ABSTRACT

Objectives: To analyze the temporal trend of mortality from sickle cell anemia in Brazil, by region, in the period 1997-2017. Methods: epidemiological study, with an ecological design, with a temporal trend, carried out with data from the Mortality Information System. For descriptive analysis, absolute and relative frequencies were used. In the correlation analysis, the ANOVA test was used, followed by Tukey's post-test. The temporal trend was obtained using the cubic polynomial regression test. Results: 6,813 deaths from sickle cell anemia were registered. Brown individuals (50.87%) were more frequent, with a predominance of males (50.4%), aged between 25 and 34 years and a higher incidence of deaths in the Midwest (0.25/100 thousand inhabitants). The time curve showed an increasing trend of deaths in the country between 1997 and 2015 (R² = 0.98). Conclusions: sickle cell anemia showed increasing mortality in the 21 years analyzed and alerts health professionals and managers.

Descriptors: Sickle Cell Anemias; Mortality; Spatio Temporal Analysis; Epidemiology; Brazil.

RESUMO

Objetivos: analisar a tendência temporal da mortalidade por anemia falciforme no Brasil, por regiões, no período compreendido entre 1997 e 2017. Métodos: estudo epidemiológico, de delineamento ecológico, de tendência temporal, realizado com dados do Sistema de Informações sobre Mortalidade. Para análise descritiva, utilizaram-se frequências absolutas e relativas. Na análise de correlação, utilizou-se o teste ANOVA seguido pelo pós-teste de Tukey. A tendência temporal foi obtida mediante o teste de regressão polinomial cúbico. Resultados: foram registrados 6.813 óbitos por anemia falciforme. Indivíduos pardos (50,87%) foram mais frequentes, com predominio do sexo masculino (50,4%), com faixa etária de 25 a 34 anos e maior incidência de óbitos no Centro-Oeste (0,25/100 mil habitantes). A curva temporal apresentou tendência crescente de óbitos no país entre 1997 a 2015 (R² = 0,98). Conclusões: a anemia falciforme apresentou mortalidade crescente nos 21 anos analisados e desperta a alerta aos profissionais de saúde e gestores.

Descritores: Anemia Falciforme; Mortalidade; Distribuição Temporal; Epidemiologia; Brasil.

How to cite this article:
Mota FM, Ferreira Júnior MA, Cardoso AIQ, Pompeo CM, Frota OP, Tsuha DH, et al. Analysis of the temporal trend of mortality from sickle cell anemia in Brazil. Rev Bras Enferm. 2022;75(4):e20210640. https://doi.org/10.1590/0034-7167-2021-0640

Corresponding author: Felipe Machado Mota
E-mail: felipemachadomota@gmail.com
INTRODUCTION

The term “sickle cell disease” (SCD) refers to a group of hereditary hemoglobinopathies resulting from a morphophysiological disorder of hemoglobin (Hb)(1). Among the types of SCD, the genetic composition with the greatest clinical impact is sickle cell anemia (SCA), a condition in which the HbS gene is inherited from both parents and culminates in the homozygous form of HbSS(2).

The pathophysiology of SCA occurs at the molecular level, due to a change in the nitrogenous base, replacing adenine (A) by thymine (T) (GAG → GTG) in the sixth codon of beta-globin. This remodeling leads to a replacement of glutamic acid with the valine residue; and, as a result, the Hb molecules start to polymerize under deoxygenation conditions, which alters the shape of the red blood cell and directly influences its functions - this structural variation of the erythrocyte is known as “sickling”. Currently, four pathological pathways are known: the polymerization of Hb; the vaso-occlusion; endothelial dysfunction mediated by hemolysis; and the sterile inflammation(14).

The main complications of SCA result from morphophysiological changes in erythrocytes after sickling. Among the main ones are pain crises, pneumonia, splenomegaly, leg ulcers, priapism, stroke, acute chest syndrome, bone changes and cholelithiasis(16).

The worldwide incidence of people carrying genes responsible for hemoglobinopathies in their structure is 5%. It is estimated that 5,476,407 children are born with sickle cell trait (SA) per year and 312,302 with HbSS. In underdeveloped countries such as those in Sub-Saharan Africa, the estimated number of live births with the HbSS gene is 235,681 births per year, but this number of people is much higher compared to developed countries such as the United Kingdom, which has a rate of 300 births; and the United States of America (USA), with approximately 3 thousand births(6-7).

In Brazil, it is estimated that around 3,000 children are born with SCD per year. The incidence is 1 per thousand newborns with SCD; on the other hand, the proportion of sickle cell trait is much lower, 1 per 35. In a study carried out in the Brazilian Federal District from January 2004 to December 2006, from a total of 116,271 blood samples collected in the neonatal screening program, 3,760 identified sickle cell trait carriers and 109 samples identified the HbSS gene corresponding to SCA(8-9).

Over the years, new research was carried out and interventions were proposed so that life expectancy would increase for people with SCA, however what is observed in recent research is the increase in mortality in this population. In Rio de Janeiro, in 15 years of follow-up at a hematology center, a total of 281 deaths among adults and children were identified; and, of these, 10.48% represented the mortality of patients under 18 years of age. In Brazil, researches show that, even with the implementation of the neonatal screening program for early diagnosis, the mortality rate of children with SCA in the country has not decreased and is higher than that of developed countries(10-11).

In the United States, between 1979 and 2005, while the SCA mortality rate in children decreased, the number of deaths in adults increased gradually, the mortality rates in the population over 19 years old increased 1% per year, and the age mean of deaths was 33.4 years for men and 36.9 years for women(12).

Among the main causes of death for people with SCA, the following were identified: acute respiratory failure mainly due to pneumonia; multiple organ failure resulting from infections and sepsis; septic shock; cardiogenic shock; and stroke(13).

Currently, there are no Brazilian studies that have globally assessed the trend in mortality in patients with SCA. Therefore, evaluating the impact of mortality from this disease in the country over the years, and describing the profile of patients who died, is of paramount importance so that lines of care can be traced to improve the survival of this population.

OBJECTIVES

To analyze the temporal trend of mortality from SCA in Brazil, by region, in the period between 1997 and 2017.

METHODS

Ethical aspects

All databases are in the public domain and require prior approval by an ethics committee for research with human beings for the use of their data.

Design, study location and period

This is an epidemiological study, with an ecological design and a temporal trend. It was carried out based on data from secondary sources, obtained from the Mortality Information System (MIS) of the Informatics Department of the Unified Health System (DATASUS)(14).

In November 2019, the collection of data for the last 21 years (from 1997 to 2017) took place. The Statement of Strengthening the Report on Observational Studies in Epidemiology was used as a guide for the research method (STROBE)(15).

Population; inclusion and exclusion criteria

Data from patients with SCA with crises (DS7.0) and without crises (DS7.1) were included, according to the International Classification of Diseases – ICD 10(14). Data were collected by Federal Unit (FU) of occurrence and residence, that is, according to the UF in which the case occurred and the one in which the affected person lived. The variables collected were: year of death, sex, age and color/race. Cases prior to 1997 and after 2017 were not included, due to the lack of registration in the SIM/DATASUS database in the collection period.

Study protocol

Initially, the Brazilian territorial grid was downloaded in shapefiles (SHP) through the website of the Brazilian Institute of Geography and Statistics (IBGE). In the geosciences area of the portal, the tabs “Territory organization”, “Territorial meshes”, “Municipal mesh” and “Downloads” were accessed in sequence to extract the SHP file for the year 2017 of the UF’s in Brazil. After this process, the territorial mesh was exported to the QGIS 3.16.0 software so that the territorial layers of the country could be dissolved by the five Brazilian regions separately.
To extract data on deaths and tabulation, the electronic address TabNet Win32 3.0 was accessed. In its services tab, the pages “Transfer/download of files” and “YES/DATASUS” were accessed in order to download auxiliary files for tabulation. Then, in the same place, data from the country’s death certificates for the years 1997 to 2017 were collected from all FUs. Since this information is generated as a data compilation in DBC format, it was necessary to export it to the DATASUS Tabwin 4.1.3 software, to read and stratify this content with the help of previously obtained tab files.

The final tabulation of the data generated after filtering by Tabwin 4.1.3 was performed using Microsoft Excel® software. After this process, a table was structured according to the Brazilian region of occurrence of deaths according to the variables “gender,” “age group” and “color/race”.

Finally, population data for Brazil were collected based on IBGE information. On the IBGE’s electronic portal, in its statistics area, the “Social”, “Population”, “Population Estimates” tabs were accessed and, finally, the download area, from which the estimates published by the Federal Official Gazette were extracted (DOU) and the information provided to the Federal Court of Accounts (TCU) to contemplate the 21 years of study approach. After this process, the Excel® program was used to calculate the incidence of deaths per 100,000 inhabitants.

**Analysis of results and statistics**

To analyze the spatial distribution, the incidence of deaths previously obtained and stratified by a grouping of four periods was used: 1) between 1997 and 2002; 2) from 2003 to 2007; 3) from 2008 to 2012; and 4) from 2013 to 2017. Incidence data were exported to QGIS 3.16.0 software to unify the territorial grid with numerical data. After unification, the color gradient symbology was applied so that it was possible to observe the follow-up of the distribution of deaths in the previously established periods. The map was divided into five classes and classified by equal distribution intervals. At this stage, four maps were plotted according to the years previously mentioned.

The comparison of the frequency and incidence of cases between regions of Brazil in relation to deaths by occurrence and by residence was performed using the one-way ANOVA test, followed by Tukey’s post-test.

The temporal trend analysis was performed by obtaining the simple moving average (SMA) used as a linear filter to smooth the data, format a sequential trend indicator for the study, in addition to removing a possible seasonality bias. The SMA was calculated by cycles of five years, whose application was given by the formula

\[ \text{SMA} = \frac{(P1+P2+P3+Pn)}{n}. \]

Then, a temporal graph was constructed with the incidence of deaths for Brazil, for the individualized regions of the country and for the incidence SMA, to verify the possible shape of the trend curve to be studied.

Next, the polynomial regression models were applied, so that the model that best fit the curve was the third-degree one, as it is a sigmoid curve, represented by the formula

\[ Y = \beta_0 + \beta_1X + \beta_2X^2 + \beta_3X^3. \]

The models were chosen according to their statistical significance and coefficient of determination (R²).

The other results were presented in the form of descriptive statistics and by tables and graphs. Statistical analysis was performed using the SigmaPlot statistical program, version 12.5; and, for all tests, a significance level of 5% was considered.

**RESULTS**

Regarding the epidemiological characterization of deaths in the country, during the analyzed period, 6,813 deaths from PA with and without crisis were registered in the MIS/DATASUS, by place of occurrence. Among these records, the Southeast Region (48.39%) had the highest percentage by absolute number, followed by the North-East Regions (31.92%), North-East (10.3%), North (4.96%) and South (4.39%), respectively.

As for gender, the male population (50.4%) had a higher number of deaths compared to the female population (49.6%). This difference is observed in four of the five Brazilian regions: North (55.9%), North-East (51.4%), South (51.5%) and Mid-West (51%) (Table 1).

In relation to age, the age groups with the highest number of death records were those between 25 and 34 years old and between 15 and 24 years old, respectively. The South Region had the highest mortality rate in the country (29.8%) for the age group 25 to 34 years, but this behavior was only statistically different in relation to the North-East of the country (p = 0.001). Regarding race, there was a higher prevalence of deaths in brown individuals (50.87%), with higher mortality in this population in the North Region (72.6%) (p = 0.001), as shown in Table 1.

The global characteristics of deaths related to the place of occurrence were repeated when comparing the mortality of patients by place of residence, when male patients, aged 25 to 34 years and with mixed skin color remained as the most affected. Table 1 describes the sociodemographic characteristics of deaths from PA in the Brazilian regions.

As shown in Table 2, the records of mortality from SCA with and without crisis, in 21 years, showed the highest incidence of cases by place of occurrence in the Brazilian Midwest (0.25 per 100 thousand inhabitants; p < 0.001). In addition, a greater number of death records from PA without crisis was observed, either by place of occurrence or by residence (p < 0.001).

The spatial distribution of deaths over the 21 years of analysis showed an increasing incidence per 100,000 inhabitants. When divided by five-year periods, the period from 1997 to 2002 presented a record of 0.19, while, between the years 2013 to 2017, this number reached 0.26 cases per 100,000 inhabitants. In addition, the highest density of deaths in the country is distributed in three Brazilian regions: Mid-West, South-East and North-East (Figure 1).

In the two decades studied, Brazil experienced an increase in the records of deaths from SCA, however the year 2010 showed the highest incidence of mortality within the period observed. Among the Brazilian regions, most showed similar behavior with stability or slight ascendancy in the period (p < 0.001). The Midwest, however, was the place that had the greatest modulations and had its peak period in 2012 (Figure 2).
The trend line observed in Figure 3 demonstrates an increasing trend ($R^2 = 0.98$) in the number of registered deaths and reached its plateau in 2012. In 2015, there was a slight decline, indicative of a possible decrease in mortality in the country from this year onwards ($p < 0.001$).

The results showed a progressive increase in deaths until the year 2015, with slight fluctuations in the fall in the years 2007, 2010 and 2012, but without a major impact on the trend curve. In 2015, there was a drop of 0.9 deaths per 100,000 inhabitants which, associated with the decrease in registrations in 2012, directly impacted the line and ended the period with a slight decline.

**DISCUSSION**

This study analyzed the mortality trend of SCA in Brazil according to their regions. It was possible to observe that, although the male population was more affected in four of the five Brazilian regions, there was no significant difference regarding the female population ($p = 0.086$), a fact evidenced in other epidemiological studies that verify the absence of a relationship between SCA and the sex.$^{10,17}$

When analyzing the age group with the highest number of deaths, the population aged 15 to 34 predominated. This fact differs from what is found in foreign literature, which demonstrates that survival for people with the homozygous form of SCD, considered the most serious and with the highest mortality, in the United States is between the third and fourth decade of life.$^{18}$

However, this finding reflects the lower survival rate for patients with SCA in Brazil, a fact evidenced by other Brazilian studies: patients with this pathology die early in the country, generally between the second and third decade of life.$^{13,19}$

---

**Table 1** - Demographic characteristics of cases of death from sickle cell anemia in Brazilian regions, by place of occurrence, between 1997 and 2017, Brazil, 2021 ($N = 6,813$)

| Variable | North n (%) | North-East n (%) | Region South-East n (%) | South n (%) | Mid-West n (%) | $p^1$ Total |
|----------|-------------|-----------------|------------------------|-------------|----------------|-------------|
| Sex      |             |                 |                        |             |                |             |
| Male     | 189 (55.9)  | 1.177 (51.4)    | 1.612 (48.9)           | 154 (51.5)  | 358 (51.0)     | 0.086 6.811 |
| Female   | 149 (44.1)  | 1.058 (48.6)    | 1.685 (51.1)           | 145 (48.5)  | 344 (49.0)     |             |
| Unmentioned | 00          | 00              | 00                     | 00          | 02             |             |
| Age range (years) | | | | | | |
| < 5      | 67 (19.8)a  | 344 (15.4)a     | 322 (10.1)b            | 25 (8.4)b   | 77 (11.0)b     |             |
| 5-14     | 61 (18.0)a  | 329 (15.2)a     | 334 (10.1)c            | 28 (9.4)bc  | 78 (11.1)bc    |             |
| 15-24    | 65 (19.2)a  | 428 (19.7)a     | 667 (20.2)a            | 49 (16.4)a  | 138 (19.6)a    | 0.001 6.807 |
| 25-34    | 66 (19.5)ac | 428 (19.7)c     | 785 (23.8)ab           | 89 (29.8)a  | 178 (25.3)ab   |             |
| 35-44    | 29 (8.6)b   | 280 (12.9)ab    | 512 (15.5)a            | 47 (15.7)ab | 107 (15.2)a    |             |
| > 44     | 50 (14.8)ab | 372 (17.1)ab    | 666 (20.2)a            | 61 (20.4)ab | 125 (17.8)ab   |             |
| Ignored  | 00          | 04              | 01                     | 00          | 01             |             |
| Race/Color |           |                 |                        |             |                |             |
| White    | 44 (13.9)dc | 233 (12.8)c     | 722 (24.5)b            | 107 (38.1)  | 127 (20.2)bd   |             |
| Black    | 42 (13.2)c  | 400 (21.9)b     | 1.009 (34.2)           | 117 (41.6)  | 117 (18.6)bc   |             |
| Yellow   | 0 (0.0)a    | 6 (0.3)a        | 12 (0.4)a              | 0 (0.0)     | 2 (0.3)        |             |
| Brown    | 230 (72.6)ab| 1.179 (64.6)ab  | 1.207 (40.9)c          | 56 (19.9)d  | 383 (54.8)b    | 0.001 6.006 |
| Indigenous | 24          | 353             | 341                    | 18          | 71             |             |
| Unmentioned | 00          | 00              | 00                     | 00          | 00             |             |

$^1$One-way ANOVA test; different letters (a, b, c, d) on the same line indicate a significant difference between the regions of Brazil (Tukey’s post-test, $p < 0.05$).

**Table 2** - Deaths from sickle cell anemia in Brazilian regions by place of occurrence and residence between 1997 and 2017, Brazil, 2021 ($N = 6,813$)

| Variable | North | North-East | Region (Mean ± Standard Error) | South | Mid-West | $p^1$ |
|----------|-------|------------|--------------------------------|-------|----------|-------|
| Deaths   |       |            |                                |       |          |       |
| Incidence| 0.10±0.01c | 0.20±0.17b | 0.20±0.01b                    | 0.05±0.00d | 0.25±0.17a |       |
| Deaths   |       |            |                                |       |          |       |
| Incidence| 0.11±0.01b | 0.20±0.16a | 0.20±0.01a                    | 0.05±0.00c | 0.24±0.15a |       |
| Deaths   |       |            |                                |       |          |       |
| Incidence| 0.02±0.00ab | 0.03±0.00ab | 0.03±0.00ab                   | 0.01±0.00b | 0.04±0.01a | 0.004 |
| Deaths   |       |            |                                |       |          |       |
| Incidence| 0.02±0.00ab | 0.03±0.00ab | 0.03±0.00ab                   | 0.01±0.00b | 0.04±0.01a | 0.004 |
| Deaths   |       |            |                                |       |          |       |
| Incidence| 0.08±0.01c | 0.17±0.12b | 0.17±0.01b                    | 0.04±0.00d | 0.21±0.14a |       |
| Deaths   |       |            |                                |       |          |       |
| Incidence| 0.08±0.01b | 0.17±0.01a | 0.17±0.01a                    | 0.05±0.01b | 0.20±0.01a |       |

$^1$One-way ANOVA test; different letters (a, b, c, d) on the same line indicate a significant difference between the regions of Brazil (Tukey’s post-test, $p < 0.05$).
The Brazilian South has the highest number of death records for the age group from 24 to 35 years old, but no data were found in the scientific literature that would allow for a discussion about this variable. Although the region does not present statistical difference compared to most Brazilian regions, it differs from the North-East ($p < 0.001$). This fact demonstrates the importance of developing new research in the South of the country so that there can be a deeper and improved comparative analysis of this variable\(^\text{(21)}\).

Regarding the variable “race/color”, there was a higher mortality rate for brown people with SCA in most Brazilian regions, confirming Brazilian studies\(^\text{(21-22)}\). It is known that SCA mainly affects the Afro-descendant population; in Brazil, this population characteristic is due to the historical process of arrival of the disease at a time of racial miscegenation, a fact pointed out as preponderant in the epidemiology of the disease in the country\(^\text{(23)}\).

Another important aspect is that the brown and black population in Brazil experiences a disparity in access to health services in the country, in relation to people of other races, and encounters structural, social and ethnic/cultural barriers when looking for services, which negatively influences the access and adherence of this population to health facilities and results in greater morbidity and mortality\(^\text{(24)}\).

It is noticeable that the profile of deaths from SCA in Brazil, especially when related to race/color, follows a pattern of the racial characteristic of the country’s population. Between 2012 and 2016, the Continuous National Household Sample Survey (Continuous PNAD) showed that 72.3%, 64.7% and 37.6% of the inhabitants of the North, North-East and South-East regions, respectively, declared themselves to be brown, a number very close to the death records found in the present study\(^\text{(25)}\).

According to the 2010 IBGE census, the South and Southeast regions had a higher rate of white people; and, with the historical transition of frequent miscegenation, the Brazilian population became more homogeneous in most regions\(^\text{(25-26)}\).

The decrease in survival suggests that the transition of prevention and global health promotion actions between adolescence and adulthood is not effective for people with hemoglobinopathies. The causes can be multifactorial and be related both to the lack of access and knowledge to perform specialized care and the absence of public policies aimed at monitoring this population in the long term\(^\text{(26)}\).
process of homogenization of the Brazilian population. It is noteworthy that migration in human evolution is one of the main factors for genetic distribution to occur among populations. 

When verifying the incidence of deaths, although the Brazilian Mid-West presents the highest number by place of occurrence and residence, and this result was statistically significant, no studies were found that allowed for an in-depth discussion of this variable, either specifically for an analysis of the region itself and globally for the differences found in relation to other Brazilian regions.

The higher incidence of deaths without crises compared to those with crises may indicate flaws in hospital records, underreporting and even lack of knowledge of professionals regarding the correct use of ICD-10. This situation is corroborated by other Brazilian studies of hospitalization and mortality from SCA.

Regarding the graphic analysis of mortality, regarding its incidence and trend, there was a growing trend in the number of death records in the country until the year 2015. However, it is not possible to say that this ascendency indicates that people with SCA are dying more, but there is a possibility that under-reporting occurred in previous years due to difficult diagnosis, incorrect use of ICD-10 and lack of hospital records.

With the implementation of the National Neonatal Screening Program (PNTN) in 2001, illnesses related to sickle cell disorders gained greater evidence, in addition to a better understanding of professionals about these diseases. The increase in the number of deaths from SCA in Brazil followed the evolution of the program's coverage rate in the country, which was 81.61% in 2009 and reached 96.5% in 2020.

The fact that the PNTN coverage rate has historically suffered a gradual increase indicates that approaches created and implemented in services have universalized access to diagnosis, which directly affects the identification of new cases and, in turn, the accounting of more records.

**Study limitations**

Despite being a large study on the trend of mortality from SCA in Brazil, this research has as a limitation the use of data from secondary sources, with low quality records. As a result, this may compromise the database in part, but the large population studied makes it possible to overcome these limitations inherent to the ecological design.

In addition, another limitation was the non-use of mortality data for all sickle cell hemoglobinopathies due to the impossibility of stratifying these data by the MIS/DATASUS database.

**Contributions to the field of Nursing, Health or Public Policy**

Identifying the profile of the people who die most from SCA in Brazil, the temporal evolution, and the spatial distribution of these deaths by regions allows managers to offer scientific knowledge so that they can recognize the most vulnerable groups and key years with the highest mortality rates. This makes it possible to search for alternatives that enable greater quality and survival for this population.

**CONCLUSIONS**

It is possible to conclude that, although mortality from SCA was predominant in men, statistically the disease did not show a higher incidence among women. Another important fact was the lower survival rate in the country, as mortality was higher between the second and third decades of life. In addition, mortality from the disease follows a process of population miscegenation and was present in a greater number of brown individuals.

It was possible to notice the occurrence of a transition in the number of cases between regions; and, in the period between 1997 and 2017, the Midwest had the highest incidence of deaths. In addition, the temporal trend of mortality in the country showed that, historically, Brazil has experienced an increase in the number of death records, which may be related to an improvement in the notifications of these cases.

The growing trend of deaths also raises an alert to health professionals and managers. Continuous monitoring of cases is necessary, as well as rapid intervention and treatment for those who show signs of worsening of the disease, to prevent early deaths and improve the survival of this population.

It is important to emphasize that, although SCA has more than 110 years of scientific report, this pathology still involves many stigmas and lack of knowledge on the part of health professionals. Carrying out actions to give more visibility to the disease is an extremely necessary conduct; with this, it is expected the emergence of new proposals for training health teams that imply improvement in interventions for this public.

**SUPPLEMENTARY MATERIAL**

Machado Mota, Felipe; Ferreira Júnior, Marcos Antônio; Insabralde de Queiroz Cardoso, Andréia; Mariana Pompeo, Carolina; Pereira Frota, Oleci; Tsuha, Daniel Henrique; Schiaveto de Souza, Albert, 2021, “Analysis of the temporal trend of mortality from sickle cell anemia in Brazil - database” , https://doi.org/10.48331/scielodata.YQJ2RK, SciELO Data, VERSÃO RASCUNHO, UNF:6:47cZ66kWLX8Sohcdgm3UWA==

**FUNDING**

This research was financed through the granting of a scientific initiation scholarship to the first author by CNPq – Conselho Nacional de Desenvolvimento Científico e Tecnológico; financed by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) – Finance Code 001; and financial support from the Universidade Federal de Mato Grosso do Sul – UFMS/MEC - Brazil.

**REFERENCES**

1. Ballas SK. Sickle cell disease: Classification of clinical complications and approaches to preventive and therapeutic management. Clin Hemanorehol Microcirc. 2018;68(2–3):105–28. https://doi.org/10.3233/CH-189002
2. Piel FB, Steinberg MH, Rees DC. Sickle Cell Disease. N Engl J Med. 2017;376(16):1561–73. https://doi.org/10.1056/nejmra1510865
3. Kato GJ, Piel FB, Reid CD, Gaston MH, Ohene-Frempong K, Krishnamurti L, et al. Sickle cell disease. Nat Rev Dis Primer. 2018;4(1):1-22. https://doi.org/10.1038/nrdp.2018.10
4. Sundd P, Gladwin MT, Novelli EM. Pathophysiology of Sickle Cell Disease. Annu Rev Pathol Mech Dis. 2019;14(1):263–92. https://doi.org/10.1146/annurev-pathmechdis-012418-012838
5. Guarda CC, Yahouédéhou SCMA, Santiago RP, Neres JSS, Fernandes CFL, Aleluia MM, et al. Sickle cell disease: a distinction of two most common genotypes (HbSS and HbSC). PLOS ONE. 2020;15(1):1-15. https://doi.org/10.1371/journal.pone.0228399
6. Chakravorty S, Williams TN. Sickle cell disease: a neglected chronic disease of increasing global health importance. Arch Dis Child. 2015;100(1):48–53. https://doi.org/10.1136/archdischild-2013-303773
7. Piel FB, Patil AP, Howes RE, Nyangiri OA, Gething PW, Dewi M, et al. Global epidemiology of sickle haemoglobin in neonates: a contemporary geostatistical model-based map and population estimates. Lancet. 2013;381(9861):142–51. https://doi.org/10.1016/S0140-6736(12)61229-X
8. Ministério da Saúde (BR). Secretaria de Atenção à Saúde. Doença Falciforme: a experiência brasileira na África histórica de um esforço de cooperação 2006-2010 [Internet]. Brasília (DF): Ministério da Saúde; 2012[cited 2020 Nov 22]. Available from: http://bvsms.saude.gov.br/bvs/publicacoes/doenca_falciforme_experiencia_brasileira_2010.pdf
9. Diniz D, Guedes C, Barbosa L, Tauli PL, Magalhães I. Prevalência do traço e da anemia falciforme em recém-nascidos do Distrito Federal, Brasil, 2004 a 2006. Cad Saúde Pública. 2009;25(1):188–94. https://doi.org/10.1590/S0102-311X2009000100020
10. Lobo CLC, Nascimento EM, Jesus LJC, Freitas TG, Lugon JR, Ballas SK. Mortality in children, adolescents and adults with sickle cell anemia in Rio de Janeiro, Brazil. Hematol Transfus Cell Ther. 2018;40(1):37–42. https://doi.org/10.1016/j.htct.2017.09.004
11. Sabarense AP, Lima GO, Silva LML, Viana MB. Characterization of mortality in children with sickle cell disease diagnosed through the Newborn Screening Program. J Pediatr (Rio J). 2015;91(3):242–7. https://doi.org/10.1590/jped.2014.08.006
12. Lanzkron S, Carroll CP, Haywood C. Mortality Rates and Age at Death from Sickle Cell Disease: U.S., 1979–2005. Public Health Rep. 2013;128(2):110–6. https://doi.org/10.1177/0033354912467255
13. Araujo OM, Ivo ML, Ferreira Júnior MA, Pontes ERJC, Bispo IMGP, Oliveira ECL. Survival and mortality among users and non-users of hydroxyurea with sickle cell disease. Rev Latino-Am Enfermagem. 2015;23(1):67–73. https://doi.org/10.1590/0104-1169.2014.01.02.1069
14. Ministério da Saúde (BR). Secretaria de Vigilância em Saúde. Departamento de Informática do SUS. Sistema de informações sobre mortalidade [Internet]. Brasília: Ministério da Saúde; 2019 [cited 2020 Nov 22]. Available from: http://bvsms.saude.gov.br/bvs/sistemas-e-aplicativos/eventos-v/sim-sistema-de-informacoes-de-mortalidade
15. Malta M, Cardoso LO, Bastos FI, Magnanini MMF, Silva CMFP. Iniciativa STROBE: subsídios para a comunicação de estudos observacionais. Rev Saúde Pública. 2010;44(3):559–65. https://doi.org/10.1590/S0104-11692010000300021
16. Organização Mundial da Saúde. Classificação Estatística Internacional de Doenças e Problemas Relacionados à Saúde. 10 ed. 1200 p
17. Wierenga KJ, Hambleton IR, Lewis NA, Unit SC. Survival estimates for patients with homozygous sickle-cell disease in Jamaica: a clinic-based surveillance system, 2004 through 2008. Public Health Rep. 2016;131(2):367–75. https://doi.org/10.1177/003335491613100221
18. Paulukonis ST, Eckman JR, Snyder AB, Hagar W, Feuchtbaum LB, Zhou M, et al. Defining sickle cell disease mortality using a population-based surveillance system, 2004 through 2008. Public Health Rep. 2016;131(2):367–75. https://doi.org/10.1177/003335491613100221
19. Martins PRJ, Moraes-Souza H, Silveira TB. Morbimortalidade em doença falciforme. Rev Bras Hematol Hemoter. 2010;32(5):378–83. https://doi.org/10.1590/s1516-84842008000500010
20. Hullihan M, Hassell KL, Raphael JF, Smith-Whitley K, Thorpe P. CDC Grand Rounds: improving the lives of persons with sickle cell disease. MMWR Morb Mortal Wkly Rep. 2017;66(46):1269–71. https://doi.org/10.15585/mmwr.mm6646a2
21. Ramos JT, Paes GR, Jesus FA, Oliveira DS, Carvalho BT, et al. Mortalidade infantil por doença falciforme na Bahia: um estudo epidemiológico. Rev Saúde Coletiva. 2017;21(3):15–22. https://doi.org/10.1590/s1518-87872017000300007
22. da Silva Júnior MT, Soares FL, Souza LV, Santos FL, Acosta AX, et al. Types of Marriages, population structure and genetic disease. J Biosoc Sci. 2013;45(4):461–70. https://doi.org/10.1017/S0021932012000673
28. Loureiro MM, Rozenfeld S. Epidemiologia de internações por doença falciforme no Brasil. Rev Saúde Pública. 2005;39(6):943–9. https://doi.org/10.1590/s0034-89102005000600012

29. Martins MMF, Teixeira MCP. Análise dos gastos das internações hospitalares por anemia falciforme no estado da Bahia. Cad Saúde Coletiva. 2017;25(1):24–30. https://doi.org/10.1590/1414-462x201700010209

30. Lima ARG, Ribeiro VS, Nicolau DI. Trends in mortality and hospital admissions of sickle cell disease patients before and after the newborn screening program in Maranhão, Brazil. Rev Bras Hematol Hemoter. 2015;37(1):12–6. https://doi.org/10.1016/j.bjhh.2014.11.009

31. Mallmann MB, Tomasi YT, Boing AF. Neonatal screening tests in Brazil: prevalence rates and regional and socioeconomic inequalities. J Pediatr (Rio J). 2020;96(4):487–94. https://doi.org/10.1016/j.jped.2019.02.008

32. Nascimento ML. Situação atual da triagem neonatal para hipotireoidismo congênito: críticas e perspectivas. Arq Bras Endocrinol Metabol. 2011;55(8):528–33. https://doi.org/10.1590/s0004-27302011000800005