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Study of Prognostic Factors of Death in Children with Sickle Cell Diseases Followed at the Albert Royer National Children's Hospital Center, Dakar, Senegal

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Abstract: Objectives. The objectives of our study are: i) estimate the survival time of cases of sickle cell diseases monitored at the Albert Royer National Children's Hospital Center, Dakar, Senegal from 1990 to 2010, ii) identify prognostic factors related to deaths. Methods. Comprehensive and retrospective survival analysis of the prognostic factors of death of the 1650 patients with sickle cell disease followed in the sickle cell management unit of Albert Royer National Children's Hospital Center from January 1st, 1991 to December 31, 2010 (20 years). 17 variables were studied: gender, ethnicity, geographical origin, age of the patient at onset of the disease, age of the patient at onset of follow-up, number of vaso-occlusive crisis in the last year of follow-up duration of which is ≥72h, type of hemoglobinopathy, baseline hemoglobin level, fetal hemoglobin level at time of diagnosis, vaccination with at least one antigen, regular folic acid intake, regular penicillin intake, hydroxyurea therapy, acute complications (severe infections, severe anemia and serious vaso-occlusive accidents) in the last year of follow-up and chronic complications. The Cox model was used. Results. We conducted 1650 observations with 44 deaths, and a lethality of 2.6%. The death incidence rate is 3.51 deaths per 100 person-years. The Cox model highlighted the prognostic factors which significantly explain the model ($p < 0.05$). Vaccination with at least one antigen and the existence of chronic complications improved patient survival. However, the number of vaso-occlusive crisis in the last year of follow-up (duration is ≥72h), the existence of serious vaso-occlusive accidents in the last year of follow-up, the very low baseline hemoglobin level (≤5mg/100 mn), the early age of late follow-up (≥15 months) reduced patients survival. Conclusions. The prognosis of patients with sickle cell disease followed at the Albert Royer National Children's Hospital Center (ARNCHC) is difficult to establish. In fact, in addition to genetic, clinical and evolutionary factors, there are poorly understood environmental and socio-economic factors that affect survival. A prospective study would shed more light on the prognostic factors of death in children with sickle cell disease.

Keywords: Sickle Cell Disease, Cox Model, Survival Study, Senegal

1. Introduction

Sickle cell disease is an inherited hemoglobin disease. This genetic disease, the most frequent in the world, found on all continents, is transmitted in an autosomal recessive mode [1-5]. The highest prevalence rates are observed in Sub Saharan Africa (10 to 40% of carriers of the gene depending on the country) and the Caribbean [1-4, 6, 7]. In Senegal, nearly 10% of the population of Senegal have the sickle cell trait [8].

The natural history of sickle cell disease is marked by the early onset of acute complications that are responsible for 50%

of all death children under the age of 5 years in sub-Saharan Africa and by the chronic complications affecting certain organs such as the eye, kidney, heart, hips, etc. [3, 9-15].

The implementation of simple and cost-effective interventions [neonatal screening and early and adequate case management] have reduced the mortality and significantly increased patient life expectancy in developed countries [1, 12, 16-20]. Thus, a survival rate of 94% at 18 years is observed in the United States of America [3, 21-23]. We were not able to find a survival study conducted in Sub Saharan Africa during the research.

On the other hand, mortality in Africa remains high; 1.9 person-years mortality in a cohort followed between 2004 and 2009 in Tanzania (7.3 person-years under 5 years) [14]. In a series observed between 1997 and 2002 in Burkina Faso, a lethality of 8.7% was observed mainly among children aged 0-5 years [24]. In Senegal, a lethality of 5.4% was observed in a series between 1990 and 2000 at the Albert Royer National Children's Hospital Center [25].

There are a number of factors [genetic, biological, therapeutic and progressive] that influence survival in developing countries [9, 13, 20, 26-32].

It is therefore important to study the survival and prognostic factors of death of children with sickle cell disease (SCD) monitored at the Albert Royer National Children's Hospital Center (ARNCHC) in Dakar. The latter houses the National Reference Centre for Sickle Cell Disease. Knowledge of these factors will improve patient care and contribute to increasing patient life expectancy.

2. Material and Methods

It is a comprehensive retrospective cohort study of patients with SCD followed in the ARNCHC sickle cell unit from January 1, 1991 to December 31, 2010.

The objectives of our study are:

i. Estimate the survival time of SCD cases followed at ARNCHC,
ii. Identify prognostic factors related to deaths,

The inclusion criteria are patients with SCD followed during the study period.

Data was collected via a questionnaire based on patient records. Some interviews were conducted by phone.

The records of the National Blood Transfusion Centre (NBTC) were very useful, as patients who have reached adulthood were followed up in this facility. In fact, from the end of adolescence onwards, most patients were transferred to the adult sickle cell management unit at the NBTC. Consulting their records allowed us to see if some patients lost to ARNCHC are alive or not.

Anamnestic, clinical, therapeutic and progressive paraclinical data were collected from patients.

The data analysis was done with the computer using software R version 2.15.2.

The univariate analysis was done with a descriptive study of the data (mean, frequency, overall survival estimate using the Kaplan Meier method).

The bivariate analysis was performed with the log-rank test comparing the stratified survival curves according to the values of the variable. This test also identified variables of interest.

The multivariate analysis was performed using the multivariate Cox regression model fitted to all variables with the following variables:

i. Dependent variable: occurrence of death and time of occurrence;
ii. Independent variables: gender, ethnicity, geographical origin, age of the patient at onset of the disease, age of the patient at onset of follow-up, number of vaso-occlusive crisis (VOC) in the last year of follow-up duration of which is ≥72h, type of hemoglobinopathy, baseline hemoglobin level, fetal hemoglobin level at diagnosis, vaccination with at least one antigen, regular folic acid intake, regular penicillin intake, hydroxyurea therapy, acute complications [severe infections, severe anemia and serious vaso-occlusive accidents] in the last year of follow-up and chronic complications.

The variables were selected for the full model with significant variables ($p \leq 0.2$ in the log-rank test) and presumed prognostic risk factors from the literature [33-35].

The verification of the model assumptions (log-linearity of variables and risk proportionality hypothesis) was performed and the significance of the final model determined.

It is patient file based investigation. Confidentiality was strictly respected with anonymous numbers assigned to the files.

The limitations of the study are related to the retroactivity of the survival study. A significant number of people were lost to follow-up (37.6% of cases). This explains the importance of censored data that could potentially affect the reliability of the data and therefore the results of our study.

3. Resultats

Patients come from Senegal and some countries in the sub-region. However, 62% of them reside in the Dakar region, 31% from other regions of Senegal and 7% from neighbouring countries.

3.1. Profile of the Study Population

3.1.1. General Characteristics of Patients

We noted 856 male patients (51.8%) and 794 female patients (48.2%). It was recorded in the series 44 deaths (2.6%), 622 lost to follow-up (37.6%) and 984 live patients at peak date (59.8%). We observed a participation time of 6432.4 person-years with an average follow-up of 3.9 years per patient.

3.1.2. Anamnestic Data

Patients come from Senegal and some countries in the sub-region. However, 62% of them reside in the Dakar region 31% from other regions of Senegal and 7% from neighbouring countries.

Table 1. *Distribution of patients according to age at diagnosis of the disease and age of onset of follow-up.*

Variables	Modalities	N	n	%
Patient's age at the beginning of follow-up (in months)	[0, 60]	1650	689	42%
	[60, 120]		538	33%
	[120, 180]		350	21%
	[180, 277]		73	4%
Age of the patient at diagnosis of the disease [in months]	[0, 6]	1627 (NA: 23)	45	2,7%
	[6, 24]		414	25,4%
	[24, 60]		454	28%
	[60, 120]		465	28.5%
	[120, 180]		218	13.4%
	[180, 277]		31	2%

The average age of the patient at the beginning of the follow-up is 81.2 months. The median is 73 months of age. Age values range from 2 to 77 months.

The average age of the patient at diagnosis of the disease is 60.6 months. The median is 48 months. Age values range from 1 to 240 months.

3.1.3. Clinical Data

Table 2. *Distribution of the 1637 patients according to the number of vaso-occlusive crisis [duration ≥72h] during the last year of follow-up (NA: 16).*

Variables	Modalities	n	%
Number of vaso-occlusive crisis [duration ≥72h] during the last year of follow-up	0	879	53.7%
	1	467	28.5%
	2	191	11.6%
	3	60	3.7%
	4	27	1.7%
	>4	13	0.8

The average number of crisis observed in the last year of follow-up in our series is 0.73 and the median is 0. The number of crisis recorded in our series in patients ranges from 0 to a maximum of 7 crisis.

3.1.4. Paraclinical Data

Table 3. *Distribution of patients by type of hemoglobinopathy, baseline hemoglobin level and fetal hemoglobin level.*

Variables	Modalities	N	n	%
Type of hémoglobin	s	1647 (NA: 3)	1531	93%
	c		94	5.7%
	β		22	1.3%
Basic hemoglobin level (gr/dl)	[4, 5]	1569 (NA: 81)	2	0.2%
	[5, 7]		547	34.8%
	[7, 9]		840	53.5%
	[9, 13]		180	11.5%
Fetal hemoglobin level (%)	[0, 6]	1627 (NA: 23)	45	2.7%
	[6, 24]		414	25.4%

The average baseline hemoglobin level in our series is 7.8 gr/dl, while the median is 7.6. The basic hemoglobin levels range from 4 to 13 gr/dl.

The average fetal hemoglobin value is 10.63% and the median is 8.7%. The values in our series range from 0 to 95.8%.

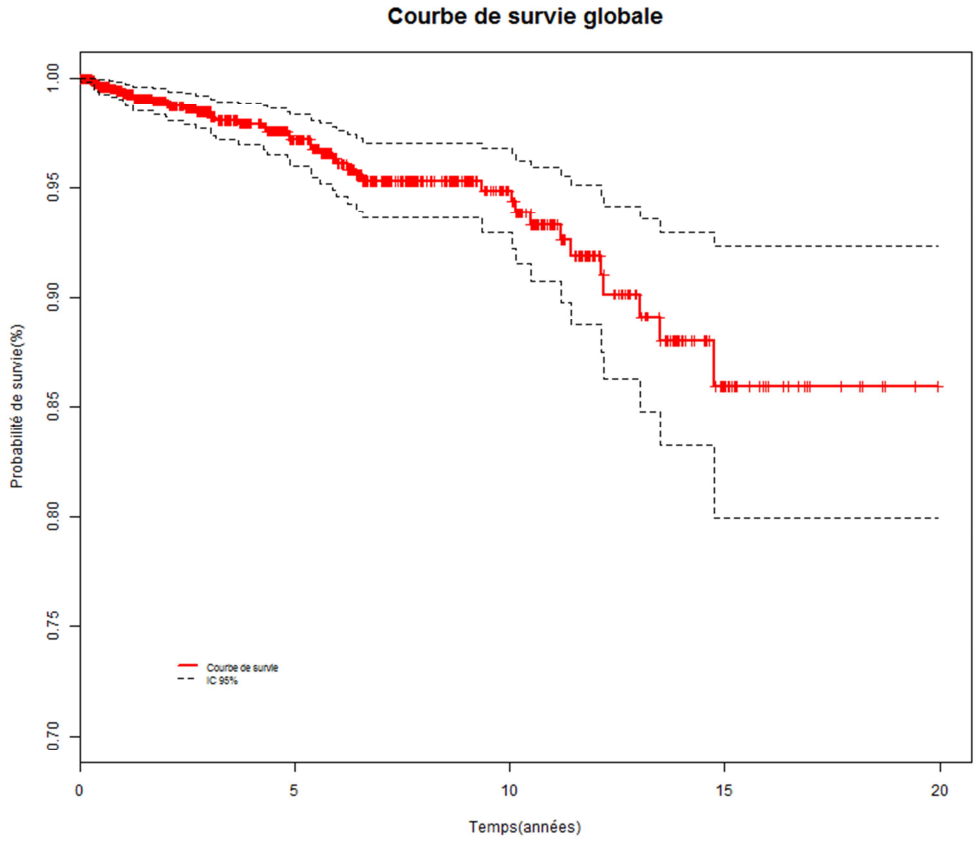

Figure 1. *Overall survival curve of patients.*

3.1.5. Therapeutic Data

Table 4. *Distribution of patients according to the different therapies received.*

Variables	Modalities	N	N	%
Vaccination [number of antigens received]	0	1650	459	27.8%
	≥1		1191	72.2%
Folic acid intake	no	1650	159	9.7%
	yes		1491	90.3%
Penicilline intake	no	1650	1391	84.3%
	yes		259	5.7%
Hydroxyurea therapy	no	1650	1627	98.6%
	yes		23	1.4%

Folic acid intake is the medication most respected by patients (90.3%) followed by antibiotic therapy (5.7%). Hydroxyurea remains the least prescribed medication (1.4%).

Vaccination with at least one antigen was followed by 72.2% of patients.

3.1.6. Evolving Data

In the last year of follow-up, serious infections (26% of patients) and anemia (22% of patients) were the most common complications in children with major sickle cell syndrome followed by serious stroke (8%) and chronic complications (7%).

3.1.7. Lethality Data

With 44 deaths, the lethality is 2.6%. The death incidence rate is 3.51 deaths per 100 person-years.

Among deceased patients, 54.5% were under 5 years of age; the age at death ranges from 18 months to 26 years with an average of 11 ± 6 years and a median of 9 years.

3.2. Survival Data

The average survival couldn't be calculated because the lethality is equal to 2.6%.

3.2.1. Estimation of Overall Survival by the Kaplan-meier Method

The log-rank test applied to all variables allowed us to identify significant variables (p less than 0.05).

Table 5. *Results of the log-rank test applied to all variables.*

VARIABLES	P VALUE
Vaccination or not with an antigen	p = 0.0157*
Number of vaso-occlusive crisis in the last year of follow-up with duration ≥72h	p = 0.0019**
Existence or not of vaso-occlusive accidents during the last year of follow-up	p = 0.0004***
Existence or not of severe anemia during the last year of follow-up [tx hb ≤5mg/dl]	p = 0.00002***
Basic hemoglobin level	p = 0.00037***
Age of patient at beginning of follow-up	p = 0.002**
Ethnicity	p = 0.505
Gender	p = 0.975
Geographic location	p = 0.308
Type of hemoglobinopathy	p = 0.654
Whether or not to take penicilline	p = 0.934
Whether or not to take folic acid	p = 0.775
Whether or not to take hydroxyurea	p = 0.239
Existence or not of generalized infection in the last year of follow-up	p = 0.464
Existence or not of chronic complications	p = 0.067
Fetal hemoglobin level at diagnosis of disease	p = 0.796
Age of the patient at diagnosis of the disease	p = 0.138

Meaning of codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 '.' 1.

The significant variables are:

i. Vaccination or not with at least one antigen.
ii. The number of vaso-occlusive crisis in the last year of follow-up (duration is ≥72h).
iii. The existence or not of serious vaso-occlusive accidents during the last year of follow-up.
iv. Whether or not there is severe anemia (hb ≤5mg/dl) in the last year of follow-up.
v. Baseline hemoglobin level (the most constant hemoglobin level on blood counts performed during a period of clinical stability (mg/dl).
vi. The age of the patient at the beginning of the follow-up.

The log-rank test also allows to compare the survival curves according to the different modalities of the significant variables.

3.2.2. Cox Model

All variables whose p-value is strictly less than 0.2 in the log-rank test were integrated into the complete model, in addition to variables from the literature data that influence the survival of sickle cell patients, to form the complete model.

Table 6. *Variables used for the full model.*

VARIABLES	P VALUE
Vaccination or not with an antigen	p = 0.0157*
Number of vaso-occlusive crisis in the last year of follow-up with duration ≥72h	p = 0.0019**

VARIABLES	P VALUE
Existence or not of vaso-occlusive accidents during the last year of follow-up	p = 0.0004***
Existence or not of severe anemia during the last year of follow-up [tx hb ≤ 5mg/dl]	p = 0.00002***
Basic hemoglobin level	p = 0.00037***
Age of patient at beginning of follow-up	p = 0.002**
Ethnicity	p = 0.654
Gender	p = 0.934
Geographic location	p = 0.775
Type of hemoglobinopathy	p = 0.239
Whether or not to take penicilline	p = 0.464
Whether or not to take folic acid	p = 0.067
Hydroxyurea therapy or not	p = 0.796
Existence or not of generalized infection in the last year of follow-up	p = 0.138

i. Results of the full adjusted Cox model.

Table 7. *Results of the adjusted Cox model.*

Variables	Coefficient	HR	IC [95%]	P value
Antigen vaccination	-1.03	0.35	0.14 - 0.86	0.021*
Number of vaso-occlusive crisis	- 0.4	1.5	1.12 - 2	0.005**
Hydroxyurea therapy	- 0.16	0.00	0	0.996
Existence of serious vaso-occlusive accidents accidents	1.032	2.8	1.21 - 6.5	0.015*
Existence of generalized infection	- 0.32	0.71	0.32 - 1.6	0.421
Existence of severe anemia	- 0.59	1.81	0.83 - 4	0.130
Existence of chronic complications	- 1.67	0.18	0.04 - 0.8	0.023*
Basic hemoglobin level [5, 7] gr/dl	- 1.67	12.78	1.56 -104	0.017*
Basic hemoglobin level [7, 9] gr/dl	1.37	3.94	0.48 - 32	0.199
Basic hemoglobin level [9, 13] gr/dl	NA	NA	NA	NA
Age at diagnosis of illness [6, 24] mois	- 0.6	0.54	0.1 - 2.6	0.447
Age at diagnosis of illness [24, 60] mois	- 0.5	0.60	0.12 - 3	0.543
Age at diagnosis of illness [60, 120] mois	- 0.8	0.44	0.07 - 2.76	0.387
Age at diagnosis of illness [120, 180] mois	- 1.89	0.14	0.01 - 2	0.153
Age at diagnosis of illness [180, 277] mois	- 1.33	0.26	0.02 - 2.72	0.262
Age at beginning of follow-up in months [60. 120] [60, 120]	- 0.11	0.89	0.3 - 2.6	0.840
Age at beginning of follow-up in months [120, 180]	- 0.11	0.89	0.2 - 3.84	0.88
Age at beginning of follow-up in months [180, 277]	1.73	5.66	1.5 - 21	0.01**

Concordance	0.823	(se = 0.06)
Rsquare	0.054	([max possible= 0.311)
Likelihood ratio test	54.81 on 17 df	p=7.363 e-06
Wald test	51.7 on 17 df	p=2.29 e-05
Score [logrank] test	60.84 on 17 df	p=7.623 e-07

Meaning of codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1.

The results of the graphical test of Schönefeld residues and the analytical test based on Schönefeld residues on the global model highlight the independence of the effect of covariates over time. The hypothesis of risk proportionality on the model is therefore verified.

ii. Résuls of the Final Model

The final model highlights the prognostic factors of death found in our series of patients with SCD followed at the ARNCHC in Dakar (the results of the significance of the variables in the final model are in the Table 8).

Table 8. *Results of the final model.*

Variables	Coefficient	HR	IC [95%]	P value
Antigen vaccination	-0.98	0.37	0.15 - 0.88	0.024*
Number of vaso-occlusive crisis	0.42	1.52	1.16 - 2	0.002**
Existence or not of vaso-occlusive accidents	1.15	3.17	1.47 - 6.83	0.003**
Existence of chronic complications	-1.67	0.18	0.04 - 0.73	0.01*
Basic hemoglobin level in gr/100ml [5, 7]	2.54	12.68	1.63 - 98	0.01*
Basic hemoglobin level in gr/100ml [7, 9]	1.27	3.58	0.45 - 28	0.22
Basic hemoglobin level in gr/100ml [9, 13]	NA	NA	NA	NA
Age at beginning of follow-up in months [60, 120]	-0.22	0.8	0.33 - 1.91	0.62
Age at beginning of follow-up in months [120, 180]	-0.64	0.52	0.14 - 1.88	0.32
Age at beginning of follow-up in months [180, 277]	1.41	4.12	1.31 -1 2	0.015*

Concordance	**0.82**	**(se = 0.06)**
Rsquare	0.047	(max possible= 0.311)
Likelihood ratio test	47.44 on 9 df	p=3.244e-07
Wald test	44.88 on 9 df	p=9.727e-07
Score (logrank) test	51.3 on 9 df	p=6.124e-08

Meaning of codes: 0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1.

The three tests [maximum likelihood test, Wald test and log-rank score test] are significant: the p-values of the 3 tests are well below 5%. This shows that the adjustment of the global Cox model is very relevant to the 5% threshold: there is a significant influence of at least one covariate on the probability of death.

The influence of the observations is estimated by comparing the order of quantities from the largest dfbeta to the coefficients. Here, they are small compared to the values of the coefficients, so no abnormally influential observations.

No interaction between covariates was observed in the final model.

4. Discussions

4.1. Profile of the Study Population

The high proportion of people lost to follow-up (37.6%) of our observations leads us to fear a weakness in the validity of the data. However, this important figure is justified, as our patients are transferred from the age of 15 to another sickle cell syndrome management unit located at the NBTC in charge of adult monitoring. However, a small number of patients continue to be followed at the ARNCHC until the age of 20 years.

Patients after their first consultation are followed for 3.9 years on average. This very short follow-up time provides us with information on the communication effort that caregivers should make to regularly follow their patients. However, in a cultural context made up of many beliefs, particularly those of traditional medicine, there remains a great deal of resistance to the continuation of patient follow-up by their parents. In addition, there are also of financial and geographical difficulties to access quality care, which reduce the number of visitors to this sickle cell reference centre.

Patients come from all regions of Senegal and neighbouring countries. This is due to the fact that the ARNCHC is home to the country's only sickle cell disease reference centre and its good reputation.

The patients come from all ethnic groups in Senegal. No study has revealed a particular sensitivity of this disease to an ethnic group in Senegal.

iii. Lethality data

In our series the lethality rate of sickle cell disease is 2.6%. Considering the participation time, the incidence rate of deaths is: 3.51 deaths per 100 person-years. Data collected on lethality in some developing countries are higher than in our series. There was high mortality with 1.9 person-years in a cohort followed between 2004 and 2009 in Tanzania (7.3 person-years under 5 years) [14]. In Zambia a lethality of 6.61% was observed in the cohort between 1987 and 1989 with a rate of 54.84% in the age group between 1 and 5 years [36]. In a series observed between 1997 and 2002 in Burkina Faso, a lethality of 8.7% was observed mainly among children aged 0 to 5 years [24]. The lethality of our series also remains below the rates observed by J. Koko in Libreville (3.6%), Kampatibe et al in Lomé (4.1%), Seeler in Chicago (8.4%) and by Rogers et al in Jamaica (11%) [8, 37-39].

These geographical differences in the rate of sickle cell death are observed even within developed countries. Thus, in the USA, sickle cell children in Florida had a higher risk of death than those living in Baltimore [40].

These differences are attributed to the quality of management of sickle cell disease (early detection, accessibility and quality of medical care, parent education, and adherence to antibiotic prophylaxis).

In our series, the peak death rate is in the age group between 0 and 5 years old with a percentage of 54%. In the literature, this peak frequency of lethality is also observed in J. Koko's series with 60.9%, in Thomas' series with 53.8% and for Seeler 68.4% [17, 38, 41].

This shows the vulnerability of children under five years of age who are paying the highest price, hence the importance of early detection and follow-up.

iv. Survival data

Mean and median survival cannot be calculated because lethality is equal to 2.6%. The 44 deceased patients were followed for 225.87 years, with an average time to death of 5.13 years.

The survival estimated by the Kaplan-Meier method is represented by the overall survival curve. The said curve is framed by its 95% confidence interval. However, the confidence interval widens at the end of the curve, showing a loss of accuracy at this level.

The censures [represented by crosses on the graph] correspond to those lost to follow-up and patients who died throughout the duration of the study (20 years). The interpretation of the censures seems delicate to us because most of lost to follow-up were in fact transferred to the adult care centre (NBTC) at the age of 15; although some patients have been followed at the child care centre (ARNCHC) well beyond the age of 15.

With the late age of follow-up, the transfer of children with SCD followed at the ARNCHC to the NBTC occurs quite early. This partly explains the low average follow-up time for children in our cohort (3,902 years).

This low average follow-up time for children is also explained by the strong belief in traditional medicine associated with poverty, which often lead parents to interrupt

therapeutic follow-up for their children with SCD at the ARNCHC.

The graph of the overall survival function fitted to the data allows to find the same trends and comments as the overall survival curve with however a better accuracy.

Vaccination with at least one antigen improves survival. The survival curves differ significantly from the Log-rank test (p = 0.0157). Vaccination in sickle cell patients, who are highly susceptible to infections, prevents the development of serious life-threatening infections [1, 20, 42].

The increasing number of vaso-occlusive crisis in the last year of follow-up, the duration of which is ≥72h, reduces survival time. In fact, the log-rank test shows a significant difference (p = 0.0019) between the different survival curves established according to the number of VOC. These results corroborate those of many authors who demonstrate a high lethality associated with a high frequency and severity of VOC [43-45].

Survival curves according to the existence or not of severe vaso-occlusive accidents show a significant difference (p = 0.0004). In fact, strokes and acute thoracic syndrome are important causes of death in young sickle-cell patients. Vaso-occlusive accidents significantly reduce the survival of patients with them [46-48].

The presence of severe anemia during the last year of follow-up in the evolution of a sickle cell patient in our series significantly reduces the probability of survival (p = 0.00002). These results are similar in almost all series [18, 22, 49]. In fact, severe anemia is the second leading cause of death in sub-Saharan African countries [10, 36, 50]. Survival curves based on baseline hemoglobin values show that the higher the baseline hemoglobin level, the greater the probability of survival with a very significant log-rank test (p = 0.00037). In fact, the very low baseline hemoglobin level increases the risk of severe, life-threatening acute anemia in sickle cell children [50-52].

The early onset of disease monitoring improves the probability of survival with a very significant log-rank test (p = 0.0029). It is recognized by all authors that the early and quality of care for sickle cell children is the essential prognostic factor improving the survival of these patients [1, 3, 4, 17, 53, 54].

4.2. Prognostic Factors of Death

The 1650 patients were followed for a total period of 6432.4 person-years, i.e. an average follow-up of 3.902 years and a median of 2.47 years (minimum: 0 year; maximum: 19.5 years).

Patients have been followed since the date of their first contact with the ARNCHC for approximately 3.902 years. This follow-up duration is very short. This may be due to insufficient information provided to parents, or to parents' inability to cope with medical costs or perhaps beliefs in traditional medicine in the face of a "disease that does not cure".

To highlight the prognostic factors of death in our study, we used the Cox model applied to all variables of interest to obtain the global model.

In this global model, vaccination with an antigen, the number of vaso-occlusive attacks during the last year of follow-up, the existence of serious vaso-occlusive accidents during the last year of follow-up, the existence of chronic complications, the low baseline hemoglobin level, the age at which follow-up begins late, significantly explain the model ($p<0.05$).

On the other hand, some variables do not seem to provide explanatory power to the model in the presence of the other covariates: hydroxyurea intake, the existence of generalized infection in the last year of follow-up, the existence of severe anemia in the last year of follow-up, the baseline hemoglobin level > 7mg/dl, the age at the beginning of the disease < 60 months and the age at the beginning of the disease ($p \geq 0.05$).

The final model highlights the prognostic factors of death found in our series of patients with SCD followed at the ARNCHC in Dakar (the results of the significance of the variables in the final model are in Table N°8).

v. The number of vaso-occlusive crisis in the last year of follow-up, the duration of which is ≥72h.

The number of vaso-occlusive crisis in the last year of follow-up, the duration of which is ≥72h, significantly increases [p = 0.002] the instant risk of death with a confidence interval of (1.16 – 2) (the value 1 is excluded from the 95% CI). Each additional vaso-occlusive crisis increases the risk of death by 1.52 times.

The existence of VOC in the last year of follow-up and their increasing number therefore reduce survival time. These results support those of many authors who demonstrate a high lethality associated with a high frequency and severity of vaso-occlusive crisis [10, 11, 55]. The number and severity of vaso-occlusive crisis are thus indicators of the severity of sickle cell disease in children [10, 44, 55, 56].

We then find it interesting to strengthen prophylactic measures for the care of children with major sickle cell disease to improve survival.

The use of hydroxy-urea in the management of sickle cell disease is once again indicated in children with frequent and severe attacks. Its use would improve the vital prognosis of these patients [57-60].

vi. Vaccination with at least one antigen

Vaccination significantly reduces the instant risk of death (p = 0.024) with a 95% confidence interval at (0.15 - 0.88). In fact, vaccination with at least one antigen multiplies by 0.37 the instant risk of death compared to an unvaccinated child.

Vaccination by its protective effect against infections plays an important role in preventing infections that are responsible for a significant part of morbidity and mortality among sickle cell disease patients, particularly children before the age of five [32].

Prevention of infections by penicillin prophylactic antibiotic therapy, vaccination with different antigens and antimalarial chemoprophylaxis in endemic areas have significantly improved infection-related morbidity and prognosis [15, 42, 61-63].

It is therefore important to strengthen the Expanded

Programme on Immunization (EPI) in our country by improving vaccine availability and accessibility in order to achieve optimal immunization coverage. It is necessary for the EPI to have a particular approach for sickle cell children, in order to make available to them all the available antigens in addition to those provided by conventional EPI. Sickle cell children should be able to benefit from antigen even outside the usual EPI vaccination schedule.

However, vaccination would be more effective when it is done early; hence the importance of early diagnosis by neonatal screening in children at risk.

vii. Existence of a serious vaso-occlusive accident during the last year of follow-up

In our series, the existence of a severe vaso-occlusive event in the last year of follow-up multiplies by 3.17 the instant risk of death in children with SCD significantly ($p = 0.003$) with a confidence interval (1.47 - 6.83).

Severe vaso-occlusive accidents are a series of complications characterized by an organic deficit [bone, nervous system, lungs, penis, etc.]. In our series only 7.8% of patients had at least one vaso-occlusive accident. The most frequent are: acute thoracic syndrome (28.4%) followed by stroke (27%) and priapism (14.6%).

The most serious are represented by osteoarticular crisis, neurological crisis, abdominal crisis, acute thoracic syndrome and priapism [1, 44, 64].

Strokes of homozygous sickle cell disease dominate the neurological manifestations of the disease; they represent one of the major causes of death in young sickle cell disease and may affect the survival of dramatic disabling sequelae [46]. They complicate approximately 4 to 13% of sickle cell disease patients, favoured by episodes of severe anemia.

Prevention and early management of serious vaso-occlusive accidents would therefore reduce the risk of death. The importance of early diagnosis and care once again demonstrates its importance.

viii. Existence of chronic complications

Paradoxically, the existence of chronic complications in our patients reduces the instant risk of death. In fact, the risk of death in a sickle cell patient with a chronic complication is multiplied by 0.18 compared to a patient free of this type of complication. The test is significant with $p < 0.05$ ($p = 0.01$) and a confidence interval that does not contain 1 (CI: [0.04 - 0.73]).

Chronic complications are more likely to occur in adolescents and adults than in children [65]. They are mainly represented by leg ulcers, bone necrosis, proliferative retinopathies, renal failure, pulmonary and cardiac complications (pulmonary infarction, pulmonary hypertension) and hepatobiliary complications. They can contribute to sickle cell disease mortality [1, 10, 26].

Chronic complications account for 7% of the observed complications. These chronic complications are relatively infrequent in our study, as they are more common in adults [32]. However, they appear in childhood and their frequency tends to increase with age. In our series we did not note any deaths due to chronic complications.

We can assume that the existence of a chronic complication in patients in our series would encourage practitioners to bring follow-up closer to patients. These same complications could also lead patients to comply more with the follow-up and care of their children, thus reducing the risk of death..

ix. The basic hemoglobin level is very low

The baseline hemoglobin level between 5 and 7 gr/100ml multiplies by 12.68 the instant risk of death in children with SCD significantly ($p = 0.01$) with a confidence interval [1.63 - 98] that does not include the value 1. However, we can report a lack of precision in the risk due to the high importance of the confidence interval.

This very low basic hemoglobin level (between 5 and 7 gr/100ml) increases the risk of severe acute anemia (hemoglobin level $\leq 5g/d\ell$); In fact, against a background of chronic anemia, the evolution of major sickle cell syndromes may be accompanied by episodes of acute anemia that can be responsible for rapid deaths [1, 10, 66].

We can deduce that, the lower the baseline hemoglobin level, the greater the risk of poor tolerance and aggravation of anemia with the possibility of decompensation, which can lead to death [1, 50, 67].

It is therefore important to prevent acute anemia by increasing the basic hemoglobin level by implementing prophylactic measures: infection prevention, a rich and balanced diet, iron and folic acid supplementation if necessary, etc..

x. The age of the patient at the beginning of late follow-up

The age of the patient at the beginning of follow-up between 180 and 277 months multiplies by 4.12 the instant risk of death in children with SCD whose follow-up age is between 120 and 180 months, significantly ($p = 0.015$) with a confidence interval [1.31-12] that does not include the value 1.

The other ages at the beginning of the follow-up ([60, 120] and [120, 180], in months) reduce the risk of death in a non-significant way ($p>0.05$).

We can therefore deduce that the later the age of children with SCD at the beginning of follow-up, the higher the risk of death.

The early age of children at the beginning of follow-up therefore implies early diagnosis [preferably neonatal screening] and comprehensive and accessible care (physical and financial accessibility to quality care). Many authors have shown that diagnosis by neonatal screening for sickle cell disease in at-risk children, early follow-up combined with parental education and comprehensive care can significantly reduce morbidity and mortality in children with SCD [20, 68].

5. Conclusions

The prognosis of patients with sickle cell disease followed at the Albert Royer National Children's Hospital Center (ARNCHC) is difficult to establish. In fact, in addition to genetic, clinical and evolutionary factors, there

are poorly understood environmental and socio-economic factors that affect survival. Our study was able to show a lethality of 2.6% and an incidence rate of deaths at 3.51 deaths per 100 person-years. The Cox model highlighted the prognostic factors that provide significant explanatory power to the model ($p < 0.05$). Vaccination with at least one antigen and the existence of chronic complications improve the survival of patients. On the other hand, the number of vaso-occlusive crisis during the last year of follow-up (duration is ≥72h), the existence of serious vaso-occlusive accidents during the last year of follow-up, the baseline hemoglobin low (≤5mg / 100 min), early onset of late follow-up (≥15 months) reduce patient survival. The retrospective nature of the study is a limit to the study. A prospective study would shed more light on the prognostic factors of death in children with major sickle cell disease.

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