

Examining the “Repletion Reflex”: The Association between Serum Potassium and Outcomes in Hospitalized Patients with Heart Failure

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BACKGROUND: In patients hospitalized with heart failure (HF) exacerbations, physicians routinely supplement potassium to maintain levels ≥ 4.0 mEq/L. The evidence basis for this practice is relatively weak. We aimed to evaluate the association between serum potassium levels and outcomes in patients hospitalized with HF.

METHODS: We identified patients admitted with acute HF exacerbations to hospitals that contributed to an electronic health record-derived dataset. In a subset of patients with normal admission serum potassium (3.5–5.0 mEq/L), we averaged serum potassium values during a 72-hour exposure window and categorized as follows: <4.0 mEq/L (low normal), 4.0–4.5 mEq/L (medium normal), and >4.5 mEq/L (high normal). We created multivariable models examining associations between these categories and outcomes.

RESULTS: We included 4,995 patients: 2,080 (41.6%), 2,326 (46.6%), and 589 (11.8%) in the <4.0 , 4.0–4.5, and

>4.5 mEq/L cohorts, respectively. After adjustment for demographics, comorbidities, and presenting severity, we observed no difference in outcomes between the low and medium normal groups. Compared to patients with levels <4.0 mEq/L, patients with a potassium level of >4.5 mEq/L had a longer length of stay (median of 0.6 days; 95% CI: 0.1 to 1.0) but did not have statistically significant increases in mortality (OR [odds ratio] = 1.51; 95% CI: 0.97 to 2.36) or transfers to the intensive care unit (OR = 1.78; 95% CI: 0.98 to 3.26).

CONCLUSIONS: Inpatients with heart failure who had mean serum potassium levels of <4.0 showed similar outcomes to those with mean serum potassium values of 4.0–4.5. Compared with mean serum potassium level of <4.0 , mean serum levels of >4.5 may be associated with increased risk of poor outcomes. *Journal of Hospital Medicine* 2019;14:729–736. © 2019 Society of Hospital Medicine

Heart failure (HF) is a leading cause of hospital admission and mortality, accounting for approximately 900,000 discharges in 2014.¹ One-year all-cause mortality risk has been estimated at 17% after hospitalization,² and roughly 50% of deaths are related to sudden cardiac death, mostly due to ventricular arrhythmia.³ Potassium abnormalities occur frequently in hospitalized patients with HF, and serum potassium levels outside of the normal reference range (<3.5 and >5.0 mEq/L) have been consistently shown to predict morbidity and mortality.⁴⁻⁹ However, confusion still surrounds the acute management of patients with potassium values in the lower normal range (3.5–4.0 mEq/L). Conventional clinical wisdom suggests that these patients must maintain a higher serum potassium, with a minimum value of 4.0 mEq/L often cited as

the target value.¹⁰ Despite the limited evidence in the acute HF population underlying this practice, clinicians often reflexively order potassium supplementation to reach this goal.

The principles underlying potassium management in acute HF are complex. Both low and high values have been linked to fatal arrhythmias, notably ventricular fibrillation, and small serum changes often reflect large total body potassium fluctuations.¹¹ Recent literature links hypokalemia to general membrane hypoexcitability, skeletal muscle hyporeflexia, and arrhythmias initiated by reduced sodium-potassium adenosine triphosphatase activity, leading to increased intracellular calcium and regional variations in action potential duration.¹² Potassium abnormalities are common at admission and may be exacerbated by both acute illness and treatments given during hospitalization, including baseline potassium, acute kidney injury, aggressive diuretic therapy, or other potassium-related treatments and conditions.¹³ The success of potassium repletion may also be affected by the choice of HF therapies.¹⁴

The belief that patients with HF must maintain a potassium >4.0 mEq/L remains pervasive, with at least one family medicine guideline recommending that patients with HF maintain

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a serum potassium level >4.0 mEq/L.¹⁵ Considering this uncertainty and that potassium repletion in hospitalized patients is a daily occurrence consuming a noteworthy amount of health-care resources, we aimed to evaluate the association between differences in normal inpatient serum potassium levels and outcomes in a large cohort of patients hospitalized for an acute HF exacerbation who presented with serum potassium within normal range (3.5-5.0 mEq/L).

METHODS

Data Sources and Cohort Definition

The Institutional Review Board at Baystate Medical Center approved this study. We identified patients with HF who were admitted for more than 72 hours between January 2010 and December 2012 to hospitals contributing to the HealthFacts database, a multihospital dataset derived from the comprehensive electronic health records of 116 geographically and structurally diverse hospitals throughout the United States (Cerner Corp.). HealthFacts—which includes date-stamped pharmacy, laboratory, and billing information—contains records of more than 84 million acute admissions, emergency room visits, and ambulatory visits. We limited the sample to hospitals that contributed to the pharmacy, laboratory, and diagnosis segments.

We included patients who had a principal International Classification of Disease (ICD-9-CM) diagnosis of HF or a principal diagnosis of respiratory failure with secondary diagnosis of HF (ICD-9-CM codes for HF: 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx¹⁶ and for respiratory failure: 518.81, 518.82, 518.84) and were 18 years or older. We ensured that patients were treated for acute decompensated HF during the hospitalization by restricting the cohort to patients in whom at least one HF therapy (eg, loop diuretics, metolazone, inotropes, and intra-aortic balloon pump) was initiated within the first two days of hospitalization. We excluded patients with a pediatric or psychiatric attending physician, those with elective admissions, and those who were transferred from or to another acute care facility because we could not accurately determine the onset or subsequent course of their illness.

Definition of Variables Describing Serum Potassium Levels

We limited the sample to patients hospitalized for longer than 72 hours in order to observe how initial potassium values influenced outcomes over the course of hospitalization. We chose an exposure window of 72 hours because this allowed, on average, three potential observations of serum potassium per patient. We further restricted the sample to those who had a normal potassium value (3.5-5.0 mEq/L) at admission (defined as 24 hours prior to admission through midnight of the day of admission) to ensure that the included patients did not have abnormal potassium values upon presentation. We identified the period of time from 24 hours prior to admission through 72 hours following admission as “the exposure window” (the time during which patients were eligible to be classified into average serum potassium levels of <4.0 , 4.0-4.5, or >4.5 mEq/L).

We excluded patients who, during this window, had fewer than three serum potassium levels drawn (“exposure” levels could be disproportionately influenced by a single value) or received sodium polystyrene (as this would indicate that the physicians felt the potassium was dangerously high). For patients with repeated hospitalizations, we randomly selected one visit for inclusion to reduce the risk of survivor bias. We calculated the mean of all serum potassium levels during the exposure window, including the admission value, and then evaluated two different categorizations of mean serum potassium, based on categories of risk previously reported in the literature:^{8,17,18} (1) <4.0 , 4.0-4.5, or >4.5 mEq/L and (2) <4.0 versus ≥ 4.0 mEq/L.

Outcomes

We assessed three outcomes: in-hospital mortality, transfer to an intensive care unit (ICU), and length of stay (LOS). Admission to the ICU was defined as any evidence, after the exposure window, that the patient received care in the ICU. We excluded patients with ICU admissions during the exposure window from the analysis of this outcome. We calculated LOS as the difference between discharge date/time and the admission date/time.

Covariates and Comorbidity Adjustment

We obtained information on patient demographics (age and race) and identified the presence of comorbid conditions using previously derived and validated models.^{19,20} We then further quantified these conditions into a single combined score to adjust for differences in presenting illness severity (including kidney disease) and help reduce confounding.²¹ To account for presenting severity of illness, we calculated the Laboratory-based Acute Physiology Score (LAPS-2).^{22,23} LAPS-2 was developed for predicting mortality risk in general medical patients, but we previously externally validated it against other published clinical HF models in a cohort of patients hospitalized with acute decompensated HF.⁵ LAPS-2 includes fourteen laboratory values at the time of admission (including blood urea nitrogen, creatinine, and anion gap) to calculate a score.^{22,23} Thus, we adjusted for differences in baseline characteristics, including admission renal function.

Potassium Repletion

We evaluated whether patients received potassium during the exposure window (defined as any supplemental potassium order during the hospital stay) and the total number of days the patient was eligible for repletion (defined as a serum potassium result that was <4.0 mEq/L). We then recorded the total number of days repletion was given (using medication orders). We also calculated the ratio of days that repletion was received to the days that the patient was eligible for repletion. We also recorded all instances in which serum potassium values were <3.5 mEq/L at any time during the exposure window.

Analysis

We evaluated the differences in patient characteristics across serum potassium categories. Categorical variables are pre-

TABLE 1. Cohort Demographics

	Mean Potassium During Exposure Window				P Value
	Overall	<4 mEq/L	4.0-4.5 mEq/L	>4.5 mEq/L	
	N = 4,995	n = 2,080 (41.6%)	n = 2,326 (46.6%)	n = 589 (11.8%)	
Age, mean (SD)	72.6 (14.1)	72.4 (14.3)	73.0 (14.1)	71.8 (13.4)	.1183
Female, n (%)	2,556 (51.2)	1,106 (53.2)	1,154 (49.6)	296 (50.3)	.0552
Race, n (%)					.0018
African American	1,157 (23.2)	456 (21.9)	540 (23.2)	161 (27.3)	
Caucasian	3,499 (70.1)	1,498 (72.0)	1,627 (69.9)	374 (63.5)	
Other	339 (6.8)	126 (6.1)	159 (6.8)	54 (9.2)	
Heart failure subtype, n (%) ^a					.0174
Diastolic	1,547 (39.0)	615 (37.1)	725 (39.0)	207 (45.8)	
Systolic	1,888 (47.6)	814 (49.1)	888 (47.8)	186 (41.2)	
Combined	532 (13.4)	229 (13.8)	244 (13.1)	59 (13.1)	
LAPS-2, mean (SD)	4.9 (5.8)	4.9 (6.0)	4.8 (5.6)	5.2 (5.6)	.2018
Combined comorbidity score, mean (SD)	4.7 (2.2)	4.6 (2.2)	4.7 (2.2)	5.1 (2.3)	<.001
Admission creatinine, mean (SD) ^b	1.6 (1.1)	1.4 (1.0)	1.6 (1.1)	2.0 (1.7)	<.001
Admission creatinine >1, n (%)	3,561 (71.3)	1,384 (66.5)	1,706 (73.3)	471 (80.0)	<.001
Admission creatinine >1 or Elixhauser code for renal insufficiency, n (%)	3,663 (73.3)	1,431 (68.8)	1,750 (75.2)	482 (81.8)	<.001
Comorbidities, n (%) ^c					
Hypertension	3,101 (62.1)	1,287 (61.9)	1,439 (61.9)	375 (63.7)	.7002
Chronic renal insufficiency	1,978 (39.6)	728 (35.0)	951 (40.9)	299 (50.8)	<.001
Chronic pulmonary disease	1,916 (38.4)	744 (35.8)	904 (38.9)	268 (45.5)	<.001
Diabetes without chronic complications	1,598 (32.0)	646 (31.1)	729 (31.3)	223 (37.9)	.0050
Deficiency anemias	1,515 (30.3)	570 (27.4)	717 (30.8)	228 (38.7)	<.001
Fluid and electrolyte disorders	1,438 (28.8)	718 (34.5)	545 (23.4)	175 (29.7)	<.001
Obesity	1,024 (20.5)	424 (20.4)	456 (19.6)	144 (24.4)	.0335
Hypothyroidism	805 (16.1)	336 (16.2)	379 (16.3)	90 (15.3)	.8348
Peripheral vascular disease	545 (10.9)	200 (9.6)	267 (11.5)	78 (13.2)	.0217
Diabetes with chronic complications	499 (10.0)	179 (8.6)	232 (10.0)	88 (14.9)	<.001
Depression	478 (9.6)	214 (10.3)	219 (9.4)	45 (7.6)	.1466
Other neurological disorders	353 (7.1)	146 (7.0)	161 (6.9)	46 (7.8)	.7495
Coagulopathy	340 (6.8)	137 (6.6)	163 (7.0)	40 (6.8)	.8575

^an = 1,028 (21%) missing a heart failure subtype category.

^bn = 9 (0.2%) missing creatinine value.

^cComorbidities <5% are not shown (weight loss, valvular disease, pulmonary circulation disease, rheumatoid arthritis, liver disease, alcohol/drug abuse, psychoses, solid tumor without metastasis, paralysis, lymphoma, chronic blood loss anemia, metastatic cancer, acquired immunodeficiency syndrome, and peptic ulcer disease).

Abbreviation: SD, standard deviation.

sented as frequencies and percentages, whereas continuous variables are presented as means and standard deviations. For binary outcomes, we used generalized estimating equations (with a binomial family and logit link and clustering by hospital) to estimate incidence and calculate unadjusted and adjusted odds ratios (ORs) and 95% confidence intervals (CIs). For LOS, we estimated the median and 95% CIs using quantile regression with clustered standard errors.²⁴ We calculated all models using both a binary exposure (<4.0 versus ≥4.0 mEq/L)

and a three-level categorization (<4.0, 4.0-4.5, and >4.5 mEq/L) to explore the effects at the highest potassium level. We adjusted all models for age, race, LAPS-2 score, and combined comorbidity score. We conducted two sensitivity analyses. First, we restricted our sample to those who never received potassium during the exposure window, as these patients may be different than patients who required potassium repletion. Second, we stratified our findings by the presence or absence of acute or chronic renal insufficiency (defined as an admission

TABLE 2. Potassium Repletion Characteristics

	Overall N = 4,995	Mean Potassium During Exposure Window			P Value
		<4 mEq/L n = 2,080 (41.6%)	4.0-4.5 mEq/L n = 2,326 (46.6%)	>4.5 mEq/L n = 589 (11.8%)	
First admission window serum potassium:					
Mean (SD)	4.3 (0.4)	4.0 (0.3)	4.4 (0.3)	4.7 (0.3)	<.001
Median (range)	4.2 (3.5, 5.0)	4.0 (3.5, 5.0)	4.4 (3.5, 5.0)	4.7 (3.7, 5.0)	<.001
Mean exposure window serum potassium					
Mean (SD)	4.1 (0.4)	3.8 (0.2)	4.2 (0.1)	4.7 (0.2)	<.001
Median (range)	4.1 (2.9, 5.8)	3.8 (2.9, 3.9)	4.2 (4.0, 4.5)	4.7 (4.5, 5.8)	<.001
Potassium <3.5 mEq/L at any point within exposure window, n (%)	1,202 (24.1)	1,054 (50.7)	146 (6.3)	2 (0.3)	<.001
Potassium repletion within exposure window, n (%)	2,588 (51.8)	1,488 (71.5)	943 (40.5)	157 (26.7)	<.001
Total days repletion eligible, n (%)					
0	1,406 (28.1)	2 (0.1)	858 (36.9)	546 (92.7)	<.001
1	1,104 (22.1)	142 (6.8)	924 (39.7)	38 (6.5)	
2	1,219 (24.4)	739 (35.5)	476 (20.5)	4 (0.7)	
3	942 (18.9)	878 (42.2)	63 (2.7)	1 (0.2)	
4	324 (6.5)	319 (15.3)	5 (0.2)	0 (0.0)	
Total days repletion given, n (%) ^a					
0	1,721 (48.0)	710 (34.2)	984 (67.0)	27 (62.8)	—
1	1,289 (35.9)	839 (40.4)	435 (29.6)	15 (34.9)	
2	456 (12.7)	410 (19.7)	45 (3.1)	1 (2.3)	
3	113 (3.1)	109 (5.2)	4 (0.3)	0 (0.0)	
4	10 (0.3)	10 (0.5)	0 (0.0)	0 (0.0)	
Ratio of days repleted/opportunities, n (%) ^a					
0	1,721 (48.0)	710 (34.2)	984 (67.0)	27 (62.8)	—
0.25	116 (3.2)	115 (5.5)	1 (0.1)	0 (0.0)	
0.33	381 (10.6)	355 (17.1)	26 (1.8)	0 (0.0)	
0.5	566 (15.8)	394 (19.0)	171 (11.6)	1 (2.3)	
0.66	222 (6.2)	211 (10.2)	11 (0.7)	0 (0.0)	
0.75	54 (1.5)	52 (2.5)	2 (0.1)	0 (0.0)	
1	529 (14.7)	241 (11.6)	273 (18.6)	15 (34.9)	

^aOnly among those who required repletion (n = 3,589). P values not able to be calculated because of sparse cells.

creatinine >1 or the presence of a diagnostic code for renal insufficiency, as defined by Elixhauser et al.).^{19,21} Statistical significance was set at an alpha of 0.05. Analysis was completed using Stata v15.1, StataCorp LP, College Station, Texas.

RESULTS

Cohort Description

We identified patients from 56 geographically diverse US hospitals, although most were located in either the northeast (n = 21; 38%) or south (n = 18; 32%). A total of 59% of the hospitals were teaching hospitals, and nearly 95% were in an urban setting. We identified 13,163 patients with HF, of which 4,995 (38.0%) met the inclusion criteria. We excluded 3,744 (28.4%) patients with LOS < 72 hours, 2,210 (16.8%) with admission potassium values outside of the defined range, and 896 (6.8%) with fewer than

three potassium values during the exposure window. Of the patients who met the inclusion criteria, 2,080 (41.6%), 2,326 (46.6%), and 589 (11.8%) were categorized in the <4.0, 4.0-4.5, and >4.5 mEq/L groups, respectively (Table 1). The groups were clinically similar in terms of age, sex, illness severity (LAPS-2), and comorbidity score. Compared with other racial groups, black patients had higher potassium values. While the <4.0 and 4.0-4.5 mEq/L groups were relatively similar, the group with mean potassium >4.5 mEq/L had higher admission creatinine and a greater prevalence of chronic kidney disease, deficiency anemias, and chronic obstructive pulmonary disease (Table 1).

Serum Potassium Values

Individuals' mean serum potassium within the 72-hour exposure window ranged from 2.9 to 5.8 mEq/L (Table 2). In the

TABLE 3. Potassium and Outcomes

	n	Events	Incidence and 95% CI ^a	Unadjusted ^{a,b}		Adjusted ^{a,b}	
				OR and 95% CI	P Value	OR and 95% CI	P Value
Mortality							
Full sample (mEq/L)							
<4	2,080	73	3.5% (2.6 to 4.4)	Referent		Referent	
4.0-4.5	2,326	83	3.6% (2.7 to 4.5)	1.04 (0.76 to 1.43)	.811	1.05 (0.75 to 1.46)	.785
>4.5	589	31	5.3% (3.4 to 7.2)	1.55 (1.01 to 2.39)	.045	1.51 (0.97 to 2.36)	.070
No repletion (mEq/L)							
<4	592	18	3.2% (1.6 to 4.7)	Referent		Referent	
4.0-4.5	1,383	52	3.9% (2.7 to 5.2)	1.24 (0.73 to 2.12)	.424	1.18 (0.66 to 2.09)	.574
>4.5	432	24	5.6% (3.3 to 8.0)	1.82 (0.98 to 3.38)	.057	1.56 (0.81 to 3.01)	.185
ICU admission							
Full sample (mEq/L)							
<4	1,723	33	1.8% (1.0 to 2.7)	Referent		Referent	
4.0-4.5	1,951	47	2.5% (1.5 to 3.4)	1.36 (0.86 to 2.14)	.192	1.30 (0.82 to 2.06)	.264
>4.5	486	18	3.8% (1.9 to 5.7)	2.10 (1.16 to 3.80)	.014	1.78 (0.98 to 3.26)	.061
No repletion (mEq/L)							
<4	512	12	2.2% (0.8 to 3.6)	Referent		Referent	
4.0-4.5	1,188	34	2.9% (1.8 to 4.0)	1.30 (0.66 to 2.57)	.444	1.25 (0.61 to 2.55)	.540
>4.5	355	13	3.8% (1.7 to 5.9)	1.71 (0.77 to 3.82)	.189	1.40 (0.60 to 3.26)	.431
Length of stay (LOS)							
Length of stay (Days)			Median and 95% CI ^a	Difference in LOS and 95% CI	P Value	Difference and 95% CI	P Value
Full Sample (mEq/L)							
<4	2,080	—	5.5 (5.3 to 5.8)	Referent		Referent	
4.0-4.5	2,326	—	5.5 (5.2 to 5.7)	-0.1 (-0.2 to 0.1)	.558	0.0 (-0.1 to 0.2)	.773
>4.5	589	—	6.1 (5.8 to 6.5)	0.6 (0.3 to 1.0)	<.001	0.6 (0.1 to 1.0)	.009
No Repletion (mEq/L)							
<4	592	—	5.2 (4.9 to 5.6)	Referent		Referent	
4.0-4.5	1,383	—	5.2 (4.9 to 5.5)	0.0 (-0.2 to 0.2)	.958	0.1 (-0.1 to 0.3)	.440
>4.5	432	—	6.1 (5.7 to 6.5)	0.9 (0.5 to 1.3)	<.001	0.6 (0.1 to 1.2)	.016

^aMortality and ICU admission: generalized estimating equation for logistic regression clustering on hospital; length of stay (LOS): quantile regression clustering on hospital.

^bAdjusted for age, race, Laboratory-based Acute Physiology Score-2, and Combined Comorbidity Score.

Abbreviation: ICU, intensive care unit; LOS, length of stay.

<4.0, 4-4.5, and >4.5 mEq/L cohorts respectively, patients had a median serum potassium of 3.8 mEq/L (2.9-3.9), 4.2 mEq/L (4.0-4.5), and 4.7 mEq/L (4.5-5.8) during the exposure window. Approximately half of the patients in the <4.0 mEq/L group had a serum potassium <3.5 mEq/L at some point during the exposure window. In contrast, <10% of the other groups had this low value during the exposure window.

Potassium Repletion

Patients in the <4.0 mEq/L group were much more likely to receive potassium repletion during the exposure window when compared with the 4.0-4.5 mEq/L (71.5% vs 40.5%) and >4.5 mEq/L (71.5% vs 26.7%) groups. On days that they were eligible for repletion (defined as a daily potassium value <4.0 mEq/L), patients with mean serum potassium >4.0 mEq/L were less likely to receive potassium repletion compared with those with values <4.0 mEq/L. There were 592 (28.5%), 1,383

(59.5%), and 432 (73.3%) patients in the <4.0, 4-4.5, and >4.5 mEq/L groups, respectively, who did not receive potassium repletion therapy during the exposure window.

Relationship of Serum Potassium Levels and Outcomes

Overall, 3.7% (n = 187) of patients died during the hospitalization, 2.4% (n = 98) were admitted to the ICU after the exposure window, and the median LOS was 5.6 days. We did not observe a significant association between mean serum potassium of <4.0 or 4.0-4.5 mEq/L and increased risk of mortality, ICU transfer, or LOS (Table 3). Our unadjusted analysis showed that patients with values >4.5 mEq/L had worse outcomes, including more deaths (5.3%; OR = 1.55; 95% CI: 1.01 to 2.39) and ICU admission (3.8%; OR = 2.10; 95% CI: 1.16 to 3.80) compared with those with values <4.0 mEq/L (Table 3). We also found that, compared with the <4.0 mEq/L group, the >4.5 mEq/L group

TABLE 4. Potassium and Outcomes Stratified by Renal Condition

	n	Events	Incidence and 95% CI ^a	Unadjusted ^{a,b}		Adjusted ^{a,b}	
				OR and 95% CI	P Value	OR and 95% CI	P Value
Mortality							
No renal condition (mEq/L)							
<4	649	20	3.1% (1.7 to 4.5)	Referent		Referent	
4.0-4.5	576	14	2.5% (1.2 to 3.9)	0.81 (0.41 to 1.61)	.545	0.91 (0.44 to 1.87)	.798
>4.5	107	8	7.4% (2.4 to 12.4)	2.52 (1.08 to 5.89)	.033	3.03 (1.27 to 7.24)	.013
Creatinine >1 or Elixhauser code for renal insufficiency (mEq/L)							
<4	1,431	53	3.7% (2.6 to 4.8)	Referent		Referent	
4.0-4.5	1,750	69	4.0% (2.9 to 5.0)	1.08 (0.75 to 1.56)	.665	1.08 (0.74 to 1.58)	.686
>4.5	482	23	4.8% (2.9 to 6.8)	1.33 (0.81 to 2.19)	.264	1.27 (0.76 to 2.13)	.366
ICU admission							
No renal condition (mEq/L)							
<4	551	10	1.9% (0.6 to 3.1)	Referent		Referent	
4.0-4.5	487	7	1.7% (0.4 to 2.9)	0.90 (0.35 to 2.26)	.815	0.83 (0.32 to 2.14)	.701
>4.5	82	5	5.9% (0.7 to 11.1)	3.30 (1.08 to 10.05)	.036	3.00 (0.95 to 9.47)	.062
Creatinine >1 or Elixhauser code for renal insufficiency (mEq/L)							
<4	1,172	23	1.8% (0.9 to 2.8)	Referent		Referent	
4.0-4.5	1,464	40	2.7% (1.6 to 3.8)	1.50 (0.88 to 2.56)	.137	1.49 (0.87 to 2.56)	.144
>4.5	404	13	3.3% (1.4 to 5.2)	1.85 (0.92 to 3.72)	.084	1.63 (0.80 to 3.32)	.175
Length of stay (Days)							
No renal condition (mEq/L)							
<4	649	—	5.1 (4.8 to 5.4)	Referent		Referent	
4.0-4.5	576	—	5.2 (4.9 to 5.5)	0.0 (−0.2 to 0.3)	.785	0.1 (−0.3 to 0.4)	.780
>4.5	107	—	5.9 (5.3 to 6.6)	0.8 (0.1 to 1.5)	.026	0.4 (0.2 to 1.1)	.210
Creatinine >1 or Elixhauser code for renal insufficiency (mEq/L)							
<4	1,431	—	5.7 (5.5 to 5.9)	Referent		Referent	
4.0-4.5	1,750	—	5.6 (5.3 to 5.9)	−0.1 (−0.3 to 0.1)	.361	0.0 (−0.2 to 0.2)	.814
>4.5	482	—	6.2 (5.8 to 6.8)	0.5 (0.2 to 0.9)	.001	0.6 (0.1 to 1.1)	.024

^aMortality and ICU admission: generalized estimating equation for logistic regression clustering on hospital; LOS: quantile regression clustering on hospital

^bAdjusted for age, race, Laboratory-based Acute Physiology Score-2, and Combined Comorbidity Score.

Abbreviations: ICU, intensive care unit; LOS, length of stay.

showed just over a half-day longer LOS (0.6 days; 95% CI: 0.0 to 1.0; Table 3). However, we found that mortality and ICU admission results were attenuated after adjustment for age, race, comorbidity score, and LAPS-2 and were no longer statistically significant, whereas the association with LOS was consistent after adjustment. When using a binary exposure (<4.0 versus ≥4.0 mEq/L), we observed no association between mean potassium value and increased risk of mortality, ICU transfer, or LOS both before and after adjustment for age, race, LAPS-2, and comorbidity score (data not shown).

Sensitivity Analyses

In the sensitivity analysis restricted to those who did not receive potassium repletion during the exposure window, we continued to observe no association between the <4.0 and 4.0-4.5

mEq/L groups and outcomes (Table 3). In adjusted models for the >4.5 versus <4.0 mEq/L groups, risk estimates for mortality were similar to the full sample, but statistical significance was lost (OR = 1.56; 95% CI: 0.81 to 3.01). Adjusted risk estimates for ICU transfer were attenuated and not statistically significant (OR = 1.40; 95% CI: 0.60 to 3.26). However, LOS estimates were very similar to that observed in the full dataset (0.6 days; 95% CI: 0.1 to 1.2).

When stratifying our results by the presence or absence of acute or chronic renal insufficiency, we continued to observe no increased risk of any outcome in the 4.0-4.5 mEq/L compared with the <4.0 mEq/L groups across all strata (Table 4). Interestingly, even after adjustment, we did find that most of the increased risk of mortality and ICU admission in the >4.5 versus <4.0 mEq/L groups was among those without renal in-

sufficiency (mortality OR = 3.03; ICU admission OR = 3.00) and was not statistically significant in those with renal insufficiency (mortality OR = 1.27; ICU admission OR = 1.63). Adjusted LOS estimates remained relatively similar in this stratified analysis.

DISCUSSION

The best approach to mild serum potassium value abnormalities in patients hospitalized with HF remains unclear. Many physicians reflexively replete potassium to ensure all patients maintain a serum value of >4.0 mEq/L.¹⁵ Yet, in this large observational study of patients hospitalized with an acute HF exacerbation, we found little evidence of association between serum potassium <4.0 mEq/L and negative outcomes.

Compared with those with mean potassium values <4.0 mEq/L (in unadjusted models), there was an association between potassium values of >4.5 mEq/L and increased risk of mortality and ICU transfer. This association was attenuated after adjustment, suggesting that factors beyond potassium values influenced the observed relationship. These findings seem to suggest that unobserved differences in the >4.5 mEq/L group (there were observed differences in this group, eg, greater presenting severity and higher comorbidity scores, suggesting that there were also unobserved differences), and not average potassium value, were the reasons for the observed differences in outcomes. However, we cannot rule out the possibility that potassium >4.5 mEq/L has some associated increased risk compared with mean potassium values of <4.0 mEq/L for patients hospitalized with acute decompensated HF.

Patients in our study routinely received exogenous potassium: more than 70% of patients received repletion at least once, although it is notable that the majority of patients in the 4.0-4.5 and >4.5 mEq/L groups did not receive repletion. Despite this practice, the data supporting this approach to potassium management for patients hospitalized with HF remain mixed. A serum potassium decline of $>15\%$ during an acute HF hospital stay has been reported as a predictor of all-cause mortality after controlling for disease severity and associated comorbidities, including renal function.²⁵ However, this study was focused on decline in admission potassium rather than an absolute cutoff (eg, >4.0 mEq/L). Additionally, potassium levels <3.9 mEq/L were associated with increased mortality in patients with acute HF following a myocardial infarction, but this study was not focused on patients with HF.²⁶ Most of the prior literature in patients with HF was conducted in patients in outpatient settings and examined patients who were not experiencing acute exacerbations. MacDonald and Struthers advocate that patients with HF have their potassium maintained above 4.0 mEq/L but did not specify whether this included patients with acute HF exacerbations.¹⁰ Additionally, many studies evaluating potassium repletion were conducted before widespread availability of angiotensin-converting enzyme (ACE) inhibitors or potassium-sparing diuretics, including spironolactone. Prior work has consistently reported that hyperkalemia, defined as serum potassium >4.5 mEq/L, is associated with mortality in patients with acute HF over the course of hospitalization (which aligned with the results from our sensitivity analysis), but concurrent

medication regimens and underlying impaired renal function likely accounted for most of this association.¹⁷ The picture is further complicated as patients with acute HF presenting with hypokalemia may be at risk for subsequent hyperkalemia, and potassium repletion can stimulate aldosterone secretion, potentially exacerbating underlying HF.^{27,28}

These data are observational and are unlikely to change practice. However, daily potassium repletion represents a huge cost in time, money, and effort to the health system. Furthermore, the greatest burden occurs for the patients, who have labs drawn and values checked routinely and potassium administered orally or parenterally. While future randomized clinical trials (RCTs) would best examine the benefits of repletion, future pragmatic trials could attempt to disentangle the associated risks and benefits of potassium repletion in the absence of RCTs. Additionally, such studies could better take into account the role of concurrent medication use (like ACEs or angiotensin II receptor blockers), as well as assess the role of chronic renal insufficiency, acute kidney injury, and magnesium levels.²⁹

This study has limitations. Its retrospective design leads to unmeasured confounding; however, we adjusted for multiple variables (including LAPS-2), which reflect the severity of disease at admission and underlying kidney function at presentation, as well as other comorbid conditions. In addition, data from the cohort only extend to 2012, so more recent changes in practice may not be completely reflected. The nature of the data did not allow us to directly investigate the relationship between serum potassium and arrhythmias, although ICU transfer and mortality were used as surrogates. We were not able to examine the relationship between acute and chronic renal failure and potassium, as this was beyond the scope of this analysis. Given the hypothesis-generating nature of this study, adjustment for additional confounders, including concurrent medication use, was beyond the scope of this analysis.

In conclusion, the benefit of a serum potassium level >4.0 mEq/L in patients admitted with HF remains unclear. We did not observe that mean potassium values <4.0 mEq/L were associated with worse outcomes, and, more concerning, there may be some risk for patients with mean values >4.5 mEq/L.

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