

**Rapid decline in estimated glomerular filtration rate in sickle cell anemia: results of a multicenter pooled analysis**

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## SUPPLEMENTARY MATERIALS

Supplementary Table 1: Baseline Demographic, Laboratory and Clinical Variables in Individual Patient Cohorts

Characteristic	N	UNC Cohort Number (%) / Median (IQR)	N	Duke Cohort Number (%) / Median (IQR)	N	UIC Cohort Number (%) / Median (IQR)	N	Methodist Cohort Number (%) / Median (IQR)
Age	236	28 (20.5, 39.5)	203	28.0 (21.0, 38.0)	94	33.3 (25.9, 43.9)	73	18 (18, 18)
Sex (female)	236	133 (56.4)	203	103 (50.7)	94	57 (60.6)	73	34 (46.6)
Weight (kg)	230	65.5 (57.1, 75.8)	178	67.4 (58.9, 76.5)	79	68.0 (61.2, 75.3)	69	58.6 (53.3, 66.2)
Height (cm)	89	170.3 (163.0, 175.9)	N/A	N/A	85	170.2 (165.1, 175.3)	72	167.7 (161.5, 174.6)
WBC (x10 <sup>9</sup> /L)	236	10.8 (8.4, 13.0)	161	10.3 (7.7, 13.5)	94	10.3 (7.9, 12.5)	73	9.2 (6.8, 13.6)
Hemoglobin (g/dL)	236	8.8 (7.8, 10.0)	161	8.6 (7.6, 9.8)	94	8.7 (7.9, 9.6)	73	9.5 (8.7, 10.2)
Hematocrit (%)	236	26.2 (22.9, 28.9)	161	24.5 (21.3, 28.0)	93	26.0 (23.0, 28.9)	72	27.6 (25.6, 30.0)
Reticulocyte Count (x10 <sup>9</sup> /L)	222	218.7 (148.5, 303.4)	142	277.8 (193.0, 403.7)	94	349.0 (243.0, 464.0)	6	160.9 (119.6, 226.4)
Platelet Count (x10 <sup>9</sup> /L)	230	427.0 (319.0, 545.0)	161	400.3 (287.7, 479.7)	94	463.0 (345.0, 549.0)	73	360 (271, 453)
Baseline eGFR (mL/min/1.73m <sup>2</sup> )	236	140.4 (120.1, 155.9)	203	143.3 (119.6, 158.1)	94	130.0 (101.0, 146.0)	73	166 (158.8, 174.8)
Blood Urea Nitrogen (mg/dL)	226	8.0 (6.0, 10.0)	N/A	N/A	94	7.0 (5.0, 11.0)	N/A	N/A
Total Bilirubin (mg/dL)	213	2.4 (1.5, 4.3)	152	2.35 (1.5, 3.9)	92	2.50 (1.65, 3.90)	73	2.4 (1.6, 3.8)
Direct Bilirubin (mg/dL)	52	0.09 (0.09, 0.10)	N/A	N/A	90	0.40 (0.30, 0.60)	66	0.3 (0.2, 0.3)
Ferritin (ng/mL)	95	307 (124, 1340)	126	491 (184, 1153)	81	566 (171, 1276)	26	984 (591, 2535)
Hemoglobinuria (Yes)	119	15 (12.6)	154	26 (16.9)	90	29 (32.2)	N/A	N/A
Proteinuria* (Yes)	131	26 (19.9)	154	42 (27.3)	N/A	N/A	N/A	N/A
Albumin-Creatinine Ratio (mcg/mg)	N/A	N/A	N/A	N/A	20	82.5 (23.5, 295.5)	N/A	N/A
Hemoglobin F (%)	112	6.15 (3.2, 10.4)	102	9.4 (4.6, 17.4)	94	6.9 (3.3, 11.4)	62	10.0 (4.0, 18.9)
H/O Acute Chest Syndrome (Yes)	226	197 (87.2)	175	133 (76)	94	45 (47.9)	73	41 (56.2)
H/O Stroke (Yes)	216	36 (16.7)	172	36 (20.9)	94	26 (27.7)	73	6 (8.2)
H/O Leg Ulcers (Yes)	197	38 (19.3)	169	35 (20.7)	94	15 (16.0)	73	0 (0)
H/O Priapism** (Yes)	86	37 (43.0)	84	(36 (42.9))	63	8 (25.8)	N/A	N/A
H/O Avascular Necrosis (Yes)	162	64 (39.5)	170	53 (31.2)	94	35 (37.2)	N/A	N/A
Systolic Blood Pressure (mm Hg)	236	119 (109, 130)	177	118 (109, 125)	94	118 (110, 128)	71	118.0 (110.0, 125.0)

Diastolic Blood Pressure (mm Hg)	236	70 (62, 76)	177	69 (63, 75)	94	69 (62, 75)	71	61.0 (57.0, 69.0)
H/O Diabetes (Yes)	236	7 (3.0)	155	0 (0)	94	4 (4.3)	73	0 (0)
Chronic RBC Transfusion (Yes)	236	11 (4.7)	174	10 (5.8)	94	11 (11.7)	73	26 (35.6)
Hydroxyurea Therapy (Yes)	234	98 (41.9)	203	105 (51.7)	94	57 (60.6)	73	61 (83.6)
RAAS Blocking Agents (Yes)	235	24 (10.2)	N/A	N/A	94	14 (14.9)	N/A	N/A

\* Proteinuria – at least 1+ by dipstick urinalysis

\*\*Male patients only

RAAS Blocking Agents – Renin-angiotensin-aldosterone system blocking agents (Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers).

WBC – White blood cell count

**Supplementary Table 2: Prevalence of Hyperfiltration and Rapid eGFR Decline in Pooled and Individual Patient Cohorts**

<b>Variable</b>	<b>Pooled Cohorts (N = 607) Number (%)</b>	<b>UNC Cohort (N = 236) Number (%)</b>	<b>Duke Cohort (N = 203) Number (%)</b>	<b>UIC Cohort (N = 94) Number (%)</b>	<b>Methodist Cohort (N = 73) Number (%)</b>
Prevalence of hyperfiltration	375 (61.9)	138 (58.5)	123 (60.6)	43 (45.7)	71 (97.3)
Prevalence of rapid eGFR decline (>3 mL/min/1.73m <sup>2</sup> per year)	216 (35.6)	80 (33.9)	74 (36.5)	28 (29.8)	34 (46.6)
Prevalence of rapid eGFR decline (>5 mL/min/1.73m <sup>2</sup> per year)	149 (24.6)	48 (20.3)	51 (25.1)	21 (22.3)	29 (39.7)
Prevalence of CKD progression (<90 mL/min/1.73 m <sup>2</sup> and ≥ 25% decline in baseline eGFR)	130 (21.5)	48 (20.3)	49 (24.1)	32 (34.0)	1 (1.37)
Prevalence of CKD progression (<90 mL/min/1.73 m <sup>2</sup> and ≥ 50% decline in baseline eGFR)	55 (9.1)	21 (8.9)	23 (11.3)	10 (10.6)	1 (1.37)

**Supplementary Table 3: Association of Clinical and laboratory Variables with eGFR Declines >3.0 mL/min/1.73 m<sup>2</sup> and >5.0 mL/min/1.73 m<sup>2</sup> per year in Individual Patient Cohorts**

<b>Association of Clinical and laboratory Variables with eGFR Declines &gt;3.0 mL/min/1.73 m<sup>2</sup> per year in Individual Patient Cohorts</b>								
<b>Characteristic</b>	<b>UNC Cohort</b>	<b>p Value</b>	<b>Duke Cohort</b>	<b>p Value</b>	<b>UIC Cohort</b>	<b>p Value</b>	<b>Methodist Cohort</b>	<b>p Value</b>
Age	1.04 (1.01, 1.06)	0.0035	1.02 (0.99, 1.04)	0.20	1.024 (0.99, 1.06)	0.22	1.028 (0.62, 1.71)	0.92
Sex (male)	1.59 (0.93, 2.74)	0.093	1.35 (0.76, 2.40)	0.30	1.23 (0.50, 3.02)	0.65	1.20 (0.48, 3.03)	0.69
WBC	0.98 (0.90, 1.06)	0.55	1.02 (0.94, 1.10)	0.64	0.97 (0.83, 1.12)	0.66	0.97 (0.89, 1.06)	0.53
Hemoglobin	0.87 (0.72, 1.04)	0.12	0.82 (0.67, 1.01)	0.066	0.72 (0.50, 1.03)	0.071	1.48 (0.98, 2.24)	0.066
Hematocrit	0.96 (0.90, 1.02)	0.21	0.93 (0.87, 1.0)	0.051	0.88 (0.79, 0.99)	0.034	1.12 (0.98, 1.29)	0.11
Reticulocyte Count	0.998 (0.995, 1.0)	0.069	1.001 (0.999, 1.003)	0.26	1.001 (0.998, 1.005)	0.35	N/A	N/A
Platelet Count	1.0 (0.998, 1.001)	0.69	0.999 (0.997, 1.001)	0.38	0.998 (0.995, 1.002)	0.32	0.998 (0.995, 1.001)	0.21
Baseline eGFR	0.98 (0.97, 0.99)	0.0015	1.01 (0.99, 1.02)	0.23	1.004 (0.99, 1.02)	0.62	1.039 (1.004, 1.075)	0.028
Blood Urea Nitrogen	1.06 (1.01, 1.12)	0.02	N/A	N/A	0.99 (0.91, 1.07)	0.76	N/A	N/A
Total Bilirubin	0.95 (0.83, 1.08)	0.42	1.03 (0.93, 1.14)	0.55	1.18 (0.99, 1.40)	0.054	0.91 (0.71, 1.19)	0.50
Direct Bilirubin	2.44 (0.54, 11.06)	0.25	N/A	N/A	3.12 (1.15, 8.42)	0.026	0.32 (0.038, 2.63)	0.29
Indirect Bilirubin	0.80 (0.56, 1.14)	0.22	N/A	N/A	1.15 (0.95, 1.39)	0.15	0.99 (0.75, 1.31)	0.96
Ferritin	1.0 (1.0, 1.001)	0.034	1.0 (1.0, 1.001)	0.018	1.0 (1.0, 1.0)	0.51	1.0 (0.999, 1.00)	0.65
Hemoglobinuria	1.41 (0.46, 4.35)	0.55	1.10 (0.45, 2.69)	0.83	7.04 (2.56, 19.4)	0.0002	N/A	N/A
Proteinuria	2.41 (0.97, 5.96)	0.057	1.35 (0.64, 2.86)	0.44	N/A	N/A	N/A	N/A
Albumin-Creatinine Ratio	N/A	N/A	N/A	N/A	1.0 (0.998, 1.003)	0.80	N/A	N/A
Hemoglobin F	0.94 (0.87, 1.01)	0.068	0.98 (0.93, 1.02)	0.31	0.98 (0.91, 1.06)	0.64	1.045 (0.98, 1.11)	0.16
Weight	1.01 (0.99, 1.03)	0.36	0.98 (0.96, 1.01)	0.16	1.006 (0.97, 1.04)	0.77	1.003 (0.97, 1.038)	0.84
Height	1.07 (0.996, 1.16)	0.062	N/A	N/A	1.03 (0.96, 1.097)	0.46	1.001 (0.95, 1.06)	0.98
H/O Acute Chest Syndrome	1.31 (0.54, 3.17)	0.55	1.42 (0.67, 3.01)	0.36	1.41 (0.54, 3.66)	0.48	0.95 (0.36, 2.49)	0.91
H/O Stroke	3.51 (1.62, 7.57)	0.0014	2.03 (0.95, 4.33)	0.068	1.295 (0.48, 3.49)	0.61	1.14 (0.21, 6.11)	0.88
H/O Leg Ulcers	0.75 (0.33, 1.73)	0.50	1.57 (0.68, 3.61)	0.29	2.99 (0.90, 9.90)	0.073	N/A	N/A
H/O Avascular Necrosis	0.99 (0.49, 2.02)	0.98	0.68 (0.32, 1.44)	0.31	1.51 (0.59, 3.88)	0.40	N/A	N/A
Systolic Blood Pressure	1.02 (0.997, 1.03)	0.11	1.01 (0.99, 1.03)	0.43	0.99 (0.96, 1.03)	0.72	0.98 (0.94, 1.02)	0.32
Diastolic Blood Pressure	1.01 (0.99, 1.03)	0.25	1.02 (0.98, 1.05)	0.38	0.99 (0.94, 1.04)	0.60	0.96 (0.91, 1.02)	0.18
H/O Diabetes	1.42 (0.28, 7.09)	0.67	N/A	N/A	0.48 (0.04, 5.38)	0.55	N/A	N/A
Chronic RBC Transfusion	2.30 (0.65, 8.10)	0.20	2.05 (0.56, 7.56)	0.28	2.43 (0.66, 8.98)	0.18	0.75 (0.28, 1.997)	0.56
Hydroxyurea Therapy	1.18 (0.67, 2.08)	0.57	0.99 (0.54, 1.80)	0.96	1.45 (0.56, 3.74)	0.45	5.71 (1.11, 29.5)	0.037
RAAS Blocking Agents	2.55 (1.0, 6.51)	0.05	N/A	N/A	1.66 (0.49, 5.61)	0.42	N/A	N/A
<b>Association of Clinical and laboratory Variables with eGFR Declines &gt;5.0 mL/min/1.73 m<sup>2</sup> per year in Individual Patient Cohorts</b>								
<b>Characteristic</b>	<b>UNC Cohort</b>	<b>p value</b>	<b>Duke Cohort</b>	<b>p value</b>	<b>UIC Cohort</b>	<b>p value</b>	<b>Methodist Cohort</b>	<b>p value</b>
Age	1.03 (1.01, 1.06)	0.011	1.01 (0.98, 1.04)	0.61	1.02 (0.98, 1.06)	0.44	1.02 (0.61, 1.70)	0.95
Sex (male)	1.24 (0.66, 2.35)	0.50	1.22 (0.65, 2.30)	0.54	1.21 (0.45, 3.23)	0.71	1.42 (0.55, 3.65)	0.47
WBC	0.99 (0.90, 1.1)	0.99	1.02 (0.94, 1.11)	0.64	1.07 (0.92, 1.26)	0.38	0.94 (0.85, 1.04)	0.21
Hemoglobin	0.82 (0.66, 1.01)	0.06	0.66 (0.51, 0.86)	0.0017	0.68 (0.46, 1.0)	0.051	1.34 (0.89, 2.03)	0.16
Hematocrit	0.95 (0.88, 1.02)	0.14	0.88 (0.81, 0.96)	0.0035	0.88 (0.77, 0.998)	0.046	1.10 (0.96, 1.27)	0.18
Reticulocyte Count	0.998 (0.994, 1.001)	0.17	1.001 (0.999, 1.003)	0.36	1.004 (1.001, 1.008)	0.017	N/A	N/A
Platelet Count	1.0 (0.999, 1.002)	0.63	0.999 (0.997, 1.002)	0.58	0.998 (0.994, 1.002)	0.36	0.997 (0.994, 1.0)	0.11
Baseline eGFR	0.98 (0.97, 0.99)	0.0006	1.0 (0.99, 1.01)	0.53	1.0 (0.99, 1.02)	0.72	1.03 (0.997, 1.06)	0.076
Blood Urea Nitrogen	1.07 (1.02, 1.13)	0.008	N/A	N/A	1.02 (0.94, 1.11)	0.70	N/A	N/A

Total Bilirubin	1.01 (0.87, 1.17)	0.90	1.09 (0.98, 1.21)	0.13	1.07 (0.90, 1.26)	0.44	0.92 (0.70, 1.20)	0.52
Direct Bilirubin	6.13 (0.41, 91.0)	0.19	N/A	N/A	2.82 (1.1, 7.15)	0.029	0.39 (0.05, 2.98)	0.36
Indirect Bilirubin	0.82 (0.52, 1.28)	0.38	N/A	N/A	1.0 (0.81, 1.24)	0.99	1.02 (0.77, 1.35)	0.92
Ferritin	1.0 (1.0, 1.001)	0.043	1.0 (1.0, 1.0)	0.018	1.0 (1.0, 1.001)	0.15	0.999 (0.999, 1.0)	0.24
Hemoglobinuria	2.22 (0.67, 7.33)	0.19	1.72 (0.68, 4.33)	0.25	11.8 (3.63, 37.98)	<0.0001	N/A	N/A
Proteinuria	3.8 (1.45, 9.98)	0.0068	1.95 (0.88, 4.32)	0.10	N/A	N/A	N/A	N/A
Albumin-Creatinine Ratio	N/A	N/A	N/A	N/A	1.0 (0.998, 1.003)	0.77	N/A	N/A
Hemoglobin F	0.97 (0.90, 1.04)	0.39	0.97 (0.92, 1.02)	0.24	0.9 (0.81, 1.0)	0.053	1.07 (0.99, 1.14)	0.052
Weight	0.99 (0.98, 1.02)	0.87	0.98 (0.96, 1.01)	0.19	1.0 (0.96, 1.04)	0.99	1.01 (0.97, 1.04)	0.75
Height	1.06 (0.98, 1.16)	0.16	N/A	N/A	1.04 (0.97, 1.12)	0.27	0.995 (0.94, 1.05)	0.85
H/O Acute Chest Syndrome	1.91 (0.61, 6.05)	0.27	1.27 (0.55, 2.93)	0.58	2.0 (0.69, 5.78)	0.20	1.12 (0.42, 3.02)	0.82
H/O Stroke	2.67 (1.17, 6.08)	0.019	1.46 (0.64, 3.3)	0.37	1.85 (0.65, 5.31)	0.25	0.71 (0.12, 4.19)	0.70
H/O Leg Ulcers	0.70 (0.26, 1.88)	0.48	1.69 (0.69, 4.16)	0.25	2.66 (0.76, 9.31)	0.13	N/A	N/A
H/O Avascular Necrosis	0.82 (0.36, 1.85)	0.63	0.61 (0.26, 1.40)	0.24	1.21 (0.43, 3.42)	0.72	N/A	N/A
Systolic Blood Pressure	1.01 (0.99, 1.03)	0.57	1.02 (0.99, 1.04)	0.09	1.01 (0.97, 1.04)	0.79	0.97 (0.93, 1.01)	0.18
Diastolic Blood Pressure	1.01 (0.98, 1.03)	0.64	1.03 (0.99, 1.06)	0.16	1.01 (0.96, 1.07)	0.59	0.93 (0.87, 0.99)	0.032
H/O Diabetes	1.35 (0.23, 7.86)	0.74	N/A	N/A	N/A	N/A	N/A	N/A
Chronic RBC Transfusion	1.15 (0.23, 5.68)	0.86	2.28 (0.60, 8.69)	0.23	3.84 (1.01, 14.6)	0.048	0.68 (0.25, 1.88)	0.46
Hydroxyurea Therapy	0.85 (0.43, 1.65)	0.63	0.95 (0.49, 1.84)	0.88	1.33 (0.47, 3.73)	0.59	N/A	N/A
RAAS Blocking Agents	1.79 (0.67, 4.78)	0.25	2.17 (1.04, 4.53)	94	2.01 (0.56, 7.21)	0.29	N/A	N/A

WBC – White blood cell count; eGFR – Estimated glomerular filtration rate; RBC – Red blood cell; RAAS Blocking Agents – Renin-angiotensin-aldosterone system blocking agents (Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers).

**Reference Ranges for Routine Laboratory Parameters in Adults**

<b>Variable</b>	<b>Normal Range</b>
White Blood Cell Count (x10 <sup>9</sup> /L)	4.2 – 10.2
Hemoglobin (g/dL)	11.5 – 14.8
Hematocrit (%)	34.6 – 43.8
Reticulocyte Count (x10 <sup>9</sup> /L)	30.0 – 90.0
Platelet Count (x10 <sup>9</sup> /L)	150 - 400
Baseline eGFR (mL/min/1.73m <sup>2</sup> )	>60
Blood Urea Nitrogen (mg/dL)	7 - 18
Total Bilirubin (mg/dL)	0.2 – 1.0
Direct Bilirubin (mg/dL)	<0.2
Ferritin (ng/mL)	8.0 – 252.0