BMC Health Services Research

RESEARCH

Open Access

Risk factors associated with pain episodes among sickle cell patients that visited Mulago National Referral Hospital-Uganda

Nassiwa Shamira[1], Asiimwe John Bosco[2], Nsimbe Dick[1] and Charles Lwanga[3*]

Abstract

Background Sickle cell disease (SCD) is a chronic hematologic disease associated with increased morbidity and mortality. The study aims to investigate the suggested socio-economic and clinical factors and their contribution to the frequency of pain episodes among sickle cell patients in Uganda.

Method We used pre-existing secondary data from sickle cell clinic records at Mulago referral hospital collected in 2019, with a sample of 2532 sickle cell patients. In support of the outcome being count data, the Negative Binomial Regression model was utilized to estimate how the independent factors affected the frequency of pain episodes among the patients.

Results The frequency of pain episodes was different among age groups as age group (16/24) experienced the highest number of pain episodes on average (Incidence Rate Ratio = 1.39; 95% CI = 1.277–1.522; $p = 0.000$) compared to young children because as individuals age, pain management declines, and repeated episodes can lead to increased sensitivity, making them more prone to pain. While increased temperature (°C) (fever) increased the frequency of pain episodes by 24% (Incidence Rate Ratio = 1.243; 95% CI = 1.147–1.348; $p = 0.000$), infection by 27% (Incidence Rate Ratio = 1.27; 95% CI = 1.191–1.354; $p < 0.000$), other chronic diseases by 11% (Incidence Rate Ratio = 1.11; 95% CI = 1.038–1.188; $p < 0.002$), malaria by 38% (Incidence Rate Ratio = 1.38; 95% CI = 1.036–1.836; $p < 0.027$). The rate of hydroxyurea usage was very high at 90%. The intake of the drug reduced the frequency of pain episodes by 34% (Incidence Rate Ratio = 0.662; 95% CI = 0.584–0.750; $p < 0.000$). According to the observations, there is a high chance that hydroxyurea also had a strong protective against malaria in SCD patients. Nevertheless, there was no evidence that being a male or female would influence the frequency of pain episodes among sickle cell patients.

Conclusions These findings are expected to add to the body of knowledge in the health sector, assist in advocacy programs, inform policy, and aid in tailored interventions.

Keywords Sickle cell disease, Pain episodes, Mulago-Kampala, Uganda

*Correspondence:
Charles Lwanga
cblwanga@gmail.com; charles.lwanga@mak.ac.ug
[1]Department of Statistical Methods & Actuarial Sciences, School of Statistics & Planning, College of Business & Management Sciences, Makerere University, Kampala, Uganda
[2]Department of Planning, School of Statistics & Planning, College of Business & Management Sciences, Makerere University, Kampala, Uganda
[3]Department of Population Studies, School of Statistics & Planning, College of Business & Management Sciences, Makerere University, Kampala, Uganda

Background

In 1910, James Herrick discovered sickle cells in human blood as unusual, elongated sickle-shaped erythrocytes in a patient with anemia [1]. Sickle cell disease (SCD) is a group of disorders that affect hemoglobin, the molecule found in red blood cells that transports oxygen throughout the body [2]. People with this disorder have atypical hemoglobin molecules known as hemoglobin S, which can cause red blood cells to distort into a sickle or crescent shape [3]. The affected blood is less able to carry oxygen and flow smoothly, resulting in a variety of health issues such as pain and a shorter lifespan [3]. Because sickle cell trait increases survival of malaria, the disease is most common in malaria-endemic parts of the ancient world, primarily Africa, the Middle East, and Southeast Asia. Equatorial African countries bear the greatest burden [4]. Extreme conditions among the patients such as severe dehydration and strenuous physical activity, continue to occasionally result in serious health problems, including sudden death among patients with the disease [5]. Individuals however with the Sickle Cell Trait (SCT), also known as carriers, do not have the disease and typically do not exhibit any of the symptoms of sickle cell disease (SCD) and lead a normal life [6].

SCD symptoms differ from person to person and change over time. Chronic anemia, recurrent pain crises with painful swelling of hands and feet (dactylics), which is often one of the first symptoms, and an increased risk of infections are among the symptoms. Infections are frequently caused by impaired spleen function as a result of recurrent pain crises and infarction. This makes a patient more vulnerable to infections associated with pain, some of which are potentially fatal, such as pneumonia. Other symptoms include delayed growth and vision [7]. The most common problems associated with SCD are SCA and pain episodes (crises). Anemia is caused by the easy breakage and death of sickled red blood cells in 10–20 days, as opposed to normal red blood cells, which live for 120 days, leaving you with an insufficient supply of red blood cells. This has a number of side effects, including stroke, acute chest syndrome, pulmonary hypertension, organ damage, blindness, leg ulcers, gall stones, and priapism [7]. Painful episodes, also known as crises, occur when sickle-shaped red blood cells block blood flow through tiny blood vessels to your chest, abdomen, and joints [8]. Similarly, bone pain is also possible and the intensity of the pain varies and can last from a few hours to a few weeks [9]. Some people have a few pain episodes each year, while others have a dozen or more [8]. If the crisis is severe enough, one may require hospitalization. This can cause bone and joint damage, as well as ulcers [7].

Approximately 5% of the world's population currently carries trait genes for hemoglobin disorders, primarily sickle cell disease and thalassemia [10]. It is most common in Africans and less common in those of Mediterranean, Latino, East Indian, and Arab descent. It is estimated that 16% of the African population suffers from sickle haemoglobinopathy, the highest proportion in the world [11]. The Americas and the East Mediterranean region have the second highest prevalence of sickle cell haemoglobinopathy. Each year, an estimated 400,000 neonates are born with sickle cell disease, including 300,000 with sickle cell anemia [12]. Sub-Saharan Africa bears the greatest burden, accounting for more than 75% of all sickle cell disease cases, with this figure expected to rise by 2050 [13]. Most African countries are affected by sickle cell anaemia, with many children suffering from the most severe form of the disease dying before the age of five. Recent estimates suggest mortality rates of 36.4% by age 5 years and 43.3% by age 10 years among children with sickle cell anaemia in sub-Saharan Africa. These deaths are primarily attributed to complications such as pain, severe infection, or blood loss [14]. According to the WHO's 2024 report, the prevalence of sickle cell trait ranges from 20 to 30% in countries like Cameroon, the Republic of Congo, Gabon, Ghana, and Nigeria, and can reach up to 45% in certain regions of Uganda [15]. According to the Uganda Bureau of Statistics and ICF, the prevalence of sickle cell disease is 0.73, while the prevalence of trait is 13.3% [16]. However, the distribution varies across the country. Trait prevalence exceeds 20% in the Mid North (Acholi and Lango), East Central (Busoga, Bugweri, Busamya, Budama, and part of Teso), and Bulisa and Bundibugyo, and disease prevalence exceeds 1%. A trait prevalence of more than 15% exists in 49 of the 112 districts. Fourteen districts, including Kampala, Gulu, Lira, Jinja, Tororo, Luweero, Wakiso, Apac, Iganga, Mayuge, Buikwe, Oyam, Masaka, and Masindi, contribute 47% of the national disease burden [17]. In Uganda, it is estimated that 33,000 babies are born each year with sickle cell disease, with 80% dying before the age of five. End-organ damage causes the survivors' lives to be cut short [18].

Pain is a defining feature of SCD, and it is unpredictable, episodic in nature, and described as one of the most excruciating forms of pain that affects humans [19]. SCD patients may experience severe pain during infancy, childhood, and adulthood [20]. It is responsible for the vast majority of hospitalizations as well as the overall negative impact on patients' health-related quality of life. Pain episodes can occur as infrequently as once a year to as frequently as once a week. The intensity and duration of pain can vary, and it can be excruciating. The vast majority of painful episodes are managed at home, with patients typically seeking

hospital care only if the pain is unbearable or analgesia is unavailable. Patients who require hospitalization may be admitted for several days [21]. Pain in sickle cell can result in bone and joint damage as well as ulcers [22]. Regarding management of pain episodes, the dosage and type of painkiller are determined by the patient's recent painkiller use, the location and intensity of the pain, other symptoms associated with the pain, and what agents and doses have worked effectively in the past and side effects [21]. Nonsteroidal anti-inflammatory drugs (NSAIDs) may be sufficient to control moderate to mild VOC. These medications may include diclofenac and ibuprofen, and if the pain persists, an opioid may be prescribed. Furthermore, opioids are commonly used to treat moderate to severe pain. Weaker opioids, such as codeine, are used to treat moderate pain. Stronger opioids, such as morphine, or equivalents such as levorphanol, methadone, oxymorphone, or fentanyl, may be used to treat severe pain. Chronic pain should be evaluated at least once a year, and treatment should be adjusted as necessary [23]. Despite numerous studies demonstrating the prevalence of sickle cell disease in Uganda [13], the use of hydroxyurea [17], knowledge and perceptions [24], studies on pain evaluation in SCD patients are lacking in Uganda, which should be the guide to drug and painkillers prescription by clinicians.

Methods

The study used secondary data from Mulago hospital sickle cell clinic for the year 2019. The hospital routinely collects data on the frequency of sickle cell pain episodes, and on, socio-demographic factors from all sickle cell patients using a special medical record form. This information is collected during clinic days and in the process, patients are given unique clinic numbers which are printed on their hospital cards. The unique numbers are used to identify patients and to avoid duplicating information from the same person, and data is later entered into the computer for proper storage. All patients presented to the clinic with pain in any part of their body were eligible for an interview. In the process of data collection, the hospital used a retrospective study design to collect previous and current patients' medical histories. The design was appropriate because it could allow tracing the origin of sickle cell pain episodes and further investigate potential relationships. In addition to frequency of pain episodes and sociodemographic factors, other information collected include patients' reasons for visiting the clinic, vital signs, measurements, history, physical examination, investigations, previously diagnosed chronic diseases, current condition, day care treatment, patient disposition, and outpatient medications. Analysis for the current study is based on a sample of 2532 sickle cell patients who visited the sickle cell clinic with body pain in the abdomen, chest, bones, and joints.

Measures of outcome

The dependent variable of the study was the frequency of pain episodes among sickle cell patients in "*one*" year as registered at Mulago sickle cell clinic. This was a count per unit time that a patient-reported pain at the clinic. The dependent variable was created from a general question, *'How many times did the patient in question report a pain episode in "2019"?'*, indicating the number of times a patient had pain when they reported to the clinic in "2019".

Measures of explanatory variables

The independent variables are sex, categorized as male and female; age, categorized as 0–7 (young children), 8–15 (children), 16–24 (young adults), 25–40 (adults), and 41 + years (older persons); fever status, categorized as Yes and No; presence of other chronic diseases, categorized as Yes and No; folic acid, categorized as Yes and No; infection status, classified as Yes and No; blood transfusion, grouped as Yes and No; hydroxyurea, categorized as Yes and No; and malaria status, grouped as Yes and No.

Statistical analysis

Diagnostic tests were performed prior to data analysis to determine whether the dependent variable follows a Poisson distribution. Although the dependent variable was count, which qualified the data to follow a Poisson distribution and be analyzed using Poisson, we had to further investigate whether the observations were independent and whether the distribution of the counts followed a Poisson distribution (or whether the mean was equal to the variance) [25]. To test for independence, the dependent variable was tested for observation independence using the Kolmogorov-Smirnov (K-S) test, which is a non-parametric test. Because the test results were significant (Asymp > 0.05), we rejected the null hypothesis that the data followed a Poisson distribution because the variable did not meet the observation independence assumption (Asymp > 0.05). We used descriptive statistics to determine whether the count distribution followed a Poisson distribution by comparing the mean value to the variance value. Our results showed that the mean value was 1.742496, variance was 1.772464 with a standard deviation of 1.3313. Since mean and variance were not equal, we concluded that there was over-dispersion in the data. Based on the above tests, we concluded that a negative binomial model was appropriate for analyzing this type of data. Furthermore, we used the variance inflation factor (VIF) to test for multi-collinearity, and the values for all covariates considered in the analysis

ranged between 1 and 5. As a result, the correlation was moderate and could not significantly bias our results. Following the diagnostic test, we analyzed our data at three levels. First, we used descriptive statistics to describe the variables in the data which were used in subsequent analysis. Results of the descriptive analysis were presented as frequency distributions and percentages of demographic and socioeconomic characteristics. Second, we used the one-way ANOVA test, with a p-value 0.05, to see if there were any statistically significant differences in the means of each independent factor at the bivariate level. Third, the negative binomial regression model was used at multivariate level to isolate the sociodemographic factors associated with the frequency of pain episodes. At this level, variables included in the final model were selected based on statistical significance, $p < 0.05$, at the bivariate level and those found to be significant in other studies. The findings are presented as Incidence Rate Ratios. The fitted model was subjected to the *link test* to examine whether the explanatory variables were specified correctly and also assess the goodness of fit of the model [26]. This *link* test uses the *hat* and *_hat-squared statistics* to compare observed and expected data. When the model describes the data correctly and is appropriate, the *_hat-squared* should not be significant (_hat-squared, $p > 0.05$). The implication is that the observed and expected data m Incidence Rate Ratio or the same.

Results

Table 1 shows that slightly more than half of the study population were male sickle cell patients (50.2%). The results also show that the majority of the respondents (38.8%) were aged between 8 and 15 years; 38.4% were aged between 0 and 7 years; about 17.0% were between 16 and 24; 5.0% were aged between 25 and 40 and nearly 0.9% were over 40 years. Table 1 further show that the majority of the patients (80.1%) reported fever when they had pain with the remaining 19.9% reporting no fever

Table 1 Frequency distribution of the factors influencing the frequency of episodes and mean number of episodes by selected sociodemographic, clinical, and form of intervention factors

Covariates	Frequency	Percentage	Mean no of pain episodes per year	*P*-value for the mean difference
Age				
Young children (0-7)	971	38.35	1.53	0.00
Children (8-15)	982	38.78	1.79	
Young adults (16-24)	430	16.98	2.05	
Adults (25-40)	127	5.02	1.93	
Older persons (41+)	22	0.87	1.82	
Sex				
Male	1261	49.80	1.78	0.18
Female	1271	50.20	1.71	
Fever status				
No	505	19.94	1.41	0.00
Yes	2027	80.06	1.83	
Infection status				
No	1185	46.80	1.52	0.00
Yes	1347	53.20	1.94	
Other chronic diseases				
No	1796	70.93	1.67	0.00
Yes	736	29.07	1.91	
Blood transfusion				
No	2312	91.31	1.73	0.10
Yes	220	8.69	1.89	
Hydroxyurea				
No	101	3.99	2.80	0.00
Yes	2431	96.01	1.70	
Malaria Status				
No	2515	99.33	1.74	0.00
Yes	17	0.67	2.82	
Folic Acid				
No	731	28.87	1.30	0.00
Yes	1801	71.13	1.92	

when they had pain. Records also show that nearly half of the patients (53.2%) had an infection when they had pain. The majority of the patients had no other chronic diseases other than SCD (70.9%). About folic acid, 71.1% were taking it; 91.3% of the sickle cell patients didn't undergo blood transfusion; 96.0% were on hydroxyurea and nearly all (99.3%) had no malaria. With the significance level ($p = 0.18 > 0.05$) there isn't a statistically significant difference in the mean frequency of pain episodes between male and female patients.

Furthermore, in light of the age of the patients, results from Table 1 show a significant difference in the mean frequency of pain episodes between age groups ($p = 0.00 < 0.05$). Specifically, the post hoc results showed that there was a significant difference between the mean frequency of pain episodes between children and Young children, young adults (16–24) and Young children, and young adults (16–24) and children. Clear observations indicate that older patients experienced often more pain crises compared to the young ones. Though the majority of children experienced moderately less pain compared to their counterparts, there was a significant difference in the mean frequency of pain episodes between patients that had a fever when they reported pain and those that had no fever when they reported pain ($p = 0.00 < 0.05$). Patients that had fever alongside pain episodes had more pain episodes - compared to those that had no fever alongside pain. With a p-value ($p = 0.00$), there was a significant difference in the mean number of pain episodes experienced by patients that had pain and other infections other than malaria as compared to those that had none alongside pain. Patients that had such infection when they had pain reported more pain episodes as compared to their counterparts. There was a significant difference in the mean number of pain episodes experienced by patients that had other chronic diseases other than sickle cell disease as compared to their counterparts as they experienced more pain episodes on average ($p = 0.00$). With the significance level ($p = 0.10$) there is no significant difference in the mean frequency of pain episodes among patients that had ever had a blood transfusion when they reported pain as compared to those that had never had a blood transfusion as they reported with pain. In other words, both groups of patients experienced the same number of pain episodes on average in that year. In addition, results in Table 1 showed a significant difference between the mean number of pain episodes' patients that were on hydroxyurea compared to those who were not on medication. Patients that were on hydroxyurea had a less number of pain episodes compared to their counterparts. The majority of the patients did not have malaria. However, patients that had malaria times reported pain at the clinic and experienced more pain episodes that year compared to those that had no malaria ($p = 0.00$). Results further show that patients who were on folic acid when they reported pain, experienced a greater number of pain episodes compared to those that were not on folic acid.

Table 2 Multivariate negative binomial results linking frequency of pain episodes among sickle cell patients to individual characteristics, in Uganda

Variable	Incidence Rate Ratio (IRR)	*P*-value	95%CI
Sex			
Male (Ref.)			
Female	1.0167	0.585	[0.9582 1.0787]
Age (in years)			
Young children (Ref.)			
Children (8-15)	1.1934	0.000	[1.1097 1.2833]
Young adults (16-24)	1.3941	0.000	[1.2773 1.5215]
Adults (25-40)	1.2466	0.001	[1.0908 1.4247]
Older persons (41+)	1.2404	0.178	[0.9067 1.6967]
Fever status			
No (Ref.)			
Yes	1.2434	0.000	[1.1467 1.3483]
Infection status			
No (Ref.)			
Yes	1.2700	0.000	[1.1914 1.3538]
Other chronic problems			
No (Ref.)			
Yes	1.1102	0.002	[1.0380 1.1875]
Hydroxyurea			
No (Ref.)			
Yes	0.6615	0.000	[0.5836 0.7497]
Malaria status			
No (Ref.)			
Yes	1.3795	0.027	[1.0364 1.8362]

Ref. Reference category, *CI* Confidence Interval

Risk factors associated with pain episodes among sickle cell patients

In identifying the net effect of each independent factor on the frequency of pain episodes in sickle cell patients, a final model was built based on the variables identified by the bivariate analysis. During the modeling process, the patient's sex, age, fever status, other chronic disease, hydroxyurea, malaria status, and infection status were all included in the final model. Patients' age and infection status were non-concave during the estimation process. They were however included in the model with the option "*difficult*," which uses a different stepping algorithm in non-concave variables [27]. A non-concave variable is one where the model fails to obtain maximum likelihood during the estimation process. This occurs when such variables do not show a clear direction. While sex was not significant at the bivariate level, it was included in the model because previous research has shown that

it influences pain [28]. Although folic acid was significant at the bivariate level, it was not included in the model because the model remained non-concave even with the "*difficult*" option. Results in Table 2 show that; Children, young adults (16–24)and adults are 19%, 39%, and 25% respectively more likely to experience greater frequency of pain episodes compared to Young children (0 - 7 yrs). The Incidence Rate Ratio of pain increased mostly among young adults (16 - 24 yrs), (Incidence Rate Ratio = 1.193; 95% CI = 1.278–1.522; p = 0.000), adults (25 - 40 yrs), (Incidence Rate Ratio = 1.247; 95% CI = 1.091–1.425; p = 0.001), and children (8 - 15 yrs), (Incidence Rate Ratio = 1.193; 95% CI = 1.110–1.283; p = 0.000).

Patients presented with fever were 24% more likely to experience frequency of pain episodes relative to those without (Incidence Rate Ratio = 1.243; 95% CI = 1.147–1.348, p = 0.000); similarly, patients presented with other infections were 27% more likely to experience pain episodes than those who did not have such infections (Incidence Rate Ratio = 1.270; 95% CI = 1.191–1.354, p = 0.000). Table 2 further show that having other chronic diseases other than sickle cell, would increase the odds of experiencing pain episodes by about 11% relative to those without (Incidence Rate Ratio = 1.110; 95% CI = 1.038–1.188, p = 0.002). A one-unit increase in Hydroxyurea intake is associated with a reduction of about 34% in the odds of frequency of pain episodes (Incidence Rate Ratio = 0.661; 95% CI = 0.584–0.750; p = 0.000). It is not surprising to find a positive association between malaria and experiencing of frequency of pain episodes. Results show a 38% more chance of experiencing frequency of pain episodes for patients with malaria relative to those without (Incidence Rate Ratio = 1.3794; 95% CI = 1.036–1.836; p = 0.027). Sex of the sickle cell patient was not associated with experiencing of frequency of pain episodes in Uganda (Incidence Rate Ratio = 1.017; 95% CI = 0.958–1.079; p = 0.585). Regarding the diagnostic test, results show that the final model was correctly specified (*_hat-squared p-value = 0.540).* This implies that the observed data as described by the sample is similar to the expected data hypothesized for the population of patients being investigated.

Discussion

The main objective of the study was to examine the risk factors associated with frequency of pain episodes in sickle cell patients in Uganda. As a result, we tested three main hypotheses regarding sickle cell patients: age and sex are less likely to be associated with the frequency of pain episodes; clinical factors including hydroxyurea and folic acid are likely to influence the frequency of pain episodes; fever status, malaria status and Infection status are more likely to influence the frequency of pain episodes. Results showed a significant association between age and frequency of pain episodes however there was no evidence that with sex of the patients. A significant association with age is consistent with the findings of the study entitled "Sickle cell disease: a natural model of acute and chronic pain" conducted in the United States which found out pain crises to increase with duration and intensity as patients age [29]. Similarly, these results are in line with those of Panepinto and colleagues in their study on, "Variation in hospitalizations and hospital length of stay in children with Vaso-occlusive crises in sickle cell disease". These researchers found a positive association between age of the patient and pain rates until early adulthood, with more frequent, painful episodes and a higher mortality rate in young adults (16–24) [30]. Two perspectives may be used to explain the observed association. The first is the accelerated aging syndrome. Since the majority of sickle cell patients are young, we argue that those who age with it suffer from what is termed as an accelerated aging syndrome. We all know that aging is a natural process which is often associated with changes in the level and lifespan of cells, tissue, and organ; and these have also been documented among sickle cell patients [31]. The second, is the loss of physical activity as people age. This increases diseases, resulting in a higher levels of morbidity, and subsequently mortality. Difference in frequency of pain episodes between males and females was not found to be significant which is contrary to studies done earlier in which Astles and his colleagues found sex to be associated with acute pain trajectories in adolescents [32]. This could be attributed to physicians' commitment to standardized protocols for the treatment of sickle cell patients in Mulago hospital.

Some characteristics of SCD patients might decrease the risk of experiencing the frequency of pain episodes. Results from the study show a 34% decrease in the frequency of pain episodes among SCD patients with each unit increase in hydroxyurea intake which is consistent with earlier studies where hydroxyurea was found to reduce Vaso-occlusive crisis (VOC) and mortality in sickle cell patients [33]. Relatedly, Maakaron and Taher, found similar results in their study entitled "What are the effects of hydroxyurea in sickle cell disease (SCD) patients" [34]. These results might be explained by two arguments. The first is that hydroxyurea intake helps SCD patients by keeping blood cells not in a sickle shape which makes it more flexible. This allows easy flow of blood as well as delivering of oxygen to the body without difficulty implying less pain episodes. Second, hydroxyurea lowers circulating leukocyte levels and as a result, pain episodes are reduced as well as the acute chest syndrome. A reduction in acute chest syndrome increases the flow of oxygen which reduces the frequency of pain episodes.

It is not surprising to find a positive association between malaria and the number of pain episodes in people with SCD. Results show that having malaria increases the likelihood of increase in the number of pain episodes for people with SCD by nearly 38%. These results are consistent with

previous studies entitled, "sickle cell disease and malaria: decreased exposure and asplenia can modulate the risk from Plasmodium falciparum". In this study, it was found out that patients with SCD have a higher risk of malaria, at least in part because of impaired splenic function and Plasmodium falciparum infection. These conditions are thought to cause pain episodes, aggravate anemia, and possibly contribute to malaria's fatal effects including death [35, 36]. The findings are also consistent with the findings of the "Sickle Cell Anemia and Malaria" study. It is argued that if AS heterozygotes are protected from malaria through failure infection, then SS homozygotes should be as well. However, the mechanism may not always apply to homozygotes (SCA) patients. These people have prototype congenital hemolytic anemia and are at risk of malaria, which is a prototype acquired hemolytic anemia. Malaria will exacerbate SCA anemia to the point where it is potentially fatal. Malaria, like any other infection, has the potential to cause pain attacks [37].

A positive association between fever and frequency of pain episodes in sickle cell patients is not surprising and might be explained by two perspectives. The first is the positive association between fever and a number of sickle cell complications including hand-foot syndrome, acute chest syndrome, and other infections [38]. Secondly, fever is frequently the first sign of a potentially fatal bacterial infection among SCDs. It is common and associated with acute chest syndrome and vaso-occlusion, and the two are responsible for recurrent pains among SCD [39]. Our study also confirms a positive relationship between the frequency of pain episodes and infections which is consistent with previous studies [40]. Having an infection, increases the risk of experiencing pain episodes by 27%. One of the argument which may be used in explaining this finding is that people with sickle cell usually have reduced immunity which makes them more vulnerable to infections. In this case, infections cause pain episodes by inducing pathological changes such as pneumonitis, pyrexia, acute-phase reaction, hypercoagulability, neutrophilia and others, all of which can act singly or in combination, to cause red cell sick resulting in pain episodes.

Our study highlights the exceptionally high hydroxyurea usage rate (90%) among individuals with SCD receiving care at Mulago Hospital. Previous clinical trials have demonstrated a protective effect of hydroxyurea against malaria using rigorously defined endpoints, though the magnitude of the effect observed in our study appears larger [41–43]. However, due to the observational nature of our analysis, we cannot definitively conclude causality. Potential confounders such as healthcare access, socioeconomic status, and concurrent interventions may have influenced the observed reduction in malaria incidence. Notably, the NOHARM trial also investigated hydroxyurea use in a malaria-endemic region, providing further insights into its potential benefits [44]. Further prospective studies with robust study designs are warranted to validate these findings and explore the broader implications of hydroxyurea use in malaria-endemic regions.

In summary, this study utilized secondary data from Mulago national referral hospital to investigate the risk factors associated with the frequency of pain episodes among Sickle cell patients. As a result, three hypotheses were tested, 'socio-demographic factors (age and sex) are unlikely to be associated with frequency of pain episodes, 'malaria, fevers and other infections as clinical conditions, are likely to be associated with frequency of pain episodes, and hydroxyurea as an intervention received by sickle cell disease patients is likely to have a negative effect on the number of pain episodes. Notably, the study identified several influential factors on the frequency of pain episodes among sickle cell patients. Malaria emerged as the most significant factor, causing the highest increase in pain episodes. In addition, the presence of fever and other infections also contributed to a higher frequency of pain episodes. In contrast, the use of hydroxyurea as an intervention demonstrated a significant reduction in the frequency of pain episodes, highlighting its effectiveness in managing pain.

There are some limitations that should be considered for future studies. First, the accuracy of the data relies on others for precise record-keeping, retrospective study designs typically suffer from recall bias and misclassification. Consequently, significant bias may impact the study's findings. Secondly, secondary data may be prone to information bias and may lack certain details necessary to address specific questions. Because in statistics, missing data influence regression coefficients, standard errors and statistical power, in this study, it was assumed that missing data were missing completely at random (MCAR) and as a result did not bias our estimates [45, 46]. Additionally, while our findings indicate a high rate of hydroxyurea usage, the study design does not allow us to establish a causal relationship between hydroxyurea and malaria protection in SCD. The observational nature of the study and potential confounders not accounted for in the analysis limit our ability to draw definitive conclusions about hydroxyurea's protective effect.

In conclusion, this study underscores the high adoption of hydroxyurea in SCD management at Mulago Hospital and contributes to the growing body of evidence regarding its potential benefits. While our findings suggest a possible protective effect of hydroxyurea against malaria, previous clinical trials have reported reductions in malaria incidence with hydroxyurea, though the impact was smaller than observed in our study [42, 43]. Caution is warranted in interpreting these results due to study design limitations. Future research should focus on controlled prospective studies to better elucidate hydroxyurea's role in malaria prevention among individuals with SCD.

Abbreviations

ASH	The American society of hematology
CDC	Centers for disease control and prevention
CHPL	Certified health information technology product list
G/dl	Grams per deciliter
GPM	Generalized poisson model
Hb	Hemoglobin
Hbf	Fetal hemoglobin
Hbss	Hanks balanced salt solution
IHTC	Indiana hemophilia & thrombosis center
Incidence Rate Ratio	Incidence rate ratio
K-S	Kolmogorov-Smirnov test
MOH	Ministry of health
NCBI	National center for biotechnology information
NIH	National Institutes of health
NSAIDs	Non-steroidal anti-inflammatory drugs
PNAS	Proceedings of the National Academy of Sciences of the United States of America
RBC	Red blood cells
SCA	Sickle cell anemia
SCD	Sickle cell disease
SCT	Sickle cell trait
UDHS	Uganda demographic and health survey
VOC	Vaso-Occlusive crisis
WBC	White blood cells
WHO	World health organization

Acknowledgements
The authors extend their sincere gratitude to Mulago referral hospital for allowing them to use the Pain Episodes Sickle Cells Patients data.

Authors' contributions
Our team's collaborative effort resulted in a multifaceted approach to this study. N.S. played a pivotal role in conceptualizing the study, curating and analyzing the data, formulating the methodology, and drafting the original manuscript. A.J.B. contributed significantly to data curation, methodology development, software implementation, validation, and provided critical input during the review and editing process. N.D.'s contributions included conceptualization, conducting investigations, managing resources, providing supervision throughout the study, and contributing to the review and editing of the manuscript. C.L spearheaded the conceptualization of the project, managed project administration, provided supervision, ensured validation of findings, and actively participated in the review and editing process to refine the manuscript. Each author's unique expertise and dedication were instrumental in the successful completion of this research endeavor. N.S (Nassiwa Shamira) A.J.B (Asiimwe John Bosco) N.D (Nsimbe Dick) C.L (Charles Lwanga).

Funding
This study received no specific grant from any funding agency, commercial entity or not-for-profit organization. However, the corresponding author is grateful to the college of Business and Management Science (CoBAMS), Makerere University, for the institutional grant, as research facilitation support, for staff.

Data availability
The datasets used and/or analyzed during the current study is available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Utilizing secondary data with person from Mulago referral hospital, the study was approved by the Mulago hospital research and ethics committee during the original survey. Moreover, informed consent was obtained from all participants or their legal guardian(s) as part of the data collection process. The study adheres to the ethical and consent procedures. All procedures contributing to this research adhered to the ethical standards set by relevant national and institutional committees for human experimentation, as well as the Helsinki Declaration of 1975, amended in 2008.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Received: 10 May 2024 / Accepted: 15 April 2025
Published online: 21 April 2025

References

1. Herrick J.B. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. Arch Intern Med. 1910;VI5:517–21. https://doi.org/10.1001/archinte.1910.00050330050003.
2. CDC. What Is Sickle Cell Disease? National Center on Births Defects and Developmental Disabilities, Center for Disease Control and Prevention. 2020;4.
3. Inusa BPD, et al. Sickle cell disease—genetics, pathophysiology, clinical presentation and treatment. Int J Neonatal Screen (Vol. 2019;5(2). https://doi.org/10.3390/ijns5020020.
4. Ndila C et al. Human candidate gene polymorphisms and risk of severe malaria in children in Kilifi, Kenya: a case-control association study. Lancet Haematol. 2018;5(8):e333- e345. https://doi.org/10.1016/S2352-3026(18)30107-8. Epub 2018 Jul 20. PMID: 30033078; PMCID: PMC6069675. 2018.
5. Editorial. Sickle cell trait. Bri Med J. 1976;1(6022):1359–1360. https://doi.org/10.1136/bmj.1.6022.1359.
6. Ojodu J, et al. Incidence of sickle cell trait–United States, 2010. MMWR Morb Mortal Wkly Rep. 2014;63(49):1155–8.
7. Onimoe G. S. Rotz 2020 Sickle cell disease: A primary care update. Cleve Clin J Med 87 1 19–27 https://doi.org/10.3949/CCJM.87A.18051.
8. Excelence N.I.C. Sickle cell acute painful episode. Sickle cell acute painful episode: Manage Acute Painful Sickle Cell Episode Hosp. 2012;143(June):1–179. https://www.ncbi.nlm.nih.gov/books/NBK126761/.
9. Treede RD, et al. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the international classification of diseases (ICD-11). Pain. 2019;160(1):19–27.
10. WHO. Sickle cell disease prevention and control - WHO| Regional Office for Africa. 2015. https://www.afro.who.int/health-topics/sickle-cell-disease.
11. WHO. F. and n.w.H. A, Sickle-Cell Anaemia Report by the Secretariat.\n. In Fifty-ninth World Health Assembly. 2006. http://apps.who.int/gb/ebwha/pdf_files/WHA59/A59_9-en.pdf.
12. Piel F.B., et al. Global burden of sickle cell anaemia in children under five, 2010–2050: modelling based on demographics, excess mortality, and interventions. PLoS Med. 2013;10(7). https://doi.org/10.1371/JOURNAL.PMED.1001484.
13. Ndeezi G, et al. Burden of sickle cell trait and disease in the Uganda sickle surveillance study (US3): a cross-sectional study. Lancet Global Health. 2016;4(3):e195–7. https://doi.org/10.1016/S2214-109X(15)00288-0.
14. Lancet Haematol. 2022;9(3):e208–16.
15. World Health Organization. WHO Sickle Cell Disease Package of Interventions. Geneva: World Health Organization. 2024. Available from: https://www.afro.who.int/health-topics/sickle-cell-disease.
16. UBOS, Uganda demographic and health survey 2016. Udhs, 625. Www. DHSprogram.comUBOS. Uganda Demographic Health Surv 2016 Udhs, 625. www.DHSprogram.com. 2016. 2016.
17. MOH. Press statement ahead of World Sickle Cell Day. 2017. https://www.health.go.ug/document/press-statement-ahead-of-world-sickle-cell-day/.
18. MOH, Uganda: Sickle Cells Disease On the Rise in Uganda| Knowledge Management Portal. In Knowledge Management Portal. 2013, p. 1. http://library.health.go.ug/news/uganda-sickle-cells-disease-rise-uganda.
19. Inusa BPD et al. Sickle cell disease—genetics, pathophysiology, clinical presentation and treatment. Int J Neonatal Screen. 2019;5(2):1–2. International Journal of Neonatal Screening. https://doi.org/10.3390/ijns5020020.
20. Kanter J, Kruse-Jarres R. Management of sickle cell disease from childhood through adulthood. Blood Rev. 2013;27(6):279–87. https://doi.org/10.1016/j.blre.2013.09.001.
21. Gillis VL. Management of an acute painful sickle cell episode in hospital: Summary of NICE guidance. BMJ (Online). 2012;345(7866):1. https://doi.org/10.1136/bmj.e4063 Gould, W., & Pitblado, W. (2010). stata.com.
22. Staff MC. Sickle cell anemia - Symptoms and causes - Mayo Clinic. In Mayo Clinic. 2020. https://www.mayoclinic.org/diseases-conditions/sickle-cell-anemia/symptoms-causes/syc-20355876.

23. SCA news. Pain management guidelines for sickle cell disease. Pain Management Guidelines for Sicke Cell Disease. 2022. https://sicklecellanemianews.com/pain-management-guidelines-for-sickle-cell-anemia/.
24. Tusuubira SK et al. Knowledge, perception and practices towards sickle cell disease: A community survey among adults in Lubaga division, Kampala Uganda. BMC Public Health. 2018;18(1):561. https://doi.org/10.1186/s12889-018-5496-4.
25. Modenesi B. Poisson distribution. In Wikipedia. 2021. https://en.wikipedia.org/wiki/Poisson_distribution.
26. Ulrich Kohler FK. Journal of statistical software. In Data Analysis Using Stata, 3rd Edition: revised. Taylor & Francis; 2012. Vols. 3. 2012. https://doi.org/10.1002/wics.10.
27. Gould W, Pitblado J, Poi B. Maximum Likelihood Estimation with Stata. 4th ed. College Station: Stata Press; 2010.
28. Mckerrell TDH, Cohen HW, Billett HH. The older sickle cell patient. J Hematol. 2004;76:101–6. https://doi.org/10.1002/ajh.20075.
29. Brandow MA, Zappia JK, Stucky LC. Sickle cell disease: a natural model of acute and chronic pain. PMC, 2017: pp. 79–84.
30. Panepinto AJ, et al. Variation in hospitalizations and hospital length of stay in children with vaso-occlusive crises in sickle cell disease. Wiley Online Library; 2004. pp. 182–6.
31. Idris, I.M., E.A. Botchwey, and H.I. Hyacinth, Sickle cell disease as an accelerated aging syndrome. Exp Biol Med (Maywood, N.J.). 2022;247(4):368–74. https://doi.org/10.1177/15353702211068522.
32. Astles RL, Gillespie Z, Lai SE, Maillis KW, Morris A, Bakshi CR. Sex and frequency of pain episodes are associated with acute pain trajectories in adolescents with sickle cell disease. Pain Rep. 2023;8(5):e1084.
33. Smith RW et al. The association between hydroxyurea treatment and pain intensity, analgesic use, and utilisation in ambulatory sickle cell anaemia patients. NLH. 2011: pp. 3–4.
34. Maakaron EJ, Taher TA. What are the effects of hydroxyurea in patients with sickle cell disease (SCD), in Medscape. 2020.
35. Mwaiswelo RO, Mawala W, Iversen PO, et al. Sickle cell disease and malaria: decreased exposure and asplenia can modulate the risk from Plasmodium falciparum. Malar J. 2020;19:165. https://doi.org/10.1186/s12936-020-03212-w.
36. Osman Mirghani H, et al. Association between sickle cell Anemia and malaria: A systematic review of previous literature: sickle cell Anemia and malaria: A systematic review. Saudi Med Horizons J. 2023;3(3):118–30. https://doi.org/10.54293/smhj.v3i3.82.
37. Luzzatto L. Sickle cell anaemia and malaria. Mediterr J Hematol Infect Dis. 2012;4(1):e2012065. https://doi.org/10.4084/MJHID.2012.065.
38. Complications and treatments of sickle cell disease. Centers Disease Control Prev. 2020:1–6.
39. Rogers ZR. UpToDate, in Management of fever in sickle cell disease. 2020.
40. St. Jude Children's Research Hospital. Infection and sickle cell disease. 2021. https://together.stjude.org/en-us/treatment-tests-procedures/symptoms-side-effects/infection-and-sickle-cell-disease.html.
41. Dei-Adomakoh YA et al. Hydroxyurea for Children and Adults with Hemoglobin SC Disease. NEJM Evid. 2025;4(2):EVIDoa2400402. https://doi.org/10.1056/EVIDoa2400402. Epub 2024 Dec 8. PMID: 39647172.
42. Tshilolo L, Tomlinson G, Williams TN, et al. Hydroxyurea for children with sickle cell anemia in sub-Saharan Africa. N Engl J Med. 2019;380:121–31. https://doi.org/10.1056/NEJMoa1813598.
43. Aygun B, Lane A, Smart LR, et al. Hydroxyurea dose optimisation for children with sickle cell anemia in sub-Saharan Africa (REACH): extended follow-up of a multicentre, open-label, phase 1/2 trial. Lancet Haematol. 2024;11:e425–35. https://doi.org/10.1016/S2352-3026(24)00078-4.
44. Opoka RO, Ndugwa CM, Latham TS, et al. Novel use of hydroxyurea in an African region with malaria (NOHARM): a trial for children with sickle cell anemia. Blood. 2017;130:2585–93. https://doi.org/10.1182/blood-2017-06-788935.
45. Houchens R. Missing Data Methods for the NIS and the SID. Agency for Healthcare Research and Quality No. 2015–01. HCUP Methods Series Report. 2015. https://www.hcupus.ahrq.gov/reports/methods/2015_01.pdf.
46. Abonazel MR, Ibrahim MG. On Estimation methods for binary logistic regression model with missing values. Int J Math Comput Sci. 2018;4(3):79–85.

Publisher's Note