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ORIGINAL ARTICLE

Assessing potassium levels in critically ill patients with heart failure: application of a group-based trajectory model

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Abstract

Aims Abnormalities in potassium homeostasis are frequently seen in hospitalized patients. A poor outcome in heart failure (HF) has been linked to both hypokalaemia and hyperkalaemia. The studies on the connection between variations in potassium levels and all-cause mortality remain scarce. We delineated trajectories of potassium levels and investigated the association of these trajectories with all-cause mortality of critically ill patients with HF.

Methods and results A retrospective analysis of blood potassium levels (9 times) in patients with HF after being admitted to the intensive care unit (ICU). Potassium levels were divided into three groups according to the first serum potassium level in ICU and thereafter categorized as follows: hypokalaemia group (n = 336) (<3.5 mmol/L), normal blood potassium-level group (n = 3322) (3.5–5.0 mmol/L), and hyperkalaemia group (n = 395) (>5.0 mmol/L). According to the group-based trajectory modelling (GBTM), the hyperkalaemia group and the normal blood potassium-level group can be divided into three trajectory groups: the low-level stable group, the medium-level stable group, and the high-level decline group. The hypokalaemia group can be divided into two trajectory groups: the low-level rise group and the high-level rise group. A total of 4053 HF patients were included (mean age 71.81 ± 13.12 years, 54.90% males, 45.10% females). After adjusting for possible confounding variables, in the hyperkalaemia group, the low-level stable group had lower 28 day [high-level decline group vs. low-level stable group hazard ratio (HR), 95% confidence interval (CI): 2.917, 1.555–5.473; $P < 0.05$] and 365 day (high-level decline group vs. low-level stable group HR, 95% CI: 2.854, 1.820–4.475; $P < 0.05$) all-cause mortality. In the normal blood potassium-level group, the medium-level stable group had lower 28 day (medium-level stable group vs. low-level stable group HR, 95% CI: 0.776, 0.657–0.918; $P < 0.05$) and 365 day (medium-level stable group vs. low-level stable group HR, 95% CI: 0.827, 0.733–0.934; $P < 0.05$) all-cause mortality. In the hypokalaemia group, the cumulative survival of the high-level rise group and the low-level rise group did not differ significantly.

Conclusions Critically ill patients with HF have blood potassium trajectories. And the trajectories are associated with all-cause mortality for hyperkalaemia and normal blood potassium-level patients. GBTM is a granular method to describe the evolution of blood potassium, which may increase the current knowledge of blood potassium-level adjustment.

Keywords Blood potassium trajectory; Heart failure; Group-based trajectory model; Prognosis

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Introduction

Heart failure (HF) is a complex, multifactorial syndrome resulting from an impaired heart function and is a serious public health problem worldwide.[1] Blood potassium disorder is a common phenomenon in patients with HF, which may be related to the complications (such as reduced potassium intake and renal insufficiency) and the drug therapy of HF (such

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as diuretics and angiotensin-converting enzyme inhibitors/angiotensin receptor antagonists).[2] Due to the essential role that potassium plays in cardiac excitability and arrhythmias, dyskalaemia is a critical clinical issue that is associated with serious life-threatening complications.[3] Hyperkalaemia is now claimed to be a direct risk indicator for the cardiovascular complications and served as an indirect biomarker of the severity of the underlying disease afflicting neurohormonal activation and renal dysfunction.[4] In patients with HF, potassium levels over 5.0 mmol/L are associated with an increased risk of all-cause mortality. Additionally, there is evidence that hypokalaemia is both common and independently associated with poor clinical outcomes in HF patients.[5] In a study of 50 203 patients with HF, it was found that the blood potassium level and mortality in patients with HF showed a U-shaped curve.[6] At the same time, the COACH, PROTECT,[7] and EVEREST[8] studies did not find that serum potassium was associated with poor prognosis of HF. However, little is known about the changes in potassium levels during hospitalization and how they relate to outcomes of patients with HF. Therefore, the objectives of the current study are to identify changes in potassium levels and assess the associations between changes in potassium levels and all-cause mortality of critically ill patients with HF. In our study, hypokalaemia is defined as serum potassium <3.5 mmol/L and hyperkalaemia as serum potassium >5 mmol/L.[9]

Methods

Study population

The protocol was approved by Massachusetts Institute of Technology and the Institutional Review Boards. We retrieved all data from an openly available critical care database named Medical Information Mart for Intensive Care III (MIMIC-III, Version 1.4),[10] which includes the demographic information, diagnoses, vital signs, medications, and other essential data of the patients admitted to intensive care unit (ICU) (53 423 distinct admissions) from June 2001 to October 2012 in Beth Israel Deaconess Medical Center (Boston). Protecting Human Research Participants' exam was passed to gain access to the MIMIC-III database, and our certificate number is 9253690.

Population selection criteria

The selected population must meet the following requirements: (i) adult patients (age $\geq$18) who were first admitted to the hospital, (ii) diagnosed with HF according to ICD-9 diagnosis code (39891, 40201, 40211, 40291, 40401, 40403, 40411, 40413, 40491, 40493, and 4280–4289), (iii) ICU stay $\geq$48 h, and (iv) blood potassium records $\geq$9.

Patients meeting the following criteria were excluded: (i) age $<$18 years, (ii) ICU stay $<$48 h, (iii) no data blood potassium within the first 48 h of admission, (iv) blood potassium records $<$9, and (v) missing data $>$10%.

Data extraction

Data were extracted from MIMIC-III database through Structured Query Language. For patients with multiple hospitalizations, only the first admission to ICU is registered. The initial baseline characteristics and laboratory results measured within 48 h after admission to the ICU were recorded and analysed. The following variables were collected: demographics (age, gender, ethnicity, and marital status), mean values of vital signs [weight, heart rate, respiratory rate, mean blood pressure (MBP), systolic blood pressure (SBP), diastolic blood pressure (DBP), percutaneous oxygen saturation, glucose, and temperature], and laboratory parameters [white blood cell (WBC) count, platelet count, haemoglobin, haematocrit, blood urea nitrogen (BUN), serum creatinine, prothrombin time, activated partial thromboplastin time, international normalization ratio, bicarbonate, serum sodium, serum potassium, serum chloride, partial pressure of oxygen, arterial pressure of carbon dioxide, potential of hydrogen (PH), and lactate]. The comorbidities included hypertension, diabetes, hyperlipidaemia, acute myocardial infarction, mitral valve disease, tricuspid valve disease, aortic disease, atrial fibrillation, atrial flutter, ventricular fibrillation, acute renal failure (ARF), peripheral vascular disease (PVD), coronary artery bypass grafting, percutaneous coronary intervention, pacemaker, depression, and anxiety. Medication included aspirin, clopidogrel, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers, loop diuretics, thiazide diuretics, mineralocorticoid antagonists, and statins. Clinical severity scales included Sequential Organ Failure Assessment Score (SOFA), Simplified Acute Physiology Score II (SAPS II), and Acute Physiology Score III (APS III). Finally, we collected the first nine times serum potassium levels of the target patients after their admission to the ICU in chronological order and the time intervals between the first and last potassium levels (time intervals 1–9). The primary outcome was 28 day mortality, and the secondary outcome was 365 day mortality. The patients were followed up for at least 1 year since admission. The date of death was based on Social Security Death Index records. Logistic regression was used for imputation of missing variables.

Statistical analysis

All the patients with HF were stratified into three groups according to the first serum potassium level in ICU (hypokalaemia, normal blood potassium levels, and

hyperkalaemia). All continuous variables in this study were non-normally distributed, and they were presented as median and inter-quartile range (IQR). Categorical data were summarized as numbers and percentages. Kruskal–Wallis and χ^2 tests were employed to compare differences in baseline features among groups of serum potassium levels.

Group-based trajectory modelling (GBTM), an established analytical approach, may provide an alternative methodology for summarizing long-term blood potassium value while accounting for the dynamic nature of this variable over time.[11] We used it to fit the first nine blood potassium levels of each subgroup patients. Because blood potassium values are continuous variables, the cnorm mode was adopted to first determine the number of trajectory groups and subsequently determine the polynomial order of each group of trajectories. We fitted the model from three group trajectories to one group trajectory, and measurement time was used as the timescale. To identify the model with optimal functional forms of distinct blood potassium trajectories, starting from the highest polynomial, the cubic, quadratic, and linear terms were considered and assessed according to the significance level. Model fit was compared using the Bayesian information criterion (BIC) and Akaike information criterion value, with the smallest negative number indicating the best fit model.[12,13]

In each group, survival rates of different trajectories were compared by log-rank tests, and the Kaplan–Meier curves were built. Multivariable Cox proportional hazard models were developed to evaluate the independent effect of blood potassium trajectories on 28 and 365 day all-cause mortality.

A two-sided $P < 0.05$ was considered statistically significant. Stata MP 16 and SPSS 25 were used to perform the statistical analyses.

Results

A total of 4053 critically ill patients with HF were enrolled in this study (*Figure 1*). They were divided into three groups according to the blood potassium level: hypokalaemia group (<3.5 mmol/L, *n* = 336), normal blood potassium-level group (3.5–5.0 mmol/L, *n* = 3322), and hyperkalaemia group (>5.0 mmol/L, *n* = 395). The results of baseline characteristics were shown in *Table 1*. The median (IQR) of the blood potassium level was 3.30 (3.10, 3.40) in the hypokalaemia group, 4.20 (3.90, 4.50) in the normal blood potassium-level group, and 5.40 (5.20, 5.70) in the hyperkalaemia group; 2225 males and 1828 females were included, and most of the patients were White. Patients with a high blood potassium level tended to have higher weight, WBC count, creatinine, and BUN and lower respiratory rate, SBP, DBP, MBP, haemoglobin, haematocrit, sodium, and bicarbonate. At the same time, patients in the hyperkalaemia group are more likely to suffer from diabetes, mitral, tricuspid, aortic valve disease, atrial fibrillation, ARF, and PVD. Besides, they received more aspirin and less ACEIs. In addition, these patients showed significantly higher SOFA, SAPS II, and APS III scores.

In the hyperkalaemia group and the normal blood potassium-level group, the model with three trajectories according to the change patterns of blood potassium level was identified as the fit by comparing the BIC and the proportion of the participants within each trajectory group. Following the same method, the hypokalaemia group was divided into two trajectories (*Figures 2–4*). In the hyperkalaemia group, 395 patients were classified as the low-level stable group, the medium-level stable group, and the high-level decline group, and blood potassium levels when admitted

Figure 1 Flow chart of study population. ICU, intensive care unit.

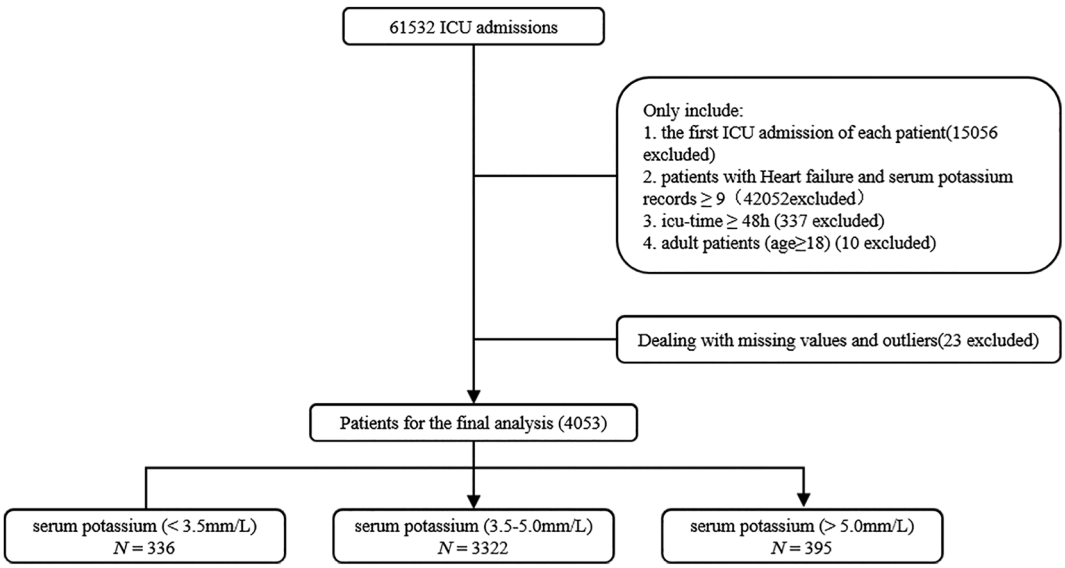

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Table 1 Baseline characteristics of the study population

Characteristics	Serum potassium			*P* value
	Hypokalaemia (n = 336) (<3.5 mmol/L)	Normal blood potassium levels (n = 3322) (3.5–5.0 mmol/L)	Hyperkalaemia (n = 395) (>5.0 mmol/L)	
Potassium	3.30 (3.10, 3.40)	4.20 (3.90, 4.50)	5.40 (5.20, 5.70)	<0.001
Age (years)	75.20 (63.28, 83.75)	74.30 (63.77, 81.96)	71.76 (63.47, 79.48)	0.021
Gender, *n* (%)				0.007
Male	161 (47.90%)	1829 (55.10%)	235 (59.50%)	
Female	175 (52.10%)	1493 (44.90%)	160 (40.50%)	
Ethnicity				0.270
White	238 (70.80%)	2398 (72.20%)	273 (69.10%)	
Black	29 (8.60%)	200 (6.00%)	28 (7.10%)	
Other	69 (20.50%)	724 (21.80%)	94 (23.80%)	
Marital status				0.270
Married	148 (44.00%)	1622 (48.80%)	203 (51.40%)	
Single	58 (17.30%)	562 (16.90%)	69 (17.50%)	
Other	130 (38.70%)	1138 (34.30%)	123 (31.10%)	
Weight (kg)	76.00 (63.35, 90.00)	78.80 (66.00, 93.60)	82.70 (66.80, 102.10)	<0.001
RR (times per minute)	19.67 (17.10, 23.08)	18.79 (16.36, 21.80)	18.26 (15.80, 21.54)	<0.001
HR (b.p.m.)	85.84 (76.13, 99.00)	85.91 (76.24, 96.67)	85.40 (77.63, 94.39)	0.750
Temperature (°C)	37.00 (36.56, 37.47)	36.87 (36.46, 37.27)	36.78 (36.38, 37.16)	<0.001
SBP (mmHg)	113.45 (103.73, 126.47)	112.41 (104.00, 123.10)	110.79 (103.69, 119.97)	0.017
DBP (mmHg)	56.63 (50.56, 63.29)	56.46 (50.82, 62.71)	55.60 (49.57, 60.82)	0.016
MBP (mmHg)	75.32 (69.28, 83.46)	74.49 (68.76, 81.22)	72.64 (67.59, 78.80)	<0.001
SpO_2 (%)	97.58 (95.92, 98.89)	97.60 (96.15, 98.72)	97.72 (96.44, 98.82)	0.160
Glucose (mg/dL)	138.42 (116.94, 163.54)	135.75 (118.00, 161.50)	135.00 (119.40, 166.86)	0.480
Laboratory parameters				
WBC (10^9/L)	11.20 (7.80, 14.90)	11.80 (8.80, 15.70)	12.60 (9.40, 16.10)	0.003
Haemoglobin (g/dL)	10.25 (9.30, 11.30)	10.30 (9.40, 11.50)	9.90 (8.90, 11.00)	<0.001
Haematocrit (%)	30.50 (27.95, 33.90)	30.70 (27.80, 33.90)	29.80 (27.20, 33.20)	0.020
Platelet (10^9/L)	186.50 (138.00, 254.50)	183.00 (130.00, 248.00)	177.00 (129.00, 252.00)	0.630
Scr (mEq/L)	1.10 (0.70, 1.60)	1.10 (0.80, 1.80)	1.90 (1.10, 3.40)	<0.001
BUN (mg/dL)	23.00 (16.00, 37.50)	25.00 (17.00, 40.00)	37.00 (23.00, 58.00)	<0.001
PT (s)	14.90 (13.50, 17.20)	14.60 (13.50, 16.50)	14.60 (13.60, 16.50)	0.100
APTT (s)	34.00 (28.80, 43.70)	34.80 (29.00, 44.90)	34.90 (29.50, 44.50)	0.600
INR	1.40 (1.20, 1.65)	1.30 (1.20, 1.60)	1.40 (1.20, 1.60)	0.200
Sodium (mmol/L)	140.00 (137.00, 143.00)	139.00 (136.00, 141.00)	137.00 (134.00, 140.00)	<0.001
Bicarbonate (mmol/L)	24.00 (21.00, 28.00)	24.00 (21.00, 27.00)	22.00 (20.00, 25.00)	<0.001
Chloride (mmol/L)	105.00 (101.00, 109.00)	105.00 (101.00, 109.00)	105.00 (101.00, 109.00)	0.130
pO_2	104.50 (76.84, 149.00)	115.00 (85.00, 153.00)	116.00 (87.00, 176.00)	0.004
pCO_2	39.00 (34.00, 46.00)	40.00 (35.00, 46.00)	41.00 (36.00, 47.00)	0.031
PH	7.40 (7.36, 7.45)	7.39 (7.34, 7.43)	7.36 (7.31, 7.40)	<0.001
Lactate	1.96 (1.40, 2.45)	1.80 (1.30, 2.43)	2.00 (1.40, 2.75)	0.003
Potassium 1	3.50 (3.20, 3.90)	4.20 (3.80, 4.60)	5.10 (4.40, 5.60)	<0.001
Potassium 2	3.50 (3.20, 3.90)	4.20 (3.80, 4.60)	5.10 (4.40, 5.70)	<0.001
Potassium 3	3.50 (3.30, 4.00)	4.10 (3.80, 4.60)	5.10 (4.40, 5.60)	<0.001
Potassium 4	3.50 (3.30, 4.00)	4.10 (3.80, 4.50)	4.90 (4.20, 5.50)	<0.001
Potassium 5	3.60 (3.40, 4.00)	4.10 (3.80, 4.50)	4.80 (4.20, 5.30)	<0.001
Potassium 6	3.60 (3.40, 4.00)	4.10 (3.70, 4.50)	4.80 (4.20, 5.30)	<0.001
Potassium 7	3.70 (3.40, 4.10)	4.10 (3.70, 4.40)	4.60 (4.10, 5.20)	<0.001
Potassium 8	3.70 (3.30, 4.00)	4.10 (3.80, 4.40)	4.60 (4.10, 5.20)	<0.001
Potassium 9	3.80 (3.40, 4.10)	4.10 (3.70, 4.40)	4.50 (4.00, 5.20)	<0.001
Time intervals 1–9 (h)	46.00 (25.00, 68.50)	42.00 (21.00, 65.00)	24.00 (11.00, 47.00)	<0.001
Comorbidities and medical history, *n* (%)				
AMI	90 (26.80%)	862 (25.90%)	110 (27.80%)	0.700
Hypertension	142 (42.30%)	1403 (42.20%)	128 (32.40%)	<0.001
Diabetes	112 (33.30%)	1139 (34.30%)	175 (44.30%)	<0.001
Hyperlipidaemia	67 (19.90%)	912 (27.50%)	109 (27.60%)	0.012
Mitral valve disease	51 (15.20%)	749 (22.50%)	90 (22.80%)	0.007
Tricuspid valve disease	16 (4.80%)	162 (4.90%)	31 (7.80%)	0.039
Aortic disease	33 (9.80%)	568 (17.10%)	87 (22.00%)	<0.001
Atrial fibrillation	141 (42.00%)	1608 (48.40%)	204 (51.60%)	0.028
Atrial flutter	14 (4.20%)	134 (4.00%)	21 (5.30%)	0.480
Ventricular fibrillation	6 (1.80%)	99 (3.00%)	10 (2.50%)	0.420
ARF	148 (44.00%)	1473 (44.30%)	219 (55.40%)	<0.001
PVD	32 (9.50%)	538 (16.20%)	68 (17.20%)	0.004
GABG	23 (6.80%)	253 (7.60%)	37 (9.40%)	0.380
Pacemaker	14 (4.20%)	190 (5.70%)	25 (6.30%)	0.420

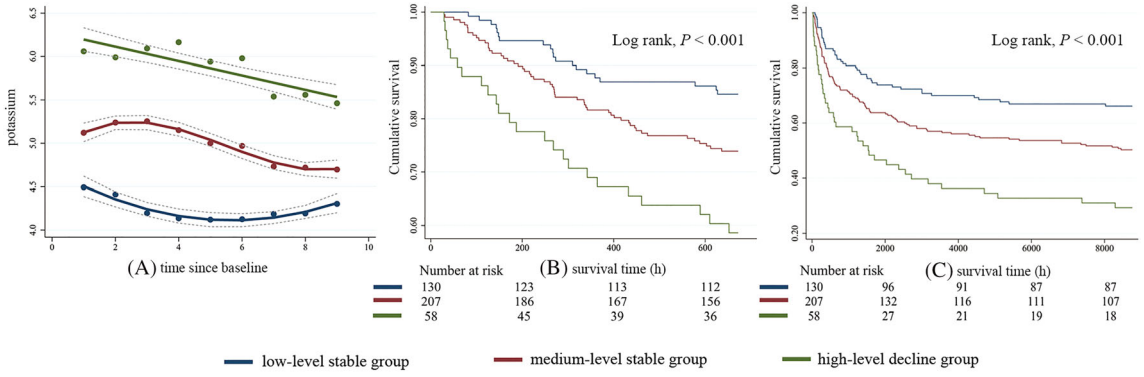
(*Continues*)

Table 1 (continued)

Characteristics	Serum potassium			*P* value
	Hypokalaemia (n = 336) (<3.5 mmol/L)	Normal blood potassium levels (n = 3322) (3.5–5.0 mmol/L)	Hyperkalaemia (n = 395) (>5.0 mmol/L)	
Anxiety	6 (1.80%)	82 (2.50%)	8 (2.00%)	0.660
Depressive	18 (5.40%)	157 (4.70%)	22 (5.60%)	0.690
Medication use, *n* (%)				
Aspirin	199 (59.20%)	2322 (69.90%)	300 (75.90%)	<0.001
Clopidogrel	69 (20.50%)	746 (22.50%)	82 (20.80%)	0.570
ACEIs	151 (44.90%)	1533 (46.10%)	149 (37.70%)	0.006
ARBs	26 (7.70%)	248 (7.50%)	34 (8.60%)	0.720
Loop diuretics	265 (78.90%)	2754 (82.90%)	286 (72.40%)	<0.001
Thiazide diuretics	36 (10.70%)	367 (11.00%)	55 (13.90%)	0.220
MRAs	19 (5.70%)	204 (6.10%)	21 (5.30%)	0.770
Statins	193 (57.40%)	2118 (63.80%)	269 (68.10%)	0.011
Scoring systems				
SOFA	5.00 (3.00, 7.00)	5.00 (3.00, 8.00)	7.00 (5.00, 9.00)	<0.001
SAPS II	40.00 (34.00, 49.00)	41.00 (33.00, 50.00)	46.00 (37.00, 56.00)	<0.001
APS III	47.00 (36.00, 61.00)	47.00 (37.00, 61.00)	56.00 (44.00, 72.00)	<0.001
Length of ICU stay (h)	143.50 (94.00, 262.00)	145.00 (93.00, 257.00)	126.00 (79.00, 218.00)	0.009
Mortality, *n* (%)				
28 day	78 (23.20%)	706 (21.30%)	98 (24.80%)	0.210
365 day	157 (46.70%)	1328 (40.00%)	188 (47.60%)	0.002

ACEIs, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; APS III, Acute Physiology Score III; APTT, activated partial thromboplastin time; ARBs, angiotensin receptor blockers; ARF, acute renal failure; BUN, blood urea nitrogen; DBP, diastolic blood pressure; GABG, coronary artery bypass grafting; HR, heart beat; ICU, intensive care unit; INR, international normalization ratio; MBP, mean blood pressure; MRAs, mineralocorticoid antagonists; pCO_2, arterial pressure of carbon dioxide; PH, potential of hydrogen; pO_2, partial pressure of oxygen; PT, prothrombin time; PVD, peripheral vascular disease; RR, respiratory rate; SAPS II, Simplified Acute Physiology Score II; SBP, systolic blood pressure; Scr, serum creatinine; SOFA, Sequential Organ Failure Assessment Score; SpO_2, percutaneous oxygen saturation; Time intervals 1–9, the time intervals between the first and ninth potassium levels; WBC, white blood cell count.
Data are described as count (percentage) for categorical variables and median (inter-quartile range) for continuous variables.

Figure 2 (A) The trajectories of hyperkalaemia group, (B) 28 day Kaplan–Meier curves of each trajectory group, and (C) 365 day Kaplan–Meier curves of each trajectory group.



to the ICU were higher in the high-level decline group. In the normal blood potassium-level group, 3322 patients were classified as the low-level stable group, the medium-level stable group, and the high-level decline group, and blood potassium levels when admitted to the ICU were lower in the low-level stable group. In the hypokalaemia group, 336 patients were classified as the high-level rise group and the low-level rise group, and blood potassium levels when admitted to the ICU were lower in the low-level stable group.

The survival curves of 28 day (log rank, $P < 0.05$) and 365 day (log rank, $P < 0.05$) all-cause mortality stratified by the trajectories of blood potassium in each group are shown in *Figures 2–4*. In the hyperkalaemia group, the low-level stable group had higher cumulative survival demonstrated significantly (*Figure 2*). In Model 1, age, gender, ethnicity, and marital status were incorporated into the regression model; compared with the low-level stable group, the highest 28 day [high-level decline group vs. low-level stable group

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Figure 3 (A) The trajectories of normal blood potassium-level group, (B) 28 day Kaplan–Meier curves of each trajectory group, and (C) 365 day Kaplan–Meier curves of each trajectory group.

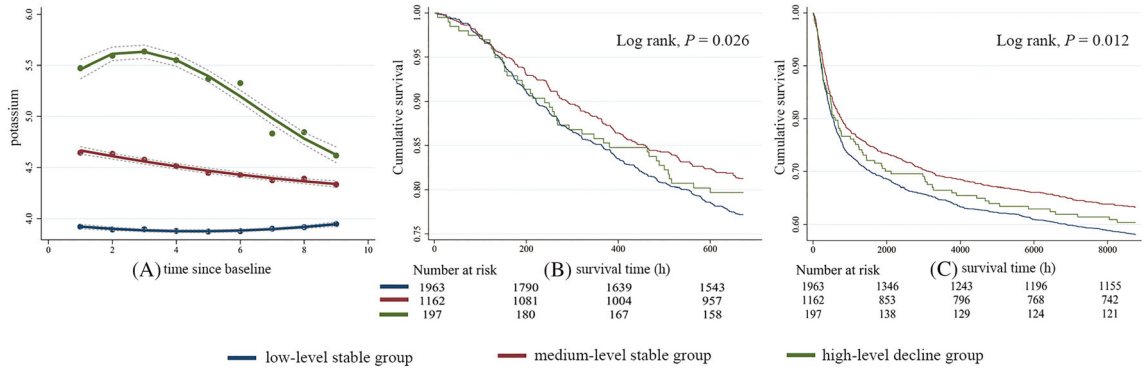
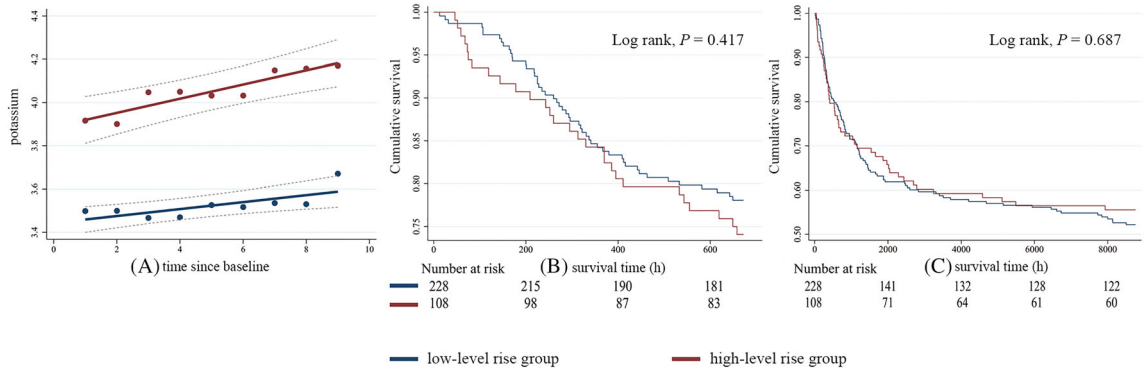


Figure 4 (A) The trajectories of hypokalaemia group, (B) 28 day Kaplan–Meier curves of each trajectory group, and (C) 365 day Kaplan–Meier curves of each trajectory group.



hazard ratio (HR), 95% confidence interval (CI): 3.210, 1.766–5.833; $P < 0.05$] and 365 day (high-level decline group vs. low-level stable group HR, 95% CI: 3.020, 1.968–4.637; $P < 0.05$) all-cause mortality was confirmed in the high-level decline group. In Model 2, age, gender, weight, respiratory rate, WBC, serum sodium, PH, ARF, SOFA, loop diuretics, and time intervals 1–9 were incorporated. The blood potassium level still associated with 28 day (high-level decline group vs. low-level stable group HR, 95% CI: 2.917, 1.555–5.473; $P < 0.05$) and 365 day (high-level decline group vs. low-level stable group HR, 95% CI: 2.854, 1.820–4.475; $P < 0.05$) all-cause mortality in patients with HF (*Table 2*).

In the normal blood potassium-level group, the medium-level stable group had higher cumulative survivals demonstrated significantly (*Figure 3*). In Model 1, compared with the low-level stable group, the lowest 28 day (medium-level stable group vs. low-level stable group HR, 95% CI: 0.805, 0.684–0.947; $P < 0.05$) and 365 day (medium-level stable group vs. low-level stable group HR, 95% CI: 0.842, 0.749–0.947; $P < 0.05$) all-cause mortality was confirmed in the medium-level stable group. In Model 2, blood potassium level still associated with 28 day (medium-level stable group vs. low-level stable group HR, 95% CI: 0.776, 0.657–0.918; $P < 0.05$) and 365 day (medium-level stable group vs. low-level stable group HR, 95% CI: 0.827, 0.733–0.934; $P < 0.05$) all-cause mortality in patients with HF (*Table 3*).

In the hypokalaemia group, the cumulative survival of the high-level rise group and the low-level rise group was demonstrated not significantly (*Figure 4*). In Model 1, compared with the low-level rise group, the 28 day (high-level rise group vs. low-level stable group HR, 95% CI: 1.238, 0.777–1.972; $P = 0.370$) and 365 day (high-level rise group vs. low-level stable group HR, 95% CI: 0.965, 0.685–1.358; $P = 0.836$) all-cause mortality in the medium-level stable group was not statistically significant. In Model 2, compared with the low-level rise group, the 28 day (high-level rise group vs. low-level stable group HR, 95% CI: 1.258, 0.772–2.049; $P = 0.356$) and 365 day (high-level rise group vs. low-level stable group HR, 95% CI: 0.917, 0.643–1.306; $P = 0.630$) all-cause mortality in the medium-level stable group was not statistically significant (*Table 4*).

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Table 2 The association between all-cause mortality and blood potassium trajectories in hyperkalaemia group

	Non-adjusted		Model 1		Model 2	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
28 day all-cause mortality						
Trajectory 1		1.0 (ref)	1.0 (ref)		1.0 (ref)	
Trajectory 2	1.812 (1.085–3.026)	0.023	1.734 (1.033–2.910)	0.037	1.403 (0.830–2.370)	0.206
Trajectory 3	3.274 (1.808–5.928)	<0.001	3.210 (1.766–5.833)	<0.001	2.917 (1.555–5.473)	0.001
365 day all-cause mortality						
Trajectory 1		1.0 (ref)	1.0 (ref)		1.0 (ref)	
Trajectory 2	1.663 (1.168–2.367)	0.005	1.629 (1.141–2.328)	0.007	1.416 (0.986–2.034)	0.059
Trajectory 3	2.943 (1.922–4.508)	<0.001	3.020 (1.968–4.637)	<0.001	2.854 (1.820–4.475)	<0.001

ARF, acute renal failure; CI, confidence interval; HR, hazard ratio; PH, potential of hydrogen; RR, respiratory rate; SOFA, Sequential Organ Failure Assessment Score; WBC, white blood cell count.
Trajectory 1: low-level stable group; Trajectory 2: medium-level stable group; and Trajectory 3: high-level decline group. Models were derived from Cox proportional hazard regression models. Non-adjusted model, adjusted for none. Adjusted Model 1, adjusted for age, gender, ethnicity, and marital status. Adjusted Model 2, adjusted for age, gender, weight, RR, WBC, serum sodium, PH, ARF, SOFA, loop diuretics, and time intervals 1–9.

Table 3 The association between all-cause mortality and blood potassium trajectories in normal blood potassium-level group

	Non-adjusted		Model 1		Model 2	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
28 day all-cause mortality						
Trajectory 1		1.0 (ref)	1.0 (ref)		1.0 (ref)	
Trajectory 2	0.802 (0.682–0.943)	0.007	0.805 (0.684–0.947)	0.009	0.776 (0.657–0.918)	0.003
Trajectory 3	0.883 (0.639–1.221)	0.453	0.926 (0.670–1.280)	0.642	0.933 (0.667–1.304)	0.685
365 day all-cause mortality						
Trajectory 1		1.0 (ref)	1.0 (ref)		1.0 (ref)	
Trajectory 2	0.837 (0.745–0.941)	0.003	0.842 (0.749–0.947)	0.004	0.827 (0.733–0.934)	0.002
Trajectory 3	0.926 (0.735–1.169)	0.519	0.971 (0.769–1.225)	0.971	1.010 (0.794–1.285)	0.936

CI, confidence interval; HR, hazard ratio.
Trajectory 1: low-level stable group; Trajectory 2: medium-level stable group; and Trajectory 3: high-level decline group. Models were derived from Cox proportional hazard regression models.

Table 4 The association between all-cause mortality and blood potassium trajectories in hypokalaemia group

	Non-adjusted		Model 1		Model 2	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
28 day all-cause mortality						
Trajectory 1		1.0 (ref)	1.0 (ref)		1.0 (ref)	
Trajectory 2	1.211 (0.762–1.923)	0.418	1.238 (0.777–1.972)	0.370	1.258 (0.772–2.049)	0.356
365 day all-cause mortality						
Trajectory 1		1.0 (ref)	1.0 (ref)		1.0 (ref)	
Trajectory 2	0.933 (0.664–1.310)	0.688	0.965 (0.685–1.358)	0.836	0.917 (0.643–1.306)	0.630

CI, confidence interval; HR, hazard ratio.
Trajectory 1: low-level rise group; Trajectory 2: high-level rise group. Models were derived from Cox proportional hazard regression models.

Discussion

Patients with HF frequently experience dyskalaemia (hypokalaemia and hyperkalaemia), which has been connected to underlying pathophysiological alterations, pharmacological therapies, and concurrent comorbidities. Both hypokalaemia and hyperkalaemia have been associated with a poor outcome in patients with HF. However, it is not known if this association is causal.[14] The main findings of the study were as follows. First, disturbances in potassium homeostasis are prevalent among critically ill patients presenting with HF. Second, we explored how blood potassium levels of patients with hyperkalaemia, hypokalaemia, and normal blood potassium levels changed over time after admission and plotted their trajectories. By using GBTM, we identified three trajectory groups in patients with hyperkalaemia, three trajectory groups in patients with normal blood potassium levels, and two trajectory groups in patients with hypokalaemia. There

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were significant differences in blood potassium levels at admission and the stability of changes in blood potassium levels during hospitalization in these groups. Third, this study demonstrated that the blood potassium trajectory was an independent risk factor of 28 and 365 day all-cause mortality in HF patients with hyperkalaemia and normal blood potassium levels at admission, even after adjusting for potential confounding variables. However, we did not observe this circumstance in HF patients with hyponatremia. As far as we know, this is the first retrospective cohort study regarding the impacts of longitudinal blood potassium patterns in patients with HF.

In fact, we can find more interesting points through the GBTM model. In the hyperkalaemia group, patients' blood potassium levels stabilized between 4.0 and 4.5 mmol/L after admission, with lower 28 and 365 day all-cause mortality than the other two trajectory groups. In the normal blood potassium-level group, patients with stable blood potassium levels of ~4.5 mmol/L had lower 28 and 365 day all-cause mortality than patients with stable blood potassium levels of 3.5–4.0 mmol/L. This is in line with the research conducted by Aldahl *et al*.[5] They found that blood potassium levels of 4.0–4.8 mmol/L were associated with the lowest risk of death in patients with chronic HF. In our study, we further included the changing trend of blood potassium level after admission. For example, in the hyperkalaemia group, the low-level stable group had a better prognosis than the high-level decline group. According to our hypothesis, potassium 'variability' may be a significant factor influencing clinical outcomes. This merits further exploration. Specifically, the association between admission potassium levels and outcomes is not merely attributable to crossing a threshold, but depends upon the dynamic changes in potassium levels.

Dyskalaemia (i.e. both hypokalaemia and hyperkalaemia) in HF is common because of HF itself and related comorbidities and because of the medications used to treat HF and these comorbidities.[15] According to a recent large observational study, 24.4% of patients experienced at least one hyperkalaemia event within 1 year, and 10.2% reported moderate or severe hyperkalaemia.[16] Additionally, 20.3% of patients experienced at least one episode of hypokalaemia event within 1 year, whereas 3.7% of them experienced severe hypokalaemia. In HF, as in other conditions, for example, myocardial infarction, hypertension, and kidney disease, or in the general population,[17–20] the relationship between K concentrations and adverse outcomes appeared to be U-shaped, where both low- and high-K levels were associated with adverse outcomes.[21–23] However, the majority of these studies simply looked at blood potassium levels of patients at a particular time point for analysis, ignoring the impact of the change of blood potassium level on the prognosis of patients. Our study found that under the influence of many factors, the blood potassium level of patients can be divided into different trajectories. At the same time, these trajectories had different effects on the prognosis of patients. In patients with hyperkalaemia, we found that the low-level stable group had higher cumulative survival demonstrated significantly. This situation is quite interesting and should be noticed. Because the patient's electrolyte level is a dynamic process, it is important to focus more on the impact of the change of blood potassium level on the prognosis of patients than the blood potassium level at a time point. Should we correct the patient's blood potassium level? In patients with HF, adjusting the blood potassium level and identifying which state is most beneficial to patients are all issues that merit more research.

Limitation

This study was a single retrospective study with MIMIC-III; inevitable bias may affect the authenticity of the results. In general, the more key variables a model contains, the more accurate its predictions will be. But constrained by the public databases, a lot of information that may affect the model was not collected like the results of cardiac ultrasound, left ventricular ejection fraction, mechanical circulatory support, estimated glomerular filtration rate, and angiotensin receptor–neprilysin inhibitor using record. And we cannot identify cardiac vs. non cardiac causes of hospitalization. These factors may affect the clinical approach and medical treatment, and we cannot further assess the patient's cardiac status. Meanwhile, we were unable to obtain blood potassium levels at regular intervals, which may have an impact on the study. Moreover, the complications and treatments will affect the blood potassium level of patients, which we are unable to collect accurately. However, considering that we studied the change trajectory of blood potassium in ICU, it is appropriate for us to do so. In addition to this, other important information was also not collected such as specific causes of death, type of myocardial infarction, type of HF, and left ventricular ejection fraction. Moreover, due to a lack of blood potassium, the sample size of this study declined significantly. In order to verify the conclusion of this study, a prospective case–control study may be needed.

Conflict of interest

None declared.

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References

1. Bragazzi NL, Zhong W, Shu J, Abu Much A, Lotan D, Grupper A, Younis A, Dai H. Burden of heart failure and underlying causes in 195 countries and territories from 1990 to 2017. *Eur J Prev Cardiol* 2021; **28**: 1682–1690.
2. McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, Burri H, Butler J, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Francesco Piepoli M, Price S, Rosano GMC, Ruschitzka F, Kathrine Skibelund A, ESC Scientific Document Group, de Boer RA, Christian Schulze P, Abdelhamid M, Aboyans V, Adamopoulos S, Anker SD, Arbelo E, Asteggiano R, Bauersachs J, Bayes-Genis A, Borger MA, Budts W, Cikes M, Damman K, Delgado V, Dendale P, Dilaveris P, Drexel H, Ezekowitz J, Falk V, Fauchier L, Filippatos G, Fraser A, Frey N, Gale CP, Gustafsson F, Harris J, Iung B, Janssens S, Jessup M, Konradi A, Kotecha D, Lambrinou E, Lancellotti P, Landmesser U, Leclercq C, Lewis BS, Leyva F, Linhart A, Løchen ML, Lund LH, Mancini D, Masip J, Milicic D, Mueller C, Nef H, Nielsen JC, Neubeck L, Noutsias M, Petersen SE, Sonia Petronio A, Ponikowski P, Prescott E, Rakisheva A, Richter DJ, Schlyakhto E, Seferovic P, Senni M, Sitges M, Sousa-Uva M, Tocchetti CG, Touyz RM, Tschoepe C, Waltenberger J, Adamo M, Baumbach A, Böhm M, Burri H, Čelutkienė J, Chioncel O, Cleland JGF, Coats AJS, Crespo-Leiro MG, Farmakis D, Gardner RS, Gilard M, Heymans S, Hoes AW, Jaarsma T, Jankowska EA, Lainscak M, Lam CSP, Lyon AR, McMurray JJV, Mebazaa A, Mindham R, Muneretto C, Piepoli MF, Price S, Rosano GMC, Ruschitzka F, Skibelund AK. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J* 2021; **42**: 3599–3726.
3. Rakisheva A, Marketou M, Klimenko A, Troyanova-Shchutskaia T, Vardas P. Hyperkalemia in heart failure: foe or friend? *Clin Cardiol* 2020; **43**: 666–675.
4. Llubani R, Vukadinović D, Werner C, Marx N, Zewinger S, Böhm M. Hyperkalaemia in heart failure—pathophysiology, implications and therapeutic perspectives. *Curr Heart Fail Rep* 2018; **15**: 390–397.
5. Aldahl M, Jensen ASC, Davidsen L, Eriksen MA, Møller Hansen S, Nielsen BJ, Krogager ML, Køber L, Torp-Pedersen C, Søgaard P. Associations of serum potassium levels with mortality in chronic heart failure patients. *Eur Heart J* 2017; **38**: 2890–2896.
6. Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, Bushinsky DA. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. *Am J Nephrol* 2017; **46**: 213–221.
7. Tromp J, ter Maaten JM, Damman K, O'Connor CM, Metra M, Dittrich HC, Ponikowski P, Teerlink JR, Cotter G, Davison B, Cleland JGF, Givertz MM, Bloomfield DM, van der Wal MHL, Jaarsma T, van Veldhuisen DJ, Hillege HL, Voors AA, van der Meer P. Serum potassium levels and outcome in acute heart failure (data from the PROTECT and COACH trials). *Am J Cardiol* 2017; **119**: 290–296.
8. Khan SS, Campia U, Chioncel O, Zannad F, Rossignol P, Maggioni AP, Swedberg K, Konstam MA, Senni M, Nodari S, Vaduganathan M, Subacius H, Butler J, Gheorghiade M, EVEREST Trial Investigators. Changes in serum potassium levels during hospitalization in patients with worsening heart failure and reduced ejection fraction (from the EVEREST trial). *Am J Cardiol* 2015; **115**: 790–796.
9. Gumz ML, Rabinowitz L, Wingo CS. An integrated view of potassium homeostasis. *New Engl J Med* 2015; **373**: 1787–1788.
10. Johnson AE, Pollard TJ, Shen L, Lehman LW, Feng M, Ghassemi M, Moody B, Szolovits P, Celi LA, Mark RG. MIMIC-III, a freely accessible critical care database. *Sci Data* 2016; **3**: 160035.
11. Nagin DS. Group-based trajectory modeling: an overview. *Ann Nutr Metab* 2014; **65**: 205–210.
12. Nagin DS, Odgers CL. Group-based trajectory modeling in clinical research. *Annu Rev Clin Psychol* 2010; **6**: 109–138.
13. Nagin DS, Jones BL, Passos VL, Tremblay RE. Group-based multi-trajectory modeling. *Stat Methods Med Res* 2018; **27**: 2015–2023.
14. Sfairopoulos D, Arseniou A, Korantzopoulos P. Serum potassium and heart failure: association, causation, and clinical implications. *Heart Fail Rev* 2021; **26**: 479–486.
15. Ferreira JP, Butler J, Rossignol P, Pitt B, Anker SD, Kosiborod M, Lund LH, Bakris GL, Weir MR, Zannad F. Abnormalities of potassium in heart failure. *J Am Coll Cardiol* 2020; **75**: 2836–2850.
16. Savarese G, Xu H, Trevisan M, Dahlström U, Rossignol P, Pitt B, Lund LH, Carrero JJ. Incidence, predictors, and outcome associations of dyskalemia in heart failure with preserved, mid-range, and reduced ejection fraction. *Jacc-Heart Failure* 2019; **7**: 65–76.
17. Krogager ML, Torp-Pedersen C, Mortensen RN, Køber L, Gislason G, Søgaard P, Aasbjerg K. Short-term mortality risk of serum potassium levels in hypertension: a retrospective analysis of nationwide registry data. *Eur Heart J* 2017; **38**: 104–112.
18. Goyal A, Spertus JA, Gosch K, Venkitachalam L, Jones PG, van den Berghe G, Kosiborod M. Serum potassium levels and mortality in acute myocardial infarction. *Jama-J Am Med Assoc* 2012; **307**: 157–164.
19. Pitt B, Rossignol P. Serum potassium in patients with chronic heart failure: once we make a U-turn where should we go? *Eur Heart J* 2017; **38**: 2897–2899.
20. Kovesdy CP, Matsushita K, Sang Y, Brunskill NJ, Carrero JJ, Chodick G, Hasegawa T, Heerspink HL, Hirayama A, Landman GWD, Levin A, Nitsch D, Wheeler DC, Coresh J, Hallan SI, Shalev V, Grams ME. Serum potassium and adverse outcomes across the range of kidney function: a CKD Prognosis Consortium meta-analysis. *Eur Heart J* 2018; **39**: 1535.
21. Hayes J, Kalantar-Zadeh K, Lu JL, Turban S, Anderson JE, Kovesdy CP. Association of hypo- and hyperkalemia with disease progression and mortality in males with chronic kidney disease: the role of race. *Nephron Clin Pract* 2012; **120**: C8–C16.
22. Shiyovich A, Gilutz H, Plakht Y. Potassium fluctuations are associated with inhospital mortality from acute myocardial infarction. Soroka Acute Myocardial Infarction II (SAMI-II). *Project Angiology* 2018; **69**: 709–717.
23. Kovesdy CP, Appel LJ, Grams ME, Gutekunst L, McCullough PA, Palmer BF, Pitt B, Sica DA, Townsend RR. Potassium homeostasis in health and disease: a scientific workshop cosponsored by the National Kidney Foundation and the American Society of Hypertension. *J Am Soc Hypertens* 2017; **11**: 783–800.