



ORIGINAL ARTICLE

Reverse pseudohyperkalemia is more than leukocytosis: a retrospective study

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ABSTRACT

Background. Hyperkalemia is a potentially life-threatening electrolyte abnormality that often requires urgent treatment. Clinicians should distinguish true hyperkalemia from pseudohyperkalemia and reverse pseudohyperkalemia (RPK). RPK has exclusively been described in case reports of patients with hematologic malignancies (HMs) and extreme leukocytosis [white blood cell (WBC) count $>200 \times 10^3/\text{mL}$].

Methods. This single-center retrospective study analyzed laboratory data from the Mount Sinai Data Warehouse between 1 January 2010 and 31 December 2016 for plasma potassium and serum potassium samples drawn within 1 h of each other, with plasma potassium ≥ 1 mEq/L of the serum potassium. Only plasma potassium ≥ 5 mEq/L were included. Samples that were documented to be hemolyzed or contaminated were excluded. Clinical history and laboratory data were collected from the identified cases.

Results. After applying the inclusion/exclusion criteria to 485 potential cases, the final cohort included 45 cases from 41 patients. There were 24 men and 17 women with a mean age of 52 years. The median plasma potassium was 6.1 mEq/L and serum potassium was 4.4 mEq/L. The median WBC count was $9.35 \times 10^3/\text{mL}$ (interquartile range $6.5\text{--}19.7 \times 10^3/\text{mL}$). Only 44% of the samples had leukocytosis, defined as $\text{WBC} > 11 \times 10^3/\text{mL}$.

Seven patients had a HM and comprised 11 of the cases (24%) with a median WBC of $181.8 \times 10^3/\mu\text{L}$. There was no difference in their plasma and serum potassium levels when compared with the total cohort, despite a higher median WBC count. Thirty-eight percent of the cases required medical management.

Conclusions. The literature on RPK is limited to case reports and series associated with extreme leukocytosis. This is the first study characterizing RPK predominantly associated with normal leukocyte counts. Further investigation is required to more precisely characterize factors associated with RPK and to elucidate RPK mechanisms.

Keywords: hyperkalemia, leukocytosis, potassium, pseudohyperkalemia, reverse pseudohyperkalemia

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INTRODUCTION

Hyperkalemia is a potentially life-threatening electrolyte disorder frequently encountered in both inpatient and outpatient settings. Hyperkalemia is associated with increased morbidity and mortality [1–5] and places a substantial clinical and economic burden to the healthcare system [6, 7]. Diagnosis and management of hyperkalemia rely on serial potassium measurements. Accordingly, hyperkalemia frequently prompts additional clinical decision-making.

Potassium is highly restricted to the intracellular component and is the most abundant intracellular ion [8]. Cell lysis *in vivo*, as occurs with hemolysis, rhabdomyolysis and tumor lysis syndrome, can release intracellular potassium and raise the extracellular concentration. Cell lysis *in vitro* can also raise the measured potassium level, as can occur in the test tube after blood collection in the setting of leukocytosis or thrombocytosis and with fist clenching, tight tourniquets and traumatic phlebotomy [9, 10].

Hyperkalemia adversely affects cardiac electrical conduction and can cause arrhythmias. Evaluation of the cardiac effects of elevated serum potassium measurements should be confirmed with an electrocardiogram (ECG). If ECG changes are consistent with hyperkalemia, then treatment to lower serum potassium and stabilize the myocardium should commence. If there are no ECG changes, then a plasma potassium level should be measured from a tube containing sodium or lithium heparin to avoid potassium release during platelet *in vitro* aggregation, to confirm the presence of true hyperkalemia prior to treatment. If the plasma potassium is not elevated, then pseudohyperkalemia is diagnosed and treatment is not indicated. Pseudohyperkalemia commonly occurs with *in vitro* hemolysis. However, a less well-described phenomenon, reverse pseudohyperkalemia, can occur when the plasma potassium is higher than the serum value [11] (Table 1). This lab discrepancy can introduce confusion in the interpretation of results. Reverse pseudohyperkalemia has been described in several case reports and case series among patients with hematologic malignancies (HMs), predominantly chronic lymphocytic leukemia (CLL) [11–22]. The mechanism for the elevated potassium concentration in plasma has been attributed to *in vitro* leukocyte lysis.

The urgency and selection of therapy for hyperkalemia should vary according to the severity and ECG changes. In the acute setting, there are multiple interventions to lower the potassium level: insulin, beta-agonists, sodium bicarbonate, loop diuretics, sodium polystyrene sulfonate (SPS), sodium zirconium cyclosilicate and dialysis. Treatment decisions based on erroneous results may place patients at risk of receiving treatment that could lead to true hypokalemia or other adverse effects. In fact, a retrospective single-center study of patients who received SPS found that it was administered without a clear indication, with absolute contraindications or with drug contraindications, and no alternative modalities to treat hyperkalemia in 71% of the patients [23]. Potential adverse effects of

the administration of SPS [24] include constipation, diarrhea, fecal impaction and rarely intestinal necrosis.

We conducted this single-center study to determine the characteristics, clinical features and treatment interventions for patients with reverse pseudohyperkalemia.

MATERIALS AND METHODS

Data collection

A retrospective analysis was performed using laboratory data from 1 January 2010 to 31 December 2016 using the Mount Sinai Data Warehouse [25], a clinical laboratory database of inpatient, outpatient and emergency department data for a large academic tertiary care hospital. This study was approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board (IRB-17-02704).

The initial cohort included cases that met the following two criteria: serum potassium and plasma potassium samples drawn on the same day from the same patient and plasma potassium greater than serum potassium. Reverse pseudohyperkalemia was then defined as serum and plasma potassium samples collected within 1 h of each other where the plasma potassium was ≥ 5 mEq/L and the plasma potassium was ≥ 1 mEq/L of serum potassium.

Laboratory testing

Approximately 75–80% of the laboratory samples reach our central laboratory via the pneumatic tube system from both the inpatient and the outpatient settings as per routine clinical practice. Serum and plasma potassium concentrations were measured using the Architect c16000 for routine labs and the ABL800 FLEX for the stat labs (Abbott Laboratories, Abbott Park, IL, USA). Serum potassium was analyzed from blood collected in a serum separator tube spun automatically for 10 min at 3000 rpm. Plasma potassium was analyzed from blood collected in a tube containing the anticoagulant lithium heparin spun manually for 5 min at 3500 rpm.

Specimens that were documented in the laboratory report to be hemolyzed or contaminated were excluded. Serum creatinine values were obtained from the same chemistry panel that reported the serum potassium. White blood cell (WBC) and platelet counts were determined from a complete blood count within 24 h before or after the identified reverse pseudohyperkalemia event. The clinical history and treatment of the patients with identified reverse pseudohyperkalemia were obtained by manual chart review of the electronic medical records.

Acute kidney injury (AKI) and chronic kidney disease (CKD) were defined according to the Kidney Disease: Improving Global Outcomes and Kidney Disease Outcomes Quality Initiative criteria [26, 27].

Electrocardiogram (EKG) interpretation

EKGs performed within 24 h of the reverse pseudohyperkalemia were manually reviewed and compared with a prior EKG not associated with reverse pseudohyperkalemia.

Table 1. Definitions of hyperkalemia [14]

Condition	Serum potassium	Plasma potassium
Hyperkalemia	High	High
Pseudohyperkalemia	Falsely high	Normal
Reverse pseudohyperkalemia	Normal	Falsely high

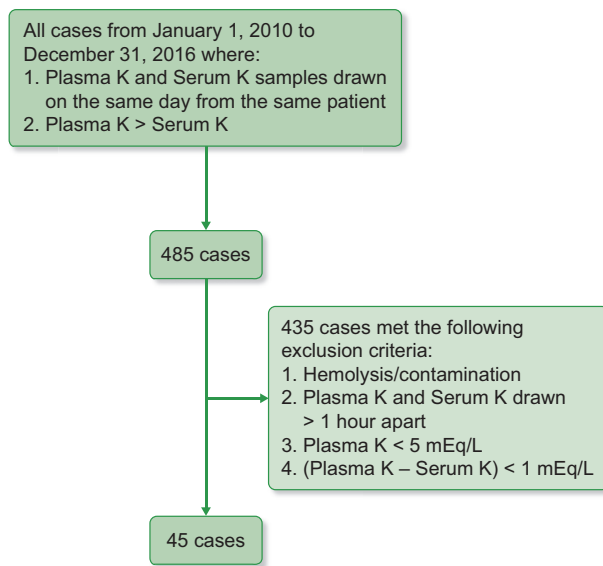


FIGURE 1: Flow chart of retrospective cohort sample selection criteria.

Determination of treatment intervention

Medication administration was evaluated at the time of reverse pseudohyperkalemia and medications dispensed for the treatment of hyperkalemia within 4 h were identified. Treatments included insulin and dextrose, albuterol, sodium bicarbonate, furosemide, SPS and/or hemodialysis.

Data analysis

Basic statistical analysis to calculate the mean, median and interquartile range (IQR) was performed using Excel version 16.17 (Microsoft, Redmond, WA, USA).

Ethics approval and consent to participate

This study was approved by the Icahn School of Medicine at Mount Sinai Institutional Review Board (IRB-17-02704). Consent was not required or obtained for this study, as the data obtained were retrospective, some of the patients in the study had already expired at the time of the study and the study analyzed data of inpatients, many of whom were from out of state with outdated patient contact information.

Availability of data and materials

The data sets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

RESULTS

A total of 485 cases within the hospital system met the initial criteria; 435 cases were then eliminated due to hemolysis or contamination, serum and plasma potassium that were drawn

Table 2. Patient characteristics

Characteristics and Values	Gender, n (%)
Male	24 (59)
Female	17 (41)
Race, n (%)	
Black/African American	14 (34)
White	17 (41)
Other/unknown	10 (24)
Age (years) ^a , mean ± SD (range)	54 ± 15.5 (1–94)
No AKI/CKD, n (%)	26 (58)
AKI, n (%)	5 (11)
CKD stage, n (%)	
3A/3B	5 (11)
4	4 (9)
5/ESRD	5 (11)
Laboratory test, median (IQR)	
Plasma K (mEq/L)	6.1 (5.5–6.6)
Serum K (mEq/L)	4.4 (4.0–5.2)
Plasma K–serum K (mEq/L)	1.4 (1.1–2.0)
WBC count (×10 ³ /μL)	9.4 (6.5–19.7)
Platelets (×10 ³ /μL)	227 (128–302)
Creatinine (mg/dL)	1.0 (0.7–2.8)

^aPatients age ≤12 months were entered as age 1 year.

>1 h apart or the difference between the plasma and serum potassium levels was <1 mEq/L (Figure 1). The final cohort included 45 cases from 41 patients. The study cohort was comprised of 59% males and 41% females. Patients ranged in age from 0 to 94 years (mean age 52 years) and, notably, seven patients were <1 year of age (Table 2). The study cohort was 41% White, 34% Black or African American and 24% were of other

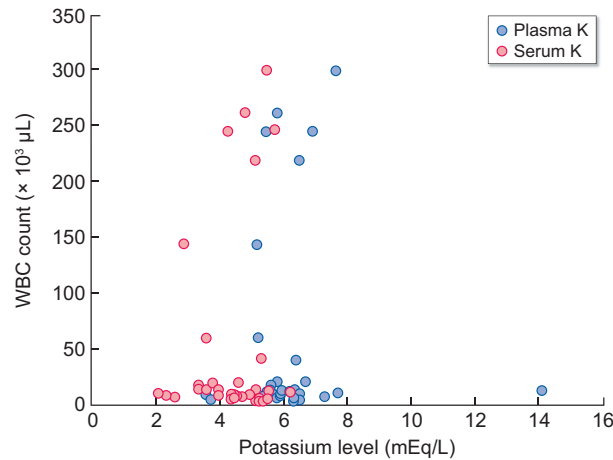


FIGURE 2: Serum and plasma potassium levels and the corresponding WBC counts in the study population.

Table 3. Comparison of the laboratory values of patients with an HM and those without an HM

Variable	HM	NHM
Cases, n	11	34
Laboratory test, median (IQR)		
Plasma K (mEq/L)	6.0 (5.3–6.7)	6.1 (5.5–6.7)
Serum K (mEq/L)	4.5 (4.0–5.1)	4.4 (4.0–5.2)
Plasma K – Serum K	1.4 (1.2–2.1)	1.5 (1.1–2.0)
WBC count ($\times 10^3/\mu\text{L}$)	181.8 (8.1–250.1)	8.5 (5.9–11.9)
Platelets ($\times 10^3/\mu\text{L}$)	101 (65–271)	253 (163–304)
Creatinine (mg/dL)	2.1 (0.9–5.1)	1.0 (0.5–2.8)

Conversion factors for units: serum creatinine in mg/dL to $\mu\text{mol/L}$, $\times 88.4$. NHM: non-hematologic malignancy.

cases. Thirty-eight cases were from the emergency department or inpatient setting, while seven of the cases were from the outpatient clinic.

Analysis of the laboratory data revealed a median plasma potassium of 6.1 mEq/L and serum potassium of 4.4 mEq/L with a median difference of 1.4 mEq/L between the two values. WBC counts were variable with a median value of $9.4 \times 10^3/\mu\text{L}$ (IQR $6.5\text{--}19.7 \times 10^3$). Of the 36 available CBC samples, only 44% of WBC counts met the laboratory's definition of the upper limit of normal ($\text{WBC} > 11.0 \times 10^3/\mu\text{L}$). No clear correlation was found between either the serum or the plasma potassium level and the corresponding WBC count (Figure 2). The median platelet count was $227 \times 10^3/\mu\text{L}$ (IQR $128\text{--}302 \times 10^3$).

Seven patients carried an established diagnosis of an HM, accounting for 24% of the cases (11/45). Diagnoses included two cases of multiple myeloma and one case each of Hodgkin's lymphoma, chronic myelomonocytic leukemia, acute myelogenous leukemia, cutaneous T-cell lymphoma (Sézary syndrome) and monoclonal gammopathy of undetermined significance. Despite substantially higher WBC counts (median of 181.8 versus 9.4 versus $8.5 \times 10^3/\mu\text{L}$) in patients with HMs compared with the total cohort and the remainder of the cohort, the median plasma potassium was 6.0 mEq/L and serum potassium was 4.5 mEq/L (Table 3). These values are similar to those of the total cohort and remainder of the cohort. The median platelet count

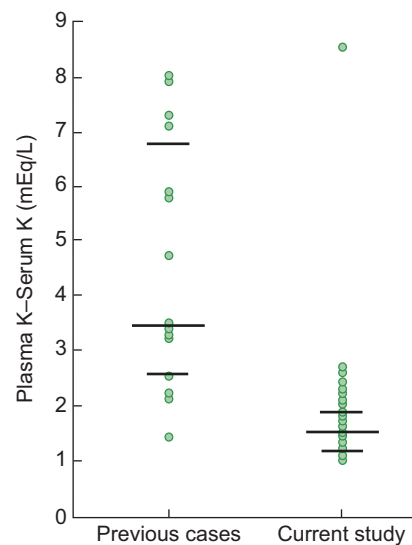


FIGURE 3: Vertical scatterplot of the 'plasma potassium – serum potassium' values comparing previous case reports/series with the current study. For each plot, the top line represents the third quartile, the longer middle line represents the median and the bottom line represents the first quartile.

for the total cohort was within the normal range at $227 \times 10^3/\mu\text{L}$. There were no cases of thrombocytopenia or platelet count $> 1000 \times 10^3/\mu\text{L}$.

Five patients had AKI (11%) while 36 patients did not. Fourteen patients had a diagnosis of CKD, of which five patients had Stage 3, four patients had Stage 4 and five patients had Stage 5 or end-stage renal disease (ESRD). Overall, the median serum creatinine was 1.0 mg/dL (IQR 0.7–2.8). Electrocardiography was performed in 22 of the 45 cases (49%) and 1 case was associated with peaked T waves. The remaining EKGs were either normal or unchanged from prior EKGs.

Potassium-lowering interventions were undertaken in 17 of the 45 cases (38%)—none of which were done between the drawing of plasma and the serum samples. These interventions included SPS in nine cases (20%), insulin in nine cases (20%), furosemide in seven cases (16%), sodium bicarbonate in five cases

Table 4. Review of the published case reports/reviews on RPK and the patients' characteristics

Case report	Age (years)	Diagnosis	Plasma K (mEq/L)	Serum K (mEq/L)	Plasma Serum K	WBC ($\times 10^3/\mu\text{L}$)	Creatinine (mg/dL)
Theparee et al. [12]	66	Mantle cell lymphoma	6.3	3.1	3.2	207	5.5
Mansoor et al. [13]	49	CLL	9.5	3.7	5.8	545	1.5
Avelar [14]	78	CLL	7.9	4.4	3.5	206	1.4
George et al. [20]	64	CLL	10.7	3.6	7.1	367	1.2
Garwicz and Karlman [15]	76	CLL	7.3	4.8	2.5	421	Normal
Garwicz et al. [16]	2	ALL	11.6	3.7	7.9	391	N/A
Meng and Krahn [17]	86	CLL	7.5	2.8	4.7	374	1.0
Lee et al. [21]	76	CLL	5.6	3.1	2.5	268	N/A
	64	CLL	6.2	4.8	1.4	371	
	93	CLL	7.8	1.9	5.9	235	
	74	CLL	6.9	3.6	3.3	218	
Abraham et al. [18]	49	CLL	10.7	2.7	8.0	364	N/A
Kellerman and Thornbery [28]	77	NHL	10.5	3.2	7.3	290	N/A
Singh et al. [11]	70	CLL	7.0	3.6	3.4	524	1.4–1.7 ^a
Huang et al. [19]	83	CLL	8.2	6.1	2.1	300	N/A
Kattamanchi et al. [22]	57	Mycosis fungoides/Sézary syndrome	6.7	4.5	2.2	246	6.5
Median (IQR)	72 (59–78)		7.7 (6.8–10.3)	3.6 (3.1–4.5)	3.5 (2.5–6.8)	332 (238–387)	

ALL: acute lymphoblastic leukemia; NHL: non-Hodgkin lymphoma.

^aIn the setting of AKI.

(11%) and hemodialysis in three cases (7%). The three cases that received urgent hemodialysis occurred in patients who had CKD Stage 5 or ESRD. The mean plasma potassium level for patients who received treatment was 7.2 mEq/L, compared with 5.8 mEq/L in the remaining 28 cases. Notably, six patients (15%) died during the same hospitalization in which the reverse pseudohyperkalemia occurred. Of these patients, four received potassium-lowering therapy and four had an HM.

DISCUSSION

This is the first retrospective cohort study to examine the clinical characteristics and treatment interventions of reverse pseudohyperkalemia. In this medical institution, both serum and plasma potassium levels are commonly obtained simultaneously in patients with or at risk for hyperkalemia.

Although pseudohyperkalemia and reverse pseudohyperkalemia can occur with measured values remaining within the reference range, we identified clinically relevant reverse pseudohyperkalemia where the potassium value was above the normal reference range. We excluded results that were within the normal range, as these values would be unlikely to prompt treatment or additional clinical decision-making.

We identified 45 cases of reverse pseudohyperkalemia over 6 years. Case reports and case series of reverse pseudohyperkalemia have all described patients with severe leukocytosis from an HM. Although neoplastic leukocytes are likely fragile and prone to *in vitro* lysis, increasing the chance of reverse pseudohyperkalemia, 44% of our cases had normal WBC counts. Although published case reports and case series describe reverse pseudohyperkalemia in the setting of severe leukocytosis associated with an HM, we demonstrated that reverse pseudohyperkalemia occurs in the absence of leukocytosis. A total of five cases (only 2 of the 41 patients) in this sample had a WBC $>200 \times 10^3/\mu\text{L}$. Furthermore, ~17% of our cohort carried an established diagnosis of a hematological disorder and less than half of the samples collected (44%) met the laboratory definition

of leukocytosis (WBC $>11.0 \times 10^3/\mu\text{L}$). Interestingly, median plasma and serum potassium levels were similar between patients with and without a known HM (6.0 versus 6.1 mEq/L and 4.5 versus 4.4 mEq/L, respectively), despite a clear difference in median WBC counts (181.8 versus $8.5 \times 10^3/\mu\text{L}$).

The literature regarding reverse pseudohyperkalemia is limited to 13 case reports and case series [11–22, 28] of patients with HMs, predominantly CLL. Among the reported cases, WBC counts have ranged between 206 and $545 \times 10^3/\mu\text{L}$ with a median of $332 \times 10^3/\mu\text{L}$ (Table 4). This is >35 -fold of the median WBC of our total cohort ($9.4 \times 10^3/\mu\text{L}$). Furthermore, the median difference between the plasma potassium and serum potassium values in the case reports was 3.5 mEq/L. This was almost double the values for both patients with and without an HM in our cohort, at 1.4 and 1.5 mEq/L, respectively (Figure 3). While these differences between potassium values may demonstrate the role of extreme leukocytosis in reverse pseudohyperkalemia, it still does not explain the consistency that we see in our cohort where those with and without an HM had median differences between their plasma and serum potassium values of 1.4 and 1.5 mEq/L, respectively.

While the underlying mechanism for the development of reverse pseudohyperkalemia remains unknown, possible mechanisms involve collection tube heparin-induced WBC membrane damage and cell lysis [17], leukocyte-induced consumption of metabolic fuels with resultant inhibition of the sodium pump (Na^+/K^+ -ATPase) and subsequent potassium release [15], lithium-induced Na^+/K^+ -ATPase dysfunction and pneumatic transport causing mechanical disruption of the WBC membrane and/or activation of mechanoactivated cell membrane potassium channels [19, 28]. Two case reports provide insights into potential mechanisms. First, a case report by Meng and Krahn [17] demonstrated that increasing heparin concentrations in the collection tubes was associated with increasing potassium and lactate dehydrogenase levels, implying increased WBC lysis, as no hemolysis was observed. A case report by Huang et al. [19] of a patient with a WBC of $300 \times 10^3/\mu\text{L}$ showed that pneumatic

tube delivery compared with hand delivery was associated with artifactually increased plasma potassium levels.

In our study, extreme leukocytosis was observed in only 5 of the 45 cases. Furthermore, given that 75–80% of the laboratory samples in this institution are delivered via the pneumatic tube system, this could have played an additional contributory role that cannot be precisely quantified with the available data. Although extreme leukocytosis is associated with both pseudohyperkalemia and reverse pseudohyperkalemia, thrombocytosis has only been associated with pseudohyperkalemia in the literature [29, 30]. This analysis did not demonstrate any cases of reverse pseudohyperkalemia associated with thrombocytosis.

Potassium-lowering interventions were undertaken in 17 of the 45 cases (38%). The most commonly used medications were SPS and insulin and dextrose, at nine cases each. These were followed by furosemide (seven cases), sodium bicarbonate (five cases) and hemodialysis (three cases). Neither sodium zirconium cyclosilicate nor patiromer were used in this patient population, since the former was not approved by the US Food and Drug Administration (FDA) during the study period and latter was approved by the FDA for the treatment of chronic hyperkalemia on 21 October 2015. Of the six patients who died during the same hospitalization as the reverse pseudohyperkalemia event, four patients received potassium-lowering therapy. The deaths occurred days after the reverse pseudohyperkalemia occurred.

Our study has several limitations that include single-center experience and an inability to distinguish pneumatic tube transport from manual transport for the individual cases. In addition, the method of phlebotomy, tourniquet use, duration of specimen transport before analysis and other potentially relevant factors are not available. We were unable to determine if specimens were obtained using an intravenous catheter compared with venipuncture, the former of which is associated with higher rates of hemolysis [31–33]. Moreover, more frequent routine simultaneous measurement of serum and plasma potassium in patients at risk will increase the frequency of assessment of both pseudohyperkalemia and reverse pseudohyperkalemia. The authors also did not look at the differences between plasma potassium and serum potassium samples drawn within 1 h of each other for patients who did not meet the inclusion criteria. Lastly, the aim was case finding within an overall denominator of laboratory data during the study period of >1 billion samples. However, we are unable to calculate a relevant denominator precisely, such as the cohort at risk for hyperkalemia. Thus the incidence of reverse pseudohyperkalemia in this study population cannot be determined with the available data.

While this study and literature review does not establish a causality for the cases of reverse pseudohyperkalemia, it is hypothesis-generating, as it demonstrates that reverse pseudohyperkalemia occurs in the absence of leukocytosis, in contrast to previously described cases. Lastly, mechanisms postulated for mechanical, chemical or metabolic WBC lysis require additional study. Of course, the mechanisms for reverse pseudohyperkalemia with a normal leukocyte count may be independent of WBC lysis.

In conclusion, hitherto the literature for reverse pseudohyperkalemia was limited to case reports associated with extreme leukocytosis. This is the first retrospective study to show reverse pseudohyperkalemia occurs frequently in the absence of leukocytosis. Recognition of this disorder may decrease potential harms associated with inappropriate treatment of both

reverse pseudohyperkalemia and pseudohyperkalemia. Further investigation is required to more precisely characterize factors associated with reverse pseudohyperkalemia and to elucidate the pathophysiologic mechanisms underlying cell lysis.

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AUTHORS' CONTRIBUTIONS

J.L.R., S.K. and J.A.V. were responsible for the research idea and study design. S.K. was responsible for data acquisition. O.E.S., J.L.R., S.K. and J.A.V. were responsible for data analysis/interpretation. O.E.S. and J.A.V. were responsible for statistical analysis. J.U. and J.A.V. were responsible for supervision or mentorship. Each author contributed important intellectual content during manuscript drafting or revision, accepts personal accountability for the author's own contributions and agrees to ensure that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

CONFLICT OF INTEREST STATEMENT

J.A.V. reports consulting fees for Janssen for type 2 diabetes and CKD epidemiology and Renalytix AI for CKD biomarker implementation.

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