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Prognostic value of nutrition status in the response of cardiac resynchronization therapy

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ABSTRACT

Background: Cardiac resynchronization therapy (CRT) is indicated in symptomatic heart failure (HF) patients after achieving optimal medical therapy. However, there are still a large percentage of patients who do not respond to CRT. Malnutrition is a frequent comorbidity in patients with HF, and it is associated with a poorer prognosis. Here, we evaluate the nutritional status of patients assessed by Controlling Nutritional Status (CONUT) score and its association with structural remodeling and cardiovascular events.

Methods: We investigated the effect of CONUT on HF/death in 302 consecutive patients with a CRT device implanted between 2005 and 2015 in a single tertiary center. We categorized the patients into three groups: normal nutritional status (CONUT 0–1), mild malnutrition (CONUT 2–4) and moderate-severe malnutrition (CONUT $\geq$ 5). Changes in nutritional status were assessed in patients with mild-to-severe malnutrition prior to CRT.

Results: One hundred and forty-eight patients exhibited normal nutritional status (49.0%), 99 patients exhibited mild malnutrition (32.8%) and 55 patients exhibited moderate-severe malnutrition (18.2%). CONUT scores of at least 2 were associated with higher risk of HF/death compared with CONUT 0–1. Significant left ventricular (LV) reverse remodeling was noted in patients with better nutritional status. In addition, those malnutrition patients at baseline that improved nutritional state exhibited fewer HF/death events at follow-up.

Conclusion: CONUT score prior to CRT was an independent risk factor of death/HF and was correlated with LV reverse remodeling. Improvements in CONUT score during long-term follow-up were associated with a reduction in the rate of HF/death.

1. Introduction

Heart failure (HF) is a highly prevalent syndrome associated with poor quality of life, frequent hospitalizations and high mortality, despite therapeutic advances [1–3]. HF-related mortality remains as high as 50% within 5 years of diagnosis [4]. In large clinical trials, cardiac resynchronization therapy (CRT) conducted in tandem with pharmacological therapy in patients with chronic symptomatic HF with left ventricular dysfunction (left ventricular ejection fraction (LVEF $\leq$ 35%) and prolonged QRS complex (QRS > 130 ms) has been associated with a significant reduction in

Abbreviations: ACEIs, Angiotensin-converting enzyme inhibitors; ARBs, Angiotensin II receptor blockers; BB, Beta-blockers; CRT, Cardiac resynchronization therapy; CRT-D, Cardiac resynchronization therapy - defibrillator; CRT-P, Cardiac resynchronization therapy - pacemaker; HF, Heart Failure; MRAs, Mineralocorticoid receptor antagonist; NYHA, New York Heart Association.

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mortality, clinical improvement and structural reverse remodeling [5–10]. However, approximately 30% of patients receiving CRT experience no benefit [11]. The non-response to CRT is multifactorial and may involve multiple pre-, peri- and post-implant factors.

Malnutrition is a frequent comorbidity in patients with HF, which is associated with more advanced disease, comorbidities and poorer prognosis [12–14]. The etiology of the malnutrition is multifactorial: immune system, proinflammatory state, neurohormonal alterations, inadequate nutrition and absorption, and it is characterized by a catabolic/anabolic imbalance [15]. Early identification of malnutrition may lead to improved nutritional status and a better prognosis; however, the accepted definition of malnutrition has not yet been established. Controlling Nutritional Status (CONUT) is a score that identifies the in-hospital nutritional status of patients [16]. This score has been shown to be a good indicator of the nutritional status of HF patients and its association with increased cardiovascular events, both in patients with chronic HF and in patients hospitalized for acute HF[17–19].

The aim of this study was to analyze nutritional status using CONUT score in symptomatic HF patients receiving CRT and its association with structural remodeling and long-term events (hospitalization for HF and/or death).

2. Material and methods

This retrospective study included 302 consecutive patients with a CRT - defibrillator (CRT-D) or a CRT - pacemaker (CRT-P) under standard clinical indications in a single tertiary institution between August 2005 and April 2015. All of the patients had demonstrated HF symptoms (New York Heart Association (NYHA) functional class II, III or ambulatory IV), with ischemic or non-ischemic cardiomyopathy, decreased LVEF (≤35%) and prolonged QRS duration (≥130 ms) at the time of implantation. They received pharmacological treatment for HF up-titrated to the maximal tolerated doses according to the guidelines recommendations for the management of HF at the discretion of the treating cardiologist. Patients with severe liver disease (Child Pugh B-C) have been excluded.

We collected the baseline characteristics of all of the patients: age, gender, NYHA functional class, atrial fibrillation, underlying heart disease, pharmacological therapy and analytical data, electrocardiographic parameters and echocardiographic parameters, which included LV end-diastolic (LVEDV) and end-systolic volume (LVESV), LVEF and left atrial diameter (LAd). We used CONUT to evaluate the nutritional status of the patients via analytical control during the month prior to the implantation of CRT. The parameters that we used included serum albumin levels (g/dl), total cholesterol levels (g/dl) and total lymphocytes (cells/ml). We accordingly evaluated protein reserve (serum albumin ≥3.5, 0 points, 3.00–3.49, 2 points, 2.50–2.99, 4 points, < 2.50, 6 points), caloric reserve (total cholesterol ≥ 180, 0 points, 140–179, 1 point, 100–139, 2 points, < 100, 3 points) and immunological defenses (≥1600, 0 points, 1200–1599, 1 point, 800–1199, 2 points, <800, 3 points). The CONUT scores ranged from 0 to 12, and the patients were classified as: having normal nutritional status (CONUT 0–1 points), mild malnutrition (CONUT 2–4 points) and moderate-severe malnutrition (CONUT ≥ 5 points).

The patients were followed up for at least one year in the Heart Failure Clinic every three or six months and in the CRT-Device Clinic every six months. Electrocardiograms and echocardiograms were also performed at the 6-month and 2-year follow-up and according to the discretion of the HF cardiologist. CONUT was calculated for all patients between 6 and 24 months after CRT. Changes in the nutritional status of patients after CRT were assessed in the follow-up. We evaluated the association of improved nutritional status with cardiovascular events and structural remodeling in patients with mild-to-severe malnutrition prior to CRT. The reduction in LVESV and increase of LVEF are markers of reverse remodeling that correlates with mortality and heart failure hospitalizations, which are well-defined criteria to assess response to CRT. Maintained or worsened nutritional status post-CRT was considered to indicate no improvement.

The study satisfied all of the requirements of local ethics committees and complied with the Declaration of Helsinki.

2.1. Statistical analysis

Continuous variables are expressed as mean ± standard deviation (SD). Categorical data are presented as numbers and percentages. We used the Mann-Whitney and the Kruskal-Wallis tests to compare continuous numerical variables among the groups. The cumulative probability of death and/or HF was calculated using the Kaplan-Meier method. We used the multivariate Cox proportional hazards model to estimate the hazard ratio (HR) and 95% confidence interval (95%CI). We made use of the Statistical Package for Social Science (SPSS) for Windows, version 20.0 (software SPSS Inc.; Chicago, Illinois, United States) package for all of the statistical analysis. We carried out statistical analyses in R using the package "survival," which is freely available at http://cran.r-project.org. A p value less than 0.05 was considered to be statistically significant.

3. Results

3.1. Baseline characteristics

Three hundred and twenty-eight CRT devices have been consecutively implanted in our center from 2005 to 2015. The study population included 302 patients (68 women and 234 men; mean age: 70 ± 10 years). Twenty six patients did not have all analytical parameters and were excluded from the study. One hundred and eight patients (35.8%) exhibited ischemic etiology, 77 patients (25.5%) were II NYHA class, 210 patients (69.5%) were III NYHA class and 15 patients (5.0%) were IV NYHA class. The mean LVEF and LVESV in our cohort were 27 ± 7% and 166 ± 60 ml, respectively. Pharmacotherapy at baseline was as follows: 262 patients (86.8%) were on angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers (ACEIs/ARBs), 254 patients (84.1%) were on beta-blockers (BBs) and 144 patients (47.7%) were on mineralocorticoid receptor antagonist (MRAs). The mean follow-up duration was 4.2 ± 2.9 years.

We calculated the nutritional status of patients with CONUT prior to CRT implantation. Patients were classified using CONUT as having normal nutritional status (148 patients; 49.0%), mild malnutrition (99 patients; 32.8%) or moderate-severe malnutrition (55 patients; 18.2%). The characteristics of the patients in terms of CONUT score are listed in Table 1. Patients with a higher CONUT score were older, exhibited lower levels of hemoglobin, lower glomerular filtration rates and higher percentage of ischemic etiology. We did not find any differences in NYHA functional class, body mass index (BMI), width and morphology of the QRS among the groups. There were also no differences in terms of medical treatment (ACEI/ARB, BB and MRA).

3.2. Structural remodeling

During follow-up, the echocardiographic parameters exhibited significant reverse LV remodeling in patients with better nutritional status. A significant (>15%) LVESV reduction was observed in 88.1% of patients with normal nutritional status, in 84.7% of patients with mild malnutrition and in 62.2% of patients with moderate-to-

Table 1
Baseline characteristics, reverse remodeling and clinical response according CONUT Score.

	Overall n = 302	CONUT 0-1	CONUT 2-4	CONUT ≥5	*p-value*
Age, (years)	70 ± 10	68 ± 10	71 ± 9	73 ± 8	*0.000*
Male, n(%)	234(77.5)	109(73.6)	79(79.8)	46(83.6)	*0.253*
NYHA class, n (%)					
II	77(25.5)	43(29.1)	21(21.2)	13(23.6)	*0.117*
III	210(69.5)	101(68.2)	73(73.7)	36(65.5)	
IV	15(5.0)	4(2.7)	5(5.1)	6(10.9)	
Ischemic etiology, n (%)	108(35.8)	41(27.7)	41(41.4)	26(47.3)	*0.013*
DM, n (%)	74(24.5)	30(20.3)	28(28.3)	16(29.1)	*0.244*
BMI	28 ± 4	28 ± 5	28 ± 4	28 ± 4	*0.639*
GFR, ml/(min x 1.73m^2)	61.2 ± 23.9	67.5 ± 54.9	54.4 ± 21.3	56.2 ± 21.7	*0.000*
Sodium, mmol/l	138 ± 4	139 ± 3	138 ± 4	137 ± 4	*0.016*
Hemoglobine, g/dl	13.2 ± 1.7	13.6 ± 1.4	13.0 ± 1.9	12.4 ± 1.9	*0.000*
AF, n (%)	114(37.7)	52(35.1)	36(36.4)	26(47.3)	*0.268*
CRT-D, n (%)	158(52.3)	87(58.8)	46(46.5)	25(54.5)	*0.087*
LBBB, n (%)	186(61.6)	90(60.8)	62(62.6)	34(61.8)	*0.959*
QRS width, ms	162 ± 26	161 ± 24	162 ± 25	165 ± 31	*0.622*
LVESV, ml	166 ± 61	163 ± 63	162 ± 56	182 ± 62	*0.141*
LVEF, %	27 ± 7	27 ± 7	27 ± 7	26 ± 8	*0.367*
LAd, mm	49 ± 9	48 ± 7	49 ± 10	52 ± 9	*0.053*
ACEI/ARB, n(%)	262(86.8)	135(91.2)	82(82.8)	45(81.8)	*0.080*
BB, n(%)	254(84.1)	121(81.8)	86(86.9)	47(85.5)	*0.535*
MRA, n(%)	144(47.7)	71(48.0)	46(46.5)	27(49.1)	*0.948*
LVEF FU, %	39 ± 13	41 ± 13	39 ± 12	34 ± 12	*0.001*
Δ LVEF, %	12 ± 13	14 ± 14	12 ± 12	8 ± 11	*0.015*
Δ LVEF > 5%, n (%)	214(63.1)	111(68.1%)	72(67.9%)	31(53.4%)	*0.106*
LVESV FU	100 ± 57	100 ± 57	106 ± 55	146 ± 75	*0.000*
Δ LVESV, ml	−50 ± 62	−57 ± 61	−52 ± 57	−25 ± 68	*0.024*
ΔLVESV>15%, n (%)	180(78.3)	96(88.1%)	61(84.7%)	23(62.2%)	*0.001*
LAd FU, mm	47 ± 10	46 ± 9	46 ± 10	52 ± 8	*0.003*
ΔLAd FU	−1±9	−1±9	−1±9	−1±10	*0.808*
Clinical Response, n (%)	220(72.8)	112(75.7)	72(72.7)	36(65.5)	*0.347*
Clinical Response, n (%)					
-Worse	4(1.3)	0 (0.0)	2(2.0)	2(3.6)	*0.378*
-No change	78(25.8)	36(24.3)	25(25.3)	17(30.9)	
-Improvement 1 class	181(59.9)	90(60.8)	61(61.6)	30(54.5)	
-Improvement 2 class	39(12.9)	22(14.9)	11(11.1)	6(10.9)	

ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; AF: atrial fibrillation; BB: beta-blockers; BMI: Body Mass Index; CRT-ICD: Cardiac Resynchronization Therapy Defibrillator; DM: diabetes mellitus; FU: Follow-up; GFR: Glomerular Filtration Rate; LAd: Left atrium diameter; LBBB: Left bundle branch block; LVEF: Left ventricle eyeccion fraction; LVESV: left ventricular end systolic volume; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association; Δ: changes.

severe malnutrition (p = 0.001). There was also a significant difference in the LVEF increase among the groups (Table 1).

3.3. Mortality/HF admissions

During the mean follow-up duration of 4.4 ± 3.0 years, HF or death occurred in 43.6, 63.2 and 69.5% (p < 0.001) of patients with a normal nutrition status, mild malnutrition and moderate-severe malnutrition, respectively. The long-term cumulative probability free of HF/death differed significantly according to nutritional status (p < 0.001) (Fig. 1).

Multivariate Cox proportional hazard model analyses revealed that age, male sex, low sodium levels and LA diameter were independent predictors of HF/death. Higher CONUT score was also associated with an increased risk of HF/death during long-term follow-up. The nutritional status prior to CRT assessed by CONUT was identified as an independent predictor of cardiovascular events at follow-up (Table 2).

3.4. CONUT in follow-up

Nutritional status was assessed after the implantation of CRT. One hundred and fifty-four patients prior to CRT had mild-to-severe malnutrition. These patients were classified into two groups depending on whether their CONUT scores improved or worsened after CRT: 90 patients (58.4%) maintained similar or worse nutritional status, and 64 patients (41.6%) improved their nutritional status post-CRT. No differences were observed in the baseline characteristics of the cohort (Table 3).

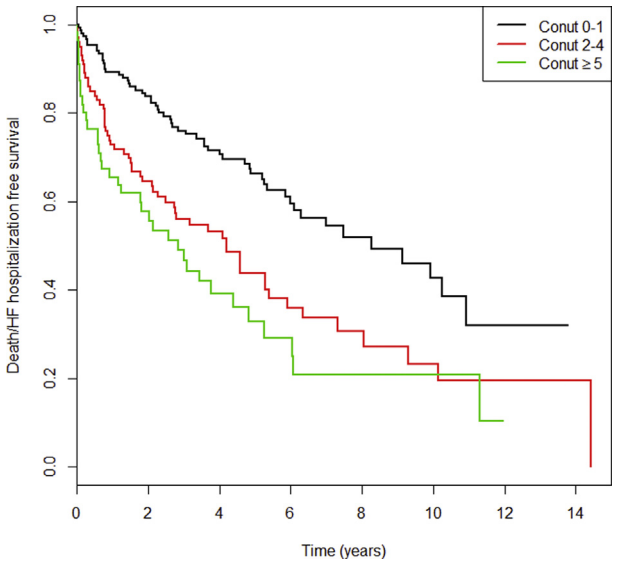

Fig. 1. Cumulative survival free of HF/death according CONUT nutritional status pre CRT.

The long-term cumulative probability of HF/death differed

Table 2
Multivariate Cox proportional hazards model for death/HF hospitalizations in patients with CRT.

	HR, CI 95%	*p-value*
Age	1.03(1.01–1.05)	*0.016*
Male	1.86(1.15–3.02)	*0.012*
Ischemic etiology	1.16(0.77–1.76)	*0.482*
AF	1.21(0.80–1.81)	*0.368*
GFR	0.99(0.98–1.00)	*0.213*
Sodium	0.95(0.91–0.99)	*0.019*
Hemoglobine	0.98(0.87–1.10)	*0.676*
CONUT		
0–1	1	*0.019*
2–4	1.63(1.08–2.48)	*0.022*
≥5	1.88(1.15–3.06)	*0.011*
LAd	1.03(1.01–1.05)	*0.005*
ACEI/ARB	0.600(0.36–1.01)	*0.053*

Gender: 0: female, 1: male. Etiology: 0: non-ischemic, 1: ischemic. Functional class: NYHA II as a reference.
ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; AF: Atrial Fibrillation; GFR: Glomerular Filtration Rat; LAd: Left atrium diameter.

significantly between those patients that improved their nutritional state and those whose nutrition state remained constant or worsened (32.6% and 43.8%, respectively; p [log-rank] = 0.02). Similar results were obtained when we analyzed HF hospitalizations and death separately according to nutritional change after CRT in patients with mild-to-severe nutrition status prior to implantation (Fig. 2). However, no improvement was observed in structural LV remodeling in those patients with poor basal nutritional status who improved their nutritional status compared with those patients who maintained poor nutritional status (ΔLVEF = 12.2 ± 12.3% and ΔLVESV = −47 ± 63 in the improved-CONUT group and ΔLVEF = 9.3 ± 11.3% and ΔLVESV = −40 ± 61 ml in the no-improved CONUT group, p = 0.138 and p = 0.582, respectively). There was also no improvement in NYHA functional class (the clinical response was 78.1% in the improved-CONUT group and 64.4% in the no-improved CONUT group, p = 0.068). The nutritional status after CRT assessed by CONUT was identified as an independent predictor of cardiovascular events at follow-up. The univariate Cox regression analysis showed relative risk reduction of cardiovascular events in improve-CONUT group (HR 0.51, 95% CI 0.33–0.78). This reduction in the hazard ratio is maintained after adjusting for several variables (HR 0.56, 95% 0.36–0.87) (Table 4).

4. Discussion

Our study provides evidence that malnutrition— assessed using the CONUT score— is common and predicts a poor outcome in patients with HF referred for CRT implantation. The CONUT score was significantly associated with cardiac events and LV reverse remodeling to CRT in patients with advanced HF. We found that an improvement in CONUT score after CRT was associated with a better outcome. We have provided the first evidence that malnutrition in HF patients receiving CRT is significantly associated with the prognosis and echocardiographic response to CRT.

Our findings may have several clinical implications. For instance, selecting patients on the basis of malnutrition may be helpful for patient selection for CRT, as it provides increased prognostic value in addition to other variables, which remains a challenging issue in clinical practice [11]. Patients with severe malnutrition, an indicator of frailty, poor outcomes and poor CRT response, can be considered for the length-of-life assessment recommended by HF guidelines for CRT recipient selection [20]. On the other hand, CRT response may improve nutritional status [21], and nutritional improvement may be considered to be a new clinical indicator of positive CRT response. CONUT should not be used as an isolated criterion to predict the CRT response, since the causes of nonresponse are multifactorial and involve several pre-, peri-, post - implant factors [11]. However, several previous studies have shown that targeted nutritional interventions could improve the response

Table 3
Differences in Baseline Characteristics between improvement and no improvement of CONUT post CRT.

	OVERALL n = 154	CONUT NO IMPROVEMENT n = 90	CONUT IMPROVEMENT n = 64	*p-value*
Age, (years)	72 ± 9	73 ± 8	71 ± 9	*0.432*
Male, n (%)	67(43.5)	41(45.6)	26(40.6)	*0.543*
NYHA class, n (%)				
II	34(22.1)	21(23.3)	13(20.3)	*0.824*
III	109(70.8)	62(68.9)	47(73.4)	
IV	11(7.1)	7(7.8)	4(6.2)	
CONUT prior CRT, n (%)				
CONUT 2-4	99(64.3)	69(76.7)	30(46.9)	
CONUT ≥5	55(35.7)	21(23.3)	34(53.1)	*0.000*
Ischemic, n (%)	67(43.5)	41(45.6)	26(40.6)	*0.543*
DM, n (%)	44(28.6)	26(28.9)	18(28.1)	*0.918*
BMI	28 ± 4	27 ± 4	29 ± 4	*0.798*
GFR, ml/(min x 1.73m^2)	55.1 ± 21.4	54.2 ± 21.5	56.3 ± 21.2	*0.904*
Sodium, mmol/l	138 ± 4	138 ± 4	138 ± 2	*0.103*
Hemoglobine, g/dl	12.8 ± 1.9	12.9 ± 2.0	12.7 ± 1.9	*0.452*
AF, n (%)	62(40.3)	34(37.8)	28(43.8)	*0.456*
CRT-D, n (%)	71(46.1)	39(43.3)	32(50.0)	*0.413*
LBBB, n (%)	96(62.3)	61(67.8)	35(54.7)	*0.098*
QRS width, ms	163 ± 27	165 ± 25	161 ± 30	*0.505*
LVESV, ml	169 ± 59	165 ± 56	176 ± 62	*0.550*
LVEF, %	27 ± 7	27 ± 7	26 ± 7	*0.772*
LA, mm	47 ± 10	49 ± 9	50 ± 11	*0.088*
ACEI/ARB, n (%)	127(82.5)	71(78.9)	56(87.5)	*0.411*
BB, n (%)	133(86.4)	76(84.4)	57(89.1)	*0.166*
MRA, n (%)	73(47.4)	45(50.0)	28(43.8)	*0.444*

ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; AF: Atrial Fibrillation; BB: beta-blockers; BMI: Body Mass Index; CRT-ICD: Cardiac Resynchronization Therapy Defibrillator; DM: Diabetes Mellitus; GFR: Glomerular Filtration Rate; LA: Left atrium; LBBB: Left bundle branch block; LVEF: Left ventricle eyeccion fraction; LVESV: left ventricular end systolic volume; MRA: mineralocorticoid receptor antagonist; NYHA: New York Heart Association.

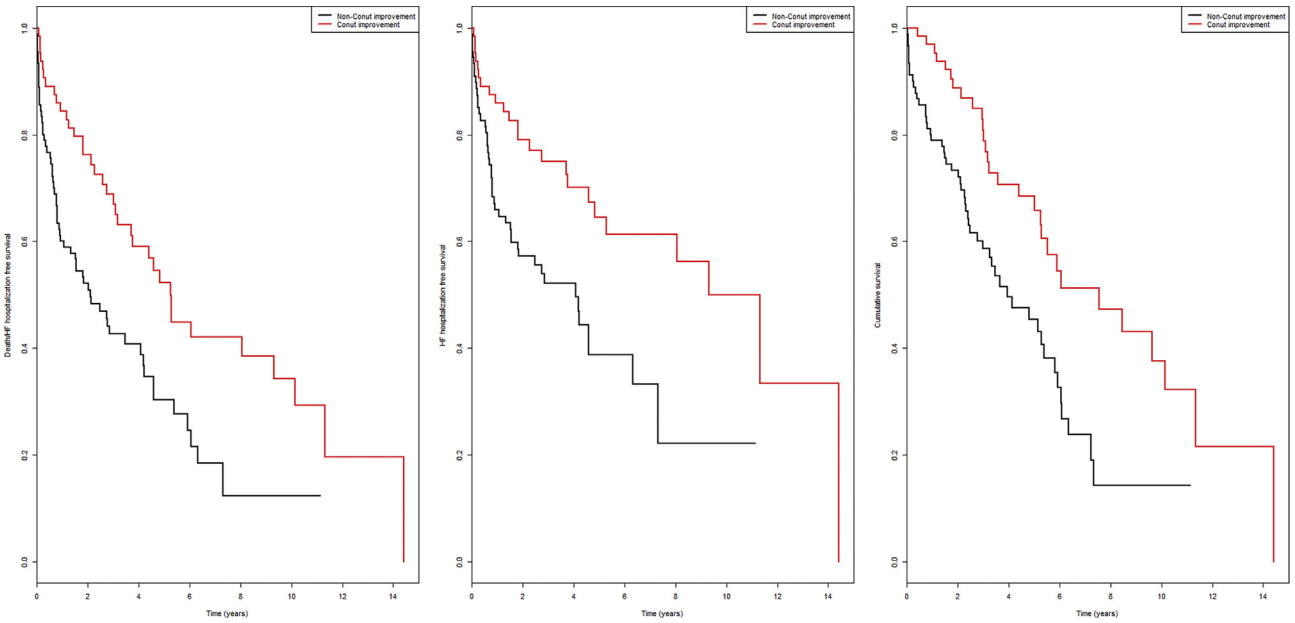

Fig. 2. A. Cumulative survival free of death or HF hospitalizations according CONUT improvement after CRT; B. Cumulative survival free of death according CONUT improvement after CRT; C. Cumulative survival free of HF hospitalizations according CONUT improvement after CRT.

Table 4
Multivariate Cox proportional hazards model for death/HF hospitalizations in patients with CRT.

	HR, CI 95%	*p-value*
Age	1.04 (1.01–1.07)	*0.003*
Male	1.26 (0.81–1.98)	*0.299*
Ischemic etiology	1.32 (0.85–2.05)	*0.217*
CRT-D	0.67 (0.43–1.04)	*0.076*
AF	1.57(1.02–2.41)	*0.039*
LBBB	0.84 (0.5301.33)	*0.454*
Δ QRS	1.00 (0.99–1.01)	*0.507*
Improve CONUT post CRT	0.54(0.34–0.85)	*0.008*
BB	0.96 (0.51–1.83)	*0.909*
MRA	1.18(0.78–1.83)	*0.447*
ACEI/ARB	0.77 (0.40–1.48)	*0.430*

Gender: 0: female, 1: male. Etiology: 0: non-ischemic, 1: ischemic.
ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers; AF: Atrial Fibrillation; BB: beta-blockers; CRT: Cardiac Resynchronization Therapy; CRT-D: Cardiac Resynchronization Therapy Defibrillator; LBBB: Left bundle branch block; MRA: mineralocorticoid receptor antagonist.

in HF patients with malnutrition and may improve outcomes [22–24]. Therefore, it is possible that a nutritional intervention helps optimize energy intake and moderate the imbalance between anabolism/catabolism, which is the result of neurohormonal and inflammatory activation of the HF. Also it might optimize the protein intake and increase protein synthesis, necessary to maintain muscle mass and serum albumin concentration. The modifications of these factors could change the evolution of the disease in the poorly nourished patient and explain the benefit of nutritional intervention.

4.1. Malnutrition and HF prognosis

Malnutrition has been identified as an independent risk factor and likely mediator of morbidity and mortality in patients with chronic and acute HF. Nutritional interventions may prevent complications and increase the quality of life of patients with HF[12–14, 25–27]. Low serum albumin [28–30] and nutrition indices [17–19,31–34] strongly predict mortality across the spectrum of HF severity from ambulatory patients to left ventricular assist device recipients. Therefore, it has been suggested that the HF can be substantially modulated by nutritional status. In turn, BMI is not a good predictor of nutritional status in HF patients [25]. However, the pathophysiological mechanisms underlying these findings remain unclear. Inflammatory and metabolic derangements of the failing myocardium could develop and worsen the progression of HF [35]. *Nakagomi* et al. [36] described that nutritional state is associated with inflammation and predicts poor outcome in patients with chronic HF. These authors found a positive correlation between the production of monocyte tumor necrosis factor (TNF) α and plasma levels of CRP with CONUT score. This myocardial imbalance might alter levels of circulating adipocytokines, including ghrelin, leptin, growth hormone and, more recently, orosomucoid [37]. This situation might contribute to the wasting process by altering appetite and energy expenditure [37–39]. The derangement of these hormone systems, potentially triggered by the effects of proinflammatory cytokines may be responsible for the development of satiety without adequate food intake and the promotion of other deleterious mechanisms in HF. *Von Haehing* et al. [40] extensively described malabsorption from the gut as being a possible result of bowel edema and reduced bowel perfusion in HF patients. Malabsorption from the gut may also play a relevant role in the progression of the wasting process and nutritional state.

4.2. Malnutrition and CRT

The implication of nutritional status in the response to CRT has thus far not yet been evaluated. Only *Obrzut* et al. demonstrated, in a prospective study consisting of 21 patients with non-ischemic cardiomyopathy who received CRT, that myocardial free fatty acid uptake flux may be a useful biomarker of non-responders due to high altered myocardial metabolism in advanced stages of HF[21]. We found that more than half of patients with CRT were malnourished according to CONUT score. Patients with higher levels of malnutrition were older, had poorer renal function and lower hemoglobin concentrations [41]. These variables were associated with a more

advanced stage of HF and greater lipotoxicity [42,43]. Remarkably, in our sample there was a direct association between the degree of malnutrition and mortality or hospitalization for HF. A high CONUT score prior to CRT was independently associated with an increased risk of death/HF and poorer ventricular remodeling after CRT. Moreover, the improvement in nutritional status after CRT was associated with a better outcome in terms of decreased rates of HF and death after adjusting for confounding variables.

There were a large percentage of patients who did not exhibit a LV reversal remodeling to CRT. Causes of non-response are multifactorial and may involve pre-, peri- and post-implant factors [11]. In our study, nutritional status assessed by CONUT score prior to CRT implantation demonstrated for the first time its association with LV reverse remodeling. Therefore, patients with better nutritional status exhibited a larger response to CRT. CONUT could easily identify patients in an advanced state of heart disease who were more likely not to respond to CRT. However, there was only a trend linking improvement in nutritional status and reverse LV remodeling. Additional studies are necessary to reveal the precise mechanisms involved in this process. It is also critically important to consider nutritional-state improvements as a new indicator of CRT response and cardiovascular outcomes.

5. Limitations

There are several limitations associated with this study. First, this investigation was a retrospective study conducted at a single center and reflects our own experience with the patients with CRT at our institution. Second, our sample size was relatively small. Third, we did not provide valid pathophysiological mechanisms for the improvement in the nutrition status after CRT.

6. Conclusions

In this follow-up study, the nutritional risk score CONUT prior to CRT was an independent risk factor of death/HF hospitalizations and was correlated with LV reverse remodeling. An improvement in CONUT score during follow-up post CRT implantation was associated with a reduction in HF hospitalizations and/or death. Our results suggest that more advanced states of malnutrition flagged by CONUT could be used to identify early non-responders to CRT and improvements in nutrition status may be a new marker of a positive response to CRT.

Conflicts of interest

None.

Relationship with the industry for this publication

No.

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