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/m², 72.1% in those with body mass index ≥25 kg/m²). 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
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. However, results are still not homogeneous in all subgroups of patients; baseline, echocardiographic, and procedural characteristics may influence outcomes.

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

 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 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/m²) and overweight/obesity (BMI ≥25 kg/m²).

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 transmural gradient <5 mmHg.

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≤0.10) with outcomes in the univariate analysis (see Table S1). To perform 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 <25kg/m²) compared with 72.1% throughout overweight/obese patients (BMI>25kg/m²) (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.

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:
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.
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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 it 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. In patients undergoing valvular heart surgery it has been reported to be in the range of 10% to 25% and it may increase up to 40% among patients with transcatheter aortic valve replacements. Likewise, in patients with HF any degree of malnutrition is described in 44%. In elderly populations of hospitalized patients this percentage ranges from 30% to 50%. 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 since patients who are malnourished have more complications, longer length of stay, and greater mortality. Different screening tools have been compared to assess nutrition risk in patients with HF. 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. 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.

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

| Variables                  | Malnutrition | P value |
|---------------------------|--------------|---------|
| Age, y                    |              |         |
| Female sex, n (%)         |              |         |
| Body mass index, kg/m²    |              |         |
| Active smoking, n (%)     |              |         |
| Arterial hypertension, n (%) |           |         |
| Dyslipidemia, n (%)       |              |         |
| Diabetes, n (%)           |              |         |
| Ischemic heart disease, n (%) |           |         |
| Peripheral artery disease, n (%) |         |         |
| Prior stroke, n (%)       |              |         |
| COPD, n (%)               |              |         |
| Atrial fibrillation, n (%) |              |         |
| Anemia, n (%)             |              |         |
| Creatinine >1.5 mg/dL, n (%) |           |         |
| Functional MR, n (%)      |              |         |
| LVEF ≤40%, n (%)          |              |         |
| PAP ≥55 mmHg, n (%)       |              |         |
| NYHA class III-IV, n (%)  |              |         |
| B-blocker, n (%)          |              |         |
| ACEI/ARB, n (%)           |              |         |
| ARNI, n (%)               |              |         |
| Antialdosterone, n (%)    |              |         |
| Diuretic, n (%)           |              |         |
| Resynchronization therapy, n (%) |         |         |
| ICD, n (%)                |              |         |

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.
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.\textsuperscript{22} Inflammation results in acute or chronic-related malnutrition\textsuperscript{6} and may be responsible for the wasting syndrome and hypoalbuminemia.\textsuperscript{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.\textsuperscript{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\textsuperscript{24} and represents a complex syndrome involving physical performance and nutrition.\textsuperscript{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.\textsuperscript{24} As malnutrition is one of the criteria included in

\begin{figure}[h]
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\includegraphics[width=\textwidth]{figure2.png}
\caption{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.}
\end{figure}
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.
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
Received July 5, 2021; accepted August 1, 2022.

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Sources of Funding
None.

Disclosures
Dr Freixa is a consultant for Abbott Vascular. Dr Arzamendi is a consultant for Abbott Vascular and Edwards Lifesciences. Drs Nombela-Francisco and De Agustín have served as proctors for Abbott. Dr Rodés-Cabau holds the Canadian Research Chair “Fondation Famille Jacques Larivière” for the development of structural heart disease. Dr Estevez-Loureiro is consultant for Abbott Vascular, Boston Scientific, and Edwards Lifesciences. The remaining authors have no disclosures to report.

Supplemental Material
Tables S1–S11

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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/Nephrilysin 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/Nepriysin 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/Nepriysin 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 \(\leq 40\%\)              | 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 \(\leq 40\%\)              | 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/Nepriysin 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/m²) | 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/m²) | Variable                        | HR   | 95% CI     | P-value |
|-------------|---------------------------------|------|------------|---------|
| < 25        | Non-malnutrition                 |      |            |         |
|             | Mild malnutrition                | 1.46 | 0.77 – 2.73| 0.243   |
|             | Moderate-severe malnutrition     | 0.87 | 0.49 – 1.54| 0.627   |
| 25-30       | Non-malnutrition                 |      |            |         |
|             | Mild malnutrition                | 2.62 | 1.34-5.15  | 0.005   |
|             | Moderate-severe malnutrition     | 0.958| 0.53 – 1.72| 0.886   |
| >30         | Non-malnutrition                 |      |            |         |
|             | Mild malnutrition                | 6.16 | 1.83-20.61 | 0.003   |
|             | Moderate-severe malnutrition     | 1.25 | 0.52 – 2.99| 0.621   |