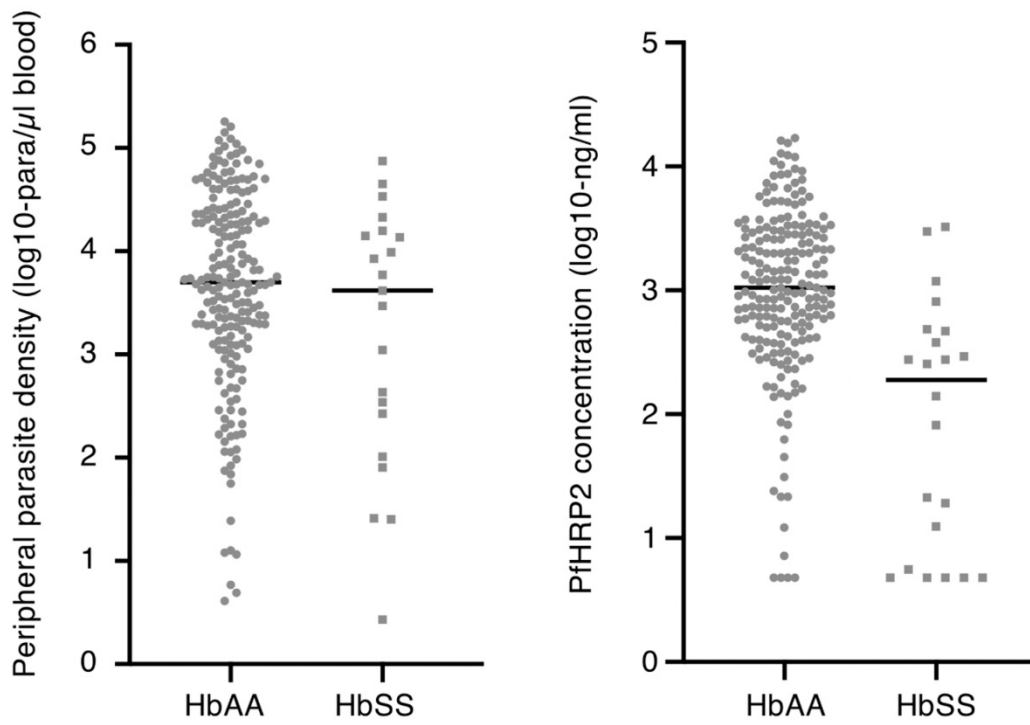**Supplemental Figure 1.** Distribution of peripheral parasite density and PfHRP-2 concentrations by beta globin genotype.

Median is denoted with a black bar.

Supplemental Table 1. Demographic characteristics of children in the CM-R01 parent study.

	SMA (n = 232)	CM (n = 267)	Community Controls (n = 216)
Baseline demographic characteristics			
Number of male patients (%)	140 (60.3)	159 (59.6)	104 (48.1)
Median age (IQR), years	2.8 (2.1, 4.4)	3.5 (2.5, 4.9)	3.6 (2.7, 4.7)
Baseline clinical characteristics			
Number with HbAA genotype (%)	208 (89.6)	264 (98.9)	175 (81.0)
Number with HbAS genotype (%)	2 (0.9)	2 (0.7)	41 (19.0)
Number with HbSS genotype (%)	22 (9.5)	1 (0.4)	0 (0)

Note: SMA, severe malarial anemia; CM, cerebral malaria; IQR, interquartile range.

Supplemental Table 2. Association between biomarkers correlated with SCA during severe anemia with *P. falciparum* parasitemia and risk of death or readmission and risk of future outpatient visit for uncomplicated malaria.

	N obs, n event	HR	95% CI	P value [b]	HR	95% CI	P value [b]
Risk of Death or Readmission [a]					Adjusted for age & Hb genotype		
Angpt-2 (pg/mL)	186, 49	1.45	0.77, 2.72	0.25	1.48	0.75, 2.92	0.25
TNFα (pg/mL)	212, 57	0.54	0.36, 0.81	**0.003**	0.55	0.36, 0.83	**0.004**
L-arg:ADMA ratio	165, 48	2.24	0.56, 8.91	0.25	2.67	0.64, 11.1	0.18
Risk of Malaria Outpatient visit [a]					Adjusted for age & Hb genotype		
Angpt-2 (pg/mL)	186, 81	1.83	1.09, 3.06	0.02	2.03	1.14, 3.59	**0.016**
TNFα (pg/mL)	212, 88	1.29	0.81, 2.06	0.28	1.33	0.82, 2.15	0.25
L-arg:ADMA ratio	165, 75	1.44	0.46, 4.47	0.53	1.77	0.55, 5.72	0.34

a. Cox regression is based on log10 transformation of biomarkers, so hazard ratio is increase in outcome for each log10 increase in biomarker

b. Significant p-values in bold, determined by FDR = 0.05

Supplemental Table 3. Number of readmission or sick visit events, including one participant who died at 1st hospital admission

	Overall (N = 227)[a]	HbSS (N = 20)	HbAA (N = 207)
Readmission and/or death	60 (26.4)	8 (40.0)	52 (25.1)
Including at admission (n=1)	61 (26.9)	8 (40.0)	53 (25.6)
Readmission	55 (24.2)	7 (35.0)	48 (23.3)
Death	8 (3.5)	1 (5.0)	7 (3.4)
Including at admission (n=1)	9 (4.0)	1 (5.0)	8 (3.9)
Malaria outpatient visit	90 (39.6)	10 50.0)	80 (38.6)

a. 3 participants did not have follow-up readmission/sick visit data (2 HbSS, 1 HbAA)

Supplemental Table 4. Baseline, steady state concentrations of inflammatory biomarkers in children with SCA enrolled in the NOHARM study at Mulago National Referral Hospital, and comparison with SCA and severe anemia with *P. falciparum* parasitemia from this study.

	HbSS, without SMA (N = 206)	HbSS, with SMA (N = 22)	HbAA, with SMA (N = 208)	P value[a,b]
Number of male patients (%)	95 (46.1)	13 (59.1)	127 (61.1)	0.25
Median Age (IQR), years	2.2 (1.5, 3.0)	4.6 (3.7, 5.7)	2.7 (2.0, 4.1)	**< 0.001**
Median C-reactive protein (IQR), mg/dL	0.67 (0.26, 1.52)	25.0 (16.7, 34.5)	44.0 (25.2, 64.7)	**< 0.001**
Median Angiopoietin-2 (IQR), ng/mL	1.8 (1.3, 2.6)	5.0 (3.6, 6.7) (n = 18)	1.7 (0.9, 2.8)	**< 0.001**

a. Determined between children with HbSS with and without SCA by use of χ^2 for categorical data, student's t test for parametric continuous data, and Wilcoxon rank-sum test for non-parametric continuous data, as appropriate.
b. Significance determined with FDR = 0.05 correction for multiple comparisons.

Supplemental Table 5. Characteristics of children with and without SCA with WHO-defined SMA[a] and without evidence of bacteremia, helminthic infection, or HIV infection.

	HbSS (n = 12)	HbAA (n = 138)	P-value[b, c]
Baseline demographic and clinical characteristics			
Number of male patients (%)	6 (50)	82 (59.4)	0.53
Median age (IQR), years	4.6 (3.0, 8.5)	2.6 (2.0, 3.9)	**0.006**
Median admission temperature (IQR), °C	38.3 (37.2, 39.2)	37.7 (36.9, 38.5)	0.20
Baseline clinical characteristics (Mean, SD)			
Hemoglobin, g/dL	3.8 (0.6)	3.8 (0.9)	0.96
WBC count, x10^3/μL	32.2 (16.0)	13.0 (8.8)	**<0.001**
Platelet count, x10^3/μL	209 (110)	163 (120)	0.21
Plasma markers of inflammation and endothelial activation (Median, IQR)			
Plasmodium falciparum HRP-2, ng/mL	276 (50, 649)	1344 (591, 3050)	**<0.001**
Parasite density in peripheral blood, parasites x10^3/μL	117 (50.4, 277)	86 (32, 282)	0.84
Circulating (x10^9)	1842 (739, 2640)	946 (377, 2500)	0.27
Sequestered (x10^9)	1365 (0, 5720)	7804 (2358, 21100)	**0.01**
Total (x10^9)	3070 (679, 6010)	9850 (4320, 22200)	**0.004**
Plasma markers of inflammation and endothelial activation (Median, IQR)			
C-reactive protein, mg/dL	25.0 (16.7, 34.5)	44.0 (25.2, 64.7) (n = 192)	**0.04**
Alpha-1 glycoprotein, mcg/mL	1380 (1140, 1890) (n = 10)	2120 (1710, 2730) (n = 114)	**<0.001**
Tumor Necrosis Factor (TNF)-α, pg/mL	62.2 (36.5, 77.8) (n = 11)	100 (57.0, 168) (n = 130)	**0.02**
Angiopoietin-1, ng/mL	6.65 (2.85, 7.63) (n = 10)	4.30 (1.92, 7.29) (n = 118)	0.36
Angiopoietin-2, ng/mL	5.98 (3.65, 8.44) (n = 10)	1.62 (0.89, 2.80) (n = 118)	**<0.001**
L-arginine, μmol/L	20 (20, 30) (n = 10)	30 (20, 30) (n = 101)	0.40
Asymmetric Dimethylarginine (ADMA), μmol/L	0.89 (0.81, 1.09)	0.73 (0.61, 0.89)	**0.006**
L-arginine:ADMA	24.2 (21.8, 27.5) (n = 10)	33.8 (25.6, 47.7) (n = 100)	**0.02**

a. Hemoglobin <5 g/dL and *P. falciparum* parasitemia >10,000 parasites/microliter

b. Determined by use of χ^2, student's t-test, or Wilcoxon rank-sum test, as appropriate.

c. Significant p-values in bold, determined by FDR = 0.05 correction for multiple comparisons.