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ORIGINAL RESEARCH ARTICLE

Serum potassium levels provide prognostic information in symptomatic heart failure beyond traditional clinical variables

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Abstract

Aims Despite of recent advances in the pharmacological treatment, heart failure (HF) maintains significant morbidity and mortality rates. While serum potassium disorders are common and associated with adverse outcomes, the exact recommended potassium level for patients with HF are not entirely established. We aimed to investigate the prognostic role of potassium levels on a cohort of patients with symptomatic chronic HF.

Methods and results Patients with symptomatic chronic HF were identified at the referral to 6 min walking test (6MWT) and were prospectively followed up for cardiovascular events. Clinical and laboratorial data were retrospectively obtained. The primary endpoint was the composite of cardiovascular death, hospitalization due to HF, and heart transplantation. The cohort included 178 patients with HF with the mean age of 51 ± 12.76 years, 39% were female, 85% of non-ischaemic cardiomyopathy, and 38% had New York Heart Association Class III with a relatively high Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) score (12.91 ± 6.6). The mean left ventricular ejection fraction was 39.98 ± 15.79%, and the mean 6MWT distance was 353 ± 136 m. After a median follow-up of 516 days, there were 22 major cardiovascular events (4 cardiovascular deaths, 13 HF admissions, and 5 heart transplants). Patients were stratified according to cut-point level of serum potassium of 4.7 mmol/L to predict combined cardiac events based on receiver operating characteristic analysis. Individuals with higher potassium levels had worse renal function (glomerular filtration rate, $K \leq 4.7$: 102.8 ± 32.2 mL/min/1.73 m^2 vs. $K > 4.7$: 85.42 ± 36.2 mL/min/1.73 m^2, $P = 0.004$), higher proportion of New York Heart Association Class III patients ($K \leq 4.7$: 28% vs. $K > 4.7$: 48%, $P = 0.0029$), and also higher MAGGIC score ($K \leq 4.7$: 12.08 ± 5.7 vs. $K > 4.7$: 14.9 ± 7.9, $P = 0.0089$), without significant differences on the baseline pharmacological HF treatment. Both potassium levels [hazard ratio (HR) 4.26, 95% confidence interval (CI) 1.59–11.421, $P = 0.003$] and 6MWT distance (HR 0.99, 95% CI 0.993–0.999, $P = 0.01$) were independently associated with the primary outcome. After adjustments for MAGGIC score and 6MWT distance, potassium levels > 4.7 mmol/L maintained a significant association with outcomes (HR 3.57, 95% CI 1.305–9.807, $P = 0.013$). Patients with $K > 4.7$ mmol/L were more likely to present clinical events during the follow-up (log rank = 0.005). Adding potassium levels to the model including 6MWT and MAGGIC significantly improved the prediction of events over 2 years (integrated discrimination index 0.105, 95% CI 0.018–0.281, $P = 0.012$ and net reclassification index 0.447, 95% CI 0.077–0.703, $P = 0.028$).

Conclusions Potassium levels were independently associated with worse outcomes in patients with chronic symptomatic HF, also improving the accuracy model for prognostic prediction when added to MAGGIC score and 6MWT distance. The potassium levels above 4.7 mmol/L might identify those patients at an increased risk of cardiovascular events.

Keywords Heart failure; Prognosis; Potassium; Renal function; Physical capacity

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Introduction

Heart failure (HF) is a common clinical syndrome characterized by a reduction in cardiac output and/or increase in intracardiac pressures at rest or during exercise, which is strongly associated to reduced functional capacity, poor quality of life, and cardiac events including cardiovascular death and hospitalization rates.[1,2] In the USA, more than 550 000 patients are diagnosed with HF yearly, and, in Brazil, HF represents one of the most frequent causes of cardiovascular hospitalization in the elderly population.[3,4] Despite having a high prevalence and newer pharmacological treatment advances, HF still maintains high morbidity and mortality rates.[3,5]

In the HF population, serum potassium disorders (hyperkalaemia and hypokalaemia) are common and frequently associated with adverse outcomes.[6] Diabetes, chronic kidney disease, and hypertension are frequent co-morbidities in individuals with HF, playing a significant role in the potassium disturbances.[7] Hyperkalaemia is markedly related to poor outcomes in patients with HF and often leads to an increased risk of life-threatening arrhythmias and to discontinuation or reduction of the renin–angiotensin–aldosterone system (RAAS) inhibitors, which may impact survival.[8,9] Likewise, hypokalaemia might also be present among patients with HF, despite the use of RAAS inhibitors.[10] In a recent study, a U-shaped relation between potassium and mortality in patients with acute HF was reported.[11] Whether potassium is an independent risk factor for worse outcomes or related to other risk factors such as chronic kidney disease or diabetes remains unclear, although hyperkalaemia has been consistently linked to mortality increase.[6,12]

With a growing number of patients with HF with associated multiple co-morbidities receiving RAAS inhibitors and also mineralocorticoid receptor antagonists, hyperkalaemia has become a common condition that impairs the initiation and up-titration of life-saving HF therapies.

Noteworthy, the ideal potassium levels that should be maintained in patients with HF have not been well established. Moreover, the impact of potassium levels in ambulatory real-world HF patients has yet to be further investigated. In this study, we aimed to assess the impact of potassium levels on the prognosis of an ambulatory chronic and symptomatic HF cohort.

Methods

Study population

Patients with symptomatic chronic HF followed at the outpatient HF clinic of a tertiary hospital (Discipline of Cardiology, Clinics Hospital, Faculty of Medical Science, University of Campinas, São Paulo, Brazil) referred for 6 min walking test (6MWT) were consecutively identified. The eligibility criteria included patients with symptomatic HF [Stage C HF with a New York Heart Association (NYHA) Class II or III] at age between 18 and 75 years receiving optimized guideline-based HF therapy. The exclusion criteria were advanced or decompensated HF, significant cardiac valve disease other than functional mitral or tricuspid regurgitation, significant asthma or chronic obstructive pulmonary disease, pregnancy, unstable clinical condition, unavailability of follow-up, and inability to perform a 6MWT.

Study design

Patients underwent a baseline evaluation, after the 6MWT, and were prospectively followed for cardiovascular events. The baseline evaluation included clinical and a single laboratorial evaluation based on the available data and tests obtained in medical records matched to the 6WMT. Left ventricular ejection fraction (LVEF) by transthoracic echocardiogram (Simpson method's) assessment and a 6MWT were available in all recruited patients. After the initial evaluation, patients were followed for major cardiovascular events (cardiac death, HF hospitalization, and heart transplantation) in a specialized HF outpatient clinic in accordance with the most recent guidelines.[13,14] Cardiac death was defined as any sudden death occurred preceding cardiovascular symptoms (syncope, chest pains, or dyspnoea).[15] HF hospitalization was defined as any hospital admission triggered by clinically decompensated HF requiring intravenous loop diuretics for more than 24 h. Cardiac events (cardiac death, HF hospitalization, and heart transplantation) were obtained based on the available medical documentation of our hospital and health care network, blinded to any clinical information. The study was conducted according to the precepts of the Helsinki Declaration and was approved by the research ethics committee of our institution (CAAE: 39500514.2.0000.5404). All patients provided consent to participate.

Echocardiogram

Cardiac ultrasound analysis was performed using a dedicated phased array transducer (1.5–4.5 MHz, Vivid-S60, GE Healthcare, Chicago, USA). Cardiac chambers and LVEF evaluation (assessed by the Simpson's method) were performed according to the current American Society of Echocardiography guidelines.[16] Left ventricular relative wall thickness (RWT) was estimated as 2*posterior wall thickness/end-diastolic diameter.[16]

Six-minute walking test

The 6MWT was performed as previously described on a surface level by a health care professional unaware of clinical, laboratorial, or echocardiographic results.[17] Each patient underwent two 6MWTs performed at the same day, with the first test performed in order to familiarize the patient with the methodology. The second test was performed with a maximal performance with instructions to cover the greatest distance during the test time, at a self-determined speed, and the patients were allowed to pause and rest if needed. Two different health care professionals objectively measured the distance covered.

Laboratory and electrocardiogram data

Twelve-lead resting electrocardiogram (ECG) was obtained through calibrated and validated equipment. Standard definitions for chamber enlargement were considered as left atrial enlargement (second deflection of P wave on V1 $>$ 1 mm), left ventricular enlargement (any of SV1 + RV5 or V6 $>$ 35 mm or RI + SIII $>$ 25 mm), right atrial enlargement (initial component of P wave on II taller than 2.5 mm), and right ventricular enlargement (any of R/S V1 $>$ 1 or RV1 $>$ 5 mm or SV5 or V6 $>$ 7 mm). Glucose, haemoglobin, sodium, potassium, urea, creatinine, triglycerides, and high-density and low-density lipoprotein cholesterol were obtained by standard methods (Beckman Coulter, AU5800 Beckman Coulter Analyzer, USA). Twelve-hour fasting was performed for glucose and lipids.

Statistical methods

Data are reported as mean ± standard deviation. All statistical analyses were performed using SAS Version 9.4 (SAS Institute, Inc., Cary, NC) and SPSS (IBM Corp, IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY). The Kolmogorov–Smirnov test was used to test whether the variables showed normal distribution. For comparison of the variable mean values, we used the Student's *t*-test. Fisher's exact test was used to test the association between the nominal variables. Clinical predictors were transformed when appropriate. Receiver operating characteristic analysis was used to obtain the ideal cut-point level of serum potassium to predict combined cardiac events. Survival analysis was performed using Kaplan–Meier curves, log-rank test, and Cox regression analysis. The Meta-Analysis Global Group in Chronic Heart Failure score (MAGGIC score),[18] 6MWT distance, and potassium levels were included in the multivariable model. Harrell's C-statistics was used to verify discrimination of risk prediction models. Continuous net reclassification index (NRI) and integrated discrimination index (IDI) were calculated as previously described.[19,20] The level of significance was set at $P < 0.05$ in all analyses.

Results

Baseline evaluation and population characteristics

The demographic, clinical characteristics and echocardiogram parameters of the study population at the baseline evaluation are summarized in *Tables 1* and *2*. The cohort included 178 patients with HF. The mean age was 51 ± 12.76 years, 39% were female, 85% of non-ischaemic cardiomyopathy, and 38% had NYHA Class III with a relatively high MAGGIC score of 12.91 ± 6.6. The mean LVEF was 39.98 ± 15.79% through Simpson's measurement, with a high mean left ventricular internal dimension in diastole (64.46 ± 11.47 mm) and an RWT of 0.31 ± 0.09. While our cohort included predominantly patients with HF with reduced ejection fraction, 31% of our patients had an LVEF $>$ 45% (n = 55) and 69% had an LVEF $\leq$ 45% (n = 123). Regarding the 6MWT, the mean achieved distance was 353 ± 136 m. Patients were well treated for HF in accordance with the most recent guidelines,[13,14] with 89% and 88% of beta-blocker and RAAS inhibitors, respectively.

Mean potassium level of the entire cohort was 4.6 ± 0.32 mmol/L, and the majority of patients (70.7%) had potassium levels within the normal range (*Table 2*). Patients with higher potassium levels were older and more symptomatic, as confirmed by higher NYHA class, had a higher MAGGIC score, and had a more advanced renal dysfunction (*Table 1*).

Patients were stratified by potassium levels below (126 patients) and above 4.7 mmol/L (52 patients) according to the receiver operating characteristic analysis for better accuracy, which showed that the potassium level of 4.7 mmol/L had the best area under the curve (*Figure 1*) to predict cardiovascular events. When considering the subgroups of potassium levels below and above 4.7 mmol/L, there were no significant differences on HF therapies, even when including the RAAS blockade with mineralocorticoid antagonists. Patients with K $\leq$ 4.7 mmol/L exhibited a higher percentage of patients under diuretic therapy and calcium channel blockers (*Table 1*). Additionally, patients with K $>$ 4.7 mmol/L demonstrated higher MAGGIC score, worse NYHA class, and more tobacco use — the subgroups characteristics and comparisons are displayed in *Tables 1* and *2*. There were no significant differences on 6MWT exercise parameters between the subgroups.

Moreover, in patients with higher potassium levels, the glomerular filtration rate was lower (patients with K $\leq$ 4.7 mmol/L presented 102.8 ± 32.2 mL/min/1.73 m^2 vs.

Table 1 Demographic, clinical, and echocardiogram characteristics of the study population stratified by levels of potassium (> or ≤4.7 mmol/L)

	All patients (*N* = 178)	Patients with K ≤ 4.7 (*N* = 126)	Patients with K > 4.7 (*N* = 52)	*P*-value
Demographics				
Age, years	51 ± 12.76	50.5 ± 12.7	54.3 ± 10.6	0.0616
Body mass index, kg/m^2	28.01 ± 6.73	27.69 ± 6.6	28.76 ± 7.0	0.3366
Female, %, (*N*)	39% (69)	38% (48)	40% (21)	0.8659
Clinical characteristics				
Prior history of stroke, %*, (*N*)	10% (18)	10% (13)	10% (5)	0.99
Prior history of angina, %*, (*N*)	2% (4)	3% (4)	0% (0)	0.3219
History of alcohol abuse, %*, (*N*)	17% (32)	16% (20)	23% (12)	0.2875
History of hypertension, %*, (*N*)	53% (94)	50% (63)	59% (31)	0.3216
Diabetes, %, (*N*)	25% (44)	25% (31)	25% (13)	0.98
Tobacco use, %, (*N*)	24% (43)	19% (24)	36% (19)	0.0204
Hyperlipidaemia, %, (*N*)	54% (97)	56% (71)	50% (26)	0.1691
Prior history of MI, %, (*N*)	14% (26)	16% (20)	11% (6)	0.4954
Prior history of CABG, %, (*N*)	3% (5)	2% (3)	4% (2)	0.97
NYHA class	2.45 ± 0.7	2.34 ± 0.6	2.69 ± 0.8	0.0029
NYHA Class ≥II	100% (178)	100% (126)	100% (52)	0.99
NYHA Class III	38% (60)	28% (35)	48% (25)	0.0029
MAGGIC score	12.91 ± 6.6	12.08 ± 5.7	14.9 ± 7.9	0.0089
Cardiomyopathy aetiology				
Ischaemic heart disease, %, (*N*)	15% (27)	15% (20)	13% (7)	0.09
Non-ischaemic heart disease, %, (*N*)	85% (151)	80% (106)	86% (45)	0.85
Medication				
Aspirin, %, (*N*)	11% (19)	8% (10)	17% (9)	0.1064
Calcium channel blockers, (*N*)	13% (23)	13% (16)	13% (7)	0.99
Beta-blocker, %, (*N*)	89% (159)	89% (111)	92% (48)	0.5925
Diuretics, %, (*N*)	72% (129)	73% (91)	73% (38)	0.98
Angiotensin receptor blocker, %, (*N*)	33% (59)	35% (44)	29% (15)	0.4854
Angiotensin-converting enzyme inhibitor, %, (*N*)	45% (81)	50% (62)	37% (19)	0.1366
Statin, %, (*N*)	50% (89)	51% (64)	48% (25)	0.7432
Insulin, %, (*N*)	10% (18)	10% (12)	12% (6)	0.7857
Oral antidiabetic, %, (*N*)	17% (30)	21% (26)	8% (4)	0.0462
Clopidogrel, %, (*N*)	8% (14)	8% (10)	8% (4)	0.99
Digoxin, %, (*N*)	30% (53)	28% (35)	34% (18)	0.4713
Warfarin, %, (*N*)	35% (63)	34% (43)	38% (20)	0.6098
Spironolactone	71% (128)	70% (88)	77% (40)	0.4619

CABG, coronary artery bypass graft; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; MI, myocardial infarction; NYHA, New York Heart Association.

85.42 ± 36.2 mL/min/1.73 m^2 in patients with K > 4.7 mmol/L, $P < 0.001$), without any significant differences on other laboratorial analysis. Nevertheless, there were no differences on 12-lead resting ECG parameters, with similar rates of atrial fibrillation, chambers' enlargement, or QRS duration. The main difference on echocardiographic parameters between the groups was the lower RWT in patients with higher potassium levels (K ≤ 4.7 mmol/L presented 0.32 ± 0.09 vs. 0.29 ± 0.08 in the K > 4.7 mmol/L group, $P < 0.0001$). It is important to highlight that both groups were also receiving similar modifiable HF therapies.

Univariate analyses for adverse outcomes

After a median follow-up period of 516 days (ranging from 39 to 1340 days), there were 22 major cardiovascular events, including 4 cardiovascular deaths, 13 HF admissions, and 5 heart transplants.

Univariate associations of clinical, laboratory, electrocardiographic, and echocardiogram variables with combined major cardiac events for the entire study cohort are presented in *Table 3*. As expected in HF, NYHA functional class and MAGGIC score, along with 6MWT distance, were significantly associated to worse cardiovascular outcomes. For laboratory parameters, sodium and potassium levels were strongly linked to cardiovascular events, as well as renal function (urea, creatinine, and glomerular filtration levels). There was no prognosis correlation regarding echocardiogram parameters, medication use, or ECG-derived data.

Survival by Kaplan–Meier and event rates analysis

Patients with potassium levels > 4.7 mmol/L had a significantly higher likelihood to experience adverse outcomes during the follow-up as compared with patients with

Table 2 Six-minute walking test exercise parameters, laboratorial analysis, and electrocardiogram and echocardiogram characteristics of the study population stratified by levels of potassium (> or ≤4.7 mmol/L)

	All patients (*N* = 178)	Patients with K ≤ 4.7 (*N* = 126)	Patients with K > 4.7 (*N* = 52)	*P*-value
Haemodynamics physical capacity				
Systolic blood pressure (resting), mmHg	119.2 ± 23.53	120.1 ± 23.89	117.1 ± 22.69	0.4494
Diastolic blood pressure (resting), mmHg	76.2 ± 13.6	76.8 ± 13.7	74.5 ± 13.4	0.3096
Systolic blood pressure (after 6MWT), mmHg	123.2 ± 27.7	125.5 ± 29.1	117.8 ± 23.6	0.0986
Diastolic blood pressure (after 6MWT), mmHg	77.2 ± 14.5	78.4 ± 14.9	74.3 ± 13.2	0.0928
Heart rate, b.p.m.	73.8 ± 14.9	74.5 ± 13.9	72.4 ± 17.1	0.4013
Distance in the 6 min walk test, m	353.0 ± 136	360.8 ± 137	334.0 ± 132.8	0.2330
Laboratory analyses				
Haemoglobin, g/dL	13.6 ± 1.82	13.6 ± 1.7	13.7 ± 1.8	0.8433
Sodium, mmol/L	138.1 ± 2.8	137.9 ± 3.8	137.0 ± 4.0	0.178
Potassium, mmol/L	4.6 ± 0.32	4.32 ± 0.29	5.08 ± 0.34	<0.001
Creatinine, mg/dL	1.1 ± 0.2	1.03 ± 0.4	1.34 ± 0.9	0.0036
Glomerular filtration rate, mL/min/1.73 m^2	97.62 ± 34.2	102.8 ± 32.2	85.42 ± 36.2	0.0040
Urea, mg/dL	42.5 ± 14.4	37.4 ± 13.3	53.1 ± 32.4	<0.0001
Total cholesterol, mg/dL	159.6 ± 39.3	159.4 ± 40.5	165 ± 45.5	0.4462
Triglycerides, mg/dL	130.7 ± 77.4	154.3 ± 130.6	144 ± 99.4	0.6363
LDL-cholesterol, mg/dL	86.3 ± 34.6	89.26 ± 34.7	90.40 ± 35.5	0.8574
HDL-cholesterol, mg/dL	41.5 ± 3.53	40.24 ± 10.2	35.62 ± 6.1	0.2410
Hb1Ac, %	6.69 ± 1.96	6.68 ± 1.93	6.7 ± 1.92	0.92
Glucose, mg/dL	110.4 ± 45.9	108.1 ± 48.5	120.3 ± 78.2	0.2437
Resting 12-lead electrocardiogram				
Atrial fibrillation, % (*N*)	8% (15)	13% (11)	11% (4)	0.99
QRS duration, ms	119.1 ± 37.12	116.4 ± 36.62	125.3 ± 38.05	0.233
QTc, ms	404.2 ± 60.1	401.7 ± 64.6	410.3 ± 47.8	0.4783
Left bundle branch block	38% (68)	56% (47)	58% (21)	0.8432
Right bundle branch block	1% (2)	1% (1)	3% (1)	0.5118
Q wave, % (*N*)	1% (1)	1% (1)	0% (0)	0.99
Left atrium enlargement, % (*N*)	19% (33)	28% (24)	25% (9)	0.8242
Left ventricular hypertrophy, % (*N*)	29% (52)	45% (37)	42% (15)	0.8418
Echocardiographic characteristics				
Ascending aorta, mm	2.73 ± 6.80	3.08 ± 7.06	1.80 ± 6.01	0.2772
Aortic root, mm	32.15 ± 4.34	31.93 ± 4.60	32.68 ± 3.73	0.3987
Left atrium dimension, mm	44.70 ± 8.10	44.21 ± 8.22	46.02 ± 7.80	0.2712
Left ventricular internal dimensions in systole, mm	33.96 ± 26.99	32.71 ± 26.66	37.02 ± 27.80	0.3372
Left ventricular internal dimensions in diastole, mm	64.46 ± 11.47	62.97 ± 11.19	67.01 ± 12.64	0.0857
Septal wall dimension, mm	9.52 ± 2.35	9.51 ± 2.28	9.55 ± 2.56	0.9234
Posterior wall dimension, mm	9.26 ± 2.44	6.27 ± 4.84	6.40 ± 4.62	0.8758
Relative wall thickness	0.31 ± 0.09	0.32 ± 0.09	0.29 ± 0.08	0.0832
Left ventricular ejection fraction, %	39.98 ± 15.79	40.63 ± 16.23	38.33 ± 14.64	0.3896

6MWT, 6 min walking test; Hb1Ac, haemoglobin A1c.

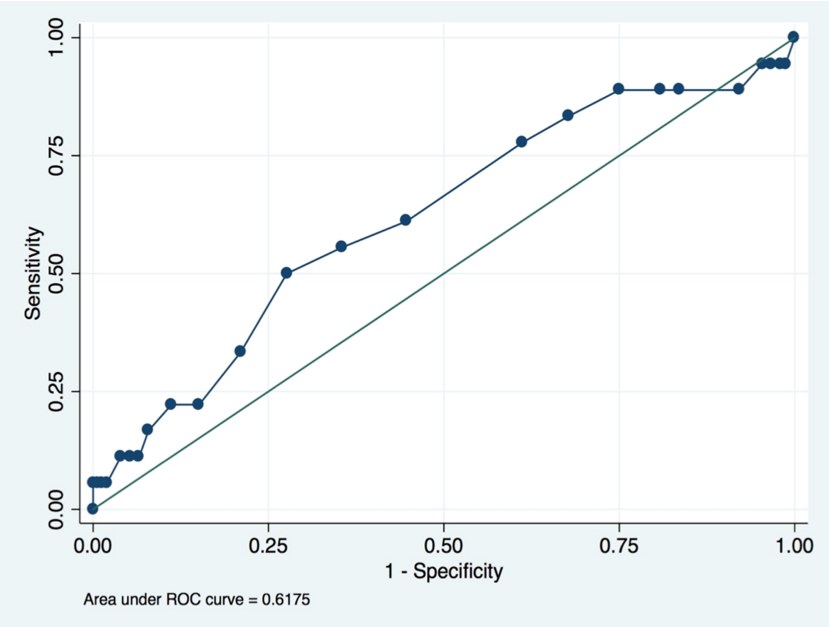
potassium levels ≤ 4.7 mmol/L (*Figure 2* demonstrates the Kaplan–Meier analysis stratified by potassium levels and MAGGIC score). Intriguingly, an analysis combining potassium levels and MAGGIC score suggested that potassium levels might offer prognostic information complementary to MAGGIC score (*Figure 2C*).

Figure 3 shows the annual event rates of adverse outcomes. Higher levels of potassium (K > 4.7 mmol/L) in either group of MAGGIC scores identified patients at a higher risk to experience adverse outcomes. While patients with HF with both high levels of potassium and MAGGIC score had an elevated annualized event rate of 15.9, patients with low levels of both K and MAGGIC had a very low annualized event rate of 1.1, highlighting the possible complementary predictive value of potassium levels in patients with symptomatic HF. Moreover, potassium levels ≤ 4.7 mmol/L along with lower MAGGIC score identified the lowest-risk group (annualized event rate of 1.1) in our cohort, which was significantly lower than the annualized event rate observed in patients with higher potassium and MAGGIC score levels (annualized event rate of 15.9, $P < 0.05$).

Multivariable analyses for adverse outcomes

After adjustments through multivariable analysis for contributing factors such as the MAGGIC score and 6MWT distance, potassium levels presented a significant association with outcomes (HR 3.57, 95% confidence interval CI 1.305–9.807, $P = 0.013$). MAGGIC score did not maintain a significant outcome prediction in this multivariate analysis (HR 1.09, 95% CI 0.996–1.200, $P = 0.06$). No other parameter included in the

Figure 1 Receiver operating characteristic (ROC) curve of the potassium levels for the outcome prediction.



multivariable model analysis other than K was significantly correlated with outcomes (age, LVEF, or 6MWT distance) (*Table 4*). Interestingly, both LVEF as a continuous variable and the presence of LVEF $>$ 45% were not associated with cardiac events (HR 0.96, 95% CI 0.931–1.005, *P* = 0.08 and HR 0.329, 95% CI 0.075–1.44, *P* = 0.14, respectively; *Table 3*). Additionally, serum potassium maintained its association with cardiovascular events even when adjusting for well-established markers of renal function, such as glomerular filtration rate and creatinine level (Supporting Information, *Tables S1* and *S2*).

We also performed a sensitivity analysis by building a multivariable Cox model including the following categorical variables: 6MWT distance (above or below 300 m), MAGGIC score (above or below 12), and potassium levels (above or below 4.7 mmol/L). Interestingly, MAGGIC score did not show any prognostic value in this analysis (HR 1.68, 95% CI 0.543–5.221, *P* = 0.367). When adding potassium levels above 4.7 mmol/L to the model as a categorical variable, this variable showed a significant association with outcomes (HR 4.109, 95% CI 1.4707–11.4849, *P* = 0.007), as well as 6MWT distance (HR 0.995, 95% CI 0.9918–0.9995, *P* = 0.029) (*Table 5*).

In order to investigate the incremental value of potassium levels, we compared the predictive power of multivariable models using Harrell's C-statistics, including MAGGIC score and 6MWT, without and with the addition of potassium levels (*Table 6*). The addition of serum K provides incremental prediction of cardiovascular events beyond established clinical variables (incremental C-statistic 0.09, *P* = 0.003). Moreover, both IDI and NRI analyses confirmed that the addition of potassium to the model including 6MWT and MAGGIC significantly improved the prediction of cardiovascular events over 2 years (IDI 0.105, 95% CI 0.018–0.281, *P* = 0.012 and NRI 0.447, 95% CI 0.077–0.703, *P* = 0.028) (*Table 6*).

Discussion

The main result of the present investigation, performed in a real-world chronic symptomatic HF cohort, was an independent association of potassium levels with combined cardiac adverse events. Moreover, potassium levels significantly improved the predictive value of prognostic models comprising MAGGIC score and 6MWT distance. Also, because serum potassium maintained its association to cardiovascular events after adjusting for renal function, its association with cardiovascular events appeared to be independent of renal function status.

Interestingly, the best accuracy prediction model showed that potassium level of 4.7 mmol/L was the best cut-off value for outcome assessment, which at our best knowledge, is a promising novel-feasible and widely available serum biomarker in symptomatic HF ambulatory population. Despite not having significant hyperkalaemia, which is an established worse prognostic factor, patients with HF in our cohort with potassium levels above 4.7 had higher likelihood to present a worse cardiovascular outcome even when potassium levels were within normal values. This result contrasts

Table 3 Univariable prognostic association with combined cardiac events

	All patients (N = 178)		
	LR χ^2 test	HR (95% CI)	P-value
Clinical characteristics			
Age, per year	0.012	1.00 (0.965–1.041)	0.91
Female	2.9254	0.34 (0.097–1.172)	0.09
Height	1.21	1.02 (0.98–1.076)	0.27
Weight	0.52	0.99 (0.964–1.017)	0.46
Body mass index, kg/m^2	1.17	0.95 (0.89–1.034)	0.27
Diabetes	1.62	0.38 (0.087–1.674)	0.20
History of hypertension	0.12	0.83 (0.312–2.254)	0.72
Hyperlipidaemia	0.46	0.67 (0.222–2.071)	0.49
Obesity	1.33	0.30 (0.04–2.296)	0.24
Prior history of stroke	2.47	2.78 (0.778–9.94)	0.11
Prior history of CABG	1.23	3.17 (0.4114–24.335)	0.26
Tabaco use	8.32	4.12 (1.574–10.788)	0.003
History of alcohol abuse	5.53	3.27 (1.22–8.807)	0.01
NYHA class	5.122	1.92 (1.092–3.393)	0.02
MAGGIC score	6.65	1.09 (1.022–1.172)	0.009
Laboratory data			
Sodium, mmol/L	10.94	0.90 (0.847–0.958)	0.0009
Potassium, mmol/L	8.30	4,26 (1.59–11.421)	0.003
Sodium/potassium	9.5	0.77 (0.663–0.913)	0.002
Potassium binary ($>$ or $\leq$4.7 mmol/L)	6.98	3.67 (1.399–09.632)	0.008
Urea, mg/dL	13.82	1.02 (1.014–1.044)	0.0002
Creatinine, mg/dL	8.56	1.83 (1.223–2.765)	0.003
Glomerular filtration rate, mL/min/1.73 m^2	8.57	0.978 (0.963–0.993)	0.0034
Total cholesterol, mg/dL	4.02	0.98 (0.974–1)	0.044
LDL-cholesterol, mg/dL	0.41	0.99 (0.98–1.01)	0.51
HDL-cholesterol, mg/dL	0.01	0.046	0.99
Triglycerides, mg/dL	0.94	0.99 (0.991–1.003)	0.33
Glucose, mg/dL	2.66	0.98 (0.963–1.004)	0.10
Hb1Ac, %	1.54	0.80 (0.568–1.135)	0.21
Haemoglobin, g/dL	1.66	0.83 (0.635–1.098)	0.19
6MWT data			
Systolic blood pressure (resting), mmHg	1.44	0.98 (0.963–1.009)	0.22
Diastolic blood pressure (resting), mmHg	0.04	0.99 (0.953–1.024)	0.50
Heart rate (resting), b.p.m.	3.15	0.97 (0.944–1.003)	0.07
Heart rate (after 6MWT), b.p.m.	0.36	0.97 (0.971–1.016)	0.54
Distance in the 6 min walk test, m	6.30	0.99 (0.993–0.999)	0.01
VO2 max (estimated)	6.28	0.77 (0.635–0.946)	0.01
Echocardiogram data			
Left ventricular internal dimensions in diastole, mm	1.57	1.03 (0.98–1.09)	0.21
Left ventricular internal dimensions in systole, mm	2.33	1.02 (0.99–1.04)	0.13
Septal wall dimension, mm	1.44	0.82 (0.597–1.131)	0.22
Posterior wall dimension, mm	0.14	1.02 (0.922–1.128)	0.70
Relative wall thickness	2.4372	0.002 (0.00–5.113)	0.12
Left ventricular ejection fraction, %	3.04	0.96 (0.931–1.004)	0.08
Left ventricular ejection fraction $>$ 45%	2.18	0.329 (0.075–1.44)	0.14
Medications			
Aspirin	0.47	1.55 (0.444–5.433)	0.49
Anti-coagulation	0.17	1.22 (0.474–3.185)	0.67
Digoxin	0.002	1.02 (0.389–2.677)	0.96
Oral antidiabetic	0.008	1.05 (0.304–3.686)	0.92
Clopidogrel	0.06	0.81 (0.182–3.679)	0.79
Insulin	0.98	1.87 (0.539–6.542)	0.32
Beta-blocker	0.97	0.46 (0.104–2.109)	0.32
Angiotensin-converting enzyme inhibitor	0.52	1.41 (0.554–3.629)	0.46
Angiotensin receptor blocker	1.04	0.57 (0.203–1.65)	0.30
12-lead resting ECG data			
Atrial fibrillation	0.15	1.36 (0.28–6.5)	0.7
Left bundle branch block	1.45	2.23 (0.604–8.28)	0.22
Right bundle branch block	3.05	6.39 (0.797–51.293)	0.08
Left ventricular hypertrophy	2.91	0.32 (0.088–1.181)	0.08
Leaf atrium enlargement	0.53	0.61 (0.167–2.271)	0.46
T inversion	0.02	0.90 (0.271–3.043)	0.87

(*Continues*)

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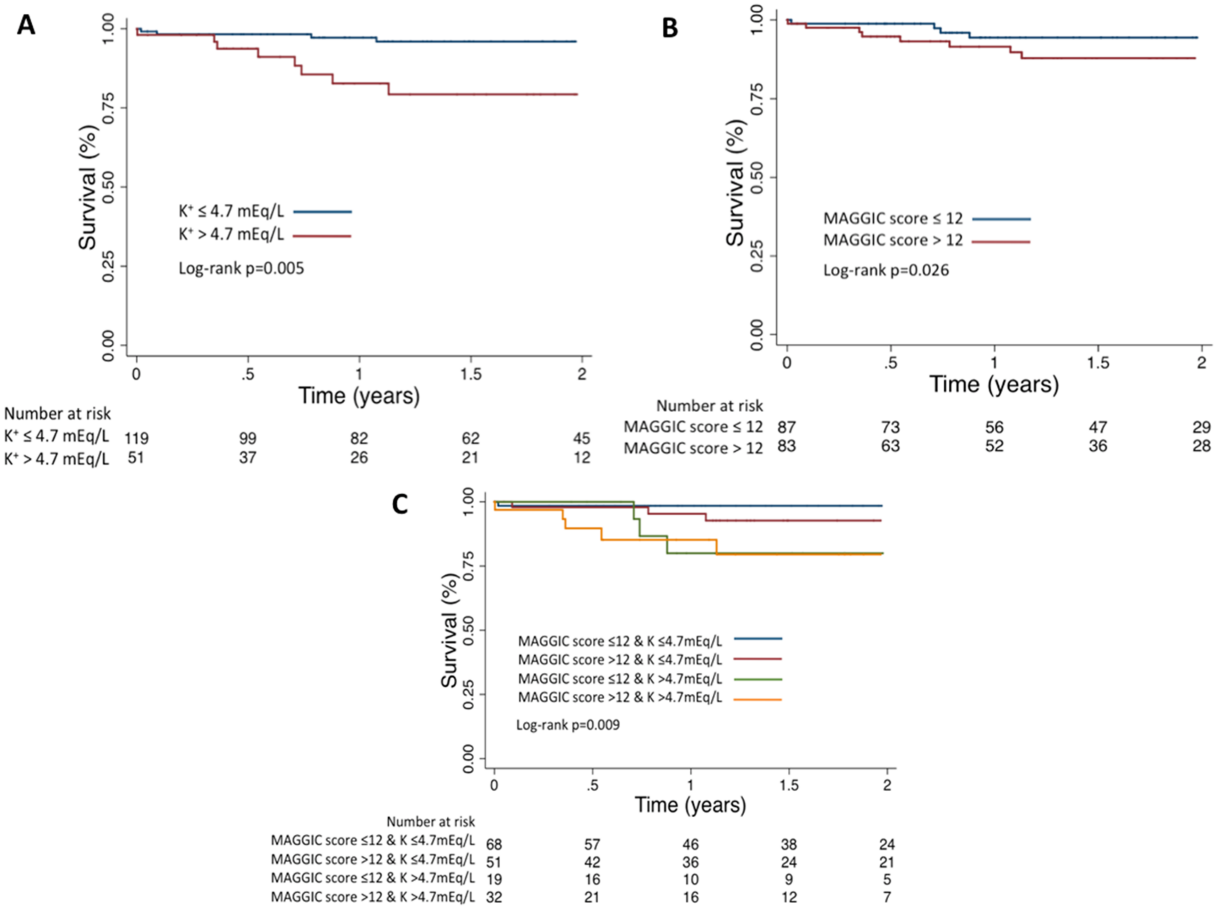
Table 3 (continued)

	All patients (N = 178)		
	LR χ^2 test	HR (95% CI)	*P*-value
ST deviation, ms	0.61	1.58 (0.502–5.006)	0.43
QRS duration, ms	2.33	1.01 (0.997–1.026)	0.005
PR duration, ms	0.20	1.00 (0.991–1.015)	0.64
Corrected QT interval, ms	7.74	1.00 (1.003–1.015)	0.005

6MWT, 6 min walking test; CABG, coronary artery bypass graft; CI, confidence interval; ECG, electrocardiogram; Hb1Ac, haemoglobin A1c; HR, hazard ratio; LR, likelihood ratio; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; NYHA, New York Heart Association.

Figure 2 The Kaplan–Meier analysis stratified by potassium levels (A), Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) score (B), and both potassium levels and MAGGIC score (C).



to other HF real-world cohorts, which showed that high-normal serum potassium levels were safe and presented an equivalent clinical outcome to normal potassium levels.[21,22]

While there are sufficient data that lower than normal potassium levels should be avoided in HF, there is no consensus on the targeted potassium levels or the upper-safety level.[21] The current study data showed that potassium levels below 4.7 mmol/L are associated with improved clinical outcomes compared with higher-normal potassium levels (above 4.7 mmol/L). When added to the lower than average MAGGIC score, the potassium below 4.7 mmol/L group identified the lowest-risk group. Also, potassium levels presented a significant and independent association with cardiac events even in patients with MAGGIC score above the cohort average. Similar to our finding, a recent cohort has concluded that the probable safest potassium interval was narrowed into 4.1–4.8 mmol/L,[23] not too low or too high potassium levels.

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Figure 3 The annual event rates of adverse outcomes in relation to Meta-Analysis Global Group in Chronic Heart Failure (MAGGIC) score and potassium levels. MACE, major cardiovascular events.

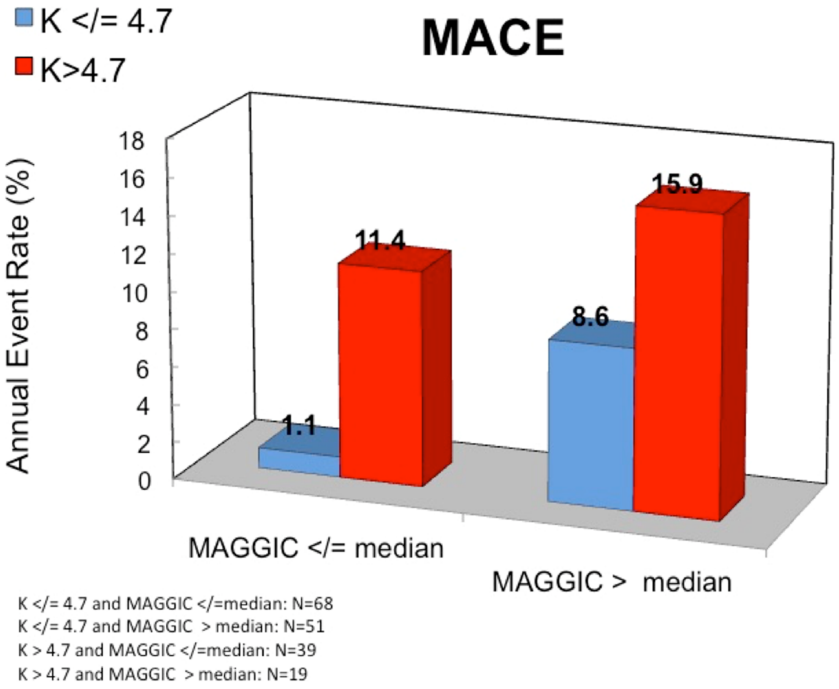

Table 4 Multivariable analysis

	LR χ2 test	HR (95% CI)	*P*-value
Potassium	6.1373	3.577 (1.305–9.807)	0.0132
MAGGIC score	3.5260	1.093 (0.996–1.200)	0.0890
Left ventricular ejection fraction	0.4250	0.985 (0.941–1.031)	0.5144
Age	1.8357	0.971 (0.931–1013)	0.1755

CI, confidence interval; HR, hazard ratio; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure.
Hazard ratio for outcome prediction including potassium levels, MAGGIC score, left ventricular ejection fraction, and age.

Table 5 Multivariable analysis for categorical variables

	HR (95% CI)	*P*-value
6MWT distance (above 300 m)	0.9956 (0.9918–0.9995)	0.029
MAGGIC score	1.68 (0.5431–5.2216)	0.367
Potassium levels (above 4.7 mmol/L)	4.109 (1.4707–11.4849)	0.007

6MWT, 6 min walking test; CI, confidence interval; HR, hazard ratio; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure.

Table 6 Incremental value of serum K in predicting cardiovascular events (cardiac death, heart failure hospitalization, and heart transplantation) beyond 6 min walking test and Meta-Analysis Global Group in Chronic Heart Failure score

Variable	C-statistic[a] (SE)	*P*-value[b]	IDI (95% CI)	*P*-value[b]	NRI (95% CI)	*P*-value[b]
Model without K: 6MWT + MAGGIC score	0.649 (0.086)	<0.001	—	—	—	—
Model with K: 6MWT + MAGGIC score + K	0.75 (0.068)	<0.001	0.105 (0.018–0.281)	0.012	0.447 (0.077–0.703)	0.028

6MWT, 6 min walking test; CI, confidence interval; IDI, integrated discrimination index; MAGGIC, Meta-Analysis Global Group in Chronic Heart Failure; NRI, net reclassification index; SE, standard error.
[a]C-statistic values were calculated considering the whole follow-up period for the composite outcome, while continuous NRI and IDI were estimated at 2 years.
[b]*P* values compared with the model containing solely clinical variables.

Additionally, our findings were not correlated with less RAAS inhibitors utilization, because there were no statistical differences on the prescribed medications between patients according to the potassium levels group (lower or higher than 4.7 mmol/L). Furthermore, these findings might bring concern for the HF outpatient treatment optimization regarding potassium, because our data suggest a possible novel threshold for potassium tolerance, independently of the MAGGIC score or 6MWT distance.

Thus, the results of the present observational, prospective study suggest that not only hyperkalaemia or hypokalaemia but also serum potassium levels above 4.7 mmol/L might be associated to adverse cardiovascular outcomes. Our results demonstrated an independent prognostic value of the potassium levels, which was additive to MAGGIC score and 6MWT distance. Whether the potassium levels were directly related to prognosis or had other confounding variables not studied in this present cohort, such as the HF severity, it demands further investigation.

Study limitations

The present study was an observational study with all the design–method-related limitations. Data regarding other ECG or echocardiogram parameters and natriuretic peptides were not available. Potassium levels were analysed at the beginning of the study and might have varied during the follow-up. Another important limitation of the current study is the small sample size, which might limit its interpretation and clinical applicability. We then tried to compensate those limitations with a prognosis-only analysis and an adjustment for clinically relevant parameters. While cardiac death was not confirmed by necropsy, typical symptoms presiding this outcome were obtained in all cases. Nevertheless, recommendations regarding lowering the threshold for alarming potassium levels cannot be done solely from the present study.

Conclusions

The study found that serum potassium levels are independently associated to worse outcomes in ambulatory patients with chronic symptomatic HF and improved the accuracy model for prognostic prediction when added to MAGGIC score and 6MWT distance. The potassium levels above 4.7 mmol/L might identify those patients at an increased risk of cardiovascular events.

Conflict of interest

C.C.T., P.V.S., L.M.S., G.S.F., F.B.C., V.C.R., L.R.P., L.M.A.C., A. C.S., J.R.M.S., R.M., W.N., L.S.F.C., and O.R.C.-F. declare no conflict of interest.

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Supporting information

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

Table S1: Multivariable analysis for outcome prediction including potassium levels, and GFR.
Table S2: Multivariable analysis for outcome prediction including potassium and creatinine level.

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