

Development of a Severity Classification System for Sickle Cell Disease

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Purpose: There is no well-accepted classification system of overall sickle cell disease (SCD) severity. We sought to develop a system that could be tested as a clinical outcome predictor.

Patients and Methods: Using validated methodology (RAND/UCLA modified Delphi panel), 10 multi-disciplinary expert clinicians collaboratively developed 180 simplified patient histories and rated each on multiple axes (estimated clinician follow-up frequency, risk of complications or death, quality of life, overall disease severity). Using ratings on overall disease severity, we developed a 3-level severity classification system ranging from Class I (least severe) to Class III (most severe).

Results: The system defines patients as Class I who are 8–40 years with no end organ damage, no chronic pain, and ≤ 4 unscheduled acute care visits due to vaso-occlusive crises (VOC) in the last year. Patients < 8 or > 40 years with no end organ damage, no chronic pain, and < 2 unscheduled acute care visits are also considered Class I. Patients any age with ≥ 5 unscheduled acute care visits and/or with severe damage to bone, retina, heart, lung, kidney, or brain are classified as Class III (except patients ≥ 25 years with severe retinopathy, no chronic pain, and 0–1 unscheduled acute care visits, who are considered Class II). Patients not meeting these Class I or III definitions are classified as Class II.

Conclusion: This system consolidates patient characteristics into homogenous groups with respect to disease state to support clinical decision-making. The system is consistent with existing literature that increased unscheduled acute care visits and organ damage translate into clinically significant patient morbidity. Studies to further validate this system are planned.

Keywords : expert panel, disease severity, vaso-occlusive crises, organ damage, chronic pain

Introduction

Sickle cell disease (SCD) is characterized by the presence of sickle hemoglobin (HbS), chronic hemolysis, inflammation and vascular adhesion, recurrent pain episodes, irreversible multi-organ damage, and early death. The clinical course of the disease varies greatly by patient depending on age, complications, comorbidities, and psychosocial health.¹ There are multiple genotypes for SCD. The HbSS and HbS β^0 -thalassemia genotypes are often associated with the most severe clinical manifestations, while HbSC and HbS β^+ -thalassemia are generally considered less severe. There are multiple compound heterozygous sickling genotypes that so vary in significance and clinical severity. Even within individual genotypes, there can be a broad range of disease severity.¹

A national or international SCD registry that can be used to characterize and classify SCD severity currently does not exist. While several researchers have developed severity classification systems to predict outcomes and mortality in SCD,^{2–5} none have been widely adopted in clinical practice in part because of the large number and complexity of variables included. While the Cooperative Study of Sickle Cell Disease (CSSCD)² and Sickle Cell Disease Assessment Instrument (SCDAI)³ models are practical because they use easily identified predictors, neither have been validated. Furthermore, the CSSCD model excludes adults and has limited contemporary validity because death, which was the second most commonly predicted severe adverse event, is now rare during childhood in high-resource nations.¹

Although there is no such classification system for SCD, there are models for classification systems in other diseases which are valid, reliable, and clinically useful. For example, the New York Heart Association (NYHA) classification, the Composite Asthma Severity Index, several cancer staging systems (such as the Eastern Cooperative Oncology Group Performance Status), and other systems for acute illnesses (such as CURB-65 for pneumonia or APACHE II for sepsis) have been developed and are widely used in clinical settings. The simplicity of the NYHA classification has led to its widespread application and while it is partially subjective, it appears to correlate reasonably well with more objective and time-consuming testing.^{6,7}

The aim of this descriptive study was to take the first step in developing a classification system for SCD using a validated expert panel process that could be implemented in a clinical setting and could be tested for its ability to predict clinical outcomes in future studies. Our goal was not to change the definition of SCD but rather to help define a conceptually sound categorization of patients with SCD.

Patients and Methods

Study Design and Participants

We used the RAND/UCLA modified Delphi panel method, which has been more fully described elsewhere.^{8–10} Briefly, this method is a formal group judgement process which systematically and quantitatively combines expert opinion and literature review evidence by asking panelists to rate, discuss, and then re-rate various patient scenarios. The primary steps in the process include identification of

the question to be answered, a literature review of the evidence, selection of expert panelists, generation of a rating form, first round survey, an in-person meeting where panelists discuss areas of disagreement, final ratings and analysis of those ratings, and development of a written summary of areas of agreement.

Our multi-disciplinary panel included 10 expert clinicians (9 Medical Doctors and 1 Doctor of Nursing Practice) from various backgrounds (5 hematologist/oncologists, 3 internists, 1 psychiatrist/public health practitioner, and 1 pulmonologist; 8 treating adults and 2 treating children). We had representatives with diverse experience in clinical, pre-clinical, and epidemiologic research and an average of 20 years of experience caring for SCD patients. We also conducted a targeted literature review summarizing evidence from the 2014 National Heart, Lung, and Blood Institute Expert Panel Report,¹¹ 4 SCD severity scoring systems,^{2–5} and 2 recent systematic literature reviews,^{12,13} focusing on factors associated with morbidity and mortality in SCD. We referred to this evidence summary when we completed our ratings.

Rating Form

We collaboratively developed the rating form through individual phone interviews. We began by developing a list of patient characteristics that the 2014 National Heart, Lung, and Blood Institute Expert Panel Report,¹¹ SCD severity scoring systems,^{2–5} and 2 recent systematic literature reviews^{12,13} listed as risk factors of morbidity and mortality in SCD. Early drafts included up to 34 characteristics. We narrowed down this list by grouping characteristics (eg, organ damage), eliminating those that on their own would not influence one's broad classification of SCD severity (eg, gender), eliminating disease modifiers (eg, alpha-thalassemia), and eliminating those that are known to affect only a small group of patients (eg, patients on chronic transfusion with alloimmunization). Using the final list of characteristics, we developed 180 distinct patient scenarios (simplified patient histories) made up of all combinations of the final characteristics chosen. We used our combined clinical experience treating patients with SCD to develop these scenarios and did not use data from patient medical records.

Scenarios differed by patient age (<8, 8–15, 16–24, 25–40, or >40 years old), hemoglobin genotype (HbSS/HbSβ⁰ or HbSC/HbSβ⁺), presence/absence of chronic pain (defined as ongoing pain on most days over the past 6 months¹⁴), and the number of unscheduled acute care visits

Table 1 Definitions of End Organ Damage Used in the Rating Form

Organ System	Mild or Moderate End Organ Damage Was Defined as Any of the Following: ^a	Severe Damage to Bone or Retina Was Defined as:	Severe Damage to Heart, Lung, Kidney, or Brain Was Defined as Any of the Following: ^b
Cardiopulmonary	<ul style="list-style-type: none"> • Hypoxia (but oxygen saturation $\geq 88\%$ at rest or sleep and no need for supplemental oxygen) • Hypertension (120–139/70–89) • TRV^c 2.5–2.9 m/sec • Venous thromboembolism (any spontaneous DVT or 1 PE) 	<ul style="list-style-type: none"> • No worse than mild or moderate damage to the heart or lung 	<ul style="list-style-type: none"> • Hypoxia (O_2 saturation $< 88\%$ at rest or sleep or need for supplemental O_2) • Hypertension ($\geq 140/90$) • Any pulmonary hypertension (confirmed by catheterization) • TRV ≥ 3 m/sec, CHF • > 1 PE
Kidney	CKD stage 1–2, where: <ul style="list-style-type: none"> • Stage 1: Kidney damage with normal kidney function (eGFR ≥ 90) and persistent (≥ 3 months) proteinuria • Stage 2: Kidney damage with mild loss of kidney function (eGFR 60–89) and persistent (≥ 3 months) proteinuria 	<ul style="list-style-type: none"> • No worse than mild or moderate damage to the kidney 	CKD stage 3–5/ESRD, where: <ul style="list-style-type: none"> • Stage 3: Mild-to-severe loss of kidney function (eGFR 30–59) • Stage 4: Severe loss of kidney function (eGFR 15–29) • Stage 5/ESRD: Kidney failure requiring dialysis or transplant for survival (eGFR < 15)
Brain	<ul style="list-style-type: none"> • TIA (in the absence of stroke) • Silent infarct • TCD velocity 170–200 cm/sec (in children) 	<ul style="list-style-type: none"> • No worse than mild or moderate damage to the brain 	<ul style="list-style-type: none"> • Overt stroke • Significant neuro-cognitive defect • TCD velocity > 200 cm/sec (in children)
Other	<ul style="list-style-type: none"> • Avascular necrosis of bone that does not limit function • Skin/leg ulcerations • Retinopathy that does not require intervention or result in blindness 	<ul style="list-style-type: none"> • Avascular necrosis of bone that limits function • Retinopathy with blindness or retinal detachment 	

Notes: ^aIn children, mild end organ damage may be identified using more subtle, or slightly different, markers (eg, microalbuminuria rather than frank proteinuria, neuro-cognitive defect demonstrated by functioning below 1 grade level, hypertension based on age/sex/height); ^bIn children, severe end organ damage may be identified using slightly different markers (eg, neuro-cognitive defect demonstrated by functioning below ≥ 2 grade levels, CNS vasculopathy defined as SWiTCH Grade ≥ 4 , hypertension based on age/sex/height); ^cSome of these items (eg, TRV and TCD velocity) are markers of increased risk rather than evidence of organ damage.

Abbreviations: CKD, chronic kidney disease; CHF, congestive heart failure; CNS, central nervous system; DVT, deep vein thrombosis; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; PE, pulmonary embolism; TCD, transcranial Doppler; TIA, transient ischemic attack; TRV, tricuspid regurgitation jet velocity.

per year due to vaso-occlusive crises (VOCs) (0–1, 2–4, ≥ 5). Acute care included unscheduled visits to out-patient offices, the emergency department, or day hospitals, as well as in-patient hospitalizations. VOCs included episodes of acute pain, priapism (sustained, unwanted, painful penile erection lasting 4 or more hours), acute chest syndrome (acute illness with a new lung infiltrate and characterized by fever and/or respiratory symptoms resembling pneumonia), splenic sequestration (blood trapped in the spleen), and hepatic sequestration (blood trapped in the liver). In addition, the simplified patient histories included three categories of end organ damage, defined as no, mild/moderate, or severe damage to organs (Table 1).

Using a 1 to 9 scale, we rated each of the 180 scenarios on multiple axes, including estimated clinician follow-up frequency, risk of additional serious complications or death

in the next 5 years (for patients ≥ 16 years old) or 10 years (for patients < 16 years old), quality of life impact, and overall disease severity (Figure 1). The final classification system was based on the responses related to overall disease severity; ratings on follow-up frequency, risk of complications, and quality of life impact were used to generate discussion about the meaning of overall disease severity. In total, 640 items were rated. We completed ratings independently before a full-day in-person meeting (first-round ratings). At the in-person meeting, we discussed the items and scenarios where our ratings differed. Ratings were completed a second time at the conclusion of the meeting (second-round ratings).

Data Analysis

Median ratings were calculated for each item and grouped into 3 categories (1–3, 4–6, 7–9). Disagreement was

In a patient 16-24 years old ^a , with:			HbSS or HbSβ ^o	HbSC or HbSβ ^o	HbSS or HbSβ ^o	HbSC or HbSβ ^o	Any genotype (HbSS, HbSβ ^o , HbSC, HbSβ ^o)	HbSS or HbSβ ^o	HbSC or HbSβ ^o
How often should this patient be seen by a SCD provider? ^b			How high is this patient's risk of any additional serious complications ^c or death in the next 5 years? ^d		How much is this patient's quality of life impacted by their disease?		Considering your answers to the previous questions, how would you rate this patient's overall level of disease severity?		
Enter a value from 1 to 9, where: 1=at a typical follow-up schedule (eg, every 6 months) 5=moderately frequently (eg, every 3 months) 9=as frequently as any patient is usually seen (eg, twice a month)			Enter a value from 1 to 9, where: 1=low risk for a patient this age with SCD 5=standard or typical risk for a patient this age with SCD 9=significant or high risk for a patient this age with SCD		Enter a value from 1 to 9, where: 1=the best quality of life you can expect in a patient this age with SCD 5=a medium impact 9=a devastating impact, as severe as you can imagine in a patient this age with SCD		Enter a value from 1 to 9, where: 1=Class I (least severe) 5=Class II 9=Class III (most severe)		
(When there is heterogeneity within a scenario, do your best to answer each question for a typical patient with those characteristics.)			A	B	C	D	E	F	G
no end organ damage, ^e	no chronic pain, ^f	0-1 2-4							
	chronic pain, ^f	0-1 2-4	unscheduled acute care visits due to VOCs ^g in the last year, with						
		≥5							
mild or moderate end organ damage, ^e	no chronic pain, ^f	0-1 2-4							
	chronic pain, ^f	0-1 2-4	unscheduled acute care visits due to VOCs ^g in the last year, with						
		≥5							
severe damage to bone or retina, ^e	no chronic pain, ^f	0-1 2-4							
	chronic pain, ^f	0-1 2-4	unscheduled acute care visits due to VOCs ^g in the last year, with						
		≥5							
severe damage to heart, lung, kidney, or brain, ^e	no chronic pain, ^f	0-1 2-4							
	chronic pain, ^f	0-1 2-4	unscheduled acute care visits due to VOCs ^g in the last year, with						
		≥5							

Figure 1 Example rating form of patient scenarios. Each cell represents 1 patient scenario. The table is read from top to bottom and left to right. For example, the first cell in column A1 reads: "In a patient with no end organ damage, no chronic pain, 0-1 unscheduled acute care visits due to VOCs in the last year, with HbSS or HbSβ^o, how often should this patient be seen by a SCD provider?" ^aThis table was replicated for each patient age group: Patient <8, 8-15 years old, 25-40 years old, >40 years old. Young children might have no history, so the classification system might not be as applicable. ^bA SCD provider includes any clinician treating SCD and its primary consequences (eg, hematologist or pulmonologist). ^cAdditional serious complications include end organ damage, sepsis, or other. ^dRisk of complications or death in the next 5 years for patients ≥16 years old and next 10 years for patients <16 years old. ^eChronic pain defined as ongoing pain present on most days over the past 6 months. ^fAcute care includes unscheduled office visits, ED visits, day hospital visits, and hospitalizations; VOCs include pain, priapism, acute chest syndrome, splenic sequestration, and hepatic sequestration. ^gRefer to Table 1 for definitions of end organ damage provided.

Abbreviations: VOC, vaso-occlusive crisis; SCD, sickle cell disease; ED, emergency department.

defined as items with ≥2 individual ratings outside the category in which the median rating fell (eg, ratings of 4, 5, 6, 7, 8, 8, 8, 8, 9, 9 would be a median of 8 with disagreement because 3 ratings were outside the range 7-9). This is a modification of the definition of disagreement used widely in Delphi panels (where disagreement is defined less stringently as ≥2 individual ratings between 1 and 3 and ≥2 individual ratings between 7 and 9). Using the second-round ratings and follow-up discussions by phone and email with the panelists to resolve any remaining areas of disagreement, we identified characteristics that the panel agreed defined a patient as having more or less severe disease. We used these characteristics to develop a 3-level severity classification system, ranging from Class I (least severe) to Class III (most severe).

Results

The proportion of scenarios with disagreement on overall severity decreased from 59% to 23% from the first to second-round ratings. In the second-round ratings, we continued to disagree on some scenarios, such as with patients with 2-4 unscheduled acute care visits due to

VOCs in the last year, patients 16-40 years old, and patients with severe damage to bone or retina and no chronic pain. These remaining disagreements were resolved by further rounds of discussion by phone and email following the in-person meeting. We then agreed on the classification definitions listed in Figure 2 and described below.

We agreed that patients 8-40 years old with no end organ damage, no chronic pain, and ≤4 unscheduled acute care visits due to VOCs in the last year should be classified as Class I (least severe disease). Patients <8 or >40 years old with no end organ damage, no chronic pain, and <2 unscheduled acute care visits due to VOCs in the last year should also be considered Class I. Patients any age with ≥5 unscheduled acute care visits due to VOCs in the last year should be considered Class III (most severe disease). Similarly, patients of any age with severe damage to bone, retina, heart, lung, kidney, or brain should be classified as Class III, with the exception of patients ≥25 years old presenting with severe retinopathy, no chronic pain, and 0-1 unscheduled acute care visits due to VOCs in the last year, who should be considered Class II (patients with severe damage to bone are unlikely to have no chronic pain and

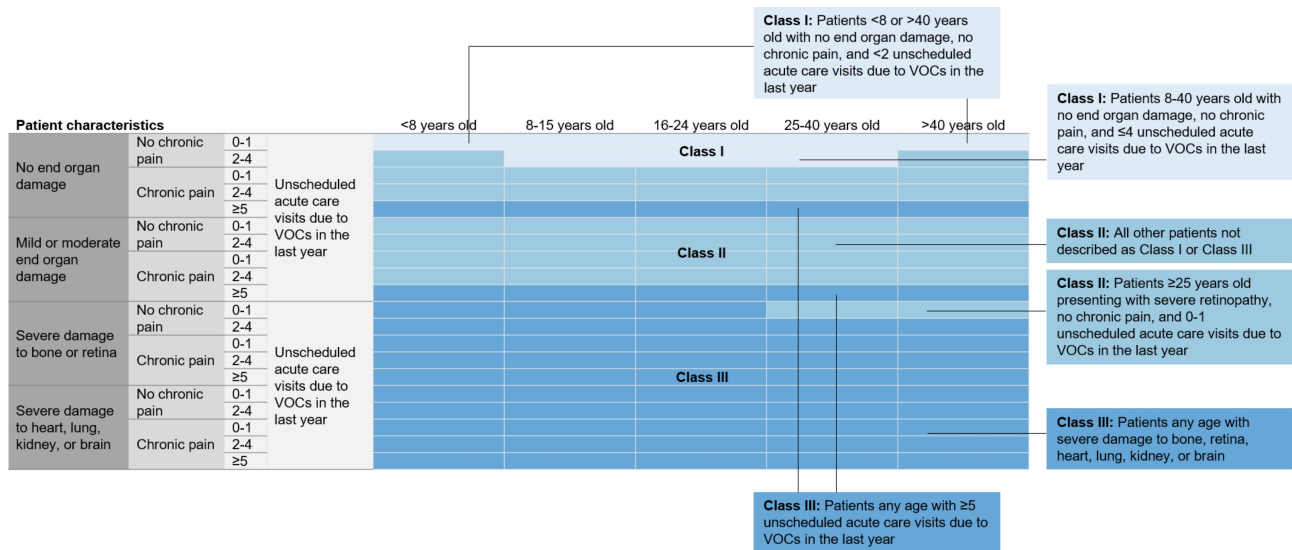


Figure 2 Expert agreement on overall disease severity classifications. Each cell represents 1 patient scenario. Class levels are color coded: The lightest blue represents Class I (least severe disease) and the darkest blue represents Class III (most severe disease).
Abbreviation: VOC, vaso-occlusive crisis.

are therefore not specified in this exclusion). All other patients are classified as Class II. Figure 3 illustrates how patients could be classified into one of these classes using only a few key clinical questions.

We agreed that genotype does not affect classification. Scenarios that differed only by hemoglobin genotype were

rated similarly, with mean differences in medians in the 0.0–0.4 range out of 9.

Discussion

A validated methodology was used to assist a multi-disciplinary expert panel in developing a 3-level severity

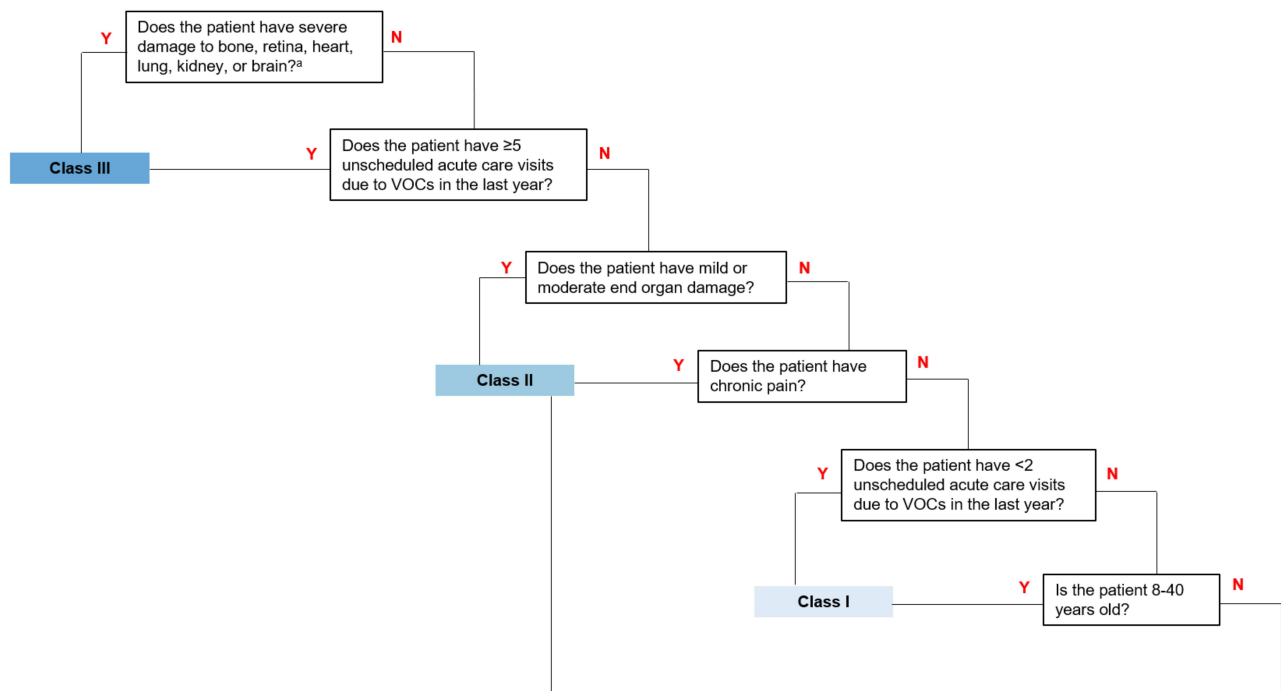


Figure 3 Patient classification flow chart. Class I represents least severe disease and Class III represents most severe disease. ^aPatients ≥25 years old presenting with severe retinopathy, no chronic pain, and <2 unscheduled acute care visits due to VOCs in the last year are Class II.
Abbreviation: VOC, vaso-occlusive crisis.

classification system for SCD. The system defines patients as Class I (the lowest severity) if they have no end organ damage or chronic pain, and infrequently (≤ 4 times/year for patients 8–40 and < 2 times/year for others) have acute care visits for VOC. The highest severity classification (Class III) is primarily reserved for patients with ≥ 5 acute care visits and/or severe damage to bone, retina, heart, lung, kidney, or brain. In this descriptive study, we developed the classification system; in later studies, we will test the validity of the system using patient data.

Our resulting classification system is consistent with existing literature. Patients classified by our system as having the most severe disease share characteristics demonstrated to be associated with worse outcomes and death. These include increased frequency of acute pain episodes (acute chest syndrome, hepatic and splenic sequestration, priapism, and thromboembolism), which has been associated with hospital readmissions,¹⁵ as well as the accumulation of organ damage,¹⁶ which can sometimes occur in the absence of VOCs.¹⁷

Patients with chronic pain were classified as at least Class II. Evidence supports that SCD patients with chronic pain have greater healthcare utilization, depression, anxiety, and poorer health-related quality of life.¹⁸ Greater opioid use is also associated with worse health-related quality of life among those with chronic pain.¹⁹ In addition, the oldest and youngest patients with frequent VOCs (≥ 2 unscheduled acute care visits) were classified as having more severe disease than patients 8–40 years old with a similar number of VOCs. Increasing age has been associated with risk of early death,^{13,20} increased acute care visits,²¹ and a higher severity score in Sebastiani et al's network analysis model (that used a cohort of 3,380 individuals from the Cooperative Study of Sickle Cell Disease to predict the risk of death).⁴ We also agreed that younger patients with frequent VOCs should be classified as more severe due to their increased risk for complications earlier in life.²⁰

Our severity classification system does not use hemoglobin genotype as an independent variable. The patient characteristics described in the scenarios accounted for the phenotypic expression of disease, regardless of genotype. This is supported by evidence that shows that there is significant phenotypic variation in disease expression and severity by genotype.¹

There are concerns about the changing standards for defining disease in a way that fundamentally changes the number of people considered to have the condition.²² This

classification system does not attempt to change the definition of SCD. Instead, we attempt to help define a conceptually sound categorization of patients with SCD. Our severity classification system uses clinical characteristics to consolidate patients into homogenous groups with respect to disease state. Some of these clinical characteristics are transient and may worsen or improve based on therapeutic interventions. Therefore, patients may move between severity classes over time.

Our system is made up of few patient characteristics that can be obtained during a clinical visit. For example, Figure 3 illustrates how patients are classified using only a few key clinical questions. In contrast, Sebastiani et al's network analysis model included 14 patient characteristics and 5 laboratory values⁴ and the pediatric severity index consisted of 12 items.⁵ If our system is validated, its simplicity may improve adoption and, hence, utility. Like other classification systems, it may help clinicians determine follow-up frequency, guide aggressiveness of therapy, or estimate disease progression. For example, the NYHA classification (based on patient reported and physician assessment of cardiac symptoms) correlates with other heart failure measures and is used in clinical settings to assess patients' functional limitation and guide therapy.²³ The Centor score (made up of 4 criteria based on patient signs and symptoms) has also been widely adopted to predict group A β -hemolytic streptococcal pharyngitis in adults and improve appropriate prescribing of antibiotics.²⁴ However, like other classification systems, our system is not intended to supersede clinical decision-making and we do not propose treatment guidelines for the different levels.

We used the RAND/UCLA modified Delphi panel method to develop this severity system. This process has been used extensively to develop quality measures and clinical guidelines in a variety of clinical areas²⁵ and there is evidence that the resultant measures have content, construct, and predictive validity.²⁶ Furthermore, modified Delphi panels have been shown to generate reproducible outcomes in ways that other methods have not: three separate panels using the method in another disease developed similar clinical guidelines.²⁷

This study had limitations. First, this study is descriptive only and the relationship between severity scores using our system and outcomes has yet to be demonstrated. Second, patient scenarios were simplified patient histories and, by design, did not use patient-reported outcomes, laboratory data, or account for the severity of acute visits (for example,

if transfusions or intensive care were required). This may have resulted in scenarios that were too broad to be interpreted consistently by experts. In addition, developing a single classification system applicable to both adults and children may make it less specific for either group; for example, markers of organ damage may be different across age groups. Our system assumes patients have access to acute care and that clinicians can obtain the characteristics used to classify patients (eg, evaluate evidence of organ damage). This may not be the case in low-resource settings. Therefore, on a global scale, our system might only be useful in a minority of cases. Lastly, although the modified Delphi technique has extensive support in the literature, panels consist of a relatively small number of clinicians who bring their individual clinical judgement, expertise, and experience to the process.

Conclusion

Using this rigorous and reproducible process, we developed a straightforward classification system that could be implemented in a clinical setting. Studies to validate this classification system and further refine the tool are planned. Specifically, retrospective studies (including medical chart reviews and/or patient registries) can be conducted to identify how clinical outcomes differ in each severity class definition. Prospective studies can be conducted to test the system's ability to predict clinical outcomes as well as explore how patients may move between severity classes. After validating this classification system, its use in a clinical setting should help support clinician decision-making and patient care by better predicting health outcomes and disease course for SCD.

Ethical Approval

This article does not describe a research study using human participants or animals, so ethical approval was not required.

Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

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