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

Chronic kidney disease (CKD), typically defined as kidney damage or decreased kidney function for 3 or more months, is common in sickle cell disease (SCD).[1] Increasing evidence suggests that the glomerulopathy of SCD is progressive.[2] CKD is associated with increased mortality in SCD.[3] Based on single center studies, we previously reported on the high prevalence of rapid decline in kidney function, defined as estimated glomerular filtration rate (eGFR) loss >3.0 mL/min/1.73 m^2 per year, in SCD.[4-6] In the present study, we further examine rapid eGFR decline in sickle cell anemia, using a pooled analysis of patients to better characterize factors associated with such decline and its association with mortality.

Patients from four centers, University of North Carolina at Chapel Hill (UNC), Duke University Medical Center (Duke), University of Illinois at Chicago (UIC), and St. Jude Children's Research Hospital/Methodist University Comprehensive Sickle Cell Center (Methodist) were analyzed.[4,5,7,8] Patients, at least 18 years old, with sickle cell anemia, were evaluated during routine visits while in "steady state". Baseline visit was defined as the first available serum creatinine measurement during the study period. Only patients with two or more measures of kidney function over the observation period were included. Mortality during the observation period was assessed by medical record review and/or by utilizing the US Social Security Death Index. Approvals were obtained from Institutional Review Boards at each institution.

Estimated GFR was calculated using the creatinine-based chronic kidney disease epidemiology collaboration (CKD-EPI) equation.[9] Rapid decline of kidney function was defined as eGFR loss of >3.0 mL/min/1.73 m^2 per year[10] or eGFR loss of >5.0 mL/min/1.73 m^2 per year.[11] Rapid decline of kidney function, using these thresholds, was ascertained based on the slope in a linear model, with eGFR as the response and time as the covariate, using all available observations from a patient. The slope was defined as the estimate of the regression coefficient for time. CKD progression was defined as a decline in eGFR to <90 mL/min/1.73m^2 and at least 25% decline from baseline,[11] or eGFR decline to <90 mL/min/1.73m^2 and at least 50% decline from baseline or requiring renal replacement therapy.[12]

Variables of interest were summarized by median and interquartile ranges (IQR) if continuous, or by counts and percentages if categorical. In order to evaluate eGFR change over time, a linear mixed effects model with subject level random effects for intercept and slope for time was fitted, adjusting for baseline age, sex and cohort. Stratified analyses according to hyperfiltration at baseline were conducted. Logistic regression analyses were employed to evaluate variables associated with rapid decline in eGFR. In multivariable analyses, variables associated with rapid decline in eGFR with P-values <0.3 in individual analyses, but without an excess of missing data (<20% missing data), were included in the initial model. Cox regression analyses were employed to evaluate the association of rapid decline in eGFR with mortality, from the period of first eGFR assessment to the last assessment.

The analysis included 606 individuals with sickle cell anemia (HbSS, HbSβ^0), 236 from UNC (followed from 2004 – 2013), 203 from Duke (followed from 2002 – 2016), 94 from UIC (followed from 2009 – 2017) and 73 from Methodist (followed from 2006 – 2017). The median observation period was 5.20 years (IQR: 1.56-7.53), with 31,286 patient-years of observation. The median patient age in the pooled analysis was 27 years (IQR: 20-38) and 327 (54.0%) were female (Table 1). Baseline laboratory and clinical data in individual cohorts are shown in the *Online Supplementary Table S1*. In evaluating the change in eGFR over time in the pooled analysis, only the main cohort effect was retained as the time-cohort interaction was not significant (P=0.19). For all patients, the change in eGFR over time, adjusted for baseline age, sex and main cohort effect, was -2.36 mL/min/1.73 m^2 per year (95% Confidence Interval [CI]: -2.68 to -2.04; P<0.0001) (Figure 1A). In patients with hyperfiltration, the time-cohort interaction was significant (P=0.008), so both main cohort and interaction effects were retained. The estimated change in eGFR over time for patients with hyperfiltration, without consideration of the time-cohort interaction, was -2.09 mL/min/1.73 m^2 per year (95% CI: -2.50 to -1.69; P<0.0001). In patients without hyperfiltration, the time-cohort interaction was not significant (P=0.97),

Table 1. Baseline demographic, laboratory and clinical variables in pooled patient cohorts with sickle cell anemia.

Variable	Total Number	Median (IQR) /Number (%)
Age (years)	606	27 (20, 38)
Sex (female)	606	327 (54.0)
Weight (kg)	556	65·8 (57.7, 75.3)
Height (cm)	246	169·5 (163.0, 175.5)
White Blood Cell Count (x10^9/L)	564	10·5 (7.9, 13.0)
Hemoglobin (g/dL)	564	8·8 (7.8, 9.9)
Hematocrit (%)	562	26·0 (22.8, 29.0)
Reticulocyte Count (x10^9/L)	464	258·7 (179.0, 364.6)
Platelet Count (x10^9/L)	558	416 (310.7, 523.0)
Baseline eGFR (mL/min/1.73m^2)	606	143·9 (120.4, 159.7)
Blood Urea Nitrogen (mg/dL)	320	8·0 (6.0, 11.0)
Total Bilirubin (mg/dL)	530	2·4 (1.5, 4.0)
Direct Bilirubin (mg/dL)	214	0·3 (0.2, 0.5)
Ferritin (ng/mL)	328	524·5 (159.5, 1308.0)
Hemoglobinuria (Yes)	363	70 (19.3)
Proteinuria* (Yes)	305	73 (23.9)
Albumin-Creatinine Ratio (mcg/mg)	20	82.5 (23.5, 295.5)
Hemoglobin F (%)	370	7.7 (3.6, 14.2)
H/O Acute Chest Syndrome (Yes)	568	416 (73.2)
H/O Stroke (Yes)	555	104 (18.7)
H/O Leg Ulcers (Yes)	533	88 (16.5)
H/O Priapism** (Yes)	201	81 (40.3)
H/O Avascular Necrosis (Yes)	426	152 (35.7)
Systolic Blood Pressure (mm Hg)	578	118 (109, 128)
Diastolic Blood Pressure (mm Hg)	578	68 (61, 74)
H/O Diabetes (Yes)	558	11 (2.0)
Chronic RBC Transfusion (Yes)	577	58 (10.1)
Hydroxyurea Therapy (Yes)	604	321 (53.2)
RAAS Blocking Agents (Yes)	329	38 (11.6)

*Proteinuria – at least 1+ by dipstick urinalysis; **Male patients only. eGFR: estimated glomerular filtration rate; RAAS: blocking agents: renin-angiotensin-aldosterone system blocking agents (Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers); IQR: interquartile range.

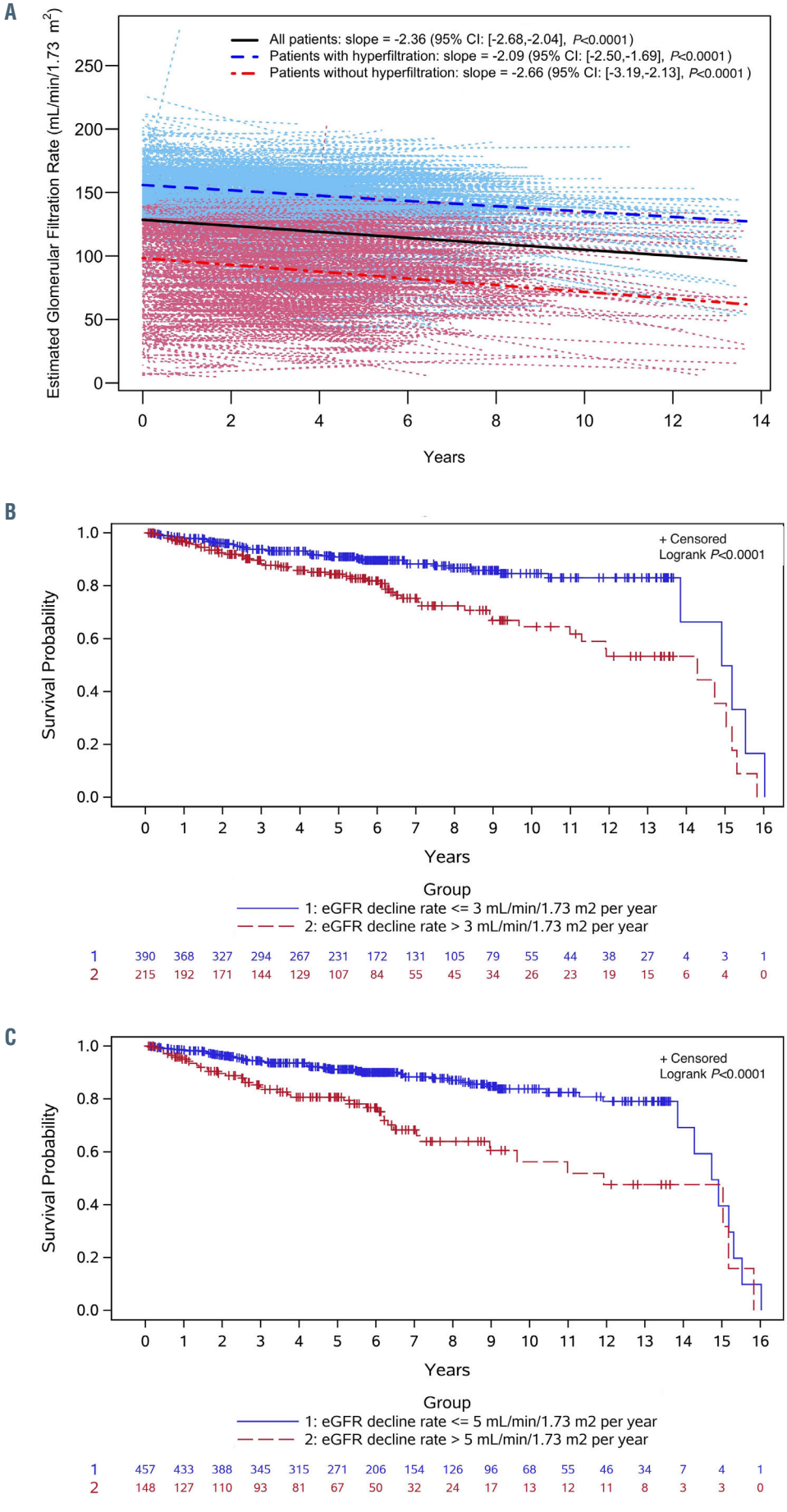

Figure 1. The slope of estimated glomerular filtration rate (eGFR) decline in sickle cell anemia and the association of rapid eGFR decline with mortality in the pooled population are shown. (A) The change in eGFR over time, adjusted for baseline age, sex and main cohort effect, was -2.36 mL/min/1.73 m^2 per year (95% Confidence Interval [CI]: -2.68 to-2.04; *P*<0.0001). (B) Kaplan-Meier estimates of the survival probabilities for rapid (>3.0 mL/min/1.73m^2 per year) and non-rapid eGFR decline groups (log-rank test; *P*<0.0001). (C) Kaplan-Meier estimates of the survival probabilities for rapid (>5.0 mL/min/1.73 m^2 per year) and non-rapid eGFR decline groups (log-rank test; *P*<0.0001). The number of patients at risk at each time point are shown in (B) and (C).

hence only the main cohort effect was retained. The change in eGFR over time was -2.66 mL/min/1.73 m^2 per year (95%CI: -3.19 to -2·13; *P*<0.0001).

Rapid decline of kidney function, defined as eGFR loss >3.0 mL/min/1.73 m^2 per year, was observed in 216 patients (35.6%), and in 149 patients (24.6%) when defined as eGFR loss >5.0 mL/min/1.73 m^2 per year (*Online Supplementary Table S2*). CKD progression was observed in 130 of 606 patients (21.5%), defined as eGFR decline to <90 mL/min/1.73 m^2 and at least 25% decline from baseline, and in 55 of 606 patients (9.1%) defined as eGFR decline to <90 mL/min/1.73 m^2 and at least 50% decline from baseline. Using a threshold of >3.0 mL/min/1.73 m^2 per year, 96 of 216 patients (44.4%) with rapid decline had CKD progression defined as ≥25% eGFR decline from baseline, while 48 of 216 patients (22.2%) had CKD progression defined as ≥50% eGFR decline from baseline. Using a threshold of >5.0 mL/min/1.73 m^2 per year, 76 of 149 patients (51.0%) with rapid decline had CKD progression defined as ≥25% eGFR decline from baseline, while 43 of 149 patients (28.9%) had CKD progression defined as ≥50% eGFR decline from baseline.

The association of baseline variables with rapid eGFR decline (>3.0 mL/min/1.73 m^2 per year) in the pooled population was examined (Table 2). Adjusted for cohort, we observed significantly increased odds of rapid decline with increasing age and male sex. Adjusted for age, sex, and cohort, there were significantly lower odds of rapid decline with higher hemoglobin and hematocrit. The odds of rapid decline in kidney function were significantly increased with higher levels of direct bilirubin and ferritin, as well as hemoglobinuria, history of stroke and use of ACE inhibitors/angiotensin receptor blockers.

Adjusted for cohort, we similarly observed significantly increased odds of rapid decline, using a threshold of >5.0 mL/min/1.73 m^2 per year, with increasing age (Table 2). Adjusted for age, sex, and cohort, there were lower odds of rapid decline with higher hemoglobin and hematocrit. The odds of rapid decline were significantly increased with higher baseline blood urea nitrogen, direct bilirubin and ferritin, as well as hemoglobinuria, proteinuria, and history of stroke. Associations of covariates with rapid decline in individual cohorts are shown in the *Online Supplementary Table S3*. Using a

Table 2. Association of clinical and laboratory variables with rapid decline of eGFR in pooled patient cohorts with sickle cell anemia.

Variable*	Rapid decline based on >3.0 mL/min/1.73 m^2 threshold		Rapid decline based on >5.0 mL/min/1.73 m^2 threshold	
	Odds ratio (95% CI)	*P*	Odds ratio (95% CI)	*P*
Age**	1.03 (1.01, 1.04)	0.0011	1·02 (1.003, 1.04)	0.02
Sex (Male)**	1.40 (1.0, 1.96)	0.05	1.25 (0.86, 1.82)	0.24
White Blood Cell Count	0.99 (0.94, 1.03)	0.52	0.99 (0.95, 1.04)	0.80
Hemoglobin	0.89 (0.79, 0.996)	0.042	0.80 (0.70, 0.92)	0.0012
Hematocrit	0.96 (0.92, 0.995)	0.029	0.93 (0.89, 0.98)	0.0029
Reticulocyte Count	1.0 (0.999, 1.001)	0.99	1.001 (0.999, 1.002)	0.39
Platelet Count	0.999 (0.998, 1.0)	0.14	0.999 (0.998, 1.001)	0.36
Baseline eGFR	1.0 (0.99, 1.01)	0.91	0.997 (0.991, 1.004)	0.44
Blood Urea Nitrogen	1.04 (0.99, 1.08)	0.054	1.06 (1.01, 1.098)	0.0089
Total Bilirubin	1.02 (0.95, 1.09)	0.58	1.05 (0.98, 1.13)	0.21
Direct Bilirubin	1.74 (1.01, 2.97)	0.044	1.99 (1.15, 3.43)	0.013
Indirect Bilirubin	1.02 (0.90, 1.16)	0.72	0.98 (0.85, 1.13)	0.79
Ferritin$^{\Phi}$	1.02 (1.01, 1.03)	0.0037	1.02 (1.01, 1.03)	0.0037
Hemoglobinuria	2.16 (1.24, 3.78)	0.007	3.20 (1.79, 5.73)	<0.0001
Proteinuria$^{\neq}$	1.68 (0.94, 2.99)	0.08	2.48 (1.34, 4.58)	0.0037
Albumin-Creatinine Ratio$^{\neq\neq}$	1.0 (0.998, 1.003)	0.80	1.0 (0.998, 1.003)	0.77
Hemoglobin F	0.99 (0.96, 1.02)	0.42	0.99 (0.96, 1.02)	0.48
Weight	1.0 (0.99, 1.01)	0.94	0.996 (0.98, 1.01)	0.55
H/O Acute Chest Syndrome	1.25 (0.82, 1.92)	0.30	1.45 (0.90, 2.35)	0.13
H/O Stroke	2.13 (1.36, 3.34)	0.001	1.77 (1.09, 2.88)	0.021
H/O Leg Ulcers	1.29 (0.77, 2.17)	0.33	1.31 (0.74, 2.32)	0.35
H/O Avascular Necrosis	0.92 (0.59, 1.43)	0.70	0.77 (0.47, 1.28)	0.32
Systolic Blood Pressure	1.01 (0.99, 1.02)	0.31	1.01 (0.99, 1.02)	0.33
Diastolic Blood Pressure	1.01 (0.99, 1.02)	0.44	1.01 (0.99, 1.02)	0.60
H/O Diabetes	0.95 (0.26, 3.47)	0.94	0.65 (0.13, 3.19)	0.60
Chronic RBC Transfusion	1.47 (0.81, 2.68)	0.20	1.39 (0.74, 2.64)	0.31
Hydroxyurea Therapy	1.28 (0.90, 1.83)	0.18	1.20 (0.81, 1.79)	0.37
RAAS Blocking Agents	2.17 (1.04, 4.53)	0.04	1.88 (0.86, 4.09)	0.11

*Results adjusted for age, sex and cohort effects, except that **are adjusted only for cohort effects; RAAS blocking agents: renin-angiotensin-aldosterone system blocking agents (Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers); $^{\neq}$proteinuria (at least 1+ by dipstick urinalysis); $^{\neq\neq}$available in only the UIC cohort; $^{\Phi}$odds ratio is provided for 100 ng/mL increase in ferritin.

threshold of >3.0 mL/min/1.73 m^2 per year, multivariable analysis showed significant associations of rapid decline with age (odds ratio [OR]: 1.03, 95%CI: 1.01-1.04; *P*=0.003), male sex (OR: 1.58, 95%CI: 1.09-2.29; *P*=0.016), and history of stroke (OR: 1.99, 95%CI: 1.25-3.15; *P*=0.004). Using a threshold of >5.0 mL/min/1.73 m^2 per year, significant associations were observed between rapid decline and hemoglobin (OR: 0.83, 95%CI: 0.72-0.96; *P*=0.009) as well as history of stroke (OR: 1.72, 95%CI: 1.03-2.86; *P*=0.038).

Ninety-eight of 605 patients died during the observation period. Adjusted for age, sex, white blood cell count, hemoglobin, baseline eGFR and use of hydroxyurea, rapid eGFR decline, at thresholds of >3.0 mL/min/1.73 m^2 per year and >5.0 mL/min/1.73 m^2 per year, was associated with increased mortality risk (hazard ratio [HR]: 2.41, 95%CI: 1.57-3.69; *P*<0.0001 and HR: 2.90, 95%CI: 1.87-4.48; *P*<0.0001, respectively). Kaplan-Meier estimates showed significantly lower survival probabilities for patients with rapid eGFR decline using both decline thresholds (log-rank test; *P*<0.0001) (Figures 1B and C).

In this multicenter analysis, we confirm accelerated eGFR loss over time in adults with sickle cell anemia, with an average eGFR loss of 2.36 mL/min/1.73 m^2 per year, representing a faster kidney function decline than is reported in African American adults.[13] The observed decline in this pooled cohort is similar to that in patients with diabetes, who have reported eGFR declines of 2.1 and 2.7 mL/min/1.73 m^2 per year, respectively, for women and men.[14] We also confirm the high prevalence of rapid eGFR decline, as well as its impact on survival. Regardless of the threshold, >3.0 mL/min/1.73 m^2 or >5.0 mL/min/1.73 m^2 per year, rapid decline is more frequent in sickle cell anemia than the reported prevalence of 10.5% after 12 years in the African American population.[13] Much like in patients with diabetes,[15] male sex was a significant risk factor for rapid eGFR decline. This is consistent with the finding in a multicenter, observational study, which reported faster kidney function decline in males with SCD.[16]

In age-, sex- and cohort-adjusted analysis, we observed an association of proteinuria with rapid decline of kidney function. However, proteinuria was not included in the multivariable analysis due to severe lack of data. Albuminuria is a known risk factor for progression of CKD.[2]

Increased hemoglobin was associated with a lower risk of rapid eGFR decline. Although not evaluated in the multivariable analysis due to substantial missing data, hemoglobinuria has previously been shown to be associated with albuminuria and CKD progression, suggesting an important role for intravascular hemolysis in the pathogenesis of SCD-related kidney disease.[17] Based on the role of intravascular hemolysis, drugs that decrease hemolysis may prevent or slow the progression of kidney disease in SCD.

Our study is limited by lack of data for several important variables. Approximately 40% of patients had only two eGFR evaluations, which may have had an impact on the estimated change in eGFR over time. Most patients did not have urine albumin-creatinine ratios, limiting assessment of the role of albuminuria.

In conclusion, this pooled analysis confirms the high prevalence of rapid decline in kidney function in adults with sickle cell anemia. The association of rapid decline in kidney function with increased mortality highlights the need for early identification of individuals at risk for such decline.

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References

1. Ataga KI, Derebail VK, Archer DR. The glomerulopathy of sickle cell disease. Am J Hematol. 2014;89(9):907-914.
2. Gosmanova EO, Zaidi S, Wan JY, Adams-Graves PE. Prevalence and progression of chronic kidney disease in adult patients with sickle cell disease. J Investig Med. 2014;62(5):804-807.
3. Thrower A, Ciccone EJ, Maitra P, et al. Effect of renin-angiotensin-aldosterone system blocking agents on progression of glomerulopathy in sickle cell disease. Br J Haematol. 2019;184(2):246-252.
4. Xu JZ, Garrett ME, Soldano KL, et al. Clinical and metabolomic risk factors associated with rapid renal function decline in sickle cell disease. Am J Hematol. 2018;93(12):1451-1460.
5. Derebail VK, Ciccone EJ, Zhou Q, et al. Progressive decline in estimated GFR in patients with sickle cell disease: an observational Cohort Study. Am J Kidney Dis. 2019;74(1):47-55.
6. Derebail VK, Zhou Q, Ciccone EJ, et al. Rapid decline in estimated glomerular filtration rate is common in adults with sickle cell disease and associated with increased mortality. Br J Haematol. 2019;186(6):900-907
7. Saraf SL, Viner M, Rischall A, et al. HMOX1 and acute kidney injury in sickle cell anemia. Blood. 2018;132(15):1621-1625.

8. Hankins JS, Estepp JH, Hodges JR, et al. Sickle Cell Clinical Research and Intervention Program (SCCRIP): a lifespan cohort study for sickle cell disease progression from the pediatric stage into adulthood. Pediatr Blood Cancer. 2018;65(9):e27228.
9. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):606-612.
10. Rifkin DE, Shlipak MG, Katz R, et al. Rapid kidney function decline and mortality risk in older adults. Arch Intern Med. 2008;168(20):2212-2218.
11. Levin A, Stevens PE. Summary of KDIGO 2012 CKD Guideline: behind the scenes, need for guidance, and a framework for moving forward. Kidney Int. 2014;85(1):49-61.
12. Feldman HI, Appel LJ, Chertow GM, et al. The Chronic Renal Insufficiency Cohort (CRIC) Study: design and methods. J Am Soc Nephrol. 2003;14(7 Suppl 2):S148-153.
13. Young BA, Katz R, Boulware LE, et al. Risk factors for rapid kidney function decline among African Americans: the Jackson Heart Study (JHS). Am J Kidney Dis. 2016;68(2):229-239.
14. Hemmelgarn BR, Zhang J, Manns BJ, et al. Progression of kidney dysfunction in the community-dwelling elderly. Kidney Int. 2006;69(12):2155-2161.
15. de Hauteclocque A, Ragot S, Slaoui Y, et al. The influence of sex on renal function decline in people with Type 2 diabetes. Diabet Med. 2014;31(9):1121-1128.
16. Olaniran KO, Allegretti AS, Zhao SH, et al. Kidney function decline among black patients with sickle cell trait and sickle cell disease: an observational cohort study. J Am Soc Nephrol. 2020;31(2):393-404.
17. Saraf SL, Zhang X, Kanias T, et al. Haemoglobinuria is associated with chronic kidney disease and its progression in patients with sickle cell anaemia. Br J Haematol. 2014;164(5):729-739.