scientific reports

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Association of potassium disorders with the mode of death and etiology in patients with chronic heart failure: the INCOR-HF study

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Observational studies suggest a U-shaped association between serum potassium (K^+) levels and mortality in patients with chronic heart failure (CHF). However, the mode of death in patients with HF and K^+ disorders remains speculative. To investigate the association between potassium disorders and the mode of death in patients with CHF. A retrospective cohort of 10,378 CHF outpatients was analyzed over an average of 3.28 ± 2.5 years. Kaplan-Meier method, Cox proportional hazards regression models, Poisson regression models adjusting for confounders, and e-value determination (e' > 1.6) were used to observe associations between potassium disorders and outcomes. Chagas etiology ($p < 0.01$) and triple HF therapy ($p < 0.01$) were associated with hyperkalemia. Atrial fibrillation was associated with hypokalemia ($p < 0.01$). Chronic kidney disease (CKD) ($p < 0.01$) and diabetes ($p = 0.03$) were associated with both. Hypertension was inversely related to hyperkalemia ($p < 0.01$); age was inversely related to hypokalemia. Associations with mortality were significant for Chagas ($p < 0.01$, e-value 2.16), stroke ($p < 0.01$, e-value 1.85), hypokalemia ($p = 0.02$, e-value 1.94), severe hyperkalemia ($p = 0.08$, e-value 1.93), and CKD ($p < 0.01$, e-value > 1.63). Decompensated HF or cardiogenic shock was the cause of death in 54% of patients with normokalemia, 67.8% with hypokalemia, 44.9% with mild hyperkalemia, 57.8% with moderate hyperkalemia, and 69% with severe hyperkalemia. Most patients with hypokalemia and severe hyperkalemia died from decompensated HF ($p = 0.007$). Data suggest hypokalemia and severe hyperkalemia, along with Chagas and CKD, are associated with death. Unexpectedly, progressive HF was the most frequent mode of death rather than arrhythmias. Further studies are needed to confirm these findings and explore the underlying mechanisms.

Keywords Heart failure, Chagas disease, Hypokalemia, Hyperkalemia, Mortality, Triple therapy

Chronic heart failure (CHF) is a prevalent clinical condition affecting millions globally, characterized by high morbidity and mortality rates. It imposes significant financial burdens on healthcare systems[1]. Potassium disorders, observed in 3 to 18% of patients in randomized clinical trials and up to 25% in observational studies, are linked to adverse outcomes in CHF, with varying impacts depending on the heart failure (HF) phenotype.

Studies have shown that serum potassium levels are independently associated with cardiovascular death, hospitalization due to HF, and heart transplantation in symptomatic CHF patients[2]. In HF with reduced ejection fraction (HFrEF), potassium disorders correlate with HF hospitalizations, with hypokalemia particularly associated with both cardiovascular and non-cardiovascular mortality, especially in patients with chronic kidney disease (CKD). Conversely, in HF with preserved ejection fraction (HFpEF), both hypokalemia and hyperkalemia are linked to increased risks of cardiovascular death, sudden death, and HF death[3]. Hyperkalemia is also a barrier to the prescription of guideline-directed medical therapy (GDMT), leading to increased cardiovascular events.

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Despite these findings, questions remain about whether potassium disorders specifically increase the risk of arrhythmias or sudden death in CHF patients[4–6]. This study aims to investigate the association between potassium disorders and the mode of death in CHF patients, exploring whether hyperkalemia and hypokalemia contribute differently to this association and examining how hydroelectrolytic disorders influence etiologies prone to sudden death or arrhythmias.

Methods

Study design and patient population

A retrospective cohort study of patients with CHF receiving outpatient care at a tertiary cardiology center between January 2013 and December 2020 was conducted. Data were collected from the electronic medical records system, encompassing patient demographics, laboratory variables (including serum potassium and other electrolytes), imaging tests, comorbidities, medication use, hospitalizations, and emergency room visits. Comorbidities were identified using ICD-10 and procedure codes, with all information verified for accuracy. Clinical data such as functional class (NYHA), weight, blood pressure, heart rate, and CHF etiology were confirmed individually in the medical records. The estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula within six months before 2013 to capture baseline laboratory information.

Inclusion and exclusion criteria

Patients were included if they had at least one serum potassium measurement within six months of the study's start. If this test was conducted before 2013, that date was considered the index consultation. Patients lacking baseline variables in medical records or those participating in other institutional protocols were excluded.

Laboratory tests

Chronic kidney disease (CKD) was classified into five stages according to the eGFR determined by KDIGO guidelines[7], without considering albuminuria due to its low testing frequency in this population. Hyperkalemia was categorized as mild ($5.0 < K^+ < 5.5$ mEq/L), moderate ($5.5 < K^+ < 6.0$ mEq/L), and severe ($K^+ > 6.0$ mEq/L). Hypokalemia was classified as mild ($3.0 < K^+ < 3.5$ mEq/L) and severe ($K^+ < 3.0$ mEq/L).

Outcomes

The primary outcome was mortality from any cause, obtained from the Death Information System (SIM) of the Health Department, adhering to confidentiality and data protection laws, This study was conducted with the approval of the Institutional Ethics Committee of the Heart Institute (InCor) at the Hospital das Clínicas, Faculty of Medicine, University of São Paulo. Mortality records from death certificates were used, with diseases or injuries contributing to death listed hierarchically. The underlying cause of death was identified, and comorbidities contributing to death were reported. Deaths were classified by location (hospital or out-of-hospital) and analyzed according to underlying potassium levels and the last potassium measurement before death. Causes of death were categorized using ICD-10 codes, focusing on cardiogenic shock, decompensated HF, and arrhythmias. All research was conducted in accordance with relevant guidelines and regulations and received ethical approval.

Control measures

Given the retrospective nature of this study, we implemented rigorous statistical controls to mitigate potential biases and confounding factors: To assess the robustness of our findings against unmeasured confounding, we performed an E-value calculation. The E-value quantifies the minimum strength of association that an unmeasured confounder would need to have with both the exposure and the outcome to explain away the observed association fully[8]. We adjusted for known confounders such as age, sex, comorbidities, medication use, and clinical variables.

Statistical analysis

Patient characteristics were summarized using descriptive statistics. Categorical variables were presented as frequencies and percentages, while continuous variables were summarized using means and standard deviations or medians and interquartile ranges, as appropriate. Univariate analyses were conducted to examine the association between baseline variables and the outcomes of interest. Variables considered in the univariate analysis included age, etiology, NYHA functional class, previous stroke, hypertension, diabetes, atrial fibrillation, use of triple therapy, CKD stages, and serum potassium levels. The associations were evaluated using chi-square tests for categorical variables and t-tests or Mann-Whitney U tests for continuous variables. To control for potential confounding factors, multivariate regression models were employed. Cox proportional hazards regression was used to assess the association between serum potassium levels and mortality. Time-to-event data were analyzed using Kaplan-Meier survival curves, and differences between groups were evaluated using the log-rank test. Variables with a p-value < 0.10 in univariate analysis were included in the multivariate Cox regression models. Logistic regression was employed to evaluate the association between potassium disorders (hyperkalemia and hypokalemia) and various covariates. The results were presented as odds ratios (ORs) with 95% confidence intervals (CIs). Given the longitudinal nature of the data, time-dependent Cox regression models were applied to account for changes in exposure status over time. This approach allowed for the assessment of how variations in serum potassium levels over time influenced mortality risk. Missing data were addressed using multiple imputation techniques. Multiple imputed datasets were created, each replacing missing values with plausible values based on observed data. The results from these datasets were combined to produce final estimates that account for the uncertainty associated with the missing data. Mortality rates were calculated using Poisson regression models, presented as deaths per person-year. This approach accommodated varying

follow-up times among patients, providing a standardized mortality rate for comparison. To assess the potential impact of unmeasured confounders, an E-value calculation was performed. The E-value quantifies the minimum strength of association that an unmeasured confounder would need to have with both the exposure (serum potassium levels) and the outcome (mortality) to explain away the observed association[9]. All statistical analyses were conducted using R version 4.2.0[10]. A two-tailed significance level of 5% was applied for all tests, with p-values < 0.05 considered statistically significant.

Handling missing data

Patients without potassium measurements, missing demographic variables, participation in other protocols, or duplicate registrations were excluded. Laboratory variables with less than 20% missing data were adjusted as covariables. Multiple imputations handled missing data by creating multiple imputed datasets, substituting missing values with plausible values based on observed data. These datasets were analyzed separately and combined to account for the uncertainty caused by missing data.

Results

Baseline characteristics

The study sample consisted of patients who were followed in a heart failure clinic, with data collected from their clinical records. Data from 10,423 CHF patients were analyzed, with a mean follow-up of 3.28 ± 2.5 years. Baseline laboratory tests were available for 92% of the patients, with an average serum potassium level of 4.5 ± 0.5 mEq/L. Hypokalemia was present in 1.6% of patients, while 13% had hyperkalemia. Most patients had HF with reduced ejection fraction (HFrEF) and were symptomatic at their first visit. Common comorbidities included coronary artery disease (CAD), dyslipidemia, hypertension, atrial fibrillation (AF), diabetes mellitus (DM), smoking, alcoholism, and acute myocardial infarction (AMI). Chagas disease accounted for 5.3% of cases. As shown in Tables 1 and 80% of the patients had a left ventricular ejection fraction (LVEF) below 50%, indicating a significant proportion of patients with reduced ejection fraction. (Table 1).

For hypokalemia recurrence, the Poisson model indicated associations with valvular etiology (aRR 1.59, 95% CI: 1.07-2.37, $p < 0.01$), AF (aRR 1.71, 95% CI: 1.39-2.10), and moderate to severe CKD (aRR 2.61-6.08, 95% CI: 1.77-6.94, $p < 0.01$). Age was weakly protective against hypokalemia recurrence (Tables 2 and 3).

Chagas etiology was associated with higher mortality risk ($p < 0.01$), hyperkalemia, and recurrence. E-value analysis yielded a value of 2.16, indicating a significant risk associated with this etiology, likely not due to unmeasured factors. Valvular and idiopathic etiologies were weakly associated with hypokalemia. In valvular cardiomyopathy patients, the risk of hypokalemia recurrence was higher ($p < 0.01$).

Outcomes

Out of 10,378 patients, 2,311 died, resulting in a mortality rate of 22.2%. The mortality incidence rate was 7.44 per 100 patient-years (95% CI: 7.16-7.74). Hospitalization incidence was 10.71 per 100 patient-years (95% CI: 10.32-11.11). First hospitalization incidence was 5.08 per 100 patient-years (95% CI: 4.83-5.34). First-time emergency room access incidence was 9.53 per 100 patient-years (95% CI: 9.17-9.9).

Independent mortality risk factors in the Cox-adjusted model included Chagas etiology, age, stroke, hypokalemia, and all levels of hyperkalemia. Adjusting for CKD, hypokalemia and severe hyperkalemia remained significant risk factors, while hypertension was weakly protective (Table 4). The Kaplan-Meier curve (Fig. 1) demonstrated cumulative mortality adjusted for baseline potassium levels and potassium ranges. The multivariate model showed the effect of potassium disorders on mortality: hypokalemia (aHR 1.96, 95% CI: 1.52-2.54, $p < 0.01$), mild hyperkalemia (aHR 1.19, 95% CI: 1.05-1.36, $p = 0.01$), moderate hyperkalemia (aHR 1.33, 95% CI: 1.04-1.70, $p = 0.02$), and severe hyperkalemia (aHR 1.49, 95% CI: 1.0-2.21, $p = 0.05$).

A cubic polynomial model adjusted for age and year of inclusion estimated a reversed J-shaped curve for baseline potassium levels, with the highest death risk at potassium levels ≤ 3 mEq/L and ≥ 6 mEq/L and the lowest risk between 4.3 and 4.6 mEq/L. Sensitivity analysis, including the e-value, is provided in Table 4.

Decompensated HF and cardiogenic shock, followed by ischemic heart disease, were the most frequent causes of death (Table 2). Electrolyte disorders contributed to 1% of deaths, with arrhythmias accounting for 6.2%. Other significant causes included septicemia/infections, stroke, pulmonary embolism, and respiratory failure. Analyzing baseline potassium levels as a predictor of death mode revealed no significant difference between potassium levels and the place of death ($p = 0.475$). However, patients with severe hypokalemia and primary hyperkalemia tended to die from HF-related causes ($p = 0.08$). To enhance the accuracy of a potential association between potassium levels and outcomes, we opted to use the most recent potassium level measured before the event. This approach ensures that the potassium measurements are temporally closer to the outcome, thereby providing a more reliable assessment of the relationship between potassium levels and the event. The last potassium measurement before death indicated that hypokalemia and hyperkalemia were associated with higher risks of death due to HF, cardiogenic shock, or arrhythmia ($p = 0.03$), with these patients often dying from decompensated HF ($p = 0.007$) (Table 5).

Potassium disorders

The incidence rate of hyperkalemia was 22.72 per 100 patient-years (95% CI: 22.01-23.48), while hypokalemia occurred at a rate of 3.56 per 100 patient-years (95% CI: 3.32-3.81). Mild hyperkalemia had an incidence rate of 19.31 (95% CI: 18.66-19.98), moderate hyperkalemia 5.07 (95% CI: 4.78-5.37), and severe hyperkalemia 1.77 (95% CI: 1.6-1.94).

Variables associated with the incidence of hyperkalemia included the Chagas disease, age, DM, use of triple therapy, and all stages of CKD (adjusted hazard ratio [aHR] range from 1.49 to 5.53, $p < 0.01$). Hypertension was inversely related to hyperkalemia (aHR 0.84, 95% CI: 0.76-0.93, $p < 0.01$). Chagas etiology, age, DM, and

Baseline variables	Total (*n*=10,378)	Normokalemia (*n*=7866)	Hyperkalemia (*n*=1193)	Hypokalemia (*n*=147)	*P*
Age; mean ± SD	54 ± 13.8 (*n*=10378)	53.6 ± 13.5 (*n*=7866)	58.5 ± 12 (*n*=1193)	55.9 ± 13.4 (*n*=147)	<0.001
Sex					<0.001
Female	35.2%	36.1%	27.2%	49%	
Male	64%	63.3%	72.3%	50.3%	
Other	0.8%	0.6%	0.5%	0.7%	
etiology					0.370
Ischemic	39.6%	39.5%	42.7%	35.4%	
Chagas	5.3%	5.5%	5.8%	5.6%	
Idiopathic	14.5%	14.6%	13.4%	13.9%	
Valvar heart disease	5.2%	5.3%	4%	6.9%	
Hypertensive	24%	24%	24.3%	25.7%	
Other	11.3%	11.1%	9.7%	12.5%	
Comorbidities					
Atrial fibrillation	29.9%	30.5%	30%	39.5%	0.059
AMI	10.6%	10.4%	12%	6.1%	0.051
CAD	39.2%	39%	42.7%	34.7%	0.024
NYHA					0.140
I	38.1%	37.9%	38.1%	46.9%	
II	39.4%	39.4%	39.2%	27.2%	
III	19.8%	19.8%	19.6%	23.1%	
IV	2.8%	2.8%	3.1%	2.7%	
Deep venous thrombosis	0.9%	0.8%	1.1%	2.7%	0.039
Anemia	4.4%	4.4%	4.2%	6.1%	0.559
Diabetes	29.4%	29.5%	34.3%	25.9%	0.002
Thyroid					0.288
Hyperthyroidism	0.1%	0.2%	0%	0%	
Hypothyroidism	2.8%	2.9%	2.1%	2.7%	
Dyslipidemia	38.1%	40.1%	42.3%	34.7%	0.094
Hypertension	36.2%	36.3%	37.2%	39.5%	0.615
Stroke					0.294
Ischemic	2.4%	2.4%	2.5%	1.4%	
Hemorrhagic	0.6%	0.7%	0.5%	0.7%	
COPD	8.3%	7.9%	8.8%	11.5%	0.031
Smoking	12.5%	12.8%	12.9%	16.3%	0.443
Alcoholism	10.7%	11.1%	11.4%	14.3%	0.450
HIV	0.1%	0.1%	0%	0%	0.551
Valvar disease	2.4%	2.4%	2%	3.4%	0.524
Connective tissue disease	0.3%	0.3%	0.1%	0%	0.374
BMI, kg/m^2	26.9 ± 4.9 (*n*=8719)	27 ± 4.9 (*n*=6756)	26.4 ± 4.4 (*n*=1025)	27.3 ± 5.1 (*n*=127)	<0.001
DBP, mmHg	75.6 ± 12.9 (*n*=8388)	75.8 ± 12.9 (*n*=6541)	74.5 ± 12.9 (*n*=977)	76.7 ± 15 (*n*=121)	0.212
SBP, mmHg	119.6 ± 21.1 (*n*=8388)	119.8 ± 21 (*n*=6541)	118.5 ± 21.6 (*n*=977)	120.5 ± 27.3 (*n*=121)	0.012
HR, bpm	72.8 ± 14.3 (*n*=8922)	72.9 ± 14.6 (*n*=6980)	71.6 ± 12.8 (*n*=1034)	76.3 ± 13.5 (*n*=128)	0.001
Ejection Fraction (n)	(*n*=3282)	(*n*=2800)	(*n*=64)	(*n*=418)	
LVEF < 40%	63.8%	63.3%	66.7%	67.2%	0.128
LVEF 40 - 50%	16.0%	15.9%	17.7%	12.5%	
LVEF > 50%	20.2%	20.9%	15.6%	20.3%	
Spironolactone	69.9%	74.4%	66.5%	74.8%	<0.001
Beta-blocker	84.4%	87.4%	91.5%	85.7%	<0.001
RAASi	66.8%	70.1%	69.6%	56.5%	0.002
ARB	26.8%	28.4%	24%	25.9%	0.006
ARNI	1.0%	1.0%	1.1%	0.9%	0.243
Thiazides	36.8%	38.8%	34.5%	65.3%	<0.001
Statin	57.7%	59.7%	66.3%	50.3%	<0.001
Anticoagulants	26.5%	27.9%	26.9%	31.3%	0.490
Continued					

Baseline variables	Total (*n*=10,378)	Normokalemia (*n*=7866)	Hyperkalemia (*n*=1193)	Hypokalemia (*n*=147)	*P*
Ivabradine	2.5%	2.8%	2.3%	1.4%	0.374
Hydralazine	35%	35.6%	44.6%	48.3%	<0.001
Nitrate	32.3%	32.8%	42.3%	42.2%	<0.001
Aspirin	41.7%	42%	51.2%	34%	<0.001
Furosemide	73.5%	76.2%	80.9%	83%	<0.001
Gliclazide	13.1%	13.8%	15.8%	8.8%	0.040
Ferrous sulphate	4%	4%	5.8%	5.4%	0.015
NSAID	0.1%	0.1%	0.1%	0%	0.936
Triple therapy (RAASi + Beta-blocker + Spironolactone)	53%	56.8%	50.5%	48.3%	<0.001
Alternative Therapy (Hydralazine/Nitrate + Beta-blocker + Spironolactone)	9%	9.3%	9.9%	17.5%	0.004
Mean GFR ± SD	64.5 ± 26.3 (*n*=6671)	66.7 ± 25.7 (*n*=5633)	52.3 ± 25.2 (*n*=829)	53.1 ± 26.6 (*n*=108)	<0.001
Normal	16.8%	18.3%	8%	10.2%	<0.001
Mild reduced	39.8%	41.9%	28.8%	26.9%	
Moderate reduced	32.9%	31.2%	42.8%	40.7%	
Severe reduced	7.5%	6.5%	12.9%	15.7%	
Terminal or dialysis	2.9%	2%	6.5%	7.5%	
Mean potassium ± SD	4.5 ± 0.5 (*n*=9206)	4.4 ± 0.4 (*n*=7866)	5.4 ± 0.4	3.2 ± 0.2	<0.001
BNP (*n*=1758)	461±820	472±800	584±1035	581±962	
Haemoglobin	13.6±1.9	13.7±1.8	13.3±2.1	13.1±1.9	
% Lymphocytes	27.6±9.3	28±9.3	25.9±8.8	25.5±9.2	
Troponin-HS (pg/mL)	2303±438	2302±441	2305±433	2324±383	

Table 1. Clinical characteristics in the index consultation. Categorical variables were compared using the chi-square method and the continuous ones using ANOVA ARNI, neprilysin receptor antagonists; ARB, angiotensin II receptor blocker; NSAID, non-steroidal anti-inflammatory drugs; SD, standard deviation; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; CKD, kidney disease; LVEF, left ventricular ejection fraction; HR, heart rate; Hb, haemoglobin; HIV, human immunodeficiency virus; ACEI, angiotensin conversion enzyme inhibitor; BMI, body mass index; AMI, acute myocardial infarction; NYHA, New York Heart Association functional class; BNP, brain natriuretic peptide; DBP, diastolic blood pressure; SBP, systolic blood pressure; GFR, glomerular filtration rate; DVT, deep vein thrombosis; Troponin-US, highly-sensitive troponin

Variable	Hyperkalemia (*n*=5446) HR (95% CI)	*P*	Hypokalemia (*n*=5446) HR (95% CI)	*P*
Chagas etiology	1.54 (1.26 - 1.89)	<0.01	1.14 (0.77 - 1.68)	0.51
Idiopathic etiology	0.87 (0.75 - 1.01)	0.07	0.81 (0.60 - 1.10)	0.18
Age	1.02 (1.01 - 1.02)	<0.01	0.98 (0.97 - 0.99)	<0.01
Hypertension	0.84 (0.76 - 0.93)	<0.01	1.02 (0.84 - 1.25)	0.81
Diabetes	1.13 (1.02 - 1.25)	0.01	1.23 (1.02 - 1.50)	0.03
Atrial fibrillation	1.03 (0.94 - 1.14)	0.52	1.67 (1.39 - 2.01)	<0.01
Triple therapy[a]	1.34 (1.21 - 1.48)	<0.01	0.86 (0.71 - 1.04)	0.12
Mild reduced CKD	1.49 (1.26 - 1.77)	<0.01	1.76 (1.24 - 2.49)	<0.01
Moderate reduced CKD	2.52 (2.12 - 3.00)	<0.01	3.08 (2.16 - 4.40)	<0.01
Severe reduced CKD	4.07 (3.26 - 5.07)	<0.01	7.76 (5.19 - 11.61)	<0.01
Terminal or dialysis CKD	5.53 (4.08 - 7.51)	<0.01	5.03 (2.81 - 8.99)	<0.01

Table 2. Multivariate Cox model for incidence of potassium disorders. All etiologies were considered, but only those with a significant association were found. CKD, chronic kidney disease; HR, hazard ratio; 95% confidence interval (95% CI). [a]Triple therapy use of RASSi + beta-blocker + spironolactone.

Variable	Hyperkalemia Relative Risk (95% CI)	*P*	Hypokalemia Relative Risk (95% CI)	*P*
Chagas etiology	1.35 (1.11 - 1.64)	<0.001	1.3 (0.87 - 1.92)	0.046
Idiopathic etiology	0.84 (0.72 - 0.99)	0.001	0.75 (0.53 - 1.06)	0.011
Valvar heart disease	0.91 (0.72 - 1.16)	0.235	1.59 (1.07 - 2.37)	<0.001
Hypertensive aetiology	0.92 (0.81 - 1.04)	0.041	0.94 (0.71 - 1.23)	0.455
Age (years)	1.01 (1.01 - 1.01)	<0.001	0.98 (0.97 - 0.99)	<0.001
Stroke	1.15 (0.91 - 1.45)	0.062	1.17 (0.74 - 1.84)	0.294
AMI	1.07 (0.92 - 1.25)	0.154	0.82 (0.57 - 1.18)	0.092
Hypertension	0.85 (0.77 - 0.95)	<0.001	1.09 (0.88 - 1.36)	0.196
Diabetes	1.07 (0.97 - 1.19)	0.029	1.14 (0.92 - 1.42)	0.058
Atrial fibrillation	1.06 (0.96 - 1.18)	0.058	1.71 (1.39 - 2.1)	<0.001
Triple therapy	1.21 (1.09 - 1.34)	<0.001	0.91 (0.74 - 1.12)	0.149
Mild reduced CKD	1.64 (1.35 – 2)	<0.001	1.4 (0.96 - 2.05)	0.007
Moderate reduced CKD	2.7 (2.21 - 3.29)	<0.001	2.61 (1.77 - 3.83)	<0.001
Severe reduced CKD	3.94 (3.12 - 4.98)	<0.001	6.08 (3.95 - 9.35)	<0.001
Terminal or dialysis CKD	4.63 (3.47 - 6.18)	<0.001	3.91 (2.2 - 6.94)	<0.001

Table 3. Poisson model for recurrence of potassium disorders. CKD, chronic kidney disease; AMI, acute myocardial infarction; 95% CI, 95% confidence interval.

Models for mortality (*n*=8901)	Multivariate HR (95% CI)	*P*	E-value
Chagas etiology	1.64 (1.35 - 1.99)	<0.01	2.16
Valvar heart disease	1.25 (1.00 - 1.58)	0.05	1.62
Age, years	1.01 (1.01 - 1.02)	<0.01	1.11
Stroke	1.41 (1.12 - 1.77)	<0.01	1.85
Hypertension	0.88 (0.79 - 0.98)	0.02	1.42
Diabetes	-	-	-
Atrial fibrillation	1.11 (1.00 - 1.23)	0.05	1.36
Use of triple therapy	0.89 (0.80 - 0.99)	0.03	1.39
Hypokalemia	1.47 (1.06 - 2.02)	0.02	1.94
Mild hyperkalaemia	1.05 (0.90 - 1.24)	0.52	1.24
Moderate hyperkalaemia	0.96 (0.70 - 1.31)	0.78	1.21
Severe hyperkalemia	1.47 (0.96 - 2.25)	0.08	1.93
Mild reduced CKD	1.26 (1.04 - 1.53)	0.02	1.63
Moderate reduced CKD	2.01 (1.65 - 2.45)	<0.01	2.61
Severe reduced CKD	3.77 (3.00 - 4.73)	<0.01	4.36
Terminal or dialysis CKD	4.32 (3.26 – 5.72)	<0.01	4.82

Table 4. Multivariable Cox model for mortality and sensitivity analysis. All variables were considered for analysis, but only those with a significant association are presented. CKD, chronic kidney disease; HR, hazard ratio; AMI, acute myocardial infarction; 95% CI%, 95% confidence interval.

use of triple therapy were positively associated with hyperkalemia (aHR 1.54, 1.02, 1.13, and 1.34 respectively, $p < 0.01$ for all) (Table 2).

In the Poisson model for hyperkalemia recurrence, associated variables were Chagas etiology (adjusted relative risk [aRR] 1.35, 95% CI: 1.11-1.64, $p < 0.01$), age (aRR 1.35, 95% CI: 1.11-1.64, $p < 0.01$), DM (aRR 1.35, 95% CI: 1.11-1.64, $p < 0.01$), use of triple therapy, and all stages of CKD (aRR 1.64-4.63, 95% CI: 1.35-6.18, $p < 0.01$) (Table 3).

Factors associated with hypokalemia incidence were DM (aHR 1.23, 95% CI: 1.02-1.50, $p = 0.03$), AF (aHR 1.67, 95% CI: 1.39-2.01, $p < 0.01$), and all stages of CKD (aHR 1.76-7.76, 95% CI: 1.24-11.61, $p < 0.01$). Age was a weak protective factor against hypokalemia incidence (Table 2).

Discussion

This study is the first to describe the association of hypokalemia and severe hyperkalemia with modes of death from heart failure or cardiogenic shock in patients with chronic heart failure. Our findings revealed an E-value greater than 1.6 for mortality associations with Chagas etiology, valvular etiology, stroke, hypokalemia,

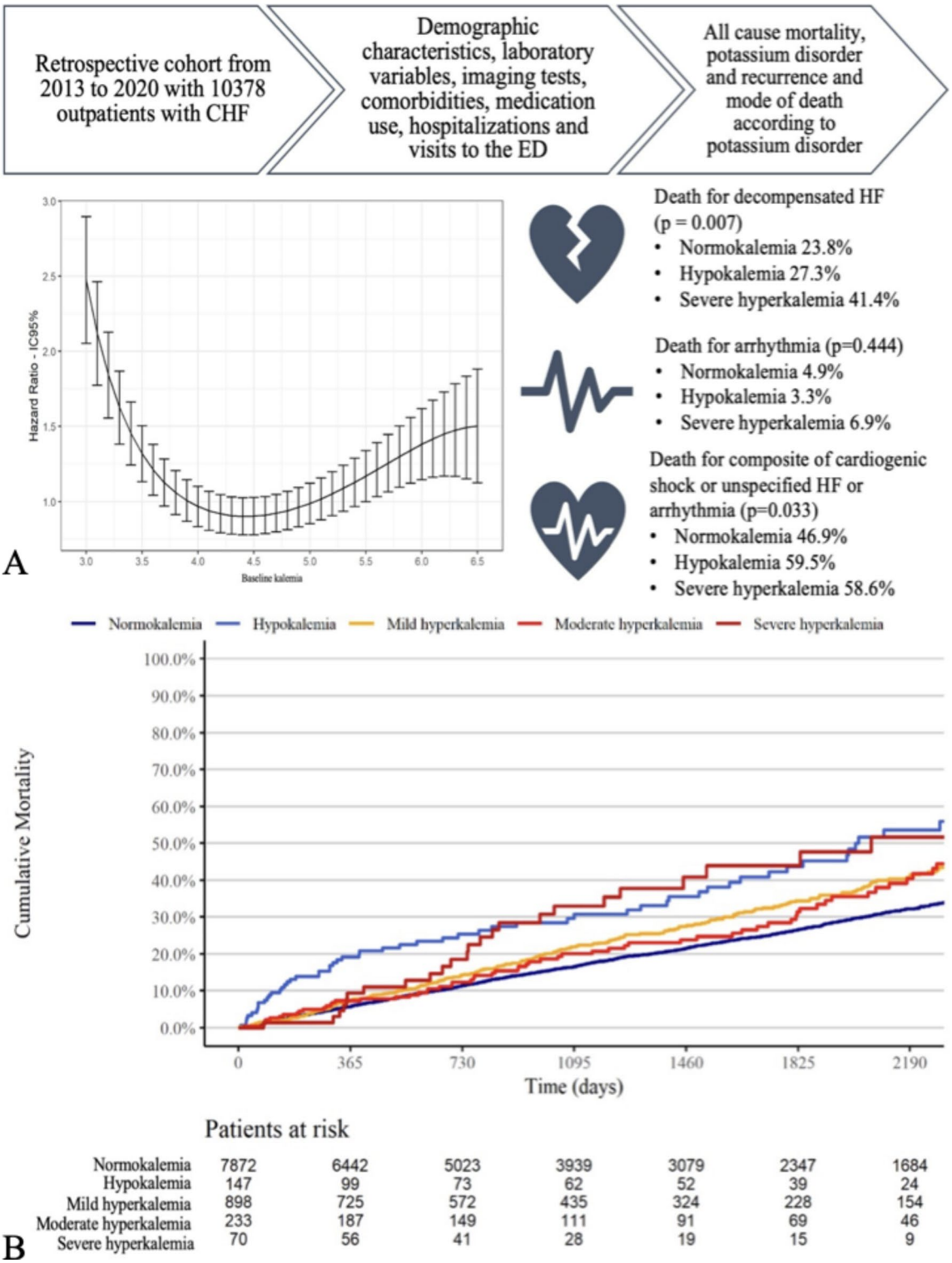

Fig. 1. Structured graphical abstract. **A** Risk curve for mortality according to baseline potassium. **B** Kaplan-Meier of cumulative mortality according to baseline kalaemia.

severe hyperkalemia, and chronic kidney disease (CKD). We observed the influence of specific etiologies on the development and recurrence of potassium disorders: Chagas etiology was linked to a higher incidence and recurrence of hyperkalemia. In contrast, valvar etiologies were more commonly associated with hypokalemia and its recurrence. Additionally, triple therapy, age, diabetes mellitus (DM), Chagas etiology, idiopathic etiology, and CKD were significantly associated with hyperkalemia, whereas hypertension was a protective factor. Conversely, DM, atrial fibrillation (AF), and CKD were associated with hypokalemia, while age served as a protective factor.

Mode of death	Normokalemia (*n*=7866)	Hypokalemia (*n*=147)	Mild hyperkalemia (*n*=898)	Moderate hyperkalemia (*n*=225)	Severe hyperkalemia (*n*=70)	Total (*n*=9206)	*P*
Cardiogenic shock or unspecified HF or arrhythmia	876/1868 (46.9%)	72/121 (59.5%)	105/243 (43.2%)	31/64 (48.4%)	17/29 (58.6%)	1101/2325 (47.4%)	0.033
Cardiogenic shock	564/1868 (30.2%)	49/121 (40.5%)	68/243 (28%)	17/64 (26.6%)	8/29 (27.6%)	706/2325 (30.4%)	0.131
Decompensated HF	444/1868 (23.8%)	33/121 (27.3%)	41/243 (16.9%)	20/64 (31.2%)	12/29 (41.4%)	550/2325 (23.7%)	0.007
Arrhythmias	91/1868 (4.9%)	4/121 (3.3%)	11/243 (4.5%)	6/64 (9.4%)	2/29 (6.9%)	114/2325 (4.9%)	0.444
Hospital death and other health establishment	1477/1687 (87.5%)	48/50 (96%)	209/238 (87.8%)	57/61 (93.4%)	22/23 (95.6%)	2033/2311 (88%)	0.475
Death at home or outside of hospital	189/1687 (11.3%)	2/50 (4%)	29/238 (12.2%)	4/61 (6.6%)	1/23 (4.4%)	250/2311 (10.8%)	

Table 5. Mode of death divided by the last kalaemia before death and local of death.

Previous studies have identified risk factors for hyperkalemia and cardiovascular mortality, including CKD, diabetes, and medication use[11,12]High-dose loop diuretics, CKD, and neurohormonal activation have been associated with hypokalemia and death. Our study found a higher incidence of mild to severe hyperkalemia (22%) and hypokalemia (3.5%) compared to previous reports[13,14], likely due to a higher percentage of patients in NYHA III/IV functional class, renal dysfunction, diuretic use, and RAASi use. Furthermore, we identified Chagas and valvular etiologies as novel risk factors for potassium disorders in this population.

Contrary to the traditional view that arrhythmias predominantly cause death in patients with potassium disorders, our findings indicate that HF or cardiogenic shock was the most frequent mode of death in patients with hypokalemia and severe hyperkalemia. Both hyperkalemia and hypokalemia were associated with a higher risk of hospitalization for HF and death from HF compared to normokalemia.

The mechanisms underlying the association between potassium disorders and death from HF and cardiogenic shock remain speculative. Potassium disorders may serve as markers of greater disease severity in CHF[15]. Hypokalemia might indicate disease progression, associated with more frequent diuretic use and insufficient neurohormonal inhibition, leading to increased activation of angiotensin II, aldosterone, and norepinephrine[16]. Severe hemodynamic disturbances may cause a catecholamine-induced drop in serum potassium[15]. Hyperkalemia, resulting from decreased potassium elimination, could be a marker of cardiorenal syndrome and other comorbidities like Chagas disease and older age, which were identified as risk factors for mortality[17–19]. Alternatively, potassium disorders could contribute to increased mortality through their effects on myocardial function, the cardiovascular system, neurohormonal activation, coagulation, and endothelial function[20–23]. Potassium can stimulate aldosterone production independently of the renin-angiotensin-aldosterone system and reduce angiotensin II-induced vasoconstriction, especially when there is low nitric oxide availability[24]. Animal and human studies suggest that low serum potassium may increase thrombosis rates, endothelial dysfunction, and platelet aggregation[25]. Additionally, serum potassium levels may influence cardiac systolic function by affecting the Na+/K+ ATPase pump, essential for maintaining cellular ion balance and myocardial contractility[26].

In agreement with these mechanisms, triple therapy medications that increase serum potassium levels and improve survival in HFrEF were also associated with hyperkalemia in our study. The suspension or dose reduction of triple therapy might explain increased mortality, although sub-analyses of the PARAGON-HF and PARADIGM-HF studies suggest that hyperkalemia-related mortality occurred despite constant sacubitril-valsartan doses[5,6].

The association between Chagas etiology and potassium disorders is significant given its prevalence in endemic regions and higher mortality compared to other CHF etiologies. Potassium disorders have not been previously identified as contributors to high mortality in Chagas disease, necessitating further research to elucidate the pathophysiological mechanisms involved[27,28].

Limitations

This retrospective observational study has limitations such as selection bias, confounding, and misclassification. However, it addresses important clinical practice issues not evaluable in clinical trials. We included various patient characteristics to reduce confounding bias and performed sensitivity analyses and e-value calculations to mitigate limitations. The database reflects real-world practice standards, limiting misclassification by reducing human interference in data capture and implementing quality control measures[29].

While the e-value has limitations, it was used to assess causality in observational studies. Retrospective data may be incomplete and non-standardized, but our missing data rate was below 20%, with all patients having at least one potassium measurement. Clinical decisions determine the variables obtained, reflecting real-world practice but potentially limiting the accuracy of certain questions. The use of death certificates to determine the mode and cause of death may introduce inaccuracies, but they provide the most accurate information closest to the time of death. The sample size was large, adjustments were made for measured confounders, and sensitivity analyses were performed for unmeasured confounders, enhancing internal validity and generalizability of results.

Conclusion

Our study underscores the importance of monitoring potassium levels in CHF patients, as both severe hypokalemia and hyperkalemia were associated with increased mortality risk. The most common causes of death related to potassium disorders were the progression of HF and cardiogenic shock. Potassium disorders may serve as therapeutic targets for managing CHF, especially in patients with Chagas, valvar disease, elderly, diabetic, chronic kidney disease, and those on triple therapy. Close monitoring and management of potassium disorders could help identify patients with a high risk of death from decompensated HF or cardiogenic shock. Further research is needed to confirm these findings and explore the underlying mechanisms.

Data availability

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

Received: 29 May 2024; Accepted: 30 September 2024
Published online: 04 December 2024

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Acknowledgements

The authors would like to express their sincere gratitude to all the participants who generously contributed

their time and effort to this study. We would also like to acknowledge the support and resources provided by AstraZeneca. We extend our appreciation to the Instituto do Coração staff and the InCor -HF research team for their invaluable assistance in data collection and analysis. Special thanks go to Professor Edimar Bocchi for their valuable insights and expertise. Lastly, we thank our families and loved ones for their unwavering support throughout this research endeavor.

Author contributions

I.G.C.V.L. and J.T.N. conceptualized, designed the study, wrote the initial manuscript, and collected the data. I.H.O collected the data. L.P.D performed the statistical analysis, S.M.A.F., and R.T.M. P.R.C., B.B., B.R.G., F.R., A.S., F.R, and E.A.B. critically reviewed the final manuscript and provided significant intellectual input. All authors reviewed and approved the final manuscript.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-74928-x.

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