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CAMILA CRISTIANE DE TOLEDO

OS NÍVEIS SÉRICOS DE POTÁSSIO FORNECEM INFORMAÇÕES PROGNÓSTICA COMPLEMENTARES EM PACIENTES COM INSUFICIÊNCIA CARDÍACA SINTOMÁTICA ALÉM DAS VARIÁVEIS E MODELOS CLÍNICOS TRADICIONAIS

SERUM POTASSIUM LEVELS PROVIDE PROGNOSTIC INFORMATION IN SYMPTOMATIC HEART FAILURE BEYOND TRADITIONAL CLINICAL

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Dissertação apresentada à Faculdade de Ciências Médicas da Universidade Estadual de Campinas como parte dos requisitos exigidos para a obtenção do título de Mestra em Ciências, Área de Concentração em Pesquisa Clínica

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Orientador: PROF. DR. OTÁVIO RIZZI COELHO FILHO

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“Nem tudo que se enfrenta pode ser modificado, mas nada pode ser modificado até que seja enfrentado.”

Albert Einstein

RESUMO

Introdução: A Insuficiência Cardíaca (IC) é uma síndrome clínica comum, com morbidade e mortalidade significativas, a despeito dos recentes avanços no tratamento farmacológico. Os distúrbios do potássio sérico, em particular a hipercalemia, são frequentemente encontrados nos pacientes com IC e podem prejudicar o início e a titulação de terapias que melhoram a sobrevida, e estão associados com eventos adversos. Além disso os níveis séricos de potássio ideal que devem ser mantidos em pacientes com IC ainda não foram estabelecidos.

Objetivo: O objetivo desse estudo foi avaliar o impacto dos níveis séricos de potássio em uma coorte ambulatorial de pacientes com IC crônica e sintomática.

Métodos: Foram avaliados 178 pacientes com IC crônica sintomáticos encaminhados para realização de teste de caminhada de 6 minutos (TC6M). Os dados clínicos e laboratoriais foram obtidos retrospectivamente. O desfecho primário para a presente análise incluiu morte cardiovascular (CV), hospitalização por IC e transplante cardíaco.

Resultados: A idade média dos pacientes incluídos foi de 51±12,76, 39% eram mulheres, 85% apresentavam cardiomiopatia não isquêmica, 38% apresentavam classe funcional III da "*New York Heart Association*" (NYHA) e escore derivado do estudo "*The Meta-Analysis Global Group in Chronic Heart Failure score*" (MAGGIC) relativamente alto de (12,91±6,6). A média da fração de ejeção do ventrículo esquerdo foi de 39,98%±15,79% e a distância percorrida no TC6M foi de 353±136 metros. Após um acompanhamento mediano de 516 dias ocorreram 22 eventos cardiovasculares, incluindo 4 mortes CV, 13 internações por IC e 5 transplantes cardíacos. Os pacientes foram estratificados de acordo com valor de corte de potássio de 4,7mmol/kg obtido pela análise ROC para predizer eventos CV. Pacientes com níveis de potássio mais elevados apresentavam pior função renal (taxa de filtração glomerular, K≤4,7: 102,8±32,2 ml/min/1,73m^2 vs. K>4,7: 85,42±36,2 ml/min/1,73m^2, p=0,004), maior proporção de pacientes com classe III da NYHA (K≤4,7: 28% vs. K>4,7: 48%, p=0,0029) e escore MAGGIC mais elevado (K≤4,7: 12,08±5,7 vs. K>4,7: 14,9±7,9, p=0,0089), sem diferenças significativas no tratamento farmacológico basal para IC. Ambos os valores do potássio (HR=4,26; IC=1,59-11,421; p=0,003) e a distância no TC6M (HR=0,99, IC=0,993-0,999, p=0,01) foram significativamente associados com o desfecho primário. Após ajuste para outros fatores contribuintes, como o escore

MAGGIC e a distância no TC6M, os valores do potássio >4,7 mmol/L mantiveram associação significativa com os desfechos considerados (HR=3,57; IC=1,305-9,807; p=0,013). Pacientes com valores de potássio >4,7 mmol/L apresentaram maior chance para eventos CV, sendo que a adição do potássio no modelo de predição, incluindo escore MAGGIC e a distância do TC6M, melhorou significativamente a predição de eventos em 2 anos IDI = 0,105 (IC95%= 0,018-0,281), p=0,012 e NRI = 0,447 (IC95%=0,077-0,703), p=0,028).

Conclusão: Os níveis séricos de potássio estão independentemente associados a piores resultados clínicos em pacientes ambulatoriais com IC crônica sintomática e melhoram o modelo de acurácia para predição prognóstica quando incorporados ao escore de MAGGIC e a distância do TC6M. Os níveis de potássio acima de 4,7 mmol/l podem identificar aqueles pacientes com risco aumentado de eventos cardiovasculares.

Palavras Chave: Insuficiência Cardíaca; Potássio Sérico; Hipercalemia; Teste de Caminhada 6 minutos

ABSTRACT

Background: 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 levels for patients with HF are not entirely established.

Aims: We aimed to investigate the prognostic role of potassium levels on a cohort of patients with symptomatic chronic HF.

Methods: Symptomatic chronic HF patients were identified at the referral to 6-minute 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.

Results: The cohort included 178 HF patients with the mean age of 51±12.76 years, 39% were female, 85% of non-ischemic cardiomyopathy and 38% had NYHA class III with a relatively high 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 meters. After a median follow-up of 516 days, there were 22 major cardiovascular events (4 CV 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 ROC analysis. Individuals with higher potassium levels had worse renal function (Glomerular filtration rate, K≤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 NYHA class III patients (K≤4.7: 28% vs. K>4.7: 48%, p=0.0029) and also, higher MAGGIC score (K≤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 (HR=4.26, CI 1.59 -11.421, p=0.003) and 6MWT distance (HR=0.99, 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, 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 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).

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.

Key Words: Heart Failure; Potassium Levels; 6-minute walking test

LISTA DE ABREVIATURAS

ECG	Eletrocardiograma
Escore MAGGIC	*The Meta-Analysis Global Group in Chronic Heart Failure score*
FEVE	Fração de ejeção do ventrículo esquerdo
HR	*Hazard ratio*
IC	Insuficiência Cardíaca
ICFEi	Insuficiência cardíaca com fração de ejeção intermediária
ICFEp	Insuficiência cardíaca com fração de ejeção preservada
ICFEr	Insuficiência cardíaca com fração de ejeção reduzida
IDI	*Integrated Discrimination Index*
MACE	Eventos cardiovasculares maiores
NRI	*Net Reclassification Index*
NYHA	*New York Heart Association*
SRAA	Sistema Renina Angiotensina Aldosterona
TC6M	Teste de caminhada de 6 minutos
VE	Ventrículo esquerdo
K+	Potássio

SUMÁRIO

1. INTRODUÇÃO

1.1. Epidemiologia da Insuficiência Cardíaca

A insuficiência cardíaca (IC) é uma síndrome clínica caracterizada por alterações estruturais e/ou funcionais cardíacas, que resultam na redução do débito cardíaco e elevadas pressões de enchimento dos ventrículos no repouso ou no esforço (1). A IC determina um comprometimento funcional que afeta também a qualidade de vida dos indivíduos. Sintomas como dispneia, fadiga, baixa tolerância ao exercício e retenção de líquidos aparecem frequentemente durante o curso da doença, determinando grande impacto não apenas na qualidade de vida mas também no período produtivo da vida profissional dos pacientes afetados (2). Apesar dos recentes avanços terapêuticos, a IC continua sendo uma importante e crescente epidemia global, com prevalência estimada de mais de 37,7 milhões de indivíduos em todo o mundo, sendo uma das principais causas de hospitalização e morte. Nos Estados Unidos mais de 550.000 indivíduos são diagnosticados com IC todos os anos (3, 4). No Brasil, no ano de 2007, as doenças cardiovasculares representaram a terceira causa de internações no SUS, com 1.156.136 hospitalizações. A IC é a causa mais frequente de internação por doença cardiovascular, e apesar dos tratamentos disponíveis as taxas de mortalidade e hospitalizações permanecem elevadas (5, 6), ocasionando altos custos hospitalares e grandes números de atendimentos em emergência, e ainda, contribuindo para a redução da qualidade de vida e aposentadorias precoces, com altos custos para o país.(7)

1.2. Caracterização da Insuficiência Cardíaca

A síndrome da IC surge como consequência de anormalidades na estrutura, função, ritmo e condução cardíaca. A IC ocorre frequentemente em pacientes idosos que apresentam morbidades múltiplas, incluindo angina, hipertensão, diabetes entre outras. O Colégio Americano de Cardiologia (ACC) e a Associação Americana de Cardiologia (AHA) definem a IC como uma síndrome clínica complexa que resulta de qualquer comprometimento estrutural ou funcional do enchimento ventricular ou da ejeção de sangue (8, 9). Os principais mecanismos

patogênicos envolvidos na IC incluem a ativação do sistema nervoso simpático e renina angiotensina aldosterona, as alterações hemodinâmicas comumente encontradas envolvem resposta inadequada do débito cardíaco e elevação das pressões pulmonar e venosa sistêmica, em resposta a realização de atividade física. O diagnóstico da IC é essencialmente clínico, sendo mandatório a realização de uma história clínica detalhada, exame físico e eventualmente realização de testes de diagnósticos adicionais (6, 10).

O sistema de classificação da IC mais utilizado na prática clínica é o da *New York Heart Association* (NYHA), que foi originalmente descrito em 1928 e atualizado em 1994, se consolidando como um método de avaliação prático com base na intensidade dos sintomas(11). Esta classificação estratifica o grau de limitação imposto pela doença para atividades cotidianas dos indivíduos com IC (6). Segundo essa classificação, os indivíduos com IC são estratificados em quatro classes: classe I - ausência de sintomas durante atividades cotidianas; classe II - sintomas desencadeados por atividades cotidianas; classe III - sintomas desencadeados em atividades menos intensas que as cotidianas; classe IV - sintomas em repouso(12). Enquanto a classificação segundo a NYHA valoriza a capacidade funcional para o exercício, a classificação por estágios da IC proposta pela ACC/AHA enfatiza o desenvolvimento e a progressão da doença. Esta última classificação inclui desde o paciente que apresenta apenas fatores de risco para desenvolver IC, cuja abordagem deve ser feita no sentido de prevenção. Por outro lado pacientes em estágios mais avançado da doença, podem necessitar de terapias específicas para IC, tais como transplante cardíaco ou dispositivos de assistência ventricular (13).

Em 2016 a Sociedade Europeia de Cardiologia (ESC) introduziu uma nova classificação para IC, a terminologia usada para classificação da IC que se baseia na fração de ejeção do ventrículo esquerdo (FEVE), sendo FEVE ≤ 40% IC de fração de ejeção reduzida (ICFEr), ≥40 e ≤49% IC de FEVE intermediária (ICFEi), e FEVE ≥ 50% IC de fração de ejeção preservada (ICFEp) (14). Sendo assim, a determinação da fração de ejeção (FE) é considerada importante etapa para pacientes com IC, uma vez que pode determinar estratégias de tratamentos diferentes (15, 16).

A ICFEr é caracterizada pela redução da contratilidade do ventrículo esquerdo (VE) e costuma ser acompanhada pela dilatação do VE. Por outro lado o diagnóstico da ICFEp é baseado em sinais e sintomas típicos de IC em pacientes

com FEVE preservada, predominando as anormalidades no relaxamento diastólico do VE, assim como, da complacência das câmeras cardíacas associado com aumento das pressões do VE (17, 18). Tanto os pacientes com ICFEr, quanto ICFEp, apresentam limitações funcionais e baixa qualidade de vida, sendo que os desfechos clínicos de ambos os fenótipos de IC (ICFEp e ICFEr) são semelhantes, incluindo morbidade hospitalar e re-intenações hospitalares, assim como mortalidade. (18)

Mais recentemente, um outro escore que quantifica a probabilidade de sobrevida IC foi desenvolvido dando origem ao escore de MAGGIC (Grupo Global de Meta-análise em Insuficiência Cardíaca Crônica)(19). Este escore de risco foi desenvolvido para oferecer uma oportunidade abrangente de avaliação do risco de eventos em pacientes com IC. Interessantemente, esse escore fornece dados prognósticos para pacientes com IC, tanto com FEVE reduzida, quanto preservada. No seu desenvolvimento foram compilados dados disponíveis de 39372 pacientes provenientes de cerca 30 estudos para obtenção da pontuação que quantifica prontamente o risco de mortalidade individual dos pacientes com IC(19). Assim, estabeleceu-se um escore de risco para prever a mortalidade em pacientes com IC, incluindo 13 características comuns encontradas em pacientes com IC. Além disso, vale salientar que esse escore é facilmente implementado, uma vez que depende de variáveis amplamente disponíveis ou de fácil obtenção na prática clínica de pacientes com IC (20). Evidências indicam que a hipercalemia pode identificar indivíduos com IC sob o maior risco de desenvolver eventos cardiovasculares maiores (MACE), mesmo após o ajuste para múltiplas variáveis, como doença renal crônica e uso de bloqueadores do receptor de angiotensina tipo 1 (BRAs), inibidores da enzima conversora de angiotensina (IECAs), e bloqueadores dos receptores de aldosterona. Apesar disso, até o momento existem poucos dados publicados que avaliaram o impacto incremental da hipercalemia no escore de MAGGIC.

1.3. Importância Clínica dos Valores do Potássio

O potássio (K) é o cátion mais abundante em humanos, 98% é intracelular e 2% é extracelular. A ingestão de potássio em uma dieta típica é de 60 a 100 mEq/dia, 10% dessa quantidade é excretada nas fezes, muito pouca é excretada pelo o suor e o restante acaba sendo excretado na urina. O potássio é essencial para

diversas funções celulares normais e as alterações na regulação do potássio sérico podem levar a anormalidades neuromusculares, gastrointestinais e cardíacas (21, 22). Alimentos são as principais fontes de ingestão de potássio e as maiores quantidades de potássio são encontradas em frutas legumes e carnes, no entanto, algumas fontes de potássio vem dos substitutos do sal e suplementos nutricionais. A ingestão de elevadas quantidades de potássio pode causar hipercalemia, especialmente se a excreção renal de potássio estiver significativamente reduzida.(23)

O potássio é de extrema importância para manter a função celular, uma vez que todas as células possuem uma bomba de Na–K ATPase que transporta de forma ativa o sódio (Na+) para o exterior da célula e o K+ para o interior, mantendo as concentrações iônicas no meio intra e extracelular (24). Para manter a homeostase iônica é necessário manter constante a excreção de potássio pela urina. No rim, o potássio é filtrado pelo glomérulo e reabsorvido ao longo do túbulo contorcido proximal e da alça ascendente espessa de Henle (Figura 1). Assim, menos de 10% da carga filtrada de potássio chega ao início do túbulo distal renal, principal sítio para o ajuste fino da homeostase do potássio, sendo a chave da homeostase de potássio a função renal (25, 26)

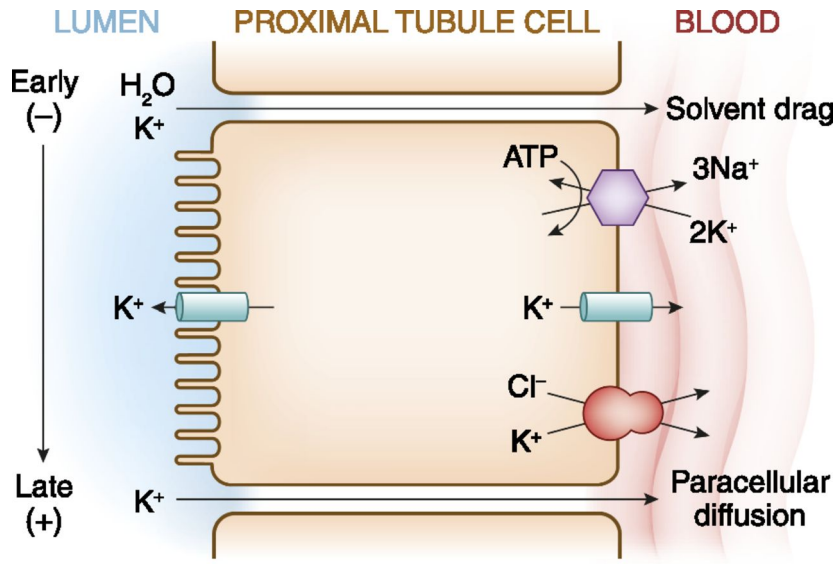

Figura 1: Modelo celular para o transporte de potássio pela alça ascendente espessa de Henle (Reproduzido de Palmer, 2015 (27)).

1.4. Valor Prognóstico do Potássio Sérico

Os distúrbios de potássio são relativamente comuns (28). A hipocalemia e hipercalemia são anormalidades eletrolíticas importantes, podendo contribuir para o aparecimento de arritmias cardíacas e aumentar o risco de morte, principalmente com pacientes com doenças cardiovasculares e renais (28). A hipocalemia se caracteriza quando a concentração de potássio sérico está abaixo de 3,5 mmol/L e costuma estar presente em situações com redução na ingesta de potássio, com aumento da translocação de potássio para o espaço intracelular, ou situações que aumentem as perdas de potássio pela urina, trato gastrointestinal e suor levando uma redução no potássio sérico (29). Os principais sintomas decorrem de alterações na polarização das membranas celulares que afetam a função dos tecidos neural e muscular, podendo levar à arritmias potencialmente fatais (30).

A hipercalemia geralmente é definida com nível de potássio sanguíneo acima de 5,0 mmol/L. Além de muito prevalente em pacientes com doença renal crônica (DRC), diabetes mellitus (DM) e IC, é uma causa comum para hemodiálise de emergência e também está associada ao aumento de risco de morte súbita (31). Os sintomas clínicos são inconstantes e inespecíficos, como fadiga e fraqueza muscular, podendo causar arritmia e parada cardíaca sem sinais prévios (25, 32). Os pacientes com IC experimentam pelo menos uma ocorrência de hipercalemia dentro de um ano (15)

1.5. Relação da Insuficiência Cardíaca e Potássio Sérico

Distúrbios séricos de potássio são frequentemente encontrados em pacientes com IC, estando comumente associados com algumas morbidades e com uso de medicamentos como terapia diurética, suplementos de potássio e bloqueadores do sistema renina-angiotensina-aldosterona, como os IECAs, BRAs, e a combinação de BRA e inibidores da neprisilina (33). A terapia com IECA ou BRA reduz a mortalidade por todas as causas em 15-30% em pacientes com IC crônica com ICFEr , sendo um dos principais componentes do tratamento de ICFEr (34). O tratamento com IECA pode aumentar os níveis de potássio (K), sendo que a hipercalemia induzida pela IECA muitas vezes limita o uso dessas drogas, reduzindo assim, seus benefícios na IC. Em pacientes hipertensos sem fatores de risco para

hipercalemia, a incidência de hipercalemia com terapia com IECA é menor que 2% e aumenta para 5% com inibição dupla e para 5 a 10% quando a terapia dupla é administrada em pacientes com IC ou doença renal crônica [18].

A espironolactona (antagonista dos receptores de aldosterona) é um diurético poupador de potássio, que constitui uma importante ferramenta terapêutica no tratamento da ICFEr. O estudo RALEs (35) que investigou o efeito da espironolactona em 1663 pacientes com ICFEr com classe funcional avançada, demonstrou que o uso de um antagonista da aldosterona reduziu em 30% o risco de morte, sendo que essa foi devido à redução de morte por progressão da IC e morte súbita. Além disso, a frequência de hospitalizações também apresentou redução significativa com o uso da espironolactona (risco relativo de hospitalização, HR=0,65; IC=95 0,54 - 0,77; P<0,001). Por fim, a espironolactona também influenciou favoravelmente os sintomas de IC, avaliado pela melhora da classe funcional da NYHA (p<0,0001). Apesar do que foi exposto, a espironolactona pode causar além da ginecomastia, efeito “colateral” indesejável em homens, é a hipercalemia, condição com consequências sérias que ocorre com frequência nos pacientes com IC, principalmente quando o paciente apresenta disfunção renal.

Um estudo populacional realizado no Canadá, após a publicação do estudo RALES, confirmou que a ocorrência de um aumento significativo da utilização da espironolactona, que era de 34 por 1000 pacientes em 1994, e aumentou para 149 por 1000 pacientes no final de 2001 (36, 37). Nesse estudo as hospitalizações por hipercalemia também aumentaram de 2,4 casos por 100 pacientes em 1994, para 11 casos por 100 pacientes em 2001 (P<0,001), com aumento da mortalidade associada à hipercalemia de 0,3 para 2,0 por 1000 pacientes (P<0,001). Esse estudo concluiu que a publicação do estudo RALES determinou um aumento expressivo da prescrição de espironolactona, com consequente aumento de eventos clínicos relacionados com a hipercalemia, sugerindo que a monitorização cuidadosa dos níveis potássio é fundamental para evitar eventos adversos, sobretudo em indivíduos com risco de hipercalemia.

A hipercalemia pode ser uma preocupação em pacientes com IC na prática clínica cotidiana. Dados recentes mostram associações da hipercalemia com o aumento da mortalidade em pacientes com IC, assim como, em pacientes internados por descompensação clínica (38). Diversos dados evidenciam que a hipercarlemia

pode induzir arritmias ventriculares, cursando com palpitações, tonturas, síncope e até mesmo morte súbita, no entanto, pode ser frequentemente detectada em uma amostra de sangue de rotina, e facilmente tratada na rotina clínica (39). A ocorrência de hipercalemia difere entre pacientes internados e ambulatoriais, estando presente em 2-4% da população em geral e em 10-55% dos pacientes hospitalizados. Na prática clínica a hipercalemia ocorre em até 73% dos pacientes com DRC avançada e em até 40% dos pacientes com IC crônica (23).

Apesar das evidências supracitadas, ainda é escasso o conhecimento sobre a ocorrência de hipercalemia e os desfechos associados em pacientes com IC (38). A hipercalemia é um evento frequentemente observado e potencialmente perigoso em pacientes com IC e tem sido identificada como um dos principais problemas de gestão médica desses pacientes (5, 25). Alguns ensaios clínicos importantes mostraram as implicações prognósticas da hipercalemia, por exemplo, em uma análise do estudo RALES os níveis de potássio >5,5 mmol/L foram associados ao risco de morte, já no ensaio TOPCAT o mesmo valor de potássio foi associado a um aumento de 1,7 vezes no risco relativo de morte. (21, 40, 41)

2. OBJETIVOS

Objetivo principal

O objetivo do presente estudo foi avaliar o valor prognóstico dos níveis do potássio sérico em pacientes com IC sintomática, euvolêmicos, e em tratamento ambulatorial otimizado pra IC, de acordo com as últimas diretrizes brasileiras (2).

Objetivos específicos

1. Comparar o valor prognóstico dos níveis do potássio sérico com as demais variáveis clínicas disponíveis.
2. Avaliar se os níveis do potássio sérico são capazes de reclassificar o risco para eventos cardiovasculares em pacientes com IC sintomática.
3. Avaliar se os níveis do potássio sérico oferecem dados prognósticos complementares ao escore MAGGIC e ao TC6M.

3. MÉTODOS E RESULTADOS

Os resultados da presente dissertação serão apresentados através do seguinte artigo:

i. "*Serum Potassium Levels Provide Prognostic Information in Symptomatic Heart Failure Beyond Traditional Clinical Variables*", submetido para publicação no periódico indexado de língua inglesa *ESC Heart Failure (Online ISSN:2055-5822, Impact factor:3.902),* estando atualmente em revisão (Ms. No. ESCHF-20-01177).

View Letter

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Date: 20 Feb 2021
To: "Otavio Coelho-Filho" tavicocoelho@gmail.com
From: "Gabor Foldes" g.foldes@imperial.ac.uk
Subject: ESCHF: Your manuscript entitled Serum Potassium Levels Provide Prognostic Information in Symptomatic Heart Failure Beyond Traditional Clinical Variables

Ref.: Ms. No. ESCHF-20-01177R1
Serum Potassium Levels Provide Prognostic Information in Symptomatic Heart Failure Beyond Traditional Clinical Variables
ESC Heart Failure

Dear Dr. Coelho-Filho,

I am writing to say that your manuscript, Serum Potassium Levels Provide Prognostic Information in Symptomatic Heart Failure Beyond Traditional Clinical Variables, has now been accepted for publication in the ESC Heart Failure. It will appear in the next available issue.

Thank you for submitting your excellent article to ESC Heart Failure.

Yours sincerely,

Gabor Foldes
Editor-in-Chief
ESC Heart Failure

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Please be aware that if you ask to have your user record removed, we will retain your name in the records concerning manuscripts for which you were an author, reviewer, or editor.

ESC Heart Failure

Serum Potassium Levels Provide Prognostic Information in Symptomatic Heart Failure Beyond Traditional Clinical Variables

--Manuscript Draft--

Manuscript Number:	ESCHF-20-01177R1
Full Title:	Serum Potassium Levels Provide Prognostic Information in Symptomatic Heart Failure Beyond Traditional Clinical Variables
Article Type:	Original Research Article
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Abstract:	Background : 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 levels for patients with HF are not entirely established. Aims : We aimed to investigate the prognostic role of potassium levels on a cohort of patients with symptomatic chronic HF .. Methods : Symptomatic chronic HF patients were identified at the referral to 6-minute 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. Results: The cohort included 178 HF patients with the mean age of 51±12.76 years,

	39% were female, 85% of non-ischemic cardiomyopathy and 38% had NYHA class III with a relatively high 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 meters. After a median follow-up of 516 days, there were 22 major cardiovascular events (4 CV 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 ROC analysis. Individuals with higher potassium levels had worse renal function (Glomerular filtration rate, K≤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 NYHA class III patients (K≤4.7: 28% vs. K>4.7: 48%, p=0.0029) and also, higher MAGGIC score (K≤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 (HR=4.26, CI 1.59 - 11.421, p=0.003) and 6MWT distance (HR=0.99, 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, 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 (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). 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.
Response to Reviewers:	Manuscript Number: Ms. No. ESCHF-20-01177 Manuscript Title: Serum Potassium Levels Provide Prognostic Information in Symptomatic Heart Failure Beyond Traditional Clinical. We thank the reviewers and editors for carefully examining our manuscript and providing us with valuable feedback. We appreciate the thoughtful comments and suggestions from the editor and the reviewers. We have addressed each of these comments below and have modified the manuscript accordingly. We feel that these revisions have added clarification and strengthened our manuscript, and we hope that you will agree that this manuscript will be of value to your readers and that it meets full criteria for publication in the ESC-HF Journal. Please find attached our point-by-point response to the reviews. The reviewers' comments are italicized, and each point is then followed by our reply, including details on how the manuscript was changed. In addition, we reviewed the manuscript for compliance with the journal's style requirements. Editor comments: Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. We would consider it again if you could respond to the points that have been raised during the review process. Response: Thank you very much for this encouraging comment! When revising your work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Please make all changes in red and bold font (If you utilize the Track Changes for Word please accept all changes before saving). Please note that you should ensure the revised manuscript is complete, ie. it should include THE FULL TEXT, TITLE PAGE, ABSTRACT, ALL FIGURES, ALL TABLES AND LEGENDS. As this may be the finally accepted version to be sent to the type-setters you should ensure the figures are print quality and you should proof-read and check the quality of all components of the paper after it has been up-loaded. Response: Thank you for these comprehensive clarifications. We have addressed each of these comments and have modified the manuscript accordingly. Please find attached our point-by-point response to the reviews. The reviewers' comments are italicized, and each point is then followed by our reply, including details on how the manuscript was changed. In addition, we reviewed the manuscript for compliance with the journal's style requirements. Editorial Office comments: The authors are required to pay particular attention to preparing their abstract as this is

a reflection of their work and may be the only part that is read by some readers. Abstracts should be prepared in accordance with author guidelines. Authors are encouraged to check their abstract again whether the key messages are presented including important facts and figures, standard deviations and p-values supporting these messages. If in doubt, add more data rather than less. Please omit all "filling words" used for style such as "thus", "therefore", "moreover" and the like. In addition, we ask you to pay particular attention for the abstract to be straight and to the point as well as in a correct English. Editors will check the abstract quality prior to final acceptance and may ask the authors to adjust according to the above criteria.
Response: We have revised the current manuscript to meet ESC-HF journal's style requirements. The revised Abstract is now divided into the following sections 'Aims', 'Methods', "Results' and 'Conclusions' respecting the limit of 400 words. We have also excluded the condensed abstract since it was not required. All modifications were highlighted using track changes.

Reviewer #1:
1) Dear Authors, I have read with interest your paper and I think it's complete and exhaustive but I think you have two issues to confirm:
Response: Thank you very much not only for the positive and encouraging comments, but also for the helpful suggestions below, highlighting all aspects requiring revision and improvements!
2) What about chronic kidney disease people.
Response: We completely agree with the reviewer that chronic kidney disease is a very relevant comorbidity in HF patients having recognized prognostic implications. In our study, the mean glomerular filtration rate (GFR) and the mean creatinine level were within the normal range (97.62±34.2mL/min/1.73 m2 and 1.1±0.2 mg/dL, respectively). While the entire cohort of our patients had an apparently normal renal function, patients with higher serum potassium, stratified by the serum potassium>4.7, demonstrated a significant reduced GFR (K≤4.7 mmol/L: 102.8±32.2 mL/min/1.73m2 vs. K>4.7: 85.42±36.2 mL/min/1.73m2, p=0.004) and increased creatinine levels (K≤4.7: 1.03±0.4 vs. K>4.7: 1.34±0.9, p=0.0036) as displayed in the Table 2 of the current manuscript. As expected and in accordance with the prior literature(1-4), including two well-designed meta-analysis(5, 6), both GFR and serum creatinine were highly associated with cardiovascular events in the present study (GFR: HR 0.978, CI 0.963- 0.993, p=0.0034 and creatinine level: HR 1.83, CI 1.223-2.765, p=0.003, Table 3 of the current manuscript).
In order to investigate whether serum potassium would provide complementary prognostic information to renal function, we built two multivariable models, including serum potassium and GFR (Model 1) and another model including serum potassium and creatinine levels (Model 2).
Model 1: Multivariable analysis for outcome prediction including potassium levels, and GFR.

	Chi-square	HR (95% CI)	p-value
Potassium, mmol/L	5.4077	3.076 (1.193 – 7.929)	0.02
Glomerular filtration rate, mL/min/1.73 m2	6.1949	0.981 (0.966 – 0.996)	0.0128

Model 2: Multivariable analysis for outcome prediction including potassium and creatinine level.

	Chi-square	HR (95% CI)	p-value
Potassium, mmol/L	5.1867	3.223 (1.177 – 8.825)	0.0228
Creatinine, mg/dL	3.8386	1.543 (1.00 – 2.380)	0.051

Both models 1 and 2 confirmed that serum potassium offered additional prognostic data over 2 well-established markers of renal function (GFR and creatinine levels). While we have to acknowledge that the current study has a relatively small sample size, imposing caution to its interpretation, these additional multivariable models confirmed that serum potassium might provide further prognostic data beyond renal function.
Although the current number of events (n=22) limits our ability to build more complex multivariable models, we decided also to construct an exploratory multivariable model, including potassium, creatinine and GFR (Model 3). Interestingly, even including two collinear variables of renal function (creatinine and GFR), serum potassium still maintained its significant association with outcomes.

Model 3: Multivariable analysis for outcome prediction including potassium, creatinine levels and GFR.

	Chi-square	HR (95% CI)	p-value
Potassium	5.4026	3.129 (1.196 – 8.185)	0.0201
Glomerular filtration rate, mL/min/1.73 m2	3.0953	0.979 (0.957 – 1.002)	0.079
Creatinine, mg/dL	0.0383	0.930 (0.447 – 1.933)	0.845

Although Model 3 brings some interesting and insightful information, we believe that this model is not suitable to be included in the current manuscript because GFR and/or creatinine are collinear variables. Moreover, we also consider inadequate to include GFR or creatinine in multivariable models including MAGGIC-score as it already comprises renal function as one of the covariates of this score (creatinine level) (7). According to the reviewer suggestion, we have added to the revised manuscript multivariable models 1 and 2, which explore the interaction between serum potassium and renal function. The following statement was also added to the Results section to highlight the fact that serum potassium was associated with cardiovascular events regardless of renal function.
“Serum potassium maintained its association to cardiovascular events even when adjusting for well-established markers of renal function, such as GFR and creatinine levels (Supplemental Online Tables 1 and 2)”.
Finally and in accordance with the reviewer comment we have also included the following sentence to the first paragraph of the Discussion:
“Also, since 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.”

3) Have you performed any ECG Holter?.
Response: We thank you the reviewer for this constructive comment! Unfortunately ECG Holter monitoring was available only in a minority of patients in our cohort (~20%), making unfeasible any analysis using this variable.

Reviewer #2:
1) In this study Toledo et al. prospectively evaluated 178 HF patients referred for 6-min walking test, and concluded that serum K greater than 4.7 mEq/L had the best discriminative power to predict subsequent adverse CV outcome. The paper is original and conclusions of interest.

Response: Thank you very much for the positive and supportive comments!

Major points:
2) Criteria for patient enrolment should be more clearly explained. In the conclusion AA refer to HFrEF patients, whereas baseline EF was 40±16 %, thus suggesting that at least a part of patients could suffer from HFpEF. Furthermore, in the Methods section, the AA stated that stage C HF patients were considered eligible. Please clarify in a better way criteria for patients enrolment, throughout the entire paper.
Response: Thank you for bringing this important point and to highlighting this oversight! As underlined by the reviewer, our cohort of patients included predominantly HF patients with reduced ejection fraction (HFrEF) but as pointed based on the reported mean LVEF of 39.98% ±15.79%, it is clear that a proportion of our cohort comprised HF patients with preserved ejection fraction (HFpEF). Although the ideal LVEF cut-point to define HF with preserved ejection fraction (HFpEF) is still under debate, a recently published clinical trial investigating the effect of an angiotensin receptor-neprilysin inhibition in patients with HFpEF (PARAGON-HF; ClinicalTrials.gov number, NCT01920711) enrolled individuals with a LVEF > 45%(8). Using the same criteria as the PARAGON-HF trial for HFpEF (LVEF > 45%), we found that 31% of our patients had a LVEF > 45% (n=55) and 69% had a LVEF </=45% (n=123) (Figure 1).

Figure 1: Proportion of patients with HFrEF and HFpEF (Figure 1 is available in the attached document).

	While the mean LVEF among individuals with LVEF</=45% was 30.78±8.01%, the mean LVEF in the group with LVEF > 45% was 59.77±8.37%. As showed in the Table 3 of the current manuscript (Table 3. Univariable Prognostic Association With Combined Cardiac Events), LVEF was not significantly associated with outcomes (LVEF as a continuous variable; LR Chi-square Test 3.04, HR 0.96, CI 0.931-1,005, p=0.08). Interestingly, the presence of LVEF > 45% was also not significantly associated with cardiac events (LVEF > 45%; LR Chi-square Test 2.18, HR 0.329, CI 0.075-1.44, p=0.14). We have decided to add the variable LVEF > 45% in the Table 3 of the revised manuscript. According to the reviewer suggestion, we have updated the inclusion criteria to improve its clarity and interpretation as follows: “The eligibility criteria included symptomatic HF patients (stage C HF with a NYHA class II or III) at age between 18 and 75 years receiving optimized guideline-based HF therapy“ We have also included the following statements in the Results section regarding the question about HFpEF. “While our cohort included predominantly patients with HFrEF, 31% of our patients had a LVEF > 45% (n=55) and 69% had a LVEF </=45% (n=123).” “Interestingly, both LVEF as a continuous variable and the presence of LVEF > 45% was not associated with cardiac events (HR 0.96, CI 0.931-1,005, p=0.08 and HR 0.329, CI 0.075-1.44, p=0.14, respectively, Table 3).” 3) How many samples were performed for estimating s-K levels for each patient? This is a crucial point, since a cut-off value of 4.7 mEq/L, and not a wider s-K range, resulted predictive of adverse CV outcome. Response: We thank the reviewer for raising this pertinent question. We have used a single sample of serum potassium obtained that was matched with the 6MWT. We have updated this information in the manuscript. 4) Interestingly, in the group with s-K lower than 4.7 mEq/L, greater eGFR was shown. Have the AA explored any interaction of eGFR with s-K in predicting CV outcome? Response: We thank the reviewer for this opportunity to further explore the interaction of GFR and serum potassium levels. We have performed additional analysis, including 3 new multivariable models, to investigate this important interaction. Serum potassium has maintained its significant association with outcome even after adjustments to baseline renal function markers (GFR and creatinine levels), suggesting that serum potassium may offer complementary prognostic data to renal function in HF patients. Please refer to our answer to question #2 of reviewer #1. Response to question #2 of reviewer #1: We completely agree with the reviewer that chronic kidney disease is a very relevant comorbidity in HF patients having recognized prognostic implications. In our study, the mean glomerular filtration rate (GFR) and the mean creatinine level were within the normal range (97.62±34.2mL/min/1.73 m2 and 1.1±0.2 mg/dL, respectively). While the entire cohort of our patients had an apparently normal renal function, patients with higher serum potassium, stratified by the serum potassium>4.7, demonstrated a significant reduced GFR (K≤4.7 mmol/L: 102.8±32.2 mL/min/1.73m2 vs. K>4.7: 85.42±36.2 mL/min/1.73m2, p=0.004) and increased creatinine levels (K≤4.7: 1.03±0.4 vs. K>4.7: 1.34±0.9, p=0.0036) as displayed in the Table 2 of the current manuscript. As expected and in accordance with the prior literature(1-4), including two well-designed meta-analysis(5, 6), both GFR and serum creatinine were highly associated with cardiovascular events in the present study (GFR: HR 0.978, CI 0.963- 0.993, p=0.0034 and creatinine level: HR 1.83, CI 1.223-2.765, p=0.003, Table 3 of the current manuscript). In order to investigate whether serum potassium would provide complementary prognostic information to renal function, we built two multivariable models, including serum potassium and GFR (Model 1) and another model including serum potassium and creatinine levels (Model 2). Model 1: Multivariable analysis for outcome prediction including potassium levels, and

GFR.

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Model 2: Multivariable analysis for outcome prediction including potassium and creatinine level.

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Potassium, mmol/L	5.1867	3.223 (1.177 – 8.825)	0.0228
Creatinine, mg/dL	3.8386	1.543 (1.00 – 2.380)	0.051

Both models 1 and 2 confirmed that serum potassium offered additional prognostic data over 2 well-established markers of renal function (GFR and creatinine levels). While we have to acknowledge that the current study has a relatively small sample size, imposing caution to its interpretation, these additional multivariable models confirmed that serum potassium might provide further prognostic data beyond renal function.

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According to the reviewer suggestion, we have added to the revised manuscript multivariable models 1 and 2, which explore the interaction between serum potassium and renal function. The following statement was also added to the Results section to highlight the fact that serum potassium was associated with cardiovascular events regardless of renal function.

“Serum potassium maintained its association to cardiovascular events even when adjusting for well-established markers of renal function, such as GFR and creatinine levels (Supplemental Online Tables 1 and 2)”.

Finally and in accordance with the reviewer comment we have also included the following sentence to the first paragraph of the Discussion:

“Also, since 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.”

5) In the Result section (subheading Baseline evaluation and ….) the AA stated that "Moreover, in patients with higher K levels, the glomerular filtration rate tended to be lower despite having higher urea levels…" (?) Please clarify, since lower eGFR is almost always associated with higher urea level, as an expression of reduced renal function.

Response: Thank you to underlining this oversight! We totally agree with the reviewer’s point of view about the association of GFR and levels of serum urea. We have revised the above-mentioned statement and we eliminated urea levels as follows:

"Moreover in patients with higher potassium levels, the glomerular filtration rate was lower (patients with K≤4.7 mmol/L presented 101.7±32.7 mL/min/1.73m2 vs. 85.4±36.9 mL/min/1.73m2 in patients with K>4.7 mmol/L, p<0.001), without any other significant

	differences on other laboratorial analysis" 6) The small sample size should be acknowledged as a limitation in the "Study Limitations" section. Response: We thank the reviewer for this constructive observation. We have added the follow sentence to Limitation section: “Another important limitation of the current study is the small sample size, which may limit its interpretation and clinical applicability.” References: 1.Dries DL, Exner DV, Domanski MJ, Greenberg B, Stevenson LW. The prognostic implications of renal insufficiency in asymptomatic and symptomatic patients with left ventricular systolic dysfunction. Journal of the American College of Cardiology. 2000 Mar 1;35(3):681-689. 2.Hillege HL, Girbes AR, de Kam PJ, Boomsma F, de Zeeuw D, Charlesworth A, Hampton JR, van Veldhuisen DJ. Renal function, neurohormonal activation, and survival in patients with chronic heart failure. Circulation. 2000 Jul 11;102(2):203-210. 3.Smilde TD, Hillege HL, Navis G, Boomsma F, de Zeeuw D, van Veldhuisen DJ. Impaired renal function in patients with ischemic and nonischemic chronic heart failure: association with neurohormonal activation and survival. American heart journal. 2004 Jul;148(1):165-172. 4.Damman K, Voors AA, Navis G, van Veldhuisen DJ, Hillege HL. The cardiorenal syndrome in heart failure. Progress in cardiovascular diseases. 2011 Sep-Oct;54(2):144-153. 5.Damman K, Valente MA, Voors AA, O'Connor CM, van Veldhuisen DJ, Hillege HL. Renal impairment, worsening renal function, and outcome in patients with heart failure: an updated meta-analysis. European heart journal. 2014 Feb;35(7):455-469. 6.Damman K, Navis G, Voors AA, Asselbergs FW, Smilde TD, Cleland JG, van Veldhuisen DJ, Hillege HL. Worsening renal function and prognosis in heart failure: systematic review and meta-analysis. Journal of cardiac failure. 2007 Oct;13(8):599-608. 7.Pocock SJ, Ariti CA, McMurray JJ, Maggioni A, Kober L, Squire IB, Swedberg K, Dobson J, Poppe KK, Whalley GA, Doughty RN, Meta-Analysis Global Group in Chronic Heart F. Predicting survival in heart failure: a risk score based on 39 372 patients from 30 studies. European heart journal. 2013 May;34(19):1404-1413. 8.Solomon SD, McMurray JJV, Anand IS, Ge J, Lam CSP, Maggioni AP, Martinez F, Packer M, Pfeffer MA, Pieske B, Redfield MM, Rouleau JL, van Veldhuisen DJ, Zannad F, Zile MR, Desai AS, Claggett B, Jhund PS, Boytsov SA, Comin-Colet J, Cleland J, Dungen HD, Goncalvesova E, Katova T, Kerr Saraiva JF, Lelonek M, Merkely B, Senni M, Shah SJ, Zhou J, Rizkala AR, Gong J, Shi VC, Lefkowitz MP, Investigators P-H, Committees. Angiotensin-Neprilysin Inhibition in Heart Failure with Preserved Ejection Fraction. The New England journal of medicine. 2019 Oct 24;381(17):1609-1620.
Author Comments:	Tuesday, January 26, 2021 Prof. Stefan D Anker M.D., Ph.D Editor-in-chief, ESC Heart Failure Berlin, Germany Dear Professor Anker, We respectfully submit our revised manuscript “Serum Potassium Levels Provide Prognostic Information in Symptomatic Heart Failure Beyond Traditional Clinical” for consideration as an original research manuscript in the esteemed ESC Heart Failure journal. We thank the reviewers and editors for carefully examining our manuscript and providing us with valuable feedback. We appreciate the helpful comments and suggestions from the editor and the reviewers. We have addressed each of these comments and have modified the manuscript accordingly. We feel that these revisions have added clarification and have strengthened our manuscript, and we hope that you will agree that this manuscript will be of value to your readers and that it meets full criteria for publication in your journal. Please find attached our point-by-point response to the reviews. The reviewers’

	comments are italicized, and each point is then followed by our reply, including details on how the manuscript was changed. All the authors have reviewed the revised manuscript and all are in agreement with regard to the validity of our data collection, analysis, results, and the scientific value of this study. No patents, products in development or marketed products are associated with the current manuscript. This paper is not under consideration elsewhere, and none of the paper's contents has been previously published. None of the authors have any potential conflicts of interest to disclose. Sincerely yours, Otavio Rizzi Coelho-Filho MD PhD MPH Assistant Professor of Medicine Discipline of Cardiology, Department of Medicine, State University of Campinas (UNICAMP), Rua Tessália Viera de Camargo, 126 Campinas - SP - Brasil - CEP 13083-887

Title: Serum Potassium Levels Provide Prognostic Information in Symptomatic Heart Failure Beyond Traditional Clinical Variables.

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Short Tile: Potassium Levels in Symptomatic Heart Failure

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Abstract (< 400 words):

Background: 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 levels for patients with HF are not entirely established.

Aims: We aimed to investigate the prognostic role of potassium levels on a cohort of patients with symptomatic chronic HF ..

Methods: Symptomatic chronic HF patients were identified at the referral to 6-minute 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.

Results: The cohort included 178 HF patients with the mean age of 51±12.76 years, 39% were female, 85% of non-ischemic cardiomyopathy and 38% had NYHA class III with a relatively high 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 meters. After a median follow-up of 516 days, there were 22 major cardiovascular events (4 CV 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 ROC analysis. Individuals with higher potassium levels had worse renal function (Glomerular filtration rate, K≤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 NYHA class III patients (K≤4.7: 28% vs. K>4.7: 48%, p=0.0029) and also, higher MAGGIC score (K≤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 (HR=4.26, CI 1.59 - 11.421, p=0.003) and 6MWT distance (HR=0.99, 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, 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 (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).

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.

Key Words: Heart Failure, Prognosis, Potassium, Renal Function, And Physical Capacity.

Abbreviations List:

6MWT = six minute walking test

AUC = area under the curve

CKD = Chronic Kidney Disease

ECG = Electrocardiogram

EF = ejection fraction

GFR = glomerular filtration rate

HF = heart failure

HFrEF = Heart Failure with Reduced Ejection Fraction

HR = hazard ratio

IDI = Integrated Discrimination Index

LV = left ventricle

LVEF = Left ventricular ejection fraction

MACE = major cardiovascular events

MAGGIC score = The Meta-Analysis Global Group in Chronic Heart Failure score

MRAs = mineralocorticoid receptor antagonists

NRI = Net Reclassification Index

NYHA = New York Heart Association

NYHA = New York Heart Association Functional Class

RAAS = renin-angiotensin-aldosterone system

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 to cardiac events including cardiovascular death and hospitalization rates (1, 2). In the United States, 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 (hyperkalemia and hypokalemia) are common and frequently associated with adverse outcomes(6). Diabetes, chronic kidney disease (CKD) and hypertension are frequent comorbidities in HF individuals playing a significant role in the potassium disturbances(7). Hyperkalemia 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, hypokalemia might also be present among HF patients, despite the use of RAAS inhibitors(10). In a recent study, a U-shaped relation between potassium and mortality in patients with acute heart failure was reported (11). Whether potassium is an independent risk factor for worse outcomes or related to other risk factors such as CKD or diabetes remains unclear, although hyperkalemia has been consistently linked to mortality increase (6, 12).

With a growing number of HF patients with associated multiple comorbidities receiving RAAS inhibitors and also mineralocorticoid receptor antagonists (MRAs), hyperkalemia 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

Symptomatic chronic HF patients 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-minute walking test (6MWT) were consecutively identified. The eligibility criteria included symptomatic HF patients (stage C HF with a 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. 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 (MACE – 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 dyspnea)(15). HF hospitalization was defined as any hospital admission triggered by clinically decompensated HF requiring intravenous loop diuretics for more than 24hs. Cardiac events (cardiac death, HF hospitalization and heart transplantation) were obtained based on the available medical documentation of our hospital and healthcare 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 (ASE) Guidelines (16). Left ventricular relative wall thickness (RWT) was estimated as 2*posterior wall thickness/end-diastolic diameter(16).

6MWT

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 was 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, hemoglobin, sodium, potassium, urea, creatinine, triglycerides, high and low-density lipoprotein cholesterol were obtained by standard methods. (Beckman Coulter, AU5800 Beckman Coulter Analyzer, United States). 12-hour fasting was performed for glucose and lipids.

Statistical methods

Data are reported as mean ± SD. 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 t test. Fischer´s exact test was used to test the association between the nominal variables. Clinical predictors were transformed where appropriate. Receiver operating characteristic (ROC) 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 Table 1 and 2. The cohort included 178 HF patients. The mean age was 51±12.76 years, 39% were female, 85% of non-ischemic 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 a RWT of 0.31±0.09. While our cohort included predominantly patients with HFrEF, 31% of our patients had a LVEF > 45% (n=55) and 69% had a LVEF </=45% (n=123). Regarding the 6MWT, the mean achieved distance was 353±136 meters. 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, 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 ROC analysis for better accuracy, which showed that the potassium level of 4.7 mmol/l had the best area under the curve (AUC; 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≤4.7mmol/L exhibited a higher percentage of patients under diuretic therapy and calcium channel blockers (Table-1). Additionally, patients with K>4.7mmol/L demonstrated higher MAGGIC score, worse NYHA class and more tobacco use - the subgroups characteristics and comparisons are display 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≤4.7 mmol/L presented 101.7±32.7 mL/min/1.73m^2 vs. 85.4±36.9 mL/min/1.73m^2 in patients with K>4.7 mmol/L, p<0.001), without any other 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. 0.28±0.08 in the K>4.7mmol/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 CV deaths, 13 HF admissions and 5 heart transplants.

Univariate associations of clinical, laboratory, electrocardiographic, and echocardiogram variables with combine 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 to patients with potassium levels ≤4.7mmol/L (Figure 2 demonstrates the Kaplan-Meyer 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 HF patients 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 HF

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, CI 1.305-9.807, p=0.013). MAGGIC score did not maintain a significant outcome prediction in this multivariate analysis (HR 1.09, CI 0.996-1.200, p=0.06). No other parameter included in the multivariable model analysis other than K was significantly correlated to 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, CI 0.931-1.005, p=0.08 and HR 0.329, 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 GFR and creatinine level (Supplemental Online Tables 1 and 2).

We also performed a sensitivity analysis by building a multivariable Cox model including the following categorical variables: 6MWT distance (above or below 300 meters, 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, 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, CI 1.4707-11.4849, p=0.007), as well as 6MWT distance HR (0.995, CI 0.9918-0.9995, p=0.029).

In order to investigate the incremental value of potassium levels, we compared the predictive power of multivariable models using Harrel'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 analysis 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, since 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 hyperkalemia, which is an established worse prognostic factor, HF patients in our cohort with potassium levels above 4.7 had higher likelihood to present a worse cardiovascular outcome even when potassium levels where within normal values. This result contrasts 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 is 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 to 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.

Additionally, our findings were not correlated with less RAAS inhibitors utilization, since 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, since 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, not only hyperkalemia or hypokalemia, 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 electrocardiogram or echocardiogram parameters and natriuretic peptides were not available. Potassium levels were analyzed 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 increased risk of cardiovascular events.

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Declaration 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.CF. declare no conflict of interest.

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Figure Legends:

Figure 1: ROC curve of the potassium levels for the outcome prediction

Figure 2: The Kaplan-Meyer analysis stratified by potassium levels (A), MAGGIC score (B) and by both potassium levels and MAGGIC score (C).

Figure 3: The annual event rates of adverse outcomes in relation to MAGGIC score and potassium levels.

Figures:

Figure 1

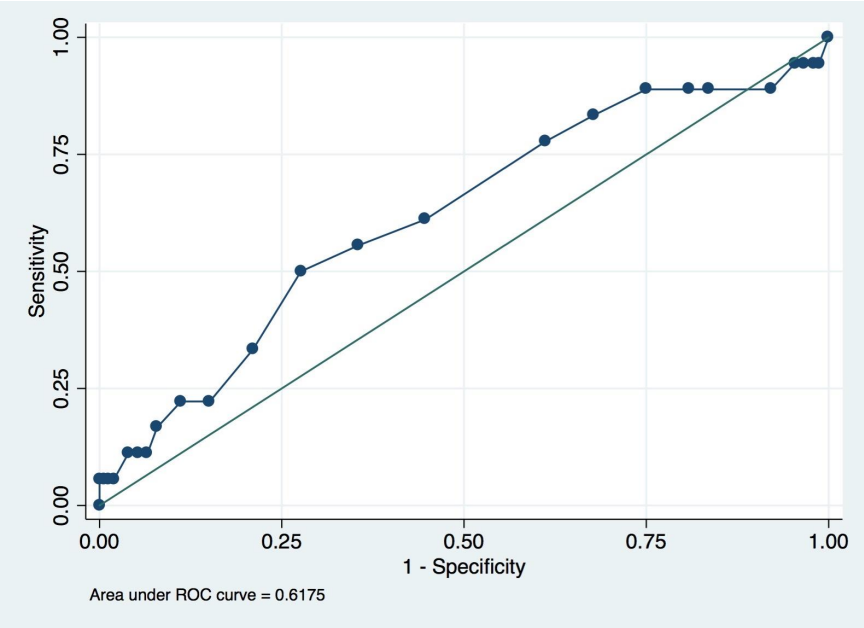


Figure 2 A-C:

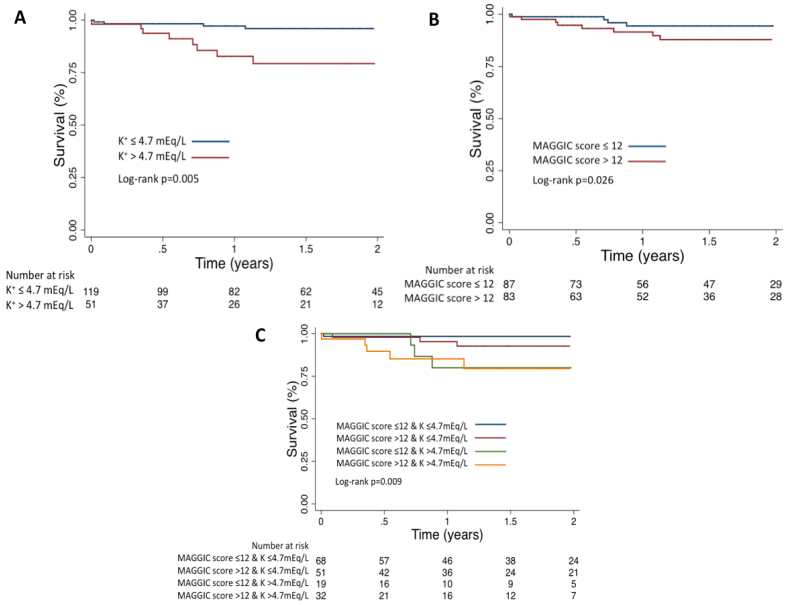
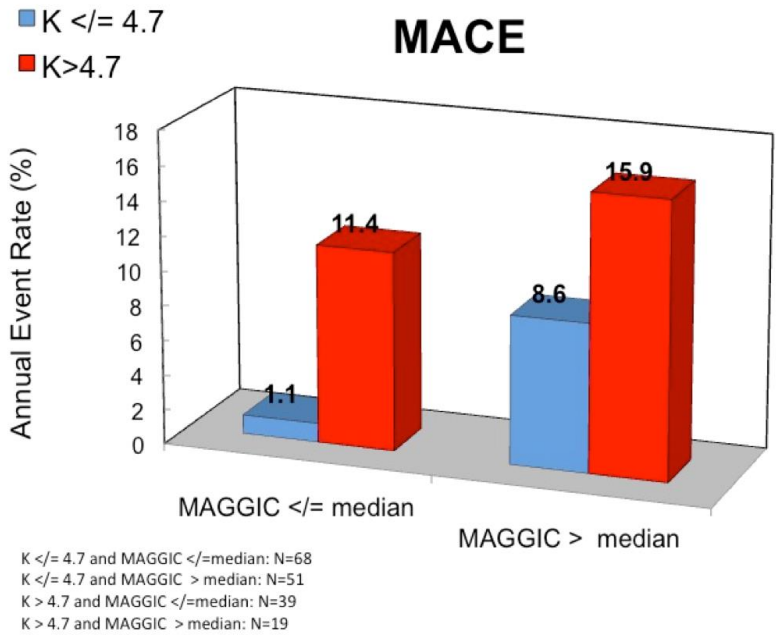

A
Survival (%)
0.00
0.25
0.50
0.75
1.00
K⁺ ≤ 4.7 mEq/L
K⁺ > 4.7 mEq/L
Log-rank p=0.005
0
.5
1
1.5
2
Time (years)
Number at risk
K⁺ ≤ 4.7 mEq/L 119 99 82 62 45
K⁺ > 4.7 mEq/L 51 37 26 21 12
B
Survival (%)
MAGGIC score ≤ 12
MAGGIC score > 12
Log-rank p=0.026
Time (years)
Number at risk
MAGGIC score ≤ 12 87 73 56 47 29
MAGGIC score > 12 83 63 52 36 28
C
Survival (%)
MAGGIC score ≤12 & K ≤4.7mEq/L
MAGGIC score >12 & K ≤4.7mEq/L
MAGGIC score ≤12 & K >4.7mEq/L
MAGGIC score >12 & K >4.7mEq/L
Log-rank p=0.009
Time (years)
Number at risk
MAGGIC score ≤12 & K ≤4.7mEq/L 68 57 46 38 24
MAGGIC score >12 & K ≤4.7mEq/L 51 42 36 24 21
MAGGIC score ≤12 & K >4.7mEq/L 19 16 10 9 5
MAGGIC score >12 & K >4.7mEq/L 32 21 16 12 7

Figure 3:


K </= 4.7
K>4.7
MACE
Annual Event Rate (%)
18
16
14
12
10
8
6
4
2
0
1.1
11.4
8.6
15.9
MAGGIC </= median
MAGGIC > median
K </= 4.7 and MAGGIC </=median: N=68
K </= 4.7 and MAGGIC > median: N=51
K > 4.7 and MAGGIC </=median: N=39
K > 4.7 and MAGGIC > median: N=19

Tables:

Table 1. Demographic, clinical and echocardiogram characteristics of the study population stratified by levels potassium (> or ≤ 4.7mmol/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
Hyperlipidemia, %, (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 Etiology				

Ischemic Heart Disease, %, (N)	15% (27)	15% (20)	13%(7)	0.09
No-ischemic 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
B-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

Table 2. 6MWT exercise parameters, laboratorial analysis, electrocardiogram and echocardiogram characteristics of the study population stratified by levels potassium (> or ≤4.7mmol/L).

	All patients (N=178)	Patients with K ≤ 4.7 (N=126)	Patients with K > 4.7 (N=52)	p-value
Hemodynamics 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, bpm	73.8 ±14.9	74.5 ±13.9	72.4±17.1	0.4013
Distance in the 6-minute walk test, m	353.0±136	360.8±137	334.0±132.8	0.2330
Laboratory analyses				
Hemoglobin, 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		116.4±36.62	125.3±38.05	0.233
QTc, ms	401.7±	401.7±64.6	410.3±47.8	0.4783
Left bundle branch block (LBBB)	38%(68)	56%(47)	58%(21)	0.8432

Right bundle branch block (RBBB)	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	33.96±26.99	32.71±26.66	37.02±27.80	0.3372

dimensions in systole, mm				
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 thickeners (RWT)	0.31±0.09	0.32±0.09	0.29±0.08	0.0832
Left ventricular ejection fraction (LVEF), %	39.98±15.79	40.63±16.23	38.33±14.64	0.3896

Table 3. Univariable Prognostic Association With Combined Cardiac Events.

All patients (N=178)			
Clinical Characteristics	LR Chi-square Test	HR (95% CI)	p-value
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
Hyperlipidemia	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 ≤ 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

Hemoglobin, 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), bpm	3.15	0.97 (0.944-1.003)	0.07
Heart rate (after 6MWT), bpm	0.36	0.97 (0.971-1.016)	0.54
Distance in the 6-minute 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 thickeners (RWT)	2.4372	0.002 (0.00-5.113)	0.1185
Left ventricular ejection fraction (LVEF), %	3.04	0.96 (0.931-1.004)	0.08
Left ventricular ejection fraction (LVEF) > 45%	2.18	0.329 (0.075-1.44)	0.14

Left ventricular ejection fraction (LVEF) > 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 anti-diabetic	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
B-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 (LBBB)	1.45	2.23 (0.604-8.28)	0.22
Right bundle branch block (RBBB)	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
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 QR interval, ms	7.74	1.00 (1.003-1.015)	0.005

Table 4. Multivariable analysis. Hazard ratio for outcome prediction including potassium levels, MAGGIC score, LVEF and age.

	Chi-square	**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 (LVEF)	0.4250	0.985 (0.941 – 1.031)	0.5144
Age	1.8357	0.971 (0.931 - 1013)	0.1755

Table 5. Multivariable analysis for categorical variables.

	HR (95% CI)	**p-value**
6MWT distance (above 300 meters)	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

Table 6. Incremental Value of Serum K in Predicting Cardiovascular Events (cardiac death, HF hospitalization and heart transplantation) Beyond 6MWT and MAGGIC score.

Variable	C-statistic † (Std Error)	P-value*	IDI (95% CI)	P-value*	NRI (95% CI)	P-Value*
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

*P values compared with the model containing solely clinical variables.

†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.

Supplemental Online Tables:

Online Table 1: Model 1: Multivariable analysis for outcome prediction including potassium levels, and GFR.

	Chi-square	HR (95% CI)	p-value
Potassium, mmol/L	5.4077	3.076 (1.193 – 7.929)	0.02
Glomerular filtration rate, mL/min/1.73 m^2	6.1949	0.981 (0.966 – 0.996)	0.0128

Online Table 2: Model 2: Multivariable analysis for outcome prediction including potassium and creatinine level.

	Chi-square	**HR (95% CI)**	**p-value**
Potassium, mmol/L	5.1867	3.223 (1.177 – 8.825)	0.0228
Creatinine, mg/dL	3.8386	1.543 (1.00 – 2.380)	0.051

Figure 1

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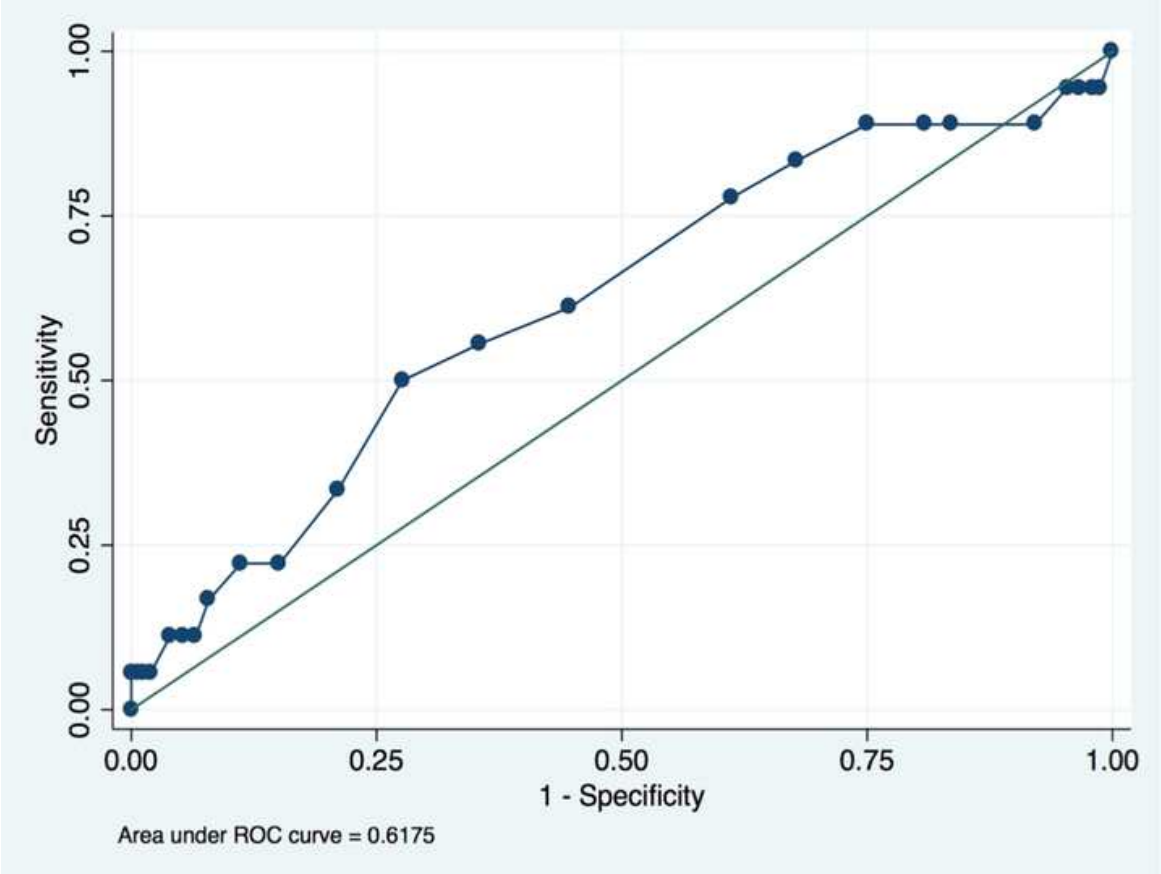

Figure 2

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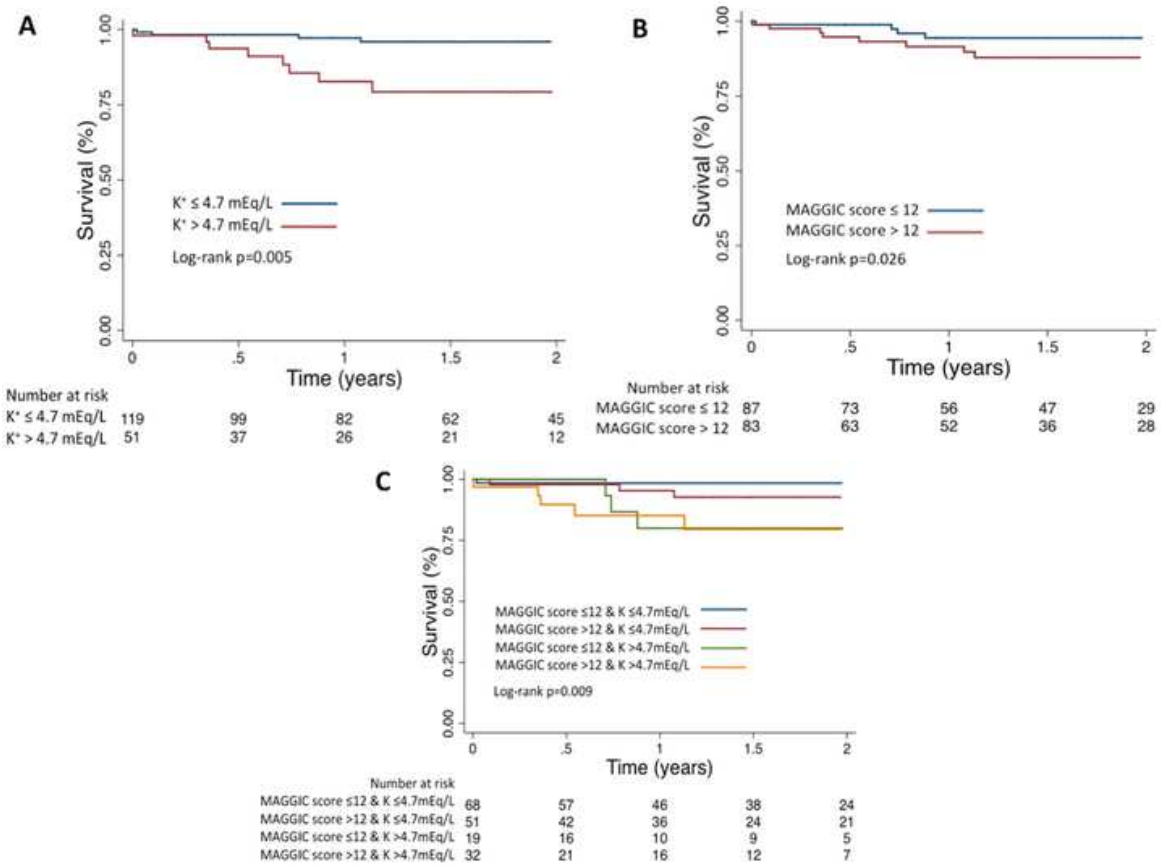

Figure 3

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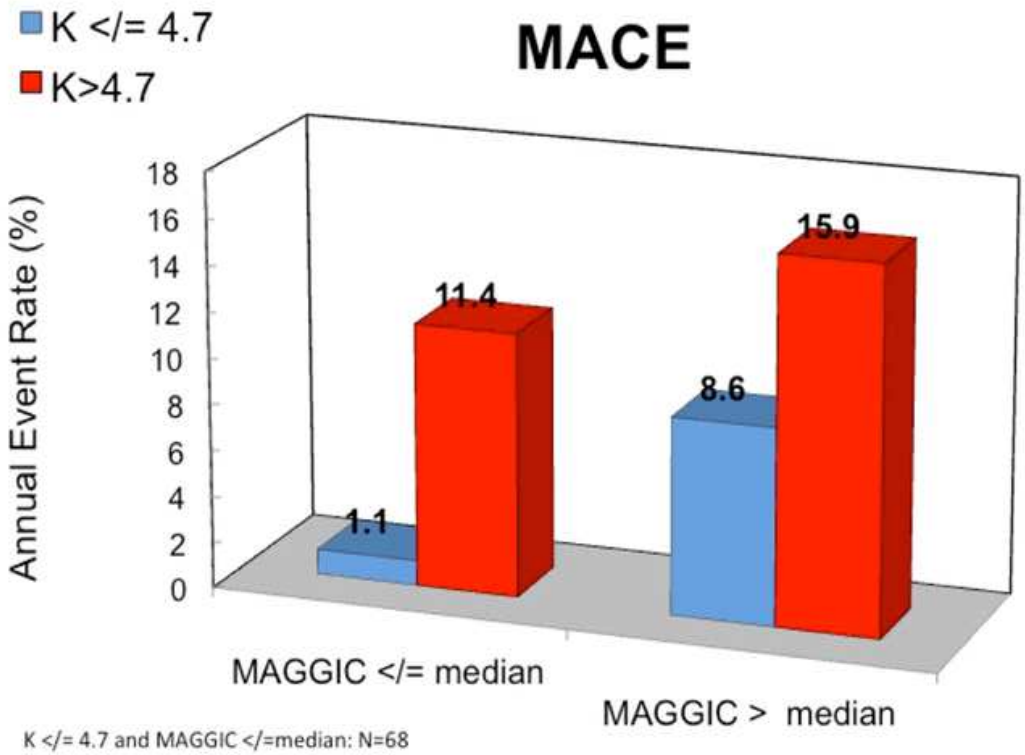

K </= 4.7 and MAGGIC </=median: N=68
K </= 4.7 and MAGGIC > median: N=51
K > 4.7 and MAGGIC </=median: N=39
K > 4.7 and MAGGIC > median: N=19

4. DISCUSÃO

O principal resultado da presente investigação, realizada em uma coorte de pacientes com IC crônica sintomática do Hospital das Clínicas da UNICAMP, foi verificação de uma robusta e independente associação dos níveis de potássio com desfechos cardíacos combinados. Além disso, os níveis de potássio aprimoraram significativamente o valor preditivo dos modelos prognósticos utilizando o escore MAGGIC e a distância do TC6M.

Interessantemente, na analise realizada o modelo de previsão de melhor precisão mostrou que o nível de potássio de 4,7 mmol/L foi o melhor valor de corte para predição de eventos. Esses dados sugerem que o potássio sérico, mesmo em níveis ainda dentro da normalidade, possa ser um novo e promissor biomarcador sérico, amplamente disponível em populações ambulatoriais com IC sintomática. Apesar da hipercalemia significativa, que é um fator de pior prognóstico estabelecido na literatura, ter sido encontrada em uma minoria dos pacientes da nossa coorte, nossos pacientes com níveis de potássio acima de 4,7 apresentaram maior probabilidade de apresentar um resultado clínico pior, mesmo quando os níveis de potássio se encontram ainda dentro dos valores considerados normais. Este resultado contrasta com outras coortes do mundo real de IC, que mostraram que os níveis séricos de potássio normais elevados eram seguros e apresentavam um resultado clínico equivalente aos níveis normais de potássio.(42, 43)

Embora existam dados suficientes suportando o conceito de que níveis de potássio abaixo do normal devem ser evitados na IC, não há consenso sobre os níveis de potássio normais ou o nível de potássio de segurança (42). Os dados do presente estudo mostraram que os níveis de potássio abaixo de 4,7 mmol/L são associados à melhores resultados clínicos, em comparação com níveis normais de potássio (acima de 4,7 mmol/L). Quando adicionado ao grupo de pacientes com escore MAGGIC inferior à média, presença de potássio abaixo de 4,7 mmol/L identificou grupo de ainda menor risco. Além disso, os níveis de potássio apresentaram uma associação significativa e independente com desfechos cardíacos, mesmo em pacientes com pontuação MAGGIC acima da média da coorte.

A hipercalemia usualmente é definida com níveis de potássio > 5mmol/L, um estudo realizado na Dinamarca, com a utilização desses níveis de potássio, que

incluiu 31.649 pacientes, mostrou que 1 em cada 4 pacientes diagnosticados com IC em hospitais desenvolveu hipercalemia no primeiro ano, sendo fortemente associada a eventos clínicos adversos(38). Outro estudo realizado no Reino Unido, com 21.334 pacientes, mostrou que tanto a hipocalemia, quanto a hipercalemia, com as concentrações de potássio fora de 4,0-5,0mmol/L, foram associadas ao aumento do risco de mortalidade (44). Similar aos nossos achados, um recente estudo de coorte concluiu que o intervalo de potássio mais seguro provável foi entre 4,1- 4,8 mmol/L (45).

Cumpri salientar, que nossos achados não foram associados com a utilização menos frequente de inibidores do sistema renina-angiotensina-aldosterona, uma vez que não foram encontradas diferenças estatísticas significativas entre medicamentos prescritos nos grupos de acordo com a estratificação pelos níveis de potássio inferior e superior a 4,7 mmol/L. Além disso, esses achados podem trazer preocupação para o paciente ambulatorial com IC para otimização do tratamento com relação ao potássio, uma vez que nossos dados sugerem uma possível inovação no limite para tolerância do potássio, independentemente do escore MAGGIC ou a distância do TC6M.

5. CONCLUSÃO

O presente estudo demonstrou que os níveis séricos de potássio estiveram associados de maneira independentemente com a ocorrência de desfechos clínicos combinados em pacientes ambulatoriais com IC crônica sintomática. A adição do potássio à modelos de predição de risco incorporando variáveis tradicionalmente associadas com pior prognóstico, como o escore MAGGIC e à distância do TC6M, melhorou significativamente a capacidade de predição de eventos. A presença de níveis de potássio acima de 4,7 mmol/L em pacientes com IC sintomática crônica identificaram indivíduos com maior risco para apresnetarem eventos cardiovasculares, o que justifica a realização de estudos subsequentes com populações maiores e mais abrangentes de pacientes com IC para avaliar a real aplicabilidade de tal achado.

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7. ANEXO

PARECER CONSUBSTANCIADO DO CEP

DADOS DA EMENDA

Título da Pesquisa: ESTUDO RETROSPECTIVO DO VALOR PROGNÓSTICO DA RESSONÂNCIA CARDÍACA EM PACIENTES COM CARDIOPATIAS

Pesquisador: Otavio Rizzi Coelho Filho

Área Temática:

Versão: 10

CAAE: 39500514.2.0000.5404

Instituição Proponente: Hospital de Clínicas da UNICAMP

Patrocinador Principal: Financiamento Próprio

DADOS DO PARECER

Número do Parecer: 3.702.463

Apresentação do Projeto:

Solicitação de emenda ao projeto original. No documento : PB_INFORMAÇÕES_BÁSICAS_1340960_E3.pdf 23/04/2019; Justificativa da Emenda: Para: Comitê de Ética em Pesquisa da Faculdade de Ciências Médicas da UNICAMP Referente: Solicitação de adendo no projeto intitulado "ESTUDO RETROSPECTIVO DO VALOR PROGNÓSTICO DA RESSONÂNCIA CARDÍACA EM PACIENTES COM CARDIOPATIAS" para inclusão de pacientes que realizaram avaliação da função ventricular esquerda com ecocardiograma. Número do Último Parecer: 1.919.912 CAA: 39500514.2.0000.5404. Prezado(a) Senhor(a), Em primeiro lugar agradecemos a cuidadosa e valorosa avaliação do nosso projeto intitulado "Estudo Retrospectivo do Valor Prognóstico da ressonância Cardíaca em Pacientes com Cardiopatias" realizado pelo Comitê de Ética em Pesquisa da UNICAMP-Campus Campinas nas avaliações já realizadas. Venho por meio desta submissão solicitar a possibilidade de inclusão de pacientes no estudo retrospectivo Que tiveram a avaliação da função ventricular realizada pelo ecocardiograma, pois estamos percebendo que números de pacientes que submetidos ressonância magnética cárdica com solicitação clínica está sendo menor do que se antevia. Dessa forma pretendemos também utilizar os dados da fração de ejeção do ventrículo esquerdo obtidos pelo ecocardiograma, que acaba sendo mais frequentemente utilizado no nosso serviço. A ecocardiografia representa atualmente um valioso método diagnóstico não-invasivo cuja aplicação na cardiologia encontrasse amplamente estabelecida. A ecocardiografia permite identificar dilatação das cavidades, espessura

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das paredes, alterações da contratilidade global e segmentar, presença de lesão de ponta e trombos intracavitários, além de estimar as alterações funcionais decorrentes do acometimento cardíaco. Solicitamos também inclusão dos seguintes novos membros da equipe de pesquisadores: Camila Toledo – Fisioterapeuta – CPF: 344637868-51 Luis Sergio Fernandes de Carvalho – Médico – CPF: 731583131-20 Essa emenda não modifica nenhum outro procedimento do estudo em vigência aprovado no ultimo parecer disponível (Número do Último Parecer: 1.919.912). Salientamos que a referida mudança só será praticada após aprovação pro parte deste CEP. Salientamos que ambos os novos membros ainda não iniciaram qualquer atividade relacionada ao presente projeto, sendo que aguardam aprovação oficial dessa ementa para integrarem o time de pesquisadores ativos do referido projeto. Ambos os novos membros já realizaram inscrição na plataforma Brasil e na plataforma Lattes, sendo pesquisadores associados à programas de pós graduação da FCM – UNICAMP. Cumpri elucidar que essa emenda não modifica nenhum procedimento do presente projeto previamente aprovado no último parecer em vigor. Todas estas informações receberão o mesmo tratamento de absoluta proposta de respeito à voluntariedade dos participantes, bem como o cuidado com o sigilo das informações obtidas com a pesquisa. Sem mais para o momento, agradeço a atenção, renovando votos de estima e consideração. Prof. Dr. Otávio Rizzi Coelho Filho Professor Assistente Doutor – MS3 Disciplina de Cardiologia – Departamento de Clínica Médica Faculdade de Ciências Médicas - UNICAMP Outros Comite de Eitca ORCF EMENDA NOVO FINAL.pdf Outros Respostas CEP1.pdf Outros Emenda_04_2019.pdf Projeto Detalhado / Brochura Investigador Projeto_RMC_revisado.pdf Projeto Detalhado / Brochura Investigador Comite de Eitca ORCF final.pdf Dat. A ecocardiografia representa atualmente um valioso método diagnóstico não-invasivo cuja aplicação na cardiologia encontrase amplamente estabelecida. A ecocardiografia permite identificar dilatação das cavidades, espessura das paredes, alterações da contratilidade global e segmentar, presença de lesão de ponta e trombos intracavitários, além de estimar as alterações funcionais decorrentes do acometimento cardíaco.

Objetivo da Pesquisa:

Objetivo principal inalterado do projeto original.

Avaliação dos Riscos e Benefícios:

Inalterado do projeto original.

Comentários e Considerações sobre a Pesquisa:

Projeto original aprovado em Número do Parecer:953.874

Data da Relatoria: 11/02/2015.
A versão 5 do projeto foi uma solicitação de emenda (2) para dispensa da aplicação do TCLE que recebeu pendências (Número do Parecer: 1.872.987 de 18 de Dezembro de 2016) e não foi respondida.
A emenda solicita:
1- inclusão de um novo grupo de participantes retrospectivos; pacientes que tiveram a avaliação da função ventricular realizada pelo ecocardiograma, assim utilizar os dados da fração de ejeção do ventrículo esquerdo obtidos pelo ecocardiograma, que é um exame mais frequentemente utilizado no serviço. Para conseguir tamanho amostral necessário.
2- inclusão de dois novos membros da equipe de pesquisadores:
-Camila Toledo – Fisioterapeuta – CPF: 344637868-51
-Luis Sergio Fernandes de Carvalho – Médico – CPF: 731583131-20

1- o projeto mantém os mesmos critérios de inclusão e característica retrospectiva (justificando que os pacientes serão identificados após realização do respectivo exames).
2- cronograma : Devido a dificuldade de obter pacientes com os critérios de inclusão, antecipamos que a colete de dados será mantida até dezembro de 2022.
3- Como relatório parcial solicitado apresenta resultados de exames e acompanhamento.
4- Ambos os novos pesquisadores irão coletar os dados nos prontuários e realizar as análises estatísticas.

Considerações sobre os Termos de apresentação obrigatória:
- TCLE_Projeto_ORCF_corrigido.pdf 26/10/2019 : adequado após pendências.
- PB_INFORMAÇÕES_BÁSICAS_1340960_E3.pdf 26/10/2019: com a solicitação da emenda.
- Respostas_Pedencias_CEP_outubro.pdf 26/10/2019 : responde as pendências do parecer anterior.

Recomendações:
Segundo a Resolução 466/12 do CNS; IV.5 - O Termo de Consentimento Livre e Esclarecido deverá, ainda: d) ser elaborado em duas vias, rubricadas em todas as suas páginas e assinadas, ao seu término, pelo convidado a participar da pesquisa, ou por seu representante legal, assim como pelo pesquisador responsável, ou pela (s) pessoa (s) por ele delegada (s), devendo as páginas de assinaturas estar na mesma folha.

Conclusões ou Pendências e Lista de Inadequações:
Em consideração ao parecer anterior, pesquisador apresenta Respostas_Pedencias_CEP_outubro.pdf 26/10/2019, onde responde a pendência e adequa o TCLE.

Conclusões: pendências atendidas com uma recomendação.
Segundo a Resolução 466/12 do CNS; IV.5 - O Termo de Consentimento Livre e Esclarecido deverá, ainda: d) ser elaborado em duas vias, rubricadas em todas as suas páginas e assinadas, ao seu término, pelo convidado a participar da pesquisa, ou por seu representante legal, assim como pelo pesquisador responsável, ou pela (s) pessoa (s) por ele delegada (s), devendo as páginas de assinaturas estar na mesma folha.

Considerações Finais a critério do CEP:
Segundo a Resolução 466/12 do CNS; IV.5 - O Termo de Consentimento Livre e Esclarecido deverá, ainda: d) ser elaborado em duas vias, rubricadas em todas as suas páginas e assinadas, ao seu término, pelo convidado a participar da pesquisa, ou por seu representante legal, assim como pelo pesquisador responsável, ou pela (s) pessoa (s) por ele delegada (s), devendo as páginas de assinaturas estar na mesma folha.

- O participante da pesquisa deve receber uma via do Termo de Consentimento Livre e Esclarecido, na íntegra, por ele assinado (quando aplicável).
- O participante da pesquisa tem a liberdade de recusar-se a participar ou de retirar seu consentimento em qualquer fase da pesquisa, sem penalização alguma e sem prejuízo ao seu cuidado (quando aplicável).
- O pesquisador deve desenvolver a pesquisa conforme delineada no protocolo aprovado. Se o pesquisador considerar a descontinuação do estudo, esta deve ser justificada e somente ser realizada após análise das razões da descontinuidade pelo CEP que o aprovou. O pesquisador deve aguardar o parecer do CEP quanto à descontinuação, exceto quando perceber risco ou dano não previsto ao participante ou quando constatar a superioridade de uma estratégia diagnóstica ou terapêutica oferecida a um dos grupos da pesquisa, isto é, somente em caso de necessidade de ação imediata com intuito de proteger os participantes.
- O CEP deve ser informado de todos os efeitos adversos ou fatos relevantes que alterem o curso

normal do estudo. É papel do pesquisador assegurar medidas imediatas adequadas frente a evento adverso grave ocorrido (mesmo que tenha sido em outro centro) e enviar notificação ao CEP e à Agência Nacional de Vigilância Sanitária – ANVISA – junto com seu posicionamento.

- Eventuais modificações ou emendas ao protocolo devem ser apresentadas ao CEP de forma clara e sucinta, identificando a parte do protocolo a ser modificada e suas justificativas e aguardando a aprovação do CEP para continuidade da pesquisa.

- Em caso de projetos do Grupo I ou II apresentados anteriormente à ANVISA, o pesquisador ou patrocinador deve enviá-las também à mesma, junto com o parecer aprovatório do CEP, para serem juntadas ao protocolo inicial.

- Relatórios parciais semestrais e final devem ser apresentados ao CEP, inicialmente seis meses após a data deste parecer de aprovação e ao término do estudo.

-Lembramos que segundo a Resolução 466/2012 , item XI.2 letra e, "cabe ao pesquisador apresentar dados solicitados pelo CEP ou pela CONEP a qualquer momento".

-O pesquisador deve manter os dados da pesquisa em arquivo, físico ou digital, sob sua guarda e responsabilidade, por um período de 5 anos após o término da pesquisa.

Este parecer foi elaborado baseado nos documentos abaixo relacionados:

Tipo Documento	Arquivo	Postagem	Autor	Situação
Informações Básicas do Projeto	PB_INFORMAÇÕES_BÁSICAS_1340960_E3.pdf	26/10/2019 16:48:45		Aceito
Outros	Respostas_Pedencias_CEP_outubro.pdf	26/10/2019 16:46:38	Otavio Rizzi Coelho Filho	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_Projeto_ORCF_corrigido.pdf	26/10/2019 16:45:13	Otavio Rizzi Coelho Filho	Aceito
Outros	Respostas_Pedencias_CEP_setembro.pdf	24/09/2019 09:05:43	CAMILA CRISTIANE DE TOLEDO	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE_Projeto_ORCF.pdf	24/09/2019 08:59:25	CAMILA CRISTIANE DE TOLEDO	Aceito
Outros	Respostas_Pedencias_CEP_Maio2019.pdf	17/07/2019 19:32:15	CAMILA CRISTIANE DE TOLEDO	Aceito
Outros	Emenda_04_2019.pdf	23/04/2019 00:19:53	Otavio Rizzi Coelho Filho	Aceito

Continuação do Parecer: 3.702.463

Projeto Detalhado / Brochura Investigador	Projeto_RMC_revisado.pdf	02/02/2017 12:38:27	THIAGO QUINAGLIA	Aceito
Outros	Resposta_pendencias.pdf	02/02/2017 12:34:22	THIAGO QUINAGLIA	Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	ADENDO_TCLE.pdf	28/11/2016 21:46:24	THIAGO QUINAGLIA	Aceito
Outros	TCLE Projeto ORCF BIOPSIA NOVO.pdf	08/04/2015 08:35:13		Aceito
Outros	OC-Letter of Collaboration.pdf	08/04/2015 08:34:45		Aceito
Outros	Carta Resposta Emenda CEP2.pdf	08/04/2015 08:34:21		Aceito
Outros	Comite de Eitca ORCF EMENDA NOVO FINAL.pdf	22/02/2015 22:03:48		Aceito
Outros	TCLE Projeto ORCF BIOPSIA.pdf	22/02/2015 22:01:29		Aceito
Outros	Carta EMENDA CEP ORCF.pdf	22/02/2015 22:00:14		Aceito
Outros	Respostas CEP1.pdf	02/02/2015 11:18:01		Aceito
Outros	Comite de Eitca ORCF novo2.pdf	02/02/2015 11:17:16		Aceito
Outros	Autorização para Coleta de Dados Cardiologia.pdf	02/02/2015 11:15:56		Aceito
Outros	TCLE Projeto ORCF novo.pdf	02/02/2015 11:13:43		Aceito
Outros	Declaração_Otavio E. C. Filho.pdf	02/02/2015 11:12:40		Aceito
Outros	Autorização para Coleta de Dados_HES.pdf	02/02/2015 11:11:43		Aceito
Folha de Rosto	Folha de rosto.pdf	20/11/2014 07:52:25		Aceito
Outros	Autorizacao Coleta Dados HES.pdf	17/11/2014 00:35:18		Aceito
Outros	Autorizacao Coleta Dados CMC.pdf	17/11/2014 00:34:25		Aceito
TCLE / Termos de Assentimento / Justificativa de Ausência	TCLE Projeto ORCF.pdf	17/11/2014 00:10:14		Aceito
Projeto Detalhado / Brochura Investigador	Comite de Eitca ORCF final.pdf	17/11/2014 00:09:38		Aceito

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Situação do Parecer:
Aprovado

Necessita Apreciação da CONEP:
Não

CAMPINAS, 13 de Novembro de 2019

Assinado por:
Maria Fernanda Ribeiro Bittar
(Coordenador(a))

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