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Validation of a composite vascular high-risk profile for adult patients with sickle cell disease

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To the Editor:

In the US, the median survival of patients with sickle cell disease (SCD) is 50 years, which is approximately two decades less than African Americans without SCD. As patients with SCD grow older, they develop end-organ damage related to vascular complications, including pulmonary hypertension, diastolic left heart disease, and nephropathy.¹ More than 50% of adult patients have dysfunction of at least one organ system, and 25% have multi-organ dysfunction. Simultaneous end-organ disease in heart, lung and kidney increased mortality by approximately 4-fold.¹ Intravascular hemolysis contributes to pulmonary vasculopathy and renal insufficiency by elaboration of free hemoglobin, which produces redox stress, inflammation, hypercoagulability, and vascular injury.² We have reported that elevated tricuspid regurgitation velocity (TRV), a non-invasive marker of elevated systolic pulmonary artery pressure, is associated with an increased risk of death in two independent cohorts.^{3,4} N-terminal-prohormone B-type natriuretic peptide (BNP) 160 pg/mL also predicts pulmonary hypertension, and is associated with high risk of mortality.⁵ Moreover, patients with chronic renal insufficiency are at higher risk of death.⁶

Hydroxyurea, the first pharmacologic agent to be approved by the FDA for treating SCD, reduces hemolysis and raises the hemoglobin level by increasing fetal hemoglobin levels. It also may improve vascular health through suppressing inflammation and favoring NO production. L-Glutamine, the only other agent approved by the FDA for treating sickle cell

disease, reportedly reduces VOC episodes by an unknown mechanism. There is no approved or consensus therapy for chronic organ dysfunction in SCD. Chronic simple red blood cell transfusions are effective at reducing the rate of stroke, acute chest syndrome and hospitalization.⁷ Currently three new classes of intervention are proposed for sickle cell disease. Antiadhesive treatments such P-selectin inhibitors focus on reducing vaso-occlusive complications such as pain episodes.⁸ Hemoglobin S polymerization inhibitors such as voxelotor aim to decrease hemolysis and increased hemoglobin concentration.⁹ Soluble guanylate cyclase activators and cyclic phosphodiesterase inhibitors aim to improve vascular health through enhanced NO signaling and vasorelaxation.¹⁰ Given the specific mechanisms of action of the new treatments, specific profiles of SCD complications according to pharmacologic action are highly relevant for future clinical trials.

The purpose of the present study is to evaluate a vascular risk profile that reflects pulmonary vasculature dysfunction, left heart failure and chronic kidney disease. A single risk profile that unifies existing knowledge of vascular complications has not been validated for SCD patients. A risk profile prediction is necessary for identifying patients with early vascular dysfunction who are at higher risk of mortality and morbidity. This risk profile is also crucial for experimental trials that focus on improving vascular health. In this paper, we use our preexisting knowledge to develop a composite vascular complication signature in SCD patients that increases risk of mortality. This will identify patients who could benefit from vascular-targeted interventions. We used existing data from two large cohorts of SCD patients to develop a composite vascular end-organ dysfunction high risk profile. These two cohorts included patients with SCD for Treatment of Pulmonary Hypertension, and SCD with Sildenafil Therapy (walk-PHaSST),⁴ and the National Institutes of Health SCD registry (NIH PH).³ For this analysis, we selected adult sickle cell anemia patients (hemoglobin SS and S-beta 0 thalassemia) to develop a composite vascular high-risk profile. This was defined as the presence of any of three specific vascular-related complications: (a) TRV 2.5–2.9 m/sec and BNP 160 pg/mL, or (b) TRV 3.0 m/sec, or (c) chronic kidney disease in SCD (CKD_{SCD}) as eGFR <90 mL/min/1.73 m² or urine albumin to creatinine ratio > 300.

In 739 (420 walk-PHaSST and 319 NIH PH) SCD patients, the frequency of TRV 2.5–2.9 m/sec and BNP 160 pg/mL was 12.9%, the frequency of TRV 3.0 m/sec was 16.2%, and the frequency of CKD_{SCD} was 24.2%, respectively. The frequency of a high-risk group defined by having any of these three criteria was 39.1% (including 42.9% in the walk-PHaSST cohort and 36.4% in NIH PH). Patients in this group were older, had higher white blood cell counts and plasma alkaline phosphatase levels. Patients in this group were less likely to have α -thalassemia gene, had a lower hemoglobin level and performed a shorter 6-minute walk distance (Table 1).

During a median follow-up of 30 months (IQR: 25–37), 70 patients died including 49 (17.0%) in the high-risk and 21 (4.7%) among the rest of the patients. The hazards ratio (HR; *P*value) of TRV 2.5–2.9 m/sec and BNP 160 pg/mL was 3.25 (*P* = .001), HR for TRV 3.0 m/sec was 6.04 (*P* < .001), and for CKD_{SCD} it was 4.22 (*P* < .001), respectively (Figure 1a). HR (95% CI) was 5.38 (3.20–9.04) for the high-risk group (Figure 1b). Population attributable mortality fraction to the high-risk group was 57%. In addition, the number of pain crises (HR = 1.34 per each crisis, *P* = .012) and increasing alkaline

phosphatase (HR = 1.04 per 10 units, $P < .001$) were significant independent prognostic factors.

We identified a risk profile including elevated TRV, and BNP, or chronic kidney disease which is observed in 40% of adult SCD patients and increases the risk of mortality by 5-fold. These high-risk patients are older, more anemic and have lower functional capacity. In addition to this risk profile, more pain crises and higher alkaline phosphatase levels independently predict higher risk of mortality.

In our study, half of the observed mortality in SCD is attributed to a high-risk profile group for vascular complications. This finding emphasizes the importance of risk stratification of patients based on risk of vascular complications, and a targeted approach to risk reducing strategies. A precision medicine approach can apply this risk profile to identify patients for more intensive interventions.

In the current study, other factors including vaso-occlusive pain crisis, and elevated serum alkaline phosphatase, remain as significant prognostic factors. The added value of these markers might improve the definition of a risk profile. In conclusion, our results suggest that measuring TRV, NT-proBNP, eGFR and urine albumin to creatinine ratio enable SCD researchers and care providers to identify patients who are at higher risk of morbidity and mortality.

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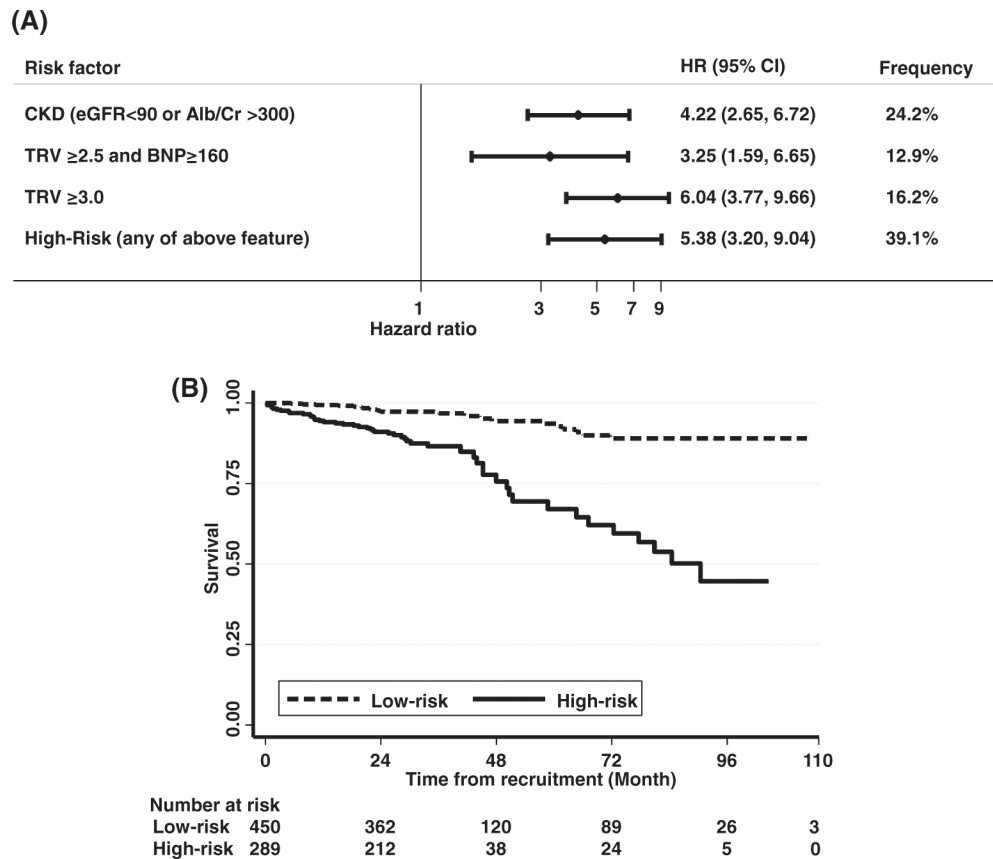


FIGURE 1.
 a) Forest plot of association between component of high risk group and mortality b) Survival of patients by study group. The high-risk group are patients with TRV 2.5–2.9 m/sec and BNP 160 pg/mL or TRV 3.0 m/sec or chronic kidney disease (eGFR <90 mL/ min per 1.73 m² or urine albumin to creatinine ratio >300). Survival was significantly lower in high-risk group (HR = 5.38, 95%CI = 3.20–9.04)

TABLE 1

Distribution of demographic and clinical variables between two groups and effect of each variable on risk of death

	Baseline group N = 450	High-risk group N = 289	Mean difference (P value) ^d	Hazard ratio (95% CI) ^b
Age, year	31 (24–40)	44 (32–52)	9 (<.001)	1.02 (1.00–1.04)
Female, n (%)	327 (55)	154 (51)	-1% (.72)	1.34 (0.84–2.16)
α-thalassemia gene deletion, n (%)	129 (30)	57 (21)	-10% (.005)	0.86 (0.49–1.51)
Pain crisis in last month, mean (SD)	0.2 (0.7)	0.2 (0.8)	0.0 (.90)	1.34 (1.07–1.67)
Hydroxyurea, n (%)	268 (60)	161 (56)	2% (.54)	0.88 (0.53–1.48)
Hemoglobin, g/L	93 (82–103)	82 (70–93)	-11 (<.001)	0.99 (0.98–1.01)
Hemoglobin F %	6.8 (3.4–12.2)	5.6 (2.1–11.0)	-0.7 (.20)	0.97 (0.93–1.01)
WBC, 10 ⁹ /L	9.7 (7.7–12.0)	10.0 (8.0–12.5)	0.2 (.48)	1.05 (0.98–1.12)
Platelet, 10 ⁹ /L	372 (286–469)	354 (274–456)	-17 (.12)	0.98 (0.96–1.00) ^c
Absolute reticulocyte count, /mm ³	25.1 (17.0–34.6)	23.4 (15.3–34.4)	-1.0 (.31)	0.99 (0.98–1.01)
Alkaline phosphatase, IU/L	85 (66–109)	100 (73–140)	26 (<.001)	1.04 (1.02–1.05)^c
Six-minute walk distance, m	470 (410–540)	411 (361–472)	-53 (<.001)	0.97 (0.92–1.02) ^c

Bold numbers indicate statistically significant ($P < .05$). Results are in median (IQR) unless otherwise specified.

^a Adjusted for study.

^b Adjusted for high-risk group.

^c Per 10 unit.