Supplemental Table 1. Characteristics of participants from ELYSIS and SCCRIP cohorts

	ELYSIS *N=170*	**SCCRIP** *N=34*	**p** [a]	**p_{FDR}** [b]
Age (years)	10.75 (3.60)	9.84 (3.85)	0.20	0.34
Sex			0.26	0.37
Male	77 (45.29)	19 (55.80)		
Female	93 (54.71)	15 (44.12)		
Genotype			>0.99	>0.99
HbSS	159 (93.50)	32 (94.12)		
HbS/β^0thalassemia	11 (6.47)	2 (5.88)		
Group			<0.001	<0.001
Group 1	55 (32.35)	3 (8.82)		
Group 2	33 (19.41)	1 (2.94)		
Group 3	57 (33.53)	15 (44.12)		
Group 4	25 (14.71)	15 (44.12)		
Splenectomy			0.01	0.03
Yes	24 (14.12)	11 (32.35)		
No	146 (85.88)	23 (67.65)		
Duration of therapy (years)	5.99 (4.33)	6.48 (3.78)	0.37	0.48
Dose of HU (mg/kg/day)	23.85 (4.08)	27.08 (1.39)	0.18	0.33
MCV at baseline (fL)	92.74 (14.71)	93.16 (12.49)	0.93	0.99
HbF at baseline (%)	13.7 (9.12)	9.46 (9.32)	<0.01	0.03
Hb at baseline (g/dL)	8.98 (1.26)	9.16 (0.91)	0.25	0.37
TRV at baseline (m/sec)	2.42 (0.29)	2.30 (0.29)	<0.01	0.03
TRV at baseline≥ 2.5m/s (%)	63 (37.06)	6 (17.65)	0.03	0.08
TRV at year 2 (m/sec)	2.36 (0.28)	2.25 (0.23)	0.03	0.08
TRV at year 2 ≥ 2.5m/s (%)	51 (30.00)	5 (14.71)	0.07	0.15

NOTE: Values presented as mean (standard deviation) for continuous variables or frequency (%); Test between group differences using Fishers Exact test for categorical variables and 2-sample T-test or Wilcoxon rank sum test for continuous variables. [a] raw p-value. [b] False Discovery Rate (FDR) adjusted p-value. MCV: mean corpuscular volume, HbF: fetal hemoglobin, Hb: hemoglobin, TRV: tricuspid regurgitant velocity

Supplemental Table 2: Characteristics of participants in Group 4 from ELYSIS and SCCRIP cohorts

	ELYSIS *N=25*	**SCCRIP** *N=15*	**p** [a]	**p_{FDR}** [b]
Age (years)	12.57 (3.30)	9.06 (4.13)	<0.01	0.04
Sex			0.15	0.40
Male	26 (45.61)	10 (66.67)		
Female	31 (54.39)	5 (33.33)		
Genotype			>0.99	>0.99
HbSS	52 (91.23)	14 (93.33)		
HbS/β^0thalassemia	5 (8.77)	1 (6.67)		
Splenectomy			0.57	0.69
Yes	7 (28)	3 (20)		
No	18 (72)	12 (80)		
Duration of therapy (years)	8.03 (3.41)	5.89 (3)	0.06	0.12
MCV at baseline (fL)	88.6 (3.51)	86.02 (3.90)	0.04	0.09
HbF at baseline (%)	3.07 (2.56)	2.99 (3.88)	0.59	0.69
Hb at baseline (g/dL)	9.74 (1.18)	9.48 (0.83)	0.46	0.69
TRV at baseline (m/sec)	2.51 (0.25)	2.23 (0.27)	<0.01	0.03
TRV at baseline≥2.5m/s (%)	13 (52)	2 (13.33)	0.02	0.09
TRV at year 2 (m/sec)	2.47 (0.28)	2.28 (0.23)	0.03	0.09
TRV at year 2 ≥2.5m/s (%)	12 (48)	3 (20)	0.10	0.18

NOTE: Values presented as mean (standard deviation) for continuous variables or frequency(group%); Test between group differences using Fishers Exact test for categorical variables and 2-sample T-test or Wilcoxon rank sum test for continuous variables. [a] raw p-value. [b] False Discovery Rate (FDR) adjusted p-value. Group 4 represents participants who are on monthly blood transfusions at both baseline and 2-year evaluation. MCV: mean corpuscular volume, HbF: fetal hemoglobin, Hb: hemoglobin, TRV: tricuspid regurgitant velocity

Supplemental Table 3. Associations between laboratory or clinical markers and TRV as a categorical (≥2.5m/sec) variable in each group and the whole cohort.

	Group 1			Group 2			Group 3			Group 4			All		
	Est	**SE**	**P**	**Est**	**SE**	**P**	**Est**	**SE**	**P**	**Est**	**SE**	**P**	**Est**	**SE**	**P**
Hb#	-0.61	0.26	0.03	-0.56	0.30	0.07	0.16	0.20	0.40	-0.21	0.33	0.53	-0.04	0.02	<0.05
ARC#	9.09	2.84	<0.01^	4.09	3.11	0.20	1.71	2.97	0.57	0.42	3.04	0.89	0.75	0.26	<0.01
LDH	0.78	0.31	0.02	0.46	0.36	0.22	0.08	0.24	0.74	0.3	0.35	0.39	0.07	0.03	<0.01
Bilirubin	0.44	0.82	0.60	0.71	1.16	0.54	1.15	0.83	0.17	1.14	1.1	0.31	0.15	0.08	0.07
WBC	0.64	0.98	0.51	-1.10	1.41	0.44	-0.99	0.95	0.30	-1.94	1.34	0.16	-0.02	0.10	0.88
Platelet	0.05	0.29	0.85	0.18	0.36	0.62	0.35	0.21	0.10	-0.22	0.37	0.56	0.04	0.03	0.12
vWF	0.29	0.40	0.46	0.30	0.56	0.59	0.32	0.42	0.45	1.23	0.84	0.16	0.07	0.05	0.13
FVIII	0.07	0.42	0.86	0.51	0.58	0.38	-0.08	0.43	0.86	0.25	0.68	0.72	0.05	0.05	0.28
CRP#	-0.19	0.41	0.65	-0.56	0.47	0.24	-0.57	0.59	0.34	1.41	2.18	0.53	-0.06	0.04	0.18
Ferritin	-0.14	0.16	0.38	-0.57	0.29	0.06	-0.24	0.15	0.11	-0.13	0.10	0.22	-0.02	0.01	0.09
E-selectin	0.50	0.34	0.15	0.21	0.48	0.67	0.20	0.42	0.64	2.19	1.12	0.07	0.08	0.04	0.09
EGF	-0.15	0.18	0.42	-0.18	0.25	0.49	0.15	0.20	0.45	-0.31	0.30	0.32	-0.02	0.02	0.34
IL7	0.74	0.52	0.16	0.85	0.75	0.27	-0.36	0.40	0.38	0.48	0.76	0.54	0.03	0.05	0.57
sVCAM	0.31	0.33	0.34	0.17	0.32	0.60	-0.16	0.23	0.50	0.68	0.48	0.17	0.01	0.03	0.68
MIP-1a	0.02	0.06	0.71	0.02	0.10	0.83	-0.03	0.09	0.72	0	0.16	0.99	0	0.01	0.92
MIP-1b	0.74	0.35	0.04	-0.08	0.49	0.87	0.50	0.36	0.17	1.67	0.74	0.04	0.10	0.04	0.01
sCD40L	0.07	0.10	0.48	0.12	0.15	0.45	-0.10	0.10	0.31	-0.01	0.17	0.97	0.01	0.01	0.58
IFNa2	0.31	0.18	0.08	0.63	0.30	<0.05	-0.02	0.18	0.91	0.50	0.36	0.19	0.05	0.02	0.03
IL4	0.21	0.24	0.39	0.70	0.39	0.09	-0.37	0.32	0.26	0.34	0.41	0.43	0.04	0.03	0.21
NT-proBNP	0.15	0.17	0.38	0.17	0.26	0.51	0.22	0.21	0.31	-0.31	0.33	0.36	0.01	0.02	0.51
UPCR	0.06	0.26	0.81	0.77	0.44	0.09	0.40	0.19	0.04	0.10	0.37	0.80	0.06	0.02	0.02
# #ACS	0.18	0.72	0.80	-1.53	0.93	0.11	-0.02	0.43	0.96	-0.15	1.08	0.89	-0.15	0.32	0.63
# #VOC	-0.13	0.16	0.42	0.20	0.10	0.06	-0.03	0.10	0.74	-0.53	0.45	0.24	0.02	0.06	0.73
# # ACS + VOC	-0.11	0.15	0.47	0.17	0.10	0.08	-0.03	0.09	0.76	-0.42	0.37	0.26	0.01	0.06	0.81

NOTE: Est (slope estimate), SE (standard error) and p value calculated using generalized linear mixed effect model (GLMM) with a binomial link function with adjusting age at baseline, gender, time point and group (only for All). #Except for Hb, ARC and CRP, the cube root of laboratory values were used in GLMM model. ##The effect of event counts (ACS: acute chest syndrome, VOC: acute pain crisis, ACS+VOC: combined ACS and VOC events) on tricuspid regurgitant velocity ≥ 2.5m/sec where the estimate is the slope of the regression curve. ^pFDR= 0.05. Hb: hemoglobin, ARC: absolute reticulocyte count, LDH: lactate dehydrogenase, WBC: white blood cell count, vWF: von willebrand factor, CRP: C-reactive protein, sVCAM: soluble vascular cell adhesion molecule, EGF: epidermal growth factor, IL-7: interleukin-7 , MIP-1a and MIP-1b: macrophage inflammatory protein, sCD40L: soluble CD40 ligand, IFNα2: interferon alpha-2, IL4: interleukin-4, NT-pro BNP: N-terminal pro-brain natriuretic factor, UPCR: urine protein creatinine ratio.