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Inpatient management and post-discharge outcomes of hyperkalemia

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ABSTRACT

Objectives: Patients with hyperkalemia are commonly treated in the inpatient setting; however, real-world evidence is limited. The purpose of this study was to describe the inpatient management and post-discharge outcomes among patients with hyperkalemia.

Methods: Electronic medical record data (2012–2018) were used to analyze US adult patients with an inpatient stay with hyperkalemia (≥ 1 potassium value >5.0 mEq/L). Patient characteristics, treatments, and monitoring six months prior to and during the inpatient stay, and hyperkalemia recurrence and inpatient readmissions post-discharge were summarized and compared among patients with mild (>5.0 – 5.5 mEq/L), moderate (>5.5 – 6.0), and severe (>6.0) hyperkalemia.

Results: Of the 21,793 patients, 69.2% had mild, 19.0% had moderate, and 11.8% had severe hyperkalemia during inpatient care. The most common inpatient treatments were temporizing agents (mild: 28.9%; moderate: 46.0%; severe: 73.0%), diuretics (32.7%; 37.1%; 34.6%), and sodium-polystyrene sulfonate (11.7%; 27.8%; 45.3%). Almost no patients (0.1%) received a potassium binder at discharge. Most patients (86.8%) had their potassium levels return to ≤ 5.0 mEq/L during the inpatient stay. Death during the inpatient stay occurred in 12.3% of mild, 15.5% of moderate, and 19.5% of severe hyperkalemic patients. Within 30 days of discharge, hyperkalemia recurred in 13.3%, 15.4%, and 18.4% of patients with mild, moderate, and severe hyperkalemia, respectively. Additionally, 19.7%, 21.5%, and 19.6% of patients were readmitted to inpatient care within 30 days post-discharge.

Conclusion: Among patients with hyperkalemia in the inpatient setting, treatment and normalization of serum potassium levels were common. However, death, readmission, and hyperkalemia recurrence were also fairly common across all cohorts. Future studies examining measures to reduce inpatient death, readmission, and hyperkalemia recurrence among patients with hyperkalemia in inpatient care are warranted.

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Clinical management; hyperkalemia; inpatient; post-discharge outcomes; real-world; recurrence

Introduction

Hyperkalemia is an electrolyte disorder characterized by elevated levels of serum potassium [1]. Symptoms include muscle weakness, paralysis, and cardiac dysfunction (e.g., arrhythmia), which may be life-threatening [2,3]. Risk factors for hyperkalemia include comorbidities (e.g., chronic kidney disease [CKD], hypertension, type 2 diabetes), medications (e.g., renin-angiotensin-aldosterone system inhibitors [RAASi]), and high potassium intake [4,5]. In 2014, the annual prevalence of hyperkalemia among adults in the general population of the United States (US) was estimated at 1.55% (3.7 million) [6]. However, the prevalence of hyperkalemia can vary by condition. For example, 6.35% of adults with CKD and/or heart failure were estimated to have hyperkalemia and 41.2% of pre-dialysis patients with end-stage kidney disease (ESKD) were estimated to have hyperkalemia [6,7]. The clinical and economic burden associated with hyperkalemia is considerable. Patients with hyperkalemia were reported to incur two to three times the all-cause health costs compared to patients without hyperkalemia (\$31,844 vs. 15,861 USD), a difference

which persisted after adjustment for comorbid conditions, age, and gender [8]. In that same analysis, patients with hyperkalemia had twice as many hospital visits and longer lengths of stay compared to patients without hyperkalemia [8]. The clinical and economic burden associated with hyperkalemia is expected to increase as the prevalence of associated risk factors continues to rise [9].

The clinical management of hyperkalemia varies based on factors such as severity, etiology, and presentation (i.e., acute vs. chronic) [10]. Treatments include a combination of dietary modifications and/or pharmacological agents [10–13]. In acute settings, treatment with calcium gluconate aids in stabilizing the cardiac membrane, use of albuterol, other inhaled beta agonists, or insulin with glucose facilitates redistribution of potassium into cells, and treatment with sodium bicarbonate helps increase potassium excretion via the kidneys [10,13]. However, these acute treatments are followed by additional agents to help eliminate excess potassium, which is important in normalizing serum potassium levels, include diuretics, cation-exchange resins (e.g., sodium-polystyrene sulfonate [SPS]), potassium binders (e.g., sodium zirconium cyclosilicate

and patiromer), and hemodialysis [10]. Regardless of the treatment received, ongoing monitoring with repeated assessments of serum potassium levels and electrocardiograms (ECGs) are recommended to mitigate potentially fatal consequences, particularly among patients with severe hyperkalemia [12].

Although hyperkalemia can be effectively managed in the outpatient setting, hyperkalemia is common in inpatient care. The REVEAL-ED observational cohort study examined treatment patterns of patients with hyperkalemia in the emergency department and found that many different treatment patterns were used and that 79% of emergency department visits resulted in hospitalization [14]. A recent study reported that the average patient with hyperkalemia is expected to have 0.44 inpatient stays per year [8,15–17]. Despite the frequent occurrence of hyperkalemia in hospitalized patients, scant recent real-world evidence is available regarding patient outcomes following hospitalization [15,18–20]. A recent study found that patients with hyperkalemia-related hospitalizations have significant post-discharge economic and readmission burdens [21,22]. However, evidence that comprehensively and longitudinally describes both the inpatient management and post-discharge outcomes by hyperkalemia severity is needed. Such insight is essential to healthcare stakeholders in order to assess treatment effectiveness and identify unmet needs among patients. To help fill this gap in knowledge, the purpose of the present study was to characterize patient characteristics, inpatient clinical management, and post-discharge outcomes among patients with mild, moderate, and severe hyperkalemia in the US.

Materials and methods

Data source

Electronic medical record (EMR) data from the US Research Action for Health Network (REACHnet) from 2012–2018 was used in this study. Formed in 2014, REACHnet is one of nine clinical research networks participating in PCORnet®, the National Patient-Centered Outcomes Research Network. EMR data is available on more than 5 million patients across all age groups and racial/ethnic groups from five health systems in Louisiana and Texas. In this study, EMR data from Tulane Medical Center and Ochsner Health System in Louisiana were used. Full ethics board approval was obtained from the New England Independent Review Board on 25 June 2018.

Sample selection

The study population in this retrospective study included adult patients with ≥ 1 inpatient stay with hyperkalemia (defined as ≥ 1 potassium laboratory value >5.0 mEq/L that occurred during the inpatient stay). For patients with several eligible inpatient stays with hyperkalemia, the index inpatient stay was randomly selected. Logical Observation Identifier Names and Code (LOINC) codes and lab names were used to identify potassium labs. The first elevated serum potassium level during the inpatient stay was used to classify the severity

of hyperkalemia (mild: >5.0 – 5.5 mEq/L; moderate: >5.5 – 6.0 mEq/L; severe: >6.0 mEq/L). These cutoffs were chosen because potassium levels >5.0 mEq/L are noted to be defined as hyperkalemia by the National Kidney Foundation [23–26]. The admission date of the inpatient stay was required to be ≥ 6 months after the start of the data availability and the date of discharge was required to be ≥ 90 days before the end of the data. Patients were also required to have ≥ 1 additional encounter with the health systems after the inpatient stay.

The index date was defined as the date of the first elevated potassium level during the inpatient stay. The baseline period was defined as the six-month period prior to the admission date of the index inpatient stay and the interval from the index date to discharge date was defined as the inpatient stay. The 90-day period following discharge was defined as the post-discharge period. It was assumed that patients who did not have any follow-up visits did not have any events during the follow-up period.

Study measures and outcomes

Across all cohorts, study measures assessed during the six month baseline period included patient characteristics, comorbidities (based on diagnosis codes from the International Classification of Diseases-Ninth/Tenth edition), prior treatments for hyperkalemia (based on RxNorm codes), and potassium laboratory values (based on LOINC codes). Since data from 2012–2018 were used, more recent hyperkalemia treatments, such as sodium zirconium cyclosilicate, which was approved by the Food and Drug Administration (FDA) in 2018, were not examined. During the inpatient stay, patient characteristics, treatments, monitoring practices, length of stay, and death were described. All-cause inpatient readmissions, hyperkalemia-related inpatient readmissions (inpatient readmissions with ≥ 1 potassium lab value >5.0 mEq/L), and hyperkalemia recurrence (≥ 1 potassium lab value >5.0 mEq/L in any setting) within 30, 60, and 90 days following discharge were described.

Statistical analysis

Study measures and outcomes were summarized using descriptive statistics. Categorical variables were summarized using counts and percentages; continuous variables were summarized using means and standard deviations (SD). Comparisons across outcomes for patients with mild, moderate, or severe hyperkalemia were made using Chi-squared tests (categorical variables) and analysis of variance tests (continuous variables). SAS 9.4 was used for all analyses.

Results

Baseline patient characteristics across hyperkalemia severity

Of the 21,793 patients included in this study, 15,083 (69.2%) had mild hyperkalemia, 4,136 (19.0%) had moderate hyperkalemia, and 2,574 (11.8%) had severe hyperkalemia (Table 1).

Table 1. Patient characteristics during the six months prior to the inpatient admission by hyperkalemia severity during the inpatient stay.

	Mild Hyperkalemia	Moderate Hyperkalemia	Severe Hyperkalemia	P-values	
	>5.0–5.5 mEq/L (N = 15,083)	>5.5–6.0 mEq/L (N = 4,136)	>6.0 mEq/L (N = 2,574)	Mild vs. Moderate	Mild vs. Severe
Demographics					
Age (years), mean (SD)	64.6 (16.4)	63.8 (16.8)	63.0 (16.7)	< 0.01 *	< 0.001 *
Female, n (%)	6,858 (45.5%)	1,892 (45.7%)	1,118 (43.4%)	0.77	0.06
Race, n (%)				<0.001 *	<0.001 *
White	8,923 (59.2%)	2,257 (54.6%)	1,342 (52.1%)		
Black or African American	5,691 (37.7%)	1,738 (42.0%)	1,138 (44.2%)		
Asian, other, or missing	469 (3.1%)	141 (3.4%)	94 (3.7%)		
Comorbidities					
CKD (stage 3–5), n (%)	6,001 (39.8%)	1,737 (42.0%)	1,167 (45.3%)	< 0.05 *	<0.001 *
CKD stage among patients with CKD, n (%)				< 0.001 *	< 0.001 *
Stage 3	3,371 (56.2%)	867 (49.9%)	492 (42.2%)		
Stage 4	996 (16.6%)	301 (17.3%)	229 (19.6%)		
Stage 5 or ESKD	1,634 (27.2%)	569 (32.8%)	446 (38.5%)		
ESKD, n (%)	559 (3.7%)	192 (4.6%)	183 (7.1%)	< 0.01 *	< 0.001 *
Acute kidney injury, n (%)	2,250 (14.9%)	672 (16.2%)	463 (18.0%)	< 0.05 *	< 0.001 *
Type 2 diabetes, n (%)	4,881 (32.4%)	1,366 (33.0%)	911 (35.4%)	0.43	< 0.01 *
Heart failure, n (%)	3,423 (22.7%)	1,013 (24.5%)	615 (23.9%)	< 0.05 *	0.19
Hypertension, n (%)	8,754 (58.0%)	2,397 (58.0%)	1,536 (59.7%)	0.94	0.13
Charlson Comorbidity Index (CCI), mean (SD)	2.1 (2.4)	2.2 (2.4)	2.3 (2.5)	0.26	< 0.05 *
Previous Treatments Used, n (%)					
Any RAASi use	4,004 (26.5%)	1,125 (27.2%)	671 (26.1%)	0.41	0.63
SPS or patiromer	550 (3.6%)	202 (4.9%)	197 (7.7%)	< 0.01 *	< 0.01 *
Any diuretics use	4,559 (30.2%)	1,290 (31.2%)	777 (30.2%)	0.24	0.99
Any dialysis	636 (4.2%)	214 (5.2%)	195 (7.6%)	< 0.01 *	< 0.001 *
Potassium Labs during Baseline					
Number of potassium labs, mean (SD)	7.1 (14.9)	7.6 (16.5)	7.3 (14.9)	0.09	0.54
Proportion with at least 1 potassium lab, n (%)	10,464 (69.4%)	2,827 (68.4%)	1,690 (65.7%)	0.21	< 0.01 *
Among patients with at least 1 potassium lab					
Any potassium labs >5 mEq/L, n (%)	1,483 (14.2%)	489 (17.3%)	416 (24.6%)	< 0.001 *	< 0.001 *
Number of potassium labs >5 mEq/L, mean (SD)	0.8 (2.3)	1.0 (2.8)	1.6 (3.9)	< 0.001 *	< 0.001 *

*p-values<0.05 were considered statistically significant; p-values for categorical variables were calculated using chi-squared tests; p-values for continuous variables were calculated using ANOVA tests. CKD, chronic kidney disease; ESKD, end-stage kidney disease; N, number; RAASi, renin-angiotensin-aldosterone system inhibitor; SD, standard deviation; SPS, sodium polystyrene sulfonate

The mean ages of patients were similar across all hyperkalemia severity levels (mild: 64.6 years old; moderate: 63.8 years old; severe: 63.0 years old) and nearly half of all patients were female (mild: 45.5%; moderate: 45.7%; severe: 43.4%). Over half of all patients were white (mild: 59.2%; moderate: 54.6%; severe: 52.1%).

The mean Charlson comorbidity index (CCI) was similar across all three severity levels (mild: 2.1; moderate: 2.2; severe: 2.3). Hypertension was the most common comorbidity and was present in over half of all patients (mild: 58.0%; moderate: 58.0%; severe: 59.7%), followed by CKD stages 3–5 (mild: 39.8%; moderate: 42.0%; severe: 45.3%). ESKD, defined as CKD 5 and dialysis, was present in 3.7% of mild, 4.6% of moderate and 7.1% of severe patients. Similar distributions of heart failure and type 2 diabetes were observed among patients with mild, moderate, and severe hyperkalemia. History of acute kidney injury in the 6 months prior to index hospitalization increased with hyperkalemia severity (14.9% – 18.0%). A similar distribution of RAASi use was observed among patients with mild, moderate, and severe hyperkalemia (26.5%, 27.2%, 26.1%, respectively). About one third of patients used diuretics (mild: 30.2%; moderate: 31.2%; severe: 30.2%) and very few used SPS or patiromer (4.4% overall for SPS, 0.0% overall for patiromer) before the inpatient stay.

Comparison of clinical characteristics across hyperkalemia severity during inpatient stay

A total of 12.3% of patients with mild hyperkalemia, 15.5% with moderate hyperkalemia, and 19.5% with severe hyperkalemia died during the inpatient stay (Table 2). During the inpatient stay, most patients (92.4%) had ≥ 2 potassium laboratory tests, with a mean of 1.5 potassium labs per day. Among these patients, most had their potassium level normalized (returned to ≤ 5.0 mEq/L) during the inpatient stay (mild: 87.7%; moderate: 86.8%; severe: 81.9%). ECG monitoring was more frequent in patients with more severe hyperkalemia (mild: 51.9%; moderate: 67.9%; severe: 82.6%). RAASi were used by 11.3% of mild patients, 11.8% of moderate patients, and 9.2% of severe patients during the inpatient stay, with about half of patients receiving a RAASi during the stay receiving a RAASi at discharge (mild: 5.7%; moderate: 6.2%; severe: 4.9%).

Hyperkalemia treatment was more frequent as the severity of the hyperkalemia increased. Temporizing agents were the most common treatment during the inpatient stay (mild: 28.9%; moderate: 46.0%; severe 73.0%) and intravenous calcium was the most common temporizing agent (mild: 16.5%; moderate: 29.8%; severe: 56.4%). SPS was commonly used and was used more frequently as hyperkalemia severity increased (mild: 11.7%; moderate: 27.8%; severe: 45.3%). Over a third of patients across hyperkalemia severities received diuretics

Table 2. Comparison of clinical characteristics among patients with mild, moderate, and severe hyperkalemia during the inpatient stay^a.

	Mild Hyperkalemia	Moderate Hyperkalemia	Severe Hyperkalemia	p-values	
	>5.0–5.5 mEq/L (N = 15,083)	>5.5–6.0 mEq/L (N = 4,136)	>6.0 mEq/L (N = 2,574)	Mild vs. Moderate	Mild vs. Severe
Death during Inpatient Stay, n (%)					
Patients who died	1,852 (12.3%)	643 (15.5%)	502 (19.5%)	< 0.001 *	< 0.001 *
Length of Inpatient Stay, mean (SD)					
Total days in inpatient care	9.1 (7.5)	8.5 (7.1)	7.5 (6.6)	< 0.001 *	< 0.001 *
Days from admission to first high potassium lab	2.6 (4.3)	1.9 (3.8)	1.2 (3.3)	< 0.001 *	< 0.001 *
Days from first high potassium lab to discharge	6.5 (6.0)	6.6 (5.9)	6.3 (5.7)	0.20	0.09
Potassium Lab Values during Inpatient Stay					
Number of potassium lab values, mean (SD)	9.1 (11.3)	10.1 (10.9)	10.9 (11.4)	< 0.001 *	< 0.001 *
Patients with ≥ 2 potassium lab values, n (%)	13,680 (90.7%)	3,965 (95.9%)	2,491 (96.8%)	< 0.001 *	< 0.001 *
Among patients with ≥ 2 lab values					
First potassium lab value, mean (SD)	5.2 (0.1)	5.8 (0.1)	6.7 (0.7)	< 0.001 *	< 0.001 *
Last potassium lab value, mean (SD)	4.3 (0.7)	4.3 (0.7)	4.4 (0.9)	0.85	< 0.001 *
Potassium lab value returned to ≤ 5.0 mEq/L during the stay, n (%)	12,000 (87.7%)	3,441 (86.8%)	2,041 (81.9%)	< 0.001 *	< 0.001 *
Monitoring during Inpatient Stay, n (%)					
Electrocardiogram ^b	6,497 (51.9%)	2,272 (67.9%)	1,773 (82.6%)	< 0.001 *	< 0.001 *
Hyperkalemia treatment during Inpatient Stay, n (%)					
Any temporizing agent	4,352 (28.9%)	1,904 (46.0%)	1,880 (73.0%)	< 0.001 *	< 0.001 *
Albuterol	947 (6.3%)	523 (12.6%)	810 (31.5%)	< 0.001 *	< 0.001 *
Calcium	2,487 (16.5%)	1,231 (29.8%)	1,452 (56.4%)	< 0.001 *	< 0.001 *
Insulin with glucose	1,220 (8.1%)	839 (20.3%)	1,251 (48.6%)	< 0.001 *	< 0.001 *
Sodium bicarbonate	2,173 (14.4%)	884 (21.4%)	975 (37.9%)	< 0.001 *	< 0.001 *
SPS	1,759 (11.7%)	1,151 (27.8%)	1,167 (45.3%)	< 0.001 *	< 0.001 *
Patiromer	2 (0.0%)	2 (0.0%)	3 (0.1%)	0.20	< 0.05 *
Diuretics	4,930 (32.7%)	1,536 (37.1%)	890 (34.6%)	< 0.001 *	0.06
Dialysis	1,709 (11.3%)	614 (14.8%)	578 (22.5%)	< 0.001 *	< 0.001 *
Hyperkalemia Treatments at Discharge, n (%)					
SPS at discharge	10 (0.1%)	6 (0.1%)	10 (0.4%)	0.21	< 0.001 *
Patiromer at discharge	0 (0.0%)	1 (0.0%)	2 (0.1%)	0.22	< 0.05 *
Diuretics at discharge	1,289 (8.5%)	376 (9.1%)	200 (7.8%)	0.28	0.20
Other treatments, n (%)					
RAASi during inpatient stay	1,702 (11.3%)	488 (11.8%)	238 (9.2%)	0.37	< 0.01 *
RAASi at discharge	860 (5.7%)	256 (6.2%)	126 (4.9%)	0.25	0.11

*p-values <0.05 were considered statistically significant.

^aVariables analyzed between the first potassium lab >5.0mEq/L during stay and the discharge date.

^bECG use was calculated among patients with ECG data available (mild hyperkalemia, n = 12,522; moderate hyperkalemia, n = 3,345; severe hyperkalemia, n = 2,147); p-values for categorical variables were calculated using chi-squared tests; p-values for continuous variables were calculated using analysis of variance tests.

ECG, electrocardiogram; n, number; SD, standard deviation; RAASi, renin-angiotensin-aldosterone system inhibitor; SPS, sodium polystyrene sulfonate

mild: 32.7%; moderate: 37.1%; severe: 34.6%). Dialysis was used by 13.3% of patients overall and use increased with hyperkalemia severity (mild: 11.3%; moderate: 14.8%; severe: 22.5%). Treatment with patiromer was rare during the inpatient stay (<0.1% overall) and very few patients were prescribed SPS (0.1%) or patiromer (<0.1%) at discharge.

Post-discharge outcomes across hyperkalemia severity

The rate of all-cause inpatient readmission was similar for patients with mild, moderate, and severe hyperkalemia 30 to 90 days following discharge (mild: 19.7% – 31.2%; moderate 21.5% – 32.1% severe: 19.6% – 31.4%; from 30–90 days respectively, Figure 1). Hyperkalemia-related readmissions, defined as inpatient readmissions with ≥ 1 potassium lab value >5.0 mEq/L, and hyperkalemia recurrence, defined as ≥ 1 potassium lab value >5.0 mEq/L in any setting, increased with hyperkalemia severity. Within 30 days of discharge, 5.5% of patients with mild hyperkalemia, 6.6% of patients with moderate hyperkalemia, and 8.3% of patients with severe hyperkalemia experienced hyperkalemia-related readmissions (mild vs. moderate p < 0.05; mild vs. severe p < 0.001), with similar trends seen for

60 days post-discharge (7.8%, 8.9%, 11.1%) and 90 days post-discharge (9.2%, 10.4%, 12.9%). Within 30 days of discharge, 13.3% of patients with mild hyperkalemia, 15.4% of patients with moderate hyperkalemia, and 18.4% of patients with severe hyperkalemia experienced hyperkalemia recurrence, defined as ≥ 1 potassium lab value >5.0 mEq/L in any setting (mild vs. moderate p < 0.01; mild vs. severe p < 0.001). Similar trends in hyperkalemia recurrence were also observed 60 days (17.3%, 19.7%, 24.6%) and 90 days (20.0%, 22.6%, 28.1%) post-discharge.

Discussion

Using a large EMR database, this study provided a contemporary characterization of both the inpatient and post-discharge outcomes stratified by hyperkalemia severity in real-world clinical practice. While previous studies on the clinical management of hyperkalemia have described the inpatient management of hyperkalemia, they often focused on specific treatments (e.g., SPS) [27–30] or outcomes only during the inpatient stay (e.g., in-hospital mortality) [15,19,20]. This study expands on previous literature by

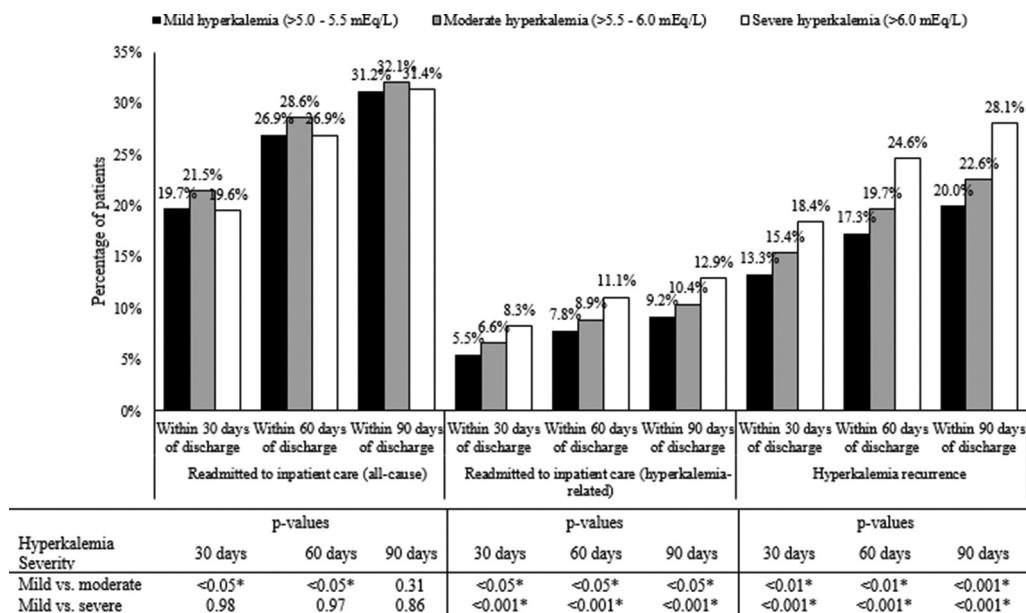


Figure 1. Post-discharge events 30, 60, and 90 days after inpatient stay by hyperkalemia severity.

*p-values <0.05 were considered statistically significant.

describing the inpatient management of hyperkalemia and post-discharge outcomes in a longitudinal cohort of hyperkalemic patients.

The inpatient setting represents an important site of care in the clinical management of hyperkalemia. The potentially life-threatening consequences associated with hyperkalemia, such as cardiac arrhythmias, may require hospitalization for immediate treatment and ongoing monitoring [18,31]. However, treatment recommendations often vary and multiple different regimens can be used to lower potassium levels (e.g., various temporizing agents and SPS) [15,18,20,30]. Similar to prior studies [15,20], temporizing agents (intravenous calcium, insulin/glucose, and sodium bicarbonate) as well as SPS were commonly used in the inpatient setting. While temporizing agents were used by 28.9–73.0% of patients in this study, their impact on hyperkalemia is more immediate and transitory rather than having a long-term impact on hyperkalemia after inpatient discharge.

In this study, SPS was also commonly used across all severity levels of hyperkalemia (mild: 11.7%; moderate: 27.8%; severe: 45.3%). Although SPS has been a mainstay hyperkalemia treatment since its approval by the US FDA in 1958, there is limited evidence regarding its real-world effectiveness. Results from a 2015 retrospective study found that while SPS lowered serum potassium levels, the authors noted that the difference may not be clinically important. Furthermore, SPS has been associated with serious adverse events (e.g., colonic necrosis) which limits its use in certain patients [27,32,33]. For example, a recent study found that older patients who used SPS had a higher incident rate of hospitalization for serious gastrointestinal events, such as intestinal ischemia, gastrointestinal ulceration or perforation, resection or ostomy, than patients matched patients not using SPS [34]. Furthermore, a systematic literature review found that SPS use may be

associated with a risk of death due to gastrointestinal events [33].

Over half of all patients in this study were monitored via ECG with increased monitoring observed for patients with moderate and severe hyperkalemia (67.9% and 82.6%, respectively). This aligns with a prospective study published in 1998 that reported ECG monitoring in up to 83% of hospitalized patients with hyperkalemia. Likely as a result of the frequent treatment and monitoring, >80% of patients had their potassium levels return to normal (≤ 5.0 mEq/L) in this study, a finding that aligns with an earlier study that reported normalization of serum potassium levels in 89% of patients with hyperkalemia [35].

However, despite frequent treatment, monitoring, and normalization of serum potassium levels during the inpatient stay, death, readmission, and hyperkalemia recurrence were fairly common across all cohorts. Furthermore, less than 1% of patients received any potassium binder treatment at discharge in this study despite the fact that approximately 18% of patients did not have normalized serum potassium levels. The lack of potassium binder treatment use at discharge as well as the subsequent high hyperkalemia recurrence and hyperkalemia-related readmissions may demonstrate the continued unmet treatment need in this patient population. However, this study was descriptive in nature and the cause of the readmissions was not examined. Currently, newer treatments, such as patiromer (approved by the FDA in 2015) and sodium-zirconium cyclosilicate (approved by the FDA in 2018), are available to patients. While not commonly used or available during this study period, these treatments have improved tolerability profiles compared to other treatments for hyperkalemia [36–38]. Further studies examining how these treatments impact potassium normalization, recurrence and readmission in real-world settings would be beneficial.

Mortality among patients with hyperkalemia in the inpatient setting is a widely recognized concern [20,25,39,40]. Across severity levels, 12.3% – 19.5% of patients died during the inpatient stay, which is higher than a prior study [20] that reported deaths among 8% of patients hospitalized for hyperkalemia. Results from an observational study found that even slight increases in serum potassium levels when admitted to critical care were associated with a considerable risk of death [40].

In this study, approximately 1 in 5 patients, irrespective of hyperkalemia severity, were re-hospitalized within 30 days of discharge. Despite largely similar all-cause readmission rates across severity levels, hyperkalemia-related readmission rates increased with hyperkalemia severity (mild: 5.5%, moderate: 6.6%, severe: 8.3% within 30 days). Hyperkalemia recurrence also increased with severity (mild: 13.3%, moderate: 15.4%, severe: 18.4% within 30 days). The post-discharge outcomes reported in this study are comparable to a retrospective cohort study that assessed the burden associated with hyperkalemia readmissions 30, 60, and 90 days post-discharge [21]. In that study, hyperkalemia-related hospitalizations were associated with significantly more readmissions than hospitalizations unrelated to hyperkalemia (30 days: 12.5% vs. 8.4%; 60 days: 18.3% vs. 12.7%; 90 days: 24.3% vs. 16.8%; all $p < 0.001$) [21]. These studies together show the large post-discharge burden of hyperkalemia.

In order to reduce the clinical burden during hospitalization and post-discharge, it's possible that improvements in the management of patients during both the inpatient and post-discharge periods are needed. During inpatient care, strategies focused on regular monitoring, particularly for high risk patients such as those with CKD and/or heart failure, may facilitate earlier interventions that could mitigate the burden of this condition. In addition to regular monitoring and acute management of hyperkalemia, long-term maintenance of serum potassium post-discharge should be considered, especially for those with high risk of hyperkalemia recurrence or readmissions. In this study, very few patients (<1%) received SPS or patiromer at discharge. With the introduction of targeted therapies with novel potassium binders, additional studies are warranted to identify patients with the greatest potential to benefit from such novel agents in the inpatient setting and at discharge and to understand the impact of long-term maintenance of serum potassium on hyperkalemia recurrence and readmission.

This study should be interpreted within the context of specific limitations. One limitation of this study is that the primary reason for each patient's inpatient admission was unknown and the cause of hyperkalemia during the inpatient stay was also unknown, similar to other studies using EMR or insurance claims databases. Additional variables, such as arterial blood gas for determination of pH, were also not examined during the stay as they were not available in the EMR which may have an impact on the outcomes of hyperkalemia. Second, hyperkalemia was defined as ≥ 1 potassium laboratory value >5.0 mEq/L that occurred during the inpatient stay, which could have been the result or an errant value due to hemolysis or other reasons. Therefore, this study may potentially overestimate the proportion of patients with

hyperkalemia in the inpatient setting. However, since most patients had at least 2 potassium laboratory values measured during the inpatient stay we anticipate errant potassium laboratory values may not be a common occurrence in patients in this study. Third, while this study included a large number of patients with hyperkalemia in the state of Louisiana, if the clinical management in Louisiana differs from other US census regions, the generalizability of the study's findings may be limited. Fourth, the inability to capture out-of-network encounters in the EMR database may have resulted in an underestimation of the baseline and post-discharge results. In spite of these limitations, use of a robust EMR database that captured longitudinal information on patients from a multitude of in-network settings and included rich laboratory data, enabled a broad assessment of clinical events during and after an inpatient stay with hyperkalemia. Overall, the results of this study have the potential to provide healthcare stakeholders with real-world insight related to the inpatient management of hyperkalemia and post-discharge outcomes.

Conclusions

In this real-world study of patients with hyperkalemia in the inpatient setting, patients were frequently monitored and treated, and over 80% of patients' serum potassium were normalized during the inpatient stay. However, approximately one in six patients with hyperkalemia managed in inpatient care died and hyperkalemia recurrence and readmissions frequently occurred. Future studies examining measures to reduce inpatient death, readmission, and hyperkalemia recurrence among patients with hyperkalemia are warranted.

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Declaration of interest

JD is an employee of AstraZeneca.

RI was an employee of AstraZeneca at the time this study was conducted.

FM, EEC, and KAB are employees of Analysis Group, Inc., which received consultancy fees from AstraZeneca for the conduct of this analysis.

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References

- Coutrot M, Depret F, Legrand M. Tailoring treatment of hyperkalemia. *Nephrol Dial Transplant*. 2019;34(Supplement_3):iii62–iii8.
- Nyirenda MJ, Tang JI, Padfield PL, et al. Hyperkalaemia. *BMJ*. 2009;339:b4114. DOI:10.1136/bmj.b4114
- Thomsen RW, Nicolaisen SK, Hasvold P, et al. Elevated potassium levels in patients with congestive heart failure: occurrence, risk factors, and clinical outcomes: a danish population-based cohort study. *J Am Heart Assoc*. 2018;7(11). DOI:10.1161/JAHA.118.008912.
- Weir MR, Rolfe M. Potassium homeostasis and renin-angiotensin-aldosterone system inhibitors. *Clin J Am Soc Nephrol*. 2010;5(3):531–548.
- Desai AS, Swedberg K, McMurray JJ, et al. Incidence and predictors of hyperkalemia in patients with heart failure: an analysis of the CHARM program. *J Am Coll Cardiol*. 2007;50(20):1959–1966.
- Betts KA, Woolley JM, Mu F, et al. The prevalence of hyperkalemia in the United States. *Curr Med Res Opin*. 2018;34(6):971–978.
- Khedr E, Abdelwhab S, El-Sharkawy M, et al. Prevalence of hyperkalemia among hemodialysis patients in Egypt. *Ren Fail*. 2009;31(10):891–898.
- Betts KA, Woolley JM, Mu F, et al. The cost of hyperkalemia in the United States. *Kidney Int Rep*. 2018;3(2):385–393.
- Dunn JD, Benton WW, Orozco-Torrentera E, et al. The burden of hyperkalemia in patients with cardiovascular and renal disease. *Am J Manag Care*. 2015;21(15Suppl):s307–15.
- Mushiyakh Y, Dangaria H, Qavi S, et al. Treatment and pathogenesis of acute hyperkalemia. *J Community Hosp Intern Med Perspect*. 2012;1(4). DOI:10.3402/jchimp.v1i4.7372
- Rosignol P, Legrand M, Kosiborod M, et al. Emergency management of severe hyperkalemia: guideline for best practice and opportunities for the future. *Pharmacol Res*. 2016;113:585–591.
- Depret F, Peacock WF, Liu KD, et al. Management of hyperkalemia in the acutely ill patient. *Ann Intensive Care*. 2019;9(1):32.
- Kovesdy CP. Management of hyperkalemia: an update for the internist. *Am J Med*. 2015;128(12):1281–1287.
- Peacock WF, Rafique Z, Clark CL, et al. Real world evidence for treatment of hyperkalemia in the emergency department (REVEAL-ED): a multicenter, prospective, observational study. *J Emerg Med*. 2018;55(6):741–750.
- Acker CG, Johnson JP, Palevsky PM, et al. Hyperkalemia in hospitalized patients: causes, adequacy of treatment, and results of an attempt to improve physician compliance with published therapy guidelines. *Arch Intern Med*. 1998;158(8):917–924.
- Paice B, Gray JM, McBride D, et al. Hyperkalaemia in patients in hospital. *Br Med J (Clin Res Ed)*. 1983;286(6372):1189–1192.
- Shemer J, Modan M, Ezra D, et al. Incidence of hyperkalemia in hospitalized patients. *Isr J Med Sci*. 1983;19(7):659–661.
- An JN, Lee JP, Jeon HJ, et al. Severe hyperkalemia requiring hospitalization: predictors of mortality. *Crit Care*. 2012;16(6):R225.
- Charytan D, Goldfarb DS. Indications for hospitalization of patients with hyperkalemia. *Arch Intern Med*. 2000;160(11):1605–1611.
- Khanagavi J, Gupta T, Aronow WS, et al. Hyperkalemia among hospitalized patients and association between duration of hyperkalemia and outcomes. *Arch Med Sci*. 2014;10(2):251–257.
- Mu F, Betts KA, Woolley JM, et al. Prevalence and economic burden of hyperkalemia in the United States medicare population. *Curr Med Res Opin*. 2020;36(8):1333–1341.
- Betts KA, Woolley JM, Mu F, et al. (2020) Postdischarge Healthcare Costs and Readmission in Patients With Hyperkalemia-Related Hospitalizations. *Kidney International Reports*.
- National Kidney Foundation (2021). Facts about high potassium in patients with kidney disease. <https://www.kidney.org/atoz/content/hyperkalemia/facts>. Accessed 2021 Mar 19.
- Kraft MD, Btaiche IF, Sacks GS, et al. Treatment of electrolyte disorders in adult patients in the intensive care unit. *Am J Health Syst Pharm*. 2005;62(16):1663–1682.
- Einhorn LM, Zhan M, Hsu VD, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med*. 2009;169(12):1156–1162.
- Knoll GA, Sahgal A, Nair RC, et al. Renin-angiotensin system blockade and the risk of hyperkalemia in chronic hemodialysis patients. *Am J Med*. 2002;112(2):110–114.
- Hagan AE, Farrington CA, Wall GC, et al. Sodium polystyrene sulfonate for the treatment of acute hyperkalemia: a retrospective study. *Clin Nephrol*. 2016;85(1):38–43.
- Kessler C, Ng J, Valdez K, et al. The use of sodium polystyrene sulfonate in the inpatient management of hyperkalemia. *J Hosp Med*. 2011;6(3):136–140.
- Batterink J, Lin J, Au-Yeung SH, et al. Effectiveness of sodium polystyrene sulfonate for short-term treatment of hyperkalemia. *Can J Hosp Pharm*. 2015;68(4):296–303.
- Fordjour KN, Walton T, Doran JJ. Management of hyperkalemia in hospitalized patients. *Am J Med Sci*. 2014;347(2):93–100.
- Montford JR, Linas S. How dangerous is hyperkalemia? *J Am Soc Nephrol*. 2017;28(11):3155–3165.
- Chaitman M, Dixit D, Bridgeman MB. Potassium-binding agents for the clinical management of hyperkalemia. *P T*. 2016;41(1):43–50.
- Harel Z, Harel S, Shah PS, et al. Gastrointestinal adverse events with sodium polystyrene sulfonate (Kayexalate) use: a systematic review. *Am J Med*. 2013;126(3):264e9–24.
- Noel JA, Bota SE, Petrich W, et al. Risk of hospitalization for serious adverse gastrointestinal events associated with sodium polystyrene sulfonate use in patients of advanced age. *JAMA Intern Med*. 2019;179(8):1025–1033.
- Grodzinsky A, Goyal A, Gosch K, et al. Prevalence and prognosis of hyperkalemia in patients with acute myocardial infarction. *Am J Med*. 2016;129(8):858–865.
- Rosano GMC, Spoletini I, Agewall S. Pharmacology of new treatments for hyperkalaemia: patiromer and sodium zirconium cyclosilicate. *Eur Heart J Suppl*. 2019;21(Supplement_A):A28–A33.
- Spinowitz BS, Fishbane S, Pergola PE, et al. Sodium Zirconium cyclosilicate among individuals with hyperkalemia. *Clin J Am Soc Nephrol*. 2019;14(6):798.
- Colbert GB, Patel D, Lerma EV. Patiromer for the treatment of hyperkalemia. *Expert Rev Clin Pharmacol*. 2020;13(6):563–570.
- Jain N, Kotla S, Little BB, et al. Predictors of hyperkalemia and death in patients with cardiac and renal disease. *Am J Cardiol*. 2012;109(10):1510–1513.
- McMahon GM, Mendu ML, Gibbons FK, et al. Association between hyperkalemia at critical care initiation and mortality. *Intensive Care Med*. 2012;38(11):1834–1842.