Development and validation of a pediatric severity index for sickle cell patients

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There is no instrument to measure severity of sickle cell disease (SCD) in pediatric patients that is generally accepted. The aim of this study was to develop and validate a severity index for SCD in children. We developed an index consisting of 12 items and tested its validity of the index using data from 92 children. We tested whether different scores were obtained for patients classified by severity both subjectively and objectively by a partially validated existing index. Furthermore, we tested whether the index could differentiate patients classified according to genotype or the number of α-gene deletions and evaluated whether the score on the index was correlated with the average number and days of hospitalizations/year, age and a risk of death score. We explored the effect of three different weighting systems (Score A, B, and C) to summarize these items. All weightings demonstrated a significant difference between the scores of mild, moderate, and severely affected patients, as classified by a subjective rating or with an existing index ($P < 0.01$). The index clearly differentiated patients by genotype ($P < 0.01$) or α-gene deletions ($P < 0.01$). The correlation with hospitalization was moderate. Age and the risk of death score were weakly associated with the pediatric severity index for SCD. This is the first pediatric SCD severity index that was developed and validated using modern clinimetric methodology. The validity and reliability of this index should be further evaluated in a prospective study including a larger cohort, preferably diagnosed at birth. Am. J. Hematol. 85:746–751, 2010. © 2010 Wiley-Liss, Inc.

Introduction

Although sickle cell disease (SCD) is caused by a single missense mutation in the β-globin gene, the clinical picture in SCD patients is heterogeneous. Patients with a severe clinical course suffer from recurrent painful vaso-occlusive crises, develop irreversible organ damage at an early age, and may die prematurely [1]. At the other end of the spectrum, there are patients who have normal life expectancy with relatively few complications [2,3].

The phenotype in patients with SCD is determined by the interaction of both genetic and environmental factors, of which some have been identified [1,4–6]. It is important to increase our understanding of factors that contribute to a severe clinical course. Knowledge of these determinants may help to unravel the pathophysiological mechanisms underlying the disease process, identify novel targets for therapeutic interventions, and enhance patient care.

Studies of determinants of disease severity may be performed efficiently if patients can already be classified as having mild or severe disease during childhood, thereby limiting follow-up time. Early classification is based on the assumption that disease severity is a characteristic of the individual that is relatively constant over time. Since children rarely manifest irreversible organ damage, a severity index that is specifically aimed at this population is needed. At present such an index does not exist.

A systematic literature review of all disease severity assessment instruments (indices) for SCD revealed that only four of the 30 identified indices were partially validated [7–9]. No fully validated indices for a pediatric age range were found.

The aim of this study was to develop and validate a severity assessment instrument for SCD in children. We define the concept of severity as "the rate and extent of reversible and irreversible damage to organs brought on by the SCD process, resulting in impairment requiring medical intervention." The ultimate goal is to develop and reach international consensus on an instrument which will serve as an outcome measure in etiological studies of SCD severity in children.

Methods

Development of a severity score. Item selection was based on a pool of 51 items retrieved from a systematic review of all disease severity assessment instruments for SCD (unpublished work). Items from this pool were rejected if the item was not applicable to children, nonspecific for SCD or confounded. An example of a confounded item is the age at diagnosis, which is determined by several other factors beside the disease severity, such as the presence of a neonatal screening program and accessibility of medical care. The final index consists of 12 items, with 6 items regarding cumulative lifetime incidence of organ damage, 2 items concerning the number of recurrences of SCD related complications over a period of 2 years and 4 laboratory items (Table I).

Definition of the items.

Cumulative lifetime incidence.

1. Bone necrosis (avascular) of the hip and/or shoulder: Pain in hip and/or shoulder and abnormalities of the hip and/or shoulder confirmed by X-ray or MRI.
2. Cerebral infarcts or vasculopathy.

Cerebral infarcts. Acute reduction or cessation of the cerebral blood flow, observed by MRI or CT-scan, resulting in focal neurological impairment lasting more than 24 hrs or without focal neurological impairment (so-called "silent infarcts").

Cerebral vasculopathy. Stenosis or occlusion of the cerebral arteries documented by MRA. MRA was performed in children with a velocity of >200 cm sec^{-1} measured by transcranial duplex ultrasound (TCD).

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Conflict of interest: Nothing to report

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Received for publication 26 October 2009; Revised 21 July 2010; Accepted 22 July 2010

Am. J. Hematol. 85:746–751, 2010.

Published online 28 July 2010 in Wiley Online Library (wileyonlinelibrary.com).
DOI: 10.1002/ajh.21846

TABLE I. The Items of the Severity Index With Different Weighting Systems

	Items	Classification	Score A Points (max 20)	Score B Points (max 47)	Score C Points (max 285)
Lifetime cumulative incidence					
1.	Bone necrosis (avascular)	if present	1	1	10
2.	Cerebral infarcts or vasculopathy	if present	1	10	50
3.	Hepatic sequestration (acute)	if present	1	10	50
4.	Pneumococcal meningitis/septicemia	if present	1	10	50
5.	Priapism	if present	1	1	10
6.	Splenic sequestration (acute)	if present	1	10	50
Number of recurrences over past 2 years					
1.	Acute chest syndrome	absent; present OR ≥ 2 over a period of 2 years	0; 1	0; 1	0; 10; 20
2.	Painful crisis	absent; present OR ≥ 2 over a period of 2 years	0; 1	0; 1	0; 5; 10
Laboratory values					
1.	Hemoglobin (g/dl)	If ≤ 6.6 g dl^{-1}	1	1	5
2.	HbF (%)	If $\leq 3.0\%$	1	1	5
3.	LDH	If > 700 U l^{-1}	1	1	5
4.	Leucocytes (10E9/l)	If $\geq 15.2 \times$ 10E9/l	1	1	5

3. Hepatic sequestration (acute): Acute reduction of hemoglobin >3.2 g dl^{-1} compared to hemoglobin values in the stable situation, combined with acute enlargement of the liver.
4. Pneumococcal septicemia and/or meningitis: Pneumococcal septicemia and/or meningitis confirmed by respectively culture of blood and/or cerebral spinal fluid.
5. Priapism: Sustained, painful, and unwanted erection of the penis that is the result of either increased arterial inflow (i.e., high flow) or, more commonly, the failure of venous outflow (i.e., low flow), resulting in blood trapping within the erectile bodies [10] for which intervention in the hospital was necessary.
6. Splenic sequestration (acute): Acute reduction of hemoglobin >3.2 g dl^{-1} compared to hemoglobin values in the stable situation, combined with acute enlargement of the spleen.

Cumulative incidence over a period of 2 years.

7. Acute chest syndrome: Presence of a new pulmonary infiltrate on chest X-ray film and/or a defect on radionuclide imaging of the chest or abnormalities on spiral CT-scan, combined with acute respiratory illness [8,11].
8. Painful crisis: Pain in the arms and legs, back, abdomen, chest, or skull that lasts for at least 2 hrs, leading to hospital admission and attributable to SCD [8].

Weighting of the items. Three different weighting systems to summarize the items of the severity index were used (Table I). First, all items were summed with an equal weight of 1, leading to Score A. Second, acute life-threatening events and neurological complications were assigned more weight, receiving a score of 10, with all other items assigned a score of 1 (Score B). Finally, items were weighted according to the severity of the different complications and the frequency of occurrence, ranging from 5 to 50 points (Score C). Both Scores B and C attributed the highest score (respectively, 10 and 50 points) to acute life threatening events or complications associated with major sequelae (i.e., pneumococcal septicemia and/or meningitis, acute hepatic sequestration, acute splenic sequestration, cerebral infarction, or vasculopathy). Although avascular bone necrosis and priapism are considered to be severe complications as well, they do not lead immediately to acute life threatening events. We therefore did not assign the maximum score of 10 for the presence of each of these items. Five points were attributed to laboratory values.

In Score C the frequency was taken into account by attributing a higher score to episodes of acute chest syndrome and painful crisis that occurred more than once over a period of 2 years. As recurrent episodes of acute chest syndrome are associated with sickle cell chronic lung disease and increased mortality [12,13], a larger weight was attributed to this complication. Cut-off values to define abnormal laboratory parameters were obtained by using the upper tenth percentile (leukocytes, LDH) or lower tenth percentile (Hemoglobin, HbF) of the values obtained in this study population.

Study population, management, and data collection. The data used to validate the index were derived from patients aged 0–18 years who were born and diagnosed with SCD (HbSS, HbSC or HbS-β-thalassemia) in the Netherlands, were seen at least twice a year at the outpatient clinic of the study center (tertiary referral hospital) and had been followed for a period of more than 2 years. Patients born outside the Netherlands were excluded to reduce potential information bias. Information on "lifetime cumulative incidence" is more likely to be missing in this group. In the study center all patients receive penicillin prophylaxis until the age of 12 years in combination with 5-yearly pneumococcal vaccination. Transcranial duplex ultrasound (TCD) is performed twice a year in children with HbSS/HbS-β^0-thalassemia and HbS-β^+-thalassemia from the age of 4 to 12 years and once every year in older children. From the age of 15 years onward all patients are screened by cardiac ultrasound and ophthalmologic examination.

Data on the cumulative incidence of organ damage and the number of recurrences of SCD related complications were retrieved from patient records over life-time and entered into a database. The number of recurrences of SCD-related complications was documented over the last two observation years or over a period of 2 years before the start of hydroxyurea therapy or regular blood transfusions. Laboratory values were taken from the outpatient clinic, when patients were in a stable phase, not using hydroxyurea and at least 4 months after the last blood transfusion. The percentage of fetal hemoglobin was assessed after the age of 2 years. If more than one laboratory value was available during a stable phase over a period of 1 year, the average of these values was taken.

All patients in the study were classified according to severity by a subjective expert classification and by the "SCD Assessment Instrument" (SCDAI) described by Day [8] and we calculated the risk of death score published by Sebastiani [14].

The subjective expert classification was performed by two experienced pediatric hematologists (HH and MP), who independently classified all patients into three categories (mild, moderate, severe) based on their experience with these patients and information from the patient files before the current index was made. Any disagreement between the two experts was discussed and consensus was reached on final classification of the patient. The "SCD Assessment Instrument" (SCDAI) consists of the number of painful episodes and the number of acute chest syndrome episodes over a period of 2 years. Its content validity, inter-rater reliability, and test-retest reliability were found to be sufficient [8]. We collected data on the number and days of all hospitalizations for SCD-related complications from the first visit to the hospital for SCD until the day of entering these data into a database and divided these by the number of observation years. The risk of death score consists of 16 items (both clinical events and laboratory tests) predicting the risk of death within 5 years. The predictive value of the death risk score was validated in two unrelated sets of patients [14].

Score validity. We assessed the validity of our index according to generally accepted criteria [15]. To assess if the Scores A, B, and C relate to other measures of the same concept, we formulated eight hypotheses. First, we expected the scores to be incrementally different for the three patient groups (mild, moderate, and severe) that were identified by the experts, with the highest score for the severe patient group. Second, we expected the scores to be incrementally different in accordance with the SCDAI score [8]. The third and fourth hypothesis specified that the scores would distinguish disease severity based on genotype (patients with HbSS/HbS-β^0-thalassemia having higher scores than those with HbSC/HbS-β^+-thalassemia) and/or number of α-gene deletions (lower scores in patients with one or more α-gene deletions), respectively. For all hypotheses, a P-value <0.01 was expected. The fifth and sixth hypotheses stated that there would be a positive correlation between the

TABLE II. Occurrence of Complications in 92 Patients

			HbSS/HbS-β^0-thalassemia (n = 68)		HbSC/HbS-β^+-thalassemia (n = 24)	
	No. of patients	No. of complications	No of complications	% of patients with complication	No of complications	% of patients with complication
Number of organ damage complications (lifetime cumulative incidence)						
Bone necrosis (avascular)		1	0	0	1	4
Cerebral infarction (asymptomatic)		3	3	4	0	0
Cerebral infarction (symptomatic)		2	2	3	0	0
Cerebral vasculopathy (stenosis/occlusion)		6	6	9	0	0
Hepatic sequestration (acute)		2	2	3	0	0
Pneumococcal meningitis/septicemia		4	3	4	1	4
Priapism		1	1	2	0	0
Splenic sequestration (acute)		5	5	7	0	0
Patients with $\geq$ 1 organ damage complications	36	57	28	41	8	33
Number of other SCD related complications (cumulative incidence over the last 2 years)						
Acute chest syndrome	8	11	8	12	0	0
Painful crisis	24	35	20	29	4	17
Patients with $\geq$ 1 other SCD related complications	32	51	28	41	4	17
Patients with $\geq$ 1 organ damage and/or other SCD related complications	56	108	45	66	11	46

scores and the average number of hospital admission days for sickle cell related complications per year and between the scores and the average number of hospitalizations for sickle cell related complications per year (Spearman's $\rho > 0.4$). Only hospital admissions for sickle cell related complications, as described in our index, were included in the analysis.

The seventh and eight hypotheses stated that there would be a positive correlation between the scores and age, between the scores and the risk of death score (Spearman's $\rho > 0.4$).

Statistics. The inter-rater agreement of the experts was assessed by weighted kappa (κ). Higher the κ value, the stronger is the agreement of the experts [16]. The Kruskal-Wallis test was used to test differences between the scores of the groups as classified by the experts. The Mann-Whitney *U* test was used for differences between the scores for groups as classified by the SCDAI, distinction between genotype and number of α-gene deletions, respectively. The fifth (higher scores in children with a larger number of hospital admission days/year), the sixth (higher scores in children with a larger number of hospitalizations/year), the seventh (higher scores in older children) and the eighth hypothesis (higher scores in children with a greater risk of death within 5 years) were tested by Spearman's correlation coefficient.

Results

Patient characteristics

This study population consisted of 92 patients (68 HbSS/HbS-β^0-thalassemia, 24 HbSC/HbS-β^+-thalassemia). The median age at the time of data assembly was 9.7 years (range 2.7–18.6 years); 58% was male.

Twenty-nine (32%) patients scored "0" on all three severity indices. There was no difference in age between this group (mean age 9.1 ± 3.5 years) and the patients who scored 1 or higher on the severity indices (mean age 10.4 ± 4.7 years).

Altogether, 108 complications had occurred in 56 (60%) patients (Table II). Seven (8%) patients only scored on laboratory values. Painful crisis was the most common complication. The following complications occurred only in HbSS/HbS-β^0-thalassemia patients: acute hepatic and splenic sequestration, central nervous system abnormalities, priapism, and acute chest syndrome.

Validity

Table III shows the Scores A, B, and C for the entire study population and for different subgroups classified in four ways. The patients were classified according to severity by experts and according to the SCDAI. The weighted κ value for inter-rater reliability of the severity classification by the two experts (pediatric hematologists) was 0.52, which indicates moderate agreement [16]. Furthermore, patients were classified based on their genotype and on the deletion of α-genes.

The Scores A, B, and C were significantly different for the three severity categories classified by the experts ($P < 0.01$, Fig. 1) and for the two severity categories of the SCDAI ($P < 0.01$). There was a significant difference in Scores A, B, and C for subgroups of patients classified according to genotype ($P < 0.01$). Patients with the severe genotype (HbSS/HbS-β^0-thalassemia) scored higher than patients with the mild genotype (HbSC/HbS-β^+-thalassemia) on Scores A, B, and C (see Fig. 2). Patients with one or two α-gene deletions scored lower than those without α-gene deletions on Scores A, B, and C. The correlation between Scores A, B, and C and the number of hospital admission days/year and the number of hospitalizations/year was moderate and statistically significant (Spearman's correlation coefficient for number of hospital admission days/year of 0.51 ($P < 0.01$), 0.53 ($P < 0.01$), and 0.55 ($P < 0.01$), respectively (see Fig. 3) and for the number of hospitalizations/year of 0.40 ($P < 0.01$), 0.49 ($P < 0.01$), and 0.51 ($P < 0.01$), respectively). There was no significant correlation between Scores A, B, and C and age (Spearman's correlation coefficient of 0.16, 0.18, and 0.19, respectively). The correlation between Scores A, B, and C and the risk of death score was significant but weak (Spearman's correlation coefficient of 0.31 ($P < 0.01$), 0.29 ($P < 0.01$), and 0.26 ($P < 0.05$), respectively; see Fig. 4). Of the three different weighting systems, Score C distinguished best among patient groups, as is evident from Figures 1 to 2.

Discussion

This is the first SCD severity index, exclusively aimed at children, that was developed using a transparent methodology. The index adequately differentiated between patient groups classified for severity by experts and by an existing index (SCDAI). Moreover, the index differentiated between patients classified by genotype (HbSS/HbS-β^0-thalassemia versus HbSC/HbS-β^+-thalassemia) or by the number of alpha-gene deletions. There was a moderate correlation between the scores and the number of hospital admission days/year and the number of hospitalizations/year. There was no significant correlation between the scores from the index and age and the correlation with the risk of death score was very weak. Score C, calculated with the most refined weighting system differentiating between items according to severity and the frequency of occurrence of complications, discriminated best between patient groups.

Contrary to our expectation we did not find a higher severity score in older children. This lack of association between age and severity has also been observed by Cameron et al., who reported no correlation between their

TABLE III. Scores of Indices A, B, and C for Patients Classified in Four Ways

	Number of patients	Score A; Median score (range) 1 (0–7)		Score B; Median score (range) 1 (0–23)		Score C; Median score (range) 5 (0–130)		
Total group	92	Median	IQR	Median	IQR	Median	IQR	*P*
Classification according to severity by experts[a]								<0.01
mild	58	1	0–1	1	0–1	5	0–6	
moderate	22	2	1–3	3	1–3	15	10–23	
severe	12	2	1–4	11	1–13	60	8–70	
Classification according to severity by SCDAI[b]								<0.01
mild/moderate	87	1	0–2	1	0–2	5	0–15	
severe	5	4	3–6	13	7–20	70	50–108	
Classification according to genotype[b]								<0.01
HbSS/HbS-β^0-thalassemia	68	1	1–3	1	1–3	10	5–20	
HbSC/HbS-β^+-thalassemia	24	0	0–1	0	0–1	0	0–5	
Classification according to presence of alpha-thalassemia[b]								<0.01
No alpha-gene deletion	56	1	1–3	1	1–3	10	5–20	
≥1 alpha-gene deletion	28	0	0–1	0	0–1	0	0–5	
missing data	8	2	1–3	2	1–3	10	3–15	

Patients were classified according to severity by**:** (1) according to severity by experts, (2) according to severity by an existing score (SCDAI), (3) by genotype (β-globin gene mutation); and (4) by the presence or absence of an alpha-gene deletion as described in the Methods section. For each subgroup of patients we calculated the median severity score and interquartile range for index A, B, and C for each subgroup. We then tested for all three indices (A, B, and C) whether there were differences in scores of the three severity subgroups identified by experts and whether patients classified as mild/moderate by the SCDAI had scores that were different from patients classified as severe by the SCDAI. Similarly differences in scores between patient groups classified by genotype (β-globin gene mutation or alpha-gene deletion) were tested.

[a] Kruskal-Wallis test.

[b] Mann-Whitney U test.

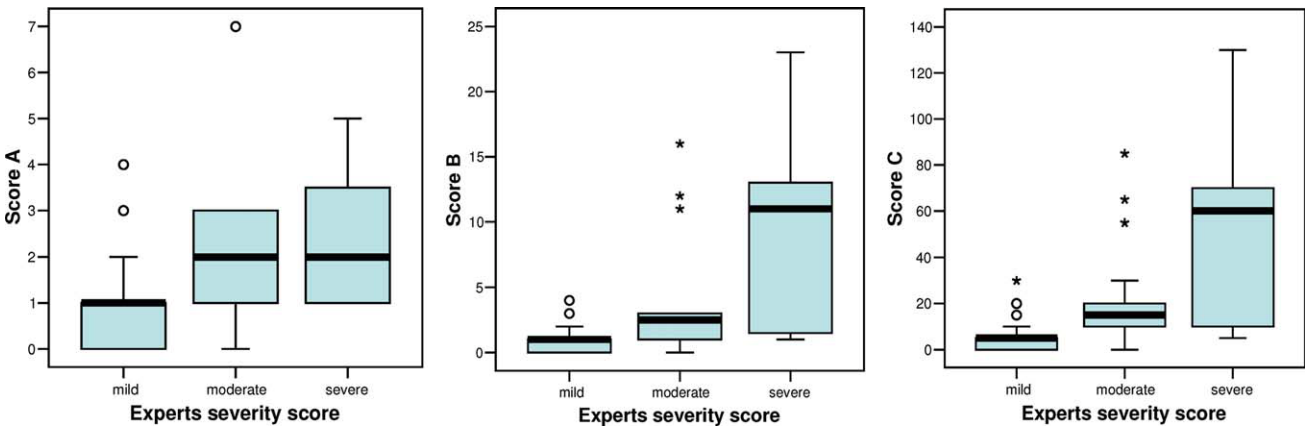

Figure 1. Results of Index A, B, and C for patients of three severity categories classified by experts (Hypothesis 1). Each boxplot shows the median, interquartile range (box length) and extreme values within a category. Circles: Cases with values between 1.5 and 3 box lengths from upper or lower edge of the box. Stars: Cases with values more than 3 box lengths from upper or lower edge of the box. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

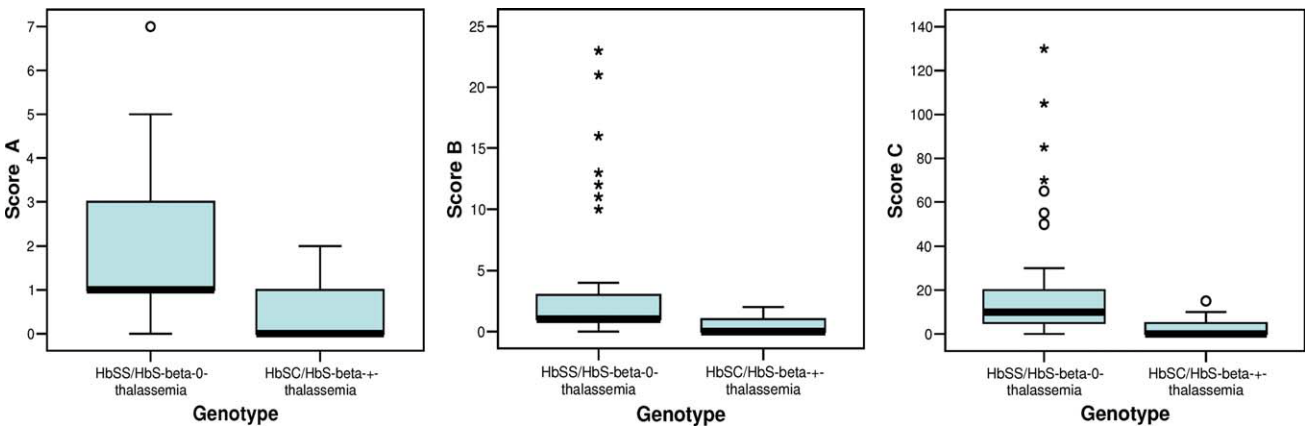

Figure 2. Association between Scores A, B, and C and genotype (Hypothesis 3). Each boxplot shows the median, interquartile range (box length), and extreme values within a category. Circles: Cases with values between 1.5 and 3 box lengths from upper or lower edge of the box. Stars: Cases with values more than three box lengths from upper or lower edge of the box. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

severity index and age in a cross-sectional study [7]. This should be interpreted as an indication of the heterogeneity in phenotype. Only a longitudinal study, following patients from early youth into adolescence can investigate an increase in severity with age. Our severity index did not correlate well with the risk of death score by Sebastiani

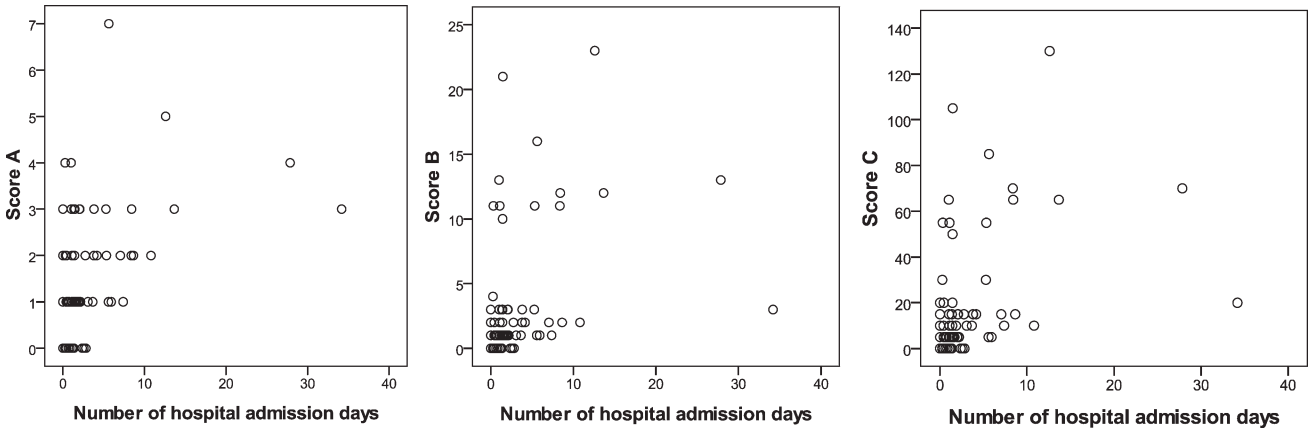

Figure 3. Correlation between Scores A, B, and C and the average number of hospital admission days/year (Hypothesis 5).

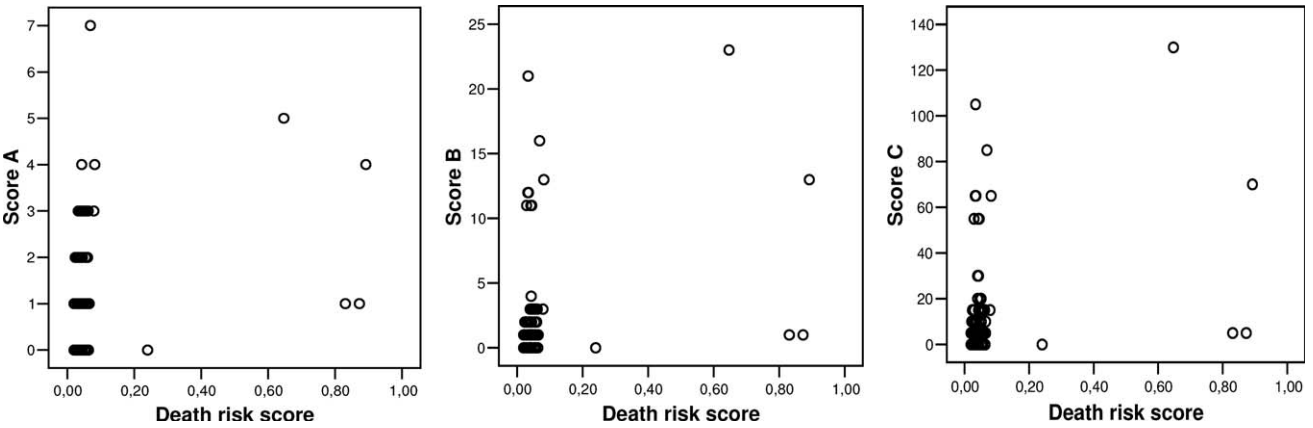

Figure 4. Correlation between Scores A, B, and C and the death risk score (Hypothesis 8).

et al. This may be due to several reasons. First, our severity index was not intended to predict death but to measure clinical disease severity. Since death rates in children with SCD are much lower than in adults, even severely affected children may not have a high risk of death within 5 years. Second, the observation period for acute chest syndrome and painful crisis in our study was restricted to a period of 2 years in contrast to the dataset used in the model predicting death, which assessed these complications over an undefined, probably longer period. Therefore, our patients may score lower on the death risk score. Third, in the death risk score sepsis was an important predictor of death. Our index attributed few points to sepsis, as the most important causes of sepsis in children with SCD can be prevented with penicillin prophylaxis and vaccination. Four of the patients in our dataset were scored as "severe" by the death risk score. All four patients had a history of sepsis. One of these patients died as result of pneumococcal sepsis due to non-compliance of penicillin prophylaxis.

There are some limitations in the selection of the sample of patients that was used for validation of our index. At the time this study was performed there was no neonatal screening program in the area of our center. Children with a severe course leading to mortality at an early age may well have been missed, resulting in selection of patients with a milder phenotype. Although every effort has been made to obtain information on previous treatment at other hospitals, missing information on the period preceding treatment at the study center cannot be completely ruled out. A history of e.g. priapism could therefore be missed, which could lead to an underestimation of this complication.

Central nervous system abnormalities may be underestimated in the HbSC group, since patients with HbSS and HbS-β-thalassemia are frequently screened for elevated cerebral blood flow by TCD in contrast to children with HbSC. This may introduce information bias concerning asymptomatic cerebral infarction. Since MRI/MRA is only performed in children with abnormal TCDs (>200 cm sec^{-1}), children with HbSC will not undergo MRI/MRA unless they are symptomatic.

In conclusion, we developed a SCD severity index by a transparent and rigorous process. Further validation is of this index is needed, e.g., in a large prospective cohort study of patients diagnosed by neonatal screening. After further refinement and adaptation of this index, it may form a base from which international consensus can be reached on outcome assessment in etiological studies of pediatric patients. It is important to use uniform outcome measures since this enhances the comparability of results across studies and enables statistical pooling in meta-analyses.

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