

Original Article

Fetal-to-sickle hemoglobin index and clinical morbidity in hydroxyurea-treated sickle cell anemia

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Abstract: Objective: Hydroxyurea improves outcomes in sickle cell anemia (SCA), but treated patients retain heterogeneous morbidity. We examined whether a fetal-to-sickle hemoglobin index integrating fetal hemoglobin (HbF), sickle hemoglobin (HbS), and total hemoglobin was associated with clinical severity. Materials and methods: This single-center retrospective study with concurrent laboratory assessment included 60 patients with HbSS or HbS/ β^0 -thalassemia receiving a stable hydroxyurea dose for at least 6 months. The index was calculated as $(\text{HbF}\% \times \text{hemoglobin [g/dL]})/\text{HbS}\%$. Annual vaso-occlusive crises (VOCs), SCA-related hospitalizations, transfusions, and infection-related admissions were obtained for the preceding 12 months. Spearman correlations used Holm correction across 36 pairwise comparisons. Adjusted negative-binomial models were used for overdispersed counts; a Poisson model was used for infection-related admissions. Receiver operating characteristic (ROC) analysis assessed high transfusion requirement ($\geq 3/\text{year}$), with the threshold selected by the Youden index. Results: The cohort included 38 patients with HbSS and 22 with HbS/ β^0 -thalassemia; the mean age was 16.0 ± 10.1 years, and 30 (50.0%) were female. The index was inversely associated with VOCs ($p = -0.50$; Holm-adjusted $P = 0.001$), hospitalizations ($p = -0.52$; adjusted $P < 0.001$), transfusions ($p = -0.45$; adjusted $P = 0.006$), and infection-related admissions ($p = -0.48$; adjusted $P = 0.002$). Per 1-g/dL higher index, adjusted event-rate ratios were 0.83 for VOCs, 0.82 for hospitalizations, 0.80 for transfusions, and 0.81 for infection-related admissions. Twenty-six patients (43.3%) had ≥ 3 transfusions/year. The AUC was 0.783 (95% CI 0.662-0.904); an exploratory Youden threshold of ≤ 2.42 g/dL yielded 73.1% sensitivity and 82.4% specificity. Conclusion: A higher fetal-to-sickle hemoglobin index was associated with lower recorded morbidity in hydroxyurea-treated SCA. The index is an exploratory measure of association, not a validated prediction rule or treatment target; prospective external evaluation is required.

Keywords: Sickle cell anemia, fetal hemoglobin, hydroxyurea, morbidity, biomarker

Introduction

Sickle cell anemia (SCA), encompassing HbSS and HbS/ β^0 -thalassemia, is caused by absent normal β -globin production in the presence of sickle hemoglobin (HbS). Deoxygenated HbS polymerizes, producing erythrocyte deformation, hemolysis, inflammation, endothelial dysfunction, and vaso-occlusion [1-3]. Its clinical expression ranges from intermittent pain to recurrent hospitalization, acute chest syndrome, infection, transfusion dependence, progressive organ injury, and premature death.

Fetal hemoglobin (HbF; $\alpha_2\gamma_2$) inhibits HbS polymerization and is an important modifier of SCA severity [4, 5]. Protection nevertheless depends on both the HbF concentration and its

cellular distribution; a favorable mean HbF percentage does not ensure that every erythrocyte contains a protective amount [5]. HbF-promoting haplotypes, including the Arab-Indian haplotype, are associated with higher average HbF but do not eliminate clinical heterogeneity [6]. This distinction between mean HbF, F-cell distribution, and intracellular HbF concentration has been emphasized in both mechanistic reviews and direct F-cell studies [7, 8].

SCA severity has no single universally accepted bedside measure. It is assessed multidimensionally using the frequency and intensity of VOCs, acute chest syndrome, hospital and emergency utilization, transfusion requirement, serious infection, stroke, and other organ complications, together with hemoglobin, hemolysis

markers, renal and cardiopulmonary findings, and treatment history. Prognostic models have combined clinical and laboratory variables, but their performance and transportability vary across age groups and care settings [9, 10]. In this study, severity was operationalized a priori as four annual count outcomes: VOCs, SCA-related hospitalizations, transfusions, and infection-related admissions.

Hydroxyurea is the principal disease-modifying treatment for SCA. In the Multicenter Study of Hydroxyurea, it reduced the median annual painful-crisis rate, delayed the first crisis, and reduced acute chest syndrome and transfusion use in adults with symptomatic HbSS [11]. The BABY HUG trial established hematologic benefit and a favorable short-term safety profile in very young children, with fewer pain, dactylitis, acute chest syndrome, hospitalization, and transfusion events in secondary analyses [12]. Guidelines consequently recommend broad use in children and use in adults with recurrent SCA complications [13]. Hydroxyurea raises HbF, increases mean corpuscular volume, reduces leukocyte and reticulocyte counts, improves rheology, and may reduce cellular adhesion and nitric oxide dysregulation [13, 14]. Greater HbF response during long-term therapy has also been associated with less organ injury and longer survival [15]. Responses remain variable because of adherence, dose intensity, pharmacokinetics, marrow reserve, genotype, and baseline disease biology. Long-term follow-up studies have further associated sustained hydroxyurea exposure with reduced morbidity and mortality, while pediatric data indicate that attaining higher HbF during hydroxyurea therapy is associated with fewer hospitalizations [16-18]. Recent reviews continue to identify hydroxyurea as a cornerstone of disease-modifying therapy in SCA [19].

We developed the fetal-to-sickle hemoglobin index as $(\text{HbF}\% \times \text{total hemoglobin})/\text{HbS}\%$. Biologically, HbF represents an anti-polymerization fraction, HbS represents the polymerizing hemoglobin burden, and total hemoglobin approximates oxygen-carrying capacity and hematologic reserve. Mathematically, $\text{HbF}\%/\text{HbS}\%$ is a dimensionless protective-to-pathogenic fraction ratio; multiplying this ratio by hemoglobin retains the unit g/dL. The index therefore increases when HbF or total hemoglobin rises and decreases when HbS predomi-

nates. It is not intended to represent cellular HbF distribution or mechanistic polymerization kinetics. We examined whether the index was associated with recorded clinical morbidity among hydroxyurea-treated patients with SCA. Because many proposed SCD biomarkers have not progressed to external clinical validation, any composite laboratory index requires rigorous independent evaluation before clinical implementation [20].

Materials and methods

Study design and setting

This single-center retrospective observational study with a cross-sectional laboratory assessment was conducted from January 2020 through December 2021 at Khalij-e-Fars Hospital, a tertiary referral center affiliated with Bushehr University of Medical Sciences, Iran. Consecutive eligible patients were identified through pediatric hematology inpatient and outpatient services. Clinical events during the 12 months preceding the index laboratory assessment were abstracted from hospital and clinic records.

Participants

Patients were eligible if they were aged ≥ 4 years, had HbSS or HbS/ β^0 -thalassemia confirmed by hemoglobin electrophoresis or high-performance liquid chromatography (HPLC), had received hydroxyurea continuously for ≥ 6 months without a dose change during the assessment period, and had concurrent HbF%, HbS%, and total hemoglobin results. Exclusion criteria were documented adherence $< 80\%$, red-cell transfusion during the preceding 3 months, HbSC or HbS/ β^+ -thalassemia, and another hematologic or chronic disorder expected to materially alter hemoglobin concentration or blood counts. Written consent was obtained from adults or guardians; assent was obtained from minors when applicable.

Hydroxyurea treatment and monitoring

Hydroxyurea was prescribed as routine care. Treatment was generally initiated at 10-15 mg/kg/day and increased according to clinical response and hematologic tolerance. Complete blood counts and reticulocytes were monitored during initiation and dose escalation; treatment was temporarily withheld or reduced for

clinically significant cytopenia according to the institutional protocol. At assessment, 28 patients received 500 mg/day and 32 received 1,000 mg/day. Dose category, duration ≥ 6 months, and adherence $\geq 80\%$ were verified from prescriptions, clinic documentation, and patient or caregiver interview. No treatment was assigned or changed for this study. Treatment-related evaluation included hemoglobin, HbF%, HbS%, reticulocyte percentage, recorded adverse cytopenias, and the four annual morbidity outcomes.

Clinical severity outcomes

A VOC was an acute sickling-attributable pain episode requiring emergency-department or inpatient management. SCA-related hospitalization included admission for VOC, acute chest syndrome, acute anemia or sequestration, or another acute sickle complication. Transfusions comprised simple or exchange packed-red-cell transfusions. Infection-related admissions included pneumonia or infection-triggered acute chest syndrome, osteomyelitis, sepsis, or another clinically significant infection requiring inpatient treatment. Counts referred to distinct documented events during the same 12-month window. These four outcomes constituted the study's operational assessment of clinical severity; no previously validated composite severity score was applied.

Laboratory measurements and index calculation

A concurrent complete blood count and reticulocyte percentage were measured using a Sysmex XN analyzer. HbF%, HbS%, and HbA₂ were measured by HPLC using the Bio-Rad Variant II system under routine calibration and quality-control procedures. Laboratory personnel were unaware of the aggregated annual event counts. The prespecified index was calculated as: fetal-to-sickle hemoglobin index (g/dL) = [HbF (%) $\times$ hemoglobin (g/dL)]/HbS (%). Because the percentage units cancel in the ratio, the index retains the unit g/dL. Values were calculated using the numeric percentages reported by HPLC.

Sample size

All 60 consecutive patients meeting the eligibility criteria and having complete data during the study period were included. No separate confir-

matory sample-size calculation was performed because this was an exploratory candidate-index analysis. Results, particularly the ROC threshold, were therefore considered hypothesis-generating.

Statistical analysis

Continuous variables are summarized as mean $\pm$ standard deviation (SD), median (interquartile range [IQR]), and range; categorical variables are reported as n (%). Spearman coefficients quantified monotonic associations. For the nine-variable correlation matrix, Holm correction was applied to the 36 unique pairwise tests; raw coefficients and Holm-adjusted *p*-values are reported. Correlations between the index and HbF%, HbS%, or hemoglobin were regarded as mathematically induced by the formula and were not interpreted as independent evidence of validity.

Annual outcomes were counts. Poisson dispersion was assessed using the Pearson χ^2 statistic divided by residual degrees of freedom. VOCs, hospitalizations, and transfusions were overdispersed (1.66, 1.63, and 1.70, respectively) and were modeled by negative-binomial regression. Infection-related admissions had a dispersion of 1.03 and were modeled by Poisson regression. Models adjusted for age, sex, hydroxyurea dose category (1,000 vs. 500 mg/day), reticulocyte percentage, and genotype (HbS/ β^0 -thalassemia vs. HbSS). Associations are expressed as adjusted incidence-rate ratios (IRRs) with 95% confidence intervals (CIs).

ROC analysis evaluated whether lower index values discriminated high transfusion requirement, defined a priori as ≥ 3 transfusions/year. The AUC and 95% CI were calculated by the nonparametric DeLong method. The exploratory cutoff maximized the Youden index (sensitivity + specificity - 1); sensitivity and specificity were calculated in the same development sample. A two-sided *P* < 0.05 was considered significant. Analyses were conducted using SPSS version 21.0 and independently reproduced for revision using Python 3.12 with SciPy 1.17 and scikit-learn 1.8.

Ethical considerations

The Institutional Ethics Committee of Bushehr University of Medical Sciences approved the study (IR.BPUMS.REC.1399.094). Data were

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Table 1. Participant laboratory values and annual clinical outcomes (N = 60)

Variable	Mean $\pm$ SD	Median (IQR)	Range
Age (years)	16.03 $\pm$ 10.07	13.50 (9.75-19.00)	4-57
Hemoglobin (g/dL)	9.59 $\pm$ 1.24	9.40 (8.85-10.23)	6.80-13.40
HbF (%)	23.50 $\pm$ 12.22	24.90 (16.00-32.40)	0.00-46.50
HbS (%)	68.53 $\pm$ 15.25	70.60 (60.20-79.25)	28.20-97.30
Reticulocytes (%)	3.09 $\pm$ 3.12	1.85 (1.18-3.85)	0.40-14.80
Fetal-to-sickle index (g/dL)	3.53 $\pm$ 2.31	3.27 (1.83-4.55)	0.00-9.29
VOCs/year	5.77 $\pm$ 4.16	5.00 (2.00-8.00)	1-20
Hospitalizations/year	5.92 $\pm$ 4.25	5.00 (2.00-8.00)	1-20
Transfusions/year	3.40 $\pm$ 3.25	2.00 (1.00-4.00)	0-12
Infection admissions/year	1.38 $\pm$ 1.38	1.00 (0.00-2.00)	0-6

HbF, fetal hemoglobin; HbS, sickle hemoglobin; IQR, interquartile range; SD, standard deviation; VOC, vaso-occlusive crisis. Decimal places are standardized by data category.

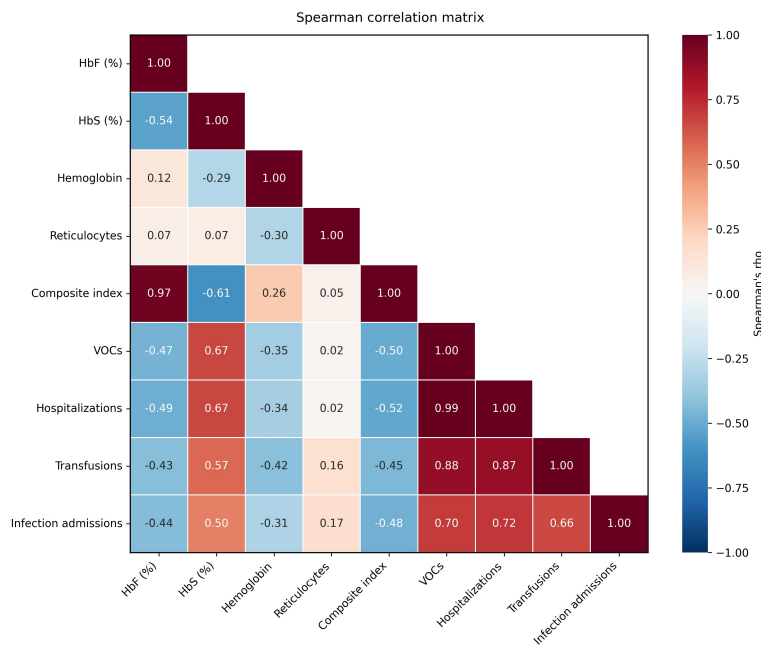


Figure 1. Spearman correlation matrix (N = 60). Coefficients are shown in the lower triangle. Holm correction was applied across 36 unique pairwise tests. Correlations between the composite index and HbF%, HbS%, or hemoglobin are structurally influenced by the formula and are not interpreted as independent validation.

de-identified, and the study followed the Declaration of Helsinki and applicable national guidance.

Results

Participant and laboratory characteristics

The analysis included 60 patients: 38 (63.3%) with HbSS and 22 (36.7%) with HbS/ β^0 -thalassemia. Mean age was 16.0 $\pm$ 10.1 years (range 4-57); 42 (70.0%) were younger than 18

years, and 30 (50.0%) were female. Eighteen patients (30.0%) had undergone splenectomy. Twenty-eight (46.7%) received hydroxyurea 500 mg/day, and 32 (53.3%) received 1,000 mg/day. The mean index was 3.53 $\pm$ 2.31 g/dL, and the median was 3.27 g/dL (IQR 1.83-4.55; Table 1).

Clinical morbidity and correlations

Mean annual counts were 5.77 $\pm$ 4.16 VOCs, 5.92 $\pm$ 4.25 SCA-related hospitalizations, 3.40 $\pm$ 3.25 transfusions, and 1.38 $\pm$ 1.38 infection-related admissions. The index was inversely correlated with VOCs (p = -0.502; raw P < 0.001; Holm-adjusted P = 0.001), hospitalizations (p = -0.522; raw P < 0.001; adjusted P < 0.001), transfusions (p = -0.450; raw P < 0.001; adjusted P =

0.006), and infection-related admissions (p = -0.477; raw P < 0.001; adjusted P = 0.002). Figure 1 displays the full matrix. Formula-determined correlations of the index with HbF%, HbS%, and hemoglobin are descriptive only and are not interpreted as independent validation.

Adjusted count models

After adjustment for age, sex, hydroxyurea dose, reticulocyte percentage, and genotype,

Table 2. Adjusted association between the fetal-to-sickle hemoglobin index and annual count outcomes

Outcome	Model	Dispersion	Adjusted IRR	95% CI	p value
VOCs	Negative binomial	1.66	0.83	0.77-0.89	< 0.001
Hospitalizations	Negative binomial	1.63	0.82	0.77-0.88	< 0.001
Transfusions	Negative binomial	1.70	0.80	0.72-0.88	< 0.001
Infection admissions	Poisson	1.03	0.81	0.72-0.91	< 0.001

IRR is reported per 1-g/dL higher index. All models were adjusted for age, sex, hydroxyurea dose category, reticulocyte percentage, and genotype. Dispersion is Pearson's χ^2 /residual degrees of freedom from the Poisson model.

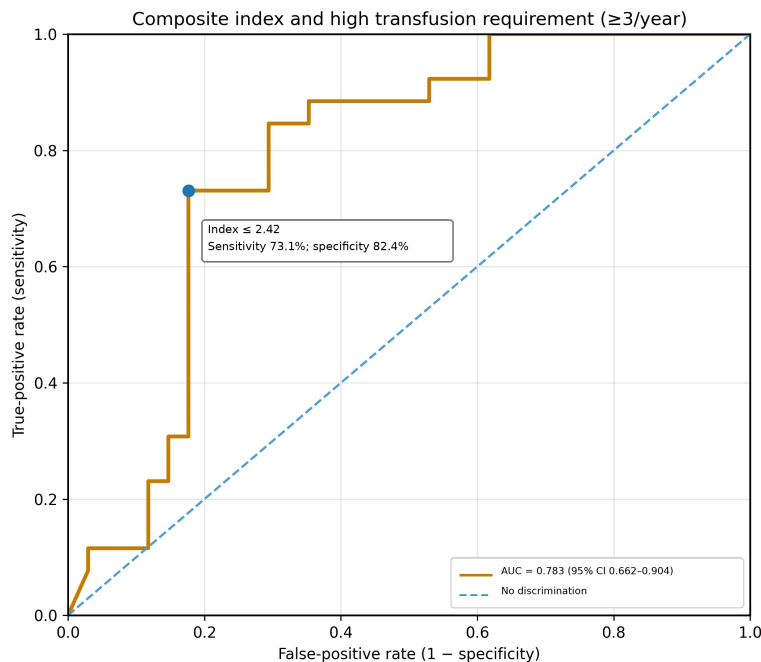


Figure 2. ROC curve for lower fetal-to-sickle hemoglobin index identifying high transfusion requirement (≥ 3 transfusions/year). Twenty-six patients (43.3%) met the outcome. AUC = 0.783 (95% CI 0.662-0.904). The Youden-selected exploratory threshold was index ≤ 2.42 g/dL (sensitivity 73.1%; specificity 82.4%). Same-sample threshold performance requires external validation.

each 1-g/dL higher index was associated with a 17% lower VOC rate (IRR 0.83, 95% CI 0.77-0.89), an 18% lower hospitalization rate (IRR 0.82, 95% CI 0.77-0.88), a 20% lower transfusion rate (IRR 0.80, 95% CI 0.72-0.88), and a 19% lower infection-related admission rate (IRR 0.81, 95% CI 0.72-0.91; **Table 2**). These estimates describe adjusted associations and do not establish a causal effect of the index or its components.

ROC analysis

Twenty-six patients (43.3%) had a high transfusion requirement (≥ 3 /year). Lower index values

showed moderate discrimination, with an AUC of 0.783 (95% CI 0.662-0.904). Maximization of the Youden index selected an exploratory cutoff of ≤ 2.42 g/dL, yielding sensitivity of 73.1% and specificity of 82.4% in this sample (**Figure 2**). Because the threshold was selected and evaluated in only 60 patients from the same center, it is vulnerable to optimism and is not proposed for clinical decision-making.

Discussion

In this cohort of hydroxyurea-treated HbSS and HbS/ β^0 -thalassemia, a higher fetal-to-sickle hemoglobin index was associated with fewer recorded VOCs, hospitalizations, transfusions, and infection-related admissions. The associations remained after covariate adjustment using models appropriate for count outcomes.

These findings support further evaluation of the index but do not validate it as a prognostic tool, surrogate endpoint, or treatment target.

The clinical benefit of hydroxyurea is well established. The pivotal adult trial demonstrated reductions in painful crises, acute chest syndrome, and transfusion exposure [11], while BABY HUG showed laboratory benefit and fewer important clinical events in very young children [12]. Guideline and implementation studies support escalation toward an individualized tolerated dose with hematologic monitoring [13, 14]. Long-term observational evidence further links hydroxyurea-associated HbF increas-

es with less organ damage and longer survival [15]. Our patients nevertheless had substantial recorded morbidity. This does not indicate hydroxyurea failure: the cohort came from a tertiary referral service, exposure was represented by only two fixed daily-dose categories rather than mg/kg/day or maximum tolerated dose, and event ascertainment was retrospective. More severely affected patients may also have received the higher dose, producing confounding by indication.

The direction of association is biologically coherent with previous HbF research. HbF inhibits HbS polymerization [4, 5] and can mitigate ineffective erythropoiesis [21]. However, HbF% alone does not represent its distribution among red cells, and patients with HbF-promoting haplotypes can retain clinically important disease [6, 22, 23]. The proposed index combines the HbF-to-HbS fraction ratio with total hemoglobin. This construction may summarize a favorable hematologic balance, but it is intentionally simple and cannot capture F-cell distribution, intracellular HbS concentration, oxygen affinity, α -thalassemia, hemolysis, vascular biology, adherence, or organ damage.

The adjusted IRRs were similar across the four morbidity domains. Their consistency should be interpreted cautiously because VOCs and hospitalizations were closely related clinical processes, and the same laboratory variables generated the index. Moreover, correlations between the index and its component variables are structurally induced by the formula and should not be interpreted as independent validation. Holm adjustment reduced the risk of false-positive interpretation in the correlation matrix, although multiplicity and the exploratory design remain relevant.

The AUC of 0.783 indicates moderate same-sample discrimination for ≥ 3 transfusions/year. The exploratory Youden cutoff of ≤ 2.42 g/dL was selected from the observed patient-level data using an explicit optimization rule. Its sensitivity and specificity are apparent, not externally validated performance. A clinically usable threshold would require prespecification, internal resampling, external validation, calibration analysis, and assessment of whether the index improves prediction beyond its individual components and established clinical variables.

This study has limitations. Its retrospective, single-center design precludes causal inference and is susceptible to documentation and referral bias. The modest sample permitted only limited covariate adjustment and yielded an imprecise ROC estimate. Hydroxyurea exposure was not available as mg/kg/day, cumulative exposure, drug concentration, or maximum tolerated dose, and adherence assessment was based on routine records. Cellular HbF distribution, α -thalassemia, β -globin haplotype, leukocyte and platelet counts, organ-function measures, and socioeconomic variables were unavailable. Outcomes may recur within individuals and were summarized over only one year. Finally, the index was derived and evaluated in the same dataset, so its added predictive value over HbF%, HbS%, and hemoglobin remains unknown.

Future prospective multicenter studies should measure hydroxyurea exposure and adherence rigorously, prespecify outcomes, compare the index directly with its components and established severity measures, assess calibration and incremental value, and validate any threshold in an independent cohort.

Conclusion

The fetal-to-sickle hemoglobin index was inversely associated with four recorded morbidity counts in hydroxyurea-treated HbSS and HbS/ β^0 -thalassemia. Count-regression and corrected correlation analyses support an association, not causality or validation. The index should remain an exploratory candidate measure until its reproducibility, incremental value, and clinical thresholds are established prospectively.

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Disclosure of conflict of interest

None.

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