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Xandra Willemijn van den Tweel, Johanna H van Der Lee, Harriët Heijboer,
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► **To cite this version:**

Xandra Willemijn van den Tweel, Johanna H van Der Lee, Harriët Heijboer, Marjolein Peters, Karin Fijnvandraat. Development and validation of a pediatric severity index for sickle cell patients. American Journal of Hematology, 2010, 85 (10), pp.746. 10.1002/ajh.21846 . hal-00560294

HAL Id: hal-00560294

<https://hal.science/hal-00560294>

Submitted on 28 Jan 2011

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Journal:	<i>American Journal of Hematology</i>
Manuscript ID:	AJH-09-0708.R2
Wiley - Manuscript type:	Research Article
Date Submitted by the Author:	21-Jul-2010
Complete List of Authors:	van den Tweel, Xandra; Emma Children's Hospital/Academic Medical Center, Pediatric Hematology van der Lee, Johanna; Emma Children's Hospital/Academic Medical Center, Department of Pediatric Clinical Epidemiology Heijboer, Harriët; Emma Children's Hospital/Academic Medical Center, Pediatric Hematology Peters, Marjolein; Emma Children's Hospital/Academic Medical Center, Pediatric Hematology Fijnvandraat, Karin; Emma Children's Hospital/Academic Medical Center, Pediatric Hematology; Emma Children's Hospital/Academic Medical Center, Department of Pediatric Clinical Epidemiology
Keywords:	Sickle cell disease, Pediatric hematology/oncology

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

Xandra W. van den Tweel¹ MD PhD, Johanna H. van der Lee² MD PhD, Harriët Heijboer¹ MD PhD, Marjolein Peters¹ MD PhD, Karin Fijnvandraat^{1,2} MD PhD

Running title: Pediatric severity index for sickle cell patients

¹ Department of Pediatric Hematology, Emma Children's Hospital, Academic Medical Center, P.O. Box 22660, 1100 DD Amsterdam, the Netherlands

² Department of Pediatric Clinical Epidemiology, Emma Children's Hospital, Academic Medical Center, P.O. Box 22660, 1100 DD Amsterdam, the Netherlands

Correspondence to:

Dr. X.W. van den Tweel

Department of Pediatric Hematology, Emma Children's Hospital, Academic Medical Center, Room G8-205, P.O. Box 22660, 1100 DD Amsterdam, the Netherlands

Email: x.w.vandentweel@amc.nl

Tel: +31-20-5662727

Fax: +31-20-6912231

Abstract word count: 247

Word count: 2989

Number of tables: 3

Number of figures: 4

Keywords: sickle cell anemia, severity index, morbidity

20-07-2010

Abstract

Introduction. 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.

Methods. 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 alpha-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.

Results. 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 alpha-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.

Conclusion. 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.

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.

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

19 ***Development of a severity score***

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

46 **Cumulative lifetime incidence**

- 47 1. Bone necrosis (avascular) of the hip and/or shoulder: Pain in hip and/or shoulder and abnormalities
48 of the hip and/or shoulder confirmed by X-ray or MRI.
- 49 2. Cerebral infarcts or vasculopathy
50 Cerebral infarcts: Acute reduction or cessation of the cerebral blood flow, observed by MRI or CT-
51 scan, resulting in focal neurological impairment lasting more than 24 hours or without focal
52 neurological impairment (so-called “silent infarcts”).
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3 Cerebral vasculopathy: Stenosis or occlusion of the cerebral arteries documented by MRA. MRA
4 was performed in children with a velocity of > 200 cm/s measured by transcranial duplex ultrasound
5 (TCD).
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3. Hepatic sequestration (acute): Acute reduction of hemoglobin > 3.2 g/dl 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 (ie, high flow) or, more commonly, the failure of venous outflow (ie, 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 compared to hemoglobin values in the stable situation, combined with acute enlargement of the spleen.

28 **Cumulative incidence over a period of two years**

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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 two hours, leading to hospital admission and attributable to SCD [8].

43 **Weighting of the items**

44 Three different weighting systems to summarize the items of the severity index were
45 used (Table I). First, all items were summed with an equal weight of 1, leading to score
46 A. Secondly, acute life-threatening events and neurological complications were assigned
47 more weight, receiving a score of 10, with all other items assigned a score of 1 (score B).
48 Finally, items were weighted according to the severity of the different complications and
49 the frequency of occurrence, ranging from 5-50 points (score C). Both scores B and C
50 attributed the highest score (respectively 10 and 50 points) to acute life threatening
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3 events or complications associated with major sequelae (i.e. pneumococcal septicemia
4 and/or meningitis, acute hepatic sequestration, acute splenic sequestration, cerebral
5 infarction or vasculopathy). Although avascular bone necrosis and priapism are
6 considered to be severe complications as well, they do not lead immediately to acute life
7 threatening events. We therefore did not assign the maximum score of 10 for the
8 presence of each of these items. Five points were attributed to laboratory values.
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10 In score C the frequency was taken into account by attributing a higher score to
11 episodes of acute chest syndrome and painful crisis that occurred more than once over a
12 period of two years. As recurrent episodes of acute chest syndrome are associated with
13 sickle cell chronic lung disease and increased mortality [12;13], a larger weight was
14 attributed to this complication. Cut-off values to define abnormal laboratory parameters
15 were obtained by using the upper tenth percentile (leucocytes, LDH) or lower tenth
16 percentile (Hemoglobin, HbF) of the values obtained in this study population.
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33 ***Study population, management, and data collection***

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36 The data used to validate the index were derived from patients aged 0-18 years who
37 were born and diagnosed with SCD (HbSS, HbSC or HbS- β -thalassemia) in the
38 Netherlands, were seen at least twice a year at the outpatient clinic of the study center
39 (tertiary referral hospital) and had been followed for a period of more than two years.
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41 Patients born outside the Netherlands were excluded to reduce potential information
42 bias. Information on "lifetime cumulative incidence" is more likely to be missing in this
43 group. In the study center all patients receive penicillin prophylaxis until the age of 12
44 years in combination with five-yearly pneumococcal vaccination. Transcranial duplex
45 ultrasound (TCD) is performed twice a year in children with HbSS/HbS- β^0 -thalassemia
46 and HbS- β^+ -thalassemia from the age of 4 to 12 years and once every year in older
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3 children. From the age of 15 years onwards all patients are screened by cardiac
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5 ultrasound and ophthalmologic examination.
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10 Data on the cumulative incidence of organ damage and the number of recurrences of
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12 SCD related complications were retrieved from patient records over life-time and entered
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14 into a database. The number of recurrences of SCD related complications was
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16 documented over the last two observation years or over a period of two years before the
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18 start of hydroxyurea therapy or regular blood transfusions. Laboratory values were taken
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20 from the outpatient clinic, when patients were in a stable phase, not using hydroxyurea
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22 and at least four months after the last blood transfusion. The percentage of fetal
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24 hemoglobin was assessed after the age of two years. If more than one laboratory value
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26 was available during a stable phase over a period of one year, the average of these
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28 values was taken.
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33 All patients in the study were classified according to severity by a subjective expert
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35 classification and by the “SCD Assessment Instrument” (SCDAI) described by Day [8]
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37 and we calculated the risk of death score published by Sebastiani [14].
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42 The subjective expert classification was performed by two experienced pediatric
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44 hematologists (HH and MP), who independently classified all patients into three
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46 categories (mild, moderate, severe) based on their experience with these patients and
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48 information from the patient files before the current index was made. Any disagreement
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50 between the two experts was discussed and consensus was reached on final
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52 classification of the patient. The “SCD Assessment Instrument” (SCDAI) consists of the
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54 number of painful episodes and the number of acute chest syndrome episodes over a
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56 period of two years. Its content validity, inter-rater reliability and test-retest reliability were
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3 found to be sufficient [8]. We collected data on the number and days of all
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5 hospitalizations for SCD related complications from the first visit to the hospital for SCD
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7 until the day of entering these data into a database and divided these by the number of
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9 observation years. The risk of death score consists of 16 items (both clinical events and
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11 laboratory tests) predicting the risk of death within 5 years. The predictive value of the
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13 death risk score was validated in two unrelated sets of patients [14].
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18 **Score validity**

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20 We assessed the validity of our index according to generally accepted criteria [15]. In
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22 order to assess if the scores A, B and C relate to other measures of the same concept,
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24 we formulated eight hypotheses. First, we expected the scores to be incrementally
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26 different for the three patient groups (mild, moderate and severe) that were identified by
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28 the experts, with the highest score for the severe patient group. Secondly, we expected
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30 the scores to be incrementally different in accordance with the SCDAI score [8]. The
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32 third and fourth hypothesis specified that the scores would distinguish disease severity
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34 based on genotype (patients with HbSS/HbS- β^0 -thalassemia having higher scores than
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36 those with HbSC/HbS- β^+ -thalassemia) and/or number of alpha-gene deletions (lower
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38 scores in patients with one or more alpha-gene deletions), respectively. For all
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40 hypotheses, a p-value <0.01 was expected. The fifth and sixth hypotheses stated that
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42 there would be a positive correlation between the scores and the average number of
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44 hospital admission days for sickle cell related complications per year and between the
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46 scores and the average number of hospitalizations for sickle cell related complications
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48 per year (Spearman's $\rho > 0.4$). Only hospital admissions for sickle cell related
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50 complications, as described in our index, were included in the analysis.
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3 The seventh and eight hypotheses stated that there would be a positive correlation
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5 between the scores and age, between the scores and the risk of death score
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7 (Spearman's $\rho > 0.4$)
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10 11 **Statistics**

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

40 **Patient characteristics**

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42 This study population consisted of 92 patients (68 HbSS/HbS- β^0 -thalassemia, 24
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44 HbSC/HbS- β^+ -thalassemia). The median age at the time of data assembly was 9.7 years
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46 (range 2.7-18.6 years); 58% was male.
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50 Twenty-nine (32%) patients scored "0" on all three severity indices. There was no
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52 difference in age between this group (mean age 9.1 ± 3.5 years) and the patients who
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54 scored 1 or higher on the severity indices (mean age 10.4 ± 4.7 years).
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3 Altogether, 108 complications had occurred in 56 (60%) patients (Table II). Seven (8%)
4 patients only scored on laboratory values. Painful crisis was the most common
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6 patients only scored on laboratory values. Painful crisis was the most common
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8 complication. The following complications occurred only in HbSS/HbS- β^0 -thalassemia
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10 patients: acute hepatic and splenic sequestration, central nervous system abnormalities,
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12 priapism and acute chest syndrome.
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14 15 16 **Validity**

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18 Table III shows the scores A, B and C for the entire study population and for different
19
20 subgroups classified in four ways. The patients were classified according to severity by
21
22 experts and according to the SCDAI. The weighted K value for inter-rater reliability of the
23
24 severity classification by the two experts (pediatric hematologists) was 0.52, which
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26 indicates moderate agreement [16]. Furthermore, patients were classified based on their
27
28 genotype and on the deletion of alpha-genes.
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33 The scores A, B and C were significantly different for the three severity categories
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35 classified by the experts ($p < 0.01$, Figure 1) and for the two severity categories of the
36
37 SCDAI ($p < 0.01$). There was a significant difference in scores A, B and C for subgroups
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39 of patients classified according to genotype ($p < 0.01$). Patients with the severe genotype
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41 (HbSS/HbS- β^0 -thalassemia) scored higher than patients with the mild genotype
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43 (HbSC/HbS- β^+ -thalassemia) on scores A, B and C (Figure 2). Patients with one or two
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45 alpha-gene deletions scored lower than those without alpha-gene deletions on scores A,
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47 B and C. The correlation between scores A, B and C and the number of hospital
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49 admission days/year and the number of hospitalizations/year was moderate and
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51 statistically significant (Spearman's correlation coefficient for number of hospital
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53 admission days/year of 0.51 ($p < 0.01$), 0.53 ($p < 0.01$) and 0.55 ($p < 0.01$, respectively
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55 (Figure 3) and for the number of hospitalizations/year of 0.40 ($p < 0.01$), 0.49 ($p < 0.01$)
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3 and 0.51 ($p < 0.01$), respectively). There was no significant correlation between scores A,
4 B and C and age (Spearman's correlation coefficient of 0.16, 0.18 and 0.19,
5 respectively). The correlation between scores A, B and C and the risk of death score
6 was significant but weak (Spearman's correlation coefficient of 0.31 ($p < 0.01$), 0.29
7 ($p < 0.01$) and 0.26 ($p < 0.05$), respectively) (Figure 4). Of the 3 different weighting
8 systems, score C distinguished best among patient groups, as is evident from Figure 1
9 and 2.
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20 Discussion

21 This is the first SCD severity index, exclusively aimed at children, that was developed
22 using a transparent methodology. The index adequately differentiated between patient
23 groups classified for severity by experts and by an existing index (SCDAI). Moreover, the
24 index differentiated between patients classified by genotype (HbSS/HbS- β^0 -thalassemia
25 versus HbSC/HbS- β^+ -thalassemia) or by the number of alpha-gene deletions. There was
26 a moderate correlation between the scores and the number of hospital admission
27 days/year and the number of hospitalizations/year. There was no significant correlation
28 between the scores from the index and age and the correlation with the risk of death
29 score was very weak. Score C, calculated with the most refined weighting system
30 differentiating between items according to severity and the frequency of occurrence of
31 complications, discriminated best between patient groups.
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49 Contrary to our expectation we did not find a higher severity score in older children. This
50 lack of association between age and severity has also been observed by Cameron et al.,
51 who reported no correlation between their severity index and age in a cross-sectional
52 study [7]. This should be interpreted as an indication of the heterogeneity in phenotype.
53 Only a longitudinal study, following patients from early youth into adolescence can
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3 investigate an increase in severity with age. Our severity index did not correlate well with
4 the risk of death score by Sebastiani et al. This may be due to several reasons. First, our
5 severity index was not intended to predict death but to measure clinical disease severity.
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7 Since death rates in children with SCD are much lower than in adults, even severely
8 affected children may not have a high risk of death within 5 years. Secondly, the
9 observation period for acute chest syndrome and painful crisis in our study was
10 restricted to a period of two years in contrast to the dataset used in the model predicting
11 death, which assessed these complications over an undefined, probably longer period.
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13 Therefore, our patients may score lower on the death risk score. Third, in the death risk
14 score sepsis was an important predictor of death. Our index attributed few points to
15 sepsis, as the most important causes of sepsis in children with SCD can be prevented
16 with penicillin prophylaxis and vaccination. Four of the patients in our dataset were
17 scored as “severe” by the death risk score. All four patients had a history of sepsis. One
18 of these patients died as result of pneumococcal sepsis due to non-compliance of
19 penicillin prophylaxis.
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38 There are some limitations in the selection of the sample of patients that was used for
39 validation of our index. At the time this study was performed there was no neonatal
40 screening program in the area of our center. Children with a severe course leading to
41 mortality at an early age may well have been missed, resulting in selection of patients
42 with a milder phenotype. Although every effort has been made to obtain information on
43 previous treatment at other hospitals, missing information on the period preceding
44 treatment at the study center cannot be completely ruled out. A history of e.g.
45 symptomatic gall stones or priapism could therefore be missed, which could lead to an
46 underestimation of these complications.
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3 Central nervous system abnormalities may be underestimated in the HbSC group, since
4 patients with HbSS and HbS- β -thalassemia are frequently screened for elevated
5 cerebral blood flow by TCD in contrast to children with HbSC. This may introduce
6 information bias concerning asymptomatic cerebral infarction. Since MRI/MRA is only
7 performed in children with abnormal TCDs (>200 cm/s), children with HbSC will not
8 undergo MRI/MRA unless they are symptomatic.
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18 In conclusion, we developed a SCD severity index by a transparent and rigorous
19 process. Further validation of this index is needed, e.g. in a large prospective cohort
20 study of patients diagnosed by neonatal screening. After further refinement and
21 adaptation of this index, it may form a base from which international consensus can be
22 reached on outcome assessment in etiological studies of pediatric patients. It is
23 important to use uniform outcome measures since this enhances the comparability of
24 results across studies and enables statistical pooling in meta-analyses.
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38 **List of abbreviations**

39 SCD	SCD
40 TCD	Transcranial Duplex Ultrasound
41 SCDAI	SCD Assessment Instrument

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- (1) Platt OS, Brambilla DJ, Rosse WF et al. Mortality in sickle cell disease. Life expectancy and risk factors for early death. *N Engl J Med* 1994;330:1639-1644.
- (2) Steinberg MH, Dreiling BJ, Morrison FS, Necheles TF. Mild sickle cell disease. Clinical and laboratory studies. *JAMA* 1973;224:317-321.
- (3) Serjeant GR, Higgs DR, Hambleton IR. Elderly survivors with homozygous sickle cell disease. *N Engl J Med* 2007;356:642-643.
- (4) Miller ST, Sleeper LA, Pegelow CH et al. Prediction of adverse outcomes in children with sickle cell disease. *N Engl J Med* 2000;342:83-89.
- (5) Steinberg MH, Rodgers GP. Pathophysiology of sickle cell disease: role of cellular and genetic modifiers. *Semin Hematol* 2001;38:299-306.
- (6) Sebastiani P, Ramoni MF, Nolan V et al. Genetic dissection and prognostic modeling of overt stroke in sickle cell anemia. *Nat Genet* 2005;37:435-440.
- (7) Cameron BF, Christian E, Lobel JS, Gaston MH. Evaluation of clinical severity in sickle cell disease. *J Natl Med Assoc* 1983;75:483-487.
- (8) Day SW. Development and evaluation of a sickle cell assessment instrument. *Pediatr Nurs* 2004;30:451-458.
- (9) Pearson SR, Alkon A, Treadwell M et al. Autonomic reactivity and clinical severity in children with sickle cell disease. *Clin Auton Res* 2005;15:400-407.
- (10) Nolan VG, Wyszynski DF, Farrer LA, Steinberg MH. Hemolysis-associated priapism in sickle cell disease. *Blood* 2005;106:3264-3267.
- (11) Vichinsky EP, Neumayr LD, Earles AN et al. Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. *N Engl J Med* 2000;342:1855-1865.
- (12) Powars D, Weidman JA, Odom-Maryon T et al. Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. *Medicine (Baltimore)* 1988;67:66-76.
- (13) Castro O, Brambilla DJ, Thorington B et al. The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease. *Blood* 1994;84:643-649.
- (14) Sebastiani P, Nolan VG, Baldwin CT et al. A network model to predict the risk of death in sickle cell disease. *Blood* 2007;110:2727-2735.
- (15) Terwee CB, Bot SD, de Boer MR et al. Quality criteria were proposed for measurement properties of health status questionnaires. *J Clin Epidemiol* 2007;60:34-42.

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(16) Altman DG. Practical statistics for medical research. London: Chapman & Hall; 1991.

For Peer Review

Table I. The items of the severity index with different weighting systems

Items	Classification	Score A	Score B	Score C
<i>Lifetime cumulative incidence</i>		Points	Points	Points
		(max 20)	(max 47)	(max 285)
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
<i>Number of recurrences over past two years</i>				
7. Acute chest syndrome	absent; present OR ≥ 2 over a period of 2 years	0; 1	0; 1	0; 10; 20
8. Painful crisis	absent; present OR ≥ 2 over a period of 2 years	0; 1	0; 1	0; 5; 10
<i>Laboratory values</i>				
9. Hemoglobin (g/dl)	If ≤ 6.6 g/dl	1	1	5
10. HbF (%)	If ≤ 3.0 %	1	1	5
11. LDH	If > 700 U/l	1	1	5
12. Leucocytes ($10^9/l$)	If $\geq 15.2 \times 10^9/l$	1	1	5

Table II. Occurrence of complications in 92 patients

	No of patients	No of complications	<i>HbSS/HbS-β⁰-thalassemia (n=68)</i>		<i>HbSC/HbS-β⁺-thalassemia (n=24)</i>	
			No of complications	% of patients with complication	No of complications	% of patients with complication
<i>Number of organ damage complications (lifetime cumulative incidence)</i>						
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 ≥ 1 organ damage complications	36	57	28	41	8	33
<i>Number of other SCD related complications (cumulative incidence over the last 2 years)</i>						
Acute chest syndrome	8	11	8	12	0	0
Painful crisis	24	35	20	29	4	17
Patients with ≥ 1 other SCD related complications	32	51	28	41	4	17
Patients with ≥ 1 organ damage and/or other SCD related complications	56	108	45	66	11	46

Table III. Scores of indices A, B and C for patients classified in four ways: 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

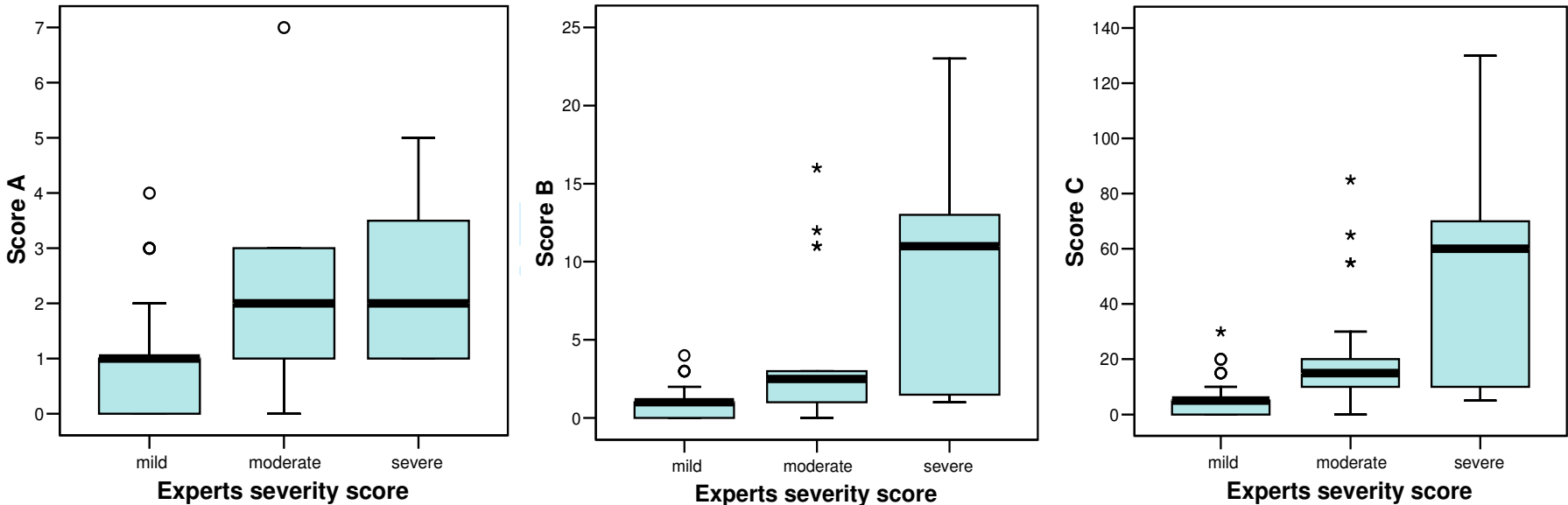
	<i>Number of patients</i>	<i>Score A Median score (range)</i>		<i>Score B Median score (range)</i>		<i>Score C Median score (range)</i>		
		Median	IQR	Median	IQR	Median	IQR	p
Total group	92	1	0-7	1	0-23	5	0-130	
Classification according to severity by experts*								<0.01
- mild	58	1	0-1	1	0-1	5	0-6	
- 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†								<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†								<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-thalassaemia†								<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 experts, an existing score (SCDAI), genotype (β -globin gene mutation or 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.

*Kruskal-Wallis test

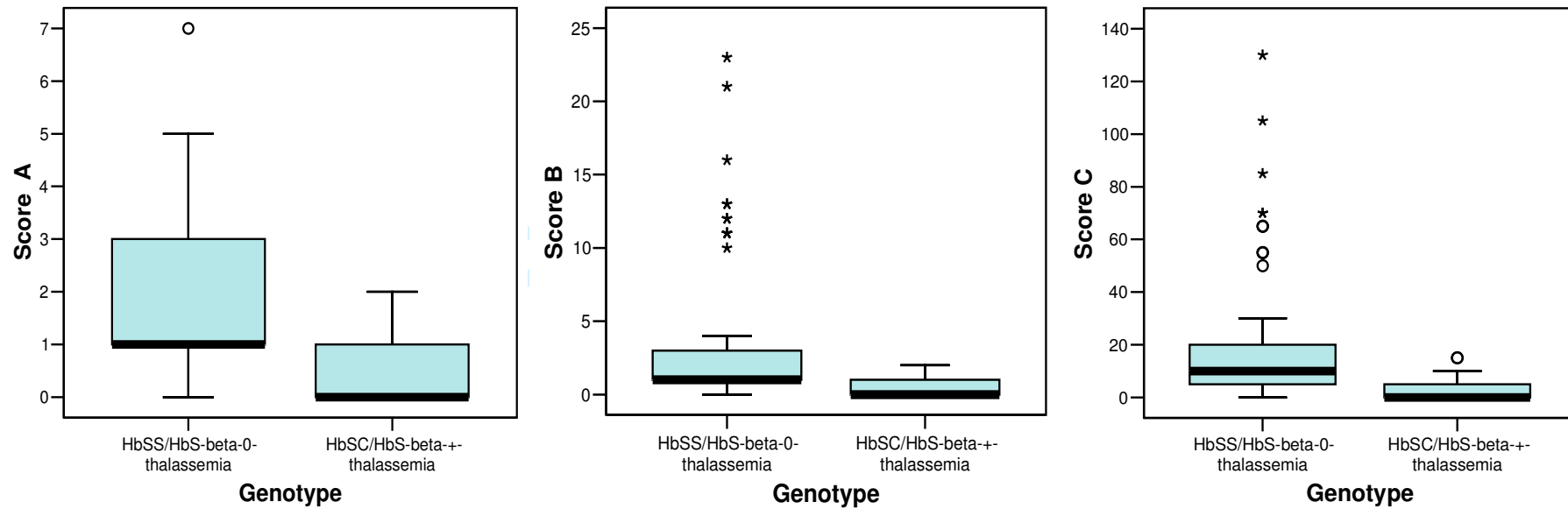
†Mann-Whitney U test

Figure 1. Results of index A, B and C for patients of three severity categories classified by experts (Hypothesis 1)



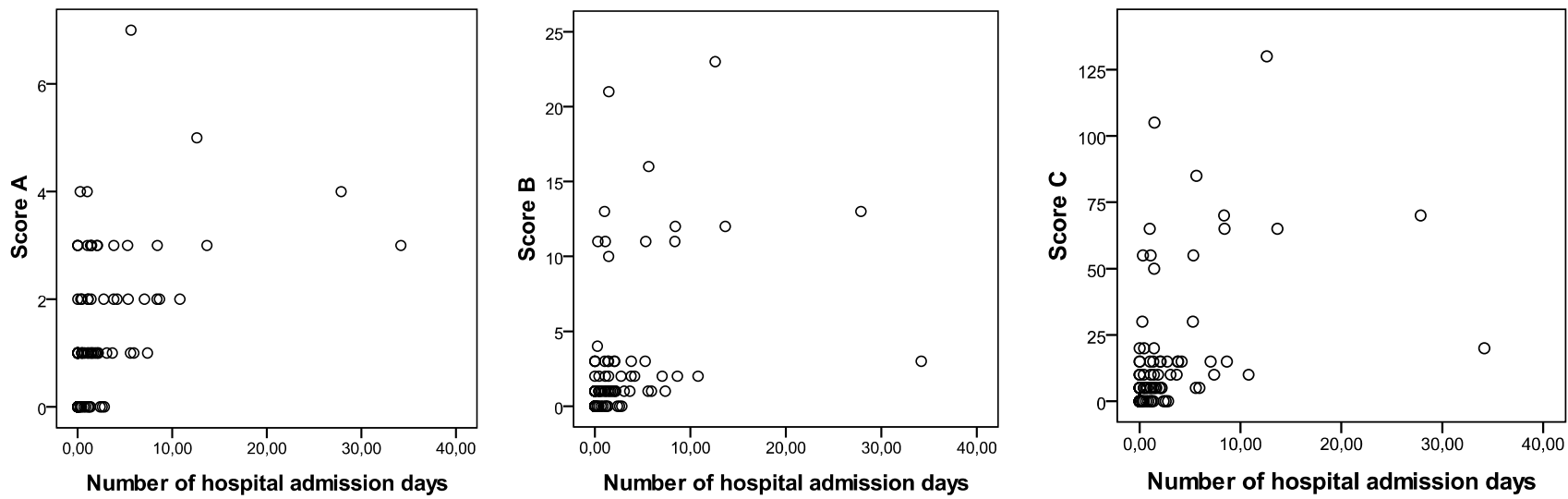
Each boxplot shows the median, interquartile range (box length) and extreme values within a category.
 Circles: Cases with values between 1.5 and 3 box lengths from upper or lower edge of the box.
 Stars: Cases with values more than 3 box lengths from upper or lower edge of the box.

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 3 box lengths from upper or lower edge of the box.

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



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

