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Hyperkalemia and Metabolic Acidosis Occur at Higher Estimated Glomerular Filtration Rates in Sickle Cell Disease

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Santosh Saraf, Vimal Derebail, Xu Zhang, Roberto Machado, Victor Gordeuk, James Lash, and Jane Little

Key Points:
*Hyperkalemia and metabolic acidosis are more common in severe & moderate SCD compared to age & sex-matched African Americans from NHANES

*Hyperkalemia and metabolic acidosis occur at higher eGFR thresholds in SCD compared to age & sex-matched African Americans from NHANES

Abstract:
Background: People with sickle cell disease (SCD) have an elevated estimated glomerular filtration rate (eGFR) compared to the general population and this may alter the usual creatinine-based eGFR cutoffs for which physiologic evidence of kidney dysfunction is apparent. This study aimed to identify eGFR thresholds for hyperkalemia and metabolic acidosis in patients with SCD. Methods: This was a cross-sectional analysis of 733 patients with severe (hemoglobin SS or Sβ0-thalassemia) SCD genotype, 238 patients with moderate (hemoglobin SC or Sβ+-thalassemia) SCD genotype, and 1,333 age- and sex-matched African Americans from the National Health and Nutrition Examination Survey (NHANES). The prevalence of hyperkalemia and metabolic acidosis were compared by eGFR category. Cutoffs for hyperkalemia and metabolic acidosis were determined using generalized additive models. Results: Hyperkalemia and metabolic acidosis were more common in those with severe SCD genotype (13% and 21%, respectively) compared to in NHANES (0.3% and 5%, respectively); the prevalence rates in the moderate SCD genotype were intermediate for hyperkalemia (3%) and metabolic acidosis (11%). The proportion of patients with hyperkalemia and metabolic acidosis progressively increased with lower eGFR category in both SCD genotype groups. The eGFR thresholds for hyperkalemia and metabolic acidosis were higher in the severe (85 and 91 mL/min/1.73m2, respectively) and moderate (52 and 102 mL/min/1.73m2, respectively) SCD genotype compared with NHANES (34 and 46 mL/min/1.73m2). Conclusions: We demonstrate that hyperkalemia and metabolic acidosis are more common and occur at higher eGFR values in patients with SCD compared to age- and sex-matched African Americans, including in eGFR ranges considered to be normal. Future studies using redefined creatinine-based eGFR thresholds for abnormal kidney function may identify high-risk patients for earlier intervention strategies and referral for specialized renal care in SCD.

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Hyperkalemia and Metabolic Acidosis Occur at a Higher Estimated Glomerular Filtration Rate in Sickle Cell Disease

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Key Points

- Hyperkalemia and metabolic acidosis are more common in severe & moderate SCD compared to age & sex-matched African Americans from NHANES
- Hyperkalemia and metabolic acidosis occur at higher eGFR thresholds in SCD compared to age & sex-matched African Americans from NHANES

Abstract

Background: People with sickle cell disease (SCD) have an elevated estimated glomerular filtration rate (eGFR) compared to the general population and this may alter the usual creatinine-based eGFR cutoffs for which physiologic evidence of kidney dysfunction is apparent. This study aimed to identify eGFR thresholds for hyperkalemia and metabolic acidosis in patients with SCD

Methods: This was a cross-sectional analysis of 733 patients with severe (hemoglobin SS or Sβ^0-thalassemia) SCD genotype, 238 patients with moderate (hemoglobin SC or Sβ^+ thalassemia) SCD genotype, and 1,333 age- and sex-matched African Americans from the National Health and Nutrition Examination Survey (NHANES). The prevalence of hyperkalemia and metabolic acidosis were compared by eGFR category. Cutoffs for hyperkalemia and metabolic acidosis were determined using generalized additive models.

Results: Hyperkalemia and metabolic acidosis were more common in those with severe SCD genotype (13% and 21%, respectively) compared to in NHANES (0.3% and 5%, respectively); the prevalence rates in the moderate SCD genotype were intermediate for hyperkalemia (3%) and metabolic acidosis (11%). The proportion of patients with hyperkalemia and metabolic acidosis progressively increased with lower eGFR category in both SCD genotype groups. The
eGFR thresholds for hyperkalemia and metabolic acidosis were higher in the severe (85 and 91 mL/min/1.73m$^2$, respectively) and moderate (52 and 102 mL/min/1.73m$^2$, respectively) SCD genotypes compared with NHANES (34 and 46 mL/min/1.73m$^2$).

**Conclusions:** We demonstrate that hyperkalemia and metabolic acidosis are more common and occur at higher eGFR values in patients with SCD compared to age- and sex-matched African Americans, including in eGFR ranges considered to be normal. Future studies using redefined creatinine-based eGFR thresholds for abnormal kidney function may identify high-risk patients for earlier intervention strategies and referral for specialized renal care in SCD.
Introduction

Sickle cell disease (SCD) is a recessively inherited red blood cell disorder characterized by abnormal hemoglobin polymerization resulting in vaso-occlusion and hemolytic anemia. The renal system is particularly susceptible to SCD-related damage due to the hypoxic, acidotic, and hyperosmolar environment in the kidney medulla, all conditions which potentiate hemoglobin polymerization. These conditions promote red blood cell sickling and lead to diverse pathologic renal manifestations.

In the general population, the risks for hyperkalemia and metabolic acidosis increase once the eGFR is \(< 30 \text{mL/min/1.73m}^2\). A high prevalence of metabolic acidosis (42%) and defects in tubular acidification (52%) have been observed in SCD cohorts with eGFR > 60 mL/min/1.73m². The differences in eGFR thresholds may be related to lower serum creatinine levels due to reduced muscle mass, abnormal tubular secretion of serum creatinine, and/or high cardiac output from the hemolytic anemia. Consequently, we hypothesize that eGFR thresholds for the development of hyperkalemia and metabolic acidosis are higher for patients with SCD as compared to individuals without SCD. Evaluating this issue may be clinically important to guide treatment strategies in this population of patients at high risk for kidney dysfunction.

We investigated the eGFR values at which hyperkalemia or metabolic acidosis became evident in patients with severe (Hb SS or Hb Sβ⁰-thalassemia) or moderate (Hb SC or Hb Sβ⁺-thalassemia) SCD genotypes and in African Americans from the National Health and Nutrition Examination Survey (NHANES).
Methods:

The study was approved by the institutional review boards of the participating institutions and the subjects provided written informed consent in accordance to the Declaration of Helsinki. The University of Illinois at Chicago (UIC) cohort included 280 Hb SS or Hb Sβ₀-thalassemia and 90 Hb SC or Hb Sβ⁺-thalassemia patients recruited into a registry between August 2010 and March 2016. Baseline clinical data were obtained from the electronic medical charts at the time of enrolment. The Walk-Treatment of Pulmonary Hypertension and Sickle Cell Disease with Sildenafil Therapy (Walk-PHaSST) cohort included 471 Hb SS or Hb Sβ₀-thalassemia and 153 Hb SC or Hb Sβ⁺-thalassemia patients from 8 U.S. centers and 1 U.K. center that were recruited between February 2008 and June 2009. UIC was a participating site for Walk-PHaSST and patients from UIC were excluded from this cohort. The National Health and Nutrition Examination Survey (NHANES) consisted of data from 1,502 African Americans evaluated between 2009 – 2012. The NHANES cohort was selected in a 2:1 manner approximately matched for age and sex to the Hb SS or Hb Sβ₀-thalassemia cohort. We focused our analyses on those subjects with available serum potassium and bicarbonate values (Hb SS or Hb Sβ₀-thalassemia: n = 733, Hb SC or Hb Sβ⁺-thalassemia: n = 238, NHANES: n = 1,333).

The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (2021) which did not include the race coefficient. The following standard definitions were applied: hyperkalemia = serum potassium ≥ 5 mEq/L, metabolic acidosis = serum bicarbonate < 22 mmol/L.

In a cross-sectional analysis, we compared continuous and categorical variables between the severe SCD genotypes, hemoglobin SS or Sβ₀-thalassemia, or moderate SCD genotypes, hemoglobin SC or Sβ⁺-thalassemia, to NHANES controls using the Kruskall-Wallis and Chi square test. The associations between the annual frequency of vaso-occlusive crises requiring
medical attention (acute care center, emergency room, or hospitalization) with eGFR and between LDH and serum potassium were performed using linear regression analysis. The LDH was log-transformed for this analysis. The association between eGFR category and hyperkalemia or metabolic acidosis were analyzed using Cochran’s linear trend test. These analyses were performed using Systat 13 (Chicago, IL).

To investigate differences in the non-linear relationship between eGFR and each binary outcome (hyperkalemia and metabolic acidosis) across the three groups, a series of additive logistic regression models were fit for each outcome. In unadjusted models, independent variables included group membership (categorical, three levels) and three separate penalized cubic regression splines for group-specific nonlinear eGFR effects, with a maximum basis dimension of k = 10 and evenly placed knots. Models were fit by REML using the mgcv package in R. Each model was then adjusted for age, gender, hypertension, and diabetes. In adjusted models, age was fit as a cubic regression spline to permit nonlinear effects. “Variable missing” was treated as a separate category for hypertension and diabetes during model estimation. For each model, group-specific partial effects of eGFR were estimated along a range of plausible eGFR values, with standard errors based on the uncertainty corrected posterior distribution of model coefficients. Approximate 95% credible intervals (95% CIs) were calculated for partial eGFR effect at each eGFR value. The magnitude of the partial effect at each eGFR value represents the contribution of eGFR to the expected outcome for individuals with that eGFR value. Partial effect terms are centered around zero and represent expected increases or decreases in outcomes relative to the group-specific mean. Partial effects are additive contributors to the linear predictor (log-odds of the outcome); as such, estimates are reported on the log-odds scale.
(i.e., 95% CI for the smooth term does not contain zero) were identified. Estimates and intervals were plotted, with non-zero portions of each partial effect smooth highlighted and labeled. These non-zero segments of partial smooths represent ranges of eGFR over which the outcome is expected to be higher or lower than the group-specific mean. We conducted a sensitivity analysis for the potassium and bicarbonate generalized additive models excluding patients being treated with angiotensin converting enzyme inhibitors (ACEi) or angiotensin receptor blockers (ARBs), since these classes of medications may affect serum potassium$^{10}$ and bicarbonate levels.$^{13}$
Results:

Patient Characteristics

Baseline characteristics of the patients are provided in Table 1 and the distribution of serum potassium and bicarbonate concentrations in all three groups are provided in Supplementary Figure 1. The eGFR was not associated with the frequency of vaso-occlusive crises in either the severe or moderate SCD genotypes (P ≥ 0.4). Patients with severe SCD genotype (hemoglobin SS or Sβ0-thalassemia) had a higher prevalence of hypertension, a lower prevalence of diabetes, and were more frequently on RAAS blockers or NSAIDs compared to the NHANES controls. Additionally, patients with severe SCD genotype had a higher serum potassium concentration and more frequent hyperkalemia, a lower serum bicarbonate level and more frequent metabolic acidosis, a lower hemoglobin and a higher LDH concentration, and a higher eGFR and urine albumin concentration compared to NHANES.

Patients with moderate SCD genotype (hemoglobin SC or Sβ+-thalassemia) were older, had a higher prevalence of hypertension and more frequent NSAID use, and a higher systolic blood pressure compared to the NHANES controls. Additionally, patients with moderate SCD genotype had a higher serum potassium concentration and prevalence of hyperkalemia, a higher prevalence of metabolic acidosis, a lower hemoglobin and a higher LDH concentration, and a higher urine albumin concentration compared to NHANES.

Potassium

Hyperkalemia, defined as a serum potassium ≥ 5 mEq/L, was observed in 0.3% of African Americans from NHANES, in 13% of patients with severe SCD genotype and in 3% of
patients with moderate SCD genotype (Table 1). Progressively higher proportions of patients with hyperkalemia were observed with lower eGFR category in the severe (P < 0.001) and moderate (P = 0.04) SCD genotypes (Figure 2A). In the subgroup of patients with urine albumin < 30 mg/g and eGFR ≥ 60 mL/min/1.73 m², hyperkalemia occurred in 7.2% and 1.8% of patients with severe or moderate SCD, respectively, which was higher than the prevalence in NHANES controls (0.1%) (P < 0.001). Serum LDH was directly associated with serum potassium concentration in both the severe (natural log, β 0.26 ± 0.04; P < 0.001) and moderate (natural log, β 0.19 ± 0.06; P = 0.003) SCD genotypes. In the generalized additive models, significantly higher proportions of patients with hyperkalemia were observed at eGFR cutoffs of < 34 mL/min/1.73m² in NHANES, < 85 mL/min/1.73m² in the severe SCD genotype cohort, and < 52 mL/min/1.73m² in the moderate SCD genotype cohort (Figure 3A). The eGFR ranges for hyperkalemia were similar in the sensitivity analyses excluding those on ACEi/ARB in the NHANES (< 33 mL/min/1.73m²) and severe SCD genotype (< 85 mL/min/1.73m²) cohorts, while no significant eGFR threshold for hyperkalemia was identified in the moderate SCD genotype cohort.

**Serum Bicarbonate**

Metabolic acidosis, defined as a serum bicarbonate < 22 mmol/L, was observed in 5% of African Americans from NHANES, in 21% of patients with severe SCD genotype, and in 11% of patients with moderate SCD genotype (Table 1). Progressively higher proportions of patients with metabolic acidosis were observed with lower eGFR category in the severe (P < 0.001) and moderate (P = 0.008) SCD genotypes (Figure 2B). In the subgroup of patients with urine albumin < 30 mg/g and eGFR ≥ 60 mL/min/1.73 m², the prevalence of metabolic acidosis was
18.1% and 13.3% in patients with severe or moderate SCD, respectively, which was higher than in the NHANES controls (4.0%) (P < 0.001). In the generalized additive models, significantly higher proportions of patients with metabolic acidosis were observed at eGFR cutoffs of < 46 mL/min/1.73m² in NHANES, < 91 mL/min/1.73m² in the severe SCD genotype cohort, and < 102 mL/min/1.73m² in the moderate SCD genotype cohort compared to group-specific averages (Figure 3B). The eGFR ranges for metabolic acidosis were similar in the sensitivity analyses for all three cohorts (NHANES: < 51 mL/min/1.73m², severe SCD genotype: < 92 mL/min/1.73m², moderate SCD genotype: < 103 mL/min/1.73m²).
Discussion:

We demonstrate that there is a greater prevalence of hyperkalemia and metabolic acidosis in SCD patients compared to age- and sex-matched African Americans from NHANES. Furthermore, hyperkalemia and metabolic acidosis occurs at eGFR values that are higher in SCD patients compared to in NHANES and above the standard eGFR thresholds currently used to define chronic kidney disease in the general population.\(^{14}\)

Hyperkalemia is a risk factor for adverse cardiovascular events or discontinuation of kidney protective renin-angiotensin-aldosterone blockers in the general population.\(^ {15}\) Higher serum potassium concentrations have been recently described in people with severe SCD genotypes compared to those with moderate SCD genotypes or healthy controls from Ghana.\(^ {16}\) Hyperkalemia in SCD may be due to impaired distal tubular function\(^ {1}\) and was previously described in a small cohort of SCD patients with a mean GFR of 47.8 ± 12.5 mL per minute.\(^ {17}\) Potassium is an intracellular cation and hemolytic anemia could result in hyperkalemia. The degree of intravascular hemolysis, as assessed by serum LDH, was associated with higher serum potassium concentrations in both the severe and moderate SCD genotypes. We demonstrate that hyperkalemia is present in 13% of patients with severe SCD genotype and 3% of patients with moderate SCD genotype and that the proportion of SCD patients with hyperkalemia increases with lower eGFR.

Metabolic acidosis has been linked to more rapid progression of chronic kidney disease,\(^ {18,19}\) bone buffering leading to osteopenia,\(^ {20}\) protein-energy malnutrition,\(^ {21}\) reduced cardiac contractility and congestive heart failure,\(^ {22}\) and early mortality in the general population.\(^ {23}\) Metabolic acidosis may be particularly relevant in the pathobiology of SCD because acidosis alters oxygen affinity, precipitates hemoglobin polymerization, and promotes
red blood cell sickling. A high prevalence of metabolic acidosis has been observed in other cohorts of severe SCD genotype. For example, a serum bicarbonate of < 23 mmol/L was observed in 42% and ≤ 20 mmol/L in 16% of patients with severe SCD genotype. The prevalence of metabolic acidosis in patients with moderate SCD genotype is less clear. Etiologies for metabolic acidosis in SCD may include impaired ammonium availability, hyporeninemic hypoaldosteronism, or impaired distal tubular acidification capacity.

Consistent with the literature, we observed a higher prevalence of metabolic acidosis in patients with severe SCD genotype (21%), as well as a higher prevalence of metabolic acidosis in patients with moderate SCD genotypes (11%), compared to African Americans from NHANES (5%). Furthermore, the prevalence of metabolic acidosis increased with lower eGFR in both SCD genotype groups.

The clinical implications for identifying patients at risk for hyperkalemia or metabolic include earlier referral to a nephrologist and implementation of prevention and treatment strategies, such as dietary potassium restriction, initiating sodium bicarbonate replacement therapy, patient and provider behavior modification (e.g. avoiding non-steroidal anti-inflammatory drugs). In patients with non-SCD-related CKD, metabolic derangements from tubular dysfunction are usually a late manifestation that occur when the eGFR is < 30 mL/min/1.73m². The eGFR cutoffs for hyperkalemia and metabolic acidosis in SCD are less clear. We demonstrate that hyperkalemia and metabolic acidosis occur at higher eGFR values, often considered in the normal eGFR range, in SCD patients compared to the general NHANES population. In patients with severe SCD genotype, the risks of hyperkalemia and metabolic acidosis were increased once the eGFR was < 85 and 91 mL/min/1.73m², respectively. These eGFR cutoffs are much higher than in the NHANES controls. Our findings highlight the need
for close monitoring of serum potassium and bicarbonate once the eGFR is < 120 mL/min/1.73m² and to consider initiating more aggressive measures once the eGFR is < 90 mL/min/1.73m². A more stringent cutoff for kidney dysfunction (serum creatinine of > 0.9 g/dL in men and > 0.77 g/dL in women) in severe SCD genotypes has been recommended in the literature,²⁸ and our data strongly supports this practice, relative to actionable decrements in tubular function. The higher eGFR cutoffs were also consistent for metabolic acidosis in those with moderate SCD genotype.

There are several limitations to our study. This is a cross-sectional analysis and future studies longitudinally monitoring changes in eGFR, serum potassium, and serum bicarbonate are needed. Metabolic acidosis was defined by serum bicarbonate < 22 mmol/L and we lacked blood pH measurements. Our definition may have included compensatory metabolic acidosis due to respiratory alkalosis, a known feature of SCD,²⁹ although a prior study demonstrated that low serum bicarbonate in patients with SCD is associated with a low pH but not with a low arterial partial pressure of carbon dioxide.⁵ We did not have measurements of urine anion gap or NH₄ excretion and this will also need to be studied in prospective studies. Another limitation is that the GFR was estimated and not directly measured, although prior studies have shown that the 2009 CKD-EPI formula without race correlates relatively well with measured GFR in SCD patients.⁷,³⁰ We applied the 2021 CKD-EPI formula for eGFR, determined using serum creatinine and without race, which is a commonly available clinical tool and our eGFR cutoffs can be readily applied to most clinical settings. Although the frequency of vaso-occlusive crises was not associated with eGFR, acute kidney injury may accelerate the rate of eGFR decline in SCD.³¹ Assessing the relationship between acute kidney injury, hyperkalemia, and metabolic acidosis should be evaluated in future studies.
In conclusion, hyperkalemia and metabolic acidosis are common and occur at eGFR cutoffs that are much higher, including eGFR values considered to be in the normal range, in patients with SCD. Future studies using redefined eGFR thresholds for abnormal kidney function may help identify high-risk patients for earlier intervention strategies, avoidance of potential nephrotoxins, and earlier referral for specialized renal care.
Disclosures: S. Saraf reports the following: Consultancy Agreements: Novartis, Global Blood Therapeutics; Research Funding: Pfizer, Novartis, Global Blood Therapeutics; Honoraria: Novartis, Global Blood Therapeutics; Scientific Advisor or Membership: Novartis; and Speakers Bureau: Global Blood Therapeutics. V. Derebail reports the following: Consultancy Agreements: Novartis; Travere; Bayer; Research Funding: Site PI for Clinical Trials (Retrophin, Chemocentryx, Gilead, Infla-RX, Vertex); and Honoraria: American Society of Nephrology, RTI International, UpToDate. V. Gordeuk reports the following: Consultancy: Global Blood Therapeutics; Forma; Vifor; and Research Funding: Shire. J. Lash reports the following: Advisory or Leadership Role: Kidney360. J. Little reports the following: Patents or Royalties: SCD Biochip, licensed with Biochip Labs - I get no honoraria, but am on the patent. The remaining authors have nothing to disclose.

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Authorship: Santosh Saraf: Conceptualization; Data curation; Formal analysis; Funding acquisition; Methodology; Project administration; Resources; Supervision; Writing - original draft; Writing - review and editing. Vimal Derebail: Conceptualization; Investigation; Methodology; Writing - original draft; Writing - review and editing. Xu Zhang: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Writing - original draft; Writing - review and editing. Roberto Machado: Conceptualization; Investigation; Methodology; Writing - original draft; Writing - review and editing. Victor Gordeuk: Conceptualization; Formal analysis; Investigation; Methodology; Writing - original draft; Writing - review and editing. James Lash: Conceptualization; Methodology; Supervision; Writing - original draft; Writing - review and editing. Jane Little: Conceptualization; Formal analysis; Investigation; Methodology; Writing - original draft; Writing - review and editing.

Supplemental Material: Supplemental Figure 1
References:


24. Chatel B, Messonnier LA, Bendahan D. Do we have to consider acidosis induced by exercise as deleterious in sickle cell disease? *Exp Physiol*. 2018;103(9):1213-1220.


<table>
<thead>
<tr>
<th>Table 1: Patient characteristics</th>
<th>NHANES (N = 1,333)</th>
<th>Severe SCD (N = 733)</th>
<th>Moderate SCD (N = 238)</th>
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<td>Age (years)</td>
<td>35 (14)</td>
<td>35 (12)</td>
<td>39 (15)*</td>
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<tr>
<td>Females</td>
<td>55%</td>
<td>54%</td>
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<td>27%</td>
<td>34%*</td>
<td>47%*</td>
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<tr>
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<td>7%</td>
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<td>4%</td>
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<td>Hydroxyurea (%)</td>
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<td>4%</td>
<td>3%</td>
<td>7%</td>
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<td>RAAS blocker</td>
<td>4%</td>
<td>11%*</td>
<td>6%</td>
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<td>NSAIDs</td>
<td>1%</td>
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<td>31%*</td>
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<tr>
<td>Systolic blood pressure (mmHg)</td>
<td>121 (16)</td>
<td>119 (14)</td>
<td>123 (15)*</td>
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<td>Potassium (mmol/L)</td>
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<td>4.4 (0.5)*</td>
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<td>13%*</td>
<td>3%*</td>
</tr>
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<td>Bicarbonate (mmol/L)</td>
<td>25 (2)</td>
<td>24 (3)*</td>
<td>25 (3)</td>
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<tr>
<td>Metabolic acidosis</td>
<td>5%</td>
<td>21%*</td>
<td>11%*</td>
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<tr>
<td>Hemoglobin</td>
<td>13.4 (1.5)</td>
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<td>11.3 (1.6)*</td>
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<td>LDH (u/L)</td>
<td>128 [112 – 147]</td>
<td>386 [283 – 542]*</td>
<td>228 [193 – 291]*</td>
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<tr>
<td>eGFR (mL/min/1.73m²)</td>
<td>99 (21)</td>
<td>111 (32)*</td>
<td>99 (27)</td>
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<td>eGFR by strata</td>
<td></td>
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<td></td>
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<tr>
<td>≥ 120</td>
<td>17.6%</td>
<td>52.2%*</td>
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<tr>
<td>90 – 119</td>
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<td>60 – 89</td>
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<td>&lt; 60</td>
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<tr>
<td>Urine ACR (mg/g creatinine)</td>
<td>6 [3 – 11]</td>
<td>33 [9 – 206]*</td>
<td>10 [4 – 38]*</td>
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<td>Urine ACR by strata</td>
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<tr>
<td>&lt; 30</td>
<td>89.9%</td>
<td>47.7%*</td>
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<tr>
<td>≥ 300</td>
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<td>20%</td>
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</table>

Severe SCD = Hemoglobin genotype SS or Sβ⁰-thalassemia; Moderate SCD = Hemoglobin genotype SC or Sβ⁺-thalassemia
Mean (standard deviation) or median [interquartile ranges] provided; SCD, sickle cell disease; Hb, hemoglobin; RAAS, renin-angiotensin-aldosterone system, NSAID, non-steroidal anti-inflammatory; eGFR, estimated glomerular filtration rate; ACR, albumin-to-creatinine ratio
* Indicates P < 0.01 in a comparison to NHANES subjects;
Hyperkalemia defined as potassium ≥ 5 mEq/L; Metabolic acidosis defined as HCO₃ < 22 mmol/L
Figure Legends

**Figure 1:** Prevalence of hyperkalemia (serum potassium $\geq 5$ mEq/L) and metabolic acidosis (serum bicarbonate $< 22$ mmol/L) in relation to estimated glomerular filtration rate.

**Figure 2:** Generalized additive models for the association of eGFR ranges with hyperkalemia and metabolic acidosis. Blue and red shaded regions represent statistically significant eGFR ranges when the prevalence of abnormal tubular function was higher or lower, respectively, compared to the group-specific averages.