratory parameters: In this study, the median age for the cases was 9.5 years while the controls was 7 years. There was a significant association of age with the development of Musculoskeletal Manifestations between the cases and control ($p=0.003$) and also with age at which Sickle Cell Disease is diagnosed ($p<0.001$). Chinawa *et al.* (2013), also noted in their study that the median age for patients with Musculoskeletal Manifestations was found to be 10 years and those without was 9 year. As explained earlier, manifestations such avascular necrosis of the femoral head (AVN) have a late presentation in the paediatric age group. Monagle et al. (2006), postulated that worsening hypoxemia, repeated infarction, and the development of the coagulation system as a child grows could be some of the reasons these Musculoskeletal Manifestations are likely to present late. Late diagnosis of the Sickle Cell Disease makes the patient and their caregivers unaware of the disease. Therefore, they will not look out for possible complications.

There was also a significant association in the monthly income between the cases and controls ($p=0.03$). About 91% of the patients were coming from a low socio-economic, that is, the monthly income was K5000 or less. This could explain some why children have had a late diagnosis as some patients travel very long distances from the rural areas and have limited finances.

Vaso-occlusive Crisis is the hallmark of Sickle Cell Disease. In this study, the median of the cases (6) was 3 times more than the median of the controls (2). There was a strong association ($p<0.001$) between the number of vaso-occlusive crisis per year and the development of Musculoskeletal Manifestations. These findings are similar to the findings of the Mulago study in Uganda. According to the University Teaching Hospital Paediatric protocol of the management of Sickle Cell Disease, two disease-modifying therapies are being used: Hydroxyurea and long-term blood transfusion protocol (are used in the prevention of vaso-occlusive crisis). This is supported by a review done by, Yawn et al. (2014), who reported that use of Hydroxyurea and transfusion protocol are highly recommended for patients who have Sickle Cell Disease to prevent vaso-occlusive crisis. However, Mahadeo et al. (2008), reported that there was a 16.5% prevalence of avascular necrosis of the femoral head in Sickle Cell Disease patients on Hydroxyurea. It was noted in this study that, about 10% of patients who presented with avascular necrosis of the femoral head were on Hydroxyurea. However, this study could not be established whether these patients had been commenced on Hydroxyurea before or after the development of the avascular necrosis.

In terms of genotype, the majority (98%) of the patients had homozygous haemoglobin ss (Hb ss). Hernigou et al. (2010), found that Sickle Cell Disease patients who presented with Septic Arthritis, 94.9% of them had Haemoglobin ss. However, there was no significant association between the cases and the controls with regards to the genotype ($p=0.31$). Nevertheless, It was noted that there was a strong significant association ($p<0.001$) in the amount (or proportion or percentage) of haemoglobin s each patient had. Patients with Haemoglobin ss are the most affected in terms of severity of disease (Ashley-Koch, Yang, & Olney, 2000).

Other parameters such Haemoglobin($p=0.08$), White Cell Count ($p=0.057$), Neutrophil count($p=0.08$), Lymphocyte count ($p=0.09$) had no significant association. This was similar to the findings in the Mulago study except for the Lymphocyte count which was significant. In this study, the controls could have had other infective processes which could explain why there were no significant findings between the two groups. For the liver function test, only AST had a significant association ($p=0.01$). These patients could also have had possible liver pathology seeing that in Sickle Cell Disease there is chronic haemolysis (Rees, Williams, & Gladwin, 2010).

For the multivariable regression, it can be noted that, in this study, age, frequency of vaso-occlusive crisis per year and percentage of Haemoglobin ss were the strongest predictors of these Musculoskeletal Manifestations. In this study, these are the predictors of Musculoskeletal Manifestations and the predictive margins of these variables are shown in the results section.

CHAPTER SIX: CONCLUSION AND RECOMMENDATIONS

6.1 Conclusion

This study revealed that:

1. Musculoskeletal Manifestations are common among the paediatric population in our environment.
2. The commonest Musculoskeletal Manifestation of Sickle Cell Disease at the University Teaching Hospital in Lusaka was Chronic Osteomyelitis and the Tibia was the commonest site for Osteomyelitis. The B – stage of Chronic Osteomyelitis according to the Beit Cure classification was the commonest presentation.
3. The following variables had a significant association: Monthly income, age, age at diagnosis, percentage of Haemoglobin s, frequency of blood transfusion and AST.
4. Age, frequency of vaso-occlusive crisis per year and the percentage of Haemoglobin s were the main predictors of Musculoskeletal Manifestations of Sickle Cell Disease established in this study.

6.2 Recommendations

1. The Ministry of Health should provide screening programmes for the early diagnosis of the Sickle Cell Disease to prevent the development of Musculoskeletal Manifestations.
2. Medical officers (especially from referring centres) should diagnose early or have a high index of suspicion for these Musculoskeletal conditions in these patients. This will help prevent long term sequelae of the disease such as Chronic Osteomyelitis and avascular necrosis of the femoral head.

3. Paediatricians should continue using disease-modifying therapies such as the use of hydroxyurea and transfusion protocols. These treatment modalities should be rolled out to many Sickle Cell Disease patients to reduce the frequency of vaso-occlusive crisis.
4. Further studies should be done on the prevalence of avascular necrosis of the femoral head in patients on Hydroxyurea.

REFERENCES

- Akakpo-Numado, G. (2013). Osteoarticular complications of sickle cell disease in children. *Hard Tissue*, 2(3). <https://doi.org/10.13172/2050-2303-2-3-486>
- Akaro, I. L., Madewo, G., Orwotho, N., Nankund, J., Byanyima, R., & Samoyo, P. T. K. (2016). The prevalence and factors associated with musculoskeletal disorders, in patients with sickle cell anaemia, at Mulago National Referral Hospital, Uganda. *East and Central African Journal of Surgery*, 21(1), 96–112. <https://doi.org/10.4314/ecajs.v21i1.139039>
- Alli, N. A., Patel, M., Alli, H. D., Bassa, F., Coetzee, M. J., Davidson, A., ... Wainwright, R. (2014). Recommendations for the management of sickle cell disease in South Africa. *South African Medical Journal*, 104(11), 743–751.
- Barclay, G. P. T., Jones, H., & Splaine, M. (1970). A survey of the incidence of sickle cell trait and glucose-6-phosphate dehydrogenase deficiency in Zambia. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 64, 78–93. [https://doi.org/10.1016/0035-9203\(70\)90197-5](https://doi.org/10.1016/0035-9203(70)90197-5)
- Bender, M. A. (2017). *Sickle Cell Disease*. University of Washington, Seattle. Retrieved from <https://www.ncbi.nlm.nih.gov/sites/books/NBK1377/>
- Chinawa. (2013). Musculoskeletal Complications Among Children with Sickle Cell Admitted in University of Nigeria Teaching Hospital Ituku - Ozalla Enugu: A 58 Month Review. Retrieved May 22, 2018, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3868124/>
- Chowa, M. M. (2013). *Factors influencing the outcome of acute Haematogenous Osteomyelitis (AHO) at The University Teaching Hospital, Lusaka* (Thesis). Retrieved from <http://dspace.unza.zm/xmlui/handle/123456789/2010>

- Clarke, A., Pulikottil-Jacob, R., Grove, A., Freeman, K., Mistry, H., Tsertsvadze, A., ...
Sutcliffe, P. (2015). *Key studies reporting costs for total hip replacement*. NIHR Journals
Library. Retrieved from <https://www.ncbi.nlm.nih.gov/books/NBK273973/>
- Ejindu, V. C., Hine, A. L., Mashayekhi, M., Shorvon, P. J., & Misra, R. R. (2007).
Musculoskeletal Manifestations of Sickle Cell Disease. *RadioGraphics*, 27(4), 1005–
1021. <https://doi.org/10.1148/rg.274065142>
- Joseph E Maakaron, MD; Chief Editor: Emmanuel C Besa, MD. (2018). Sickle Cell Anemia:
Practice Essentials, Background, Genetics. Retrieved from
<https://emedicine.medscape.com/article/205926-overview>
- Lepage, P., Dresse, M. F., Forget, P., Schmitz, V., & Hoyoux, C. (2004). [Infections and
antibiotic prophylaxis in sickle cell disease]. *Revue medicale de Liege*, 59(3), 145–148.
- Machila, N. (2016). *Prevalence and Risk Factors of Chronic Kidney Disease in Steady State
Sickle Cell Anaemia Patients Aged 5 and 16 Years at the University Teaching
Hospital. Lusaka, Zambia* (Thesis). University of Zambia. Retrieved from
<http://dspace.unza.zm/xmlui/handle/123456789/4873>
- Mahadeo, K. M., Oyeku, S., Moody, K., Rajpathak, S. N., Groner, A., Santizo, R., & Driscoll,
M. C. (2008). Hydroxyurea Use Is Associated with Avascular Necrosis of the Femoral
Head among Children with Sickle Cell Disease. *Blood*, 112(11), 2477–2477.
- Makani, J., Ofori-Acquah, S. F., Nnodu, O., Wonkam, A., & Ohene-Frempong, K. (2013). Sickle
Cell Disease: New Opportunities and Challenges in Africa [Research article].
<https://doi.org/10.1155/2013/193252>
- Miller, M. D. (Ed.). (2012). *Review of orthopaedics* (6th ed). Philadelphia, PA:
Elsevier/Saunders.

- Monagle, P., Barnes, C., Ignjatovic, V., Furmedge, J., Newall, F., Chan, A., ... Rowlands, S. (2006). Developmental haemostasis. Impact for clinical haemostasis laboratories. *Thrombosis and Haemostasis*, 95(2), 362–372. <https://doi.org/10.1160/TH05-01-0047>
- Nchimba, L. (2015). *Prevalence of Hepatitis B and C in Sickle-Cell disease patients at University Teaching Hospital, Lusaka, Zambia* (Thesis). Retrieved from <http://dspace.unza.zm/xmlui/handle/123456789/3726>
- Nwadiaro, H. C., Ugwu, B. T., & Legbo, J. N. (2000). Chronic osteomyelitis in patients with sickle cell disease. *East African Medical Journal*, 77(1). <https://doi.org/10.4314/eamj.v77i1.46370>
- Piel, F. B., Steinberg, M. H., & Rees, D. C. (2017). Sickle Cell Disease. *New England Journal of Medicine*, 376(16), 1561–1573. <https://doi.org/10.1056/NEJMra1510865>
- Stark, J. E., Glasier, C. M., Blasier, R. D., Aronson, J., & Seibert, J. J. (1991). Osteomyelitis in children with sickle cell disease: early diagnosis with contrast-enhanced CT. *Radiology*, 179(3), 731–733. <https://doi.org/10.1148/radiology.179.3.2027983>
- Stevenson, A. J., Jones, H. W., Chokotho, L. C., Beckles, V. L., & Harrison, W. J. (2015). The Beit CURE Classification of Childhood Chronic Haematogenous Osteomyelitis—a guide to treatment. *Journal of Orthopaedic Surgery and Research*, 10. <https://doi.org/10.1186/s13018-015-0282-9>
- Tsukanaka, M., Halvorsen, V., Nordsletten, L., EngesæTer, I. Ø., EngesæTer, L. B., Marie Fenstad, A., & Röhr, S. M. (2016). Implant survival and radiographic outcome of total hip replacement in patients less than 20 years old. *Acta Orthopaedica*, 87(5), 479–484. <https://doi.org/10.1080/17453674.2016.1212180>

Vaishya. (2015). Musculoskeletal Manifestations of Sickle Cell Disease: A Review. Retrieved May 22, 2018, from <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4659689/>

Van de Velde, S. K., Loh, B., & Donnan, L. (2017). Total hip arthroplasty in patients 16 years of age or younger. *Journal of Children's Orthopaedics*, *11*(6), 428–433.
<https://doi.org/10.1302/1863-2548.11.170085>

WHO. (2006, April 24). Sickle-cell anaemia. WHO. Retrieved from apps.who.int/gb/archive/pdf_files/wha59/a59_9-en.pdf Yawn, B. P., Buchanan, G. R., Afenyi-Annan, A. N., Ballas, S. K., Hassell, K. L., James, A. H., ... John-Sowah, J. (2014). Management of Sickle Cell Disease: Summary of the 2014 Evidence-Based Report by Expert Panel Members. *JAMA*, *312*(10), 1033–1048.
<https://doi.org/10.1001/jama.2014.10517>

APPENDICES

Appendix 1: Participant Information Sheet

Title of Study:

Potential Predictors of Musculoskeletal Manifestations in Paediatric Patients with Sickle Cell Disease at the University Teaching Hospital, Lusaka.

Principal Investigator:

Name: Dr Raymond M. Musowoya

Dept.: Surgery

Phone: 0977480425

Introduction

I am a postgraduate student in Orthopaedic Surgery and Trauma at the school of Medicine, University of Zambia. I request your participation in the above-mentioned research study. This study is in partial fulfilment for the award of a Master in Orthopaedic Surgery and Trauma (MMED).

The reason you have been invited to participate in this study is that your child fulfils the criteria in the enrolment of the participants.

You are kindly requested to read this document carefully; If you have any clarifications please ask me. I would like you to understand the purpose of this study and what is expected of you.

Please remember that participation in this study is voluntary.

If you agree to take part in this study, you will be asked to sign the consent form in the presence of a witness.

Purpose of the Study

The purpose of the study is to explore the Potential Predictors of Musculoskeletal Manifestations in Paediatric Patients with Sickle Cell Disease presenting to the University Teaching Hospital in Lusaka. This study will look at the factors that are likely to contribute to the development of conditions that affect the bones and the muscles in children that have Sickle Cell Disease. Many studies that have been done before show that there are a lot of these conditions affecting the bones and muscles. However, most of these studies have not given much information on the factors that are likely to contribute to the development of these conditions. The results of this study will help identify these factors and in turn help us in the prevention and management of these conditions that affect the muscles and bones in children with Sickle Cell Disease. Ultimately, this research will be published and presented as a paper.

Description of the Study Procedures

In this study, two groups of patients with Sickle Cell Disease will be recruited: In one group, the patients that will be recruited are those already with conditions that affect the bones and muscles. In the other group, patients with Sickle Cell Disease but do not have these conditions that affect the bones and muscles will be recruited. This will be done to compare the two groups on the possible factors that affect or contribute to the development of conditions of the bones and muscles in children who have Sickle Cell Disease.

This study is targeting children with Sickle Cell Disease who are 16 years and below who are seen at the University Teaching Hospital in Lusaka.

If you agree to be in this study, you will be asked to do the following things:

- Sign the consent or assent (where applicable) form.

- Respond to questions as laid down in the attached data collection tool. The questionnaire takes about 5 minutes to administer.
- Review of the patient's medical records/ diagnostic images.
- Collection of blood samples (such as the HIV test) and cultures (in cases of infection) will be done for laboratory investigations. The results of the HIV test and other results will be kept confidential and if the patient wishes to know the results, the patient will first be counselled before and after the testing. The blood that will be collected will all be used for the tests and after testing, the blood samples will be discarded according to the hospital guidelines of medical waste disposal. Meaning that the samples will be incinerated or burnt just like any other blood samples collected during normal clinical practice.

Confidentiality

Any information about your identity will not be collected or retained. The records of this study will be kept strictly confidential. Research records will be kept in a locked file, and all electronic information will be coded and secured using a password-protected file. No information will be included in any report that will be published that would make it possible to identify you.

Payments or benefits

There will be no payment for participation in this study. Any information gathered that will have a bearing on patient management will be made available to the units responsible for that patient.

Right to Refuse or Withdraw

The decision to participate in this study is entirely up to you. You may refuse to take part in the study at any time without affecting your relationship with the investigators of this study or the University Teaching Hospital. Your decision will not result in any loss of benefits to which you are otherwise entitled. You have the right not to answer any single question, as well as to withdraw completely from the interview at any point during the process; additionally, you have the right to request that the interviewer not use any of your interview material.

Right to Ask Questions and Report Concerns

You have the right to ask questions about this research study and to have those questions answered by Principle Investigator before, during or after the research. If you have any further questions about the study, at any time, feel free to contact the Principle Investigator or the Head of Surgery Department at University Teaching Hospital, Lusaka. If you like, a summary of the results of the study will be sent to you. The contact details are as shown in the table below.

Risks/Discomforts of Being in this Study

The discomfort may be the minimal pain you will feel when drawing blood with the needle from your arm and some physical examination may be a little bit uncomfortable.

Injury clause

In the event that you get injured during the course of the research study, for example, an injury to the arm caused by the needle prick when drawing blood, immediately notify the Principal Investigator or the Chairperson of **ERES Converge IRB office** at the following physical

address: 33 Joseph Mwilwa Road, Rhodes Park, Lusaka, Zambia. If you believe that your injury directly resulted from the research procedures of this study, you can file a complaint against the principal investigator. For a description of this process, contact the Chairperson of the Research Biomedical Ethics Committee.

The following are the contact details:

<p>Dr Raymond Musowoya, Surgical Registrar Principal Investigator Department of Surgery University Teaching Hospital Lusaka, Zambia +260977480425 raymondmusowoya@gmail.com</p>	<p>Dr James Munthali Head of Department Supervisor Department of Surgery University of Zambia School of Medicine Lusaka, Zambia +260966765422 jcmunthali@yahoo.com</p>	<p>The Chairperson, ERES Converge IRB office 33 Joseph Mwilwa Road Rhodes Park Lusaka, Zambia. Phone Number: +260 955 155633 or +260 955 155634 Email: eresconverge@yahoo.co.uk</p>
--	--	--

Appendix 2: Participant Information Sheet (Bemba)

Umutwe we lyashi uleti:

Ukufwailikisha ifichibilo ifyaku mwenako amalwele yamafupa na umupuli mubana abanono abakwata amalwele yakukama umulopa ayo batila Sickle Cell Disease, pa cipatala icikalamba ico batila University Teaching Hospital icisangwa mu Lusaka.

Incenshi Ikalamba:

Shing'anga Raymond M.

Ishina: Musowoya

Iciputulwa: Surgery

Kamusange: 0977480425

Mukubala

Ine nine umusambi umukalamba uwa amasambililo ayamalwele aya mafupa pa isukulu likalamba batila University of Zambia mu cipani ica masambililo aya Bushing'anga. Ndelombako ngacakuti kuti mwasendamo lubali muku censha pamalwelele insosele pakubala.

Ici cikangafwa ukuti bakampele ama pepala ayabukalapashi mulibushing'anga ubwakundapa amalwele ayamafupa na ukucenwa ayo batila MMED.

Namita mukwai ukuti imwe umwana wenu mwinga ibimba muli uyu mulimo pantu umwana wenu nakwata fyonse ifilefwaikwa pali aya amasomo.

Lyo namilomba ukweba ati mubelenge ici cipepala na umutekatima ukuti mumfwikishe efyo cilesosa. Nga cakweba ukuti mwaba na amepusho nalomba ukweba ati mwanjipusha. Icikalamba ndefwaya ukuti mumfwikishe na ukwishiba ubukankala na ubuyo bwa uku kucensha na fintu fyonse ifikafwaikwa ukufuma kuli imwe na umwana wenu.

Icikankala ndefwaya mwishibe ukuti ukusendamo ulubali muli uyu mulimo tatu patikisha. Kukonka fye nefyo umutima wenu ulefwaya.

Nga cakweba ati mwasuminisha ukusendamo ulubali muli uku kucensha, nala mipusha ukuti mundebeleko amashina yenu nangula ukufwatika pacipepala ica kweba ukuti namusuminisha ukuibimbamo. Mwala cita ici pameso aya bakamboni.

Umulandu nshi uku ukucensha kuka fikilisha

Umulimo uyo uku ukucensha kwalafikilisha waku fwailikisha ifishibisho ifyakumwenako ukwishiba amalwele aya umunofu na amafupa mubana aba ububwele ubwakukama umulopa ubo batila Sickle Cell Disease pacipatala cikalamba ica University Teaching Hospital muno mu Lusaka. Pali ici tulemubula ukweba ati, tulefwaya ukwishiba ifintu ifilenga ukuti aya amalwele ukuti yese mubana aba. Amasomo ayengi yalicitwa pamalwele aya munshita yakunuma, lelo fingi ifintu ifishaishibikwa nangula ukusomwa pali aya amalwele na ifyo yesa.

Ukukucensha kukafwilisha ukusanga ifi ifintu ifishaishibikwa; Elyo kukafwa na uku cingilila na ukundapa aya amalwele mubana aba. Kumpela kwa uyu umulimo, ifyo tukasnga ifilenga aya amalwele fikalembwa na ukushimikwa ukuti fikaishibikwe.

Intampulo tukasenda nali uku ukucensha

Aba abana abakaibimbamo muli umulimo bakabikwa mutu bungwe tubili. Akabungwe kakubali kakakwata abana abo basanga na ubulwele ubwa amafupa na umunopu. Aka bungwe ka cibili kakakwata abana abakwata ubulwele ubwa ukukama umulopa ubo batila Sickle Cell Disease; Lelo aba bana muli aka akabungwe tabakakwate aya amalwele ayamafupa na umunofu. Ifi

fikacitwa mukweba ati tukamone ngapali ifipaleneko nangula ifipuseneko pali aya amabumba yabili.

Muli ukukucensha tulefwaya abana abali na ubulwele ubwakukama umulopa abali na imyaka ikumi limo na yisano na ukwisa panshi abo aba abamonwa pacipatala icikalamba ica University Teaching Hospital (UTH).

Nga mwasumina ukukwatamo ulubali muli uku ukucensha, mwala lombwa ukwata ifi:

- Ukulemba amashina yenu nangula ukufwatika pacipepala mwalapelwa ico cilelanga ukuti mwalisumina uku ibimbamo muli uyu umulimo. Umwana wenu nao alafwaikwa ukucita ici ngacakuti nakwanisha imyaka
- Ukwasuka amepusho ayo ayalembwa ayo mwalapelwa. Aya amepusho yalasenda fye akashita akanono (Insa Shisano)
- Incenshi yikalamba yikala loleshapo pamapepala na amakadi yamwana aya kucipatala.
- Bashu Ng'anga bakala sendako umulopa na ukupima amalwele yamoyamo ayapala ubu ubulwele ubwakondoloka ubo batila HIV. Ifikalatumbukamo muli uku kupima fikaba fyankama. Ngacakuti mwebene mwafwaya ukwishiba, tukalafwaikwa ukwikala pamo na ukulanshanya apo tatulamyeba aya ama results (ifyakutumbukamo)

Amafisakanwa

Lyose ilyashi na ama results likalaba lyashi lyamatwi yesu fye fweka (imwe na ine epela). Fyonse ifikadi nama pepala fikala komenwa. Elyo ilyashi lyonse ilyo tukasambilila pa mulwele wenu ilyo tukamona ukweba ukuti kuti lya afwilisha mukundapa uyu mulwele likapelwa kuli ba shing'anga aba umwana wenu.

Amalipilo nangula ifyo mukasombolamo

Takuli takwakabe amalipilo ayali yonse ayakatumbukamo (ayo muka lipilwa) muli uku kuibimbamo. Elo ilyashi lyonse ilyo tukasambilila pa mulwele wenu ilyo tukamona ukweba ukuti kuti Iya afwilisha mukundapa uyu mulwele likapelwa kuli ba shing'anga aba umwana wenu.

Insambu ishakukana ikuibimbamo nangula ukulekela pakati ukuibimbamo

Uku senda ulutampulo ukukwatamo ulubali muli uku ukucensha cili kuli imwe mukawai. Nga mwatemwa kuti mwakana. Ici tacaka lete ububi ubuli bonse. Pakumfwane kwesu imwe na ine, na umwana wenu aka undapa cimo cine na uyo uwo abafya basumina uku sendamo ulubali muli uyu umulimo.

Na mu kwata insambu ukukana asuka ilipusho ilili lyonse. Elyo muli aba kakulwa uku leka uku sendamo ulubali muli uyu umulimo, inshita iyili yonse iyo mwatemwa. Muli abantungwa ukwipusha incenshi uku kana bonfya ilyashi ilili lyonse ilyo ya sombola muli ubu ubucenshi na amepusho.

Insambu isha kwipusha amepusho na ukutwala umulandu nangula amasakamiko kuntungulushi

Muli na insambu isha kwipusha amepusho pali uku censha ino inshita nangu umuya inshiku. Elyo namukwata na amaka na insambu ishakumona ine nangula abakalamba aba milimo muciputulwa caba shing'anga aba bomfya umwele na uku putula mukundapa amalwlele (Department of Surgery), pacipatala cikalamba ica University Teaching Hospital. Ngamulefwaya ukwishiba ifyo tukasangamo muli aya amasomo, ifwe tuli na insansa ukumitotoshako.

Kamusange na akeyala apakuntumina nangu ukundembela nangu ukunsanga na filembwa panshi pa ili ibula lya ipepala.

Ifingalenga ubusanso na uku kalipwa nolo ukutompokwa kwa mubili muli ubu ubucenshi nangula amasomo

Utunkofyo nkofyo mwinga sangamo muli uku ukuibimbamo muli ubu ubucenshi fintu nga uku kalipwa kwamubili pakufumya umulopa, ukupimwa pamubili limbi kuti nako kwalenga tamumfwile bwino panono

Nga cakuti kwaba ubusanso

Nga kwaba ubusanso munshita ya ubu ubucenshi, ubwapala ukuicena na inyeleti pakufumya umulopa, incenshi nabambipo bakalafwaikwa ukwishibisha incenshi ikalamba nangula shimucindikwa uwa kucipuna ica akabungwe kaba lolekesha pafyo ubucenshi bule enda mu calo cesu, abo batila ba ERES Converge IRB, abo aba sangwa pa akeyala 33 Joseph Mwilwa Road, Rhodes Park, Lusaka, Zambia. Ngacakweba ati uwaicena amona ukuti ubusanso bwafuma mubucenshi, uyo afwile uku twala ukuilishanya ku incenshi ikalamba. Ifyashala kuti balundapo aba ku cipuna ica bucenshi ica ERES Converge IRB.

Ikayala kabantu tulumbwile pamulu kali nga ifi:

<p>Dr Raymond Musowoya, Surgical Registrar Principal Investigator Department of Surgery University Teaching Hospital Lusaka, Zambia +260977480425 raymondmusowoya@gmail.com</p>	<p>Dr James Munthali Head of Department Supervisor Department of Surgery University of Zambia School of Medicine Lusaka, Zambia +260966765422 jcmunthali@yahoo.com</p>	<p>The Chairperson, ERES Converge IRB office 33 Joseph Mwilwa Road Rhodes Park Lusaka, Zambia. Phone Number: +260 955 155633 or +260 955 155634 Email: eresconverge@yahoo.co.uk</p>
--	--	--

Appendix 3: Parent/Guardian Consent Form

Title of Study:

Potential Predictors of Musculoskeletal Manifestations in Paediatric Patients with Sickle Cell Disease at the University Teaching Hospital, Lusaka.

Investigators:

Name: Dr Raymond M. Musowoya **Dept:** Surgery **Phone:** 0977480425

Consent

- Your signature below indicates that you have decided to volunteer your child to be a research participant for this study and that you have read and understood the information provided above. You will be given a signed and dated copy of this form to keep, along with any other printed materials deemed necessary by the study investigators.

Subject's Name (print): _____

Subject's Signature/ thumbprint: _____ Date: _____

Investigator's Signature: _____ Date: _____

Appendix 4: Child Assent Form

I am Dr Raymond Mpanjilwa Musowoya from the University Teaching Hospital. I am doing a study to find out the Potential Predictors of Musculoskeletal Manifestations of Sickle Cell Disease in children like you presenting to our hospital. By this it means, this study is looking at the factors that are likely to contribute to the development of conditions that affect the bones and the muscles in children like you that have Sickle Cell Disease.

Some questions will be asked about your condition and then an examination will be done on you to find out if you are presenting with any condition that affects the bones and muscles. This will be a routine clinical examination done in a child presenting with your condition.

If you happen to present with any conditions that affect the bones and muscles, you will receive the same treatment as any other child who presents to our hospital with a similar condition.

Whether or not you present with any of these conditions, your blood samples will be taken for different tests. The blood tests are taken to compare between those that have developed these conditions and those without. Minimal pain will be caused by the injection during the collection of blood.

If you do not want to take part in this study, you do not have to, and if you feel as though you would like to stop at any point during the study, you are free to do so.

You should discuss with your parent/guardian before you agree to take part. Your parent/guardian will be spoken to and will be asked for permission for you to participate, but if you do not want to, you do not have to.

If you have any questions, feel free to ask them, now or later, and the Principle Investigator will answer them. If you think of a question later, you or your parents can contact the Principle

Investigator on the phone number provided above, or you can find the Principle Investigator at the University Teaching Hospital in the Department of Surgery. Sign this form only if you:

- Have understood what will happen to you during the study
- Have had all your questions answered
- Have talked to your parents/ guardian about the study
- Agree to take part in this study

I _____ (Participants name) in the presence of my parents/guardian and with their consent, do agree voluntarily to participate in this study.

Signature/thumb print: _____

Date _____

Investigators name: _____

Signature/thumb print: _____

Date: _____

Appendix 5: Participant Evaluation Form

Questionnaire number:.....

Name of the person administering tool:.....

Section A: Demographic Data (Please circle):

1. **Age:**
2. **Sex:** 1) Male 2) Female
3. **Caregiver:** 1. Both Parents 2. Mother Only 3. Father only 4. Other Guardians
4. **Social Economic Status (Monthly Income):** 1) K1000 and below 2) k1001-K5000
3) K5001- K10000 4) Above K10,000
5. **Referring Hospital/District/Province:**
6. **Patient Category:** (a) New patient.....
(b) follow-up patient

Section B: Nature of Pathology (Diagnosis)

7. **Age of Diagnosis of Sickle Cell Disease:.....**
8. **Any Musculoskeletal manifestations? (Please circle): 1. Yes 2. No.**
(If No, skip to question 12)

9. Current Musculoskeletal Manifestations (Please tick):

	Diagnosis	Comment
1	Osteomyelitis:	
	Acute	
	Post-Acute	
	Sub-Acute	
	Chronic	
2	Avascular Necrosis (AVN)	
	Femoral Head	
	Spine Vertebra	
	Other	
3	Leg Ulcers	
4	Septic Arthritis	
6	Pathological Fractures	
8	Other (Dactylitis, Tb arthritis)	

Question 10: Site of Pathology (Please tick)

Site	Unilateral		Bilateral
	Right	Left	
Humerus			
Radius			
Ulna			
Femur			
Tibia			
Shoulder			
Elbow			
Hip			
Knee			
Spine			
Other			

Question 11: Classification/ Staging of Pathology

a. Infection:

Causative Organism:.....

Sensitivity:.....

Beit Cure Classification of Chronic Osteomyelitis (Please tick)

Stage: Radiological appearance of bone segment	Comment
A: Abscess type, osteolytic area(s), no sequestrum, no involucrum	
B1: Peripheral, localized cortical sequestrum, minimal/no involucrum	
B2: Sequestrum present, stable, normal-looking cortical involucrum	
B3: Sequestrum present, stable, sclerotic involucrum	
B4: Sequestrum present, unstable, inadequate involucrum	
C: No sequestrum visible on plain x-ray, densely, diffusely sclerotic bone segment; abscess may be present	
Unclassifiable: Inadequate x-ray/ disease onset > 6 months/ Previous surgery	

b. Long term complications of the Orthopaedic pathologies:

Chronic pain.....

Contracture.....

Gait Disturbances.....

Leg length Discrepancy.....

Amputations.....

Other.....

Section C: Blood investigations

Question 12: Haematological Parameters

Parameter	Reference Range	Patient's Reading	Comment
Hb			
PLTs			
WBC			
DC			
Neutrophils			
Lymphocytes			
Monocytes			
Basophils			
Eosinophils			

Question 13: Liver Function Tests (LFTs)

Parameter	Reference Range	Patient's Reading	Comment
Alanine transaminase (ALT)			
Aspartate transaminase (AST)			
Alkaline phosphatase (ALP)			

Gamma-glutamyl transpeptidase (GGT)			
Total Bilirubin			
Direct Bilirubin			
Lactate dehydrogenase (LDH)			

Question 14: HIV status (Please tick)

Reactive:

Non- Reactive.....

Question 15: Genotype:.....

Section D: Use of Hydroxyurea

- a. Is Patient on hydroxyurea? 1. Yes 2. No
- b. If yes, what is the dose?.....
- c. How long has the patient being on hydroxyurea?.....
- d. Has the patient experienced recurrent fevers in the past one year? 1. Yes 2. No

- e. If a patient has experienced recurrent fevers, what is the frequency in the past year?.....
- f. Any history of bone pain during these recurrent fevers? 1. Yes 2. No

Section E: Frequency of Vaso-occlusive crisis

- a. The number of blood transfusions in the past one year?.....
- b. The number of Vaso-occlusive crisis in the past one year?.....
- c. Any other crisis apart from vaso-occlusive crisis in the past one year?.....
- d. Any other associated comorbidities?.....