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Is Severity Score Associated with Indication for Hematopoietic Stem Cell Transplantation in Individuals with Sickle Cell Anemia?

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MVFP, MCO, ICGM, SK, VR analyzed the data

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Summary

Manifestations of sickle cell disease (SCD) begin early in childhood and cause morbidity and decreased life expectancy. Hematopoietic stem cell transplantation (HSCT) is curative but associated with risk of mortality attributable to the transplant. This risk should be counterbalanced with SCD morbidity and mortality. A severity score using a Bayesian network model was previously validated to predict the risk of death in adult individuals with SCD. We compared severity scores between cohort members with (n=431) and without (n=1632) HSCT indications in the Recipient Epidemiology and Donor Evaluation Study-III (REDS-III) Brazil SCD cohort based on Brazilian Ministry of Health transplant criteria. Scores were not different in adult participants with ≥1 HSCT indication when compared to those with no indication (mean= 0.342 vs. 0.292; median=0.194 vs. 0.183, p=0.354) and ROC curves did not demonstrate an obvious threshold to differentiate participants with or without HSCT indications. Severity score may predict risk of death but does not differentiate HSCT candidates. Current indications should be evaluated to ensure patients with more severe disease who might benefit from HSCT are appropriately identified.

Keywords

sickle cell disease; sickle cell anemia; hematopoietic stem cell transplantation; HSCT; candidates; Bayesian model; severity score; cohort

Introduction

Sickle cell disease (SCD) is a hemoglobinopathy with increasing prevalence, and is considered a global public health problem by the World Health Organization (WHO).[1, 2] Manifestations of SCD begin early in childhood and can progress throughout life, causing significant morbidity with substantial impact on quality of life and decreased life expectancy. A wide spectrum of acute and chronic complications occur and are influenced by genetic, sociodemographic, and environmental characteristics, which can modify outcomes among individuals.[3] The role of the diversity of such modifiers and their influence on severity of the disease is limited.[2]

Newborn screening, early diagnosis, supportive care, penicillin prophylaxis, vaccines, transcranial Doppler (TCD) imaging, and treatment with blood transfusions and hydroxyurea (HU) can improve survival, reduce prevalence of complications, and improve quality of life, yet morbidity and mortality due to SCD remains high. Hematopoietic stem cell transplantation (HSCT) with a matched sibling donor is a curative treatment, but is not available to the majority of individuals with SCD due to lack of donor availability as well as socio cultural and economic barriers.[4] Other emerging treatments such as HSCT with haploidentical or unrelated donors can be curative, but are associated with poorer survival, higher rates of graft failure and increased transplant associated morbidity such as graft vs. host disease (GVHD). Most of these alternative HSCT donor sources as well as promising gene therapies are still considered experimental and being studied in clinical trials.[5]

HSCT using HLA matched sibling donors has been performed in the US, Europe and other countries in more than 1000 people with SCD with favorable results[4] though mortality risk is higher in adults than children. Recently, Eapen showed a lower overall and event free survival in patients ≥13 years old compared to younger children, and also when an alternative HSCT donor such as an unrelated or haploidentical donor was used compared to a related donor.[6, 7] With improved GVHD prevention prophylaxis, new conditioning regimens with minimal toxicity and use of alternative donors are under investigation, the number of transplants and transplant opportunities for patients with SCD is expected to increase. Currently, HSCT indications are established according to published studies on severity of the disease and risk of death due to SCD but can also be based on expert opinion. Indications were described many years ago when alternative donors and current HSCT strategies were not available. The most commonly defined indications for HSCT are stroke, cerebrovascular disease, frequent vaso-occlusive episodes (VOE) and acute chest syndrome (ACS), priapism, severe alloimmunization, avascular necrosis (AVN), retinopathy, pulmonary and kidney disease.[8–12] As patients with classic indications for transplant typically have more severe disease, a severity score measuring the risk of death could serve as a practical tool for periodically assessing candidacy for transplant.

The objective of this study is to calculate the severity scores of participants in a multi-center cohort of Brazilians with SCD, using a previously published Bayesian network-derived score, associated with risk of death and then compare the severity scores between participants with and without an indication for HSCT as defined by the Brazilian Ministry of Health (MoH) criteria. [12, 13] This severity score has been validated in adult populations

with SCD, but not to the same degree in pediatric populations. We estimated the utility of the severity score assessment in adult members of the SCD cohort and conducted an exploratory analysis of the performance of the severity score for pediatric members of the cohort. Our hypothesis is that adult candidates for transplant have higher severity scores than non-candidates, and for pediatric patients that severity score is associated with HSCT indications.

Methods

1. REDS-III Brazil SCD Cohort

The REDS-III SCD cohort is a multicenter study conducted in six cities in Brazilian where individuals with SCD were recruited at routine healthcare visits from 2013–2015 and followed for two years to investigate clinical outcomes. The clinical and genetic ancestry profile of the cohort have been described elsewhere.[14]

2. Identification of cohort participants with an indication for HSCT

We have previously published results of a study that identified and characterized REDS-III participants who had an indication for HSCT according to a Brazilian Ministry of Health (MoH) Ordinance, which was developed by a panel with expertise in SCD.[12]

These criteria included homozygous SS or Sβ0 individuals with at least one of the following: stroke, cerebrovascular disease, more than two alloantibodies while on chronic transfusion therapy (CTT), or one or more of the following despite treatment with hydroxyurea (HU): more than two vaso-occlusive episodes (VOE) or acute chest syndrome (ACS) episodes in the last year, more than one episode of priapism, and avascular necrosis (AVN) of more than one joint.

Exclusion criteria of the MoH Ordinance were cerebral vasculopathy (Moya-Moya) and other comorbidities that could compromise the results of the transplant according to the evaluation and definition of the transplantation team. The Ordinance highlights ages < 16y should be a priority because of the improved survival of transplants in this age (sic). Patients younger than 16 years were defined as children and those 16 or older were considered adults in our analysis because of the original MoH policy. This threshold was chosen because the first MoH policy indicated HSCT was appropriate only for children under 16 years old based on evidence of improved HSCT outcomes in children younger than 16 with thalassemia with less severe iron overload.[9, 11, 15, 16], though the policy was later expanded to include all ages. Therefore, for the current analysis we used <16y and ≥16y age categories based on this Brazilian context. From the 2063 SS/Sβ0 participants included in the REDS-III cohort, 431 (279 adults and 152 children) had at least one indication for transplant.[17]

3. A Bayesian network model to predict the risk of death in SCD

Sebastiani and colleagues developed a Bayesian network model of severity scores to predict the risk of death within 5 years in individuals with sickle cell disease.[13] Data from participants of the US Cooperative Study of Sickle Cell disease (CSSCD) were the primary data source used to construct the model. Twenty-five clinical events and laboratory tests

with hierarchical relationships were included in the model, but a reduced set of sixteen predictive variables sufficient to compute the risk of death was identified: SCD genotype, age, gender, ACS, blood transfusion, pain, priapism, sepsis, avascular necrosis, stroke, systolic blood pressure (SysBP), bilirubin, lactate dehydrogenase (LDH), mean corpuscular volume (MCV), reticulocyte and white blood count (WBC). Patients who died (n=283) were used to compute the risk of death. The model was later validated in two populations of individuals with SCD, one of them had only adults, and the second had 140 participants, mean age 21.4 y ± 14.91. The severity score ranges from 0 (least severe) to 1 (most severe) [13] and it can be obtained through the *Disease severity score calculator* available at: http://bios.ugr.es/dss-calculator. Sebastiani et al. defined scores <0.4 as mild for all ages, moderate when scores ranged from 0.4–0.6 for individuals <40y and from 0.4–0.8 for those >40y, and severe for scores ≥0.6 for individuals ≤40y and >0.8 in those >40y.[18]

4. Severity score applied to REDS-III Brazil participants

Data collected from the enrollment visit of the REDS-III Brazil SCD cohort were used to calculate the severity score (generated by *Bayesware calculator*) for all participants. We compared severity scores between adults with and without a HSCT indication according to Brazilian MoH (described above). The severity scores were also calculated and compared between children with and without HSCT indications.

The calculator uses age ranges of<18y, 18–40, >40y. For the current analysis we used <16y and ≥16 age categories based on the Brazilian context, guided by the MoH Ordinance. In sensitivity analysis, we restricted the severity score calculation to ≥18y to assess the impact of including 16- and 17-year-old patients in the adult analysis.

REDS-III cohort participants with genotypes SS, S-Beta0, SD and S-Quebec-Chori were clustered in the same group (*sickle cell anemia, SCA*) due to their similar severity.[19–23] The calculator has only two options for genotype: SS* and SC. The *SCA* group was identified in the calculator as SS* (apart from SC).

We next measured the sensitivity and specificity of the severity score to predict if participants were a HSCT candidate with Receiver Operating Characteristic (ROC) curves, a graphical plot that illustrates the diagnostic ability of a binary classifier system as its discrimination threshold varies. We investigated if there was a specific severity score threshold to indicate HSCT within REDS-III participants.

We also explored the distribution of severity scores among age groups to compare to the distributions described in other studies.[18, 24]

In order to highlight the similarities and differences between the variables included in the severity score and criteria to define a candidate for transplant, Supplemental chart 1 displays parallel lists of the variables included in each. In addition, all variables included in the severity score were compared between the participants who were or were not transplant candidates by the defined criteria.

5. Statistical analysis

Categorical clinical variables were presented as frequencies and numeric variables as mean +/− standard deviation (median). Numeric variables were assessed for normality using the Shapiro-Wilk test. To evaluate the association between two categorical variables we used Chi-Square and Fisher's exact test. Comparison of numeric variables between two groups was made by using Students t-test for independent samples or Wilcoxon Mann- Whitney test. The Receiver Operating Characteristic (ROC) curve was performed to evaluate the ability of the severity score to identify the cases with at least one HSCT indication. The results were shown as area under the curve (AUC) with respective 95% confidence intervals (CI). The analysis was performed in R version 4.0 and we considered a p value <0.05 as statistically significant.

6. Ethics

The REDS-III Brazil SCD cohort study was approved by national and local Brazilian ethics committees (CONEP and CEP-FMUSP), and the institutional review boards at the University of California San Francisco and Research Triangle Institute, International (the data coordinating center for REDS-III).

Results

Of the 2793 participants included in the REDS-III cohort, 2063 participants with SCA (1090 adults and 974 children) were included in this analysis. The median age was 16 years and the majority had mixed (58%) or black (28%) skin color (the self-report race categories are those used by the Brazilian Institute of Geography and Statistics, *IBGE*). Sociodemographic characteristics are described in Table 1. There were 1,632 participants without indication for transplant (821 adults and 811 children) and 431 with at least one indication (279 adults and 152 children).

There was no significant difference between median severity scores of adults with ≥1 or no HSCT indication. (Table 2) In children, median scores were significantly higher in those without an indication when compared to those with an indication. We illustrated the results in numbers singly in Table 2.

No obvious distinction in severity scores between groups with 0 and ≥1 HSCT indication for transplant was evident as shown in box plots in Figure 1. There was a high number of participants with high severity scores but no indication for transplant (outliers) (159 adults ≥16y and 52 children <16y with score above 0.481). Characteristics of participants without an indication for HSCT are shown in Table 1 of the Supplemental material.

Either for adults or children, the area under the ROC was close to 50%, indicating poor accuracy of the severity score model to define HSCT candidates. A cut point of severity score that could differentiate individuals with and without indication for transplant was not identified. (Figure 2)

Among children (n=973), the frequency of milder severity scores was higher than other scores. In the ages 16 to 40y (n= 914), the distribution of severity scores was not normally

distributed for children or adults. Higher numbers of participants demonstrated extremes of low and high severity scores. The age > 40y (n= 176) group showed a greater number of individuals with higher severity scores. (Figure 3)

The results of the sensitivity analysis restricting to only those 18y or older were not significantly different from results using 16y or older (Supplement Table 2). The comparison of severity scores of participants with and without transplant indication, divided in all ages' groups (<16; 16–40; ≥40y) did not show any difference (Table 3 - Supplemental material).

The profile of participants' variables included in the Disease severity score calculator showed that all variables included in the severity score were significantly different between candidates and non-candidates except for systolic BP and LDH. These data are presented in Table 4 - Supplemental material.

Discussion

We did not find a significant difference between severity scores of adults with or without indication for HSCT. In exploratory analysis, severity scores were higher in children without a transplant indication. Additionally, the ROC curves showed limited ability for the severity score to predict a participant as a candidate for transplant. The objective of our study was to investigate if this score could predict whether an individual with SCA was eligible for a HSCT based on Brazilian MoH criteria. However, the score does not demonstrate a diagnostic ability as a binary classifier to discriminate a threshold or a specific value to determine if a patient is a candidate for transplant or not, thus this score alone cannot be used as a marker to indicate if a patient with SCD is eligible for a transplant. The Bayesian model was developed in the Cooperative Study of SCD cohort participants recruited from 1978–1988 and then validated in two cohorts, and one of them had only adults.[13] It was applied to a group of 50 patients in London in 2009, confirming the positive predictive value of the model, when the scores were compared with severity assessed by clinicians.[25] Belini et al. (2015) also showed a high sensitivity and positive predictive value of the score in a group of 500 patients in Brazil.[24] In our study, we calculated scores for children and adults and hypothesized that patients with indications for transplant would have more severe disease, and therefore higher severity scores compared to patients without any indication. Results of this analysis could be used to clarify the defined HSCT indications as markers of severity and to establish a cut-off score that could indicate transplant for an individual

The reasons why severity scores that predict death do not appear to predict HSCT indication for adults warrant further consideration. Presumably individuals with more severe disease would be the population targeted for HSCT. However, there might be differences between the original cohorts used to define the score and the REDS-III Brazil SCD cohort regarding genetic, sociodemographic, and educational characteristics, as well as access to supportive care, diagnostic tests and medication availability, in particular because the severity score used data collected primarily in the 1980s decades before the REDS-III cohort was established. Current mortality is driven by age and disease progression, with cardiopulmonary complications a leading cause [26] compared to sepsis as a primary cause of morality in prior decades. Another reason might be that indications for transplant are

based on opinions of experts in transplant and SCD who define disease severity by the frequency of severe complications.[9, 10, 12] The Bayesian model does not include only these complications, but instead integrates many clinical and laboratory findings and provides a quantitative estimate of disease severity and risk of mortality.[13]

We found a high number of individuals with very high severity scores without any indication for transplant. We consider these individuals to be outliers. These individuals may have not yet experienced a specific complication defined by MoH as an indication for transplant yet have other disease progression markers or precursors defined to be important for predicting risk of death based on the published score. One important question is whether patients with high severity scores should be considered for HSCT regardless of specific listed indications. Our results suggest that other factors should be considered to determine if a transplant is indicated for a patient, and indications should continue to be evaluated and revised, based on results of emerging HSCT treatment modalities with improving outcomes.[10, 27]

In our study, we found that older patients had higher distribution of more severe scores than younger patients. This result was expected. Increasing age is a variable highly predictive of death in the model.[13] The lack of association between severity scores of older patients with at least one indication for transplant may be due to survivor bias, as patients with severe disease may die before they have manifested an indication for the procedure. Disease mortality should be balanced against the risk of the transplant particularly in adults, who may experience rapid disease progression with severe complications, chronic pain and premature mortality[8] and a HSCT may become an appropriate therapeutic option.[28]

We believe additional tools are needed to identify appropriate candidates in this population because of the lower overall and event-free-survival and substantial rates of toxicity and GVHD in adult HSCT recipients that still occur, especially using alternative donors (such as unrelated and haploidentical donors) and modified conditioning regimens. [29, 30] A dynamic score using variables such as those included in the severity score used in this analysis, measured periodically, to assess degree or rate of change in severity, may better identify high risk individuals who should be considered for curative therapies than currently defined criteria.[4, 30] Ideally this score should also include variables related to quality of life and functional capacity in addition of mortality risks. Additionally, due to the low likelihood of finding a compatible donor for individuals with SCD in national registries, [31, 32] older patients who could benefit from alternative treatments should be identified based on a more sensitive disease severity measurement, so treatment could start as soon as possible. This treatment could involve disease modifying therapies such as regular red blood cell transfusion, hydroxyurea, or recently approved medications such as voxelotor. These treatments may modify some parameters measured by severity score or prevent complications that define transplant criteria. Therefore the accessibility, cost and success rates of disease modifying therapies compared to transplant also have to be considered, and this multifaceted balance is difficult to achieve.

We focused this analysis on adults as the validation of the severity score has been performed in two cohorts, one of them only with adult patients. However, we explored the relationship of the severity score to HSCT indications in our pediatric patients because indications

for HSCT are the same in children and adults and variables included to calculate the score are present in all ages. However, the risk of death in children with SCD is different than adults, and children might not have sufficient mortality to be able to validate the score. Two other scores for children had been constructed using clinical and laboratory variables more specific to pediatric patients,[33, 34] but the Bayesian model has shown to be more specific than expert clinician assessment alone.[13] There is an opportunity to define a comprehensive model for children by identifying complications, genetic markers, and clinical care laboratory value data from early in a patient's life that could better define the severity in this age group. These data may help to define candidates for curative therapy. As discussed by Meier, if a reliable predictive model for severity existed, HSCT (or other curative treatments) could be offered prior to the onset of severe complications, such as vasculopathy and organ damage.[35] Prevention of these morbidities may be especially applicable for children under 13 years old, who have excellent overall and event-free survival after HSCT with a compatible HLA donor.[4, 6, 10, 29, 36]

This study has limitations. The difference of age categorization used in this study and those of Sebastiani and colleagues who developed the severity score. In our analysis we included persons over the age of 16 as adults. Our sample has 135 patients (6.5% of the sample) 16 and 17 years old, therefore this low number of patients did not change the analysis in either of the age groups we used, as the sensitivity analysis did not modify the interpretation of our findings.

In conclusion, in this analysis, we could not define a severity score that establishes a threshold to identify a patient who is a candidate for HSCT transplant, therefore, severity scores measured at one point in time cannot function as a measure to indicate HSCT for SCD patients according to Brazilian MoH criteria. As the validated severity score has been shown to predict death, we therefore question if the current criteria adequately capture all individuals with SCD with severe disease who should be considered for HSCT.

We believe severity scores could be useful if regularly measured to predict the risk of death, because the status of patients may change over time. Pediatric patients may not have had time to develop indications for transplant, but information on severity scores tracked over time as part of clinical care can inform treating physicians of disease progression short of frank indications for HSCT. Similarly, as adults have increasing disease severity with increasing age, evaluation of severity scores can indicate when curative treatment to avoid major morbidity or mortality should be considered. For both pediatric and adult population further investigation of the trajectory of severity scores measured at different times is warranted. Perhaps the rate of change in severity score may prove to be a useful tool for identifying candidates for HSCT.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Authors of the manuscript "How Ancestry Influences the Chances of Finding Unrelated Donors: An Investigation in Admixed Brazilians": Kelly Nunes, Vitor R. C. Aguiar, Marcio Silva, Alexandre C. Sena, Danielli C. M. de Oliveira, Carla L. Dinardo, Fernanda S. G. Kehdy, Eduardo Tarazona-Santos, Vanderson G. Rocha, Anna Barbara F. Carneiro-Proietti, Paula Loureiro, Miriam V. Flor-Park, Claudia Maximo, Shannon Kelly, Brian Custer, Bruce S. Weir, Ester C. Sabino, Luıs Cristovão Porto, Diogo Meyer

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References

1. Organization WH. Fifty-ninth World Health Assembly: resolutions and decisions, annexes Geneva: World Health Organization; 2006.
2. Piel FB, Steinberg MH, Rees DC. Sickle Cell Disease. N Engl J Med 2017;377(3):305.
3. Habara A, Steinberg MH. Minireview: Genetic basis of heterogeneity and severity in sickle cell disease. Exp Biol Med (Maywood) 2016;241(7):689–96. [PubMed: 26936084]
4. Gluckman E Sickle cell disease: an international survey of results of HLA-identical sibling hematopoietic stem cell transplantation. Blood 2017;129(11):1548–56. [PubMed: 27965196]
5. Houwing ME, de Pagter PJ, van Beers EJ, Biemond BJ, Rettenbacher E, Rijneveld AW, et al. Sickle cell disease: Clinical presentation and management of a global health challenge. Blood Rev 2019;37:100580. [PubMed: 31128863]
6. Eapen M, Brazauskas R, Walters MC, Bernaudin F, Bo-Subait K, Fitzhugh CD, et al. Effect of donor type and conditioning regimen intensity on allogeneic transplantation outcomes in patients with sickle cell disease: a retrospective multicentre, cohort study. Lancet Haematol 2019;6(11):e585–e96. [PubMed: 31495699]
7. Brazauskas R, Scigliuolo GM, Wang HL, Cappelli B, Ruggeri A, Fitzhugh CD, et al. Risk score to predict event-free survival after hematopoietic cell transplant for sickle cell disease. Blood 2020;136(5):623–6. [PubMed: 32518950]
8. Platt OS, Brambilla DJ, Rosse WF, Milner PF, Castro O, Steinberg MH, et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. N Engl J Med 1994;330(23):1639–44. [PubMed: 7993409]
9. Walters MC, Patience M, Leisenring W, Eckman JR, Scott JP, Mentzer WC, et al. Bone marrow transplantation for sickle cell disease. N Engl J Med 1996;335(6):369–76. [PubMed: 8663884]
10. Angelucci E, Matthes-Martin S, Baronciani D, Bernaudin F, Bonanomi S, Cappellini MD, et al. Hematopoietic stem cell transplantation in thalassemia major and sickle cell disease:

indications and management recommendations from an international expert panel. Haematologica 2014;99(5):811–20. [PubMed: 24790059]

11. Simões BP, Pieroni F, Costa T, Barros GN, Darrigo G, Grecco CS, et al. Allogenic bone narrow transplantation in sickle-cell diseases. Rev Assoc Med Bras (1992) 2016;62 Suppl 1:16–22.
12. Md Saúde. PORTARIA CONJUNTA No 05, DE 19 DE FEVEREIRO DE 2018. ANEXO: PROTOCOLO CLÍNICO E DIRETRIZES TERAPÊUTICAS DA DOENÇA FALCIFORME Brasilia 2018.
13. Sebastiani P, Nolan VG, Baldwin CT, Abad-Grau MM, Wang L, Adewoye AH, et al. A network model to predict the risk of death in sickle cell disease. Blood 2007;110(7):2727–35. [PubMed: 17600133]
14. Carneiro-Proietti ABF, Kelly S, Teixeira CM, Sabino EC, Alencar CS, Capuani L, et al. Clinical and genetic ancestry profile of a large multi-centre sickle cell disease cohort in Brazil. British Journal of Haematology 2018.
15. Portaria 1321 Transplante de células-tronco hematopoiéticas alogênico do tipo mieloablativo no tratamento da doença falciforme, (2015).
16. Lucarelli G, Galimberti M, Polchi P, Angelucci E, Baronciani D, Durazzi S. Bone Marrow Transplantatin in Thalassemia. The Pesaro experience. Haematologica 1989;74:266–70. [PubMed: 2512212]
17. Flor-Park MV, Kelly S, Preiss L, Custer B, Carneiro-Proietti ABF, Araujo AS, et al. Identification and Characterization of Hematopoietic Stem Cell Transplant Candidates in a Sickle Cell Disease Cohort. Biology of Blood and Marrow Transplantation 2019;25:2103–9. [PubMed: 31229639]
18. Sebastiani P, Solovieff N, Hartley SW, Milton JN, Riva A, Dworkis DA, et al. Genetic modifiers of the severity of sickle cell anemia identified through a genome-wide association study. Am J Hematol 2010;85(1):29–35. [PubMed: 20029952]
19. JFJr K, JO P, HC K, WA S. Life-threatening complications in a child with hemoglobin SD-Los Angeles disease. Hemoglobin 1984;8(3):203–13. [PubMed: 6547933]
20. RG S, S U, JB A, WC L, RT J, B B. Hemoglobin D Los Angeles in Two Caucasian Families: Hemoglobin SD Disease ans Hemoglobin D Thalassemia. Blood 1968;32(2).
21. Sturgeon P, HA I, WR B. Clinical Manifestations of Inherited Abnormal Hemoglobins I. The Interactions of Hemoglobin-S with Hemoglobin-D. Blood 1955;X(5).
22. VN T, CM B, Luo H-y, DHK C, MM H. Sickle Cell Disease caused by Hemoglobin S/Québec-CHORI: Treatment with hydroxyurea and response. Pediatric Blood and Cancer 2007;49(2).
23. HE W, BH L, Y B, al e. Sickle Cell Disease in a Patient with Sickle Cell Trait and Compound Heterozygosity for Hemoglobin S and Hemoglobin Quebec-Chori. New England Journal of Medicine 1991;325:1150–4. [PubMed: 1891024]
24. Belini Junior E, Silva DGnH, Torres LdS, Okumura JsV, Lobo CLdC, Bonini-Domingos CR. Severity of Brazilian sickle cell disease patients: Severity scores and feasibility of the Bayesian network model use Blood Cells, Molecules and Diseases 2015;54:321–7.
25. ANOOP P, BEVAN DH, CHAKRABARTI S. Usefulness and limitations of Bayesian network model as a mortality risk assessment tool in sickle cell anemia American Journal of Hematology 2009:312–3. [PubMed: 19338040]
26. Payne AB, Mehal JM, Chapman C, Haberling DL, Richardson LC, Bean CJ, et al. Trends in Sickle Cell Disease-Related Mortality in the United States, 1979 to 2017. Ann Emerg Med 2020;76(3S):S28–S36. [PubMed: 32928459]
27. Hulbert ML, Shenoy S, Leonard A, Tisdale JF, Gluckman E, Cappelli B, et al. Hematopoietic stem cell transplantation for sickle cell disease: Progress and challenges. Pediatr Blood Cancer 2018;65(9):e27263. [PubMed: 29797658]
28. Krishnamurti L, Neuberg DS, Sullivan KM, Kamani NR, Abraham A, Campigotto F, et al. Bone marrow transplantation for adolescents and young adults with sickle cell disease: Results of a prospective multicenter pilot study. Am J Hematol 2019;94(4):446–54. [PubMed: 30637784]
29. Cappelli B, Volt F, TozattoMaio K, Scigliuolo G, Ferster A, Dupont S, et al. Risk factors and outcomes according to age at transplantation with an HLA-identical sibling for sickle cell disease. Haematologica 2019;104:e543. [PubMed: 31018975]

30. Walters MC, De Castro LM, Sullivan KM, Krishnamurti L, Kamani N, Bredeson C, et al. Indications and Results of HLA-Identical Sibling Hematopoietic Cell Transplantation for Sickle Cell Disease. Biol Blood Marrow Transplant 2016;22(2):207–11. [PubMed: 26500093]

31. Nunes K, Aguiar V, Silva M, Sena A, de Oliveira D, Dinardo D, et al. How Ancestry Influences the Chances of Finding Unrelated Donors: An Investigation in Admixed Brazilians. Frontiers of Immunology 2020;11.

32. Gragert L, Eapen M, Williams E, Freeman J, Spellman S, Baitty R. HLA match likelihoods for hematopoietic stem-cell grafts in the U.S. registry N Engl J Med 2014;371:339–48.

33. Development Day S. and evaluation of a Sickle Cell Disease Assessmtne Instrument. Pediatr Nurs 2004;30:451–8. [PubMed: 15704592]

34. van den Tweel XW, van der Lee JH, Heijboer H, Peters M, Fijnvandraat K, Sebastiani P, et al. Development and validation of a pediatric severity index for sickle cell patients. A network model to predict the risk of death in sickle cell disease. Am J Hematol 85. United States: © 2010 Wiley-Liss, Inc.; 2010. p. 746–51. [PubMed: 20806231]

35. Meier ER, Fasano RM, Levett PR. A systematic review of the literature for severity predictors in children with sickle cell anemia. Blood Cells Mol Dis 2017;65:86–94. [PubMed: 28185829]

36. Bernaudin F. Why, Who, When, and How? Rationale for Considering Allogeneic Stem Cell Transplantation in Children with Sickle Cell Disease Journal of Clinical Medicine 2019;8.

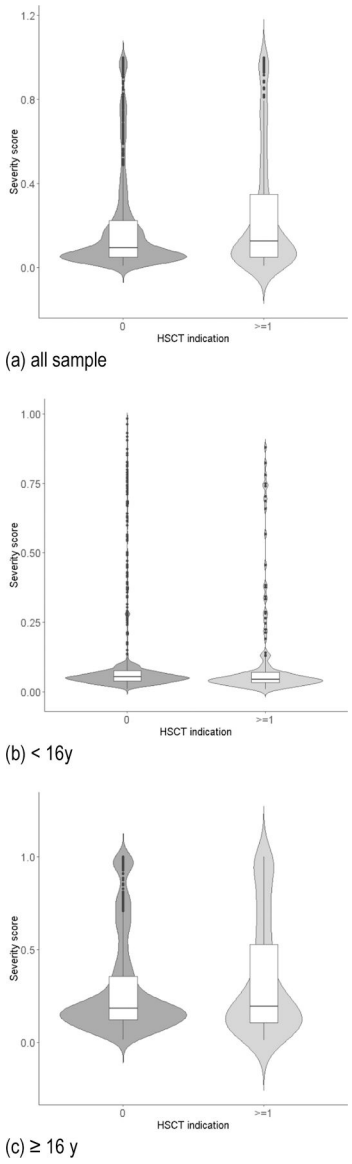
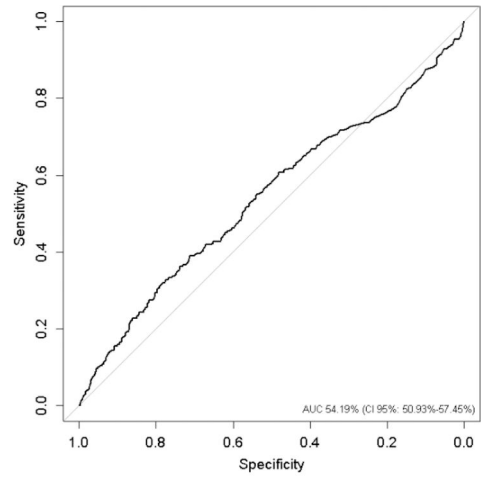
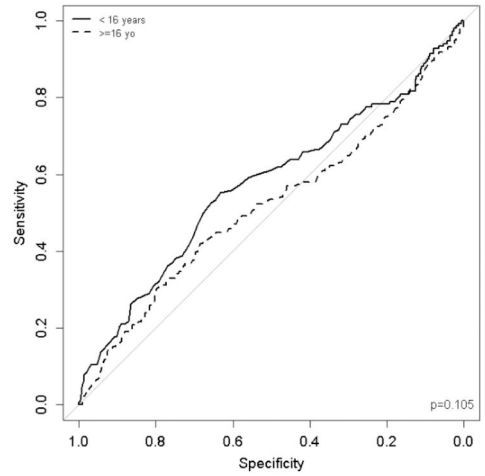


Figure 1.

Severity score distribution of 2063 REDSIII *SCA* individuals, divided into two groups: patients with 0 and ≥ 1 HSCT indication and (a) for all sample; (b) for patients with < 16 y, (c) for patients ≥ 16 y. P value refers to Wilcoxon Mann Whitney test



(a)All ages



(b) Age groups: _____ < 16y
- - - - - - ≥16y

Figure 2.

ROC curve for severity scores of 2063 REDSIII individuals with 0 and≥ 1 HSCT indication (a) all ages (b) age groups: < 16y (N= 973); ≥16y (N=1090). For age groups, patients with < 16 years AUC 57.4% (CI 95% 51.98%-62.82%) and patients ≥ 16 years old AUC 51.86% (CI 95%: 47.65%-56.07%).

Cut point (all sample): score 0.1075 (mean sensitivity and specificity 54.37%)

Cut point (<16y): score 0.0475 (mean sensitivity and specificity 59.24%)

Cut point (≥16y): score 0.1905 (mean sensitivity and specificity 53.23%)

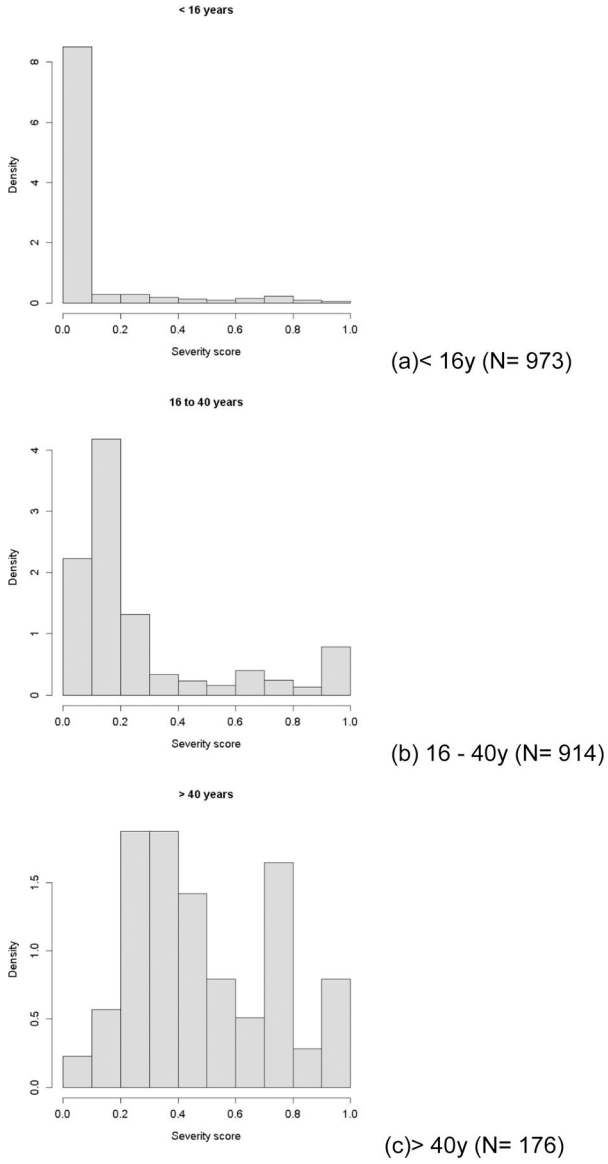


Figure 3.
Distribution of severity scores of 2063 REDSIII *SCA* individuals by age groups

Table 1.

Sociodemographic characteristics of 2063 REDSIII individuals with SCA with 0 and ≥1indication for HSCT

Characteristics	0 HSCT indication N = 1,632	≥1 HSCT indication N = 431	P value	Total N = 2,063
Gender			<0.001[C]	
F	895 (55)	197 (46)		1,092
M	737 (45)	234 (54)		971
Age[*]	19 ± 13(15)	22 ± 12 (20)	<0.001[W]	19 ± 13 (16)
<16	821 (50)	152 (35)		973 (47)
16–40	675 (41)	239 (56)		914 (44)
>40	136 (8)	40 (9)		176 (9)
Skin color[**] (n=2,059)			0.799[C]	
Black	454 (28)	123 (29)		577
Mixed	948 (58)	251 (58)		1,199
White	167 (10)	37 (9)		204
Unknown	62 (4)	17 (4)		79
SCD type			0.392[C]	
SS	1,549 (95)	414 (96)		1,963
Other severe genotypes[***]	83 (5)	17 (4)		100
Marital status (n=953[****])			0.011[C]	
Single	423 (59)	156 (65)		579
Married/Living together	264 (37)	68 (28)		332
Separated/divorced	20 (3)	15 (6)		35
Widower	6 (1)	1 (1)		7
Education (n=1,834[****])			0.448[C]	
Incomplete elementary/ Adult's literacy or less	626 (44)	177 (42)		803
Completed elementary	271 (20)	74 (18)		345
High school/ technical course	430 (30)	144 (34)		574
Graduation / Post-graduation	89 (6)	23 (6)		112
Monthly income[*****] (n=1,990[****])			0.374[C]	
< R$ 700.00	304 (19)	64 (16)		368
Between R$ 700 and R$ 1,400	927 (59)	242 (60)		1,169
Between R$ 1,400 and R$ 3,000	286 (18)	83 (20)		369
> R$ 3,000	67 (4)	17 (4)		84
Hemocenter			<0.001[C]	
HBH	361 (22)	140 (32)		501
JFO	162 (10)	29 (7)		191
MOC	212 (13)	24 (6)		236
HEMOPE	371 (23)	104 (24)		475
HEMORIO	466 (28)	111 (26)		577
HCFMUSP	60 (4)	23 (5)		83

Values are N (%) unless otherwise defined; age presented as mean in years ± 2SD (median);

*
age (y), N (%)

**
self-declared skin color is preferred in Brazilian Census instead of race;

***
other severe genotypes: 86 SB0, 7 SD, 1 S-Quebec-Chori, 2 SC, 2 SB+, 2 SB+ severe;

****
some data were not obtained from all patients, percentages are related to categories;

*****
exchange conversion in 2014 related to BRL and USD: 1 BRL (Reais) = .43 USD; Marital status only for adults ≥ 18y; HBH indicates Hemocenter of Belo Horizonte; JFO, Hemocenter of Juiz de Fora, HEMORIO, Hemocenter of Rio de Janeiro; HEMOPE, Hemocenter of Pernambuco; HCFMUSP, Hospital das Clínicas- Faculdade de Medicina da USP, Instituto da Criança

Table 2.

Comparison between severity scores of REDSIII individuals with SCA with and without an indication for HSCT

Age	0 HSCT Indication	≥1 HSCT Indication	P value
< 16y	0.111 ± 0.176 (0.053)	0.112 ± 0.183 (0.045)	0.004
≥16y	0.292 ± 0.263 (0.183)	0.342 ± 0.308 (0.194)	0.354

Data presented as mean ± standard deviation (median). P values refer to Wilcoxon Mann-Whitney test.