Faculdade de Medicina de São José do Rio Preto

Programa de Pós-Graduação em Ciências da Saúde

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"EVOLUÇÃO CLÍNICA DA INSUFICIÊNCIA CARDÍACA SISTÓLICA CRÔNICA SECUNDÁRIA À DOENÇA DE CHAGAS COMPARADA ÀS DEMAIS CARDIOMIOPATIAS DE ETIOLOGIAS NÃO-CHAGÁSICAS"

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Evolução Clínica da Insuficiência Cardíaca Sistólica Crônica Secundária à Doença de Chagas Comparada às Demais Cardiomiopatias de Etiologias Não-Chagásicas

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Orientador: Prof. Dr. Reinaldo B. Bestetti

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Evolução Clínica da Insuficiência Cardíaca Sistólica Crônica Secundária à Doença de Chagas Comparada às Demais Cardiomiopatias de Etiologias Não-Chagásicas

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Sumário

Dedicatória

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Epígrafe

“A fé em Deus nos faz crer no incrível, ver o invisível e realizar o impossível.”

Autor desconhecido

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Lista de abreviaturas e símbolos

AUC	Area Under the Curve
CC	Chagas Cardiomyopathy
CHF	Chronic Heart Failure
CKD	Chronic Kidney Disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CI	Confidence Interval
CrCl	Creatinine Clearance
GFR	Glomerular Filtration Rate
HR	Hazard Ratio
ICD	Implantable Cardioverter-Defibrillator
LAFB	Left Anterior Fascicular Block
LVEF	Left Ventricular Ejection Fraction
LVDD	Left Ventricular end-Diastolic Diameter
LVRR	Left Ventricular Reverse Remodeling
NYHA	New York Heart Association
OH	Odds Ratio
ROC	Receiver-Operating Characteristic

Resumo

Introdução: A Insuficiência Cardíaca Sistólica Crônica (ICC) é causa líder de morbidade e mortalidade em todo o mundo, representando um dos maiores problemas de saúde pública, com crescente elevação de incidência e prevalência. A probabilidade de sobrevida pode variar dentre as diferentes etiologias e cenários de pacientes com ICC. Neste contexto, ICC secundária à Cardiomiopatia Chagásica (CC) mostra um pior prognóstico comparado às demais etiologias, principalmente na América Latina onde a doença é endêmica. **Objetivos:** [Artigo1] determinar se a presença de Remodelamento Reverso Ventricular Esquerdo poderia predizer mortalidade a longo prazo em pacientes com CC; [Artigo 2] avaliar a performance de predição de risco da equação Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) e anemia em pacientes com ICC secundária a CC; [Artigo 3] desenvolver e validar um método simples para predizer mortalidade a longo prazo em nível ambulatorial de pacientes com ICC em área endêmica de Doença de Chagas. **Material e Métodos:** De Janeiro a Dezembro de 2010, [Artigo 1] o prontuário médico de 159 pacientes foram revisados. Remodelamento Reverso Ventricular Esquerdo foi definido como um aumento da fração de ejeção ventricular esquerda associada a uma redução do diâmetro diastólica final do ventrículo esquerdo por ecocardiografia bidimensional. O modelo de riscos proporcionais de Cox foi utilizado para avaliar a habilidade do Remodelamento Reverso Ventricular Esquerdo predizer mortalidade por todas as causas; [Artigo 2] um total de 232 pacientes foram estudados. O clearance de creatinina foi estimado de acordo com a equação CKD-EPI e doença renal crônica foi definida como clearance de creatinina <60 mL/min/1.73m^2. Anemia foi definida como hemoglobina <12 g/dL para mulheres e <13 g/dL para homens. O modelo

de riscos proporcionais de Cox foi utilizado para estabelecer preditores independentes de mortalidade a longo prazo; [Artigo 3] a cohort de desenvolvimento incluiu 450 pacientes prospectivamente seguidos sob tratamento otimizado para ICC. Fatores prognósticos independentes foram identificados usando análises de regressão logística e os grupos foram estratificados como de baixo, moderado e alto risco. O escore de risco CALLM foi validade em uma coorte retrospectiva independente com 228 indivíduos. **Resultados:** (Todos os Artigos) Remodelamento Reverso Ventricular Esquerdo, Doença Renal Crônica e Anemia não foram associados com mortalidade tardia, hospitalizações, choque cardiogênico, ou indicação para transplante cardíaco. O escore de risco CALLM mostrou boa discriminação e consistente calibração em predizer mortalidade em nossa casuística. **Conclusões:** (Todos os Artigos) Remodelamento Reverso Ventricular Esquerdo, Doença Renal Crônica e Anemia não têm impacto nos desfechos de nossos pacientes com CC. O escore de risco CALLM representa um método simples que permite predizer sobrevida em população de mundo real em nível ambulatorial de pacientes com ICC em área na qual a Doença de Chagas é endêmica. O modelo providencia acurácia para identificar um subgrupo de pacientes de alto risco que deveria ser manuseado de maneira mais rigorosa.

Palavras-chave: Doença de Chagas; Cardiomiopatia Chagásica; Insuficiência Cardíaca; Prognóstico; Mortalidade.

Abstract

Introduction: Chronic heart failure (CHF) is a leading cause of morbidity and mortality worldwide, representing a major public health issue, with an increasing incidence and prevalence. The likelihood of survival may vary significantly among different etiologies and subsets of patients with CHF. In this context, CHF secondary to Chagas cardiomyopathy (CC) shows a poorer prognosis compared to other etiologies, mainly in Latin American where the disease is endemic. **Objectives:** [Article 1] to determine whether the presence of Left Ventricular Reverse Remodeling (LVRR) could predict long-term mortality in patients with CC; [Article 2] to evaluate the risk prediction performance of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and anemia in patients with CHF secondary to CC; [Article 3] to develop and to validate a simple method for predicting long-term mortality in ambulatory CHF patients in an area where Chagas disease is endemic. **Material and Methods:** From January 2000 to December 2010, [Article 1] the medical charts of 159 patients were reviewed. LVRR was defined as an increase of left ventricular ejection fraction and a decrease of left ventricular end-diastolic diameter by 2D-echocardiography. A Cox proportional hazards model was used to evaluate the ability of LVRR to predict all-cause mortality; [Article 2] a total of 232 patients were studied. The creatinine clearance was estimated according to CKD-EPI equation and CKD was defined as CrCl<60 mL/min/1.73m^2. Anemia was defined as hemoglobin <12 g/dL for women and <13 g/dL for men. Cox proportional hazards models were used to establish independent predictors for long-term mortality; [Article 3] The development cohort included 450 patients receiving evidence-based treatment for CHF, prospectively followed. Independent prognostic factors were

identified using logistic regression analysis and thresholds defined to stratify low-, intermediate-, and -high-risk groups. The CALLM Risk Score was validated in an independent retrospective cohort with 228 individuals. **Results:** [All Articles] LVRR, chronic kidney disease (CKD) and anemia were not associated with late-mortality, hospitalizations, cardiogenic shock, or heart transplantation indication. The CALLM risk score showed good discrimination and consistent calibration to predict mortality in our series. **Conclusions:** [All Articles] LVRR, CKD and anemia have no impact on outcomes of patients with CC. The CALLM risk score represents a simple method that allows prediction of survival in a real-world in ambulatory CHF patients in an area where Chagas disease is endemic. The model provides an accurate identification of a subgroup of high-risk patients who should be closely managed.

Key words: Chagas Disease; Chagas Cardiomyopathy; Heart Failure; Prognosis; Mortality.

Introdução:

A Insuficiência Cardíaca Sistólica Crônica (ICC) é causa líder mundial de morbidade e mortalidade, representando atualmente um dos maiores problemas de saúde pública, com incidência e prevalência em constantes elevações (1-3). A probabilidade de sobrevida desta condição pode variar dentre as diferentes etiologias e cenários de pacientes avaliados. A doença de Chagas é a causa mais frequente de ICC por disfunção sistólica do ventrículo esquerdo em áreas endêmicas, e o prognóstico da síndrome é pior nos pacientes chagásicos comparado a não chagásicos (4-9), seja naqueles com ICC leve a moderada ou mesmo naqueles com ICC terminal (9, 10). A ICC pode acometer de 4 a 8% dos indivíduos chagásicos provenientes de zona endêmica para a doença, cerca de10% dos pacientes de uma amostra hospitalar aleatória de nível secundário e até 76% de pacientes acompanhadas em centros de referência em nível terciário (9).

A doença de Chagas é causada pelo parasita *Trypanosoma cruzi*, transmitido aos seres humanos pelas fezes de insetos hematófagos, da subfamília *Triatominae*, popularmente conhecidos como “barbeiros”, que adquirem o agente ao se alimentar de animais infectados, transmitindo-o através da contaminação da mucosa ou pele após a picada, pelas fezes com tripanonossomas (20). Outros mecanismos de transmissão são transfusão sanguínea (21, 22), transplante de órgãos (23, 24), acidentes de laboratório, transmissão oral através de comida contaminada (24, 25) e verticalmente de mãe para filho (24).

Estima-se que 6 a 7 milhões de pessoas estejam infectadas pelo parasita na América Latina, e cerca de 70 milhões estejam sob o risco de infecção, sendo, por isso,

um sério problema econômico e de saúde pública, principalmente nos países da América Central e do Sul, particularmente no Brasil e Argentina (26). Contudo, com a emigração de pacientes com a doença para áreas não endêmicas, hoje pode-se encontrar a doença na América do Norte, Europa, Ásia e Oceania (27, 28).

Após a picada do inseto e a inoculação dos tripanosomas, o protozoário se multiplica, e em 10% dos casos ocorre uma doença aguda, fatal em 10% dos pacientes (29). A doença, então, entra em fase de latência e, em média, 20 anos após a infestação inicial, aproximadamente 30% dos indivíduos infectados desenvolverão sintomas da doença de Chagas crônica, que apresenta um amplo espectro de manifestação, desde anormalidades ao eletrocardiograma convencional até a doença cardíaca avançada, caracterizada por cardiomegalia, insuficiência cardíaca congestiva, arritmias, distúrbios de condução, fenômenos tromboembólicos, dor torácica atípica e morte súbita (30).

A doença isquêmica do coração é a principal causa de ICC no mundo ocidental (10), caracterizando-se pela presença de extensa doença arterial coronária proximal e múltiplas anormalidades do movimento segmentar da parede (11) ou hipocinesia difusa do ventrículo esquerdo, provocando redução importante na fração de ejeção do ventrículo esquerdo. A sobrevida dos pacientes com essa condição aparenta ser pior que o observado naqueles sem cardiomiopatia isquêmica, excluindo os pacientes com doença de Chagas (12, 13).

Embora constatemos escassez de dados na literatura sobre concomitância entre hipertensão arterial sistêmica e Doença Chagásica crônica, alguns estudos apontaram semelhantes taxas de hipertensão arterial em pacientes chagásicos quando comparados à população geral (14, 15). Assim, demonstraram taxas variando de 26% a 33% de

hipertensos dentre os pacientes portadores de Doença de Chagas crônica, com cerca de 8% deles apresentando ICC (14).

A cardiomiopatia dilatada idiopática é incidente em cerca de 17,9/100000 habitantes na população geral (16). Recebe esta denominação quando a específica etiologia da cardiomiopatia dilatada não pode ser identificada, podendo atingir até 50% dos casos em algumas populações (17). Mundialmente, é apontada como a terceira maior causa de ICC (18), com uma taxa de mortalidade anual em torno de 69% nas coortes de referência terciária (19).

A fisiopatologia da disfunção sistólica observada na Cardiomiopatia Chagásica (CC) é semelhante à detectada na cardiomiopatia de etiologia não chagásica. O aspecto macroscópico da ICC na doença de Chagas é caracterizado por dilatação de câmaras, trombose mural e aneurisma apical ventricular esquerdo, na ausência de coronariopatia obstrutiva. Histologicamente, material de necrópsia e de corações transplantados revelam focos extensos de fibrose repadora, associados a inflamação miocárdica crônica, entremeados com áreas de miocárdio normal, e o *T. cruzi* é raramente visto no miocárdio nessa fase. Como resultado do processo de remodelamento, uma disfunção sistólica irreversível leva à ativação neuro-hormonal e níveis elevados de atividade da renina plasmática e de noradrenalina, semelhantes aos encontrados nos pacientes com ICC não chagásicos, resultando em aumento da toxicidade miocárdica e consequente remodelamento ventricular, assim como observado em modelos animais de cardiomiopatia catecolaminérgica (9).

O remodelamento reverso ventricular esquerdo é caracterizado pela redução das dimensões, normalização da anatomia e melhoria da função sistólica ventricular esquerda

(31). Uma favorável resposta à terapêutica atualmente disponível, incluindo inibidores da enzima conversora de angiotensina, betabloqueadores e antagonistas da aldosterona tem sido relatadas, inclusive com completa reversão do remodelamento ventricular (32-34). Embora a Doença de Chagas tenha sido extensivamente estudada nos últimos 20 anos, um número limitado de estudos (35, 36) avaliou quantitativamente a influência do remodelamento ventricular esquerdo na mortalidade destes indivíduos.

A doença renal crônica tem sido considerada como uma das maiores questões de saúde pública em todo o mundo, com altas prevalências e grande impacto econômico nas diversas sociedades (37). Além disso, tem sido associada com aumento significativo do risco de acometimentos cardiovasculares, até mesmo em estágios precoces da doença (38). A taxa de filtração glomerular é o melhor índice para se avaliar a função renal, inclusive para diagnóstico, avaliação e manejo da doença renal crônica (39). Em meados de 2009, uma nova equação para se estimar a taxa de filtração glomerular foi proposta pelo grupo Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (40), internamente e externamente validada, providenciando estimativas mais acuradas e melhores predições de risco que as pré-existentes (41). Além disso, a anemia, uma condição comum entre indivíduos com ICC, também tem sido também descrita por sua associação com piores desfechos clínicos (42, 43). Quando associada à doença renal crônica, mostrou-se em algumas populações como preditor independente de mortalidade (44), embora tal fato não tenha sido confirmada em outros estudos (45-47).

Em um cenário de prática clínica onde os índices prognósticos utilizados para pacientes com ICC mostram-se limitados, baseando-se muitas vezes em variáveis extremamente específicas e até mesmo em medidas invasivas e de difícil verificação (48-

50), ou mesmo pela ausência de similaridade dentre as populações estudadas (51-53), que raramente contemplam pacientes chagásicos em seu desenvolvimento e validação, dificultando desta maneira a ampliação destas ferramentas na prática clínica local, constamos a necessidade de avaliar rigorosamente a nossa casuística ambulatorial, visando estabelecer critérios prognósticos que pudessem auxiliar na predição de risco dos indivíduos portadores de ICC em área endêmica para a Doença de Chagas.

Objetivos

Os objetivos dos nossos estudos foram:

1. Determinar se a presença de Remodelamento Reverso Ventricular Esquerdo poderia predizer mortalidade a longo prazo em pacientes com Cardiomiopatia Chagásica Crônica.
2. Avaliar a performance de predição de risco da equação Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) e de anemia em pacientes com Insuficiência Cardíaca Sistólica Crônica secundária a Cardiomiopatia Chagásica.
3. Desenvolver e validar um método simples para predizer mortalidade a longo prazo em nível ambulatorial de pacientes com Insuficiência Cardíaca Crônica em área endêmica para Doença de Chagas.

Artigos Científicos

Artigo 1: Impact of Left Ventricular Reverse Remodeling on Outcome of Patients with Chagas Cardiomyopathy with Chronic Heart Failure.

Autores: Marcelo Arruda Nakazone, Ana Paula Otaviano, Maurício Nassau Machado, Reinaldo Bulgarelli Bestetti.

Periódico: International Journal of Cardiology

Artigo 2: Prognostic Significance of Chronic Kidney Disease (CKD-EPI equation) and Anemia in Patients with Chronic Heart Failure Secondary to Chagas Cardiomyopathy

Autores: Marcelo Arruda Nakazone, Maurício Nassau Machado, Ana Paula Otaviano, Ana Maria Silveira Rodrigues, Augusto Cardinalli-Neto, Reinaldo Bulgarelli Bestetti.

Periódico: International Journal of Cardiology

Artigo 3: The CALLM Risk Score: a Tool to Predict Long-Term Mortality in Heart Failure Patients in an Endemic Area for Chagas Disease

Autores: Marcelo Arruda Nakazone, Ana Paula Otaviano, Maurício Nassau Machado, Reinaldo Bulgarelli Bestetti.

Periódico: International Journal of Cardiology

Artigo 1: Impact of Left Ventricular Reverse Remodling on Outcome of Patients with Chagas Cardiomyopathy with Chronic Heart Failure.

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Abstract

Background: The impact of left ventricular reverse remodeling (LVRR) on the prognosis of Chagas Cardiomyopathy (CC) is unknown. We aimed to determine whether the presence of LVRR could predict long-term mortality in patients with this condition. Methods: From January 2000 to December 2010, the medical charts of 159 patients were reviewed. LVRR was defined as an increase of left ventricular ejection fraction (LVEF) and a decrease of left ventricular end-diastolic diameter (LVDD) by 2D-echocardiography. No patient underwent cardiac resynchronization therapy or mechanical ventricular assistance. A Cox proportional hazards model was used to evaluate the ability of LVRR to predict all-cause mortality. Results: At baseline, median (25th – 75th) LVDD was 64mm (59 – 70), and median LVEF was 33.2% (26.4 – 40.1). LVRR was detected in 24.5% of patients in a 40-month median follow-up (26 – 64). In the LVRR group, LVDD decreased from 64mm (59 – 68) to 60mm (56 – 65; P < 0.001), and LVEF increased from 31.3% (24.1 – 39.0) to 42.5% (32.2 – 47.7; P < 0.001). However, LVRR was not associated with heart failure hospitalization, cardiogenic shock, need to heart transplantation, or long-term mortality (P > 0.05 for all comparisons). Cox proportional hazard model analysis identified cardiogenic shock (HR=2.41, 95%CI 1.51-3.85; P<0.001) and serum sodium level (HR=0.91, 95%CI 0.86-0.96; P<0.001) as independent predictors of all-cause mortality. Conclusions: LVRR occurs in one quarter of patients with CC, and have no impact on outcome of patients with this condition.

Keywords	Left Ventricular Reverse Remodeling; Chagas Cardiomyopathy; Heart Failure; Prognosis; Mortality.
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August, 10th, 2017.

Prof. Dr. Paolo G. Camici, MD, FESC, FACC, FAHA, FRCP
Editor-in-Chief of
International Journal of Cardiology

Dear Prof. Dr. Camici,

We are sending a manuscript entitled "Impact of left ventricular reverse remodeling on outcome of patients with Chagas Cardiomyopathy with chronic heart failure" for evaluation of publication in *International Journal of Cardiology*.

In the 21st century, Chagas disease still is a major health problem in Latin America, where about 6 million people are carriers of the disease, and about 10,000 people die of the disease annually. Chronic heart failure secondary to Chagas Cardiomyopathy has a poorer prognosis than that observed in other etiologies.

Left ventricular reverse remodeling (LVRR) is characterized by a decrease in left ventricular dimension, normalization of left ventricular shape and improvement of systolic function. A favorable response to adequate drug therapies has been described, with almost complete reversal of left ventricular dysfunction. Although Chagas' heart disease has been extensive and intensively studied in the past 20 years, a limited number of studies have assessed cardiac remodeling quantitatively in long-term follow-up in this setting.

In this paper, we found LVRR in about a quarter of patients, which have been followed for more than ten years. As far as we know, this is the first study to show no difference in the long-term mortality of Chagas Cardiomyopathy patients with and in those without LVRR, thus suggesting that the higher mortality associated with Chagas disease seems to dissipate the potential benefit of this condition.

Therefore, the relevance of these results prompts me to submit the paper to *International Journal of Cardiology*.

Thank you in advance for your attention.

Sincerely yours,

Reinaldo B. Bestetti, MD, PhD, FESC

Title Page

Impact of left ventricular reverse remodeling on outcome of patients with Chagas cardiomyopathy with chronic heart failure ☆

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☆The authors report no relationship that could be construed as a conflict of interest.

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Short title: Left Ventricular Reverse Remodeling in Chagas Cardiomyopathy

Key words: Left Ventricular Reverse Remodeling; Chagas Cardiomyopathy; Heart Failure; Prognosis; Mortality.

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Abstract

Background: The impact of left ventricular reverse remodeling (LVRR) on the prognosis of Chagas Cardiomyopathy (CC) is unknown. We aimed to determine whether the presence of LVRR could predict long-term mortality in patients with this condition.

Methods: From January 2000 to December 2010, the medical charts of 159 patients were reviewed. LVRR was defined as an increase of left ventricular ejection fraction (LVEF) and a decrease of left ventricular end-diastolic diameter (LVDD) by 2D-echocardiography. No patient underwent cardiac resynchronization therapy or mechanical ventricular assistance. A Cox proportional hazards model was used to evaluate the ability of LVRR to predict all-cause mortality.

Results: At baseline, median (25^{th} – 75^{th}) LVDD was 64mm (59 – 70), and median LVEF was 33.2% (26.4 – 40.1). LVRR was detected in 24.5% of patients in a 40-month median follow-up (26 – 64). In the LVRR group, LVDD decreased from 64mm (59 – 68) to 60mm (56 – 65; $P < 0.001$), and LVEF increased from 31.3% (24.1 – 39.0) to 42.5% (32.2 – 47.7; $P < 0.001$). However, LVRR was not associated with heart failure hospitalization, cardiogenic shock, need to heart transplantation, or long-term mortality ($P > 0.05$ for all comparisons). Cox proportional hazard model analysis identified cardiogenic shock (HR=2.41, 95%CI 1.51-3.85; $P<0.001$) and serum sodium level (HR=0.91, 95%CI 0.86-0.96; $P<0.001$) as independent predictors of all-cause mortality.

Conclusions: LVRR occurs in one quarter of patients with CC, and have no impact on outcome of patients with this condition.

1. Introduction

In the 21st century, Chagas disease still is a major health problem in Latin America, where about 10 million people are carriers of the disease, and about 10,000 people die of the disease each year (1). In view of international immigration, Chagas disease has spread throughout the world, and the global costs associated with this disease are about US 7.2 billion anually, higher than that observed in several types of cancer (2).

The disease is caused by *Trypanosoma cruzi*, a protozoan transmitted to humans through the feces of a sucking bug. Infection usually occurs in infancy. Approximately two decades after infection, about 30% of infected patients develop chronic cardiomyopathy and severe complications, as precordial chest pain (3), conduction disturbances, ventricular dysrhythmias (4), cardiac thrombosis (5), thromboembolism (6), chronic systolic heart failure (7), and sudden cardiac death (8).

Chronic heart failure (CHF) secondary to Chagas cardiomyopathy (CC) has a poor prognosis compared to patients with ischemic cardiomyopathy (9), hypertensive cardiomyopathy (10), or idiopathic dilated cardiomyopathy (11, 12). The histopathological findings in the chronic stage of CC are focal myocarditis that leads to myocyte loss, structural remodeling with intense fibrosis, geometric changes, and ventricular dysfunction (13).

Left ventricular reverse remodeling (LVRR) is characterized by a decrease of left ventricular dimensions, normalization of left ventricular shape and improvement of systolic function (14). A favorable response to drug therapy with angiotensin converting enzyme inhibitors, beta-blockers and aldosterone antagonists has been reported, with almost complete reversal of left ventricular dysfunction (15-17). Although Chagas' heart disease has been extensive and intensively studied in the past 20 years, a limited number

of studies has assessed cardiac remodeling quantitatively in long-term follow-up in this setting (18, 19). Male gender and systemic blood pressure seem to be independent predictors of cardiac remodeling (20).

The ability of the treatment of heart failure to decrease left chamber size and to improve left ventricular ejection fraction (LVEF) can identify patients with CC with a modifiable condition and a better long-term prognosis. Accordingly, the aim of this study was to determine whether LVRR could predict all-cause mortality in patients with CC in the long-term follow up.

2. Methods

2.1 Patients selection

This single-center study retrospectively evaluated the medical charts of patients with two positive serologic tests for Chagas disease (ELISA and indirect immunofluorescence) according to the World Health Organization recommendation (21). The clinical diagnosis of heart failure was made by the attending physicians based on Framingham Criteria for the diagnosis of CHF (22). After the clinical diagnosis of CHF, a 2-D echocardiography was used for each patient to confirm the clinical diagnosis, quantify this condition using LVEF, and guide treatment. Individuals with the clinical diagnosis of CHF secondary to CC and LVEF $< 55\%$ on first 2-D echocardiography confirming left ventricular systolic dysfunction were initially screened for this study. Patients with a concomitant disease that could potentially cause heart disease by itself were excluded.

This study was conducted in accordance with the Declaration of Helsinki and approved through the local Human Research Ethics Committee of São José do Rio Preto Medical School (CAAE - 02716112.6.0000.5415). The need for individual informed

consent was waived, as this study was a retrospective analysis of prospectively collected data for routine care, and breach of privacy or anonymity did not occur.

2.2 Baseline measurements and 2D-Echocardiographics conditions

The demographics data, New York Heart Association (NYHA) functional class, heart rate, systemic arterial pressure, medical history, standard laboratory tests, 12-lead resting electrocardiogram and cardiac electronic implantable devices information were obtained at study entry, and retrieved from the records of the medical charts.

Local specialists in 2D-Echocardiography did the echocardiographic examination with patients in left lateral position. Standard parasternal, apical and subcostal views were obtained. Routinely, physicians did placing the transducer as far laterally and caudally as possible in the apical windows to maximize left ventricular cavity size and avoid foreshortening during measures. LVEF was measured by Simpson's method in the apical 4-chamber view, which was used for the main analyses, as well as the apical 2-chamber view when possible. Wall motion abnormalities analyses, left ventricular end-systolic diameter, left ventricular end-diastolic diameter (LVDD), and right ventricular dimension were measured according to the American Society of Echocardiography recommendations (23).

LVRR was defined by the simultaneous presence of the following conditions: a) occurrence of an increase of LVEF concomitant with a decrease in LVDD; b) this improvement occurred in the absence of cardiac resynchronization therapy or mechanical ventricular assistance, as previously described (14).

2.3 Prospective follow-up

The patients were routinely followed at the cardiomyopathy outpatient service in a Brazilian Medical School facility from January, 2000 to December, 2010. The heart failure medical therapy information was retrieved from a prospectively collected database of patients. All patients received evidence-based treatment for CHF, according to international guidelines of the time. Thus, treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blocks and beta-blockers at targeted or maximal tolerated doses was considered for all patients. Those with pitting edema received furosemide, while those in the NYHA Class III/IV with a LVEF < 30% were treated with digoxin. Patients usually visited the outpatient service each four months, and a senior heart failure specialist supervised the treatment given. Patients were followed until the close study; they were also censored at heart transplantation or death.

2.4 Data Analysis

The data were analyzed using the IBM SPSS Statistical Package v.21 (IBM Corporation, Armonk, NY). The variables are presented as absolute numbers and percentages and median and interquartile ranges (25^{th} and 75^{th} percentile) when applicable. Due to the lack of Gaussian distribution, continuous variables were compared using the nonparametric Mann-Whitney test. Chi-square or Fisher's exact tests were used to compare categorical variables.

A Cox proportional hazards model was used to evaluate the ability of LVRR to independently predict all-cause mortality during a long-term follow-up. In the multivariable model, variables with a P value < 0.10 in the univariate model and those with known prognostic significance were entered a backward stepwise approach to establish independent predictors of death. The Spearman test was used to stablish

correlation between continuous variables. The variable who correlated with others and with the highest Wald coefficient remained in the model, whereas the other were ruled out. Thus, each variable entered the multivariable model in a proportional at least to 10 events in an attempt to avoid overfitting. The adjusted Odds Ratio (OR) and 95% confidence intervals (95% CI) were calculated for the predictors.

Cumulative survival graphics (Kaplan-Meier) were constructed to demonstrate differences in event-free survival (mortality from all-causes). *P* values < 0.05 were considered statistically significant (two-tailed).

3. Results

Two hundred thirty-four patients were screened for potentially taking part in this investigation. However, a total of 75 individuals (32%) were excluded because they did not undergo another comparative 2D-echocardiography during the follow-up. In this context, the study evaluated 159 patients (64.2% male) who had a median age of 57 years (47 - 66), and were followed over a period more than 10 years. The baseline characteristics of the patients are shown in Table 1. These individuals were divided into two groups: with and without LVRR by echocardiographic evaluations. A similarity (P > 0.05) for all variables was observed in our series.

Our population received maximal tolerated daily doses of medications, considering samples from drugs classes with known prognostic impact in ventricular remodeling. LVRR group received mean daily dose (mg/day) of Enalapril (15.0 ± 5.8), Captopril (106.3 ± 49.6), Losartan (44.2 ± 11.0), Carvedilol (27.6 ± 21.1), Metoprolol Succinate (116.7 ± 58.7), Spironolactone (33.3 ± 24.3) and non-LVRR group received mean daily dose of Enalapril (14.3 ± 8.7; *P* = 0.357), Captopril (75.8 ± 38.0; *P* = 0.120), Losartan (50.0 ± 24.2; *P* = 0.789), Carvedilol (26.3 ± 17.9; *P* = 0.860), Metoprolol

Succinate (128.1 ± 63.6; $P = 0.585$), Spironolactone (27.5 ± 12.4; $P = 0.346$), showing no difference between groups for optimized therapeutic, according to guideline recommendations during the long-term of follow-up.

Thirty-nine patients (24.5%) with CC presented LVRR during their follow-up. Comparing the first and the last 2D-echocardiography, this group showed a median of 3.0mm (1 to 6 mm) for absolute reduction of LVDD, representing a median of 5.1% (1.7 to 10%) of reduction. For this group, we also detected a median of absolute improvement for LVEF of 7.0% (4.0 to 11.6%), representing around 23.6% (12.7 to 39.7%) of improvement. There was significant difference between this group and the group of individuals with LVRR ($P < 0.001$) for all previous measures. Right ventricle diameter and wall motion abnormality did not differ between groups (Table 2).

Standard laboratory tests, 12-lead resting electrocardiographic findings and using cardiac electronic implantable devices observed at study entry were not associated with LVRR occurrence. Moreover, patients with LVRR showed no difference for hospitalization due to acute decompensated heart failure (59.0%), cardiogenic shock (17.9%), and need to heart transplantation (10.3%) compared to patients without LVRR (65.8%, $P = 438$; 29.2%, $P = 0.167$; and 8.3%, $P = 0.747$; respectively).

Cox proportional hazards model showed similar situation for late-mortality (over period more than 10 years) between individuals without LVRR (54.2%) compared to individuals with LVRR (46.2%, $P = 0.384$). After adjustment, six variables were used in the multivariate model: age (years), gender (male), cardiogenic shock, left anterior fascicular block, serum sodium level, and LVRR. Only two variables were retained as independent predictors of long-term mortality: cardiogenic shock (HR = 2.41, 95% CI 1.51 to 3.85; $P < 0.001$) and serum sodium level (HR = 0.91, 95% CI 0.86 to 0.96; $P < 0.001$; Table 3).

Kaplan-Meier survival analysis of the patients with and without LVRR during follow-up is shown in Figure 1. No difference between both groups was observed regarding survival.

4. Discussion

In this study, we evaluated the LVRR in CC as a predictor of long-term mortality. To the best of our knowledge, this is the first study of a cohort of patients with CHF secondary to CC evaluating the role of LVRR on outcome in a more than 10-year follow up. Our study shows no survival improvement in despite of LVRR, thus confirming the dismal prognosis and the severity of CHF secondary to CC.

Cardiac reverse remodeling with medical treatment of CHF is well stablished, with demonstrable decreases in left ventricular diameter and improvement in left ventricular function (24-29). It should be noted that, although the volumetric measurements seem to provide the most powerful data, LVEF measurements are simpler to obtain and are indeed a marker of the remodeling process. As left ventricular volume increases, there is a tendency for a concomitant and usually parallel decrease in LVEF, which can be used, itself, as a marker of the remodeling process (30). Interestingly, similar to the results provided by Ramasubbu et al. (31) using the echocardiography database from the ESCAPE trial (32), our study demonstrated that changes in these parameters are not associated with improvement outcome (long-term mortality) in patients with CC as well.

Only two previous study including patients with CC aiming at assessing clinical predictors for long-term cardiac remodeling was previous performed in similar cohort. In both studies (18, 20), in contrast to our results, no significant reduction for LVDD was observed during the follow-up. It is possible that the optimized clinical treatment

provided to patients in our study, including targeted or maximal tolerated doses of angiotensin converting enzyme inhibitors and spironolactone associated to beta-blockers, can account for these discrepant results. Moreover, our findings are similar to those observed in other populations (33, 34).

The therapeutic agents, mainly angiotensin converting enzyme inhibitors and beta-blockers, modify the remodeling process and frequently add other clinically relevant benefits in reducing morbidity and mortality in cardiomyopathy patients (35). Several clinical trials using a variety of beta-blockers have demonstrated improvements in symptoms, ventricular function, functional capacity, and survival in patients with CHF due to ischemic and dilated cardiomyopathies (36-38). Some studies with beta-blockers that included patients with CC showed similar benefits (39-43).

Experimentally, a recent study designed to evaluate the role of carvedilol in the context of Chagas' disease concluded that the drug did not attenuate cardiac remodeling or mortality in a model of CC (13). This contrasts with other experimental study in which metoprolol was capable to revert electrocardiographic abnormalities in a rat model of Chagas disease probably because the reversal of catecholamine toxicity in this model (44, 45). In fact, parasympathetic derangement is believed, along with microvascular dysfunction and autoimmunity, to play a central role in the pathogenesis of chronic Chagas heart disease (46). Thus, in our study, the optimized pharmacological treatment confirmed its association with LVRR, considering reduction of LVDD and improvement of LVEF, although it has not been positively impacted on survival.

Inotropic support and serum sodium level were independent predictors for mortality in our investigation. These findings probably reflect the severity of our study population in which about a quarter of individuals showed cardiogenic shock during follow-up. Therefore, this may account, at least in part, for the ability of inotropic support

to predict hyponatremia in patients with CC and, consequently, ventricular remodeling (47, 48).

4.1 Limitations

There are several limitations to our study. This study is a retrospective analysis of prospectively collected single-center data and thus carries the inherent disadvantages of retrospective studies. All echocardiographic parameters were not available in all patients, and therefore only parameters that had paired measurements (at baseline and follow-up) were used for the analysis, resulting in a smaller sample size. Finally, intra- and interobserver variability for the echocardiography lab was not mentioned. Therefore, it was difficult to determine whether the mean changes in parameters fell within the measurement variability or reflected true changes. Additionally, our multivariate analysis included only those factors available in our database. Some factors that have an effect on prognosis might not have been examined. Thus, our results may not be applicable to other specific patient cohorts without further study into the various subgroups.

5. Conclusions

Our study shows that LVRR does not predict a reduction in the long-term mortality in patients with CC. This is the first study to show that the severity of disease progression seems to dissipate the potential benefit of LVRR in patients with CC. Further research, however, with larger sample sizes, should be conducted to confirm these findings.

References

1. Chagas disease (American trypanosomiasis) - fact sheet (revised in August 2012). Wkly Epidemiol Rec. 2012;87(51/52):519-22.

2. Lee BY, Bacon KM, Bottazzi ME, Hotez PJ. Global economic burden of Chagas disease: a computational simulation model. Lancet Infect Dis. 2013;13(4):342-8.

3. Bestetti RB, Restini CB. Precordial chest pain in patients with chronic Chagas disease. Int J Cardiol. 2014;176(2):309-14.

4. Bestetti RB, Santos CR, Machado-Junior OB, Ariolli MT, Carmo JL, Costa NK, et al. Clinical profile of patients with Chagas' disease before and during sustained ventricular tachycardia. Int J Cardiol. 1990;29(1):39-46.

5. Bestetti RB, Corbucci HA, Cardinalli-Neto A. Massive right-sided cardiac thrombosis in Chagas' heart disease without left ventricular dysfunction. Acta Cardiol. 2011;66(1):67-9.

6. Samuel J, Oliveira M, Correa De Araujo RR, Navarro MA, Muccillo G. Cardiac thrombosis and thromboembolism in chronic Chagas' heart disease. Am J Cardiol. 1983;52(1):147-51.

7. Bestetti RB, Theodoropoulos TA, Cardinalli-Neto A, Cury PM. Treatment of chronic systolic heart failure secondary to Chagas heart disease in the current era of heart failure therapy. Am Heart J. 2008;156(3):422-30.

8. Bestetti RB, Cardinalli-Neto A. Sudden cardiac death in Chagas' heart disease in the contemporary era. Int J Cardiol. 2008;131(1):9-17.

9. Vilas Boas LG, Bestetti RB, Otaviano AP, Cardinalli-Neto A, Nogueira PR. Outcome of Chagas cardiomyopathy in comparison to ischemic cardiomyopathy. Int J Cardiol. 2013;167(2):486-90.

10. Bestetti RB, Otaviano AP, Fantini JP, Cardinalli-Neto A, Nakazone MA, Nogueira PR. Prognosis of patients with chronic systolic heart failure: Chagas disease versus systemic arterial hypertension. Int J Cardiol. 2013;168(3):2990-1.

11. Pereira Nunes Mdo C, Barbosa MM, Ribeiro AL, Amorim Fenelon LM, Rocha MO. Predictors of mortality in patients with dilated cardiomyopathy: relevance of chagas disease as an etiological factor. Rev Esp Cardiol. 2010;63(7):788-97.

12. Barbosa AP, Cardinalli Neto A, Otaviano AP, Rocha BF, Bestetti RB. Comparison of outcome between Chagas cardiomyopathy and idiopathic dilated cardiomyopathy. Arq Bras Cardiol. 2011;97(6):517-25.

13. Pimentel Wde S, Ramires FJ, Lanni BM, Salemi VM, Bilate AM, Cunha-Neto E, et al. The effect of beta-blockade on myocardial remodelling in Chagas' cardiomyopathy. Clinics (Sao Paulo). 2012;67(9):1063-9.

14. Amorim S, Rodrigues J, Campelo M, Moura B, Martins E, Macedo F, et al. Left ventricular reverse remodeling in dilated cardiomyopathy- maintained subclinical myocardial systolic and diastolic dysfunction. Int J Cardiovasc Imaging. 2017;33(5):605-13.

15. Arnold RH, Kotlyar E, Hayward C, Keogh AM, Macdonald PS. Relation between heart rate, heart rhythm, and reverse left ventricular remodelling in response to carvedilol in patients with chronic heart failure: a single centre, observational study. Heart. 2003;89(3):293-8.

16. Greenberg B, Quinones MA, Koilpillai C, Limacher M, Shindler D, Benedict C, et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD echocardiography substudy. Circulation. 1995;91(10):2573-81.

17. Boccanelli A, Mureddu GF, Cacciatore G, Clemenza F, Di Lenarda A, Gavazzi A, et al. Anti-remodelling effect of canrenone in patients with mild chronic heart failure (AREA IN-CHF study): final results. Eur J Heart Fail. 2009;11(1):68-76.

18. Benchimol-Barbosa PR. Cardiac remodeling and predictors for cardiac death in long-term follow-up of subjects with chronic Chagas' heart disease: a mathematical model for progression of myocardial damage. Int J Cardiol. 131. Netherlands2009. p. 435-8.

19. Davila DF, Rossell O, de Bellabarba GA. Pathogenesis of chronic chagas heart disease: parasite persistence and autoimmune responses versus cardiac remodelling and neurohormonal activation. Int J Parasitol. 32. England2002. p. 107-9.

20. Bestetti RB. Predictors of unfavourable prognosis in chronic Chagas' disease. Trop Med Int Health. 2001;6(6):476-83.

21. Control of Chagas disease. World Health Organ Tech Rep Ser. 2002;905:i-vi, 1-109, back cover.

22. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation. 1993;88(1):107-15.

23. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr. 1989;2(5):358-67.

24. Cintron G, Johnson G, Francis G, Cobb F, Cohn JN. Prognostic significance of serial changes in left ventricular ejection fraction in patients with congestive heart failure. The V-HeFT VA Cooperative Studies Group. Circulation. 1993;87(6 Suppl):Vi17-23.

25. Yusuf S, Pitt B, Davis CE, Hood WB, Cohn JN. Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. N Engl J Med. 1991;325(5):293-302.

26. Wong M, Staszewsky L, Latini R, Barlera S, Volpi A, Chiang YT, et al. Valsartan benefits left ventricular structure and function in heart failure: Val-HeFT echocardiographic study. J Am Coll Cardiol. 2002;40(5):970-5.

27. Firth BG, Dehmer GJ, Markham RV, Jr., Willerson JT, Hillis LD. Assessment of vasodilator therapy in patients with severe congestive heart failure: limitations of measurements of left ventricular ejection fraction and volumes. Am J Cardiol. 1982;50(5):954-9.

28. Massie B, Kramer BL, Topic N, Henderson SG. Hemodynamic and radionuclide effects of acute captopril therapy for heart failure: changes in left and right ventricular volumes and function at rest and during exercise. Circulation. 1982;65(7):1374-81.

29. Shah PK, Abdulla A, Pichler M, Shellock F, Berman D, Singh BN, et al. Effects of nitroprusside-induced reduction of elevated preload and afterload on global and regional ventricular function in acute myocardial infarction. Am Heart J. 1983;105(4):531-42.

30. Udelson JE. Ventricular remodeling in heart failure and the effect of beta-blockade. Am J Cardiol. 2004;93(9a):43b-8b.

31. Ramasubbu K, Deswal A, Chan W, Aguilar D, Bozkurt B. Echocardiographic changes during treatment of acute decompensated heart failure: insights from the ESCAPE trial. J Card Fail. 2012;18(10):792-8.

32. Binanay C, Califf RM, Hasselblad V, O'Connor CM, Shah MR, Sopko G, et al. Evaluation study of congestive heart failure and pulmonary artery catheterization effectiveness: the ESCAPE trial. Jama. 2005;294(13):1625-33.

33. Cohn JN, Fowler MB, Bristow MR, Colucci WS, Gilbert EM, Kinhal V, et al. Safety and efficacy of carvedilol in severe heart failure. The U.S. Carvedilol Heart Failure Study Group. J Card Fail. 1997;3(3):173-9.

34. Packer M, Colucci WS, Sackner-Bernstein JD, Liang CS, Goldscher DA, Freeman I, et al. Double-blind, placebo-controlled study of the effects of carvedilol in patients with moderate to severe heart failure. The PRECISE Trial. Prospective Randomized Evaluation of Carvedilol on Symptoms and Exercise. Circulation. 1996;94(11):2793-9.

35. Cohn JN, Ferrari R, Sharpe N. Cardiac remodeling--concepts and clinical implications: a consensus paper from an international forum on cardiac remodeling. Behalf of an International Forum on Cardiac Remodeling. J Am Coll Cardiol. 2000;35(3):569-82.

36. Packer M, Bristow MR, Cohn JN, Colucci WS, Fowler MB, Gilbert EM, et al. The effect of carvedilol on morbidity and mortality in patients with chronic heart failure. U.S. Carvedilol Heart Failure Study Group. N Engl J Med. 1996;334(21):1349-55.

37. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9-13.

38. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353(9169):2001-7.

39. Botoni FA, Poole-Wilson PA, Ribeiro AL, Okonko DO, Oliveira BM, Pinto AS, et al. A randomized trial of carvedilol after renin-angiotensin system inhibition in chronic Chagas cardiomyopathy. Am Heart J. 2007;153(4):544.e1-8.

40. Davila DF, Angel F, Arata de Bellabarba G, Donis JH. Effects of metoprolol in chagasic patients with severe congestive heart failure. Int J Cardiol. 2002;85(2-3):255-60.

41. Bestetti RB, Otaviano AP, Cardinalli-Neto A, da Rocha BF, Theodoropoulos TA, Cordeiro JA. Effects of B-Blockers on outcome of patients with Chagas' cardiomyopathy with chronic heart failure. Int J Cardiol. 2011;151(2):205-8.

42. Issa VS, Amaral AF, Cruz FD, Ferreira SM, Guimaraes GV, Chizzola PR, et al. Beta-blocker therapy and mortality of patients with Chagas cardiomyopathy: a subanalysis of the REMADHE prospective trial. Circ Heart Fail. 2010;3(1):82-8.

43. Theodoropoulos TA, Bestetti RB, Otaviano AP, Cordeiro JA, Rodrigues VC, Silva AC. Predictors of all-cause mortality in chronic Chagas' heart disease in the current era of heart failure therapy. Int J Cardiol. 2008;128(1):22-9.

44. Bestetti RB, Sales-Neto VN, Pinto LZ, Soares EG, Muccillo G, Oliveira JS. Effects of long term metoprolol administration on the electrocardiogram of rats infected with T cruzi. Cardiovasc Res. 1990;24(7):521-7.

45. Bestetti RB, Ramos CP, Figueredo-Silva J, Sales-Neto VN, Oliveira JS. Ability of the electrocardiogram to detect myocardial lesions in isoproterenol induced rat cardiomyopathy. Cardiovasc Res. 1987;21(12):916-21.

46. Bestetti RB. Role of parasites in the pathogenesis of Chagas' cardiomyopathy. Lancet. 1996;347(9005):913-4.

47. Bestetti RB, Cardinalli-Neto A, Otaviano AP, Nakazone MA, Bertolino ND, Nogueira PR. Hyponatremia in Chagas disease heart failure: Prevalence, clinical characteristics, and prognostic importance. CTRSC 2015;11:6-9.

48. Bristow MR. The adrenergic nervous system in heart failure. N Engl J Med. 1984;311(13):850-1.

Figure Legends

Figure 1. Kaplan-Meier survival analysis of patients with and without left ventricular reverse remodeling considering reduction of left ventricle end-diastolic diameter and improvement of left ventricular ejection fraction.

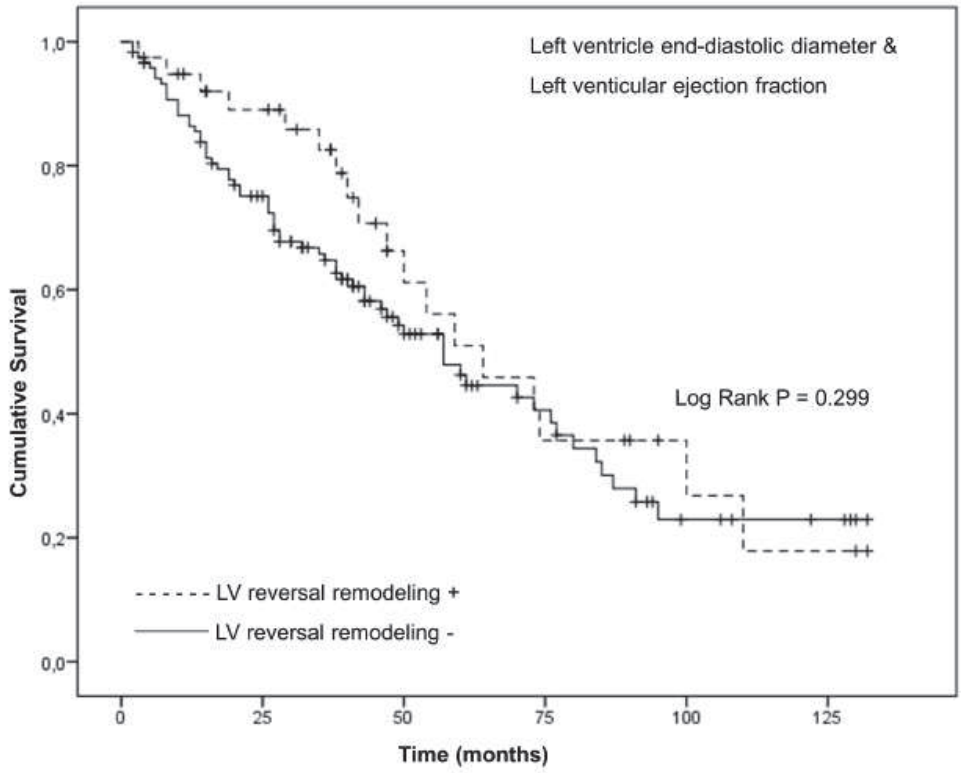
Left ventricle end-diastolic diameter &
Left venticular ejection fraction
Log Rank P = 0.299
LV reversal remodeling +
LV reversal remodeling -
Cumulative Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
25
50
75
100
125
Time (months)

Table 1. Baseline characteristics of 159 patients analyzed for occurrence of Left Ventricular Reverse Remodeling.

Baseline characteristics	All patients (159)	LVRR+ (39)	LVRR- (120)	P Value
	Median (25th - 75th) or N (%)			
Variable				
Age (years)	57 (47 - 66)	58 (52 - 67)	56 (45 - 65)	0.159
Gender (male)	102 (64.2)	23 (59.0)	79 (65.8)	0.438
NYHA Classes I and II	118 (74.2)	33 (84.6)	85 (70.8)	0.087
NYHA Classes III and IV	41 (25.8)	6 (15.4)	35 (29.2)	0.087
Heart rate (beats/min)	68 (60 - 78)	68 (60 - 80)	68 (60 - 76)	0.681
SBP (mmHg)	110 (100 - 120)	110 (100 - 120)	110 (100 - 120)	0.667
DBP (mmHg)	70 (60 - 80)	70 (70 - 80)	70 (60 - 80)	0.136
Diabetes Mellitus	4 (2.5)	2 (5.1)	2 (1.7)	0.252
Laboratory analysis				
Hemoglobin (g/dL)	13.2 (12.0 - 14.0)	13.8 (12.0 - 14.1)	13.2 (12.0 -14.0)	0.877
Sodium (mg/dL)	141 (138 - 144)	141 (137 - 144)	141 (138 - 144)	0.794
Potassium (mg/dL)	4.4 (4.1 - 4.8)	4.4 (3.9 - 4.8)	4.4 (4.1 - 4.8)	0.869
Creatinine (mg/dL)	1.2 (1.0 - 1.4)	1.1 (1.0 - 1.3)	1.2 (1.0 - 1.4)	0.157
CKD-EPI (mL/min/1.73m²)	63.5 (51.1 - 78.6)	65.3 (52.2 - 78.6)	63.3 (50.6 - 79.2)	0.658
Electrocardiography				
Atrial fibrillation	41 (25.8)	12 (30.8)	29 (24.2)	0.413
ICD	23 (14.5)	6 (15.4)	17 (14.2)	0.851
Pacemaker	84 (52.8)	18 (46.2)	66 (55.0)	0.336
LBBB	21 (13.2)	3 (7.7)	18 (15.0)	0.242
RBBB	63 (39.6)	16 (41.0)	47 (39.2)	0.837
LAFB	59 (37.1)	15 (38.5)	44 (36.7)	0.840
Low voltage of QRS	9 (5.7)	1 (2.6)	8 (6.7)	0.455
VPC	71 (44.7)	19 (48.7)	52 (43.3)	0.557

LVRR=Left ventricular reverse remodeling; N=number of individuals; NYHA=New York Heart Association functional class; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; CKD-EPI=estimated glomerular filtration rate according Chronic Kidney Disease Epidemiology Collaboration; ICD=Implantable cardioverter defibrillator; LBBB=Left bundle branch block; RBBB=Right bundle branch block; LAFB=Left anterior fascicular block; VPC=Ventricular premature contraction.

Table 2. Comparison between first and last 2D-echocardiography during follow-up.

Baseline characteristics	All patients (159)	LVRR+ (55)	LVRR- (104)	P Value
	Median (25^{th} - 75^{th}) or N (%)			
First 2D-ECHO				
LVDD (mm)	64 (59 - 70)	64 (59 - 68)	64 (59 - 71)	0.605
LVSD (mm)	54 (49 - 60)	56 (50 - 60)	54 (48 - 60)	0.440
RVD (mm)	23 (19 - 28)	24 (20 - 29)	23 (18 - 28)	0.272
WMA	54 (34.0)	12 (30.8)	42 (35.0)	0.628
LVEF (%)	33.2 (26.4 - 40.1)	31.3 (24.1 – 39.0)	33.5 (27.0 - 40.8)	0.223
Last 2D-ECHO				
LVDD (mm)	66 (60 - 72)	60 (56 - 66)	67 (62 - 74)	<0.001
LVSD (mm)	56 (49 - 63)	49 (42 - 55)	58 (52 - 64)	<0.001
RVD (mm)	25 (20 - 33)	27 (22 - 35)	25 (19 - 32)	0.485
WMA	50 (31.4)	11 (28.2)	39 (32.5)	0.616
LVEF (%)	31.7 (24.8 - 41.8)	42.2 (32.2 - 47.7)	30.0 (22.7 - 36.7)	< 0.001
Comparison LVDD				
Absolute difference (mm)	1.0 (-1.0 to 4.0)	-3.0 (-6.0 to -1.0)	2.0 (0.0 to 5.0)	<0.001
Relative difference (%)	1.4 (-1.8 to 6.0)	-5.1 (-10.0 to -1.7)	3.2 (0.0 to 8.1)	<0.001
Comparison LVEF				
Absolute difference (mm)	0 (-7.8 to 6.4)	7.0 (4.0 to 11.6)	-3.1 (-10.6 to 3.2)	<0.001
Relative difference (mm)	0 (-23.3 to 23.6)	23.6 (12.7 to39.7)	-8.4 (-28.8 to 12.0)	<0.001

LVRR=Left ventricular reverse remodeling; N=number of individuals; 2D-ECHO=two-dimensional echocardiography; LVDD=Left ventricular end-diastolic diameter; LVSD=Left ventricular systolic diameter; RVD=Right ventricular diameter; WMA=Wall Motion Abnormalities; LVEF=Left ventricular ejection fraction.

Table 3. Cox proportional hazard model for independent predictors of long-term mortality.

	Univariate			Multivariate		
All patients	HR	95%CI	*P* Value	HR	95%CI	*P* Value
Age (years)	1.00	0.98 – 1.01	0.688			
Gender (male)	1.43	0.89 – 2.30	0.142			
LVRR status	0.76	0.45 – 1.28	0.303			
Cardiogenic shock	2.49	1.58 – 3.91	< 0.001	2.41	1.51 – 3.85	< 0.001
Left anterior fascicular block	1.72	1.12 – 2.65	0.014			
Serum sodium level	0.91	0.86 – 0.96	0.001	0.91	0.86 – 0.96	< 0.001

HR=Hazard ratio; CI=Confidence interval; LVRR= Left ventricular reverse remodeling.

Author Agreement Form – International Journal of Cardiology

Manuscript Title: Impact of left ventricular reverse remodeling on outcome of patients with Chagas cardiomyopathy with chronic heart failure.

List of all Authors: Marcelo Arruda Nakazone, Ana Paula Otaviano, Maurício Nassau Machado, Reinaldo Bulgarelli Bestetti

Corresponding Author: Reinaldo Bulgarelli Bestetti

This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*.

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. Int. J. Cardiol. 170 (2014) 253-254 DOI:10.1016/j.ijcard.2013.11).

On behalf of all Co-Authors, the corresponding Author shall bear full responsibility for the submission. Any changes to the list of authors, including changes in order, additions or removals will require the submission of a new author agreement form approved and signed by all the original and added submitting authors.

All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: "The authors report no relationships that could be construed as a conflict of interest".

Artigo 2: Prognostic Significance of Chronic Kidney Disease (CKD-EPI equation) and Anemia in Patients with Chronic Heart Failure Secondary to Chagas Cardiomyopathy

Autores: Marcelo Arruda Nakazone, Maurício de Nassau Machado, Ana Paula Otaviano, Ana Maria Silveira Rodrigues, Augusto Cardinalli-Neto, Reinaldo Bulgarelli Bestetti.

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Abstract

Background: Despite advances in knowledge about the impact of chronic kidney disease (CKD) and anemia in chronic heart failure (CHF), few studies have been conducted in Chagas Cardiomyopathy (CC). We aimed to evaluate the risk prediction performance of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and anemia in patients with CHF secondary to CC. Methods: From January 2000 to December 2010, a total of 232 patients were studied. The creatinine clearance (CrCl) was estimated according to CKD-EPI equation and CKD was defined as CrCl<60 mL/min/1.73m2. Anemia was defined as hemoglobin <12 g/dL for women and <13 g/dL for men. Cox proportional hazards models were used to establish independent predictors for long-term mortality. Results: At baseline, 98 individuals (42.2%) had criteria for CKD, and 41 (17.7%) had criteria for anemia. During follow-up, 136 patients (58.6%) of our population died. Independently, CKD and anemia were not associated with late-mortality, hospitalizations, cardiogenic shock, or heart transplantation indication. However, when they coexisted, an additional risk was attributed to CHF patients. Cox Proportional Hazard Models analysis identified systolic blood pressure (HR=0.99, 95%CI 0.98-1.00; P=0.015), implantable cardioverter-defibrillator (HR=0.48, 95%CI 0.27-0.85; P=0.012), left anterior fascicular block (HR=1.52, 95%CI 1.08-2.13; P=0.017), left ventricular end-diastolic diameter (HR=1.04, 95%CI 1.02-1.06; P<0.001), and serum sodium levels (HR=0.95, 95% CI 0.92-0.99; P=0.020) as independent predictors for all-cause mortality. Conclusions: CKD and anemia are not independent predictors for long-term mortality in patients with CC. In survival analysis, however, probability of survival is poorer in CKD and anemic patients than in those without.

Keywords	Chronic Kidney Disease; Anemia; Chagas Cardiomyopathy; Chronic Heart Failure; Prognosis; Mortality.
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Research Data Related to this Submission

There are no linked research data sets for this submission. The following reason is given:
Data will be made available on request

August, 13th, 2017.

Prof. Dr. Paolo G. Camici, MD, FESC, FACC, FAHA, FRCP
Editor-in-Chief of
International Journal of Cardiology

Dear Prof. Dr. Camici,

We are sending a manuscript entitled "Prognostic significance of Chronic Kidney Disease (CKD-EPI equation) and Anemia in patients with Chronic Heart Failure secondary to Chagas Cardiomyopathy" for evaluation of publication in *International Journal of Cardiology*.

Chagas disease has been found throughout the world in view of international immigration. In fact, it has been estimated that 750,000 persons with Chagas disease are living outside South America, and the global costs associated with this disease are about US 7,2 billion each year, higher than that observed in several types of cancer. A few years ago, common comorbidities as chronic kidney disease and anemia have been associated with poorer prognosis when coexist in non-Chagas Cardiomyopathy.

Recently, a new and more accurate estimating equation for glomerular filtration rate was proposed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI), internally and externally validated. Unfortunately, however, no data exist regarding the prevalence and the burden of chronic kidney disease according CKD-EPI in patients with Chagas Cardiomyopathy.

In this paper, we have shown that these patients had a similar prevalence of chronic kidney disease and anemia to those with non-Chagas disease. However, the dismal prognosis of Chagas Cardiomyopathy seems decrease the impact of these severe conditions, nulling their independent predictor potential for long-term mortality.

Therefore, the relevance of these results prompts me to submit the paper to *International Journal of Cardiology*.

Thank you in advance for your attention.

Sincerely yours,

Reinaldo B. Bestetti, MD, PhD, FESC

Title Page

Prognostic significance of Chronic Kidney Disease (CKD-EPI equation) and Anemia in patients with Chronic Heart Failure secondary to Chagas Cardiomyopathy☆

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☆The authors report no relationship that could be construed as a conflict of interest.

This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Short title: Chonic Kidney Disease and Anemia in Chagas Cardiomyopathy

Key words: Chronic Kidney Disease; Anemia; Chagas Cardiomyopathy; Chronic Heart Failure; Prognosis; Mortality.

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Abstract

Background: Despite advances in knowledge about the impact of chronic kidney disease (CKD) and anemia in chronic heart failure (CHF), few studies have been conducted in Chagas Cardiomyopathy (CC). We aimed to evaluate the risk prediction performance of the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation and anemia in patients with CHF secondary to CC.

Methods: From January 2000 to December 2010, a total of 232 patients were studied. The creatinine clearance (CrCl) was estimated according to CKD-EPI equation and CKD was defined as CrCl<60 mL/min/1.73m^2. Anemia was defined as hemoglobin <12 g/dL for women and <13 g/dL for men. Cox proportional hazards models were used to establish independent predictors for long-term mortality.

Results: At baseline, 98 individuals (42.2%) had criteria for CKD, and 41 (17.7%) had criteria for anemia. During follow-up, 136 patients (58.6%) of our population died. Independently, CKD and anemia were not associated with late-mortality, hospitalizations, cardiogenic shock, or heart transplantation indication. However, when they coexisted, an additional risk was attributed to CHF patients. Cox Proportional Hazard Models analysis identified systolic blood pressure (HR=0.99, 95%CI 0.98-1.00; P=0.015), implantable cardioverter-defibrillator (HR=0.48, 95%CI 0.27-0.85; P=0.012), left anterior fascicular block (HR=1.52, 95%CI 1.08-2.13; P=0.017), left ventricular end-diastolic diameter (HR=1.04, 95%CI 1.02-1.06; P<0.001), and serum sodium levels (HR=0.95, 95% CI 0.92-0.99; P=0.020) as independent predictors for all-cause mortality.

Conclusions: CKD and anemia are not independent predictors for long-term mortality in patients with CC. In survival analysis, however, probability of survival is poorer in CKD and anemic patients than in those without.

1. Introduction

Chronic systolic heart failure (CHF) is an insidious syndrome that results in a varying degrees of functional impairment. Although great advances have been made over the past thirty years in the management of this condition, it still carries an unfavorable outcome, despite the recognitions of predictors of left ventricular remodeling all-cause mortality, and modern CHF therapy (1, 2). CHF secondary to Chagas cardiomyopathy (CC) has a poor prognosis compared to other etiologies (3-6), and unfortunately CC remains the leading cause of CHF in areas where the disease is endemic (7, 8).

The chronic kidney disease (CKD) has emerged as a major health concern worldwide with its high prevalence and heavy economic burdens imparted on society (9). CKD is also associated with significantly increased risks of cardiovascular disease morbidity and mortality, even at its earliest stage (10). Glomerular filtration rate (GFR) is the best overall index of kidney function and is widely used in the diagnosis, evaluation and management of CKD (11). In 2009, a new estimating equation for GFR was proposed by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) (12), internally and externally validated, providing more accurate estimates and better risk predictions (13).

Anemia is a common comorbidity in CHF patients and is associated with poorer prognosis (14, 15). Al-Ahmad et al. (16) found that CKD and anemia are independent risk factors for death among patients with CHF enrolled in the Studies of LV Dysfunction (SOLVD) clinical trial, in disagreement to previous studies that did not observe contribution of anemia to the risk of death (17-19). Since CHF commonly causes renal impairment it is possible that severe CHF is a very common cause of progressive renal

failure. To this vicious circle is often added anemia, which can be produced not only by CKD but by CHF as well, thus worsening both conditions (20).

In this context, the primary purpose of this study was to evaluate the long-term mortality risk stratification performance of the CKD-EPI equation and of anemia in patients with CC. The secondary purpose was to determine the independent predictors of all-cause mortality in our population during a long-term follow-up (more than 10 years).

2. Methods

2.1 Patients selection

This single-center study retrospectively evaluated patients with two positive serologic test for Chagas disease (ELISA and indirect immunofluorescence) according to the World Health Organization recommendation (21). The diagnosis of CHF has been made by the attending physicians using the Framingham Criteria for Heart Failure Diagnosis (22). After clinical diagnosis of CHF, a 2-D echocardiography was performed in each patient to confirm the clinical diagnosis, quantify this condition using left ventricular ejection fraction (LVEF), and guide the treatment according to the classification. Individuals with clinical diagnosis for CHF secondary to CC and LVEF < 55% on 2-D echocardiography confirming left ventricular systolic dysfunction were screened for this study. Patients with a concomitant disease that could potentially cause heart disease by itself were excluded.

This study was conducted in accordance with the Declaration of Helsinki and approved through the local Human Research Ethics Committee of São José do Rio Preto Medical School (CAAE - 02716112.6.0000.5415). The need for individual informed consent was waived, as this study was a retrospective analysis of prospectively collected data for routine care, and breach of privacy or anonymity did not occur.

2.2 Baseline measurements

The demographics data, New York Heart Association (NYHA) functional class, heart rate, systemic arterial pressure, medical history, standard laboratory tests, 12-lead resting electrocardiogram and cardiac electronic implantable devices information were noted at study entry by attending physicians, and were retrieved from medical charts records.

Anemia was defined as hemoglobin < 12 g/dL for women and < 13 g/dL for men (23). The creatinine clearance was estimated according to CKD-EPI equation (12) and CKD was defined as a creatinine clearance < 60 mL/min/1.73m^2. The original estimating GFR according CKD-EPI equation [eGFR CKD-EPI] is: eGFRCKD-EPI = 141 × min (serum creatinine/k, 1)α × max (serum creatinine/k, 1)−1.209 × 0.993Age × 1.018 (if female) × 1.159 (if African American), where k is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min indicates the minimum of serum creatinine/k or 1, and max indicates the maximum of serum creatinine/k or 1. Considering that Brazilians form one of the most heterogeneous populations in the world, which is the result of five centuries of interethnic crosses of people from three continents, the specific dissection of ancestry represents serious theoretical difficulties (24), besides questions arising from preferences for self-declarations of ancestry, we considered all patients as Caucasian for eGFR CKD-EPI equation.

2.3 Prospective follow-up

The patients were routinely followed in a public referral center for CHF in a Brazilian Medical School facility from January, 2000 to December, 2010. The CHF medical therapy information was retrieved from a prospectively collected database of

patients. All patients received evidence-based treatment for CHF, according to international guidelines of the time. Thus, treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blocks and beta-blockers at targeted or maximal tolerated doses was considered for all patients. Those with pitting edema received furosemide, while those in the NYHA Class III/IV with a LVEF < 30% were treated with digoxin. Patients usually visited the outpatient service each four months, and a senior heart failure specialist supervised the treatment given. Patients were followed until the close study; they were also censored at heart transplantation or death.

2.4 Data Analysis

The data were analyzed using the IBM SPSS Statistical Package v.21 (IBM Corporation, Armonk, NY). The variables are presented as absolute numbers and percentages and median and interquartile ranges (25^{th} and 75^{th} percentile) when applicable. Due to the lack of Gaussian distribution, continuous variables were compared using the nonparametric Mann-Whitney test. Chi-square or Fisher's exact tests were used to compare categorical variables.

Univariate and multivariable Cox proportional hazards models (stepwise backward elimination method) were used to determine independent predictors for all-cause mortality during a long-term follow-up. After univariate analysis, variables with clinical relevance and $P < 0.10$ were included in the multivariate model. Continuous variables underwent the Spearman test to establish correlation among them. The variable who correlated with others and with the highest Wald coefficient remained in the model, whereas the other were ruled out. Thus, each variable entered the multivariable model in a proportional to 10 events in an attempt to avoid overfitting. The multivariate model was then adjusted for age, gender, NYHA functional class, heart rate (beats/minute), systolic

and diastolic blood pressures (mmHg), need for implantable cardioverter-defibrillator (ICD), left anterior fascicular block on 12-lead resting electrocardiography, left ventricular end-diastolic diameter (mm), serum sodium level (mEq/L), anemia status and CKD according eGFR CKD-EPI (< 60 mL/min/1.73m^2). The adjusted Hazard Ratio (HR) and 95% confidence intervals (95% CI) were calculated for the predictors. Cumulative survival graphic (Kaplan-Meier) was constructed to show differences in event-free survival (mortality from all causes) between patients with CHF secondary to CC according to the presence of CKD and anemia associated to NYHA functional classes. P-values < 0.05 were considered statistically significant (two-tailed).

3. Results

A total of 234 patients were initially screened for the study. Two patients with no hemoglobin measurement were ruled out of the investigation. Thus, 232 individuals (65.9% male) who had a median age of 56 years (45 - 66) and fulfilled inclusion criteria were entered the study. The baseline characteristics of patients are shown in Table 1.

These individuals were divided into groups: with or without CKD according eGFR CKD-EPI and with or without anemia according hemoglobin serum levels. Ninety-eight patients (42.2%) had renal dysfunction, whereas 41 (17.7%) had anemia. Patients with CKD status were older (median for age = 63 years), had higher right ventricular diameters (median = 27mm), showed lower spontaneous heart rate (median = 66 beats/min) and, consequently, they had more need for pacemaker (63.3%) at start of outpatient follow-up compared to individuals with no CKD (median for age = 52 years, P < 0.001; median = 23mm, P = 0.011; median = 70 beats/min, P = 0.026; and 44.0%, P = 0.001; respectively). Anemic patients were older (median for age = 63 years) and had higher rate (12.2%, data not shown in Table) for end-stage renal disease (eGFR CKD-

EPI < 30 mL/min/1.73m²) compared to non-anemic individuals (median for age = 55 years, P = 0.010 and 3.1%, P = 0.028; respectively). The other laboratory tests, 2D-echocardiographic and 12-lead resting electrocardiography findings observed at study entry were not associated with CKD or anemia status (Table 2).

Our population received maximal tolerated daily doses of medications, according to guideline recommendations during the long-term of follow-up, considering mean daily dose (mg/day) of Enalapril (14.8 ± 7.8), Captopril (77.6 ± 40.7), Ramipril (8.2 ± 2.8), Losartan (47.5 ± 19.9), Carvedilol (25.9 ± 18.6), Metoprolol Succinate (123.0 ± 63.5), Spironolactone (27.5 ± 12.4), Furosemide (88.7 ± 57.7), Amiodarone (229.2 ± 100.2), and Digoxin (0.182 ± 0.065).

Clinical complications as hospitalization due to acute decompensated heart failure, cardiogenic shock and need to heart transplantation were similar between patients with CKD and anemia (P > 0.05 for all subgroups). During follow-up (median 799 days, interquartile range 291 to 1441 days), 136 patients (58.6%) died. Similar rates for late-mortality (more than 10 years) were showed by individuals with CKD (60.2%) and anemia (68.3%) compared to those with no CKD (57.5%, P = 0.675) and non-anemics (56.5%, P = 0.166); respectively.

After adjustment, the Cox Proportional Hazard Model analysis identified five variables as independent predictors for all-cause mortality: systolic blood pressure (HR = 0.99, 95% CI 0.98 to 1.00; P = 0.015), use of implantable cardioverter-defibrillator (HR = 0.48, 95% CI 0.27 to 0.85; P = 0.012), left anterior fascicular block (HR = 1.52, 95% CI 1.08 to 2.13; P = 0.017), left ventricular end-diastolic diameter (HR = 1.04, 95% CI 1.02 to 1.06; P < 0.001), and serum sodium level (HR = 0.95, 95% CI 0.92 to 0.99; P = 0.020); (Table 3). Interestingly, anemia and CKD status according eGFR CKD-EPI (< 60 mL/min/1.73m²) were not retained in the multivariate model as independent predictors.

Probability of survival for patients with CKD was 73.3%, 58.2%, 49.8%, and 33.6% at 12, 24, 36 and 60 months respectively, and for patients with no CKD was 83.0%, 67.3%, 56.5%, and 39.5% at 12, 24, 36, and 60 months respectively (P = 0.254). The probability of survival for individuals with anemia was 72.9%, 64.9%, 52.1%, and 29.2% at 12, 24, 36 and 60 months respectively, and for patients with no anemia was 80.3%, 63.1%, 53.9%, and 38.7% at 12, 24, 36, and 60 months respectively (P = 0.111). A lower survival probability for patients with CC according to functional classes of CHF was observed. Moreover, CKD and anemia status significantly showed an additional impact on survival for patients with CC (P < 0.001, Figure 1).

4. Discussion

In our study, we evaluated the long-term mortality risk stratification performance of CKD and anemia in outpatients individuals with CC. Although previous studies have addressed these variables on the prognosis of patients with CHF secondary to CC, this work is the first cohort of Brazilians assessed using the eGFR CKD-EPI equation, that provides more accurate estimates and better predictive power. Our investigation clearly showed that survival probabilities of patients with CHF secondary to CC, allocated into the same group for NYHA functional classes, are lower in those with CKD and anemia, particularly in severe CHF individuals. Nonetheless, neither CKD (CKD-EPI equation) nor anemia are independent predictors for all-cause mortality in patients with CC, suggesting the poorer prognosis of this condition.

The CHF secondary to CC is a major public health problem in Latin America, where about 10,000 people die of this disease annually (25), causing a profound socio-economic impact (26). CKD is a common comorbidity in CHF patients and is associated with the disease severity, worse prognosis and higher anemia prevalence (27, 28).

Nevertheless, there are few published studies relating CKD and anemia with CHF in patients with CC. In our series, the prevalence of CKD was 42.3%, similarly to that observed in non-Chagas population enrolled in clinical trials or data obtained from prospective longitudinal cohort studies (29-31).

Compared to individuals with no CKD, those with this condition were older, had higher right ventricular diameters, showed lower median for spontaneous heart rate and, consequently, more need for pacemaker, suggesting higher severity of CC. However, as previously reported by our group (32) and Ferreira et al. (33), this investigation did not confirm the isolated association between CKD and worse outcomes, including mortality. The younger status of our patients with no underlying ischemic conditions (coronary artery disease, peripheral and/or cerebrovascular diseases) may account, at least in part, for our different results. Moreover, there was higher proportion of patients on renin-angiotensin-aldosterone blockade (30) at maximal tolerated doses according guidelines recommendations and individuals with chronic systolic dysfunction only, managed in specialized heart failure outpatient clinic, facts that may have contributed to reduction of renal impairment influence on mortality.

In end-stage renal disease population, anemia is well-recognized risk factor for all-cause mortality (34), occurring mainly due to erythropoietin deficiency. In addition, anemia also occurs in individuals with less severe renal dysfunction (16) in several other disorders, as bone marrow depression, that interfere with the action of erythropoietin and cellular release and utilization of iron (35). Our investigation showed a prevalence of 17.7% of anemia in CC population, slightly higher rate compared to similar Brazilian cohort (36). However, this prevalence may vary from 4 to 69.7%, depending on the diagnostic criteria and the study population, increasing in accordance to age and severity of CHF and other comorbidities, as nutritional status and low weight patients (14, 37).

On the other hand, our data are consistent with those of Miguel et al. (38), who studied a smaller population of CC patients with CHF.

Furthermore, our findings were opposite to results described by Ferreira et al. (33) that evidenced high prevalence of anemia among patients with CHF and an isolated significant impact on their survival, even for mild degree of anemia. Although in distinct population, Al-Ahmad et al. (16) hypothesized four potential explanations for poorer prognosis in this individuals: level of hematocrit may be an additional marker of cardiac function; severe CHF may cause anemia through undefined mechanisms; reduced hematocrit may be a risk factor for ischemia, worsening this manifestation, mainly in organisms with pre-existing heart disease; and lower hematocrit may result in ventricular remodeling and cardiac dysfunction, culminating in a vicious cycle (39).

Anemic patients were older and showed higher rate for end-stage renal disease compared to non-anemic individuals, emphasizing the known association between these comorbidities (34, 40). Moreover, the subgroup analysis showed that patients allocated into the same group for NYHA functional classes, had lower survival probability when CKD and anemia coexist with CHF, evidencing the burden of these conditions. However, in our series, neither CKD nor anemia were independent predictors of worse outcomes, including hospitalization due to acute decompensated heart failure, cardiogenic shock, need to heart transplantation, and long-term mortality. This finding suggests that they are markers, and not independent risk-factors for, all-cause mortality in Brazilian patients with CC (38).

In the multivariate model, left ventricular end-diastolic diameter and left anterior fascicular block were positively associated with mortality, confirming previous findings and well-known risk factors (41). On the other hand, our investigation showed systolic blood pressure, use of ICD, and sodium serum level as independent protective factors for

mortality. In accordance with our results, there was one percent of risk reduction at each elevation of 1 mmHg of systolic blood pressure. One possible explanation for the protective effect is the fact that patients with higher blood pressure undergo pharmacologic treatment considering higher doses of renin-angiotensin-aldosterone blockade drugs and beta-blockers, therapy with known survival improvement effect (41, 42). The fact that CC may considered a type of a catecholaminergic cardiomyopathy (43), which is reversed by beta-blockers (44) lend further support to this assumption. Regarding the use of ICD, we believe that the main reason for this finding is the prevention of sudden cardiac death due to life-threatening ventricular arrhythmias, common clinical complication in patients with severe CHF secondary to CC (8, 45). Furthermore, as previously demonstrated by our group, hyponatremia is an independent predictor of all-cause mortality for this population (46, 47) and may appear as consequence of marked activation of the renin-angiotensin-aldosterone and autonomic nervous systems, which ultimately determines myocyte death, reparative fibrosis, and ventricular remodeling (48, 49). In this context, maybe be prudent avoid hyponatremia to counteract the deleterious effect of activation of the involved systems.

4.1 Strength and limitations

This study has some limitations. Our investigation was a retrospective view of a prospective patients' cohort. Therefore, unmeasured factors may have biased our findings. We did not determine the etiology and the incidence of worsening CKD. Detecting worsening renal dysfunction over time would be interesting to detect potential association with death. Moreover, we did not investigate the specific cause of anemia, including iron, folate and vitamin B12 deficiencies, dilutional anemia, and the anemia of not surveyed chronic diseases. On the other hand, the data were prospectively collected,

and the statistical analysis performed appears to have avoided the overfitting phenomenon, thus making our date reliable. Besides, our sample size was reasonable, and patients received evidence-based treatment, thus reflecting the contemporary era of heart failure treatment.

5. Conclusions

CKD and anemia are not independent predictors for long-term mortality in patients with CHF secondary to CC, by itself, has a worse prognosis. However, patients with these comorbidities have lower survival probabilities, in despite of their respective NYHA functional classifications.

References

1. Bestetti RB. Predictors of unfavourable prognosis in chronic Chagas' disease. Trop Med Int Health. 2001;6(6):476-83.

2. Bocchi EA, Bestetti RB, Scanavacca M, Cunha-Neto E, Issa VS. Chronic Chagas heart disease management: from etiology to cardiomyopathy treatment. J Am Coll Cardiol 2017, in press.

3. Vilas Boas LG, Bestetti RB, Otaviano AP, Cardinalli-Neto A, Nogueira PR. Outcome of Chagas cardiomyopathy in comparison to ischemic cardiomyopathy. Int J Cardiol. 2013;167(2):486-90.

4. Bestetti RB, Otaviano AP, Fantini JP, Cardinalli-Neto A, Nakazone MA, Nogueira PR. Prognosis of patients with chronic systolic heart failure: Chagas disease versus systemic arterial hypertension. Int J Cardiol. 2013;168(3):2990-1.

5. Pereira Nunes Mdo C, Barbosa MM, Ribeiro AL, Amorim Fenelon LM, Rocha MO. Predictors of mortality in patients with dilated cardiomyopathy: relevance of chagas disease as an etiological factor. Rev Esp Cardiol. 2010;63(7):788-97.

6. Barbosa AP, Cardinalli Neto A, Otaviano AP, Rocha BF, Bestetti RB. Comparison of outcome between Chagas cardiomyopathy and idiopathic dilated cardiomyopathy. Arq Bras Cardiol. 2011;97(6):517-25.

7. Bocchi EA, Marcondes-Braga FG, Bacal F, Ferraz AS, Albuquerque D, Rodrigues Dde A, et al. [Updating of the Brazilian guideline for chronic heart failure - 2012]. Arq Bras Cardiol. 2012;98(1 Suppl 1):1-33.

8. Bestetti RB, Theodoropoulos TA, Cardinalli-Neto A, Cury PM. Treatment of chronic systolic heart failure secondary to Chagas heart disease in the current era of heart failure therapy. Am Heart J. 2008;156(3):422-30.

9. Khan S, Amedia CA, Jr. Economic burden of chronic kidney disease. J Eval Clin Pract. 2008;14(3):422-34.

10. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375(9731):2073-81.

11. Wang Y, Katzmarzyk PT, Horswell R, Zhao W, Johnson J, Hu G. Comparison of the heart failure risk stratification performance of the CKD-EPI equation and the MDRD equation for estimated glomerular filtration rate in patients with Type 2 diabetes. Diabet Med. 2016;33(5):609-20.

12. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

13. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. Am J Kidney Dis. 55. United States2010. p. 622-7.

14. Lindenfeld J. Prevalence of anemia and effects on mortality in patients with heart failure. Am Heart J. 2005;149(3):391-401.

15. Anand I, McMurray JJ, Whitmore J, Warren M, Pham A, McCamish MA, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation. 2004;110(2):149-54.

16. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol. 2001;38(4):955-62.

17. Haber HL, Leavy JA, Kessler PD, Kukin ML, Gottlieb SS, Packer M. The erythrocyte sedimentation rate in congestive heart failure. N Engl J Med. 1991;324(6):353-8.

18. Parameshwar J, Keegan J, Sparrow J, Sutton GC, Poole-Wilson PA. Predictors of prognosis in severe chronic heart failure. Am Heart J. 1992;123(2):421-6.

19. Cowie MR, Wood DA, Coats AJ, Thompson SG, Suresh V, Poole-Wilson PA, et al. Survival of patients with a new diagnosis of heart failure: a population based study. Heart. 2000;83(5):505-10.

20. Silverberg DS, Wexler D, Blum M, Iaina A. The cardio renal anemia syndrome: correcting anemia in patients with resistant congestive heart failure can improve both cardiac and renal function and reduce hospitalizations. Clin Nephrol. 2003;60 Suppl 1:S93-102.

21. Control of Chagas disease. World Health Organ Tech Rep Ser. 2002;905:i-vi, 1-109, back cover.

22. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation. 1993;88(1):107-15.

23. Nutritional anaemias. Report of a WHO scientific group. World Health Organ Tech Rep Ser. 1968;405:5-37.

24. Parra FC, Amado RC, Lambertucci JR, Rocha J, Antunes CM, Pena SD. Color and genomic ancestry in Brazilians. Proc Natl Acad Sci U S A. 2003;100(1):177-82.

25. Chagas disease (American trypanosomiasis) - fact sheet (revised in August 2012). Wkly Epidemiol Rec. 2012;87(51/52):519-22.

26. Abuhab A, Trindade E, Aulicino GB, Fujii S, Bocchi EA, Bacal F. Chagas' cardiomyopathy: the economic burden of an expensive and neglected disease. Int J Cardiol. 2013;168(3):2375-80.

27. Hillege HL, Nitsch D, Pfeffer MA, Swedberg K, McMurray JJ, Yusuf S, et al. Renal function as a predictor of outcome in a broad spectrum of patients with heart failure. Circulation. 2006;113(5):671-8.

28. 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. J Am Coll Cardiol. 2000;35(3):681-9.

29. Waldum B, Westheim AS, Sandvik L, Flonaes B, Grundtvig M, Gullestad L, et al. Renal function in outpatients with chronic heart failure. J Card Fail. 2010;16(5):374-80.

30. McAlister FA, Ezekowitz J, Tonelli M, Armstrong PW. Renal insufficiency and heart failure: prognostic and therapeutic implications from a prospective cohort study. Circulation. 2004;109(8):1004-9.

31. Castagno D, Jhund PS, McMurray JJ, Lewsey JD, Erdmann E, Zannad F, et al. Improved survival with bisoprolol in patients with heart failure and renal impairment: an analysis of the cardiac insufficiency bisoprolol study II (CIBIS-II) trial. Eur J Heart Fail. 2010;12(6):607-16.

32. Ardito SQ, Bestetti RB, Cardinalli-Neto A, Otaviano AP, Nogueira PR. Chronic renal impairment in patients with Chagas cardiomyopathy with chronic systolic heart failure: prevalence and prognostic significance. Int J Cardiol. 152. Netherlands2011. p. 133-4.

33. Ferreira SM, Guimaraes GV, Cruz FD, Issa VS, Bacal F, Souza GE, et al. Anemia and renal failure as predictors of risk in a mainly non-ischemic heart failure population. Int J Cardiol. 141. Netherlands: Copyright 2008 Elsevier Ireland Ltd. All rights reserved.; 2010. p. 198-200.

34. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE. The impact of anemia on cardiomyopathy, morbidity, and and mortality in end-stage renal disease. Am J Kidney Dis. 1996;28(1):53-61.

35. Goicoechea M, Martin J, de Sequera P, Quiroga JA, Ortiz A, Carreno V, et al. Role of cytokines in the response to erythropoietin in hemodialysis patients. Kidney Int. 1998;54(4):1337-43.

36. Fernandes AM, Bortoncello AF, Sahade V, de Macedo CR, Borges IC, Andrade DC, et al. Malnutrition, anemia and renal dysfunction in patients with Chagasic cardiomyopathy. Int J Cardiol. 151. Netherlands2011. p. 109-10.

37. Anker SD, Sharma R. The syndrome of cardiac cachexia. Int J Cardiol. 2002;85(1):51-66.

38. Miguel CE, Bortoluzzi TB, Otaviano AP, Cardinalli-Neto A, Rocha BF, Ferrari SJ, et al. Prognostic significance of anemia in patients with chronic systolic heart failure secondary to Chagas' cardiomyopathy. Acta Trop. 2011;120(3):219-23.

39. Ronco C, Cicoira M, McCullough PA. Cardiorenal syndrome type 1: pathophysiological crosstalk leading to combined heart and kidney dysfunction in the setting of acutely decompensated heart failure. J Am Coll Cardiol. 2012;60(12):1031-42.

40. O'Riordan E, Foley RN. Effects of anaemia on cardiovascular status. Nephrol Dial Transplant. 2000;15 Suppl 3:19-22.

41. Bestetti RB, Otaviano AP, Cardinalli-Neto A, da Rocha BF, Theodoropoulos TA, Cordeiro JA. Effects of B-Blockers on outcome of patients with Chagas' cardiomyopathy with chronic heart failure. Int J Cardiol. 2011;151(2):205-8.

42. Issa VS, Amaral AF, Cruz FD, Ferreira SM, Guimaraes GV, Chizzola PR, et al. Beta-blocker therapy and mortality of patients with Chagas cardiomyopathy: a subanalysis of the REMADHE prospective trial. Circ Heart Fail. 2010;3(1):82-8.

43. Bestetti RB, Ramos CP, Figueredo-Silva J, Sales-Neto VN, Oliveira JS. Ability of the electrocardiogram to detect myocardial lesions in isoproterenol induced rat cardiomyopathy. Cardiovasc Res. 1987;21(12):916-21.

44. Bestetti RB, Sales-Neto VN, Pinto LZ, Soares EG, Muccillo G, Oliveira JS. Effects of long term metoprolol administration on the electrocardiogram of rats infected with T cruzi. Cardiovasc Res. 1990;24(7):521-7.

45. Bestetti RB, Cardinalli-Neto A. Sudden cardiac death in Chagas' heart disease in the contemporary era. Int J Cardiol. 2008;131(1):9-17.

46. Bestetti R, Cardinalli Neto A, Otaviano AP, Bertolino ND, Nakazone MA, Nogueira PR. Hyponatremia in patients with chronic heart failure secondary to Chagas cardiomyopathy in the contemporary era. European Journal of Heart Failure. 2014;16:36.

47. Bestetti RB, Cardinalli-Neto A, Otaviano AP, Nakazone MA, Bertolino ND, Nogueira PR. Hyponatremia in Chagas disease heart failure: Prevalence, clinical characteristics, and prognostic importance. 2015;11:6-9.

48. Bristow MR. The adrenergic nervous system in heart failure. N Engl J Med. 1984;311(13):850-1.

49. Tan LB, Jalil JE, Pick R, Janicki JS, Weber KT. Cardiac myocyte necrosis induced by angiotensin II. Circ Res. 1991;69(5):1185-95.

Figure Legend

Figure 1. Survival probabilities of patients with chronic heart failure secondary to Chagas Cardiomyopathy according to the presence of chronic kidney disease and anemia associated to New York Heart Association functional classes.

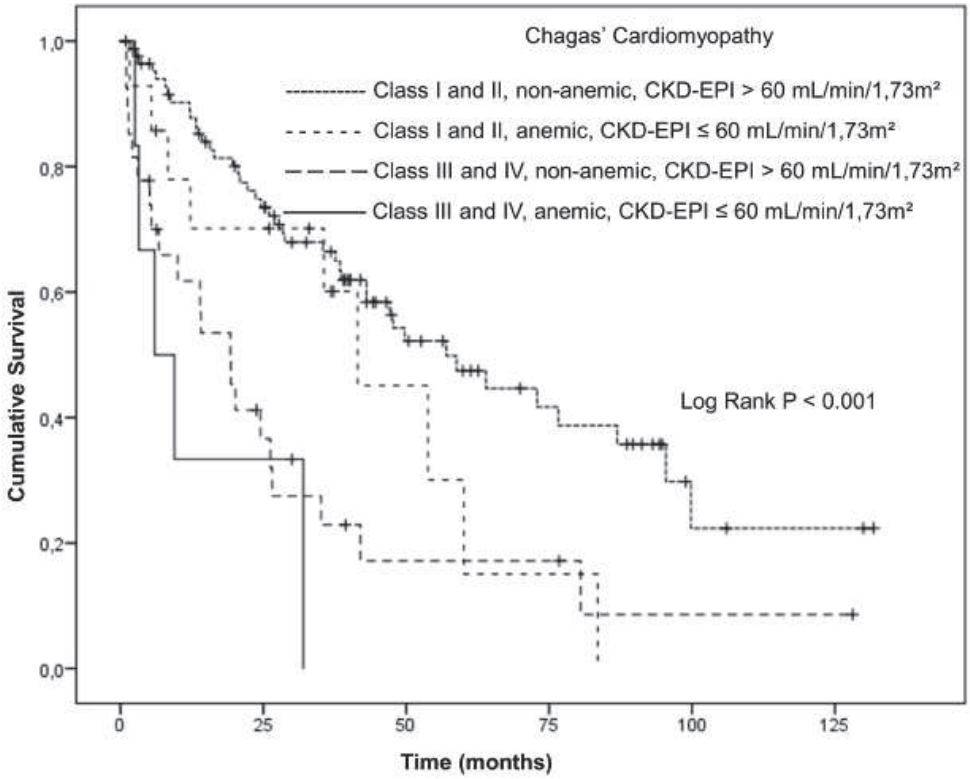
Chagas' Cardiomyopathy
Class I and II, non-anemic, CKD-EPI > 60 mL/min/1,73m²
Class I and II, anemic, CKD-EPI ≤ 60 mL/min/1,73m²
Class III and IV, non-anemic, CKD-EPI > 60 mL/min/1,73m²
Class III and IV, anemic, CKD-EPI ≤ 60 mL/min/1,73m²
Log Rank P < 0.001
Cumulative Survival
1,0
0,8
0,6
0,4
0,2
0,0
0
25
50
75
100
125
Time (months)

Table 1. Baseline characteristics of Chagas Cardiomyopathy prospective cohort (N = 232) analyzed for occurrence of chronic kidney disease and anemia.

Variable	Median (25^{th} - 75^{th}) or N (%)
Clinical characteristics	
Age (years)	56 (45 – 66)
Gender (male)	153 (65.9)
NYHA Classes I and II	157 (67.7)
NYHA Classes III and IV	75 (32.3)
Heart rate (beats/min)	68 (60 – 80)
Systolic blood pressure (mmHg)	110 (100 – 120)
Diastolic blood pressure (mmHg)	70 (60 – 80)
Type 2 Diabetes Mellitus	11 (4.7)
Laboratory analysis	
Sodium (mEq/L)	141 (138 – 144)
Potassium (mEq/L)	4.4 (4.0 – 4.8)
12-lead resting electrocardiography	
Atrial fibrillation	63 (27.2)
Implantable Cardioverter-Defibrillator	26 (11.2)
Pacemaker	124 (53.4)
Left bundle branch block	37 (15.9)
Right bundle branch block	93 (40.1)
Left anterior fascicular block	91 (39.2)
Low voltage of QRS	12 (5.2)
Ventricular premature contraction	108 (46.6)
2D-Ecochardiography	
Left ventricular end-diastolic diameter (mm)	65 (59 – 71)
Left ventricular systolic diameter (mm)	55 (50 – 61)
Right ventricular diameter (mm)	25 (20 – 30)
Wall motion abnormalities	78 (33.6)
Left Ventricular Apical Aneurysm	15 (6.5)
Left Ventricular Ejection Fraction (%)	31.7 (24.5 – 40.0)

N=number of individuals; NYHA=New York Heart Association functional class.

Table 2. Association between chronic kidney disease or anemia and other baseline characteristics.

Baseline characteristics	CKD (N = 98)	Non-CKD (N = 134)	P-value	Anemic (N = 41)	Non-anemic (N= 191)	P-value
	Median (25th - 75th) or N (%)			Median (25th - 75th) or N (%)		
Clinical characteristics						
Age (years)	63 (54 – 68)	52 (42 – 60)	< 0.001	63 (52 – 70)	55 (44 – 64)	0.010
Gender (male)	59 (60.2)	94 (70.1)	0.114	32 (78.0)	121 (63.4)	0.720
NYHA Classes I and II	61 (62.2)	96 (71.6)	0.171	25 (61.0)	132 (69.1)	0.323
NYHA Classes III and IV	37 (37.8)	38 (28.4)		16 (39.0)	59 (30.9)	
Heart rate (beats/min)	66 (60 – 74)	70 (60 – 80)	0.026	70 (60 – 79)	68 (60 – 80)	0.873
Systolic blood pressure (mmHg)	100 (90 – 120)	110 (100 – 120)	0.150	110 (90 – 120)	110 (100 – 120)	0.640
Diastolic blood pressure (mmHg)	70 (60 – 70)	70 (60 – 80)	0.097	70 (60 – 80)	70 (60 – 80)	0.523
Type 2 Diabetes Mellitus	4 (4.1)	7 (5.2)	0.764	0 (0.0)	11 (5.8)	0.220
Laboratory analysis						
Sodium (mEq/L)	141 (137 – 144)	141 (138 – 144)	0.388	141 (135 – 145)	141 (138 – 144)	0.807
Potassium (mEq/L)	4.3 (4.0 – 4.7)	4.4 (4.1 – 4.8)	0.452	4.4 (4.1 – 4.9)	4.3 (4.0 – 4.8)	0.551
12-lead resting electrocardiography						
Atrial fibrillation	30 (30.3)	33 (24.6)	0.311	13 (31.7)	50 (26.2)	0.470
ICD	10 (10.2)	16 (11.9)	0.679	5 (12.2)	21 (11.0)	0.788
Pacemaker	65 (66.3)	59 (44.0)	0.001	27 (65.9)	97 (50.8)	0.079
Left bundle branch block	12 (12.2)	25 (18.7)	0.188	7 (17.1)	30 (15.7)	0.828
Right bundle branch block	37 (37.8)	56 (41.8)	0.536	21 (51.2)	72 (37.7)	0.109
Left anterior fascicular block	36 (36.7)	55 (41.0)	0.507	16 (39.0)	75 (39.3)	0.977
Low voltage of QRS	4 (4.1)	8 (6.0)	0.521	3 (7.3)	9 (4.7)	0.449
Ventricular premature contraction	41 (41.8)	67(50.0)	0.218	24 (58.5)	84 (44.0)	0.090
2D-Ecochardiography						
Left ventricular end-diastolic diameter (mm)	66 (60 – 71)	65 (59 – 71)	0.497	64 9 59 – 74)	65 (59 – 71)	0.856
Left ventricular systolic diameter (mm)	56 (50 – 62)	55 (50 – 61)	0.544	56 (47 – 64)	55 (50 – 61)	0.839
Right ventricular diameter (mm)	27 (22 – 31)	23 (18 – 30)	0.011	25 (20 – 31)	24 (20 – 30)	0.650
Wall motion abnormalities	32 (32.7)	46 (34.3)	0.790	10 (24.4)	68 (35.6)	0.168
Left Ventricular Apical Aneurysm	5 (5.1)	10 (7.5)	0.470	2 (4.9)	13 (6.8)	1.000
Left Ventricular Ejection Fraction (%)	32.0 (23.7 – 39.0)	31.7 (25.0 – 40.8)	0.462	31.1 (24.4 – 38.3)	31.7 (24.4 – 40.1)	0.590

CKD=Chronic kidney disease; N=number of individuals; NYHA=New York Heart Association functional class; ICD=Implantable cardioverter-defibrillator.

Table 3. Cox proportional hazard model analysis for independent predictors of all-cause mortality during long-term follow-up (more than 10 years).

	Univariate			Multivariate		
All patients	HR	95% CI	P-Value	HR	95% CI	P-Value
Age (years)	1.00	0.99 – 1.01	0.876			
Gender (male)	1.27	0.88 – 1.84	0.207			
NYHA I Functional Class	0.54	0.37 – 0.77	0.001			
Heart rate (beats/min)	1.01	1.00 – 1.02	0.056			
SBP (mmHg)	0.98	0.97 – 1.00	0.006	0.99	0.98 – 1.00	0.015
DBP (mmHg)	0.98	0.96 – 1.00	0.015			
ICD	0.60	0.34 – 1.04	0.068	0.48	0.27 – 0.85	0.012
LAFB	1.63	1.16 – 2.28	0.005	1.52	1.08 – 2.13	0.017
LVDD (mm)	1.05	1.03 – 1.07	< 0.001	1.04	1.02 – 1.06	< 0.001
Serum sodium level (mEq/L)	0.93	0.89 – 0.96	< 0.001	0.95	0.92 – 0.99	0.020
Anemia status	1.31	0.86 – 2.00	0.207			
CKD status	1.21	0.86 – 1.70	0.271			

HR=Hazard ratio; CI=Confidence interval; NYHA=New York Heart Association functional class; SBP=Systolic blood pressure; DBP=Diastolic blood pressure; ICD=Implantable cardioverter-defibrillator; LAFB= Left anterior fascicular block; LVDD=Left ventricular end-diastolic diameter; CKD=Chronic kidney disease.

Author Agreement Form – International Journal of Cardiology

Manuscript Title: Prognostic significance of Chronic Kidney Disease (CKD-EPI equation) and Anemia in patients with Chronic Heart Failure secondary to Chagas Cardiomyopathy

List of all Authors: Marcelo Arruda Nakazone, Maurício Nassau Machado, Ana Paula Otaviano, Ana Maria Silveira Rodrigues, Augusto Cardinalli-Neto, Reinaldo Bulgarelli Bestetti

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This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*.

We attest that the article is the Authors' original work, has not received prior publication and is not under consideration for publication elsewhere. We adhere to the statement of ethical publishing as appears in the International of Cardiology (citable as: Shewan LG, Rosano GMC, Henein MY, Coats AJS. A statement on ethical standards in publishing scientific articles in the International Journal of Cardiology family of journals. Int. J. Cardiol. 170 (2014) 253-254 DOI:10.1016/j ijcard.2013.11).

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All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: "The authors report no relationships that could be construed as a conflict of interest".

Artigo 3: The CALLM Risk Score: a Toll to Predict Long-Term Mortality in Heart Failure Patients in an Endemic Area for Chagas Disease

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Autores: Marcelo Arruda Nakazone, Ana Paula Otaviano, Maurício de Nassau Machado, Reinaldo Bulgarelli Bestetti.

Periódico: International Journal of Cardiology

Manuscript Details

Manuscript number	IJC_2017_4319
Title	The CALLM Risk Score: a tool to predict long-term mortality in heart failure patients in an endemic area for Chagas disease
Article type	Original article

Abstract

Background: The clinical practice guidelines for chronic heart failure (CHF) recommend the use of validated risk models to estimate prognosis. We aimed to develop and to validate a simple method for predicting long-term mortality in ambulatory CHF patients in an area where Chagas disease is endemic. Methods: The development cohort included 450 patients receiving evidence-based treatment for CHF, prospectively followed for eleven years. Independent prognostic factors were identified using logistic regression analysis and thresholds defined to stratify low-, intermediate-, and -high-risk groups. The CALLM Risk Score was validated in an independent retrospective cohort with 228 individuals. Results: After multivariate analysis, five variables were independently associated with long-term mortality and subsequently included in the CALLM Risk Score: Chagas Cardiomyopathy alone (P<0.001), age ≥60 years (P=0.002), left ventricular ejection fraction <40% (P=0.027), left anterior fascicular block (P=0.005), and male gender (P=0.039). Three risk groups were identified: low-risk (score ≤4 points, 14.1% of mortality), intermediate-risk (score 5-6 points, 25.3% of mortality), and high-risk (score ≥7 points, 38.3% of mortality). The CALLM Risk Score showed discrimination characteristics with area under receiver-operating characteristic curves of 0.66 [95%CI (0.58–0.74), P<0.001] and consistent calibration [χ2 Hosmer-Lemeshow(6)=2.71, P=0.845] in the validation data set. Conclusions: The CALLM Risk Score represents a simple method with a limited number of non-invasive variables successfully predicted long-term mortality in a real-world Latin-American cohort of CHF patients in a referral center for Chagas disease. A high-risk category of patients can be easily identified in clinical practice and to alert for a rigorous management.

Keywords	Chronic Heart Failure; Chagas Cardiomyopathy; Prognosis; Mortality.
Taxonomy	Chagas Disease, Cardiomyopathy, Heart Failure
Manuscript category	Original clinical research studies, basic science/translational research papers
Manuscript region of origin	South America
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August, 21st, 2017.

Prof. Dr. Paolo G. Camici, MD, FESC, FACC, FAHA, FRCP
Editor-in-Chief of
International Journal of Cardiology

Dear Prof. Dr. Camici,

We are sending a manuscript entitled "The CALLM Risk Score: a tool to predict long-term mortality in heart failure patients in an endemic area for Chagas disease" for evaluation of publication in *International Journal of Cardiology*.

Chronic heart failure (CHF) is a leading cause of morbidity and mortality worldwide, representing a major public health problem, with an increasing incidence and prevalence. The clinical practice guidelines for CHF recommend the use of validated risk models to estimate prognosis.

However, the prognostic indices currently employed in clinical practice have several limitations. They are based on either peak oxygen consumption or invasive measures, were designed to assess patients with severe CHF in need of cardiac transplantation, were validated during hospitalization for acute decompensated heart failure, not included a substantial proportion of individuals taking contemporary evidence-based treatments, and rarely included Chagas Cardiomyopathy patients.

In this paper, we have shown that the CALLM Risk Score allows prediction of survival of ambulatory CHF patients with the use of easily obtained non-invasive variables and confirm the negative burden of Chagas etiology in CHF prognosis. Moreover, the model provides an accurate identification of a subgroup of high-risk patients who should be closely managed. The think that the paper may be of interest not only to readers from Latin America, but also to those dealing with this condition in non-endemic countries in Europe and USA.

For this reason, we are submitting the paper to *International Journal of Cardiology*.

Thank you in advance for your attention.

Sincerely yours,

Reinaldo B. Bestetti, MD, PhD, FESC

Title Page

The CALLM Risk Score: a tool to predict long-term mortality in heart failure patients in an endemic area for Chagas disease ☆

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This author takes responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

Short title: The CALLM risk score

Key words: Chronic Heart Failure; Chagas Cardiomyopathy; Prognosis; Mortality.

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Abstract

Background: The clinical practice guidelines for chronic heart failure (CHF) recommend the use of validated risk models to estimate prognosis. We aimed to develop and to validate a simple method for predicting long-term mortality in ambulatory CHF patients in an area where Chagas disease is endemic.

Methods: The development cohort included 450 patients receiving evidence-based treatment for CHF, prospectively followed for eleven years. Independent prognostic factors were identified using logistic regression analysis and thresholds defined to stratify low-, intermediate-, and -high-risk groups. The CALLM Risk Score was validated in an independent retrospective cohort with 228 individuals.

Results: After multivariate analysis, five variables were independently associated with long-term mortality and subsequently included in the CALLM Risk Score: Chagas Cardiomyopathy alone ($P<0.001$), age ≥60 years ($P=0.002$), left ventricular ejection fraction <40% ($P=0.027$), left anterior fascicular block ($P=0.005$), and male gender ($P=0.039$). Three risk groups were identified: low-risk (score ≤4 points, 14.1% of mortality), intermediate-risk (score 5-6 points, 25.3% of mortality), and high-risk (score ≥7 points, 38.3% of mortality). The CALLM Risk Score showed discrimination characteristics with area under receiver-operating characteristic curves of 0.66 [95%CI (0.58–0.74), $P<0.001$] and consistent calibration [χ^2 Hosmer-Lemeshow(6)=2.71, $P=0.845$] in the validation data set.

Conclusions: The CALLM Risk Score represents a simple method with a limited number of non-invasive variables successfully predicted long-term mortality in a real-world Latin-American cohort of CHF patients in a referral center for Chagas disease. A high-

risk category of patients can be easily identified in clinical practice and to alert for a rigorous management.

1. Introduction

Chronic heart failure (CHF) is a leading cause of morbidity and mortality worldwide, representing a major public health problem, with an increasing incidence and prevalence (1-3). The likelihood of survival may vary significantly among different etiologies and subsets of patients with CHF. In this context, CHF secondary to Chagas cardiomyopathy (CC) shows a poorer prognosis compared to other etiologies (4-7), mainly in Latin American where the disease is endemic (3, 8, 9).

The prognostics indexes currently employed in clinical practice have some limitations. They based on either peak oxygen consumption or invasive measurements, are designed to assess patients with severe CHF in need of cardiac transplantation (10-12), and were validated during hospitalization for acute decompensated heart failure (13-15). Furthermore, most of these models have not included a substantial proportion of individuals taking contemporary evidence-based treatments, including beta-blockers, angiotensin-converting enzyme inhibitors / angiotensin-receptor blockers, and spironolactone at target doses. Finally, a few models include CC patients, an important CHF etiology in our region.

The purpose of this investigation was to develop and validate a multivariate risk model for predicting long-term mortality in an independent, non-clinical trial, outpatient CHF population using variables easily assessable (demographic, 12-lead resting electrocardiogram, and 2D-echocardiography data) in clinical practice.

2. Methods

2.1 Study population

In São José do Rio Preto city/Brazil and neighboring towns, management of CHF involves general and specialized outpatient services, emergency departments, intermediate and intensive care units, covering a population of 2 million inhabitants. In our service, the diagnosis of CHF has been made by the attending physicians using the Framingham Criteria for Heart Failure Diagnosis (16). Chagas disease was confirmed by two positive serologic test for Chagas (ELISA and indirect immunofluorescence) according to the World Health Organization recommendation (17). After clinical diagnosis of CHF, a 2-D echocardiography was performed in each patient to confirm the clinical diagnosis, quantify this condition using left ventricular ejection fraction (LVEF), and guide the treatment according to the classification. Individuals with clinical diagnosis for CHF and LVEF < 55% on 2-D echocardiography confirming left ventricular systolic dysfunction were screened for this study. Patients with a concomitant disease that could potentially cause heart disease by itself were excluded.

For development cohort, all eligible patients were routinely followed in a public referral center for CHF in a Brazilian Medical School facility from January, 2000 to December, 2010. The CHF medical therapy information was retrieved from a prospectively collected database of patients. All patients received evidence-based treatment for CHF, according to international guidelines of the time. Thus, treatment with angiotensin converting enzyme inhibitors or angiotensin receptor blocks and beta-blockers at targeted or maximal tolerated doses was considered for all patients. Those with pitting edema received furosemide, while those in the NYHA Class III/IV with a LVEF < 30% were treated with digoxin. Patients usually visited the outpatient service each four months, and a senior heart failure specialist (RBB) supervised the treatment

given. Patients were followed until the close study; they were also censored at heart transplantation or death. For validation, we used separate local sample. There was no patients data overlap between the two samples.

This study was conducted in accordance with the Declaration of Helsinki and approved through the local Human Research Ethics Committee of São José do Rio Preto Medical School (CAAE - 02716112.6.0000.5415). The need for individual informed consent was waived, as this study was a retrospective analysis of prospectively collected data for routine care, and breach of privacy or anonymity did not occur.

2.2 Data collection

The demographics data, New York Heart Association (NYHA) functional class, heart rate, systemic arterial pressure, medical history, standard laboratory tests, 12-lead resting electrocardiogram and cardiac electronic implantable devices information were noted at study entry by attending physicians, and were retrieved from medical charts records. The available definition and data collection approaches were constant during the period of the study. The methodology of this investigation is consistent with the STROBE checklist for observational studies (18).

2.3 Outcome

The primary outcome was the long-term (more than 10 years) mortality based on review of hospital records or confirmed by telephone contacts with first-degree patients' relatives.

2.4 Statistical Analysis

Descriptive statistics was used to assess characteristics of two samples. Continuous data with normal distribution was expressed as mean and standard deviation,

whereas categorical variables were expressed as absolute numbers and percentages. Comparisons used the *t*-test for continuous variables and the Chi-square test for categorical variables.

We set up a model from the development cohort using multivariate analysis, including factors with clinical relevance or that were found significant at $P < 0.10$ in univariate analysis, using a stepwise backward elimination method. The first-order interactions in multivariable analysis were investigated ($P < 0.05$). Then, we stablished a scoring system based on the variables independently associated with mortality, attributing weights according to the odds ratio (exp(logistic regression β-coefficients)). Secondarily, the model was retested for validation, using bootstrap (19), with 1000 re-samples. We evaluated the discrimination using the area under the receiver-operating characteristic (ROC) curve, in the development and the validation cohorts. To assess the calibration, Hosmer-Lemeshow goodness-of-fit tests using deciles of poor outcome were performed on the development, validation cohort and on 1000 bootstrapping re-samples. *P*-values > 0.1 were considered to indicate good agreement (20). We defined the three risk groups for mortality (low-, intermediate-, and high-risk) by splitting the scoring system in tertiles of patients. Cumulative survival graphic (Kaplan-Meier) was constructed to show differences in event-free survival (mortality from all-causes) according The CALLM Risk Score.

All tests were two-sided with a *P*-value considered as significant if < 0.05 and were performed using IBM SPSS Statistical Package v.21 (IBM Corporation, Armonk, NY).

3. Results

3.1 Development cohort

The CALLM study included 450 ambulatory patients (64.7% male) with CHF, aged 49 – 68 years (mean 58 ± 14). Most patients (68.2%) were in NYHA functional classes I or II at study entry. Chagas etiology of CHF was present in 34.4% of individuals, followed by Hypertensive (19.1%), Chagas-Hypertensive association (15.8%), Idiopatic Dilated Cardiomyopathy (14.9%), Ischemic (11.8%), and Chagas-Ischemic association (4.0%). Mean left ventricular ejection fraction (LVEF) was 35.2 ± 10.6% (range 28.0 – 43.0%), and most patients (63.1%) presented LVEF < 40%. About 30.4% of patients had atrial fibrillation, 33.1% had left anterior fascicular block (LAFB), 34.2% needed pacemaker and 6.4% had implantable cardioverter-defibrillator. Among laboratory analysis, anemia [hemoglobin < 12 g/dL for women and < 13 g/dL for men] and glomerular filtration rate < 60 mL/min/1.73m^2 [according Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI)] was observed in 30.0% and 47.0% of patients, respectively.

This cohort received maximal tolerated daily doses of medications, according to guideline recommendations during the long-term of follow-up, considering mean daily dose (mg/day) of Enalapril (16.2 ± 8.3), Captopril (93.7 ± 44.1), Ramipril (8.5 ± 2.7), Losartan (50.3 ± 23.3), Carvedilol (32.2 ± 19.9), Metoprolol Succinate (127.7 ± 67.7), Spironolactone (28.0 ± 15.2), Furosemide (80.2 ± 54.2), Amiodarone (222.3 ± 89.8), and Digoxin (0.189 ± 0.067).

Hospitalization due to acute decompensated heart failure, cardiogenic shock, and need to heart transplantation rates were 74.0%, 26.4%, and 6.0%, respectively. During follow-up (1554 ± 1106 days), 197 CHF patients (43.8%) died.

The final multivariate model, which area under the curve (AUC) yielded 0.71 [95% CI 0.66 – 0.76] in the development cohort, identified five independent predictors for long-term mortality (Table 1): Chagas Cardiomyopathy etiology (OR=3.00, 95% CI

1.99 – 4.54; P<0.001), Age ≥ 60 years (OR=1.91, 95%CI 1.27 – 2.87; P=0.002), LVEF < 40% (OR=1.62, 95% CI 1.06 – 2.49; P=0.027), LAFB (OR=1.84, 95%CI 1.20 – 2.83; P=0.005), and male gender (OR=1.57, 95%CI 1.02 – 2.40; P=0.039). Comparison of baseline characteristics between development and validation cohorts are shown in Table 2. After, the Table 3 shows the good calibration of The CALLM Score, considering the predicted versus observed mortality rates. The simplest method to estimate the risk score for long-term mortality in CHF ambulatory patients consists in adding 3 points for Chagas etiology, 2 points each for any of the following: age ≥ 60 years, LVEF < 40%, and LAFB, and 1 point for male gender (Table 4).

3.2 Validation cohort

The external validation cohort analysis confirmed that the model performed as much in calibration [χ^2Hosmer-Lemeshow (6) = 2.71, P = 0.845] and discrimination characteristics [area under ROC curve 0.66, 95%CI 0.58 – 0.74]. The CALLM Risk Score performance for predicting long-term mortality in CHF patients, stratifying the risk in three categories (low-, Intermediate-, or high-risk) included: 85 patients (37.3%) in the low-risk subgroup, showing an average long-term mortality of 14.1%. The intermediate-risk subgroup considered 83 individuals (36,4%), showing a mortality rate about of 25.3%, and the high-risk subgroup, that included 60 patients (26.3%), showed that the long-term mortality could reach rates around 38.3%.

The long-term survival probabilities of patients with CHF according risk stratifications (low-, intermediate-, and high-risk) provided by the CALLM Risk Score are shown in Figure 1.

4. Discussion

In the present study, we enrolled a large ambulatory CHF population cohort with a wide spectrum of etiologies and left ventricular systolic function. Importantly, a large proportion of the study population was comprised of patients with CC, which reflects the everyday clinical practice in an area where CC is endemic. The novelty of this work is that we developed and validated the CALLM Risk Score, a simple risk model based on commonly obtained and non-invasive variables for predicting long-term mortality.

The CALLM Risk Score accurately discriminated three groups of risk for CHF patients, and offered an interesting tool for early, reliable, and easily assessment of prognosis in ambulatory clinical practice. In this sense, therefore, our study is not only of interest for physicians working in areas where CC is endemic, but also to those working in USA and Europe, where Chagas disease immigration is important.

Importantly, our validation cohort included patients with the full range of etiologies like Chagas cardiomyopathy, hypertensive, idiopatic and ischemic heart disease as well as the association of Chagas disease with hypertensive or ischemic heart disease. The heart failure symptoms ranged from NYHA functional class I to IV and the LVEF at the study entry ranged from 27.4% to 42.0%. Our validation cohort also included a significant amount of patients at intermediate and high risk in whom the risk prediction could be more challenging (21), representing the population in whom validation results may be most widely applicable.

Our multivariate model yielded an AUC of 0.71 and Hosmer-Lemeshow goodness-of-fit test (P=0.845) in the development cohort. It is important to highlight that the calibration (the agreement between observed and predicted risk, obtained by Hosmer-Lemeshow test) is also very important in prognostic settings, considering that the main purpose is to predict future risk of the target population (22), as observed for the CALLM Risk Score. On the other hand, the discrimination (useful for separating people with

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disease from without disease, for example; obtained by c-indexes) would be more important in diagnostic settings.

The score indicated that CC alone, age ≥ 60 years, LVEF < 40%, LAFB, and male gender had independent predictive power. Although with some variations in cut-off points, LVEF was similarly obtained as independent predictors for mortality by The MUSIC Risk Score (23), beyond age and male gender by The Seattle Heart Failure Model (21). Differently, our risk model highlighted CC alone and LAFB presence in 12-lead resting electrocardiogram, very common and associated finding with CC, as independent predictors for mortality, suggesting the negative burden of Chagas etiology in CHF prognosis (4, 6, 24). Furthermore, our investigation did not identify NYHA functional class and renal dysfunction as risk predictors in CHF patients, as demonstrated previously (21, 25). Among other aforementioned limitations, previous models (10, 25-27) did not include a substantial number of individuals with optimized medical therapy according current guidelines (1-3), and/or were derived in hospitalized patients (13-15), and have been developed in participants from clinical trials (21, 28), limiting their use in daily clinical practice.

Previous studies have shown that the etiology of Chagas disease is by itself an independent predictor of all-cause mortality in patients with CHF (4-7, 29). However, the impact of the etiology of CC on all-cause mortality has never been previously reported in a model like we used in this study, with proper calibration and external validation. Therefore, our study suggests that patients with CC with CHF need to be closely followed and aggressively treated in view of the poor prognosis of this condition

Early prognostication of poor outcome in CHF patients remains unsolved challenge. Predicting an individual's risk in daily clinical practice requires only adding up the points of the predictors verified in that patient to calculate the long-term mortality

risk score. Moreover, we known that an adequate stratification could help for decisions and may permit a better allocation of resources. Indeed, this possibility may lead to faster adjust the treatments and anticipate the management of these most severe patients in specialized CHF units, whereas most low-risk CHF patients could require a less intensive follow-up. In this context, the CALLM Risk Score can represent a simple tool for everyday clinical practice in areas where CC is endemic and non-endemic, aiming to improve the standardization of care and decision-making.

4.1 Strength and limitations

There are some limitations to our investigation. The CALLM Risk Score was derived in a cohort of CHF patients prospectively followed in a single-center and may not be generalizable to a wider population. Its benefit in diastolic heart failure is uncertain, because this score was derived and validated only in patients with systolic heart failure. On the other hand, the model was developed based on a large ambulatory cohort with a wide spectrum of CHF etiologies and left ventricular systolic function, mainly CC patients, as seen in everyday clinical practice in areas where CC is endemic and non-endemic, showing good performance for predicting long-term mortality in CHF patients, stratifying the risk in three categories (low-, intermediate-, or high-risk). Furthermore, the CALLM Risk Score was well validated in a separate cohort, including also real-word population. Further studies are needed with validation of the CALLM Risk Score in other CHF cohorts to confirm its value as a generalizable clinical prediction tool.

5. Conclusions

The CALLM Risk Score allows prediction of survival of ambulatory CHF patients with the use of easily obtained non-invasive variables and confirm the negative burden of

Chagas etiology in CHF prognosis. The model provides an accurate identification of a subgroup of high-risk patients who should be closely managed.

References

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.
2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147-239.
3. Bocchi EA, Marcondes-Braga FG, Bacal F, Ferraz AS, Albuquerque D, Rodrigues Dde A, et al. [Updating of the Brazilian guideline for chronic heart failure - 2012]. Arq Bras Cardiol. 2012;98(1 Suppl 1):1-33.
4. Vilas Boas LG, Bestetti RB, Otaviano AP, Cardinalli-Neto A, Nogueira PR. Outcome of Chagas cardiomyopathy in comparison to ischemic cardiomyopathy. Int J Cardiol. 2013;167(2):486-90.
5. Bestetti RB, Otaviano AP, Fantini JP, Cardinalli-Neto A, Nakazone MA, Nogueira PR. Prognosis of patients with chronic systolic heart failure: Chagas disease versus systemic arterial hypertension. International Journal of Cardiology. 2013;168(3):2990-1.

6. Pereira Nunes Mdo C, Barbosa MM, Ribeiro AL, Amorim Fenelon LM, Rocha MO. Predictors of mortality in patients with dilated cardiomyopathy: relevance of chagas disease as an etiological factor. Rev Esp Cardiol. 2010;63(7):788-97.

7. Barbosa AP, Cardinalli Neto A, Otaviano AP, Rocha BF, Bestetti RB. Comparison of outcome between Chagas cardiomyopathy and idiopathic dilated cardiomyopathy. Arq Bras Cardiol. 2011;97(6):517-25.

8. Bocchi E, Bestetti R, Scanavacca M, Cunha-Neto E, Issa V. Chronic Chagas heart disease management: from etiology to cardiomyopathy treatment. J Am Coll Cardiol2017. p. in press.

9. Bestetti RB, Theodoropoulos TA, Cardinalli-Neto A, Cury PM. Treatment of chronic systolic heart failure secondary to Chagas heart disease in the current era of heart failure therapy. Am Heart J. 2008;156(3):422-30.

10. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation. 1997;95(12):2660-7.

11. Gronda EG, Barbieri P, Frigerio M, Mangiavacchi M, Oliva F, Quaini E, et al. Prognostic indices in heart transplant candidates after the first hospitalization triggered by the need for intravenous pharmacologic circulatory support. J Heart Lung Transplant. 1999;18(7):654-63.

12. Campana C, Gavazzi A, Berzuini C, Larizza C, Marioni R, D'Armini A, et al. Predictors of prognosis in patients awaiting heart transplantation. J Heart Lung Transplant. 1993;12(5):756-65.

13. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. Jama. 2003;290(19):2581-7.

14. Fonarow GC, Adams KF, Jr., Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. Jama. 2005;293(5):572-80.

15. Varadarajan P, Pai RG. Prognosis of congestive heart failure in patients with normal versus reduced ejection fractions: results from a cohort of 2,258 hospitalized patients. J Card Fail. 2003;9(2):107-12.

16. Ho KK, Anderson KM, Kannel WB, Grossman W, Levy D. Survival after the onset of congestive heart failure in Framingham Heart Study subjects. Circulation. 1993;88(1):107-15.

17. Control of Chagas disease. World Health Organ Tech Rep Ser. 2002;905:i-vi, 1-109, back cover.

18. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Bmj. 2007;335(7624):806-8.

19. Steyerberg EW, Harrell FE, Jr., Borsboom GJ, Eijkemans MJ, Vergouwe Y, Habbema JD. Internal validation of predictive models: efficiency of some procedures for logistic regression analysis. J Clin Epidemiol. 2001;54(8):774-81.

20. Hosmer DW, Lemeshow S, RX. S. Applied Logistic Regression. Hoboken, NJ, USA: Willey Interscience.

21. Levy WC, Mozaffarian D, Linker DT, Sutradhar SC, Anker SD, Cropp AB, et al. The Seattle Heart Failure Model: prediction of survival in heart failure. Circulation. 2006;113(11):1424-33.

22. Steyerberg EW, Vickers AJ, Cook NR, Gerds T, Gonen M, Obuchowski N, et al. Assessing the performance of prediction models: a framework for traditional and novel measures. Epidemiology. 2010;21(1):128-38.

23. Vazquez R, Bayes-Genis A, Cygankiewicz I, Pascual-Figal D, Grigorian-Shamagian L, Pavon R, et al. The MUSIC Risk score: a simple method for predicting mortality in ambulatory patients with chronic heart failure. Eur Heart J. 2009;30(9):1088-96.

24. Silva CP, Del Carlo CH, Oliveira Junior MT, Scipioni A, Strunz-Cassaro C, Ramirez JA, et al. Why do patients with chagasic cardiomyopathy have worse outcomes than those with non-chagasic cardiomyopathy? Arq Bras Cardiol. 2008;91(6):358-62.

25. Brophy JM, Dagenais GR, McSherry F, Williford W, Yusuf S. A multivariate model for predicting mortality in patients with heart failure and systolic dysfunction. Am J Med. 2004;116(5):300-4.

26. Kearney MT, Nolan J, Lee AJ, Brooksby PW, Prescott R, Shah AM, et al. A prognostic index to predict long-term mortality in patients with mild to moderate chronic heart failure stabilised on angiotensin converting enzyme inhibitors. Eur J Heart Fail. 2003;5(4):489-97.

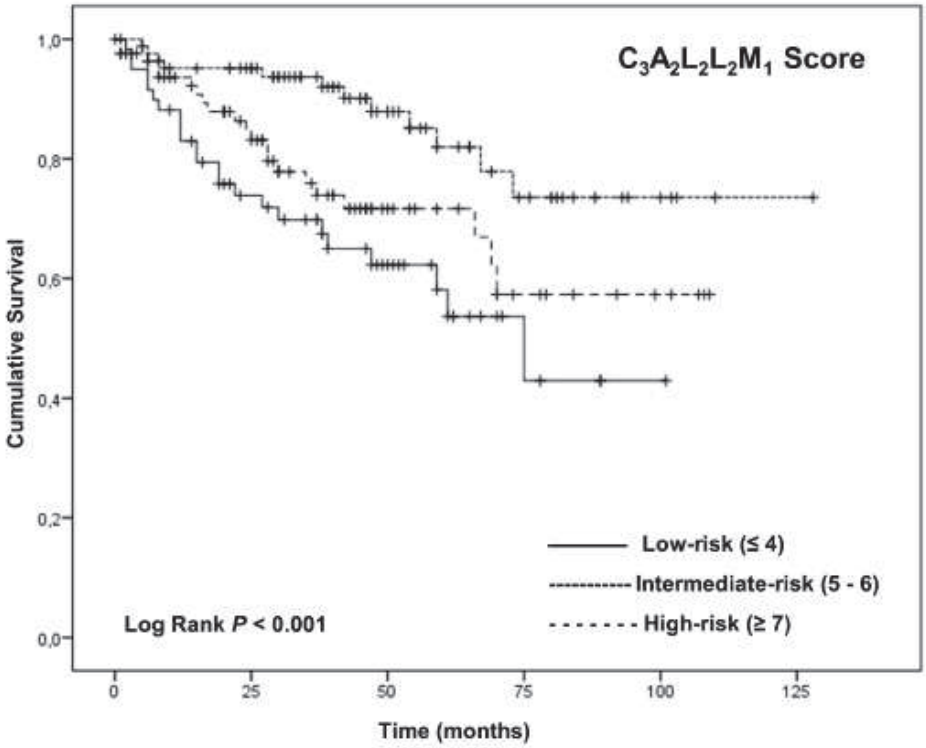
27. Bouvy ML, Heerdink ER, Leufkens HG, Hoes AW. Predicting mortality in patients with heart failure: a pragmatic approach. Heart. 2003;89(6):605-9.

28. Pocock SJ, Wang D, Pfeffer MA, Yusuf S, McMurray JJ, Swedberg KB, et al. Predictors of mortality and morbidity in patients with chronic heart failure. Eur Heart J. 2006;27(1):65-75.

29. Freitas HF, Chizzola PR, Paes AT, Lima AC, Mansur AJ. Risk stratification in a Brazilian hospital-based cohort of 1220 outpatients with heart failure: role of Chagas' heart disease. Int J Cardiol. 2005;102(2):239-47.

Figure Legend

Figure 1. Long-term Survival probabilities of patients with chronic heart failure according risk stratifications (low-, intermediate-, and high-risk) provided by the CALLM Risk Score.



Number Exposed to Risk						
Low-risk	84	68	35	16	4	1
Intermidiate-risk	82	52	20	9	4	0
High-risk	59	37	19	4	1	0

Table 1. Univariate and multivariate analysis of prognostic factors associated with long-term mortality in the development cohort (N=450 individuals).

Parameters	N (%)	Univariate			Multivariate		
		OR	95% CI	P-Value	OR	95% CI	P-Value
Chagas Cardiomyopathy alone	155 (34.4)	3.38	2.28 - 5.02	< 0.001	3.00	1.99 - 4.54	< 0.001
Age ≥ 60 years	223 (49.6)	1.82	1.25 - 2.65	0.002	1.91	1.27 - 2.87	0.002
Left Ventricular Ejection Fraction < 40%	284 (63.1)	1.70	1.15 - 2.52	0.008	1.62	1.06 - 2.49	0.027
Left Anterior Fascicular Block	298 (66.2)	2.24	1.50 - 3.34	< 0.001	1.84	1.20 - 2.83	0.005
Male (gender)	291 (64.7)	1.47	0.99 - 2.18	0.057	1.57	1.02 - 2.40	0.039

N=Number of individuals; OR=Odds ratio; CI=Confidence interval.

Table 2. Comparison of baseline characteristics between development and validation cohorts.

Predictors	All patients (N=678) n (%)	Development Cohort (N=450) n (%)	Retrospective Validation (N=228) n (%)	*P*-value
Chagas Cardiomyopathy	234 (34.5)	155 (34.4)	79 (34.6)	0.958
Age ≥ 60 years	306 (45.1)	223 (49.6)	83 (36.4)	0.001
Left Ventricular Ejection Fraction < 40%	440 (64.9)	284 (63.1)	156 (68.4)	0.171
Left Anterior Fascicular Block	434 (64.0)	298 (66.2)	136 (59.6)	0.386
Male (gender)	459 (67.7)	291 (64.7)	168 (73.7)	0.018

N=number of individuals.

Table 3. Calibration of the CALLM Score.

			Death		Alive	
Risk	Points	N	Observed N	Predicted N	Observed N	Predicted N
Low	≤4	85	12	11.72	73	73.28
Medium	5-6	83	21	20.67	62	62.33
High	≥7	60	23	23.61	37	36.39

Hosmer-Lemeshow Goodness-of-fit test ($P = 0.845$).
N=number of individuals.

Table 4. Risk of long-term mortality expressed as a point-based scoring system, with the acronym $C_3A_2L_2L_2M_1$ Score.

Risk factor	Score
Chagas Cardiomyopathy alone	3
Age ≥ 60 years	2
Left Ventricular Ejection Fraction < 40%	2
Left Anterior Fascicular Block	2
Male (gender)	1

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This statement is to certify that all authors have seen and approved the manuscript being submitted, have contributed significantly to the work, attest to the validity and legitimacy of the data and its interpretation, and agree to its submission to the *International Journal of Cardiology*.

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All authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations within three years of beginning the submitted work that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, the COI should read: "The authors report no relationships that could be construed as a conflict of interest".

Conclusões

(Artigo 1) Nosso estudo mostra que Remodelamento Reverso Ventricular Esquerdo não prediz redução de mortalidade a longo prazo em pacientes com Cardiomiopatia Chagásica. Este é o primeiro estudo a mostrar que a gravidade da progressão da doença parece anular o potencial benefício do Remodelamento Reverso Ventricular Esquerdo em pacientes com Cardiomiopatia Chagásica. Futuras pesquisas, entretanto, com número populacional adequado, deveriam ser conduzidas a fim de confirmar estes achados.

(Artigo 2) Doença Renal Crônica e Anemia não são preditores independentes de mortalidade a longo prazo em pacientes com Insuficiência Cardíaca Sistólica Crônica secundária a Cardiomiopatia Chagásica que, por si só, tem pior prognóstico. Entretanto, pacientes com estas comorbidades tem menores probabilidades de sobrevida, a despeito de suas respectivas classificações funcionais NYHA.

(Artigo 3) O Escore de Risco CALLM permite predizer sobrevida ambulatorial em pacientes com Insuficiência Cardíaca Sistólica Crônica a partir de variáveis não invasivas e de fácil acesso, confirmando o impacto negativo da Cardiomiopatia Chagásica no prognóstico da Insuficiência Cardíaca Sistólica Crônica. O modelo providencia uma acurada identificação de um subgrupo de alto risco que deveria ser manejado rigorosamente.

Conclusões gerais

Remodelamento Reverso Ventricular Esquerdo, Doença Renal Crônica e Anemia não têm impacto nos desfechos de pacientes com Cardiomiopatia Chagásica Crônica, sugerindo pior desfecho clínico inerente à esta condição.

É possível estratificar adequadamente pacientes portadores de Insuficiência Cardíaca Crônica em nível ambulatorial com métodos simples e não invasivos, como os sugeridos pelo escore de risco CALLM, desenvolvido e validado em coorte de área endêmica para Doença de Chagas.

Referências Bibliográficas:

1. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC)Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37(27):2129-200.

2. Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE, Jr., Drazner MH, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2013;62(16):e147-239.

3. Bocchi EA, Marcondes-Braga FG, Bacal F, Ferraz AS, Albuquerque D, Rodrigues Dde A, et al. [Updating of the Brazilian guideline for chronic heart failure - 2012]. Arq Bras Cardiol. 2012;98(1 Suppl 1):1-33.

4. Vilas Boas LG, Bestetti RB, Otaviano AP, Cardinalli-Neto A, Nogueira PR. Outcome of Chagas cardiomyopathy in comparison to ischemic cardiomyopathy. Int J Cardiol. 2013;167(2):486-90.

5. Bestetti RB, Otaviano AP, Fantini JP, Cardinalli-Neto A, Nakazone MA, Nogueira PR. Prognosis of patients with chronic systolic heart failure: Chagas disease versus systemic arterial hypertension. International Journal of Cardiology. 2013;168(3):2990-1.

6. Pereira Nunes Mdo C, Barbosa MM, Ribeiro AL, Amorim Fenelon LM, Rocha MO. Predictors of mortality in patients with dilated cardiomyopathy: relevance of chagas disease as an etiological factor. Rev Esp Cardiol. 2010;63(7):788-97.

7. Barbosa AP, Cardinalli Neto A, Otaviano AP, Rocha BF, Bestetti RB. Comparison of outcome between Chagas cardiomyopathy and idiopathic dilated cardiomyopathy. Arq Bras Cardiol. 2011;97(6):517-25.

8. Bocchi E, Bestetti R, Scanavacca M, Cunha-Neto E, Issa V. Chronic Chagas heart disease management: from etiology to cardiomyopathy treatment. J Am Coll Cardiol2017. p. in press.

9. Bestetti RB, Theodoropoulos TA, Cardinalli-Neto A, Cury PM. Treatment of chronic systolic heart failure secondary to Chagas heart disease in the current era of heart failure therapy. Am Heart J. 2008;156(3):422-30.

10. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Bohm M, Dickstein K, et al. ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. Eur J Heart Fail. 2012;14(8):803-69.

11. Dash H, Johnson RA, Dinsmore RE, Harthorne JW. Cardiomyopathic syndrome due to coronary artery disease. I: Relation to angiographic extent of coronary disease and to remote myocardial infarction. Br Heart J. 1977;39(7):733-9.

12. Bart BA, Shaw LK, McCants CB, Jr., Fortin DF, Lee KL, Califf RM, et al. Clinical determinants of mortality in patients with angiographically diagnosed ischemic or nonischemic cardiomyopathy. J Am Coll Cardiol. 1997;30(4):1002-8.

13. Ng AC, Sindone AP, Wong HS, Freedman SB. Differences in management and outcome of ischemic and non-ischemic cardiomyopathy. Int J Cardiol. 2008;129(2):198-204.

14. Gurgel CB, Miguel Junior A, Mendes CR, Zerbini CO, Carcioni TM. Frequency of hypertension in chronic Chagas' disease: retrospective clinical study. Arq Bras Cardiol. 2003;81(6):545-8, 1-4.

15. Guariento ME, Ramos Mde C, Gontijo JA, Carvalhal Sdos S. [Chagas disease and primary arterial hypertension]. Arq Bras Cardiol. 1993;60(2):71-5.

16. Codd MB, Sugrue DD, Gersh BJ, Melton LJ, 3rd. Epidemiology of idiopathic dilated and hypertrophic cardiomyopathy. A population-based study in Olmsted County, Minnesota, 1975-1984. Circulation. 1989;80(3):564-72.

17. Felker GM, Thompson RE, Hare JM, Hruban RH, Clemetson DE, Howard DL, et al. Underlying causes and long-term survival in patients with initially unexplained cardiomyopathy. N Engl J Med. 2000;342(15):1077-84.

18. Maron BJ, Towbin JA, Thiene G, Antzelevitch C, Corrado D, Arnett D, et al. Contemporary definitions and classification of the cardiomyopathies: an American Heart Association Scientific Statement from the Council on Clinical Cardiology, Heart Failure and Transplantation Committee; Quality of Care and Outcomes Research and Functional Genomics and Translational Biology Interdisciplinary Working Groups; and Council on Epidemiology and Prevention. Circulation. 2006;113(14):1807-16.

19. Sugrue DD, Rodeheffer RJ, Codd MB, Ballard DJ, Fuster V, Gersh BJ. The clinical course of idiopathic dilated cardiomyopathy. A population-based study. Ann Intern Med. 1992;117(2):117-23.

20. Hagar JM, Rahimtoola SH. Chagas' heart disease. Curr Probl Cardiol. 1995;20(12):825-924.

21. Leiby DA, Lenes BA, Tibbals MA, Tames-Olmedo MT. Prospective evaluation of a patient with Trypanosoma cruzi infection transmitted by transfusion. N Engl J Med. 1999;341(16):1237-9.

22. Bern C, Montgomery SP, Katz L, Caglioti S, Stramer SL. Chagas disease and the US blood supply. Curr Opin Infect Dis. 2008;21(5):476-82.

23. Chagas disease after organ transplantation--Los Angeles, California, 2006. MMWR Morb Mortal Wkly Rep. 2006;55(29):798-800.

24. Dias JC, Amato Neto V, Luna EJ. [Alternative transmission mechanisms of Trypanosoma cruzi in Brazil and proposals for their prevention]. Rev Soc Bras Med Trop. 2011;44(3):375-9.

25. Pereira KS, Schmidt FL, Guaraldo AM, Franco RM, Dias VL, Passos LA. Chagas' disease as a foodborne illness. J Food Prot. 2009;72(2):441-6.

26. Chagas disease in Latin America: an epidemiological update based on 2010 estimates. Wkly Epidemiol Rec. 2015;90(6):33-43.

27. Ramos JM, Ponce Y, Gallegos I, Flores-Chavez M, Canavate C, Gutierrez F. Trypanosoma cruzi infection in Elche (Spain): comparison of the seroprevalence in immigrants from Paraguay and Bolivia. Pathog Glob Health. 2012;106(2):102-6.

28. Hagar JM, Rahimtoola SH. Chagas' heart disease in the United States. N Engl J Med. 1991;325(11):763-8.

29. Parada H, Carrasco HA, Anez N, Fuenmayor C, Inglessis I. Cardiac involvement is a constant finding in acute Chagas' disease: a clinical, parasitological and histopathological study. Int J Cardiol. 1997;60(1):49-54.

30. Rossi MA, Bestetti RB. The challenge of chagasic cardiomyopathy. The pathologic roles of autonomic abnormalities, autoimmune mechanisms and microvascular changes, and therapeutic implications. Cardiology. 1995;86(1):1-7.

31. Amorim S, Rodrigues J, Campelo M, Moura B, Martins E, Macedo F, et al. Left ventricular reverse remodeling in dilated cardiomyopathy- maintained subclinical myocardial systolic and diastolic dysfunction. Int J Cardiovasc Imaging. 2017;33(5):605-13.

32. Arnold RH, Kotlyar E, Hayward C, Keogh AM, Macdonald PS. Relation between heart rate, heart rhythm, and reverse left ventricular remodelling in response to carvedilol in patients with chronic heart failure: a single centre, observational study. Heart. 2003;89(3):293-8.

33. Greenberg B, Quinones MA, Koilpillai C, Limacher M, Shindler D, Benedict C, et al. Effects of long-term enalapril therapy on cardiac structure and function in patients with left ventricular dysfunction. Results of the SOLVD echocardiography substudy. Circulation. 1995;91(10):2573-81.

34. Boccanelli A, Mureddu GF, Cacciatore G, Clemenza F, Di Lenarda A, Gavazzi A, et al. Anti-remodelling effect of canrenone in patients with mild chronic heart failure (AREA IN-CHF study): final results. Eur J Heart Fail. 2009;11(1):68-76.

35. Benchimol-Barbosa PR. Cardiac remodeling and predictors for cardiac death in long-term follow-up of subjects with chronic Chagas' heart disease: a mathematical model for progression of myocardial damage. Int J Cardiol. 131. Netherlands2009. p. 435-8.

36. Davila DF, Rossell O, de Bellabarba GA. Pathogenesis of chronic chagas heart disease: parasite persistence and autoimmune responses versus cardiac remodelling and neurohormonal activation. Int J Parasitol. 32. England2002. p. 107-9.

37. Khan S, Amedia CA, Jr. Economic burden of chronic kidney disease. J Eval Clin Pract. 2008;14(3):422-34.

38. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE, et al. Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet. 2010;375(9731):2073-81.

39. Wang Y, Katzmarzyk PT, Horswell R, Zhao W, Johnson J, Hu G. Comparison of the heart failure risk stratification performance of the CKD-EPI equation and the MDRD equation for estimated glomerular filtration rate in patients with Type 2 diabetes. Diabet Med. 2016;33(5):609-20.

40. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.

41. Levey AS, Stevens LA. Estimating GFR using the CKD Epidemiology Collaboration (CKD-EPI) creatinine equation: more accurate GFR estimates, lower CKD prevalence estimates, and better risk predictions. Am J Kidney Dis. 55. United States2010. p. 622-7.

42. Lindenfeld J. Prevalence of anemia and effects on mortality in patients with heart failure. Am Heart J. 2005;149(3):391-401.

43. Anand I, McMurray JJ, Whitmore J, Warren M, Pham A, McCamish MA, et al. Anemia and its relationship to clinical outcome in heart failure. Circulation. 2004;110(2):149-54.

44. Al-Ahmad A, Rand WM, Manjunath G, Konstam MA, Salem DN, Levey AS, et al. Reduced kidney function and anemia as risk factors for mortality in patients with left ventricular dysfunction. J Am Coll Cardiol. 2001;38(4):955-62.

45. Haber HL, Leavy JA, Kessler PD, Kukin ML, Gottlieb SS, Packer M. The erythrocyte sedimentation rate in congestive heart failure. N Engl J Med. 1991;324(6):353-8.

46. Parameshwar J, Keegan J, Sparrow J, Sutton GC, Poole-Wilson PA. Predictors of prognosis in severe chronic heart failure. Am Heart J. 1992;123(2):421-6.

47. Cowie MR, Wood DA, Coats AJ, Thompson SG, Suresh V, Poole-Wilson PA, et al. Survival of patients with a new diagnosis of heart failure: a population based study. Heart. 2000;83(5):505-10.

48. Aaronson KD, Schwartz JS, Chen TM, Wong KL, Goin JE, Mancini DM. Development and prospective validation of a clinical index to predict survival in ambulatory patients referred for cardiac transplant evaluation. Circulation. 1997;95(12):2660-7.

49. Gronda EG, Barbieri P, Frigerio M, Mangiavacchi M, Oliva F, Quaini E, et al. Prognostic indices in heart transplant candidates after the first hospitalization triggered

by the need for intravenous pharmacologic circulatory support. J Heart Lung Transplant. 1999;18(7):654-63.

50. Campana C, Gavazzi A, Berzuini C, Larizza C, Marioni R, D'Armini A, et al. Predictors of prognosis in patients awaiting heart transplantation. J Heart Lung Transplant. 1993;12(5):756-65.

51. Lee DS, Austin PC, Rouleau JL, Liu PP, Naimark D, Tu JV. Predicting mortality among patients hospitalized for heart failure: derivation and validation of a clinical model. Jama. 2003;290(19):2581-7.

52. Fonarow GC, Adams KF, Jr., Abraham WT, Yancy CW, Boscardin WJ. Risk stratification for in-hospital mortality in acutely decompensated heart failure: classification and regression tree analysis. Jama. 2005;293(5):572-80.

53. Varadarajan P, Pai RG. Prognosis of congestive heart failure in patients with normal versus reduced ejection fractions: results from a cohort of 2,258 hospitalized patients. J Card Fail. 2003;9(2):107-12.