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ORIGINAL RESEARCH

Prognostic Impact of Nutritional Status After Transcatheter Edge-to-Edge Mitral Valve Repair: The MIVNUT Registry

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BACKGROUND: Malnutrition is associated with poor prognosis in several cardiovascular diseases. However, its prognostic impact in patients undergoing transcatheter edge-to-edge mitral valve repair (TEER) is not well known. This study sought to assess the prevalence, clinical associations, and prognostic consequences of malnutrition in patients undergoing TEER.

METHODS AND RESULTS: A total of 892 patients undergoing TEER from the international MIVNUT (Mitral Valve Repair and Nutritional Status) registry were studied. Malnutrition status was assessed with the Controlling Nutritional Status score. The association of nutritional status with mortality was analyzed with multivariable Cox regression models, whereas the association with heart failure admission was assessed by Fine-Gray models, with death as a competing risk. According to the Controlling Nutritional Status score, 74.4% of patients with TEER had any degree of malnutrition at the time of TEER (75.1% in patients with body mass index <25 kg/m^2, 72.1% in those with body mass index ≥25 kg/m^2). However, only 20% had moderate–severe malnutrition. TEER was successful in most of patients (94.2%). During a median follow-up of 1.6 years (interquartile range, 0.6–3.0), 267 (29.9%) patients died and 256 patients (28.7%) were admitted for heart failure after TEER. Compared with normal nutritional status moderate–severe malnutrition resulted a strong predictor of mortality (adjusted hazard ratio [HR], 2.1 [95% CI, 1.1–2.4]; P<0.001) and heart failure admission (adjusted subdistribution HR, 1.6 [95% CI, 1.1–2.4]; P=0.015).

CONCLUSIONS: Malnutrition is common among patients submitted to TEER, and moderate–severe malnutrition is strongly associated with increased mortality and heart failure readmission. Assessment of nutritional status in these patients may help to improve risk stratification.

Key Words: CONUT ■ heart failure ■ malnutrition ■ mortality ■ transcatheter edge-to-edge repair

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CLINICAL PERSPECTIVE

What Is New?

- Most patients undergoing transcatheter edge-to-edge mitral valve repair have malnutrition, even those who are overweight.
- Moderate–severe malnutrition is independently associated with an increased probability of mortality and heart failure admission in patients undergoing transcatheter edge-to-edge mitral valve repair.

What Are the Clinical Implications?

- Improvement of preprocedural nutritional status may help improve the prognosis of patients undergoing transcatheter edge-to-edge mitral valve repair.

Nonstandard Abbreviations and Acronyms

CONUT	Controlling Nutritional Status
MIVNUT	mitral valve repair and nutritional status
MR	mitral regurgitation
TEER	transcatheter edge-to-edge mitral valve repair

Transcatheter edge-to-edge mitral valve repair (TEER) has become an alternative to mitral valve surgery in patients with primary mitral regurgitation (MR) deemed at high-risk or inoperable, being the first-line strategy for those patients with secondary MR who remain symptomatic despite guideline-directed medical therapy.[1] However, results are still not homogeneous in all subgroups of patients; baseline, echocardiographic, and procedural characteristics may influence outcomes.[2–5]

Malnutrition is common in patients with heart failure (HF) leading to poor quality of life and increased mortality.[6] Likewise, it has been linked to worse clinical outcomes in patients with acute coronary syndromes,[7] and is getting increasing relevance in patients with valvular heart disease.[8–10]

Nonetheless, no information on nutritional status has been provided for patients referred for TEER. Therefore, we sought to assess the prevalence and prognostic relevance of malnutrition in a cohort of patients referred for TEER.

METHODS

The data, methods used in the analysis, and materials used to conduct the research are available to any researcher for purposes of reproducing the results or replicating the procedure, after formal request to the corresponding author.

Study Population

This study is based on a multicentric international MIVNUT (Percutaneous Mitral Valve Repair and Nutritional Status) registry, which included 1119 patients referred for TEER between 2012 and 2020 from 12 centers in Europe and Canada. Two hundred and twenty-seven patients were excluded by missing data about nutritional status. Final cohort comprised 892 patients. All patients gave informed consent and the local ethics committee approved the protocol.

Patients were classified according to nutritional status by the CONUT (Controlling Nutritional Status) score[11] which assess serum albumin, cholesterol, and total lymphocyte count. A score of 0 to 1 was considered normal; scores of 2 to 4, 5 to 8, and 9 to 12 reflected mild, moderate, and severe malnutrition, respectively. For this study, because of the low number of patients with severe degree of malnutrition (n=13), the moderate and severe categories were merged into a single category (moderate–severe malnutrition).

Body mass index (BMI) was calculated before the procedure for all patients, defined as the body mass (kilograms) divided by the square of the body height (in meters). Patients were classified according to BMI in 2 groups: normal weight (BMI <25 kg/m^2) and overweight/obesity (BMI ≥25 kg/m^2).

Procedure

An interdisciplinary heart team in each institution discussed indication of TEER. The procedure was performed according to standard practices, including fluoroscopic and transesophageal echocardiographic guidance. The number of clips implanted and the selection of the type of device were left to the operators' discretion, as well as medical treatment. Technical success was defined as the successful deployment of at least one clip in the absence of procedural mortality. Acute procedural success was defined as reduction of MR to a grade ≤2+ with a mean transmitral gradient <5 mm Hg.

End Points

Primary end point was all-cause mortality. Secondary end points were HF readmission and composite event of mortality and HF readmission. Patients were followed up since the procedure date. In the absence of outcomes, time was censored at the last medical contact in primary or secondary care.

Statistical Analysis

Patients were analyzed separately according to nutritional status. Continuous data were presented as

mean±SD and compared using unpaired *t* tests. Categorical data were presented as counts (proportions) and compared using Chi-square tests. The incidence of mortality was estimated using Kaplan–Meier curves. We used Cox proportional hazard regression models to estimate the association of nutritional status with all-cause mortality. For HF admission, death served as a competing risk. Therefore, the incidence of HF admission was estimated using weighted cumulative incidence curves. Furthermore, the association between nutritional status with the hazards and cumulative incidence of HF admission was modeled using Fine-Gray proportional subdistributions hazards model. The proportionality assumption was verified by testing for an interaction between the exposure variable and time, and no relevant violations were found. All analyses were adjusted for age, sex, and all those variables with a statistical association ($P \leq 0.10$) with outcomes in the univariate analysis (see Table S1). To perfom parsimonious multivariate models, continuous variables were dichotomized and possible nonlinear associations for the Cox proportional hazards model were tested, without significant interactions were found (Bonferroni-corrected *P* value was >0.05). Effect estimates from Cox models were reported as hazard ratios (HRs) while those from Fine-Gray models were reported as subdistribution HRs (sHRs) along with 95% CIs. Statistical analyses were conducted using *STATA* software, version 15 (Stata Corp, College Station, Texas, USA). A 2-sided $P<0.05$ was considered statistically significant.

RESULTS

Malnutrition Prevalence and Baseline Characteristics

According to nutritional status 237 patients (26.6%) had a normal nutritional status, 477 patients (53.4%) had mild malnutrition, and 178 patients (20%) were classified as moderate–severe malnutrition (Figure 1). We found malnutrition in 75.1% of normal weight patients (BMI <25 kg/m^2) compared with 72.1% throughout overweight/obese patients (BMI>25 kg/m^2) ($P=0.312$). Baseline characteristics of the study population according to nutritional status are presented in Table.

Rate of functional MR was similar among the 3 nutritional groups (134 patients with normal nutritional status (56.6%), 297 patients with mild malnutrition (62.3%) and 111 patients with moderate–severe malnutrition (62.4%), $P=0.299$). Interestingly, anemia, impaired renal function and poorer functional New York Heart Association class were significantly higher among moderate–severe malnourished patients.

Procedural Data

Procedural success was achieved in 94.2% of the patients without significant difference between groups: 94.5%, 94.7% and 92.7%, respectively, for normal, mild, and moderate–severe malnutrition ($P=0.080$) and significantly different compared with preprocedure for each nutritional status (Figure 2A). However, the percentage of grade 3–4+ MR was higher as nutritional status worsened (10.5%, 14.1% and 17.5% in patients with normal nutrition, mild malnutrition, and moderate–severe malnutrition, respectively).

Malnutrition and Outcomes

During a median follow-up of 1.6 years, interquartile range of 0.6–3.0, 267 patients (29.9%) died. Information about the variables associated with all-cause mortality in univariate analysis is shown in Table S1–S11. After adjusting for those variables, age and sex, moderate–severe malnutrition (but not mild) was independently associated with all-cause mortality during follow-up after TEER (HR, 2.07 [95% CI, 1.39–3.07]) (Figure 3A). The complete multivariate analysis is shown in Tables S2 and S3.

During the follow-up, 256 patients (28.7%) were admitted to hospital for HF. After a competing risk analysis, moderate–severe malnutrition emerged as independent predictor of HF admissions (HR, 1.61 [95% CI, 1.09–2.37]) (Figure 3B). Univariate and multivariate analysis for HF admission is shown in Tables S4 through S6.

Moreover, moderate–severe malnutrition was associated with the combined end-point of mortality and HF admission (Figure 3C; Tables S7 and S8).

Despite the differences in patient characteristics between the different hospitals (Table S9), there was no variation in the results of the multivariate analysis after including the different hospitals as a confounding variable.

The analysis of the impact of malnutrition according BMI strata is shown in Tables S10 and S11.

The event rate of the combined end point (mortality and/or HF admission) was higher as the CONUT score increased (HR, 1.07 [95% CI, 1.02–1.13]; $P=0.008$) (Figure 4).

Figure 2B shows the functional improvement at 6 months before and after the procedure for each nutritional status. Although functional class at 6 months improved in all 3 nutritional groups it is greater for patients with mild malnutrition (81.5% of patients New York Heart Association I or II) compared with 74% and 67.4% for mild and moderate–severe malnutrition ($P<0.001$).

DISCUSSION

To our knowledge, this is the first study to assess the impact of malnutrition on TEER outcomes. The main findings of our study can be summarized:

Figure 1. Population distribution according to nutritional status.
BMI indicates body mass index.

1. Most of the patients undergoing TEER have malnutrition, even in those overweight, and 1 out of 5 patients have moderate–severe malnutrition.
2. The risk of mortality and/or HF increases as the nutritional status worsens, making the CONUT score a good predictor of adverse events in this population.

Table 1. Baseline Characteristics of Percutaneous Mitral Valve Repair Population According to Nutritional Status

Variables	Malnutrition			*P* value
	No	Mild	Moderate–Severe	
Age, y	72.3±11.2	73.9±10.2	74.2±9.0	0.081
Female sex, n (%)	96 (40.5)	143 (30.0)	54 (30.3)	0.014
Body mass index, kg/m^2	26.7±4.9	26.2±4.7	25.6±4.3	0.054
Active smoking, n (%)	48 (20.3)	109 (22.9)	30 (16.9)	0.233
Arterial hypertension, n (%)	157 (66.2)	354 (74.2)	132 (74.2)	0.065
Dyslipidemia, n (%)	136 (57.4)	282 (59.1)	98 (55.1)	0.636
Diabetes, n (%)	62 (26.2)	186 (39.0)	72 (40.4)	0.001
Ischemic heart disease, n (%)	112 (47.3)	274 (57.4)	115 (65.0)	0.001
Peripheral artery disease, n (%)	22 (11.5)	81 (19.7)	37 (22.8)	0.013
Prior stroke, n (%)	22 (9.3)	52 (10.9)	20 (11.2)	0.758
COPD, n (%)	58 (24.5)	101 (21.2)	33 (18.5)	0.334
Atrial fibrillation, n (%)	135 (57.0)	286 (60.0)	107 (60.1)	0.717
Anemia, n (%)	90 (38.0)	262 (54.0)	134 (75.3)	<0.001
Creatinine >1.5 mg/dL, n (%)	55 (23.2)	190 (39.8)	69 (38.8)	<0.001
Functional MR, n (%)	134 (56.5)	297 (62.3)	111 (62.4)	0.299
LVEF ≦40%, n (%)	132 (55.7)	290 (60.8)	116 (65.2)	0.142
PAP ≧55 mm Hg, n (%)	77 (32.5)	135 (28.3)	61 (34.3)	0.258
NYHA class III-IV, n (%)	184 (77.6)	423 (89.7)	164 (92.2)	<0.001
B-blocker, n (%)	189 (79.7)	383 (80.3)	128 (71.9)	0.058
ACEI/ARB, n (%)	136 (57.4)	261 (54.7)	79 (44.4)	0.022
ARNI, n (%)	22 (9.3)	45 (9.4)	13 (7.3)	0.684
Antialdosteronic, n (%)	130 (54.9)	232 (48.6)	87 (48.9)	0.268
Diuretic, n (%)	182 (76.8)	400 (83.9)	150 (84.3)	0.047
Resynchronization therapy, n (%)	33 (13.9)	106 (22.2)	29 (16.3)	0.018
ICD, n (%)	58 (24.5)	168 (35.2)	46 (25.8)	0.004

ACEI indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor/neprilysin inhibitors; COPD, chronic obstructive pulmonary disease; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; and PAP, pulmonary artery pressure.

3. Moderate–severe malnutrition is independently associated with an increased probability of mortality and HF admission

The relevance of malnutrition is given by the fact that is a common finding in patients admitted to hospitals by any cause and it is of special relevance in those linked to the cardiovascular field.[12] In patients undergoing valvular heart surgery it has been reported to be in the range of 10% to 25%[13] and it may increase up to 40% among patients with transcatheter aortic valve replacements.[9] Likewise, in patients with HF any degree of malnutrition is described in 44%.[14] In elderly populations of hospitalized patients this percentage ranges from 30% to 50%.[15] Of interest, in our study this percentage is even higher, around 70%, reflecting probably a more complex profile of patients in which advanced HF, poorer functional class, increased age, frailty, and comorbidities are merging.

The Academy of Nutrition and Dietetics and the American Society for Parenteral and Enteral Nutrition suggest screening for malnutrition in hospitalized patients[16] since patients who are malnourished have more complications, longer length of stay, and greater mortality.[13,17,18] Different screening tools have been compared to assess nutrition risk in patients with HF.[14,19] Nevertheless, simple malnutrition scores not considering anthropometric factors were more related to outcomes than other scores including BMI, not only for patients with HF but also for patients with acute coronary syndrome.[7,14]Taking this into account we selected the CONUT score as the tool for screening malnutrition in our population and simple measures including serum albumin, cholesterol, and lymphocyte count correlated accurately with malnutrition degrees.[11]

It is well recognized that malnutrition has been linked to poor prognosis in the cardiovascular scope.[7–10,20,21] Our population represents a special subset of patients with chronic HF, with a significant proportion of functional patients with MR in advanced functional status, with frequent previous readmissions

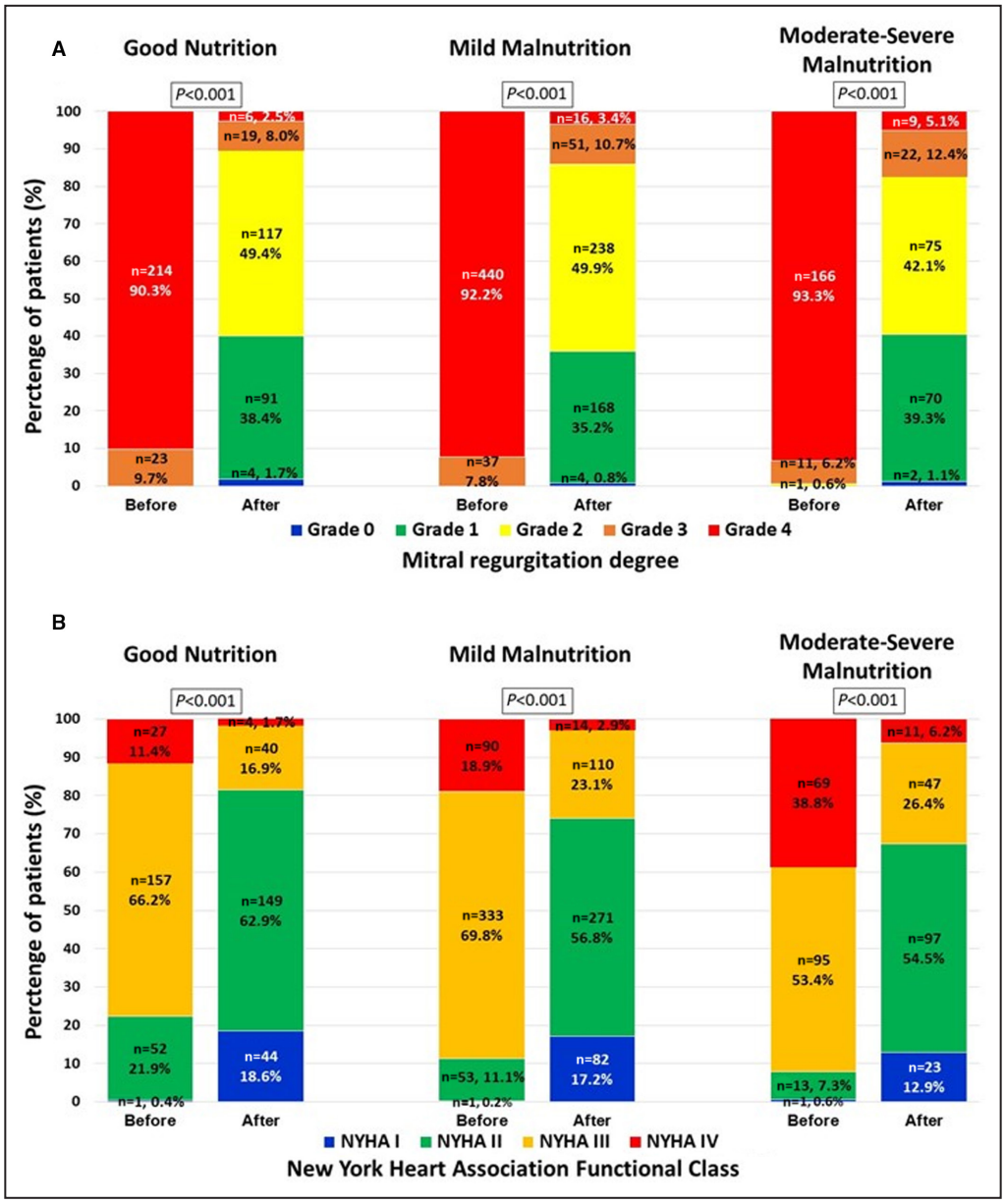

Figure 2. Improvement of the mitral regurgitation grade and functional class according to nutritional status.

A, Change in mitral regurgitation grade before and after procedure for each nutritional status; **B**, Change in 6-month New York Heart Association functional class for each nutritional group before and after the procedure. NYHA indicates New York Heart Association.

and with symptoms uncontrolled under optimal medical therapy. It is in this type of patient with MR where malnutrition is more frequently found. Advanced HF involves several mechanisms including the presence of chronic inflammation.[22] Inflammation results in acute or chronic-related malnutrition[6] and may be responsible for the wasting syndrome and hypoalbuminemia.[23] It has been also described an improper activation of oxidative processes in patients with chronic HF leading to more tissue damage and more chronic inflammation, thus creating a vicious circle that might be responsible for an impaired prognosis.[23] Another potentially relevant factor connecting nutrition and adverse prognosis is the link between nutritional status and frailty. Frailty concerns around 46% of patients undergoing TEER[24] and represents a complex syndrome involving physical performance and nutrition.[25] Frailty per se is associated with 3-times increased risk of death and twice the risk of death or HF hospitalization in patients with TEER.[24] As malnutrition is one of the criteria included in

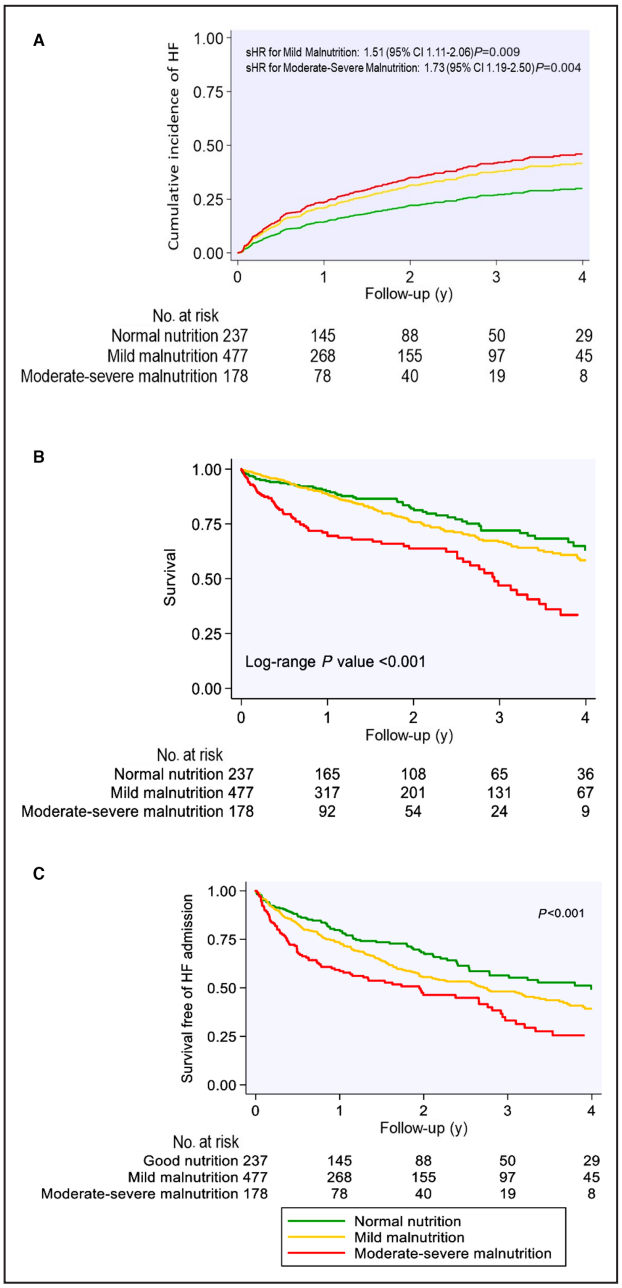

Figure 3. Primary, secondary, and combined end points according to nutritional status.
A, All-cause mortality; **B**, heart failure readmission; **C**, mortality and heart-failure readmission.

the frailty assessment, we can assume that a proportion of our patients are overlapping those syndromes therefore contributing to the increasing rates of mortality and HF readmission. Thus, we speculate that these features might be responsible for the increased adverse cardiovascular events in patients who are malnourished, irrespective of an adequate MR treatment. On the other hand, it is important to stress that, as it was pointed out by our data and data by Metze and colleagues,[24] both patients with malnourished and frailty can be successfully treated by TEER with significant reduction of MR and improvement in New York Heart Association functional class and quality of life. According to nutritional status we can identify patients with greater mortality risk and work to ameliorate it. Therefore, although relevant, malnutrition per se must not be a contraindication for referring patients for percutaneous repair.

The role of assessing malnutrition in our population is relevant because it can be a modifiable factor. It has been reported that nutritional interventions appear to benefit hospitalized patients, by reducing hospital length and readmissions.[26] In addition, there are preliminary data supporting a potential benefit from oral nutritional supplements in patients with HF, with significant reduction in the rate of mortality and hospital readmissions.[27,28] It has been recently reported that those patients who are malnourished undergoing transcatheter aortic valve replacement that improve their nutritional status after the intervention have better prognostic outcomes.[29] This fact may be seen as a signal for a potential target to improve outcomes both in aortic and mitral population, if the nutrition status can be optimized beforehand. Unfortunately, we did not assess nutritional status change after mitral repair, and this hypothesis is speculative. However, given the potential benefit of such strategy we should consider future trials based on nutritional interventions for optimizing TEER outcomes.

Study Limitations

This is a multicenter retrospective investigation with the subsequent disadvantages secondary to its nature. In addition to this, data about nutritional status were available in 892 from 1119 patients (79.7%). This fact could be a source of selection bias. The rest of data for all analyzed variables were available in all patients. Since malnutrition is a complex issue, especially in older adults, because of diversity in cause and a wide range of determinants, a more complex comprehensive nutritional assessment would be recommendable. We did not evaluate the association of malnutrition scores with inflammatory markers, nor with body composition. However, CONUT score is easy to calculate and to implement as part of routine in clinical practice and does not require specific anthropometric measurements or subjective questionnaires. In this sense, operators can be more prone to use this tool because of the aforementioned advantages. Moreover, given that the nutritional evaluation was conducted only in a single time point, we did not investigate the changes in nutritional status over time and their relationship with cardiovascular outcomes. Information about frailty status and its correlation with malnutrition would be interesting; however, unfortunately, data about frailty were not available

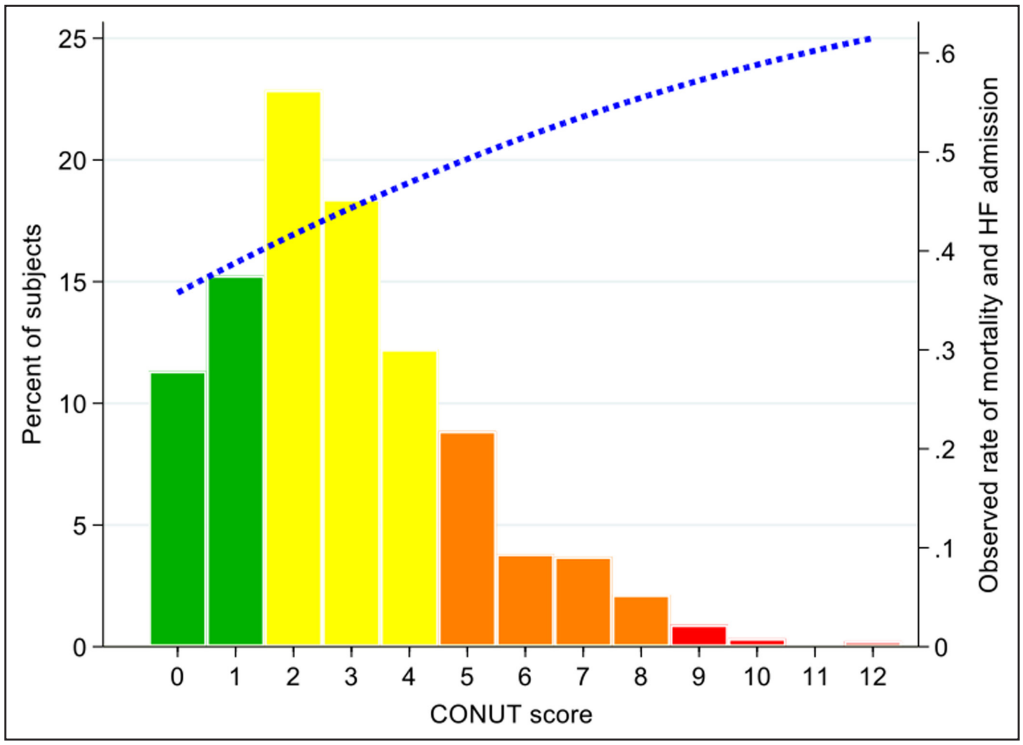

Figure 4. Rate of mortality and heart failure admission according to Controlling Nutritional Status score.
CONUT indicates Controlling Nutritional Status; and HF, heart failure.

in the MIVNUT database. Moreover, we have no data about infective endocarditis during the follow-up. And regarding medical therapy, we only had data about treatment at discharge. Confirmation of our findings by other investigators and other countries with different health care and social systems would be welcome.

ARTICLE INFORMATION

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Supplemental Material

Tables S1–S11

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SUPPLEMENTAL MATERIAL

Table S1. Univariate analysis for all-cause mortality.

Variables	HR	95% CI	P-value
Age, per 1 year	1.03	1.01 - 1.04	<0.001
Male sex	1.32	1.01 - 1.73	0.046
BMI >= 25 kg/m2	0.83	0.65 - 1.06	0.131
Active smoking	0.83	0.62 - 1.10	0.196
Arterial hypertension	1.16	0.88 – 1.53	0.297
Dyslipidemia	1.06	0.83 – 1.35	0.650
Diabetes mellitus	1.38	1.08 – 1.76	0.009
Ischemic heart disease	1.52	1.19 – 1.95	0.001
Peripheral artery disease	2.29	1.74 – 3.03	<0.001
Prior stroke	1.19	0.83 – 1.71	0.349
COPD	1.21	0.92 – 1.59	0.180
Malnutrition	**1.58**	**1.17 - 2.13**	**0.002**
Atrial fibrillation	1.06	0.81 – 1.23	0.430
Anemia	1.91	1.48 – 2.46	<0.001
Creatinine > 1.5 mg/dL	1.55	1.22 – 1.98	<0.001
Functional MR	1.03	0.80 - 1.32	0.836
LVEF <= 40%	1.39	1.07 – 1.80	0.015
Systolic PAP >= 55 mmHg	1.10	0.85 – 1.41	0.480
NYHA class III-IV	1.89	1.23 – 2.90	0.004
Successful procedure	0.59	0.31-0.76	0.002
B-blocker	0.83	0.63 – 1.10	0.194
ACEI/ARB	0.57	0.45 – 0.73	0.001
ARNI	0.71	0.38 – 1.35	0.303
Antialdosteronic	0.94	0.74 – 1.20	0.624
Diuretic	1.25	0.85 – 1.83	0.254
CRT	1.46	1.10 – 1.95	0.010
ICD	0.98	0.76 – 1.27	0.901

ARNI: Angiotensin Receptor/Neprilysin Inhibitors; ACEI: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; CRT: Cardiac Resynchronization Therapy; ICD: Implantable Cardioverter-Defibrillator; LVEF: Left Ventricular Ejection Fraction; MR: Mitral Regurgitation; NYHA: New York Heart Association; PAP: Pulmonary artery pressure.

Table S2. Multivariate analysis all-cause mortality.

Variables	HR	95% CI	P-value
Age, per 1 year	1.04	1.02 - 1.06	<0.001
Male sex	1.27	0.94 - 1.71	0.125
Diabetes mellitus	1.6	0.80 – 1.39	0.700
Ischemic heart disease	1.24	0.94 – 1.64	0.121
Peripheral artery disease	2.00	1.49 – 2.69	<0.001
Malnutrition			
Mild	**0.98**	**0.69 - 1.39**	**0.900**
Moderate-severe	**2.07**	**1.39 – 3.07**	**<0.001**
Anemia	1.22	0.92 – 1.62	0.162
Creatinine > 1.5 mg/dL	1.18	0.90 – 1.54	0.222
LVEF ≦ 40%	1.63	1.19 – 2.23	0.002
NYHA class III-IV	1.41	0.88 – 2.24	0.153
Successful procedure	0.68	0.41 - 1.12	0.128
ACEI/ARB	0.63	0.49 – 0.82	0.001
Resynchronization therapy	1.48	1.05 – 2.08	0.025

ARNI: Angiotensin Receptor/Neprilysin Inhibitors; ACEI: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; CRT: Cardiac Resynchronization Therapy; ICD: Implantable Cardioverter-Defibrillator; LVEF: Left Ventricular Ejection Fraction; MR: Mitral Regurgitation; NYHA: New York Heart Association; PAP: Pulmonary artery pressure.

Table S3. Multivariate analysis all-cause mortality with CONUT.

Variables	HR	95% CI	P-value
Procedural success	0.65	0.39 – 1.06	0.085
Age, per 1 year	1.04	1.03 - 1.06	<0.001
Male sex	1.23	0.91 - 1.66	0.181
Diabetes mellitus	1.1	0.81 – 1.40	0.643
Ischemic heart disease	1.26	0.95 – 1.66	0.103
Peripheral artery disease	1.93	1.44 – 2.59	<0.001
Anemia	1.22	0.92 – 1.62	0.161
Creatinine > 1.5 mg/dL	1.14	0.88 – 1.49	0.325
LVEF ≦40%	1.69	1.24 – 2.32	0.001
NYHA class III-IV	1.35	0.85 – 2.16	0.208
Successful procedure	0.65	0.39-1.06	0.085
ACEI/ARB	0.66	0.50 – 0.85	0.002
CRT	1.37	0.98 – 1.93	0.068
CONUT score	1.13	1.06 - 1.21	<0.001

ARNI: Angiotensin Receptor/Neprilysin Inhibitors; ACEI: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; CRT: Cardiac Resynchronization Therapy; ICD: Implantable Cardioverter-Defibrillator; LVEF: Left Ventricular Ejection Fraction; MR: Mitral Regurgitation; NYHA: New York Heart Association; PAP: Pulmonary artery pressure.

Table S4. Univariate Analysis of HF readmission.

Variables	sHR	95% CI	P-value
Age, per 1 year	1.00	0.99 - 1.01	0.877
Male sex	1.11	0.84 - 1.45	0.465
BMI >= 25 kg/m2	1.11	0.87 - 1.42	0.405
Active smoking	1.06	0.80 - 1.43	0.659
Arterial hypertension	1.26	0.94 – 1.69	0.114
Dyslipidemia	1.12	0.87 – 1.44	0.369
Diabetes mellitus	1.47	1.15 – 1.89	0.002
Ischemic heart disease	1.10	0.86 – 1.41	0.437
Peripheral artery disease	1.08	0.79 – 1.47	0.649
Prior stroke	1.14	0.78 – 1.67	0.502
COPD	1.28	0.96 – 1.70	0.087
Malnutrition	**1.57**	**1.16 - 2.11**	**0.003**
Atrial fibrillation	1.01	0.87 – 1.18	0.849
Anemia	0.95	0.75 – 1.22	0.707
Creatinine > 1.5 mg/dL	1.44	1.12 – 1.84	0.004
Functional MR	0.93	0.72 - 1.20	0.588
LVEF ≦ 40%	1.24	0.96 – 1.61	0.100
PAP >= 55 mmHg	1.12	0.87 – 1.46	0.375
NYHA class III-IV	2.01	1.30 – 3.11	0.002
Successful procedure	0.52	0.32 – 0.85	0.008
B-blocker	0.96	0.72 – 1.29	0.800
ACEI/ARB	0.79	0.62 – 1.02	0.063
ARNI	1.52	0.99 – 2.32	0.051
Antialdosteronic	1.03	0.81 – 1.32	0.809
Diuretics	1.89	1.22 – 2.93	0.004
CRT	1.50	1.12 – 2.01	0.007
ICD	1.32	1.03 – 1.70	0.027

ARNI: Angiotensin Receptor/Neprilysin Inhibitors; ACEI: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; CRT: Cardiac Resynchronization Therapy; ICD: Implantable Cardioverter-Defibrillator; LVEF: Left Ventricular Ejection Fraction; MR: Mitral Regurgitation; NYHA: New York Heart Association; PAP: Pulmonary artery pressure.

Table S5. Multivariate analysis for HF readmission.

Variables	sHR	95% CI	P-value
Age, per 1 year	1.00	0.99 - 1.01	0.573
Male sex	0.94	0.71 - 1.26	0.693
Diabetes mellitus	1.45	1.12 – 1.87	0.005
COPD	1.37	1.03 – 1.83	0.031
Malnutrition			
Mild	**1.18**	**0.86 - 1.65**	**0.304**
Moderate-severe	**1.61**	**1.09 - 2.37**	**0.015**
Creatinine > 1.5 mg/dL	1.34	1.03 – 1.73	0.027
LVEF ≦ 40%	1.03	0.75 – 1.42	0.855
NYHA class III-IV	1.80	1.14 – 2.83	0.011
Successful procedure	0.56	0.34-0.92	0.021
ACEI/ARB	0.81	0.62 – 1.06	0.126
ARNI	1.36	0.85 – 2.18	0.196
Diuretic	1.68	1.06 – 2.66	0.027
CRT	1.40	0.99 – 1.99	0.060
ICD	1.05	0.74 – 1.49	0.780

ARNI: Angiotensin Receptor/Neprilysin Inhibitors; ACEI: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; CRT: Cardiac Resynchronization Therapy; ICD: Implantable Cardioverter-Defibrillator; LVEF: Left Ventricular Ejection Fraction; MR: Mitral Regurgitation; NYHA: New York Heart Association; PAP: Pulmonary artery pressure.

Table S6. Multivariate Analysis of HF readmission with CONUT.

Variables	sHR	95% CI	P-value
Procedural success	0.55	0.33 - 0.90	0.020
Age, per 1 year	1.02	1.00 – 1.03	0.027
Male sex	1.06	0.79 - 1.41	0.716
Diabetes mellitus	1.38	1.07 – 1.79	0.015
COPD	1.19	0.89 – 1.59	0.248
Creatinine > 1.5 mg/dL	1.31	1.01– 1.70	0.042
LVEF ≦ 40%	1.12	0.81 – 1.53	0.495
NYHA class III-IV	1.64	1.04 – 2.59	0.034
Successful procedure	0.55	0.33-0.90	0.017
ACEI/ARB	0.80	0.61 – 1.05	0.112
ARNI	2.69	1.66 – 4.38	< 0.001
Diuretics	1.57	0.99 – 2.49	0.0053
CRT	1.51	1.05 – 2.16	0.025
ICD	0.84	0.60 – 1.19	0.339
CONUT score	1.10	1.03 – 1.17	0.003

ARNI: Angiotensin Receptor/Neprilysin Inhibitors; ACEI: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; CRT: Cardiac Resynchronization Therapy; ICD: Implantable Cardioverter-Defibrillator; LVEF: Left Ventricular Ejection Fraction; MR: Mitral Regurgitation; NYHA: New York Heart Association; PAP: Pulmonary artery pressure.

Table S7. Multivariate analysis for mortality and HF readmission.

Variables	HR	95% CI	P-value
Age, per 1 year	1.01	1.00 - 1.03	0.022
Male sex	1.07	0.83 - 1.37	0.614
Diabetes mellitus	1.21	0.96 – 1.53	0.100
Ischemic heart disease	1.26	0.99 – 1.58	0.054
Peripheral artery disease	1.41	1.09 - 1.81	0.009
COPD	1.33	1.04 – 1.70	0.025
Malnutrition			
Mild	**1.04**	**0.78 - 1.39**	**0.773**
Moderate-severe	**1.63**	**1.17 - 2.28**	**0.004**
Anemia	1.00	0.79 – 1.26	0.993
Creatinine > 1.5 mg/dL	1.28	1.02 – 1.60	0.031
LVEF ≦ 40%	1.27	0.97 – 1.67	0.079
NYHA class III-IV	1.54	1.05 – 2.25	0.028
Successful procedure	0.60	0.40 – 0-90	0.014
ACEI/ARB	0.67	0.54 – 0.84	<0.001
ARNI	0.91	0.58 – 1.40	0.655
Diuretic	1.48	1.02 – 2.13	0.037
CRT	1.65	1.21 – 2.26	0.002
ICD	0.91	0.67 – 1.23	0.532

ARNI: Angiotensin Receptor/Neprilysin Inhibitors; ACEI: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; CRT: Cardiac Resynchronization Therapy; ICD: Implantable Cardioverter-Defibrillator; LVEF: Left Ventricular Ejection Fraction; MR: Mitral Regurgitation; NYHA: New York Heart Association; PAP: Pulmonary artery pressure.

Table S8. Multivariate analysis for mortality and HF readmission with CONUT.

Variables	HR	95% CI	P-value
Procedural success	0.57	0.38 – 0.86	0.007
Age, per 1 year	1.02	1.01 - 1.04	< 0.001
Male sex	1.12	0.87 - 1.44	0.370
Diabetes mellitus	1.11	0.89 – 1.39	0.354
Ischemic heart disease	1.35	1.07 – 1.71	0.011
Peripheral artery disease	1.58	1.23 – 2.06	< 0.001
COPD	1.14	0.88 – 1.47	0.318
Creatinine > 1.5 mg/dL	1.17	0.93 – 1.46	0.173
LVEF ≦ 40%	1.41	1.08 – 1.85	0.012
NYHA class III-IV	1.40	0.96 – 2.06	0.082
Successful procedure	0.57	0.38 – 0.86	0.007
ACEI/ARB	0.69	0.55 – 0.86	0.001
ARNI	1.42	0.91 – 2.20	0.120
Diuretics	1.35	0.94 – 1.95	0.105
CRT	1.73	1.26 – 2.37	0.001
ICD	0.77	0.57 – 1.05	0.099
CONUT score	1.12	1.06 – 1.18	< 0.001

ARNI: Angiotensin Receptor/Neprilysin Inhibitors; ACEI: Angiotensin-Converting Enzyme Inhibitors; ARB: Angiotensin Receptor Blocker; BMI: Body Mass Index; COPD: Chronic Obstructive Pulmonary Disease; CRT: Cardiac Resynchronization Therapy; ICD: Implantable Cardioverter-Defibrillator; LVEF: Left Ventricular Ejection Fraction; MR: Mitral Regurgitation; NYHA: New York Heart Association; PAP: Pulmonary artery pressure.

Table S9. Descriptive information among centers.

Center	Age (years)	Female (%)	BMI (kg/m2)	CONUT (score)	Malnutrition (%)	Functional MR (%)	LVEF ≤ 40% (%)	Follow-up (years)	Mortality (%)
Center 1	72.9±10.8	69.2	24.4±3.8	3.5± 2.2	79.2	69.2	65.8	2.6±2.2	40.0
Center 2	74.5±10.1	69.0	26.4±4.8	2.4±1.9	64.7	79.3	63.8	2.6±1.6	31.9
Center 3	69.4±10.4	61.5	26.6±4.5	2.6±1.5	78.0	60.6	62.4	2.5±1.6	33.9
Center 4	75.9±8.5	64.2	27.2±4.4	2.9±2.1	65.4	63.0	53.1	1.7±1.2	23.5
Center 5	76.8±10.7	65.1	27.0±4.4	3.3±2.0	81.9	43.4	42.2	1.9±1.8	30.1
Center 6	70.8±14.0	83.3	23.5±3.9	3.8±0.4	100.0	100.0	66.7	3.8±1.4	16.7
Center 7	75.6±7.9	65.5	27.9±5.3	3.6±2.7	81.0	59.5	50.0	1.4±1.1	21.4
Center 8	68.2±9.8	80.6	25.2±4.0	2.8±1.6	86.1	80.6	72.2	1.1±0.7	27.8
Center 9	77.1±7.7	63.6	26.3±4.7	1.9±1.9	53.2	32.5	49.4	1.4±1.2	31.2
Center 10	77.2±8.3	66.7	26.4±4.1	2.8±1.8	80.4	49.0	58.8	0.2±0.1	0
Center 11	66.8±10.1	84.7	24.6±4.3	3,1±2.2	81.2	80.0	95.3	2.0±1.8	36.5
Center 12	75.4±11.3	43.2	27.2±5.9	2.2±2.2	52.3	25.0	40.9	2.8±2.4	38.6

Table S10. Univariate analysis for BMI categories and CONUT.

BMI (kg/m^2)	Variable	HR	95% CI	P-value
< 25	CONUT score	1.08	0.98 - 1.19	0.139
25-30	CONUT score	1.16	1.04 - 1.30	0.008
>30	CONUT score	1.23	1.03 – 1.48	0.022

Table S11. Multivariate analysis for BMI categories and Malnutrition.

BMI (kg/m^2)	Variable	HR	95% CI	P-value
	Non-malnutrition			
< 25	Mild malnutrition	1.46	0.77 – 2.73	0.243
	Moderate-severe malnutrition	0.87	0.49 – 1.54	0.627
	Non-malnutrition			
25-30	Mild malnutrition	2.62	1.34-5.15	0.005
	Moderate-severe malnutrition	0.958	0.53 – 1.72	0.886
	Non-malnutrition			
>30	Mild malnutrition	6.16	1.83- 20.61	0.003
	Moderate-severe malnutrition	1.25	0.52 – 2.99	0.621