

# Impact of Cardiovascular Treatments and Systolic Dysfunction on Nutritional Risk in Patients with Ischemic and Valvular Heart Disease

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## Original Research

# Impact of Cardiovascular Treatments and Systolic Dysfunction on Nutritional Risk in Patients with Ischemic and Valvular Heart Disease

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**Key words:** nutritional risk screening, NRS-2002, heart failure, systolic dysfunction, cardiovascular risk

**Objective:** There is a limited knowledge about connections existing between impaired systolic function and nutritional risk. The aim of our study was to evaluate nutritional risk in patients recently treated for valvular or ischemic heart disease, depending on the impairment of left ventricle systolic function and chronic cardiovascular therapy.

**Methods:** Nutritional risk screening was applied using a nutritional risk screening (NRS)-2002 [1] tool in cross-sectional study settings on patients scheduled for cardiovascular rehabilitation. There were 105 patients with impairment of left ventricle systolic function ( $LVEF \leq 40$ ) vs 145 consecutive matching peers with preserved LVEF. Percentage weight loss history (WLH) from preceding cardiovascular treatments was available for more than 85% of studied patients.

**Results:** Mean WLH was  $7.7 \pm 4.6\%$ , and NRS-2002 was  $3.6 \pm 1.5$ . Significant differences in percentage WLH and NRS-2002 were found for age groups ( $p < 0.001$ ,  $p < 0.001$ , respectively), cardiovascular treatments ( $p < 0.001$ ,  $p < 0.001$ , respectively), and grades of renal function ( $p < 0.001$ ,  $p < 0.001$ , respectively), whereas there was no difference on the basis of systolic function preservation (both  $p > 0.05$ , respectively). Utilization of proton pump inhibitors, loop diuretics, and calcium channel antagonists increased the odds for pronounced nutritional risk, 2.60 (95% confidence interval [CI], 1.23–5.47),  $p = 0.012$ , vs 2.15 (95% CI, 1.00–4.62),  $p = 0.049$ , vs 2.18 (95% CI, 1.01–4.68),  $p = 0.046$ , respectively. Conversely, angiotensin-converting enzyme (ACE) inhibitors exhibited protective effects to the nutritional risk, 0.20 (95% CI, 0.05–0.89),  $p = 0.035$ .

**Conclusion:** Clinically, most evocative connections of nutritional risk screening and unintentional weight loss were found in relation to invasiveness of preceding cardiovascular treatments, rather than preservation of systolic function. Protective effects on nutritional risk were found for ACE inhibitors, whereas loop diuretics and proton pump inhibitors increased the nutritional risk and unintentional loss of weight.

## INTRODUCTION

Heart failure is one of the most notorious issues in cardiology [2]. Prevalence continues to rise, following aging of the population and increasing number of cardiovascular risk factors or coexisting comorbidities [2]. Advanced forms of heart failure include dysfunction of several organ systems beyond the cardiovascular, which has a significantly negative impact on quality of life, rate of hospitalizations, and prevalence of major adverse cardiovascular events. These are particularly

pronounced with the development of cardiorenal syndrome, worsening of respiration dynamics, along with the development of cardiac cachexia [3,4].

Although complex connections of pathophysiological processes acting within development of cardiac cachexia are not fully understood, they include loss of appetite, malnutrition, malabsorption, drug-induced changes, metabolic disturbances, activation of neurohumoral and inflammatory processes, as well as others [5]. Heart failure cachexia leads to wasting of several body compartments by means of lean, fat, and bone

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tissue loss [6]. Furthermore, the mass of left ventricle in patients with chronic heart failure was shown to be negatively correlated with loss of body weight [7]. One study recently reported on the reciprocal correlation of right ventricle systolic function with cachexia and overall prognosis in patients with heart failure [8]. Similarly, unintentional weight loss was found to be landmark of underprivileged prognosis in several other chronic disorders, as well as in heart failure [9]. Loss of weight in conjunction with disease or treatment intensity basically sets the grounds for several nutritional risk screening (NRS) tools [1], which are considered to be well reproducible clinical tools for assessment of nutritional risk and guiding of therapeutic interventions [10]. A number of earlier studies showed that increased nutritional risk was related to the course of the disease and clinically relevant points such as admission to hospital, length of hospital stay, and incurred costs of treatment [11].

Interestingly, only a paucity of studies addressed nutritional risk in patients with systolic heart failure prior to development of an overt and potentially irreversible cardiac cachexia. In addition, there is a limited data regarding the associations between impaired systolic function and nutritional risk in patients with various cardiovascular disorders.

The aim of our study was to systematically analyze nutritional risk in patients with impaired systolic function of the left ventricle compared to matched controls, following acute treatment for valvular or ischemic heart disease. Secondly, characteristics of nutritional risk screening were assessed in connection with invasiveness of cardiovascular treatments, prevalence of comorbidities, and clinical diagnostics.

## **PATIENTS AND METHODS**

### **Study Outline**

This was cross-sectional study on consecutive patients with decreased systolic function of left ventricle; that is, ejection fraction (LVEF  $\leq$  40%). A control group was formed from a comparable number of consecutive patients in the same period from an in-house registry. Both groups were scheduled for cardiovascular rehabilitation during the period January 2012 to March 2013, 1–5 months after treatment for ischemic, valvular, or combined (ischemic and valvular) heart disease. Diagnostics included conventional echocardiography, lung function tests, anthropometrics, cardiovascular laboratory tests, and electrocardiography. Medical records from acute treatment were available for the entire studied population, and baseline weight was documented or known for more than 85% of the studied patients. Drug utilization analyzes included prevalence and daily defined doses for common cardiovascular group of drugs. A group of proton pump inhibitors was included in the analysis due to frequent use after discharge from hospital.

### **Anthropometrics**

Measurements were performed on a calibrated medical standing scale; body weight was measured in kilograms and height in meters, and body mass index (BMI) was calculated using the standard formula ( $\text{kg}/\text{m}^2$ ). Percentage weight loss history (%WLH) was calculated as the difference in kilograms in the period from acute cardiovascular treatments (baseline weight) to commencement of rehabilitation, which was divided by baseline weight. Waist circumference (WC) and hip circumference (HC) were measured in centimeters using a measuring tape, including calculation of the waist-to-hip ratio (WHR).

Nutritional risk screening was assessed with a standardized screening tool the NRS-2002, endorsed by the European Society For Clinical Nutrition and Metabolism [12]. The questionnaire included a summary of the amount and timeline of unintentional percentage weight lost and relative disease severity; an additional point was given for age over 70 years (range 0–7). The population was divided in 2 groups according to the existence of increased nutritional risk, defined as  $\text{NRS-2002} \geq 3$ .

Laboratory analyses were performed on early morning samples from fasting patients, including complete blood count, and biochemistry (electrolytes, urea, creatinine, lipid profile, and thyroid stimulating hormone). Echocardiographic examinations were done using a Toshiba Artida with a PST30BT 3 MHz cardiology transducer (Toshiba Co., Tokyo, Japan) by 2 experienced high-throughput cardiologists.

### **Exclusion Criteria**

Patients with acute cardiovascular treatment more than 5 months prior to rehabilitation were not included in this study. In addition, patients with typical contraindications for cardiovascular rehabilitation were excluded. Contraindications specifically included congestive heart failure, unregulated diabetes, thyroid dysfunction, end-stage renal or respiratory disease, neoplasms, hemodynamic instability, or malignant disorders of heart rhythms.

### **Ethical Issues**

This study was approved by the Ethical Committee of the hospital and patients were included after signing a written informed consent.

### **Statistical Analyses**

The studied groups were analyzed with descriptive statistics and results are presented as means and standard deviations. Population demographics, comorbidities, and nutritional risk outcomes for the studied groups were calculated using Pearson's chi-square tests. Data on anthropometrics, laboratory testing, echocardiography, and remainder numeric data were tested for differences by Mann-Whitney U test or Kruskal-

Wallis. Correlation of the NRS-2002 score with clinical diagnostics and outcomes was done using Spearman's rho. Partial nonparametric correlations were controlled for utilization of diuretics and LVEF. Odds of an NRS-2002  $\geq 3$  considering drug utilization analyses were calculated using multivariate logistic regression. Receiver operating characteristics curves of LVEF were analyzed for the groups at increased nutritional risk. A  $p$  value less than 0.05 was considered significant. Statistical analyses were performed by a professional statistician using Statistica v.10 for Windows (StatSoft Inc., Tulsa, OK, USA), MedCalc v. 12.2 for Windows (MedCalc Software Co., Mariakerke, Belgium), and IBM-SPSS12 v. 20 (IBM Co., Chicago, IL, USA).

## RESULTS

### Patients

The study sample included 247 patients scheduled for cardiovascular rehabilitation. Mean age was  $62.7 \pm 10.6$  years (range 32–86), with 104 (42.1%) older than 65 years. In the studied sample there were more male than female patients, 201 (81.4%) and 46 (18.6%), respectively. The average patient had  $5.4 \pm 1.5$  (0–9) cardiovascular risk factors: 52 (21.1%) had chronic renal disease, 30 (12.1%) were glucose intolerant, 84 (34.0%) had diabetes mellitus (treated), and 86 (35.0%) were obese. Ninety-five (38.5%) patients had never smoked and 69 (27.9%) were active cigarette users or recent quitters; 50 (20.2%) had known chronic obstructive pulmonary disease. Two hundred thirty-two patients (93.9%) had coronary artery disease, 204 (82.6%) had survived myocardial infarction, 60 (24.3%) had known atherothrombotic disorder (including history of peripheral artery disease, carotid disease, cerebrovascular stroke, or thromboembolism), and 37 (15.0%) had permanent atrial fibrillation. Mean BMI was  $28.7 \pm 3.9$  kg/m<sup>2</sup> (19.4–46.0); most of the patients (117, 47.6%) were overweight (BMI range 25–30 kg/m<sup>2</sup>) and only 44 (17.9%) had BMIs  $< 25$  kg/m<sup>2</sup>. WC was  $102.2 \pm 10.1$  cm (71.0–124.0), HC was  $103.0 \pm 8.5$  cm (64.0–136.0), and WHR was  $0.99 \pm 0.08$  (0.71–1.30). Most of the laboratory outputs were within referral values or in line with chronic comorbidities in a steady phase: hematocrit  $0.40 \pm 0.05$  (0.27–0.50), serum glucose  $6.9 \pm 2.0$  mmol/L, triglycerides  $1.54 \pm 0.73$  mmol/L, total cholesterol  $4.27 \pm 2.36$  mmol/L, low-density lipoprotein (LDL) cholesterol  $2.23 \pm 1.04$  mmol/L, high-density lipoprotein (HDL) cholesterol  $0.93 \pm 0.42$  mmol/L, urea  $7.7 \pm 3.1$  mmol/L, and creatinine  $115.2 \pm 45.5$   $\mu$ mol/L.

Etiologies of cardiovascular diseases were classified into groups as follows: ischemic heart disease, 211 (85.4%); valvular heart disease, 13 (5.3%); and combined (ischemic and valvular) heart disease in 23 (9.3%). Cardiovascular treatments included percutaneous coronary intervention (PCI) in 114 (46.2%),

cardiovascular surgery in 112 (45.3%), and conservatively treated myocardial infarction in 21 (8.5%). There were no cases of overt gastrointestinal bleeding or peptic ulcer disease, verified by endoscopy, including during the preinclusion period.

### Systolic Function of the Left Ventricle

Mean LVEF was  $45.6 \pm 10.1$  (range 20.0–65.0); systolic dysfunction (LVEF  $\leq 40\%$ ) was present in 105 (42.5%) patients and there were 142 (57.5%) controls. Significant differences between the groups with impaired systolic function vs controls was found for prevalence of PCI treatments, 41/105 (39.0%) vs 74/142 (52.1%),  $p = 0.042$ , respectively.

There was no significant difference between the groups on the basis of left ventricle systolic dysfunction for most of the studied comorbidities (increased nutritional risk, age, gender, BMI, heart disease etiology, acute settings treatments, arterial hypertension, dyslipidemia, chronic renal disease, diabetes, glucose intolerance, cigarette smoking, chronic obstructive pulmonary disease, coronary artery disease, survived myocardial infarction, or atrial fibrillation), all  $p > 0.05$ .

Drug utilization analyses revealed significant differences in prevalence of therapy with acetylsalicylic acid, 95/105 (90.5%) vs 141/142 (99.3%),  $p < 0.001$ ; calcium channel antagonists, 17/105 (16.2%) vs 55/142 (38.7%),  $p < 0.001$ ; loop diuretics, 61/105 (58.1%) vs 33/142 (23.2%),  $p < 0.001$ ; and aldosterone antagonists, 22/105 (21.0%) vs 0 (0%),  $p < 0.001$ . The remainder of the studied drugs had similar utilization profiles for patients with systolic dysfunction and controls (renin–angiotensin–aldosterone antagonists, beta blockers, trimetazidine, statins, proton pump inhibitors, warfarin, clopidogrel, oral antidiabetics, and insulin, all  $p > 0.05$ ).

Analyses of patient characteristics and clinical diagnostics for the groups with left ventricle systolic function are presented in Table 1.

### Percentage Weight Loss and Nutritional Risk Screening

Mean %WLH was  $7.7 \pm 4.6\%$  (range 0–26.0%), and NRS-2002 was  $3.6 \pm 1.5$  (range 0–7). A high grade of correlation was found between the NRS-2002 and WLH ( $\rho = 0.840$ ;  $p < 0.001$ ).

Significant differences in %WLH and NRS were found for age groups ( $p < 0.001$ ,  $p < 0.001$ , respectively), cardiovascular treatments ( $p < 0.001$ ,  $p < 0.001$ , respectively), and grade of renal function ( $p < 0.001$ ,  $p < 0.001$ , respectively), whereas there was no difference on the basis of preservation of left ventricle systolic function (both  $p > 0.05$ ); see Table 2.

There was no significant cutoff value of LVEF for increased nutritional risk in receiver operating characteristic curve analyses ( $p > 0.05$ ). In addition, there were no significant differences in NRS-2002 according to BMI ( $< 25$ ,

**Table 1.** Patient Characteristics According to Left Ventricle Systolic Function

	LVEF ≤ 40% <i>n</i> = 105 Mean ± SD	LVEF > 40% <i>n</i> = 142 Mean ± SD	Mann-Whitney U test
Percentage WLH	8.1 ± 5.1	7.3 ± 4.3	0.386
Nutritional risk screening (NRS-2002)	3.6 ± 1.5	3.7 ± 1.5	0.834
BMI (kg/m <sup>2</sup> )	28.4 ± 4.1	28.9 ± 3.8	0.450
Erythrocytes count ( <i>n</i> * 10 <sup>12</sup> )	4.39 ± 0.64	4.39 ± 0.61	0.908
Hematocrit ( <i>n/n</i> )	0.39 ± 0.05	0.40 ± 0.05	0.732
Mean corpuscular volume (fL)	88.9 ± 10.2	89.4 ± 11.7	0.136
Leukocytes ( <i>n</i> * 10 <sup>12</sup> )	8.22 ± 2.35	8.08 ± 2.21	0.599
Platelets ( <i>n</i> * 10 <sup>9</sup> )	294.5 ± 107.8	317.7 ± 129.7	0.415
Serum glucose (mmol/L)	6.9 ± 1.9	6.9 ± 2.0	0.717
Bilirubin (μmol/L)	13.9 ± 6.0	13.5 ± 6.8	0.281
Urea (μmol/L)	8.4 ± 3.5	7.2 ± 2.7	0.002*
Creatinine (mmol/L)	120.5 ± 48.8	111.4 ± 42.8	0.124
Uric acid (mmol/L)	366.0 ± 106.1	336.3 ± 87.0	0.032*
Triglycerides (mmol/L)	1.42 ± 0.63	1.62 ± 0.79	0.025*
Cholesterol (mmol/L)	3.92 ± 1.13	4.53 ± 2.93	0.004*
HDL cholesterol (mmol/L)	0.91 ± 0.41	0.94 ± 0.43	0.531
LDL cholesterol (mmol/L)	2.08 ± 0.98	2.34 ± 1.07	0.019*
AST (IU/L at 37°C)	25.7 ± 14.2	27.9 ± 19.9	0.569
ALT (IU/L at 37°C)	38.9 ± 29.0	41.0 ± 28.6	0.282
GGT (IU/L at 37°C)	64.7 ± 72.2	63.8 ± 101.5	0.944
TSH (mIU/L)	3.0 ± 3.4	2.6 ± 4.1	0.349
LVEDd (mm)	57.5 ± 7.3	52.9 ± 4.2	<0.001*
LVEDs (mm)	42.4 ± 10.4	35.1 ± 6.0	<0.001*
IVS (mm)	11.5 ± 2.1	11.7 ± 2.0	0.374
LVPW (mm)	10.7 ± 1.5	11.0 ± 1.9	0.029*
LVEF (%)	35.7 ± 5.6	52.9 ± 5.4	<0.001*
Early filling (m/s)	0.81 ± 0.32	0.73 ± 0.22	0.117
Atrial filling (m/s)	0.69 ± 0.26	0.78 ± 0.22	0.001*
E/A	1.24 ± 0.72	0.98 ± 0.35	0.069
Left atrium-APD (mm)	45.5 ± 5.6	42.2 ± 4.4	<0.001*
Pulmonary artery pressure (mmHg)	35.3 ± 8.5	27.7 ± 5.7	<0.001*
Tiffneau index (FEV1/FVC)	83.7 ± 6.5	83.1 ± 7.8	0.618

LVEF = left ventricle ejection fraction, WLH = weight loss history, BMI = body mass index, HDL = high-density lipoprotein, LDL = low-density lipoprotein, AST = aspartate transaminase, ALT = alanine transaminase, GGT = gamma glutamic transpeptidase, TSH = thyroid stimulating hormone, LVEDd = left ventricle end diastolic dimension, LVEDs = left ventricle end systolic dimension, IVS = interventricular septum thickness, LVPW = left ventricle posterior wall thickness, E = early ventricular filling velocity, A = late (atrial) filling velocity, APD = anteroposterior dimension, FEV1 = forced expiratory volume in the first second, FVC = forced vital capacity. \**p* < 0.001.

25–29, 30–34, >35 kg/m<sup>2</sup>); that is, 3.7 ± 1.9, 3.6 ± 1.4, 3.7 ± 1.5, 3.2 ± 1.2, respectively, *p* = 0.564. Correlations of patient characteristics undergoing nutritional risk screening are presented in Table 3.

**Drug Utilization and Nutritional Risk**

Odds for developing increased nutritional risk (NRS-2002 ≥ 3) for the analyzed group of drugs were calculated using a multivariate logistic regression model; the use of proton pump inhibitors, loop diuretics, and calcium channel antagonists increased the odds by 2.60 (95% confidence interval [CI] 1.23–5.47), *p* = 0.012, vs 2.15 (95% CI, 1.00–4.62), *p* = 0.049, vs 2.18 (95% CI, 1.01–4.68), *p* = 0.046, respectively. Conversely, ACE inhibitors showed protective effects: odds ratio (OR) = 0.20 (95% CI, 0.05–0.89), *p* = 0.035. The remainder of the studied drugs, including beta blockers,

acetylsalicylic acid, and both groups of antidiabetic drugs had an insignificant impact on the prevalence of increased nutritional risk in the model.

Changes in %WLH and NRS-2002 for patients using ACE inhibitors vs controls was also significant: %WLH = 10.5 ± 3.5 vs 6.9 ± 4.6, *p* < 0.001, and NRS-2002 = 4.4 ± 1.2 vs 3.4 ± 1.5, *p* < 0.001, respectively.

The utilization of loop diuretics revealed significant difference in prevalences between groups of patients with increased nutritional risk and controls without nutritional risk (83/190 or 43.7% vs 11/57 or 19.3%, respectively, *p* < 0.001). This was supported by significant partial correlation of %WLH and NRS-2002, controlled for utilization of loop diuretics (cc = 0.892; *p* < 0.001).

The impact of left ventricle systolic function and utilization of loop diuretics on the parameters of nutritional risk screening are presented in Table 4.

**Table 2.** Influence of Age, Earlier Cardiovascular Treatment, Grade of Renal Function, and Systolic Function of the Left Ventricle on the Studied Parameters in Nutritional Risk Screening<sup>a</sup>

	Percentage WLH		NRS-2002	
	Mean ± SD	Kruskal-Wallis	Mean ± SD	Kruskal-Wallis
Age (years)				
<44	4.6 ± 2.8	<b>&lt;0.001</b>	2.3 ± 1.3	<b>&lt;0.001</b>
44–65	6.7 ± 4.4		3.2 ± 1.4	
≥65	9.3 ± 4.7		4.4 ± 1.4	
Treatments				
Conservative	4.6 ± 2.7	<b>&lt;0.001</b>	2.8 ± 1.0	<b>&lt;0.001</b>
PCI	4.2 ± 1.8		2.6 ± 1.1	
Surgery	11.8 ± 3.3		4.9 ± 1.0	
Renal function				
No renal disease	7.1 ± 4.5	<b>&lt;0.001</b>	3.4 ± 1.5	<b>&lt;0.001</b>
Chronic renal disease	9.7 ± 4.7		4.4 ± 1.3	
Systolic function of the left ventricle				
Reduced (LVEF ≤ 40%)	8.1 ± 5.1	0.385	3.6 ± 1.5	0.830
Preserved (LVEF > 40%)	7.4 ± 4.3		3.7 ± 1.5	

WLH = weight loss history, NRS-2002 = nutritional risk screening, PCI = percutaneous coronary intervention, LVEF = left ventricle ejection fraction.  
<sup>a</sup>Significant differences are shown in bold.

## DISCUSSION

The prevalence of increased nutritional risk in patients with systolic heart failure is generally unknown. Standardized screening tools are rarely used in routine clinical practice, although there is significant evidence regarding the prognostic significance of this relevant comorbidity [13]. Our study systematically analyzed characteristics of nutritional risk screening in a cross-sectional study of clinically stable patients with recent treatment for ischemic or valvular heart disease, depending on the impairment of left ventricle systolic function and drug utilization analyzes.

In the studied set of patients, mean unintentional weight loss was 7.7 ± 4.6%, and NRS-2002 was 3.6 ± 1.5. Surgical

treatments were generally correlated with increased nutritional risk (NRS-2002 ≥ 3) but not with PCI or conservatively treated myocardial infarctions, which in general were within the non-risk range of NRS-2002. The extent and prevalence of nutritional risk were congruent with studies that included patients from general surgery or internal medicine hospital wards [14]. Weight loss greater than 5% from baseline represents one of the input parameters of NRS-2002 and its conceptualization to more specifically detect prognostically significant weight loss [10,15]. Patient age had a significant and proportionate impact on NRS-2002 and WLH. There were no correlations between either screening parameter with LVEF, which might be explained by the inclusion of relatively stable patients.

**Table 3.** Correlation of Nutritional Risk Screening Parameters with Studied Patient Characteristics<sup>a</sup>

Spearman's rho	Age	Height	Weight	BMI	Waist circumference	Hip circumference	Hematocrit	Platelets	Serum glucose	Urea
NRS-2002										
Rho	<b>0.405</b>	<b>-0.186</b>	<b>-0.179</b>	-0.052	-0.081	-0.124	<b>-0.459</b>	<b>0.265</b>	<b>0.126</b>	<b>0.267</b>
p	<b>&lt;0.001</b>	<b>0.003</b>	<b>0.005</b>	0.417	0.209	0.053	<b>&lt;0.001</b>	<b>&lt;0.001</b>	<b>0.049</b>	<b>&lt;0.001</b>
% WLH										
Rho	<b>0.333</b>	<b>-0.174</b>	<b>-0.263</b>	<b>-0.145</b>	<b>-0.180</b>	<b>-0.155</b>	<b>-0.450</b>	<b>0.304</b>	0.082	<b>0.217</b>
p	<b>&lt;0.001</b>	<b>0.006</b>	<b>&lt;0.001</b>	<b>0.023</b>	<b>0.005</b>	<b>0.015</b>	<b>&lt;0.001</b>	<b>&lt;0.001</b>	0.202	<b>0.001</b>
	Creatinine	LVE	PAP	LVEF	PPI	OAD	Insulin	ACE inhibitors	Beta blockers	Loop diuretics
NRS-2002										
Rho	<b>0.348</b>	-0.081	0.126	-0.013	<b>0.398</b>	0.060	0.060	<b>-0.261</b>	-0.073	<b>0.321</b>
p	<b>&lt;0.001</b>	0.210	0.051	0.837	<b>&lt;0.001</b>	0.347	0.347	<b>&lt;0.001</b>	0.256	<b>&lt;0.001</b>
% WLH										
Rho	<b>0.309</b>	-0.051	<b>0.175</b>	-0.082	<b>0.411</b>	0.071	0.021	<b>-0.327</b>	-0.033	<b>0.307</b>
p	<b>&lt;0.001</b>	0.428	<b>0.006</b>	0.196	<b>&lt;0.001</b>	0.267	0.748	<b>&lt;0.001</b>	0.600	<b>&lt;0.001</b>

BMI = body mass index, NRS-2002 = nutritional risk screening, %WLH = percentage weight loss history, LVEDd = left ventricle end diastolic dimension, PAP = pulmonary artery systolic pressure; LVEF = left ventricle ejection fraction; PPI = proton pump inhibitor; OAD = oral antidiabetic drugs; ACE = angiotensin-converting enzyme.

<sup>a</sup>Significant differences are shown in bold.

**Table 4.** Impact of Left Ventricle Systolic Function and Use of Loop Diuretics on the Parameters of Nutritional Risk Screening (NRS-2002)

	Percentage WLH Mean ± SD	NRS-2002 Mean ± SD
Systolic dysfunction (LVEF ≤ 40%)		
Loop diuretics		
No	6.8 ± 5.9	3.2 ± 1.5
Yes	9.0 ± 4.2	3.9 ± 1.5
Preserved systolic function (LVEF > 40%)		
Loop diuretics		
No	6.6 ± 4.1	3.3 ± 1.4
Yes	9.9 ± 3.9	4.9 ± 1.0
Systolic dysfunction (LVEF ≤ 40%)		
ACE inhibitors		
No	10.4 ± 3.1	4.0 ± 1.2
Yes	7.4 ± 5.3	3.4 ± 1.6
Preserved systolic function (LVEF > 40%)		
ACE inhibitors		
No	10.6 ± 4.0	4.8 ± 1.2
Yes	6.7 ± 4.1	3.4 ± 1.5
Systolic dysfunction (LVEF ≤ 40%)		
Calcium channel blockers		
No	7.9 ± 5.3	3.5 ± 1.6
Yes	9.1 ± 3.8	4.2 ± 1.2
Preserved systolic function (LVEF > 40%)		
Calcium channel blockers		
No	7.9 ± 4.5	3.7 ± 1.6
Yes	6.5 ± 3.9	3.6 ± 1.4

NRS-2002 = nutritional risk screening, WLH = weight loss history, LVEF = left ventricle ejection fraction, ACE = angiotensin-converting enzyme.

Inputs of nutritional risk screening were significantly correlated with utilization of loop diuretics, although patients with congestive heart failure or clinically overt edema were not included in our study. Greater prevalence of diuretic therapy utilization was found among patients with increased nutritional risk (NRS ≥ 3), as well as the group with decreased systolic function, where both opposed to their controls. The water loss effect of loop diuretic therapy was shown to be a substantial challenge for reproducibility of nutritional risk screening; hence, clinical assessments of nutritional risk in similar groups of patients warrants a more cautious approach. In addition, a similarly meticulous approach should be taken in patients with chronic kidney disease, where both utilization of loop diuretics and kidney disease influence the inputs of nutritional risk screening [16]. The latter also seems to be more pronounced due to postoperative changes in body compartments and complex connections caused by the effects of loop diuretics, as well as due to the negative impact of lowered systolic function on the dynamics of cardiorenal syndrome [17].

The use of proton pump inhibitors revealed a somewhat inquisitive profile of consumption, which was positively correlated with unintentional loss of weight and nutritional risk assessed by NRS-2002. Furthermore, the connection was also in line with the dynamics of hematocrit, which was also inversely correlated with greater WLH and NRS. Earlier studies consistently reported the well-established negative implications of anemia in patients with chronic heart failure [18]. Because there were no cases of overt gastrointestinal causes of bleeding during the study or within the period of acute treatments, the effects could be related to the pro-anemic effects of proton pump inhibitors via suppression of gastric acid secretion [19]. Paradoxically, proton pump inhibitors were most likely initiated due to postoperative anemia, advanced age, and generally poor condition during the postoperative period, which in part stemmed from pronounced nutritional risk and underlying inflammatory-reparative reactions, catabolism of protein, or other disturbances in body compartments due to invasive treatment [20]. Therefore, the safety profile of proton pump inhibitors might be questionable, due to potential bone loss, impaired iron metabolism, gut dysbiosis, as well as the increased prevalence of infection [21–23].

ACE inhibitors showed relatively potent ameliorative clinical effects on the unintentional loss of weight and nutritional risk screening, with statistically significant differences, inverse correlations, and protective odds for developing increased nutritional risk. This observation was in line with previous reports concerning nutritional aspects of ACE inhibitors [8]. ACE inhibitors display multiple beneficial effects within cardiovascular system, which extends beyond antihypertensive effects, improving endothelial function, mediating metabolism of proteins, improving insulin resistance, delaying the onset of diabetes, and hypertrophy of the left ventricle [24]. Pleiotropic effects of ACE inhibitors not surprisingly include the decrease in prevalence for numerous major adverse cardiovascular events [25]. In addition, subgroup analyses showed that the protective effects of ACE inhibitors were consistent for both impaired and preserved systolic function of the left ventricle, which was not described in earlier studies. Though these preliminary results might be inspiring, results ought to be reassessed in prospective controlled randomized settings on a sufficient number of patients, in order to objectively qualify the level of evidence and clinical significance.

Beta blockers did not show any clinically significant mediation in nutritional risk screening, although effects could have been expected due to reports from earlier investigations. Although an increase in body weight in terms of nutritional risk would be desirable, beta blockers seem to have an undesirable effect with an increase in body fat content, due to decreased energy expenditure, influencing glucose and insulin metabolism, as well as inhibiting catecholaminergic- and aldosterone-induced lipolysis [26].



Calcium channel blockers showed a somewhat intriguing connection with an increase in recorded unintentional loss of weight and NRS-2002, in favor of increasing nutritional risk. Due to the ameliorative effects on endothelial function and to some degree insulin resistance and chronic inflammatory processes, one might also expect mediation of the nutritional risk profile [27]. However, some clinically minor effects were found depending on the systolic function of the left ventricle. In subgroup analyses, the protective effects for both parameters of nutritional risk screening were found in patients with preserved systolic function, whereas unintentional weight loss and NRS-2002 were both increased in patients with impairment of systolic function. Because only amlodipine was shown to be non-inferior for prognosis of systolic heart failure and dilatative cardiomyopathy, this clinically minor effect does not influence earlier evidence-based recommendations [28].

Remarkably, neither conventional anthropometrics showed any clinically meaningful correlation with NRS-2002 score or its inputs. Nutritional risk evidently acts on a shorter timescale than cardiovascular risk and is underrecognized by conventional anthropometrics or traditional risk factors from the cardiovascular disease continuum [29]. Assessment of nutritional risk in patients with impaired systolic function could be recommended on a quarterly basis due to reproducibility and dynamics of NRS-2002 clinical inputs. Additional reassessments would be reasonable in the case of more pronounced acute illness, clinical deterioration, or following major invasive treatments [30].

In conclusion, clinically most evocative connections of nutritional risk screening and unintentional weight loss were found in relation with invasiveness of earlier cardiovascular treatments, rather than preservation of systolic function. Surgical treatments yielded the uppermost score of nutritional risk screening, contrary to percutaneous coronary interventions and conservatively treated myocardial infarctions. Interesting connections of unintentional weight loss were found for groups of drugs that are commonly used in chronic treatment of diseases from the cardiovascular disease continuum. Protective effects on nutritional risk were found for ACE inhibitors and calcium channel blockers in the subgroup of patients with preserved systolic function. On the other hand, loop diuretics, proton pump inhibitors, and calcium channel blockers, in particular in group of the patients with impaired systolic function, caused different degrees of increasing effect to the nutritional risk screening parameters. This study was limited due to post hoc uncontrolled settings and the relatively low number of patients; however, future studies regarding characteristics of nutritional risk screening in cardiology might improve medical care, quality of life, or even prognosis. This is particularly desirable in the growing number of patients with chronic heart failure.

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