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*ORIGINAL ARTICLE*

# Factors Associated with Sickle Cell Disease Mortality among Hospitalized Angolan Children and Adolescents

## *Facteurs liés à la drépanocytose mortalité chez les Hospitalisé angolais enfants et des adolescents*

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**ABSTRACT**

BACKGROUND: **Sickle cell disease complications are an important mortality cause in children mainly in Africa and India. Notwithstanding the magnitude of the problem on the African continent, studies identifying factors related to the adverse outcomes of sickle cell disease in the pediatric population are still scarce.**

OBJECTIVE: **To identify prognostic factors associated with mortality in children and adolescent aged under fifteen years with diagnosis of sickle cell disease.**

METHODS: **Patients meeting inclusion criteria were listed and randomly selected. Clinical and laboratory data collected at time of admission were collected from medical records through the use of standard forms. The association between mortality and explanatory variables was tested using univariable and multivariable analysis.**

RESULTS: **The overall mortality rate was 64(12.9%), and bacterial infections 26(40.1%) were the most common cause of death. Place of residence out of Luanda, lack of outpatient follow-up, symptoms onset more than three days, disease manifestation before age of eighth months and hemoglobin level of < 7 g/dl were independent risk factors related to death. In the study population, sickle cell related deaths were related to quality of health care and access to care.**

CONCLUSION: **The creation of regional sickle cell disease centers to support those afflicted by the disorder and their families would contribute to reduce the burden associared with the disease. WAJM 2007; 26(4): 269–273.**

Keywords: ***Sickle cell anemia, hospital mortality, children, adolescents, hospital records, Angola.***

***RESUME***

***CONTEXTE:*** *Drépanocytose complications sont une importante cause de mortalité chez les enfants, principalement en Afrique et en Inde. Nonobstant l'ampleur du problème sur le continent africain, des études liées à l'identification des facteurs d'issues défavorables de la drépanocytose dans la population pédiatrique sont encore rares.*

***OBJECTIF:*** *Identifier des facteurs liés à la mortalité des enfants et des adolescents âgés de moins de quinze ans, avec le diagnostic de la drépanocytose.*

***MÉTHODES:*** *Les patients répondant aux critères d'inclusion ont été répertoriés et choïsis au hasard. Cliniques et de laboratoire données recueillies au moment de l'admission ont été recueillies à partir de dossiers médicaux grâce à l'utilisation de formulaires standard. L'association entre la mortalité et les variables explicatives a été testé au moyen univariable et analyse multivariables.*

***RÉSULTATS:*** *Le taux de mortalité global a été 64 (12,9%), les infections bactériennes et 26 (40,1%) ont été la cause la plus fréquente de décès. Lieu de résidence hors de Luanda, le manque de suivi ambulatoire, de l'apparition de symptômes plus de trois jours, la maladie avant l'âge de la manifestation huitième mois et des taux d'hémoglobine <7 g / dl étaient indépendantes des facteurs de risque liés à la mort. Dans la population étudiée, les décès liés à la drépanocytose sont liés à la qualité des soins de santé et l'accès aux soins*

***CONCLUSION:*** *La création de partenariats régionaux drépanocytose centres de soutenir les personnes touchées par la maladie et leur famille contribuerait à réduire le fardeau associared avec la maladie.* ***WAJM 2007; 26(4): 269–273.***

***Mots-clés:*** *Sickle l'anémie falciforme, de l'hôpital de mortalité, des enfants, des adolescents, des dossiers de l'hôpital, de l'Angola.*

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## INTRODUCTION

Sickle cell anemia is an inherited hematological disorder characterized by the production of abnormal hemoglobin, and a leading cause of death in childhood.[1, 2] The disease is widely distributed throughout the World, affecting populations in the Mediterranean, Mid-West, North America, Latin America and principally India and Africa.[3,4] In Africa where sickle cell anemia prevalence reaches levels up to 40%, disease complications, usually resulting from unfavorable environmental conditions and deficient health care, are an important public health problem.[5] The estimate is that in African countries with high prevalence of the disease, over 50% of the children affected die in the first years of life specially from bacterial infections.[6-8]

Some clinical and hematological factors have been associated with unfavorable outcome of sickle cell disease. These include early onset of the disease[9], hemoglobin concentration below 7 g/dl[9], extended hospitalization[10] and leukocytes count over 15.000 cells per cubic millimeter.[11] Notwithstanding the magnitude of the problem in African countries, reports on identifying factors associated with adverse outcomes in children affected by the condition are still scarce in the continent. This paper had the aim to investigate the prognostic factors associated with sickle cell disease-related deaths among hospitalized Angolan.

## PATIENTS AND METHODS

This was a retrospective hospital-based study performed in the Pediatric Hospital of Luanda, a national child care service located in the capital city of Angola. The subjects were children and adolescents under 15 years of age admitted to hospital between January 1997 and December 2002, with a diagnosis of sickle cell disease confirmed by hemoglobin electrophoreses with alkaline pH. Patients with congenital disorders that could have a negative influence on outcome such as congenital heart disease, nephropathy, diabetes, as well as the ones who had been vaccinated against type B *Streptococcus pneumoniae* or *Haemophillus influenzae* were excluded from the study. Patients meeting inclusion criteria were listed and randomly selected.

Sample size calculation was carried out based on parameters established through a pilot study involving 150 randomly selected patients with the sickle cell disease admitted to the hospital. Sample size was calculated considering the following parameters: alpha error of 5%, power of 80%, risk ratio of 1.5, exposed: non-exposed ratio at 3:1 and attack rate among non-exposed of 23.9%, resulting in n= 493 (370 exposed and 123 non-exposed).

Clinical and laboratory data obtained at time of admission were collected from medical records through the use of standard forms. Exposure variables studied were age, sex, place of residence, age at symptoms onset, follow-up in outpatient care, history of blood transfusion, previous hospitalization, duration of signs and symptoms at the time of admission, predominant clinical features, hemoglobin levels and leukocyte count at admission. Death during hospitalization was considered the outcome.

The crude relative risk for the association of sickle cell disease death and each of the independent variables was calculated and the statistical significance of the associations tested by the chi-square test and p value. To control for influence of confounding variables, the adjusted measure of effect was estimated by multiple logistic regression analysis, which included all factors associated to the variable response with p value less than 0,20. Sample calculation, data entry and analysis were performed using the statistical programs EPI-INFO 6.04 (CDC, Atlanta) and SPSS for Windows (version 11.0).

The study had the approval of the Ethical Commission of the Instituto Materno Infantil de Pernambuco (IMIP) and of the Pediatric Hospital of Luanda.

## RESULTS

From a total of 580 clinical reports randomly selected, 87 were excluded. Of the 493 children and adolescents studied, 64 (12.9%) died during hospitalization and bacterial infection was the most common cause of death followed by anemia (Table 1).

**Table1: Frequency distribution of main causes of death among children and adolescents with sickle cell disease. Pediatric Hospital of Luanda, 1997-2002.**

| Cause of Death | N | % |
|---|---|---|
| **Bacterial Infection** | **26** | **40.6** |
| Meningitis | 12 | 18.8 |
| Septicaemia | 8 | 12.5 |
| Pneumonia | 4 | 6.3 |
| Pyelonephritis | 2 | 3.1 |
| **Anaemia** | **19** | **29.7** |
| Splenic sequestration | 11 | 17.2 |
| Aplastic crisis | 7 | 10.9 |
| Hemolytic crisis | 1 | 1.6 |
| Vaso-occlusive crisis | 5 | 7.8 |
| Acute chest syndrome | 4 | 6.3 |
| Bone Crisis | 1 | 1.6 |
| **Other Infections** | **9** | **14.1** |
| Malaria | 4 | 6.3 |
| Hepatitis B | 4 | 6.3 |
| AIDS | 1 | 1.6 |
| **Other diagnosis*** | **3** | **4.7** |
| **No diagnosis** | **2** | **3.1** |
| **Total** | **64** | **100.0** |

*Heart failure, transfusion reaction, and renal failure

Table 2 shows the distribution of deaths by biological factors, clinical histories and place of residence, the estimated crude RR, 95% Confidence Interval and p-values. There was no statistically significant association between age and unfavorable outcome. Boys had a significantly higher death risk in relation to girls. The age of symptoms onset, history of blood transfusion, previous hospitalization, follow-up in outpatient care, duration of signs and symptoms at the time of admission and area of residence in the capital were strongly related to mortality.

Table 3 depicts the frequency distribution and univariate analysis results for the association between death and predominant clinical features and haematological features at admission. Palor, neurological alterations and circulatory instability were statistically associated with mortality. No association

**Table 2: Biological, Clinical and Healthcare Access Factors and Mortality in Hospitalized Children and Adolescent with Sickle Cell Anemia. Pediatric Hospital of Luanda, 1997-2002**

| Variable | Outcome N (%) | | | | |
|---|---|---|---|---|---|
| | Deaths | Survivors | Crude RR | CI 95% | p value |
| **Age (years)** | | | | | |
| < 3 | 27 (16.9) | 133 (83.1) | 1.52 | 0.96-2.40 | 0.0749 |
| ≥ 3 | 37 (11.1) | 296 (88.9) | 1.00 | | |
| **Sex** | | | | | |
| Male | 43 (16.0) | 225 (84.0) | 1.72 | 1.05-2.81 | 0.0273 |
| Female | 21 (9.3) | 204 (90.7) | 1.00 | | |
| **Age at symptoms onset (months)** | | | | | |
| <8 | 39 (17.2) | 188 (82.8) | 1.83 | 1.14-2.92 | 0.0104 |
| ≥ 8 | 25 (9.4) | 241 (90.6) | 1.00 | | |
| **Duration of signs symptoms at admission** | | | | | |
| > 3 (days) | 47 (24.9) | 142 (75.1) | 4.45 | 2.63-7.51 | 0.0000 |
| ≥ 3 (day) | 17 (5.6) | 287 (94.4) | 1.00 | | |
| **History of transfusion** | | | | | |
| Yes | 54 (17.7) | 251 (82.3) | 3.33 | 1.74-6.37 | 0.0000 |
| No | 10 (5.3) | 178 (94.7) | 1.00 | | |
| **Previous Hospitalization** | | | | | |
| Yes | 41 (17.3) | 196 (82.7) | 1.93 | 1.19-3.11 | 0.0061 |
| No | 23 (9.0) | 233 (91.0) | 1.00 | | |
| **Follow-up in outpatient Care** | | | | | |
| Yes | 45 (23.4) | 147 (76.6) | 3.71 | 2.24-6.15 | 0.0000 |
| No | 19 (6.3) | 282 (93.7) | 1.00 | | |
| **Area of residence** | | | | | |
| Out of the capital | 38 (20.5) | 147 (79,5) | 2.43 | 1,53-3.87 | 0.0001 |
| Capital | 26 (8.4) | 282 (91.6) | 1.00 | | |

**Table 3: Predominant Clinical Features and Laboratorial Results at Admission and Mortality among Hospitalized Children and Adolescents With Sickle Cell Anemia. Pediatric Hospital of Angola, 1997-2002.**

| Variable | Outcome N (%) | | | | |
|---|---|---|---|---|---|
| | Deaths | Survivors | Crude RR | CI 95% | p value |
| **Fever** | | | | | |
| Yes | 41 (14.7) | 237 (85.3) | 1.38 | 0.85-2.22 | 0.1849 |
| No | 23 (10.7) | 192 (89.3) | 1.00 | | |
| **Palor** | | | | | |
| Yes | 24 (23.8) | 77 (76.2) | 2.33 | 1.48-3.68 | 0.0003 |
| No | 40 (10.2) | 352 (89.8) | 1.00 | | |
| **Dyspnea** | | | | | |
| Yes | 11 (12.9) | 74 (87.1) | 1.00 | 0.54-1.83 | 0.9902 |
| No | 53 (13.0) | 355 (87.0) | 1.00 | | |
| **Pain Crisis** | | | | | |
| Yes | 6 (8.8) | 62 (91.2) | 0.65 | 0.29-1.44 | 0.2723 |
| No | 58 (13.6) | 367 (86.4) | 1.00 | | |
| **Jaundice** | | | | | |
| Yes | 5 (8.2) | 56 (91.8) | 0.60 | 0.25-1.44 | 0.2353 |
| No | 59 (13.7) | 373 (86.3) | 1.00 | | |
| **Splenomegaly** | | | | | |
| Yes | 10 (19.2) | 42 (80.8) | 1.57 | 0.85-2.89 | 0.1567 |
| No | 54 (12.2) | 387 (87.8) | 1.00 | | |
| **Neurological Alterations** | | | | | |
| Yes | 6 (37.5) | 10 (62.5) | 3.08 | 1.57-6.07 | 0.0003 |
| No | 58 (12.2) | 419 (87.8) | 1.00 | | |
| **Circulatory Instability** | | | | | |
| Yes | 3 (75.0) | 1 (25.0) | 6.01 | 3.26-11.1 | 0.0002 |
| No | 61 (12.5) | 428 (87.5) | 1.00 | | |
| **Haemoglobin level (g/dl)** | | | | | |
| < 7 | 56 (15.1) | 314 (84.9) | 2.33 | 1.14-4.74 | 0.0137 |
| ≥ 7 | 8 (6.5) | 115 (93.5) | 1.00 | | |
| **Leukocytes Count (/mm³)** | | | | | |
| ≤ 15,000 | 21 (18.1) | 95 (81.9) | 1.59 | 0.98-2.56 | 0.0608 |
| ≥ 15,000 | 43 (11.4) | 334 (88.6) | 1.00 | | |

of death related with fever, dyspnea, pain crisis, jaundice and splenomegaly was found. As for laboratory data, hemoglobin level below 7 g/dl was statistically associated with mortality, while no association with death was found for leukocytes count.

Table 4 relates to the adjusted *Odds Ratio*, Confidence Intervals of 95% and p values for the association between death and predictor variables included in the multiple regression model. Among the factors that were associated in the univariate analysis with death, age at symptoms onset, follow-up in outpatient care, duration of clinical features at the time of admission, place of residence and hemoglobin concentration under 7 g/dl maintained the statistical association after adjustment for other prognostic factors of mortality.

## DISCUSSION

The mortality among children and adolescents with sickle cell disease found in this study was considered high as compared with the results of other hospital-based studies in Africa whose case fatality rates ranged from 3.4% to 6.6%.[7, 12, 13] This high mortality could be partly explained by the complexity of care provided by the Pediatric Hospital of Luanda, a reference service for treating severe disease cases with more chances of death. In addition, lack of access to primary healthcare and poor quality of health services provided to those affected by the disease may have equally contributed to the increased death rate.

In agreement with the results of previous studies in Africa,[7, 12, 14] Europe and United States [15-17] infections were the leading cause of death, representing almost half of the total deaths. Genetic factors are considered important predictors of sickle cell disease severity, as well as its complications [1, 18]. Nevertheless, in developing countries, poor quality of healthcare and unfavorable environmental conditions, also play an important role.[5] In this study, the lack of preventive measures such as prophylaxis with penicillin and vaccination against *Pneumococcus* and *Haemophillus influenza* type B given to the pediatric population affected by sickle cell disease possibly favored the occurrence of

**Table 4: Final Logistic Model of Characteristics of Patients and Mortality Among Hospitalized Children and Adolescents with Sickle Cell Anemia. Pediatric Hospital of Luanda, 1997-2002**

| Variable N=493 | Adjusted OR | CI 95% | P value |
|---|---|---|---|
| **Area of residence** | | | |
| Out of the capital | 2.93 | 1.55-5.52 | 0.001 |
| Capital | 1.00 | | |
| **Outpatient follow-up** | | | |
| No | 3.71 | 1.05–7.05 | 0.000 |
| Yes | 1.00 | | |
| **Duration of signs and symptoms at admission (days)** | | | |
| > 3 | 5.25 | 2.73–10.10 | 0.000 |
| ≥ 3 | 1.00 | | |
| **Age of symptoms onset (months)** | | | |
| < 8 | 2.19 | 1.17–4.10 | 0.014 |
| ≥ 8 | 1.00 | | |
| **Hemoglobin (g/dl)** | | | |
| < 7 | 4.17 | 1.67–10.42 | 0.002 |
| ≥ 7 | | | |

**Age, sex, previous hospitalization, history of transfusions, fever, palor, splenomegaly, neurological alterations, circulatory instability and leukocyte count were excluded from the model due to the absence of a statistically significant association.**

deaths caused by infection.

In relation to sex, although univariate analysis showed a higher mortality risk among boys, statistical association did not remain after the adjustment for other explanatory variables. The differences among genders related to sickle cell disease mortality remain controversial. Some authors found higher mortality rates in the female gender,[13, 19] while in other studies mortality was higher among males.[15, 20] Our data suggest there are no differences among the genders related to mortality risk in hospitalized children and adolescents with sickle cell anemia.

Corroborating the findings of previous studies,[9, 12] early onset of signs and symptoms was a predictive factor for death during hospitalization. The onset of signs and symptoms in sickle cell disease is associated with a reduction of fetal hemoglobin concentration that acts by inhibiting hemoglobin S polymerization and consequently ameliorating the severity of clinical manifestations.[18, 21] For this reason, patients with low fetal hemoglobin production tend to exhibit more severe forms of the disease and increased risk for vaso-occlusive complications.[18] Therefore, the result of this study reinforces the importance of considering this clinical predictor during assessment and treatment of children and adolescents with sickle cell disease.

As for clinical signs on admission, although univariate analysis showed a significant association between death outcome and palor, neurological alterations and circulatory instability, no association was found when the effect of these variables was adjusted in the multiple regression model. Regardless of the limitations on the data quality obtained from medical reports, the results suggest that these clinical manifestations appear not to be predictive factors of death outcome in the study population. In agreement with other studies that have found an association between early death in sickle cell disease and low hemoglobin concentration,[9,16] hemoglobin concentration of less than 7 g/l was an independent prognostic factor for mortality among the patients studied. The relation between acute anemia and death due to sickle cell disease is still not very clear. However, the accentuated drops in the hemoglobin level were also observed in some complications of the disease such as splenic sequestration, a frequent event in children under two years of age which often leads to death due to hypovolemic shock.[22] Therefore, the observed association between anemia and death in sickle cell anemia may be reflecting the effect of other predictor factors such as splenic sequestration not considered in the analysis.

Although high white blood cell (WBC) count has been related to the adverse outcome in sickle cell anemia,[9, 10] no association was found between mortality and leukocyte count higher than 15.000/ $mm^3$ in this study. These differences among study results could be explained by variations in basal level of the white cells blood between different populations which are, in part, genetically determined.[23]

Multivariate analysis showed that patients living out of the capital were almost three times more likely to die during the hospitalization. Differences in mortality rates due to sickle cell disease among regions have been reported, and associated with social and economic factors as well as healthcare-related factors. [8] In this study, the increased death risk among the patients living out the capital was possibly influenced by the lower quality, and less access to medical care in addition to worse quality of life of patients living in rural communities.

The lack of outpatient follow-up was a prognostic factors strongly related to mortality in sickle cell disease. This result indicates that children and adolescents regularly evaluated by outpatient services were the ones who most benefited though better information about the disease and its complications as well as from easier access to prophylactic medications.

Long duration of signs and symptoms at admission was also an independent risk factor for death. Besides the lack of access to specialized care, delay in seeking care also results from lack of information concerning the disease. As a consequence, the seeking of medical care only takes place after many attempts at self-medication at home

In summary, the data suggest that mortality among hospitalized children and adolescents with sickle cell disease in Angola is mostly related to problems of poor access and low quality of health care. These results point to the urgent need for implementing regional public heath programmes, emphasizing early diagnosis and pre-clinical intervention, as well as

improving the quality of care in tertiary services. These public health measures will prevent complications and improve the survival of those affected by the disease in Angola.

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