Minireview

Clinical severity in sickle cell disease: the challenges of definition and prognostication

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Abstract

Sickle cell disease (SCD) is a monogenic, yet highly phenotypically variable disease with multisystem pathology. This manuscript provides an overview of many of the known determinants, modifiers, and correlates of disease severity in SCD. Despite this wealth of data, modeling the variable and multisystem pathology of SCD continues to be difficult. The current status of prediction of specific adverse outcomes and global disease severity in SCD is also reviewed, highlighting recent successes and ongoing challenges.

Keywords: Biomarkers, disease severity, phenotype, prediction, prognosis, sickle cell disease, sickle cell anemia, prevention, survival, outcomes, models

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Introduction

Sickle cell disease (SCD) is an inclusive term for a group of related β-hemoglobinopathies characterized by the predominance of sickle hemoglobin (HbS) within erythrocytes. The HbS (β^S) mutation is a single nucleotide substitution in the β-globin gene (*HBB*) that yields a mature β-globin protein with a hydrophobic valine instead of a hydrophilic glutamic acid at the sixth amino acid position. HbS is prone to polymerization upon deoxygenation, and this property underlies all the pathophysiology of SCD. Erythrocytes undergo cycles of oxygenation and de-oxygenation in circulation, so polymers of HbS repeatedly form and damage the membrane. Consequently, erythrocytes become dehydrated, inflexible, and abnormally adhesive and have a greatly shortened lifespan. The net result is a chronic hemolytic anemia, with intravascular and extravascular components, and a tendency for microvascular obstruction or vaso-occlusion. The ischemia, infarction, and ischemia-reperfusion injury of multiple organs and tissues also produces a chronic inflammatory response and endothelial dysfunction.

SCD includes a number of different diseases (Table 1). The most common and severe form of SCD is the homozygous state for the β^S mutation called sickle cell anemia (HbSS). Other forms of SCD are compound heterozygous states with the β^S mutation and one of several other abnormal *HBB*s. The most common interacting Hb variants are HbC and several β^+-thalassemia and β^0-thalassemia mutations, giving rise to sickle-hemoglobin C disease (HbSC), sickle-β^+-thalassemia ($HbS\beta^+$), and sickle-β^0-thalassemia ($HbS\beta^0$). In general, HbSS and $HbS\beta^0$ are the most severe forms of SCD, and they may have an indistinguishable phenotype. Indeed, some use the term ''sickle cell anemia'' to include both the HbSS and $HbS\beta^0$ genotypes. In contrast, HbSC and $HbS\beta^+$ are usually less severe forms of SCD, especially when comparing across populations (Table 2). However, even within individual genotypes, there can be a broad range of disease severity (Figure 1).

Survival with SCD has improved substantially over the past 50 years.[1–3] It was once considered a fatal disease of children, but in the past several decades it has been transformed into a chronic disease by early detection, preventive measures, and disease-modifying therapies (e.g. hydroxyurea and chronic transfusions). Indeed, with contemporary multidisciplinary care in an experienced center in a high-resource nation, nearly all children are expected to survive to adulthood. This has produced a growing population of adults with SCD, to whom the burden of morbidity and mortality has now shifted. Long-term survival estimates (beyond childhood) are less accurately known, but are estimated to be in the fifth and sixth decades of life for those with sickle cell anemia.[4,5] Individuals with HbSC and $HbS\beta^+$ have survival estimates that approximate the general population.[6]

While it is true that SCD is a disease of the blood whose hallmark is the painful vaso-occlusive episode, if one focuses on the hematologic (e.g. anemia) and painful manifestations of the disease, then the true burden of this protean disease is underestimated. SCD affects all organ systems.

Table 1 Overall disease severity and typical hematologic features of the common genotypes of SCD

Genotype	Abbreviation	Name	Typical peripheral blood findings in untreated patients				Overall disease severity[b]
			Main Hbs	Hb (g/dL)	MCV (fL)	Reticulocytes (%)	
β^S/β^S	Hb SS	Sickle cell anemia[c]	S	6–9	Normal[a]	10–25	+++
β^S/β^0	Hb Sβ^0	Sickle-β^0-thalassemia[c]	S	6–9	Decreased	10–25	+++
β^S/β^C	Hb SC	Sickle-Hb C disease	S ≈ C	9–12	Normal[a]	5–10	++
β^S/β^+	Hb Sβ^+	Sickle-β^+-thalassemia	S > A	10–13	Decreased	2–10	+

[a]Coinheritance of α-thalassemia trait will produce microcytosis in HbSS and HbSC. Some individuals with HbSC without α-thalassemia trait may be mildly microcytic.
[b]A population-based generalization that may not apply to the individual.
[c]Some use the term ''sickle cell anemia'' to apply to both HbSS and HbSβ^0.
Hb: hemoglobin; Hbs: hemoglobins; MCV: mean cell volume; SCD: sickle cell disease.

Table 2 Incidence of complications across the common genotypes of SCD

Complication	Incidence by β-globin genotype			
	HbSS	HbSβ^0	HbSC	HbSβ^+
Acute painful episode	80	100	4	4
Acute chest syndrome	12.8	9.4	5.2	3.9
Stroke (infarction)	0.6	0.1	0.2	0.1

Incidence rates are expressed as number per 100 patient-years. Data are from the Cooperative Study of Sickle Cell Disease.

There are bony, cardiac, pulmonary, renal, central nervous system, hepatic, splenic, genitourinary, ocular, dermatologic, endocrine, and other manifestations and complications of the SCD. This multisystem organ injury begins in early infancy and accumulates over the lifetime of the individual. Nevertheless, SCD is quite phenotypically variable. Some patients develop particular complications, but not others. Likewise, some individuals have frequent or severe SCD-related complications and very early mortality, whereas others with the same SCD genotype have fewer overt manifestations and a longer—but not necessarily normal—lifespan. One example of marked phenotypic variability is the frequency of acute painful episodes and acute chest syndrome (ACS) (Figure 1). All of this variability presents at least two challenges. The first is how to best counsel and treat patients considering this range of disease expression and the limits to our prognostication—that is, should we treat all patients the same or individualize therapy in some manner? The second is how to avoid under-classification of disease severity when only a fraction of the manifestations of the disease are overt or readily quantifiable (e.g. death, number of painful events, or degree of anemia). So, not only is it challenging to predict many complications of SCD, it is likewise difficult to define—especially quantitatively—what it means to have ''severe'' disease.[7]

Determinants, modifiers, and correlates of disease severity

β-globin genotype

The β-globin genotype—that is, the genotype of SCD—is the main determinant of disease severity, especially when considered at the level of the population rather than the individual (Table 1). Overall, HbSS and HbSβ^0 are the most severe forms of SCD, while HbSC and HbSβ^+ are generally milder diseases (Table 2). This difference is largely explained by the fraction of total Hb that is HbS in each condition, which is highest in HbSS and HbSβ^0 and less in HbSC and HbSβ^+. It is important to remember that this ranking of disease severity by genotype is a population-based generalization that may not apply to individuals. Some patients with HbSC have severe and life-threatening complications, while individuals with HbSS and high levels of fetal Hb (HbF) may have a relatively mild disease.

HbF and β-globin haplotype

HbF is the most important and best-characterized modifier of disease severity in SCD, particularly in the HbSS and HbSβ^0 genotypes.[8] HbF inhibits the polymerization of deox-HbS and, depending on its level and distribution across erythrocytes, HbF can ameliorate or prevent nearly all complications of SCD. The protective effects of HbF in SCD were first appreciated in newborns with SCD, who are asymptomatic, and in the compound heterozygous state for HbS and gene-deletion $(\delta\beta)^0$-hereditary persistence of fetal hemoglobin (HbS/$[\delta\beta]^0$-HPFH). In hematologically normal individuals and most people with SCD, HbF is not uniformly distributed across all erythrocytes, but restricted to a small sub-population called F-cells (a heterocellular distribution). In rare individuals with HbS/$(\delta\beta)^0$-HPFH and, more commonly, individuals with SCD and certain co-inherited non-gene-deletion forms of HPFH, there are high levels of HbF (15–40%) in most erythrocytes (a pancellular distribution). Therefore, the degree of protection afforded by HbF is a function of both the fraction of total Hb that is HbF and the pattern of distribution of HbF across all red cells.[9]

The post-natal switch from predominantly γ-globin (HbF) to β-globin (e.g. HbA and HbS) synthesis is delayed in SCD, and HbF levels continue to decline until at least 5–6 years of age.[10] Most individuals with SCD have persistently elevated levels of HbF throughout life, but the amount is quite variable—from slight (2–3%) to marked (20–30%). Consequently, the inter-individual variation in HbF explains a significant fraction of the phenotypical variability of SCD. This variation in HbF is largely genetically determined.[11] HbF expression is regulated by a number of determinants, both linked and unlinked to β-globin locus.

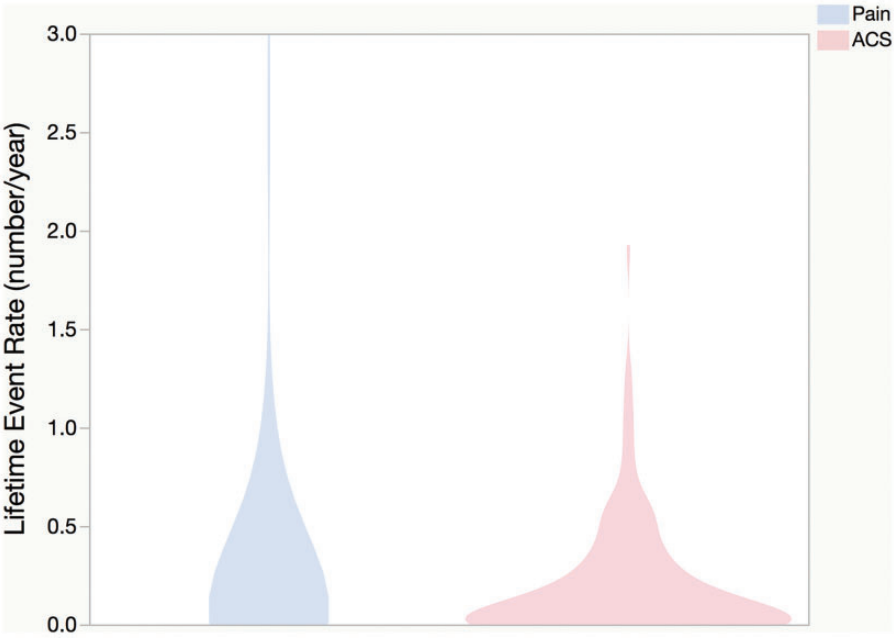

Figure 1 Phenotypic variability in the rates of acute painful episodes and acute chest syndrome (ACS). This contour plot depicts the lifetime rates of pain and ACS for members of the Dallas Newborn Cohort.[63] Acute pain is depicted in blue and ACS in red. The rate (events/year) is indicated on the *y* axis. The width of the blue and red regions is proportional to the number of subjects who have the indicated event rate

A variety of point mutations in the regulatory elements of the γ-globin genes (*HBG1*, *HBG2*), especially, give rise to non-gene-deletion forms HPFH and can be co-inherited with the β^S allele,[12] and these define the classical sickle β-globin haplotypes. The laboratory identification of these haplotypes (e.g. Benin, Senegal, Central African Republic, and Arab-Indian) is now mainly of historical interest in clinical practice, because the explanatory polymorphisms and mutations that underlie the variable HbF production upstream of *HBB* can now be directly identified instead. HbF expression is also regulated by trans-acting elements (unlinked to the β-globin locus), such as single nucleotide polymorphisms or small deletions within or near the *BCL11A* gene on chromosome 2p16, the *HBS1L-MYB* intergenic region on chromosome 6q23, and other genes.[12,13] Regardless of the source of variation, the HbF level clearly modifies the phenotype of HbSS, and increasing concentrations of HbF increasingly ameliorate the disease. Accordingly, induction of high levels of HbF continues to be an attractive therapeutic goal.

α-thalassemia

Coinherited α-thalassemia can also modify the phenotype of HbSS. Both one-gene deletion (α-thalassemia silent carrier) and two-gene deletion α-thalassemia (α-thalassemia trait) are common worldwide. The intracellular content of Hb is decreased by α-thalassemia, and this can delay the polymerization of HbS because the kinetics of this process are exquisitely sensitive to the concentration of HbS in the red cell. Consequently, the rate of hemolysis is modestly decreased in HbSS with coinherited α-thalassemia.[14] The risk of stroke is also decreased by α-thalassemia.[15–18] However, there is also evidence that α-thalassemia increases the frequency of painful episodes and avascular necrosis of bone.[19,20] Thus, α-thalassemia can modify the phenotype of sickle cell anemia in favorable and unfavorable ways, and this complicates its prognostic utility.

Glucose-6-phosphate dehydrogenase deficiency

Glucose-6-phosphate dehydrogenase (G6PD) deficiency is another commonly studied phenotypic modifier of SCD, although the data supporting its effects have sometimes been contradictory. G6PD deficiency is an X-linked disorder that affects about 10% of African-American males (the G6PD A^- variant, in particular). In the general population, the most common manifestation of G6PD deficiency is acute hemolysis with oxidant stress. In SCD, coinherited G6PD deficiency has been associated with more severe anemia and a greater frequency of acute anemic events and need for transfusions.[21,22] Its effects on cerebrovascular disease are less clear. Some studies indicate no association between G6PD deficiency and stroke or cerebral vasculopathy,[17,23,24] while others do show an increased frequency of magnetic resonance index (MRI)- or transcranial Doppler (TCD)-defined cerebral vasculopathy.[18,25,26] These conflicting data limit the prognostic utility of G6PD deficiency.

UGT1A1 promoter polymorphisms

Uridine diphosphate glucuronosyltransferase 1 family, polypeptide A1 (UGT1A1) is responsible for the conjugation (glucuronidation) of bilirubin. The *UGT1A1* gene has a polymorphic promoter region with a variable number of dinucleotide insertions (TA) in the A(TA)(n)TAA sequence (TATA box), where *n* indicates the number of TA repeats. Homozygosity for the $(TA)_7$ allele produces Gilbert

syndrome, which a genetic yet usually benign form of mild unconjugated hyperbilirubinemia. SCD is characterized by a chronic hemolytic anemia and variable degrees of unconjugated hyperbilirubinemia. Some patients also form bilirubinate gall stones. A number of studies have shown that *UGT1A1* polymorphisms modify the phenotype of SCD. In particular, $(TA)_7$ and $(TA)_8$ alleles are associated with greater hyperbilirubinemia, development of cholelithiasis, and need for cholecystectomy.[27–32] Moreover, an earlier age of onset of cholelithiasis has been associated with the $(TA)_7/(TA)_7$ and $(TA)_7/(TA)_8$ genotypes.[33,34] This is another example of a monogenic disease whose phenotype is modified by common, coinherited genetic polymorphisms. However, the practical clinical utility of this phenotypic modifier remains to be proven.

Clinical features and common laboratory measures

A host of common laboratory test results and clinical events have been correlated with numerous outcomes in SCD.[7,35] A complete review of all these associations is beyond the scope of this manuscript, but Table 3 summarizes many of the predictors identified in the landmark Cooperative Study of Sickle Cell Disease (CSSCD). In general, individuals with HbSS were more likely to have severe disease if they had lower levels of Hb and HbF and higher total leukocyte counts. However, the association of Hb concentration with outcomes was not simple. Those with lower Hb concentrations were more likely to die, suffer stroke, or have leg ulcers, while those with higher Hb were more likely to have frequent pain, ACS, and avascular necrosis of bone.[15,19,20] Similar to α-thalassemia, Hb concentration can be associated with both favorable and unfavorable outcomes, and this complicates its prognostic utility. Besides HbF, these many laboratory and clinical predictors are not particularly useful for individual patients.

Biomarkers

A biomarker has been defined by different groups as ''a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention'' or ''any substance, structure, or process that can be measured in the body or its products and influence or predict the incidence of outcome or disease.''[36] So, many if not all of the laboratory measures in the preceding section, such as HbF and Hb concentration, can be considered biomarkers. Bearing in mind this artificial distinction, a large number of other potential biomarkers have been studied recently and associated with SCD itself or various manifestations of the disease.

For example, a study of the monocyte proteome of children HbSS identified several putative biomarkers of the rate of painful events requiring hospitalization over a 5-year period.[37] The monocyte proteome was chosen because leukocytes in general, and monocytes in particular, are involved in the pathogenesis of vaso-occlusion. The abundance of several monocyte membrane and cytosolic proteins were found to correlate positively or negatively with the pain rate (Figure 2). This was a proof of principle study in 10 individuals, so these biomarkers need to be validated in large, representative studies. Table 4 lists a number of other biomarkers of SCD or complications of SCD that have been reported. These many factors are involved in adhesion, inflammation, coagulation, oxidative stress, growth, and other processes. Some of these biomarkers are proteins, or aggregates of macromolecules with proteins, or transcripts of proteins, and others are metabolites. While these biomarkers of particular complications or phenotypes have provided pathophysiological insights, none has achieved clinical utility.

The challenge of defining and predicting outcomes in SCD

The ability to predict ''severe disease'' depends on the ability to define it specifically and reproducibly. This can be a challenge in SCD because it is a protean disease that affects all organ systems with varying expression across the entire (and increasing) lifespan of the individual. Some adverse outcomes tend to appear at characteristic ages, some are insidious, and some seem to be stochastic. Many potential determinants, modifiers, and markers of disease severity are also available for study, as reviewed above. So, it is challenging to integrate all this information, and we are surely still missing key pieces of information.

Many studies that have identified predictors or correlates of ''disease severity'' in SCD have actually used the pain or ''crisis'' rate (rate of painful events), intentionally or unintentionally, as a proxy for overall disease severity. This is problematic for many reasons, not the least being that the subset of painful events that require hospitalization

Table 3 Predictors of adverse clinical outcomes identified in the Cooperative Study of Sickle Cell Disease

Outcomes	Laboratory predictors	Clinical predictors
Adult mortality	↓Hb, ↓HbF, ↑leukocyte count	Renal failure; pain rate; acute anemia; ACS rate
Pediatric mortality	↓Hb, ↓Hb F, ↑reticulocytes, ↑leukocyte count	Stroke
Stroke (infarction)	↓Hb, absence of α-thalassemia	TIA, acute anemia, ACS, hypertension
Acute chest syndrome	↓Hb, ↑HbF, ↑leukocyte count	
Acute pain rate	↑Hb, ↓HbF	
Avascular necrosis of bone	↑Hb, ↑AST, ↓MCV, presence of α-thalassemia	Pain rate
Leg ulcers	↓Hb, ↓HbF,	

ACS: acute chest syndrome; AST: aspartate transaminase; Hb: hemoglobin; HbF: fetal Hb; MCV: mean cell volume; TIA: transient ischemic attack.

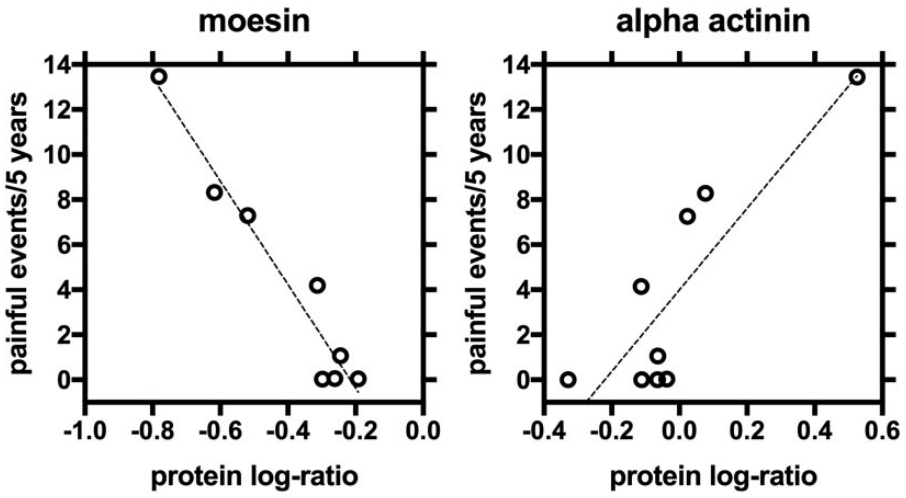

Figure 2 Putative biomarkers of painful events identified in the monocyte proteome of children with HbSS. Two representative biomarkers (proteins) from the study are shown.[37] Membrane moesin correlated negatively with pain rate (inpatient painful events/5 years), and cytosolic alpha actinin correlated positively with pain rate. (Data for the graphs obtained from Hryniewicz-Jankowska *et al*.[37])

Table 4 Reported biomarkers of SCD and complications of SCD.

SCD (compared to healthy controls)		Acute chest syndrome	Painful episodes (Vaso-occlusive Crisis)	Central Nervous System complications
Lactate dehydrogenase	Citrulline^{M}	L-selectin	L-selectin	L-selectin
D-dimer	Nuclear factor-erythroid 2-related factor mRNA^{T}	Thrombospondin-1	Thrombospondin-1	Thrombospondin-1
Thrombin-antithrombin complexes	Superoxide dismutase 1 mRNA^{T}	Secretory phospholipase A2	Leukotriene B4	Glial acidic fibrillary protein
Prothrombin fragment 1 + 2	Catalase mRNA^{T}	C-reactive protein	Vinculin	Platelet-derived growth factor
Growth differentiation factor	miR-144^{T}	Integrin $\alpha_M\beta_2$	Phosphoglycerate kinase	Brain-derived neurotrophic factor
Ubiquinated spectrin		Plasma free heme	P-selectin	Interleukin-1β
Glutathione^{M}		Neutrophil extracellular traps	Neutrophil extracellular traps	Erythrocyte and Platelet-derived microparticles
Adenosine^{M}		CD163	CD163	ADAMTS13
Sphingosine-1-P^{M}		Toll-like receptor 4	Vascular cell adhesion protein 1	Tissue plasminogen activator antigen
Spermine^{M}			Alipoprotein A1	
Spermidine			Endothelin-1	

Most of these biomarkers have been studied in the context of the HbSS genotype of SCD. This list is not exhaustive.
M: Metabolites; T: Transcripts; SCD: Sickle cell disease.

is only one characteristic of the expression of a multisystem disease. Of course, it is relatively easily to quantify painful events and ACS, making them easier to study. To avoid this narrow focus, several investigators have used composite measures of disease severity (e.g. combinations of acute event rates and laboratory test results).[38] Few have taken the steps to develop and validate such a composite measures with rigor. Notably, van den Tweel *et al*.[39] used explicit methods to develop a severity index for children with SCD. This severity scale has 12 items that include the occurrence of acute and chronic complications and common laboratory test results. The scale has been used as a primary measure in at least one study to date, and it appears to underestimate disease severity when chronic therapies, such as regular transfusions, have been instituted.[40]

In general, it has been easier to predict individual and readily quantified adverse outcomes (e.g. overt cerebral infarction) in SCD than a global measure of severe disease. This section reviews some of the successes and challenges to date.

Table 5 Evaluation of secretory phospholipase A2 (sPLA2) as a predictor of acute chest syndrome in HbSS

Study	Number of patients	sPLA2 threshold (ng/mL)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Styles *et al*.[52]	21	≥100	100	67	55	100
Naprawa *et al*.[54]	72	≥13.7	74	87	67	90
Styles *et al*.[57]	203	≥48	73	71	24	96

NPV, negative predictive value; PPV, positive predictive value.

Specific adverse outcomes

Overt stroke. Prediction of clinically overt stroke by screening TCD ultrasonography and primary prevention of stroke with chronic transfusion therapy has been a remarkable success for children with HbSS. TCD measures cerebral arterial blood flow velocities and can detect dynamic or fixed cerebral arterial stenosis that can be an antecedent of overt stroke.[41] An abnormal TCD status identifies children (2–18 years of age) at the highest risk of overt stroke, indicating about a 10% risk of stroke per year for 3 years after the test. The Stroke Prevention Trial in sickle cell anemia (STOP trial) showed that chronic transfusions decreased the rate of first stroke in children with abnormal TCD by 92% compared to observation (number needed to treat = 7).[42] In the decade after the publication of the STOP study (1999–2009), the mean annual incidence of hospitalization for overt stroke in children with SCD in the USA decreased by 45%.[43] Now, one of the greatest challenges is to limit the burden of chronic transfusions for primary stroke prevention, especially because most children with abnormal TCD velocities will not actually suffer a stroke (if untreated). The recently published TWiTCH trial demonstrated that hydroxyurea was non-inferior to chronic transfusions for the maintenance of TCD velocities in children who have received at least 1 year of transfusions and have no severe vasculopathy detected by magnetic resonance angiography.[44] So, the transition from chronic transfusions to hydroxyurea in the manner of this study should only improve the risk-benefit profile of primary stroke prevention programs.

Pulmonary hypertension. Echocardiography has also been shown to have prognostic utility in adults with HbSS, although not in the same, direct manner as TCD screening for risk of overt stroke in children. Echocardiographic measurement of tricuspid regurgitant jet velocity (TRV) can estimate pulmonary artery pressure (PAP) as a screening tool for pulmonary hypertension (PH). Mildly increased PAP occurs in 30% of adults and children with SCD when estimated by a TRV >2.5 m/s. However, right-sided heart catheterization, the gold standard for the diagnosis of PH, demonstrates that only 30% of patients with increased TRV have PH.[45] Moreover, only 40% of these patients with PH substantiated by catheterization have pulmonary arterial hypertension. Most (60%) actually have pulmonary venous hypertension, indicating left-sided heart disease rather than pulmonary disease.[45] So, echocardiography is not particularly useful as a screening tool for PH, and pulmonary arterial hypertension in particular, in SCD. However, elevated TRV, regardless of cause, has been reproducibly associated with early mortality in adults with HbSS.[46–48] However, there has been no association with early mortality in children.[49–51] Although not a robust predictor of PH, *per se*, screening echocardiography may be useful as a screening tool for adults at increased risk of early mortality. Whether addition or intensification of therapy can prevent early mortality in patients identified at high risk by echocardiography remains to be determined.

Acute chest syndrome. ACS is an acute pulmonary illness in an individual with SCD. It can be life-threatening, especially in adolescents and adults. ACS may not be present or apparent at the time of admission to the hospital for another reason (e.g. surgery or a painful episode).

Several groups have shown that secretory phospholipase A2 (sPLA2) is elevated in ACS and may be a biomarker for impending ACS (Table 5).[52–55] A pilot study even suggested that a simple transfusion of packed red blood cells could prevent ACS predicted by increased sPLA2 levels in children with HbSS hospitalized for acute pain episodes.[56] The largest study to date, however, indicated that sPLA2 had only a 24% positive predictive value for ACS (Table 5).[57] This initially promising biomarker has not performed as well as expected and has not entered common clinical practice.

Global disease severity and mortality

Because individuals with SCD can have so many different complications of their disease, whether in isolation, combined with other complications, or occurring sequentially, there are many ways to have ''severe'' disease. Consequently, investigators have used composite measures of disease severity, such as combinations of acute event rates and laboratory test results. Other than the pediatric severity index published by van den Tweel *et al*.,[39] most such composite outcomes are arbitrary or rely on face validity alone. Mortality can also be considered a ''global'' marker of severity, because death from SCD is unquestionably severe, and there are so many underlying processes that can lead to death from SCD. This section highlights two important efforts to predict global disease severity in SCD.

The CSSCD was one of the first groups to take on this formidable challenge. Miller *et al*.[38] took advantage of the CSSCD infant cohort to develop a predictive model for severe disease that manifested in later childhood. Severe disease was defined as death, stroke, frequent pain, or

recurrent ACS. The probability of experiencing one of these adverse outcomes by 10 year of age could be calculated using a multivariable model that included the following predictors: dactylitis in the first year of life (''early dactylitis''), the mean steady-state Hb concentration in the second year of life, and the mean steady-state total leukocyte count in the second year of life (Figure 3). This model was practical because it used readily identified predictors in early life. However, the potential clinical utility of the model was limited because only a small proportion of children (3%) were identified as highest risk, so only a minority might benefit from early preventive therapy. This model was not validated in a later, independent cohort, the Dallas Newborn Cohort.[58] It is possible that CSSCD model has limited contemporary validity because the second most commonly predicted adverse outcome, death, is now rare during childhood in high-resource nations.

On the understated premise that modeling the pathology of SCD is difficult, Sebastiani *et al.*,[59] undertook a comprehensive and sophisticated analytical approach to predict the risk of death in SCD. These investigators took advantage of the entire CCSCD cohort (3380 individuals with the common genotypes of SCD) and applied Bayesian network modeling to understand the relationships among many correlates of disease severity: 13 laboratory tests, 7 clinical events, and demographic and treatment information (Figure 4). This network analysis identified previously known risk factors for death, including renal insufficiency and leukocytosis, but also found that laboratory markers of hemolysis and clinical complications associated with

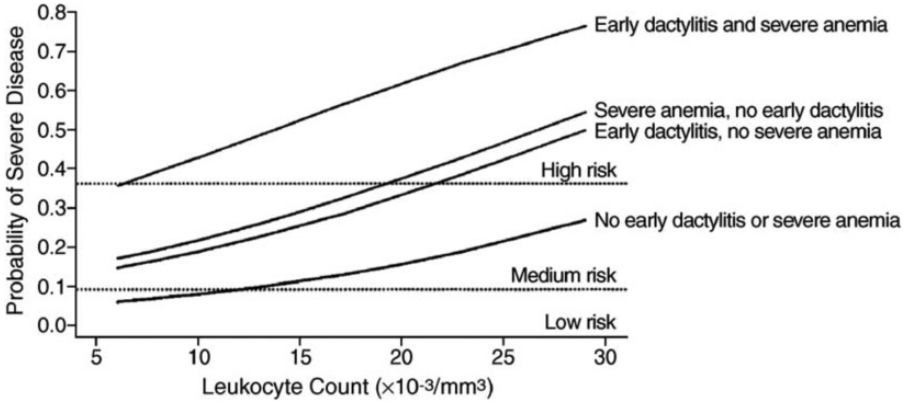

Figure 3 The CSSCD early predictive model. The estimated probability of severe SCD by 10 years of age is shown according to the leukocyte count in the second year of life, occurrence of severe anemia during the second year of life, and the occurrence of dactylitis before 1 year of age. In the CSSCD infant cohort, 3% were classified as high risk, 53% were classified as medium risk, and 44% were classified as low risk. (Reproduced with permission from Miller *et al.*[38])

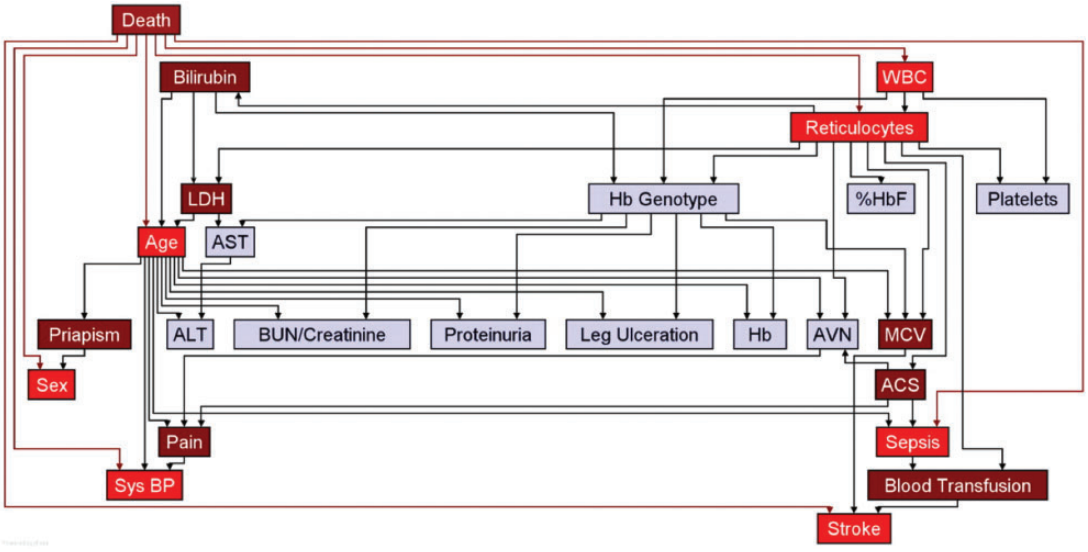

Figure 4 The network of associations among death, clinical complications, and laboratory values in SCD. The factors colored in red are sufficient alone to predict the risk of near-term death. The factors colored in blue are associated with predictive factors in red. Abbreviations: ACS, acute chest syndrome; AVN, avascular necrosis; BUN/creatinine, ratio of BUN to creatinine; Sys BP, systolic blood pressure; Hb, total hemoglobin concentration; %HbF, percentage of fetal hemoglobin; WBC, white blood cell (total leukocyte) count; Hb genotype, the genotype of SCD. (Reproduced with permission from Sebastiani *et al.*[59])

hemolysis were also risk factors near-term mortality. The probability of death within 5 years could then be computed for each individual. The predictive value of this model was corroborated in two unrelated sets of patients. Of note, the investigators considered the calculated probability of near-term death to be a continuous disease severity score, and they hoped that this model would be used by others to compute ''personalized disease severity scores'' to direct therapy for patients based on their prognosis. To this end, the model has been made freely available to the public as an online calculator (http://bios.ugr.es/dss-calculator/index.php). This network model did not consider the genetic polymorphisms that likely underlie or modulate the laboratory variables and clinical events included in model, and this provides opportunities for ongoing research.

Conclusions

In summary, the prediction of single, distinct adverse outcomes, like overt stroke, remains easier than prediction of globally severe SCD, however defined. Sophisticated and comprehensive modeling that incorporates ''multi-omic'' (e.g. genomic, proteomic, and metabolomic) factors may advance this effort. When seeking to define and predict ''severe'' HbSS, however, we must remember that this is a relative assessment—a matter of degree—because HbSS is altogether a severe disease. Almost all with HbSS will suffer from their disease. Hydroxyurea is the least burdensome of currently available therapies, and multiple lines of evidence demonstrate that it decreases complications and prolongs life in both children and adults.[3,60–62] We should not withhold a safe and effective therapy like hydroxyurea from people with a severe disease while awaiting a better model to predict who will be the sickest of the sick. Every person living with HbSS (as young as six to nine months of age), with the exception of the small subpopulation with genetically determined high, pancellular HbF expression, deserves at least a trial of some form of disease-modifying therapy. Although it can now be argued that every young child who has an HLA-matched sibling donor is a candidate for hematopoietic stem cell transplantation, predictive models are at least needed for higher-risk therapies available now or in development.

Finally, we need to remember that predictive models are not clinically useful in isolation and should not be considered the ''end product'' of research. Instead, predictive models should be used to identify individuals at high risk of an adverse outcome, and this pre-symptomatic identification should then inform a specific change in therapy, and this intervention should prevent the adverse outcome in most. All of these steps, not just the development of the model, need rigorous study and validation to improve the outcomes of individuals with SCD. Simply put, it is not enough to predict an adverse outcome; we also need to do something to prevent it. The prediction and prevention of overt stroke using screening TCD programs to direct the initiation of chronic transfusion therapy has been a remarkable success, even if imperfect, but we need many more such successes.

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DECLARATION OF CONFLICTING INTERESTS

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