Esc Anna Nery 2020;24(2):e20190194

REVIEW | REVISÃO

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Risk factors for mortality in patients with sickle cell disease: an integrative review

Fatores de risco para mortalidade em pacientes com doença falciforme: uma revisão integrativa

Factores de riesgo para la mortalidad en pacientes con enfermedad falciforme: una revisión integradora

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ABSTRACT

Objective: To summarize the risk factors and mortality indicators in sickle cell disease patients. **Method:** Integrative review searched publications in journals in CINAHL, PubMed/MEDLINE, Science Direct/SCOPUS, SciELO, and Web of Science databases. The guiding question was elaborated through the Population, Variable, Outcome (PVO) strategy and the search was from October-to-November 2018, at the Coordination of Higher Level Personnel Improvement Periodicals' Gate. The keywords anemia, sickle cell "and" mortality "and" survival and their synonyms were used. **Results:** From 18/19 articles were cohort and one randomized controlled trial. The sample consisted mostly of females and HbSS genotype. The cumulative mortality rate and the overall mortality curve were the most repeated. Seven studies identified risk factors with a statistically significant association with death. The most frequent were low hemoglobin level, liver variables (alkaline phosphatase and oxalacetic glutamic transaminase enzymes) and cardiovascular variables (tricuspid valve regurgitation speed ≥ 2.5m/s). **Conclusion and implications for practice:** Mortality indicators are tools for better management of sickle cell disease's patient, prevention of risks and complications. There is a need for further studies on the factors related to mortality of these patients. Preventing the causes that lead to death will certainly improve the quality of life and survival of this population.

Keywords: Sickle Cell Disease; Causes of death; Rates, rations and proportions.

RESUMO

Objetivo: Sumarizar fatores de risco e indicadores de mortalidade em pacientes com doença falciforme. **Método**: Revisão integrativa em periódicos indexados nas bases de dados CINAHL, PubMed/MEDLINE, *Science Direct*/SCOPUS, SciELO e *Web of Science*. A questão norteadora foi elaborada por meio da estratégia *Population, variable, outcome (PVO). A* busca ocorreu no portal de periódicos da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior entre outubro e novembro de 2018. **Resultados:** Dos 19 artigos, 18 eram coorte e um ensaio clínico randomizado. A amostra foi constituída, em sua maioria, pelo sexo feminino e genótipo HbSS. Se repetiram mais a taxa de mortalidade cumulativa e a curva de mortalidade global. Sete estudos identificaram fatores de risco com associação estatisticamente significativa para morte. Os mais frequentes foram o baixo nível de hemoglobina, variáveis hepáticas (enzimas fosfatase alcalina e transaminase glutâmico oxalacética) e cardiovasculares (velocidade de regurgitação da válvula tricúspide ≥ 2,5m/s). **Conclusão e implicações para a prática**: Indicadores de mortalidade constituem ferramentas de manejo de pacientes com doença falciforme e prevenção de riscos e complicações. Há necessidade de estudos sobre os fatores relacionados à mortalidade desses pacientes. A prevenção do óbito, certamente, promoverá uma melhoria na qualidade de vida e na sobrevida dessa população.

Palavras-chave: Doença falciforme; Causas de morte; Taxas, razões e proporções.

RESUMEN

Objetivo: Resumir los factores de riesgo y los indicadores de mortalidad en pacientes con enfermedad de células falciformes. **Método:** revisión integradora de publicaciones en las bases de datos CINAHL, PubMed/MEDLINE, Science Direct/SCOPUS, SciELO y Web of Science. La pregunta guía basada en *Population, variable, outcome (PVO*) conduciu la búsqueda en el Portal de revistas de la Coordinación de Mejoramiento de Personal de Nivel Superior, entre octubre-noviembre de 2018, con los descriptores *anemia, sickle cell* "and" *mortality* "and" *survival* y sus sinónimos. **Resultados:** De 18/19 artículos son cohortes y un ensayo controlado aleatorio. La muestra consistió en mujeres y genotipo HbSS. La tasa de mortalidad acumulada y la curva de mortalidad general fueron más repetidas. Siete estudios identificaron factores de riesgo con asociación estadísticamente significativa con la muerte. Los más frecuentes fueron el bajo nivel de hemoglobina, variables hepáticas (fosfatasa alcalina y enzimas glutámicas transaminasas oxalacéticas) y variables cardiovasculares (velocidad de regurgitación de la válvula tricúspide ≥ 2.5m/s). **Conclusión e implicaciones para la práctica:** Los indicadores de mortalidad son herramientas de manejo de los pacientes con esta enfermedad, la prevención de factores de riesgo y complicaciones. Hace necesidad de estudios sobre los factores relacionados con la mortalidad. La prevención de las muertes mejorará la calidad de vida y la supervivencia.

Palabras clave: Enfermedad falciforme; Causas de muerte; Tasas, razones y proporciones.

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Submitted on 07/03/2019.
Accepted on 12/20/2019.

DOI: 10.1590/2177-9465-EAN-2019-0194

INTRODUCTION

Sickle Cell Disease (SCD) is a broad term used to group together several inherited hematological conditions that result from a single genetic mutation that can lead to the formation of abnormal erythrocytes. It is a multiple system disease, whose abnormal cells in the presence of deoxygenation can suffer from damage in their shape and ability to carry blood gases, and generate several vessels occlusion that can lead to numerous changes in body organs.[1]

The inheritance of sickle alleles that determines the forms of SCD, whose most common and severe is the homozygous HbSS, called Sickle Cell Anemia. Other forms include heterozygous HbSC, HbSβ-thalassaemia, HbSD, and HbSOArab, which are compound hemoglobinopathies and variant β-globins that also exhibit expression of the HbS gene capable of causing sickling.[2]

Despite advances in the diagnosis and treatment of SCD, the average survival has not yet reached the fifth decade of life, with an estimated overall life expectancy of around 30 years old, especially in regions where early diagnosis, access to penicillin prophylaxis and pneumococcal immunization, as well as treatment with Hydroxyurea are more difficult.[1]

Mortality from SCD is still a haunting reality worldwide, especially in countries of the African continent, where the high prevalence of the disease and the high mortality rates are alarming. Among the Brazilian regions, the lowest mortality rate per 100,000 inhabitants was observed in the South and North regions of 0.05 and 0.19, respectively. On the other hand, the largest rate was found in the Midwest region, with 0.35, highlighting the highest concentration in the state of Goiás, which expresses a rate of 0.48 deaths per 100,000 inhabitants. Similar value to that found in the state of Bahia, which has the highest mortality rate in the northeast region, also with 0.48 deaths per 100,000 inhabitants.[3]

In addition, the number of studies on the subject in Brazil is still limited. By the year of 2017, eight articles had been published on mortality of people with SCD, with no significant increase in publications the following year.[4] These addressed characteristics and causes of mortality in only five of the 26 Brazilian states. In more than 50% of these researches the populations studied were specific, such as children, pregnant women and users of hydroxyurea. Only one addressed the risk factors for death in pregnant women with SCA.

Thus, when considering the global and national mortality rates, the low life expectancy of individuals with SCD and the gaps in relation to the aspects involving their mortality, it is necessary to investigate the worldwide studies on the mortality and its risk factors subject in order to produce indicators that may contribute to the increase of survival of this population.

In this context, this study proposes to produce a robust reference in order to compile the existing studies that address in a specific and regionalized way the data on mortality due to SCD and present a global analysis on the subject. From the identification of risk factors that increase the chances of death, it is intended to identify those capable of receiving interventions by the multidisciplinary team, especially from nursing, as a way to decrease the early mortality of patients with SCD and increase survival guaranteeing a better quality of life for these individuals.

Thus, the objective of this study was to summarize the risk factors and mortality indicators in patients with Sickle Cell Disease.

METHOD

This is an integrative literature review study consisting of a rigorous method that uses predefined criteria regarding the guiding question, extraction, analysis and discussion of data.[5] Furthermore, it allows the combination of various methods and enables the researcher to analyze and synthesize scientific knowledge about the object of study in order to identify existing gaps.[6]

For the operationalization of this research, the following steps were performed: elaboration of the guiding question, establishment of inclusion and exclusion criteria, searching or sampling in the literature, data collection, categorization of studies, critical analysis of included studies, discussion of results and presentation of the study integrative review.[7]

The guiding question was elaborated using the PVO strategy, where P (*population*) corresponds to the population of patients with Sickle Cell Disease, the V (*variable*) refers to the variable of interest that relates to risk factors and mortality indicators, lastly the O (*outcome*) is the result, here considered mortality.[8] Thus, the following guiding question was constructed: What are the risk factors and indicators related to mortality in patients with Sickle Cell Disease?

The database search took place in October and November 2018 and was performed by two independent researchers to avoid selection bias. The Proxy licensed by the Federal University of Rio Grande do Norte was used through the Coordination for Improvement of Higher Level Personnel (CAPES) (http://www.capes.gov.br/), which was accessed via the CAPES Journal Portal (http://www-periodicos-capes-gov-br.ez18.periodicos.capes.gov.br/), on the same days and times.

Data were collected from the following databases: CINAHL, PubMed, *Science Direct*, SciELO, Scopus and *Web of Science*. Disagreements were resolved by consensus, comparing search results and verifying differences in findings.

The following indexed descriptors and their respective synonyms were used for searching the *Medical Subject Headings* (MeSH) databases: **#1** Anemia, Sickle Cell (HbS Disease OR Hemoglobin S Disease OR Sickle Cell Anemia OR Sickle Cell Disease OR Sickle Cell Disorders OR Sickling Disorder Due to Hemoglobin S) AND **#2** Mortality (age-specific death rate OR case fatality rate OR death rate OR decline, mortality OR

determinants, mortality OR differential mortality OR excess mortality OR mortality decline OR mortality determinants OR mortality rate OR mortality, differential OR mortality, excess) AND **#3** Survival.

This research has as its main object of study the mortality of patients with SCD. However, the database search strategy used the descriptor "survival" in order to increase the number of articles that addressed the theme, since by studying survival it is possible to identify mortality data for a given population.

The crossings of MeSH terms in the databases were combined with each other via the Boolean connector "AND", whereas the *entry terms* were combined by the Boolean connector "OR". The crossover adopted on all bases was #1 AND #2 AND #3.

Comprehensive articles, available in the adopted databases, addressing risk factors and their mortality rates in SCD, in any language and without time frame, in order to make the most of publications on the subject that include prospective follow-up design, intervention studies or systematic review with meta-analysis, as these produce more accurate mortality indicators, because these studies make it possible to produce incidence measures and therefore direct risk measures.[9]

For data analysis and extraction an instrument was developed specifically for the purposes of this study with the following information: type of study, country, language, area of knowledge, institution host, design, journal or scientific journal of publication, population, sampling and purpose of the study, in addition to the variables to be investigated.

The search and selection process of the articles in the final sample is described in Figure 1. The results are presented descriptively and in a chart.

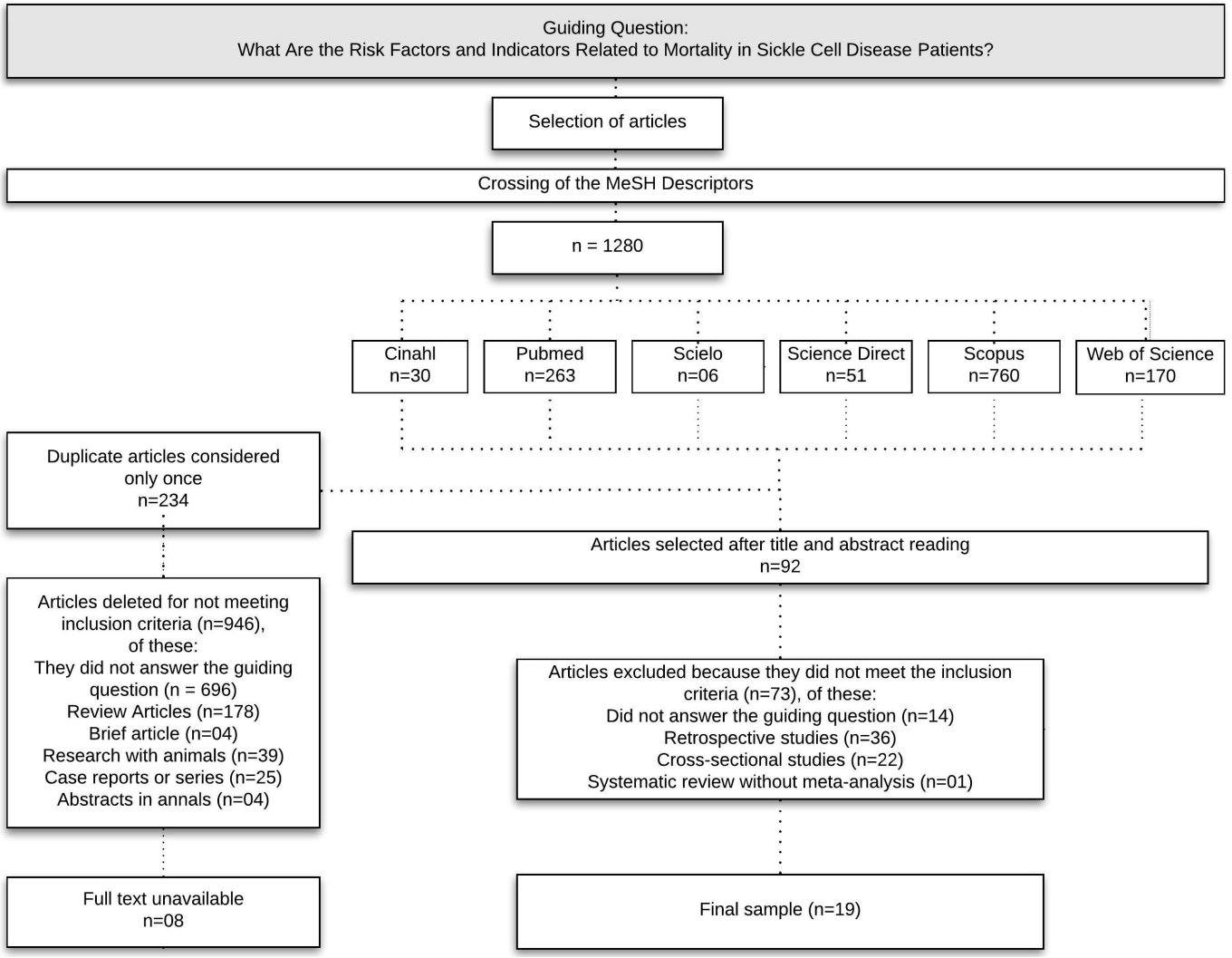

Figure 1. Search flowchart for sample composition of the integrative review study.
Source: Research data. Campo Grande/MS, Brazil, 2019.

RESULTS

The search in the databases initially totaled 1,280 articles. After applying the inclusion and exclusion criteria, 19 articles[10-28] were selected for the composition of the final sample, all published in the English language.

Of this, 10 articles were indexed in the databases *Web of Science*/Scopus,[10,12,14,15,17-19,21,23,27] three in PubMed/Scopus/*Web of Science*,[16,26,28] two in Scopus[20,22] and the others published only once in PubMed databases,[24] *Web of Science*,[25] PubMed/Scopus[13] and CINAHL/Scopus/*Web of Science*,[11] respectively.

Regarding geographic and temporal distribution, it was observed that eight studies (42.1%) were conducted in the United States of America (USA),[12,13,15-17,24,26,28] three in Jamaica,[14,20,25] two in the United Kingdom[20,27] and Tanzania,[19,21] and one in Nigeria,[22] France,[23] Netherlands[18] and Canada/United States.[11] The years with the most publications were 2013[12,20,27] and 2011[18,19,21] with three publications each and the years 2005,[17,22] 2010,[15,28] and 2015[14,16] with two publications each. The oldest publication was published in 2001[25] and the two most recent studies in the year of 2015.[14,16]

After analyzing and synthesizing the articles selected for this review, in order to facilitate reading and understanding, the results were grouped into three categories: (A) Genotypes of study participants; (B) Mortality indicators and (C) Risk factors for death, the latter divided into laboratory factors and clinical factors, sociodemographic and comorbidities.

Chart 1 shows the distribution of the 19 articles analyzed in the final sample, according to database, first author, reference number, year of publication, journal, country where it was developed, study design, study objective and main results.

Genotypes of Study Participant

The final sample comprised a total of 14,594 individuals participating in the research, except for controls, followed by an average of 8.6 years. Of this total, 6,059 (51.7%) were female and 5,660 (48.3%) male, even with a male predominance in eight studies.[13,15,16,18,23,24,26,28] In five, gender was not informed.[10,11,20-22] All articles in which the genotype was described[10,12,14-16,18,20-28] had HbSS as the study population, which totaled 11,394 individuals and constituted 91.6% of the total studied. The other described genotypes were observed, in a smaller number of publications,

Chart 1. Characterization of the Final Sample Studies of the Integrative Review.

Database	First author, reference number, year, journal, country	Designing	Objectives	Main results
Scopus, Web of Science	Telfer et al.[10] **Haematologica Journal** United Kingdom	Prospective cohort study	To investigate the results in a neonatal cohort as a reference for care of children with Sickle Cell Disease.	The overall mortality rate for HbSS was 0.13 per 100 patients/year. The probability of survival at 10 and 20 years for HbSS was 99% and the mortality rate was 0.27 per 100 patients/year.
CINAHL, Scopus, Web of Science	Steinberg et al.[11] **JAMA Network** Canada and United States of Ameria	Prospective cohort study	To determine if hydroxyurea attenuates mortality in patients with Sickle Cell Anemia.	The cumulative mortality at 09 years was 28% for fetal hemoglobin levels <0.5g/dL and 15% for ≥0.5g/dL (p<0.03). Reticulocyte count <250,000/mm^3 and hemoglobin <9g/dL increased mortality (p=0.002).
Scopus, Web of Science	Mehari et al.[12] **American journal of respiratory and critical care medicine** United States of America	Prospective cohort study	To identify risk factors associated with mortality and to estimate expected survival in a cohort of patients with Sickle Cell Anemia with Pulmonary Hypertension (PH).	Mortality was higher in patients with PH compared to those without PH (p<0.001). The cumulative mortality rate in 5-year for patients with PH was 31.7% while patients without PH had 14.4% mortality. The median of survival for Sickle Cell Disease with PH was 6.8 years from diagnosis.
PubMed, Scopus	McClellan et al.[13] **British journal of haematology** United States of America	Prospective cohort study	To test the hypothesis that pre-End-Stage Renal Disease care is associated with lower mortality among individuals with Sickle Cell Disease (SCD).	Patients with SCD and End-Stage Renal Disease (ESRD) were at a higher risk of death compared to patients with ESRD without SDF (*HR*=2.80). The mortality rate in ESRD was almost three times higher in individuals with SCD.

Chart 1. Continued...

Database	First author, reference number, year, journal, country	Designing	Objectives	Main results
Scopus, Web of Science	King et al.[14] **The Journal of pediatrics** Jamaica	Prospective cohort study	To compare mortality in children <5 years old with Sickle Cell Disease in Jamaica.	There were eight deaths in children under five years old. The average age of death was 2.0 ± 1.5 years. The mortality rate was 3.1 per 1000 people/year with a standardized mortality rate of 0.52.
Scopus, Web of Science	Quinn et al.[15] **Blood Journal** United States of America	Prospective cohort study	To estimate survival at 18 year for newborns with Sickle Cell Anemia and document changes in causes and ages of death over time.	For patients with HbSS/HbSβº the estimated survival probability at 18 years was 93.9% and for HbSC/HbSβ+ was 98.4% (p=0.009). The probability of survival at five years of age was 96.8% (1983-1990), 97.5% (1991-2000) and 99.2% (2001-2007).
PubMed, Scopus, Web of Science	Van Beers et al.[16] **Circulation research** United States of America	Prospective cohort study	To assess the relationship between iron, inflammation and early death in Sickle Cell Disease.	Survival curves for C-Reactive Protein (CRP) levels were statistically different between groups with higher mortality at levels ≥0.8mg/dL (p=0.0017), and each increase in CRP was associated with risk rate up to 3.0 for death (p<0.0001).
Scopus, Web of Science	Shankar et al.[17] **American journal of haematology** United States of America	Prospective cohort study	To evaluate the pattern of medical care utilization and mortality in children and adults with Sickle Cell Disease.	For children under five years old with SCD the mortality rate did not differ from the other black children in the studied population. Mortality was higher for ages 10 and 19 years. Between 20- and 49-years mortality was higher for males (p<0.001)
Scopus, Web of Science	Van der Plas et al.[18] **British journal of haematology** Netherlands	Prospective cohort study	To Collect information on mortality rate and causes of death in children with sickle cell anemia in the Netherlands prior to neonatal screening.	The overall mortality rate was 0.27 deaths per 100 patients/year and the estimated survival probability at 03 and 18 years was 98.2% and 97.3%, respectively.
Scopus, Web of Science	Makani et al.[19] **PloS One Journal** Tanzânia	Prospective cohort study	To determine the incidence and factors associated with death from Sickle Cell Disease in Dar-es-Salaam.	The overall mortality rate for the cohort was 1.9 per 100 people/year and for children under five and over 20 years old it was 7.3 and 1.8 respectively. Independent risk factors for death were low hemoglobin (p<0.001) and elevated total bilirubin levels (p=0.020).
Scopus	Knight-Madden et al.[20] **Lung Journal** Jamaica	Prospective cohort study	To determine whether asthma, reduced lung function, episodes of acute chest syndrome and/or smoking predict mortality in patients with Sickle Cell Anemia.	The mortality rate for the study population was 1.6 per 100 patients/year. The mortality rate among patients with Sickle Cell Anemia was higher than the controls (p=0.03). Among the risk factors for death included current asthma status (p=0.002) and smoking (p=0.006).
Scopus, Web of Science	Cox et al.[21] **Haematologica Journal** Tanzânia	Prospective cohort study	To determine if poor nutritional status predicts morbidity and mortality in a cohort of patients with Sickle Cell Anemia.	Lower levels and hemoglobin were associated with increased chance of malnutrition in SCD. The mortality rate was 2.5 per 100 people/year and was not associated with any anthropometric measurements.

Chart 1. Continued...

Database	First author, reference number, year, journal, country	Designing	Objectives	Main results
Scopus	Akinyanju et al.[22] **Clinical and Laboratory Haematology** Nigeria	Prospective cohort study	To examine the outcome of holistic care in mortality rates, hospital admission and blood transfusion.	There was a constant decrease in the mortality rate from 20.7% in 1988 to 0.6% in 1995 (p<0.0001). With the implementation of holistic care there was a decrease in hospitalizations (p<0.0001) and blood transfusions (p<0.00001).
Scopus, Web of Science	Mekontso Dessap et al.[23] **American Journal of Respiratory and Critical Care Medicine** France	Prospective cohort study	To evaluate changes in pulmonary pressures and cardiac biomarkers during severe acute chest syndrome and their associations with death.	Overall mortality for patients with pulmonary hypertension was 12.9% and survival was significantly lower for patients with tricuspid valve jet regurgitation velocity ≥3m/s when compared to values <3m/s during acute thoracic syndrome (p=0.007).
PubMed	Meier et al.[24] **American Journal of Hematology** United States of America	Prospective cohort study	To test the hypothesis that early detection (childhood) of reticulocytosis, anemia or leukocytosis is predictive of major adverse events in Sickle Cell Anemia.	The mean age at death was 3.4 ± 3.4 years. Reticulocyte count was an independent risk factor for death (p=0.011). Individuals with lower hemoglobin levels had a higher mortality rate (24.7%).
Web of Science	Wierenga et al.[25] **The Lancet** Jamaica	Prospective cohort study	To study the life expectancy of Jamaican patients with homozygous Sickle Cell Disease.	Of the 3,301 patients, 290 died. The median survival calculated by simulating the excess mortality rate was 53 years for men and 58.5 for women.
PubMed, Scopus, Web of Science	Quinn et al.[26] **Blood Journal** United States of America	Prospective cohort study	To determine contemporary survival data for children with Sickle Cell Anemia.	The overall mortality rate was 0.59 per 100 patients/year. HbSC and HbSβ+ genotypes had longer survival than HbSS and HbSβº (p=0.02). The event-free survival for all genotypes was 100% at six months and 88.5% at 18 years.
Scopus, Web of Science	Zimbarra Cabrita et al.[27] **British Journal of Haematology** United Kingdom	Prospective cohort study	To determine the survival of a cohort of patients with Sickle Cell Anemia based on Tricuspid Valve Jet (TVJ) regurgitation velocity and to describe the differences between those with elevated and normal TVJ.	TVJ values ≥ 2.5 m/s were associated with a fourfold higher risk of death. The cumulative survival at five-year rate was 95%. Age (p=0.03), hemoglobin levels (p=0.006), hematocrit (p=0.002), mean corpuscular volume (p=0.004) and mitral valve deceleration time (p<0.001) were considered risk factors to death.
PubMed, Scopus, Web of Science	Steinberg et al.[28] **American Journal of Hematology** United States of America	Randomized Controlled Trial	Examine the risks and benefits of prolonged use of hydroxyurea.	The overall mortality rate was 4.4 per 100 people/year. The mortality decreased with increasing exposure. Between 10 and 15 years was 1.78 per 100 people/year and after 15 years, reached zero.

in a total of 1,047 individuals surveyed. In three studies the genotype was not reported.[11,13,17]

Mortality Indicators

The total number of deaths found in the studies was 1,100, which corresponded to 7.5% of the sample analyzed. Of these, 1,057 deaths occurred in individuals with HbSS genotype (96.1%) and two studies did not report the absolute number of deaths.[16,22]

The most repeated mortality rates were the cumulative mortality rate observed in nine studies[11-13,16,22-24,27,28] and the overall mortality rate per 100 people/year, found in seven[10,15,18-21,26] of 19 studies.

These rates were stratified by reticulocyte count,[11,14] fetal hemoglobin (HbF) level, annual episodes of acute chest syndrome (STA) and pain,[11] pulmonary hypertension,[12] C-Reactive Protein (CRP),[16] holistic care period,[22] hemoglobin (Hb) levels,[24] tricuspid valve jet regurgitation speed,[27] severe Sickle Cell Anemia[23] and End-Stage Renal Disease[13] for the cumulative mortality rate. And more and less severe genotypes,[15,26] Sickle Cell Anemia[21] and SCD[18-21] for the overall mortality rate.

In addition to these, we found the standardized mortality rate (SMR)[14,19] and the calculation of excess mortality,[25] as well as the specific mortality rates: by age,[10,14,17,19,28] by age and year,[15] age and gender,[17] age and genotype.[26]

Among the curves found in the studies were the global mortality curve,[18] Sickle Cell Disease-related mortality curve[26] and the curve of cumulative hydroxyurea stratified mortality *versus* placebo, HbF levels, neutrophil count, reticulocyte count, acute chest syndrome, pain episodes[11] and SCR levels.[16]

Among the mortality rates found, it was possible to observe that the overall mortality rate for all forms of SCD, the lowest value observed among the studies was 0.15[17] and the highest 4.4[28] for 100 people/year. The stratified specific mortality rate for the most severe genotypes HbSS and HbSβº ranged from 0.52[15] to 0.59[15,26] and for the HbSC and HbSβ+ genotypes from 0.1[15] to 0.4[26] per 100 people/year.

The application of holistic care for the patient with SCD led to a cumulative mortality rate reduction from 20.7% to 0.6% at seven years,[22] while non-treatment with hydroxyurea implied a rate of 46.9% over a period of 17.5 years.[28]

The specific mortality rate per 100 people/year found for children up to one year old ranged from 0.55[14] to 4.98.[22] The highest mortality rate observed among children under two years old was 0.72 for the HbSS genotype[26] and for children under five years old ranged from 0.36[17] at 6.77[28] with a cumulative mortality rate of 55.7% over a period of 17.5 years.[28] It was also observed that the mortality rate of SCD increased with increasing age from the age of five years with 0.36 for children under five years old, from 3.5 for adults from 40 to 49 years and from 7.8 for elderly over 60.[17]

In addition, a higher mortality rate was found for males from the age of five years, with a higher mortality rate in the age groups 40 to 49 years and 50 to 59 years with 6.3 and 6.4 per 100 people/year, respectively. For the same ages in females, the mortality rate, in the same order, was 2.5 and 4.8.[17]

It was possible to observe in the studies that the higher mortality of SCD is directly related to the presence of risk factors. The cumulative mortality rate at different periods by HbF level presented the highest level of 32% when the HbF level was low compared to the highest level where the rate was 15%.[11] The same can be observed in reticulocyte count > than 250,000/mm^3 with a rate of 38%[11] and 4.7%[24] for <150,000/mm^3 count, low CRP level (<0.2mg/dL) at 12.4% and 25.8% for levels greater than 0.8mg/dL,[16] hemoglobin with level <10 g/dL showed a rate of 24.7% and 7.3% for levels> 10g/dL,[24] tricuspid valve jet regurgitation velocity >2.5m/s cumulative mortality rate was 16.7% and for values <2.5m/s observed rate was 6.9%.[27]

In addition, some complications were also associated with a higher cumulative mortality rate, such as the presence STA episodes with rate of 32% when compared to their absence with 18%, three or more annual episodes of pain presented the rate of 27%, while that for less than three episodes of pain in the year the mortality rate was 17%.[11] Pulmonary hypertension implied a cumulative mortality rate of 31% and 14.4% in its absence.[12] Severe Sickle Cell Anemia and SCD associated with end-stage renal disease are associated with a rate of 12.9%[23] and 44%,[13] respectively.

Risk factors for death in Sickle Cell Disease

Nine (47.3%) studies assessed risk factors for death,[12,13,16,19-21,23,24,27] seven (88.8%) with statistically significant findings.[12,16,19,20,23,24,27] A total of 23 variables grouped into laboratory and clinical risk factors, sociodemographic and comorbidities were identified in this study and associated with higher mortality in SCD.

Among the laboratory factors associated with the higher risk of death, the low Hb[19,24,27] hematological variable found in three studies was highlighted. In addition to that, it was associated with the risk of death the highest mean corpuscular volume[27] and reticulocytosis.[24]

Hepatic laboratory factors found were increased direct bilirubin,[12,19] total bilirubin,[19] alkaline phosphatase,[12] glutamic oxaloacetic transaminase (SGOT)[12] and ferritin.[12] It was also observed as increased risk of death the increased CRP levels.[16]

Among the cardiovascular factors associated with higher mortality, the presence of heart failure with functional class of the *New York Heart Association* (NYHA) II or III,[12] the walking capacity of 6-minute <100 meters[12] and echocardiographic findings such as: continuous tricuspid jet regurgitation[26] and the tricuspid valve jet regurgitation speed> 2.5 m/s,[23,27] increased pulmonary artery pressure[12] and increased pulmonary vascular resistance index.[12]

Current asthma status,[20] elevated age,[27] presence of smoking[20] and the HbSS genotype[12] were also associated with increased risk of death.

DISCUSSION

The present review sought to globally investigate the indicators and risk factors for death in SCD and provide a comprehensive overview of the literature. The data found were similar to those reported in other studies. Although gender does not present

a genetic predominance in SCD, female predominance was observed in the population.[29] Likewise, the observed data regarding genotype are also in line with the worldwide literature that shows that HbSS is the most prevalent genotype in Brazil and worldwide and can reach about 70% of all cases of SCD diagnosed.[30,31]

Regarding mortality, the data were also similar. The highest overall mortality rate found was similar to that observed in a study conducted in the state of Bahia with 5.4:100 people/year,[32] region with one of the highest mortality rates from SCD of the country.

In this context, although the decline in deaths from holistic patient care and the initiation of hydroxyurea therapy has been observed, SCD still maintains high mortality rates, with a cumulative mortality rate of 50.7% for children up to five years found in the analyzed sample. Given this, which comes against the study conducted in the state of Mato Grosso do Sul, where the cumulative four-year-old mortality rate was 48% for hydroxyurea users and 66% for nonusers.[30] These findings raise the need for global public health policies that prioritize the diagnosis and early treatment of this disease, already in the first years of life. The national neonatal screening program is an important policy in Brazil since 2001 and is responsible for the diagnosis of hemoglobinopathies in the first days after birth and ensures initiation of treatment within the first months of life.[33]

In addition, the rising mortality rate with increasing age, which can reach 7.8 per 100 people/year for older people over 60 years old, corroborates the findings from this and other studies that have observed increasing age as a risk factor for death.[34-36] These data are since older patients suffer more from progressive lesions in numerous organs resulting from chronic and frequent Sickle Cell Disease complications.[37] In an attempt to reduce these mortality data, the treatment of the disease needs to be focused on the control of these chronic complications in order to ensure a better quality of life and lower mortality for the elderly with SCD.

Regarding gender, the higher mortality rate observed for males resembles data obtained in other studies,[38,39] although several studies have also found a higher mortality rate among women, especially in the adult period, which reinforces the non-relationship between the SCD and the gender of the individuals.

Another important factor observed was the direct relationship between the highest mortality rates and the presence of risk factors. The highest death rate among the most severe genotypes, especially HbSS, has been observed in several studies worldwide and reaffirms the information that homozygous Sickle Cell Disease remains as the most severe genotype.[40,41] This statement can be justified by the pathophysiology of SCD, since when deoxygenated the HbS polymerizes, which changes the shape of the erythrocyte and decreases its deformability potential, a fundamental event in all pathophysiology of SCD. Thus, as homozygous disease tends to have a higher amount of HbS, clinical events and complications are more frequent, often severe and may culminate in death.[42]

HbF plays an important role in inhibiting HbS polymerization. Thus, a greater amount of this hemoglobin in the blood circulation may be associated with a decrease in symptoms and complications of the disease. Currently, the only drug capable of inducing HbF production is hydroxyurea, although the mechanism by which this induction occurs is unclear, the benefit of its use has already been proven and the protocol of use is warranted in the treatment of the disease.[43]

Regarding risk factors, a total of 10 laboratory variables were identified. The decreased red blood cell count, evidenced by low hematocrit percentage, besides the low Hb level and reticulocytosis[34,44,45] present themselves as risk factors for death in several researches, as well as a higher average corpuscular volume.[46] The increasing white cell numbers[44,45,47,48] have also been associated with a higher risk of death.

Low Hb levels are associated with serious complications as they are related to a lower ability to carry oxygen which may lead to deoxygenation of HbS and consequent vessel occlusion. The main treatment focuses on blood transfusion, in particular simple transfusion of red blood cells.[49]

Similarly, reticulocytes are associated with the presence of important clinical events and are considered predictors of disease severity. In addition, they act as markers of hemolysis and are prematurely eliminated in the bloodstream. Its high levels indicate active hemolysis process[50] and make it an important laboratory marker in clinical practice.

Other laboratory variables such as liver function, with increased direct and total bilirubin,[51] alkaline phosphatase,[35,51] ferritin[35,51,52] and the SGOT,[35] together with increased levels of CRP,[40] considered an inflammatory marker, have also been found in other studies as associated with greater risk of death.

In addition, it was observed that the association of some laboratory variables found in isolation in this study, when taken together, also appeared as a risk factor for death in other studies. The variable derived from the association between reticulocyte count, Lactate Dehydrogenase (LDH), SGOT and bilirubin is called hemolytic component, and this was responsible for the increase in mortality in several studies.[35,53]

Liver disease occurs in about 10 to 40% of patients with SCD. Hepatic sickling crisis is often responsible for acute and severe hepatobiliary disease. In addition, the increase in serum iron levels, which results mainly from the numerous blood transfusions, may lead to liver overload and complications resulting from this condition[54] and its dosage should be considered in the laboratory control of the disease. These variables are also related to intravascular hemolysis, which is considered one of the main characteristics of sickle cell anemia and which can lead to severe and difficult to control organ dysfunction.[55]

Among the clinical, sociodemographic and comorbidities risk factors, 13 variables were identified. The cardiovascular variables, tricuspid valve jet regurgitation velocity >2.5m/s[34,35,45,52] and continuous tricuspid valve jet regurgitation and NYHA II or III functional class heart failure[35] were associated to a greater risk of dying. These and other variables, which also reflect diastolic ventricular dysfunction and consequent pulmonary hypertension, were observed as a risk factor for death in a study done by Gladwin, which provided data from a large prospective cohort

of 513 patients with pulmonary hypertension performed by the *National Institutes of Health*.[56] A higher risk of death was also associated with current asthma,[57] increased age,[34-36] besides the HbSS genotype which is considered the most serious among the others.

The chronic evolution of SCD with frequent episodes of vessel occlusion and hemolysis leads to progressive target organ lesions, especially to the cardiovascular system with complications including pulmonary hypertension, pulmonary artery pressure elevation, and left ventricular diastolic dysfunction, which may culminate in heart failure and even arrhythmias and sudden death.[37] Thus, routine clinical and cardiological evaluation in patients with SCD with early management of these chronic complications is important by stratifying the risk of cardiovascular severity and assessing the biomarkers of cardiac injury.

It was observed that the data obtained by this study showed a high mortality rate of SCD, especially in view of the risk factors common to the pathophysiology of the disease, which maintains a high mortality rate especially after the third decade of life. Early recognition of risk factors and predictors of mortality enables appropriate and prompt treatment. Thus, the need for training of health professionals for the early recognition of signs that lead to clinical worsening and rapid intervention in these complications becomes imperative.

CONCLUSION

Mortality indicators remain as tools that point to better management of patients with SCD, as well as to the prevention of risk factors and their complications. Thus, by clarifying the main factors related to morbidity and mortality of patients with Sickle Cell Disease, it is possible to identify the main points to be addressed as investment items in order to increase survival and reduce premature life losses. However, further studies on the subject are necessary to advance knowledge and improve the quality and life expectancy of this population.

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