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ORIGINAL RESEARCH ARTICLE

Hypokalaemia and outcomes in older patients hospitalized for heart failure

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Abstract

Aims Hypokalaemia is a risk factor for ventricular arrhythmias and sudden death in ambulatory patients with chronic heart failure (HF). The objective of this study was to examine the association between hypokalaemia and outcomes in hospitalized patients with decompensated HF in whom sudden death is less common.

Methods and results Of the 5881 hospitalized patients with HF, 1052 had consistent hypokalaemia (both admission and discharge serum potassium <4.0 mmol/L), and 2538 had consistent normokalaemia (both admission and discharge serum potassium 4.0–5.0 mmol/L). Propensity scores for consistent hypokalaemia, estimated for each of 3590 (1052 + 2538) patients, were used to assemble a matched cohort of 971 pairs of patients with consistent hypokalaemia vs. consistent normokalaemia, balanced on 54 baseline characteristics (mean age, 75 years; 60% women; 28% African American). We repeated the above process to assemble 2327 pairs of patients with discharge potassium <4.0 vs. 4.0–5.0 mmol/L and 449 pairs of patients with discharge serum potassium <3.5 vs. 4.0–5.0 mmol/L. Hazard ratios (HR) and 95% confidence intervals (CIs) associated with hypokalaemia were estimated in matched cohorts. 30 day all-cause mortality occurred in 5% and 4% of patients with consistent normokalaemia vs. consistent hypokalaemia, respectively (HR, 0.78; 95% CI, 0.52–1.18; $P = 0.241$). HRs (95% CI) for 30 day mortality associated with discharge serum potassium <4.0 and <3.5 mmol/L were 0.90 (0.70–1.16; $P = 0.419$) and 1.69 (0.94–3.04; $P = 0.078$), respectively. Hypokalaemia (<4.0 or <3.5 mmol/L) had no association with long-term mortality or other outcomes.

Conclusions In hospitalized older patients with HF, compared with normokalaemia (serum potassium 4.0–5.0 mmol/L), hypokalaemia (<4.0 or <3.5 mmol/L) had no significant associations with outcomes.

Keywords Heart failure; Potassium; Mortality; Hospitalization; Propensity score

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Introduction

Hypokalaemia is common in heart failure (HF) and is often attributed to the renal loss of potassium due to neurohormonal activation and use of diuretics. Potassium homeostasis is essential for resting transmembrane potential and maintenance of a normal cardiac rhythm, and hypokalaemia may increase the risk of ventricular arrhythmias and sudden cardiac death.[1] In ambulatory patients with mild to moderate chronic HF, serum potassium levels <4.0 mmol/L have been shown to be associated with a higher risk of death.[2–4] Sudden cardiac death is a more common mode of death in early stage mild to moderate HF, but with disease progression, death because of pump failure may become relatively more common.[5–7] In the current study, we examined the association of hypokalaemia with clinical outcomes in hospitalized older patients with acute HF who would be expected to have more advanced disease.

Methods

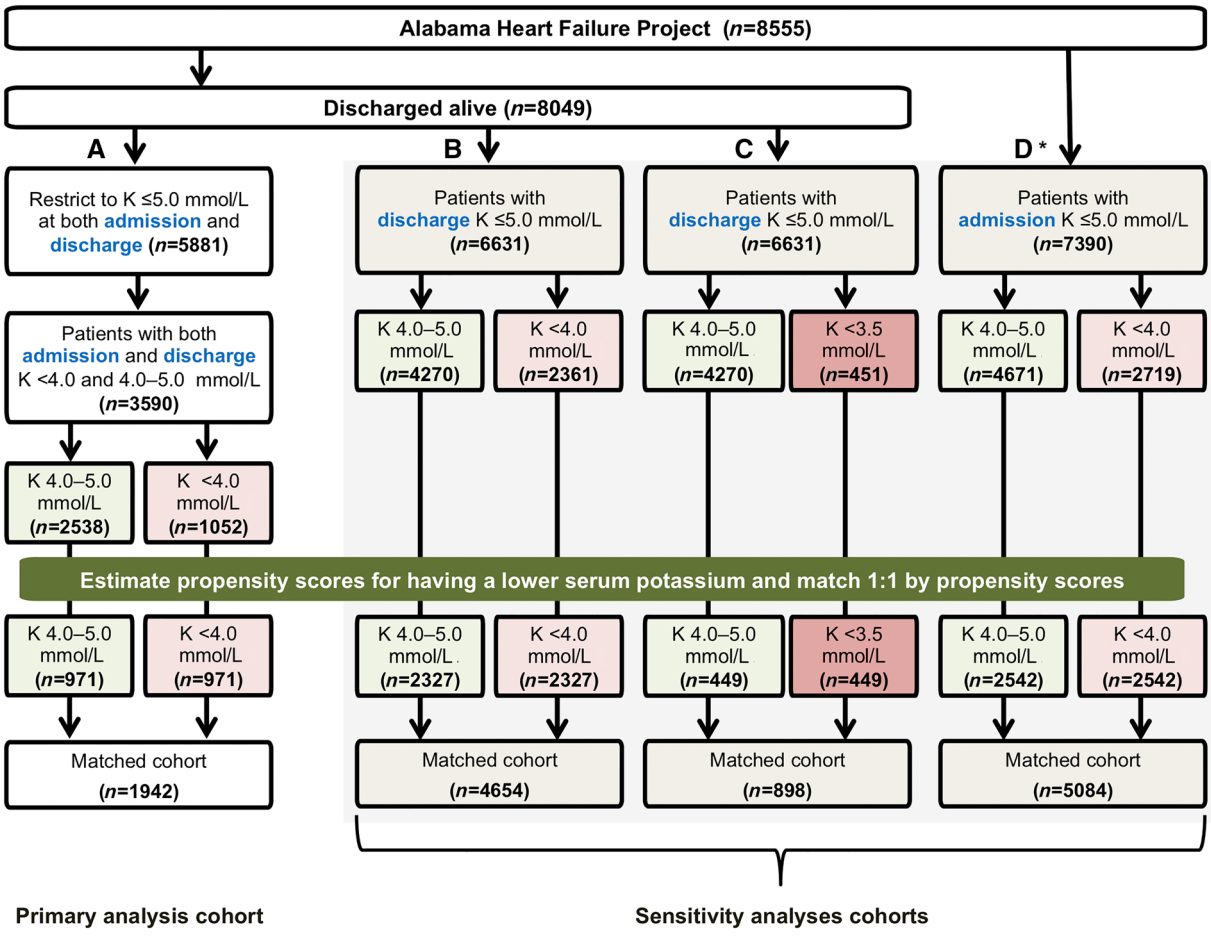
Study design and patients

We conducted a nonrandomized propensity score-matched study of the Alabama Heart Failure Project, the details of which have been described previously.[8] Briefly, 9649 medical records of fee-for-service Medicare beneficiaries discharged from 106 Alabama hospitals between 1998 and 2001 with a principle discharge diagnosis code of HF were abstracted. Charts of patients with dialysis, those transferred to another acute care hospital, or discharged against medical advice were excluded. Reliability of the abstraction process was assessed through internal and external reabstractions of 40 charts per month and had agreement values >80% and Kappa values >0.60.[8] Extensive data on demographics, past medical history, medication use, hospital course, and discharge disposition were collected.[9,10] The 9649 hospitalizations occurred in 8555 unique patients. Of the 8555 patients, 8049 were discharged alive. Of these, 7006 had data on both admission and discharge serum potassium levels.

Data on serum potassium

The Alabama Heart Failure Project is unique among large HF registries in that it collected data on admission and discharge serum potassium from laboratory reports, emergency room record, history and physical report, intensive care unit flow sheet, nursing flow sheet, diabetic flow sheets, graphic sheet, and progress notes. We excluded 1125 patients whose admission or discharge serum potassium levels were >5.0 mmol/L (*Figure 1*) as these values are associated with poor outcomes.[1,2,4,11] The remaining 5881 patients had mean (±SD) admission and discharge serum potassium levels of 4.1 (±0.49) and 4.1 (±0.45) mmol/L, respectively. Among these patients, 1052 had consistent hypokalaemia, defined as both admission and discharge serum potassium <4.0 mmol/L, and 2538 had consistent normokalaemia, defined as both

Figure 1 Flow chart displaying assembly of propensity score-matched cohorts of patients with heart failure by serum potassium. *Sensitivity cohort (D) also includes patients who were deceased during index hospitalization to allow for assessment of in-hospital mortality.



admission and discharge serum potassium levels 4.0–5.0 mmol/L (*Figure 1A*). Thus, our final prematch cohort consisted of 3590 patients, of whom 1052 had consistent hypokalaemia. These patients had mean (±SD) admission and discharge serum potassium levels of 4.2 (±0.48) and 4.2 (±0.45) mmol/L, respectively. Among the 1052 prematch patients with consistent hypokalaemia, 258 (25%) had a discharge serum potassium <3.5 mmol/L, and 15 (1.4%) had a discharge serum potassium <3.0 mmol/L. Of the 5881 patients with both admission and discharge serum potassium <5.0 mmol/L, only 82 (1.4%) had both admission and discharge serum potassium <3.5 mmol/L.

Study outcome

The primary outcome for the current study was all-cause mortality at 30 days, 1 year, and during overall follow-up of 8.8 (median, 3.3) years. Secondary outcomes included all-cause and HF readmissions, and the combined endpoints of all-cause readmission or all-cause mortality and HF readmission or all-cause mortality. All outcomes data were collected from Medicare data. Patients who were admitted to out-of-state hospitals or those who did not have Medicare pay for their hospitalizations were not included.

Assembly of a balanced cohort

Because patients with hypokalaemia and normokalaemia would have different baseline characteristics that could introduce bias, we used propensity scores to assemble a cohort in which these two groups of patients would be well-balanced on key measured baseline covariates.[12,13] We estimated propensity scores of hypokalaemia for each of the 3590 patients using a nonparsimonious multivariable logistic regression model. In that model, hypokalaemia was the dependent variable, and all 54 baseline characteristics displayed in the Supporting Information, *Figure S1*, were included as covariates. In addition, the model was also adjusted for a significant interaction between discharge use of angiotensin-converting enzyme inhibitors and potassium supplements. No outcome variable was used in the model so that the process of assembling a balanced cohort was outcome blinded.

Using a greedy matching protocol, we were able to match 971 (92%) of the 1052 patients who had hypokalaemia with 971 patients with normokalaemia who had the same propensity scores between one and five decimal points.[14] For example, if two patients had propensity scores of 0.12345 and 0.12346, then they would be rounded to 0.1235 and matched. Similarly, if they had propensity scores of 0.12342 and 0.12339, then they would be rounded to 0.1234 and matched. We then assessed balance in baseline characteristics of the postmatch cohort by estimating absolute standardized differences between the two potassium groups and presented them as a love plot (*Figure S1*).[15] An absolute standardized difference of 0% indicates no residual bias and differences <10% are considered inconsequential.

Assembly of sensitivity cohorts

We repeated the above steps to assemble three sensitivity cohorts to determine if the results from our main cohort would vary if we used different definitions and approaches. First, we separately examined the associations of discharge serum potassium <4.0 and <3.5 mmol/L (regardless of admission serum potassium level), thus assembling two propensity score-matched cohorts of 4654 and 898 patients (*Figure 1B* and *1C*). Then we examined the association of admission serum potassium <4.0 mmol/L (regardless of discharge serum potassium level), assembling a propensity score-matched cohort of 5084 patients (*Figure 1D*). The latter cohort also includes patients who died during index hospitalization to allow for assessment of in-hospital mortality.

Statistical analysis

Baseline characteristics of matched cohorts were compared using Pearson's χ^2 and Wilcoxon rank sum tests, as appropriate. Cox proportional hazard models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for outcomes associated with hypokalaemia in matched cohorts. The association of hypokalaemia with all-cause mortality in the primary matched cohort was examined using Kaplan–Meier survival analysis. For survival analysis of mortality, for patients who died we estimated time to event from date of hospital discharge to date of death, and patients who survived were censored at hospital readmission or study end, whichever came first. For survival analysis of readmission, for those who were readmitted, time to event was estimated from date of hospital discharge to date of hospital readmission, and patients without a readmission were censored at death or study end, whichever came first.

To examine if there was a non-linear relationship between discharge serum potassium and all-cause mortality during 8.8 years of follow-up, we fitted restricted cubic spline models with three knots at serum potassium values 3.0, 3.5, 4.0 (reference), and 4.5 mmol/L using matched primary cohort data and prematch data adjusting for propensity scores. Subgroup analyses were conducted to assess potential heterogeneity of association between hypokalaemia and all-cause mortality in several subgroups of matched patients in the primary cohort. A two-tailed *P* value <0.05 was considered significant for all analyses. All statistical analyses were conducted using IBM SPSS Statistics for Windows software, version 24 (IBM Corp., Armonk, NY, USA), and SAS software for Windows, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics

Matched patients (n = 1942) had a mean age (±standard deviation) of 75 (±11) years, 60% were women, and 27% were African American. Before matching, patients with hypokalaemia were more likely to be younger, women, and African American but less likely to have coronary artery disease and diabetes. They were also more likely to have a higher mean systolic blood pressure, lower mean serum creatinine, and receive discharge prescriptions for potassium supplements but less likely to receive angiotensin-converting enzyme inhibitors, digoxin, and potassium-sparing diuretics (*Table 1*). These and other between-group differences in baseline characteristics were balanced after matching (*Table 1*) and absolute standardized differences for all 54 baseline characteristics were <10% (*Figure S1*). Among the 971

Table 1 Baseline characteristics of hospitalized patients with heart failure by serum potassium levels

	Before propensity score matching (n = 3590)			After propensity score matching (n = 1942)		
	Both admission and discharge serum potassium (mmol/L)			Both admission and discharge serum potassium (mmol/L)		
n (%) or mean (SD)	4.0–5.0 (n = 2538)	<4.0 (n = 1052)	P value	4.0–5.0 (n = 971)	<4.0 (n = 971)	P value
Age (years)	76 (±11)	75 (±11)	<0.001	75 (±11)	75 (±11)	0.827
Women	1407 (55%)	637 (61%)	0.005	598 (62%)	581 (60%)	0.430
African American	551 (22%)	302 (29%)	<0.001	261 (27%)	269 (28%)	0.684
Admission from nursing home	159 (6%)	65 (6%)	0.923	60 (6%)	60 (6%)	1.000
Left ventricular ejection fraction						
< 45%	1039 (41%)	359 (34%)		344 (35%)	335 (35%)	
≥ 45%	774 (31%)	333 (32%)	<0.001	303 (31%)	309 (32%)	0.908
Unknown	725 (29%)	360 (34%)		324 (33%)	327 (34%)	
Past medical history						
Smoking history	298 (12%)	121 (12%)	0.839	118 (12%)	113 (12%)	0.726
History of heart failure	1798 (71%)	788 (75%)	0.014	706 (73%)	725 (75%)	0.328
Hypertension	1756 (69%)	780 (74%)	0.003	710 (73%)	711 (73%)	0.959
Coronary artery disease	1441 (57%)	524 (50%)	<0.001	479 (49%)	494 (51%)	0.496
Atrial fibrillation	730 (29%)	283 (27%)	0.259	241 (25%)	263 (27%)	0.255
Left bundle branch block	360 (14%)	139 (13%)	0.444	129 (13%)	127 (13%)	0.893
Diabetes mellitus	1136 (45%)	429 (41%)	0.029	407 (42%)	400 (41%)	0.747
Stroke	505 (20%)	208 (20%)	0.932	186 (19%)	189 (20%)	0.863
Chronic obstructive pulmonary disease	921 (36%)	365 (35%)	0.365	349 (36%)	340 (35%)	0.669
Dementia	227 (9%)	93 (9%)	0.921	77 (8%)	86 (9%)	0.461
Cancer	54 (2%)	20 (2%)	0.664	24 (3%)	19 (2%)	0.441
Clinical and laboratory findings						
Pulse (bpm)	90 (±23)	90 (±22)	0.646	89 (±21)	90 (±22)	0.629
Systolic blood pressure (mmHg)	148 (±32)	151 (±33)	0.009	151 (±32)	151 (±33)	0.756
Diastolic blood pressure (mmHg)	79 (±19)	81 (±19)	0.001	81 (±19)	81 (±19)	0.753
Lower-extremity oedema	1760 (69%)	804 (76%)	<0.001	725 (75%)	730 (75%)	0.794
Pulmonary oedema by chest x-ray	1794 (71%)	731 (70%)	0.474	666 (69%)	678 (70%)	0.555
Serum potassium, admission (mmol/L)[a]	4.4 (±0.3)	3.6 (±0.3)	<0.001	4.4 (±0.3)	3.6 (±0.3)	<0.001
Serum potassium, discharge (mmol/L)[a]	4.4 (±0.3)	3.6 (±0.3)	<0.001	4.3 (±0.3)	3.6 (±0.3)	<0.001
Serum creatinine (mg/dL)	1.6 (±1.1)	1.4 (±1.0)	<0.001	1.4 (±1.1)	1.4 (±1.0)	0.830
In-hospital events						
Pneumonia	639 (25%)	251 (24%)	0.405	238 (25%)	233 (24%)	0.791
Acute myocardial infarction	119 (5%)	40 (4%)	0.240	29 (3%)	37 (4%)	0.316
Pressure ulcer	234 (9%)	70 (7%)	0.012	71 (7%)	66 (7%)	0.658
Discharge medications						
ACE inhibitors or ARBs	1603 (63%)	589 (56%)	<0.001	548 (56%)	566 (58%)	0.409
Beta blockers	794 (31%)	297 (28%)	0.070	267 (28%)	274 (28%)	0.723
Loop diuretics	2079 (82%)	890 (85%)	0.053	815 (84%)	816 (84%)	0.951
Aldosterone antagonists	414 (16%)	115 (11%)	<0.001	117 (12%)	115 (12%)	0.889
Potassium supplements	1072 (42%)	638 (61%)	<0.001	563 (58%)	560 (58%)	0.890
Digoxin	1146 (45%)	400 (38%)	<0.001	358 (37%)	382 (39%)	0.262
Antiarrhythmic drugs	355 (14%)	97 (9%)	<0.001	75 (8%)	93 (10%)	0.146
Hospital length of stay (days)	7 (±5)	6 (±4)	<0.001	6 (±5)	6 (±4)	0.628
Hospital characteristics						
Rural hospital	721 (28%)	352 (34%)	0.003	299 (31%)	313 (32%)	0.494
Cardiology care	1466 (58%)	516 (49%)	<0.001	480 (49%)	487 (50%)	0.751
Intensive care	102 (4%)	37 (4%)	0.478	25 (3%)	35 (4%)	0.190

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.
[a]Because patients are categorized based on serum potassium values, they are expected to be imbalanced after matching and only displayed for descriptive purposes.

matched patients with consistent hypokalaemia, 229 (24%) had a discharge serum potassium <3.5 mmol/L, and 11 (1.1%) had a discharge serum potassium <3.0 mmol/L.

Admission and discharge hypokalaemia

30 day all-cause mortality occurred in 5% and 4% of matched patients with serum potassium levels 4.0–5.0 vs. <4.0 mmol/L at both admission and discharge, respectively (HR associated with hypokalaemia, 0.78; 95% CI, 0.52–1.18; *P* = 0.241; *Table 2*). The association of serum potassium <4.0 mmol/L with all-cause mortality remained unchanged during 1 year follow-up (*Table 2*) and 8.8 years of follow-up (*Table 2* and *Figure 2*). Findings from our restricted cubic spline analysis demonstrate that there was no evidence of a non-linear relationship between serum potassium and all-cause mortality during 8.8 years of follow-up in the matched cohort (*P* for non-linearity, 0.15), but adjusted for propensity scores, the association appeared non-linear in the prematch cohort (*P* = 0.04; *Figure 3*). Consistent hypokalaemia had no significant association with all-cause readmission, HF readmission, or combined endpoints at any of the time points (*Table 2*).

Subgroup analyses

Findings of our subgroup analyses demonstrate that the association between serum potassium <4.0 mmol/L and 8.8 year mortality in our matched cohort was homogenous across various clinically relevant subgroups of patients except for by kidney function (*P* for interaction, 0.042; *Figure S2*). Among the 1120 matched patients with estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2, all-cause mortality occurred in 68% and 69% of those with serum potassium 4.0–5.0 vs. <4.0 mmol/L, respectively (HR, 1.07; 95% CI, 0.93–1.23; *P* = 0.366). In contrast, among the 822 matched patients with eGFR ≥60 mL/min/1.73 m^2, all-cause mortality occurred in 59% and 51% of those with potassium 4.0–5.0 vs. <4.0 mmol/L, respectively (HR, 0.84; 95% CI, 0.70–1.01; *P* = 0.061; *Figure S2*).

Findings from sensitivity cohorts

Consistent with findings from our primary cohort, findings from our sensitivity cohorts demonstrate that regardless of timing of serum potassium measurement (admission or discharge) or severity of hypokalaemia (<4.0 or <3.5 mmol/L), hypokalaemia had no association with mortality or other outcomes (*Table 3*).

Discussion

Findings from our study demonstrate that in older adults hospitalized for worsening HF, low serum potassium levels during hospitalization had no significant independent association with short-term or long-term outcomes. This lack of an association between hypokalaemia and poor outcomes in older hospitalized patients with acute HF is in contrast with the association of a higher risk of death observed in ambulatory

Table 2 Outcomes in 1942 propensity score-matched patients with heart failure by serum potassium levels

	% (number) of events		Hazard ratio associated with serum potassium <4.0 mmol/L (95% confidence interval)
	Both admission and discharge serum potassium (mmol/L)		
	4.0–5.0 (*n* = 971)	<4.0 (*n* = 971)	
30 days			
All-cause mortality	5% (51)	4% (40)	0.78 (0.52–1.18); *P* = 0.241
All-cause readmission	18% (172)	20% (190)	1.12 (0.91–1.37); *P* = 0.299
Heart failure readmission	6% (57)	7% (69)	1.21 (0.85–1.72); *P* = 0.283
All-cause readmission or all-cause mortality	21% (205)	22% (214)	1.05 (0.87–1.28); *P* = 0.588
Heart failure readmission or all-cause mortality	11% (102)	10% (101)	0.99 (0.75–1.31); *P* = 0.951
1 year			
All-cause mortality	27% (264)	29% (285)	1.10 (0.93–1.30); *P* = 0.260
All-cause readmission	64% (623)	66% (643)	1.09 (0.98–1.22); *P* = 0.129
Heart failure readmission	31% (300)	31% (299)	1.03 (0.88–1.21); *P* = 0.747
All-cause readmission or all-cause mortality	73% (704)	74% (718)	1.08 (0.97–1.19); *P* = 0.169
Heart failure readmission or all-cause mortality	48% (469)	50% (489)	1.08 (0.95–1.22); *P* = 0.265
8.8 years (median, 3.3 years)			
All-cause mortality	65% (627)	61% (596)	0.96 (0.86–1.08); *P* = 0.507
All-cause readmission	87% (847)	87% (844)	1.03 (0.94–1.13); *P* = 0.540
Heart failure readmission	59% (572)	57% (554)	1.00 (0.89–1.12); *P* = 0.993
All-cause readmission or all-cause mortality	97% (938)	96% (928)	1.02 (0.93–1.12); *P* = 0.633
Heart failure readmission or all-cause mortality	87% (845)	87% (842)	1.03 (0.93–1.13); *P* = 0.574

Figure 2 Kaplan–Meier plots displaying all-cause mortality associated with admission and discharge serum potassium <4.0 mmol/L (vs. admission and discharge serum potassium 4.0–5.0 mmol/L; left panel) and discharge serum potassium <3.5 mmol/L (vs. discharge serum potassium 4.0–5.0 mmol/L; right panel), respectively, in 971 pairs and 449 pairs of propensity score-matched patients with heart failure. HR, hazard ratio; CI, confidence interval.

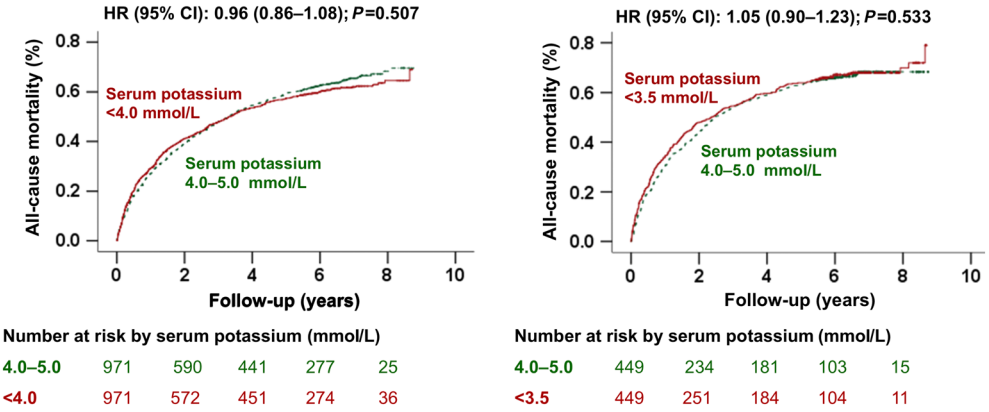
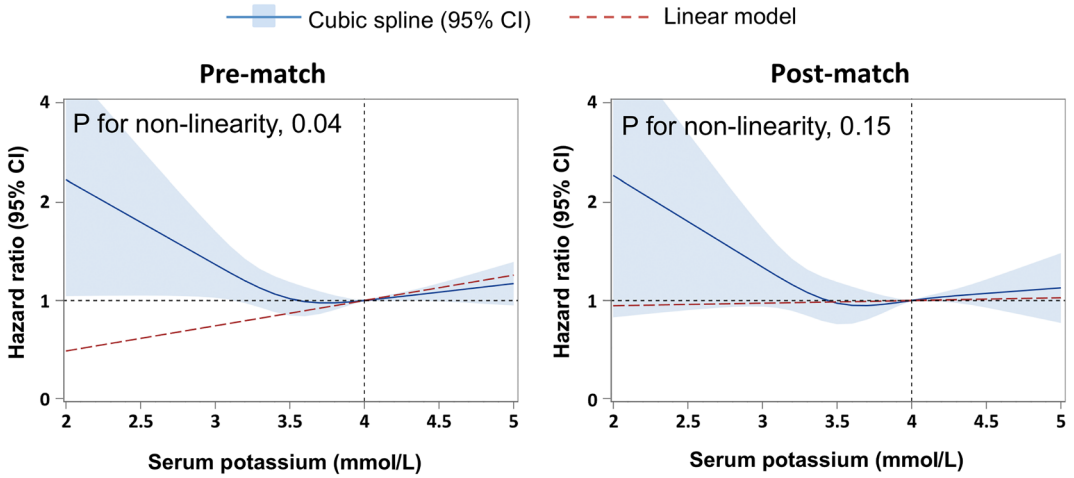


Figure 3 Cubic spline plots displaying association between discharge serum potassium and all-cause mortality during 8.8 years of follow-up, with three knots at serum potassium values 3.0, 3.5, 4.0 (reference), and 4.5 mmol/L, among 3590 prematch patients adjusted for propensity scores (left panel) and 1942 propensity score-matched patients balanced on 54 baseline characteristics (right panel). Solid blue lines represent hazard ratios and the area with the blue shade represent 95% confidence intervals (CI). Only 15 of the 3590 prematch patients and 11 of the 1942 matched patients had discharge serum potassium of <3 mmol/L.



patients with chronic HF.[2–4] These findings are important as they demonstrate that the relationship between hypokalaemia and outcomes is not homogenous in patients with HF and may vary according to patient characteristics. If these findings can be consistently replicated, that would suggest that it may not be necessary to strictly target serum potassium to values at or above 4.0 mmol/L in older patients hospitalized for decompensated HF.

One potential explanation for the lack of an independent association between hypokalaemia and outcomes in older patients hospitalized for HF in our study is that these patients have more advanced HF and thus are more likely to die from pump failure than from sudden cardiac death.[5–7] In patients with mild to moderate HF in the MERIT-HF (Metoprolol CR/XL Randomized Intervention Trial in congestive Heart Failure) trial, 58% of all deaths were sudden cardiac deaths, and 24% were pump failure deaths.[5] In contrast, in patients with more advanced and symptomatic HF in the RALES (Randomized Aldactone Evaluation Study) trial, 29% of all deaths were sudden cardiac deaths, and 47% were pump failure deaths.[5] In the EVEREST (Efficacy of Vasopressin Antagonism in Heart Failure Outcome Study with Tolvaptan) trial that included relatively younger (mean age, 66 years) hospitalized HF patients, more deaths were due to pump failure (41%) than sudden

Table 3 Outcomes by serum potassium levels in propensity score-matched patients with heart failure in three sensitivity cohorts

	Hazard ratio associated with hypokalaemia (95% confidence interval)		
Serum potassium	Discharge only	Discharge only	Admission only[a]
N for matched cohort	4654	898	5084
Hypokalaemia	Serum potassium <4.0 mmol/L	Serum potassium <3.5 mmol/L	Serum potassium <4.0 mmol/L
Normokalaemia	Serum potassium 4.0–5.0 mmol/L	Serum potassium 4.0–5.0 mmol/L	Serum potassium 4.0–5.0 mmol/L
30 days			
All-cause mortality	0.90 (0.70–1.16); *P* = 0.419	1.69 (0.94–3.04); *P* = 0.078	1.12 (0.93–1.35); *P* = 0.227
All-cause readmission	1.00 (0.88–1.14); *P* = 0.995	0.81 (0.61–1.08); *P* = 0.146	0.98 (0.86–1.11); *P* = 0.736
Heart failure readmission	1.08 (0.87–1.33); *P* = 0.502	0.80 (0.51–1.25); *P* = 0.323	0.92 (0.75–1.12); *P* = 0.396
All-cause readmission or all-cause mortality	0.99 (0.88–1.12); *P* = 0.871	0.88 (0.68–1.15); *P* = 0.340	1.01 (0.91–1.12); *P* = 0.906
Heart failure readmission or all-cause mortality	0.98 (0.83–1.16); *P* = 0.833	1.01 (0.70–1.45); *P* = 0.967	1.00 (0.87–1.15); *P* = 0.995
1 year			
All-cause mortality	1.05 (0.95–1.16); *P* = 0.390	1.17 (0.93–1.47); *P* = 0.179	1.04 (0.94–1.15); *P* = 0.423
All-cause readmission	1.00 (0.93–1.07); *P* = 0.952	0.98 (0.84–1.15); *P* = 0.834	1.02 (0.95–1.09); *P* = 0.615
Heart failure readmission	0.94 (0.85–1.04); *P* = 0.250	0.92 (0.74–1.15); *P* = 0.473	1.01 (0.91–1.12); *P* = 0.835
All-cause readmission or all-cause mortality	1.00 (0.94–1.07); *P* = 0.972	1.01 (0.87–1.17); *P* = 0.942	1.02 (0.96–1.09); *P* = 0.461
Heart failure readmission or all-cause mortality	0.99 (0.91–1.07); *P* = 0.793	1.09 (0.91–1.30); *P* = 0.348	1.03 (0.96–1.11); *P* = 0.438
8.8 years (median, 3.3 years)			
All-cause mortality	0.99 (0.93–1.07); *P* = 0.853	1.05 (0.90–1.23); *P* = 0.533	0.97 (0.91–1.04); *P* = 0.416
All-cause readmission	0.97 (0.91–1.03); *P* = 0.303	0.97 (0.84–1.11); *P* = 0.624	1.00 (0.94–1.06); *P* = 0.981
Heart failure readmission	0.92 (0.85–0.99); *P* = 0.025	0.95 (0.80–1.13); *P* = 0.541	0.99 (0.92–1.06); *P* = 0.754
All-cause readmission or all-cause mortality	0.97 (0.92–1.03); *P* = 0.331	0.98 (0.86–1.12); *P* = 0.797	1.01 (0.95–1.06); *P* = 0.862
Heart failure readmission or all-cause mortality	0.96 (0.90–1.02); *P* = 0.143	1.02 (0.89–1.18); *P* = 0.764	0.99 (0.94–1.05); *P* = 0.806

[a]Mortality in the cohort for admission hypokalaemia also includes in-hospital mortality. In-hospital mortality occurred in 4.7% and 4.3% of matched patients with admission serum potassium levels <4.0 vs. 4.0–5.0 mmol/L, respectively (odds ratio associated admission serum potassium levels <4.0 mmol/L, 1.11; 95% CI, 0.85–1.44; *P* = 0.457).

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cardiac death (26%).[7] If a higher proportion of hospitalized patients in our study had more advanced HF and died because of pump failure, then that would in part explain the lack of association of hypokalaemia with mortality. Further, nearly 60% of the patients in our study were women, in whom pump failure is a more common mode of death.[16] Finally, a higher comorbidity burden in our older hospitalized patients with HF may mean a higher proportion of noncardiovascular death, which would be less likely to be affected by a low serum potassium level.[6]

Findings from our study need to be interpreted with caution and not be used to underestimate the risk associated with very low serum potassium. Compared with discharge serum potassium 4.0–5.0 mmol/L, a discharge serum potassium <3.5 mmol/L was associated with a near-significant 69% higher risk of 30 day all-cause mortality. Findings from our spline plot analyses also suggest an incrementally higher risk of death with serum potassium under 3.5 mmol/L and specifically under 3.0 mmol/L. However, these data are extrapolated from a very small number of patients as only 0.4% (15/3590) of prematch, and 0.6% (11/1942) of matched patients in our study had a discharge serum potassium <3.0 mmol/L. These proportions would be expected to be even lower in contemporary patients with HF as a greater proportion of those patients would be receiving angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, drugs known to increase serum potassium levels. Thus, although the risk of very low serum potassium is high at an individual patient level, its attributable risk would be expected to be low at a population level.

While findings of subgroup analyses generally need to be considered exploratory,[17] the significant interaction between hypokalaemia and kidney function in older patients hospitalized for acute HF is intriguing and deserves further discussion. We have previously observed a similar significant interaction (P = 0.047) between hypokalaemia and kidney function in ambulatory younger patients with chronic HF.[2] In that study, of the 2374 propensity score-matched patients, 1062 had eGFR <60 mL/min/1.73 m^2, and among these patients, all-cause mortality occurred in 38% and 48% of those with serum potassium 4.0–5.5 vs. <4.0 mmol/L, respectively (HR, 1.40; 95% CI, 1.16–1.68; $P < 0.001$) and respective rates among the 1312 matched patients with eGFR ≥60 mL/min/1.73 m^2 were 27% and 29% (HR, 1.05; 95% CI, 0.86–1.29; P = 0.569).[2] Patients with impaired kidney function are more likely to have higher serum potassium levels; therefore, hypokalaemia in the setting of impaired kidney function may be the result of unusual electrolyte or acid–base disturbances that also increase their risk for adverse outcomes.[4]

Several studies have examined the association of hypokalaemia and outcomes in hospitalized patients with HF.[18–20] In one study, admission serum potassium levels had no independent association with outcomes in two cohorts of patients hospitalized for acute HF.[18] In another study, 77 patients had discharge serum potassium <3.5 mmol/L that was associated with a higher risk of death.[19] When adjusted for the 'entire collection of potassium values per patient', serum potassium 3.5 mmol/L had no significant association with poor outcomes, though values of 3.0 and 2.5 mmol/L had. However, it is not clear how many of the 77 had serum potassium consistently at 3.5, 3.0, and 2.5 mmol/L during follow-up.[19] In the study that reported a significant association between hypokalaemia and higher risk of inpatient mortality, hypokalaemia was defined by discharge International Classification of Diseases codes.[20] In contrast to that study, our study is based on patients who had normal or low serum potassium at both admission and discharge. In addition, our sensitivity analyses separately examined the associations of admission and discharge hypokalaemia as well as more severe discharge hypokalaemia with outcomes in separately assembled propensity score-matched cohorts.

The findings of our study are important as they suggest that the prognostic implication of hypokalaemia in older patients hospitalized for HF may differ from that in ambulatory patients with chronic HF. If these findings can be replicated in more contemporary populations of HF with longitudinal data on serum potassium, that would suggest that serum potassium levels ≥3.5 mmol/L may be safe in hospitalized patients with decompensated HF.

Our study has several limitations. These data are based on HF patients hospitalized over 20 years ago, which may limit generalizability. However, many important patient characteristics in our study such as age and ejection fraction are similar to a study based on more contemporary patients.[19] The prevalence of hypokalaemia was lower in that study (3.6% vs. 6.8% in our study), which is likely because of a higher use of neurohormonal antagonists known to raise serum potassium levels in that study. Another limitation of our study is the lack of data on serum potassium during follow-up. However, evidence suggests that most patients with HF who had hypokalaemia during hospitalization remain hypokalaemic during follow-up.[19] We also did not have data on cause of death. Finally, residual measured and unmeasured confounding may have influenced the findings.

Conclusions

In older patients hospitalized for decompensated HF, compared with a normal serum potassium level of 4.0–5.0 mmol/L, serum potassium values <4.0 or <3.5 mmol/L had no significant association with short-term or long-term mortality or readmission. Additional studies are needed to

further evaluate the relationship between serum potassium levels and outcomes among hospitalized patients with HF.

Conflict of interest

S.D.A reports consulting honoraria from Servier, Novartis, St. Jude Medical, Bayer, Boehringer Ingelheim, and Vifor Pharma. M.V., S.P., P.H.L., C.F., C.A., Y.C., R.M.A., S.V.H., and A.A. have nothing to declare.

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Supporting information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Figure S1. Love plot displaying absolute standardized differences comparing 54 baseline characteristics in patients with heart failure by serum potassium <4.0 mmol/L versus 4.0–5.0 mmol/L, before and after propensity score matching. ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers.

Figure S2. Hazard ratios and 95% confidence intervals (CI) for all-cause mortality associated with serum potassium <4.0 (versus 4.0–5.0) mmol/L in subgroups of propensity score-matched patients with heart failure. BP, blood pressure; GFR, glomerular filtration rate; EF, ejection fraction; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers.

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