Malnutrition and Left Ventricular Systolic Function in Hospitalized Elderly Patients with and without Heart Failure

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Abstract: Heart failure (HF) is highly prevalent among older subjects and it is associated with poor prognosis. HF frequently coexists with malnutrition. Objectives of our work were to assess nutritional status of old inpatients with and without HF and to study the association of malnutrition markers with echocardiographic parameters of left ventricular function and geometry. We enrolled 165 patients (72 men, 93 women; mean age: 80±7 years) consecutively admitted to Cardiology ward of our geriatric research hospital. For all subjects we performed clinical examination, echocardiogram and laboratory tests. Nutritional status was assessed evaluating anthropometric and laboratory markers of malnutrition (BMI ≤ 24 kg/m^2 and/or serum albumin ≤ 3.2 g/dL). We found high prevalence of HF (67.3%) and malnutrition (28.5%). Mean serum albumin and mean BMI were 3.6±0.5 g/dL and 25.8±5.2 kg/m^2 respectively. T-Student tests showed lower values of serum albumin in patients with HF compared with patients without HF (3.5±0.6 g/dL vs 3.7±0.4 g/dL; p:0.043). Conversely BMI values were not significantly different. We found significant association between serum albumin and ejection fraction (EF) of left ventriculum (r:0.311; p:0.001). An independent correlation between EF and serum albumin was confirmed by multivariate analysis (β:0.301; p:0.027). Our study highlights that malnutrition is common among elderly inpatients with HF. Lower albumin was associated with worse systolic left ventricular function. Efforts should be made in the research setting to better understand the pathophysiology of malnutrition in HF and to identify useful management strategies for nutritional assessment and supplementation.

Keywords: Heart failure, Malnutrition, Elderly, Albumin, Systolic function.

1. INTRODUCTION

Heart failure (HF) is a complex clinical syndrome characterized by symptoms such as dyspnoea and fatigue and evidence of cardiac systolic and/or diastolic dysfunction. It results from the inability of the heart to sufficiently supply the metabolic demands of tissues, or do so only with elevated filling pressures. HF is currently one of the major causes of hospitalization in Western Countries. It affects approximately 5% of the adult population of Western Europe, and approximately 5 million persons in the United States have HF, with more than 550000 new patients diagnosed each year [1-3]. As a result of population ageing and better medical care that contribute to longer life expectancy, HF occurs more and more frequently in the elderly.

It is now well established that malnutrition is common in chronic HF, with numerous patients showing malnourishment on the basis of anthropometric measurements and plasma protein levels [4-6]. Reduced left ventricular ejection fraction (EF) is an independent predictor of an adverse prognosis in elderly patients with HF [7]. However, few data concerning relationships between markers of malnutrition and echocardiographic parameters of systolic left ventricular function and geometry in elderly patients are available as yet.

The aim of the present study was to evaluate nutritional status of old hospitalized patients with and without HF and to search for associations, if any, between malnutrition markers and echocardiographic parameters of systolic left ventricular function.

2. MATERIALS AND METHODS

We enrolled 165 elderly patients (72 male, 93 female; mean age: 80 ± 7 years), consecutively admitted to Cardiology Unit of our geriatric research hospital (I.N.R.C.A. Fermo, Italy) from October 2010 to May 2012. Recruited patients were hospitalized in our cardiology ward on indications of their family physician or after admission to emergency rooms for cardiovascular diseases. Since the mission of our Institute comprises the care of old people, for admission to our Unit, age ≥ 65 years was required.

Baseline data including demographics, medical and family history, atherosclerotic risk factors and medications were collected during interview at admission. For all subjects at admission we performed clinical examination, blood pressure measurement, ECG and laboratory tests including serum albumin, serum creatinine, haemoglobin and high sensitivity C-

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reactive protein (hs-CRP). All subjects underwent standard echocardiographic examination. HF was defined according Heart Failure Society of America Criteria [8]. All participants gave written informed consent for all procedures.

2.1. Blood Pressure (BP) Measurements

Clinical BP were measured using a mercury sphygmomanometer with the patients supine after 5 minutes of rest. The mean value obtained from three BP readings taken at 2- to 5-minute intervals, was used for analysis.

2.2. Laboratory Assessments

Fasting blood samples were obtained to measure serum levels of albumin, total cholesterol, triglycerides, serum electrolytes and blood cells count. Renal function was evaluated by serum creatinine by standardized methods IDMS (Isotope Dilution Mass Spectroscopy). Furthermore hs-CRP was determined by Immunoturbidimetric Assay.

2.3. Estimation of Glomerular Filtration Rate

In all participants glomerular filtration rate (eGFR) was estimated from Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) formula.

Estimated GFR = 141 x $\min(Scr/\kappa, 1)^{\alpha}$ × $\max(Scr/\kappa, 1)^{-1.209}$ × 0.993^{age} × 1.018 [if woman] _ 1.159 [if black], where Scr is serum creatinine, κ is 0.7 for women and 0.9 for men, α is -0.329 for women and -0.411 for men, min is minimum of Scr/κ or 1, and max is maximum Scr/κ or 1 [9].

2.4. Nutritional Status

According to a standardized protocol, trained examiners collected anthropometric measurements of height and weight and the body mass index (BMI) was calculated [weight (kg)/height (m^2)]. In patients with HF, BMI was determined after the acute phase, so that the confounding effect of acute HF-related fluid retention could be minimized.

Assessment of nutritional status was obtained in each subject in relation of the presence or absence of anthropometeric and laboratory markers of malnutrition. Malnutrition was defined as presence of BMI ≤ 24 kg/m^2 (according to a cut-off value recommended for elderly) [10] and/or serum albumin ≤ 3.2 g/dL (cut-off previously used for screening of elderly with protein energy malnutrition) [11].

2.5. Echocardiography

All patients underwent echocardiography while taking optimized medical therapy after the acute phase of their heart disease was over. The echocardiographic study was performed with commercially available machine (Vivid Seven digital ultrasound system™; GE Medical Systems) according to standard laboratory procedures. The M-mode echocardiographic study of the left ventriculum was performed under 2-dimensional control according to the American Society of Echocardiography recommendations. Only frames with optimal visualization of interfaces and simultaneously showing septum, left ventricular diameters and posterior wall were used for readings. Tracings were read by 2 observers who were unaware of patients' clinical data, and the mean value from at least 5 measurements per observer was computed. Left ventricular mass was calculated according to Devereux et al. and normalized by body surface area. Left ventricular systolic function was estimated measuring EF by the quantitative 2-dimensional biplane volumetric Simpson method from 4- and 2-chamber views [12].

2.6. Statistical Analysis

Data are expressed as mean ± SD or as percent frequency. Comparisons between groups were made by T-Student test or the χ^2 test as appropriate. Relationships between paired parameters were analyzed by Pearson product moment correlation coefficient.

Since serum albumin resulted significantly associated with EF in bivariate correlation, to test the independent relationship between left ventricular systolic function and serum albumin, we constructed a multivariate model (multiple linear regression) based on a series of traditional factors potentially influencing EF [age, history of hypertension and diabetes, ischemic heart disease, renal function, COPD (chronic obstructive pulmonary disease), hs CRP as index of inflammation, use of ACE inhibitors or AT2 receptors inhibitors]. Data are expressed as standardized regression coefficient (β). On the basis of a statistical power calculation, we found that, given a p value of 0.05, the number of predictors included in the model (n = 9), an observed adjusted R^2 of 0.450 and a sample size of 165, multiple regression analysis achieved a post-hoc statistical power > 0.8.

A p value of 0.05 was considered significantly different. All calculations were made with a standard statistical package (SPSS for Windows version 10.0).

3. RESULTS

Demographic, clinical, biochemical and echocardiographic data of patients are shown in Table **1**. Statistical analysis revealed high prevalences of HF (67.3%) and malnutrition (28.5%) in the study inpatients. Mean serum albumin and mean BMI were 3.6 ± 0.5 g/dL and 25.8 ± 5.2 kg/m^2 respectively.

Patients were grouped according to whether they had or had not HF (Table **2**). HF patients were older and presented significantly worse renal function indices compared with patients without HF.

As expected, T-Student tests showed significantly lower values of serum albumin in patients with HF compared with patients without HF (3.55 ± 0.56 g/dL vs 3.75 ± 0.42 g/dL; p: 0.043) (Figure **1**).

Conversely BMI values were not significantly different in the examined groups (Figure **2**).

Prevalence of malnutrition was significantly higher in patients with HF (33% vs 18.5% p: 0.048) (Figure **3**).

As shown in Table **3** associations analysis evidenced a significant direct correlation between

Table 1: Demographic, Clinical, Biochemical and Echocardiographic Characteristics of Patients (n: 165)

Age (years)	80.4 ± 7.4
Gender (M/F)	72/93
Heart failure (%)	67.3
Malnutrition (%)	28.5
Hypertension (%)	71.5
Diabetes (%)	23.6
IHD (%)	37
COPD (%)	27
ACE I/AT2R I (%)	46
Systolyc blood pressure (mm hg)	127.2 ± 21.1
Diastolic blood pressure (mm hg)	72.3 ± 11.3
BMI (Kg/m^2)	25.8 ± 5.2
Serum albumin (g/dL)	3.6 ± 0.5
Serum Creatinine (mg/dL)	1.2 ± 0.5
eGFR (mL/min)	56.9 ± 21.3
Hb (g/dL)	12.3 ± 1.9
Cholesterol (mg/dL)	170 ± 43.5
Triglycerides (mg/dL)	130.3 ± 76.4
Hs CRP(mg/dL)	2.3 ± 3.1
Sodium (mEq/L)	140.6 ± 4.6
Potassium (mEq/L)	3.9 ± 0.5
Echocardiographic parameters	
LVDd (mm)	48.4 ± 6.4
IVSDd (mm)	13.5 ± 2.3
PWDd (mm)	11.8 ± 1.9
RWT	0.52 ± 0.1
LVM (g)	271.7 ± 83
iLVM (g/m^2)	156.5 ± 39.3
EF (%)	52.6 ± 10

IHD: ischemic heart disease; COPD: chronic obstructive pulmonary disease; ACE- I/AT2R-I: use of ACE inhibitors/angiotensin 2 receptor inhibitors; BMI: body mass index; eGFR: estimated glomerular filtration rate; Hb: haemoglobin; hs CRP: high sensitivity C-reactive protein; LVDd: left ventricular diastolic diameter; IVSDd: interventricular septum diastolic diameter; PWDd: posterior wall diastolic diameter; RWT: relative wall thickness; LVM: left ventricular mass; iLVM: indexed left ventricular mass; EF: ejection fraction.

Table 2: Demographic, Clinical, Biochemical and Echocardiographic Data of Patients Divided on the Basis of Diagnosis of Heart Failure

	Patients with heart failure (n: 111)	Patients without heart failure (n: 54)	P
Age (years)	81.9 ± 7.2	77.4 ± 6.7	0.000
Gender (Male %)	44	28	0.138
Systolic blood pressure (mm hg)	123.7 ± 19.8	133.4 ± 22.2	0.057
Diastolic blood pressure (mm hg)	70.4 ± 12.3	75.6 ± 8.2	0.053
Hypertension (%)	69	76	0.381
Diabetes (%)	23	26	0.629
IHD (%)	43	24	0.017
COPD (%)	31	20	0.165
ACE I/AT2R I (%)	46	47	0.923
Serum Creatinine (mgdL)	1.2 ± 0.5	1 ± 0.5	0.043
eGFR (mL/min)	52.3 ± 18.4	67.1 ± 23.7	0.000
Hb (g/dL)	12.2 ± 1.9	12.4 ± 1.7	0.469
Cholesterol (mg/dL)	170.6 ± 44.6	168.7 ± 41.7	0.821
Triglycerides (mg/dL)	129.6 ± 69	132 ± 91.1	0.869
Hs CRP (mg/dL)	2.7 ± 3.4	1.4 ± 2.2	0.133
Sodium (mEq/L)	140.6 ± 5.2	140.7 ± 3	0.917
Potassium (mEq/L)	3.9 ± 0.5	4 ± 0.4	0.851
Echocardiographic parameters			
LVDd (mm)	49.1 ± 7.1	47.1 ± 4.7	0.238
IVSDd (mm)	13.9 ± 2.4	12.8 ± 1.9	0.029
PWDd (mm)	12.2 ± 2	11.3 ± 1.7	0.062
RWT	0.54 ± 0.1	0.51 ± 0.1	0.329
LVM (g)	290.6 ± 89.9	237.9 ± 59.6	0.027
iLVM (g/m^2)	168.3 ± 42.2	139.9 ± 28.3	0.014
EF (%)	50.2 ± 10.3	57.7 ± 7.3	0.000

IHD: ischemic heart disease; COPD: chronic obstructive pulmonary disease; ACE- I/AT2R-I: use of ACE inhibitors/angiotensin 2 receptor inhibitors; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; hs CRP: high sensitivity C- reactive protein; LVDd: left ventricular diastolic diameter; IVSDd: interventricular septum diastolic diameter; PWDd: posterior wall diastolic diameter; RWT: relative wall thickness; LVM: left ventricular mass; iLVM: indexed left ventricular mass; EF: ejection fraction.
Data are expressed as mean ± SD or as percent frequency, and comparisons among groups were made by T-Student Test or the χ^2 test as appropriate.

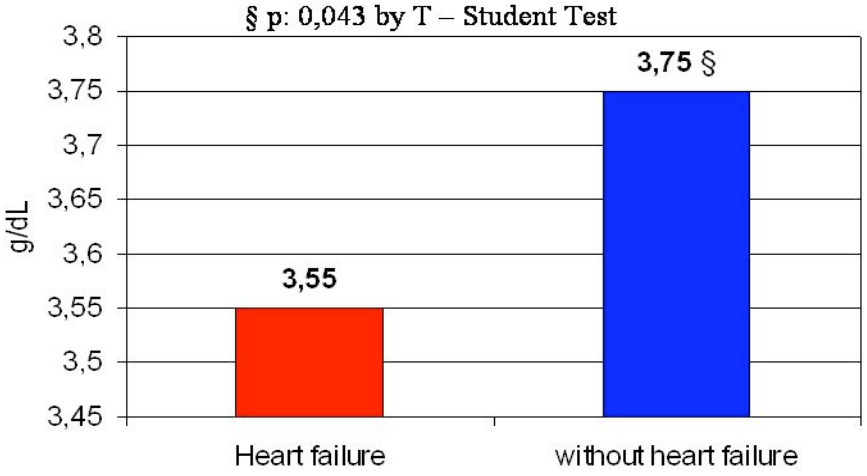

Figure 1: Comparison of mean serum albumin values in study groups.

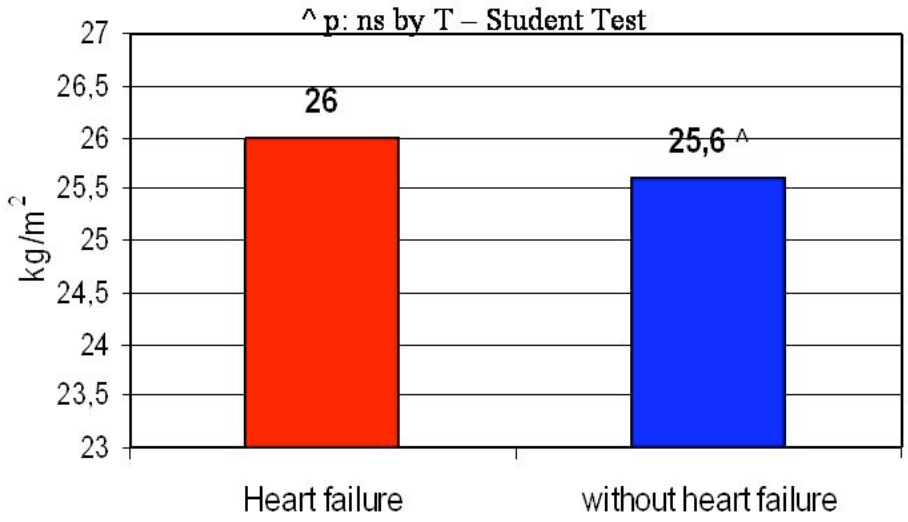

Figure 2: Comparison of mean BMI values in study groups.

serum albumin and EF of left ventriculum (r: 0.311; p:0.001). Moreover a significant inverse correlation was found between serum albumin levels and left ventricular diastolic diameter (r: - 0.297; p: 0.031) and iLVM (r: - 0.398; p: 0.015).

BMI was not significantly associated with EF. LVM resulted the only echocardiographic parameter significantly associated with BMI (r: 0.452; p: 0.002) (Table **3**).

3.1. Multivariate Analysis

To test the independence of the associations between left ventricular systolic function and serum albumin from other covariates, we performed multiple regression analyses that included demographic and cardiovascular risk factors. Serum albumin ranked as the fourth correlate of left ventricular EF, after estimated eGFR, ischemic heart disease and age (Table **4**).

4. DISCUSSION

In our study malnutrition was common among elderly hospitalized patients. In fact it was diagnosed in almost one-third of the participants. Of note, HF patients presented significantly higher prevalence of malnutrition compared with subjects without HF.

4.1. Heart Failure and Malnutrition

Malnutrition can be defined as a condition characterized by poor nourishment deriving from insufficient, unbalanced, or inappropriate diet or from impairment in absorption, assimilation, or use of foods.

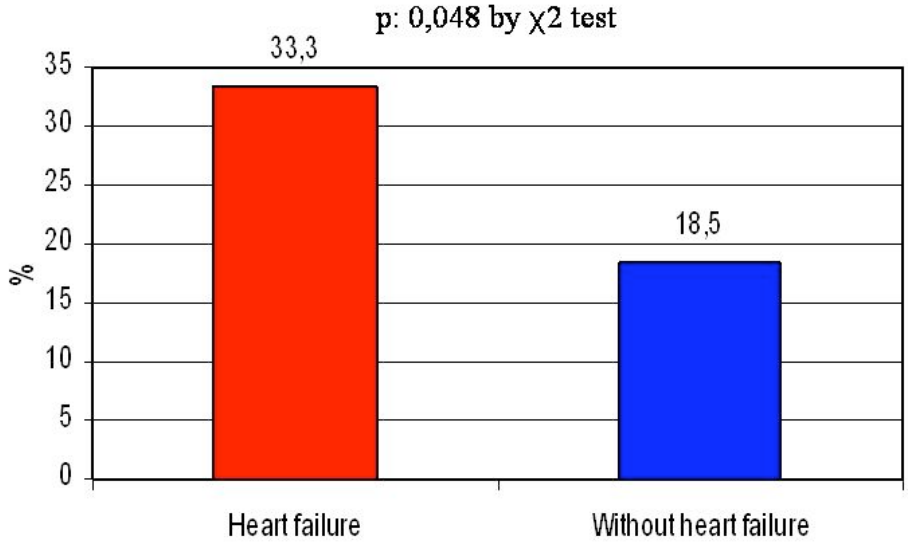

Figure 3: Prevalence of malnutrition in study groups.

Table 3: Bivariate Associations Between Malnutrition Markers and Echocardiographic Parameters

	BMI		Serum albumin	
	R	P	R	P
LVDd (mm)	0.240	0.093	-0.297	0.031
IVSDd (mm)	0.247	0.078	-0.094	0.452
PWDd (mm)	0.234	0.099	0.234	0.099
RWT	0.038	0.797	0.098	0.493
LVM (g)	0.452	0.002	-0.291	0.062
iLVM (g/m^2)	0.038	0.806	-0.398	0.015
EF (%)	0.018	0.893	0.311	0.001

BMI: body mass index; LVDd: left ventricular diastolic diameter; IVSDd: interventricular septum diastolic diameter; PWDd: posterior wall diastolic diameter; RWT: relative wall thickness; LVM: left ventricular mass; iLVM: indexed left ventricular mass; EF: ejection fraction.

Table 4: Multivariate Analysis: Dependent Variable: Left Ventricular Ejection Fraction

	β	P
eGFR	0.674	0.000
IHD	-0.413	0.001
Age	0.369	0.014
Serum albumin	0.301	0.027
Hs PCR	0.213	0.168
ACE-I/AT2R-I	0.118	0.372
Diabetes	0.083	0.483
COPD	-0.055	0.651
Hypertension	-0.012	0.929

eGFR: estimated glomerular filtration rate; IHD: ischemic heart disease; hs CRP: high sensitivity C- reactive protein; ACE- I/AT2R-I: use of ACE inhibitors/angiotensin 2 receptor inhibitors, COPD: chronic obstructive pulmonary disease.

Chronic HF often results in a malnourished state potentially culminating in body wasting (ie, cardiac cachexia) as a serious complication.

The prevalence of protein energy malnutrition associated with chronic HF, has been estimated to range from 10% to 25%, depending on the type of HF patients studied [13-18]. Importantly, malnutrition in patients with HF is associated with elevated mortality rates [19-21]. Pathophysiologic mechanisms, traditionally proposed as leading to cardiac cachexia, include reduction of appetite, secondary portal hypertension with venous stasis in the hepatic-splanchnic district in association with dyspepsia, malabsorption of lipids and loss of proteins in the gut and abnormalities in catecholamine kinetics [22-26]. Other contributors to cardiac cachexia comprise cytokine-triggered catabolism, in conjunction with neuroendocrine abnormalities [27-32]. It has been suggested that pro-inflammatory cytokines generated in response to fluid overload, chronic infections and other inflammatory stimuli have a pivotal role in the genesis of malnutrition in HF patients. In particular cytokines may cause malnutrition by mediating increased protein hydrolysis and muscle protein breakdown [33].

Our study evidenced that individuals with HF had significantly lower serum albumin levels than subjects without HF. Hypoalbuminemia is a frequent condition in patients with HF and is mainly related to the malnutrition-inflammation complex syndrome. Other causal factors include hemodilution, nephrotic syndrome, liver dysfunction, increased transcapillary escape rate and protein-losing enteropathy. Hypoalbuminemia is also common in patients with end-stage renal disease and it is a strong predictor of an adverse prognosis [34]. A low serum albumin level has been used as a marker for malnutrition for many years and is considered to be an important risk factor for mortality especially in patients with chronic renal disease [35]. However, albumin may not be a valid nutritional marker as it is affected by inflammation and external losses [36].

We found also that BMI values were not different in elderly with HF compared with elderly without HF. It should be underlined that BMI cannot distinguish between loss of lean body mass and loss of fat mass and is not an indicator of protein-energy malnutrition [37]. Furthermore, the reference ranges used to determine level of risk are often based on data from healthy adults and data for older groups is scarce [38].

4.2. Effects of Malnutrition on Heart

Interestingly, in the present study, results from multivariate analysis showed an independent

relationship between serum albumin and ejection fraction suggesting that malnutrition could induce poorer left ventriculum performance. It has been previously observed that protein malnutrition causes a hypotrophy of the cardiac muscle proportional to the hypotrophy of the skeletal muscles [39]. In healthy individuals, this can partially be an adaptive mechanism to lower metabolic requests, which rarely produces clinical cardiac insufficiency [23]. Moreover chronic HF is associated with both malnutrition (cardiac cachexia) and increased levels of pro-inflammatory cytokines [40]. In particular the failing heart produces large quantities of TNF-α. Chronic inflammation itself may cause muscle wasting, hypoalbuminaemia and anorexia, as well as reduced cardiac contractility and atherosclerotic vascular disease. A direct relationship has been documented between the level of TNF-α expression and the severity of HF [41]. An association between cytokines and the autonomic dysfunction that characterizes chronic HF has also been reported [42]. The effects of specific nutritional deficiencies of vitamins and trace elements on the heart are not well understood. Thiamine deficiency produces peripheral vasodilation, with resultant high-output HF, and certain electrolyte deficiencies reduce cardiac contractility [43-46]. Selenium deficiency has been associated with a cardiomyopathy common in certain regions of China [47] and fatal selenium cardiomyopathy has been reported in patients receiving long-term parenteral nutrition [48-50]. Anaemia, often associated with inflammation in patients with chronic kidney disease [51], is an important risk factor for cardiomyopathy, as well as increased morbidity and mortality rates in these patients [52]. Not surprisingly estimated glomerular filtration rate ranked as the first correlate of left ventricular EF. It is well established that coexistence of renal impairment with HF with preserved or depressed ejection fraction is common. In particular type 4 cardiorenal syndrome has been described as a condition characterized by primary chronic kidney disease contributing to decreased cardiac function, ventricular hypertrophy, diastolic dysfunction, and/or increased risk of adverse cardiovascular events [53].

4.3. Limitations of the Study

The present study has several limitations. First, we adopted a cross-sectional design that does not enable us to establish the direction of causality, and therefore our observations remain to be confirmed in prospective observational and interventional studies. Second, hospitalized elderly subjects enrolled in this study are a selected population not representative of all elderly people. Third, a residual fluid retention in HF patients, can't be excluded, so measured BMI values could be affected by individual hemodynamic status. Moreover it is well known that patients with diastolic HF often present higher BMI than subjects with systolic HF. So, in our study, the inclusion of all patients with HF in a single group (not differing preserved and reduced EF) could have limited the identification of differences in BMI versus subjects without HF. Finally both inflammation and inadequate nutritional intake can decrease the concentration of albumin much of the previously reported relationship between serum albumin and left ventricular systolic function may be due to an inflammatory process rather than poor nutritional intake.

5. CONCLUSIONS

In the clinical setting, more attention should be paid to recognizing and diagnosing malnutrition in hospitalized elderly subjects and especially in patients with HF. More efforts should be dedicated in the research setting to better understand the pathophysiology of cardiac cachexia and to identify effective management strategies. Since the use of single anthropometric and biochemical markers of malnutrition in the elderly present limitations, a multiparametric approach might be more adequate. The independent relationship found between serum albumin and ejection fraction suggests that malnutrition is involved in impairment of left ventricular systolic function in elderly patients with and without HF. More research is needed to clarify the complex relationship linking malnutrition, inflammation, cytokines and chronic kidney disease in patients with HF.

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