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Prevalence and prognostic significance of malnutrition in patients with secondary mitral regurgitation undergoing transcatheter edge-to-edge repair

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Abstract

Background: Malnutrition is associated with poor prognosis in several cardiovascular diseases; however, its role in patients with secondary mitral regurgitation (SMR) is poorly known.

Aims: To evaluate the impact of nutritional status, assessed using different scores, on clinical outcomes in patients with SMR undergoing transcatheter edge-to-edge repair (TEER) in a real-world setting.

Methods: A total of 658 patients with SMR and complete nutritional data were identified from the MIVNUT registry. Nutritional status has been assessed using controlling nutritional status index (CONUT), prognostic nutritional index (PNI), and geriatric nutritional risk index (GNRI) scores. Outcomes of interest were all-cause mortality and all-cause mortality or heart failure (HF) hospitalization.

Results: Any malnutrition grade was observed in 79.4%, 16.7%, and 47.9% of patients by using CONUT, PNI, and GNRI, respectively, while moderate to severe malnutrition was noted in 24.7%, 16.7%, and 25.6% of patients, respectively. At a median follow-up of 2.2 years, 212 patients (32.2%) died. Moderate-severe malnutrition was associated with a higher rate of all-cause mortality (HR: 2.46 [95% CI: 1.69–3.58], HR: 2.18 [95% CI: 1.46–3.26], HR: 1.97 [95% CI: 1.41–2.74] for CONUT, PNI, and GNRI scores, respectively). The combined secondary endpoint of all-cause mortality and HF

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rehospitalization occurred in 306 patients (46.5%). Patients with moderate-severe malnutrition had a higher risk of the composite endpoint (HR: 1.56 [95% CI: 1.20–2.28], HR: 1.55 [95% CI: 1.01–2.19], HR: 1.36 [95% CI: 1.02–1.80] for CONUT, PNI, and GNRI scores, respectively). After adjustment for multiple confounders, moderate-severe malnutrition remained independently associated with clinical outcomes. **Conclusions:** Moderate-severe malnutrition was common in patients with SMR undergoing TEER. It was independently associated with poor prognosis regardless of the different scores used.

KEYWORDS

malnutrition, secondary mitral regurgitation, transcatheter edge-to-edge mitral valve repair

1 | INTRODUCTION

Malnutrition is a common finding in the general population and in patients with cardiovascular disease. Its association with poor prognosis has been reported in several cardiovascular settings, including heart failure (HF),[1,2] acute coronary syndrome, and valvular heart disease.[3–7]

However, the assessment of nutritional status still represents a challenge due to the multitude of available scales. The controlling nutritional status index (CONUT), the prognostic nutritional index (PNI), and the geriatric nutritional risk index (GNRI) malnutrition scores were found to be independent predictors of worsening HF and/or mortality among patients with HF.[2,8] Patients with secondary mitral regurgitation (SMR) in the setting of HF represent a population at increased risk of events, for whom treatment options are nowadays increasing.[9,10] Transcatheter edge-to-edge repair (TEER) has a major role, but patient selection remains challenging.[11–13] The assessment of nutritional status might be particularly useful in patients with SMR to improve risk stratification. CONUT was already reported to be associated with poor outcomes in patients with mitral regurgitation (MR) undergoing TEER, but without distinguishing between MR etiology (i.e., SMR).[6] In addition, GNRI was found to predict a worse prognosis in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) population, without impact on the beneficial effect of TEER.[14] However, patients included in the COAPT study were very selected and that findings may not reflect real-world practice.

Thus, the aim of this study is to evaluate the impact of nutritional status, assessed by using different scores (e.g., CONUT, PNI, and GNRI), on clinical outcomes, in a large population with SMR undergoing TEER.

2 | METHODS

2.1 | Study population

MIVNUT is a multicentric international registry including 1119 patients referred for TEER between 2012 and 2020 from 12 centers in Europe and Canada. The study design of the MIVNUT registry was described elsewhere.[6] A multidisciplinary heart team discussed the indication to TEER at each center. The procedure was performed according to current guidelines and standard practices after informed consent acquisition.

2.2 | Definitions and outcomes

Nutritional status has been assessed using the CONUT, PNI, and GNRI scores (Supporting Information S1: Table 1). The CONUT score includes serum albumin, cholesterol, and total lymphocyte count. A score of 0–1 is considered normal; scores of 2–4, 5–8, and 9–12 reflect mild, moderate, and severe malnutrition, respectively.[2,8]

The PNI is calculated using the formula: 10 × serum albumin + 0.005 × total lymphocyte count. A score >38 is considered normal; scores of 35–38 and <35 reflect moderate and severe malnutrition, respectively.[2,8] The mild malnutrition category was not defined by PNI.

The GNRI is a simple screening tool for nutritional-related morbidity and mortality.[15–17] It is computed using the following algorithm: 14.89 × serum albumin + 41.7 × (body mass index [BMI]/22). If BMI is >22 kg/m^2, BMI/22 is reported as 1. Metabolic frailty has been previously defined as a GNRI ≤ 98 in patients with cardiovascular and noncardiovascular disease,[2] so this cut-off value has been used to identify patients with malnutrition and patients with normal nutritional status. Further stratification defines mild (92–98), moderate (82–91.9), and severe (<82) malnutrition.[2,8]

In this study, due to the low number of patients with severe malnutrition, the moderate and severe categories were merged into a single category (moderate-severe malnutrition) for each score.

Procedural success was defined as reduction to mild or moderate residual regurgitation, with a mean trans mitral gradient less than 5 mmHg.

The primary outcome was all-cause mortality. The secondary outcome was the composite of mortality and HF rehospitalization. Patients lost to follow-up were censored at the last medical contact.

2.3 | Statistical analysis

Patients were stratified according to nutritional status defined by the three different scores. Continuous variables were reported as means and standard deviations and were compared using an independent *t*-test. Categorical variables were reported as counts and percentage and were compared using the χ^2 test. Pearson's correlation coefficients were used to assess the correlations between pairs of variables.

Time-to-event data were presented graphically using Kaplan–Meier curves and log-rank tests were used to compare between groups survival free of events. Univariable and multivariable analysis with Cox proportional hazard regression were used to determine significant predictors of events. Multivariate analyses included age, sex, variables associated with outcomes at univariate analysis, and those judged as clinically relevant: diabetes, ischemic heart disease, NYHA III–IV, EuroScore2, LVFE ≤ 40%, PAPs ≥55 mmHg, creatinine ≥1.5 mg/dL, hemoglobin <12 g/dL, ACE-I/ARB/ARNI, furosemide >50 mg/die, and procedural success. All statistical tests were performed two-tailed, and a $p < 0.05$ was considered the threshold for statistical significance. Statistical analysis was performed using IBM SPSS Statistics version 25.

3 | RESULTS

3.1 | Baseline characteristics

Of the 658 patients with SMR from the MIVNUT Registry, 174 patients were excluded due to a lack of data for the assessment of nutritional status (Figure 1). The CONUT score was calculated in 408 patients, of whom 324 (79.4%) were malnourished and 101 (24.7%) had moderate-severe malnutrition. PNI was determined in 461 patients; 77 (16.7%) of them had moderate-severe malnutrition. Among 484 patients with available GNRI scores, 232 (47.9%) were malnourished, and 124 (25.6%) presented moderate-severe malnutrition (Central Illustration 1). Baseline characteristics of the study population stratified according to moderate-severe malnutrition evaluated with the CONUT, PNI, and GNRI scores are presented in Table 2. Patients with moderate-severe malnutrition had higher surgical risk scores, as assessed with EuroScore2 and STS score, worse symptoms with higher NYHA class, lower hemoglobin values, and less frequently received HF guideline-directed medical therapy, especially ACE-I/ARB/ARNI.

3.2 | Procedural data and outcomes

Overall, procedural success was achieved in 94.5% of patients without significant differences according to nutritional status. The rate of in-hospital mortality was low (1.7%), with higher rates in patients with moderate-to-severe versus no (-mild) malnutrition assessed using PNI and GNRI (Table 1).

During a median follow-up of 2.2 (IQR 0.9–3.5) years, 212 patients (32.2%) died. Figure 2 shows survival curves stratified by nutritional status as assessed with different scores. Moderate-severe malnutrition was associated with a higher rate of all-cause mortality (unadjusted HR: 2.46 [95% CI: 1.69–3.58], HR: 2.18 [95% CI: 1.46–3.26], HR: 1.97 [95% CI: 1.41–2.74], for CONUT, PNI, and GNRI scores, respectively) (Table 2). Variables associated with all-cause mortality in univariate analysis are shown in Supporting Information S1: Table 2. After adjusting for several variables moderate-severe malnutrition remained independently associated with all-cause mortality during follow-up (adjusted HR: 2.18 [95% CI:

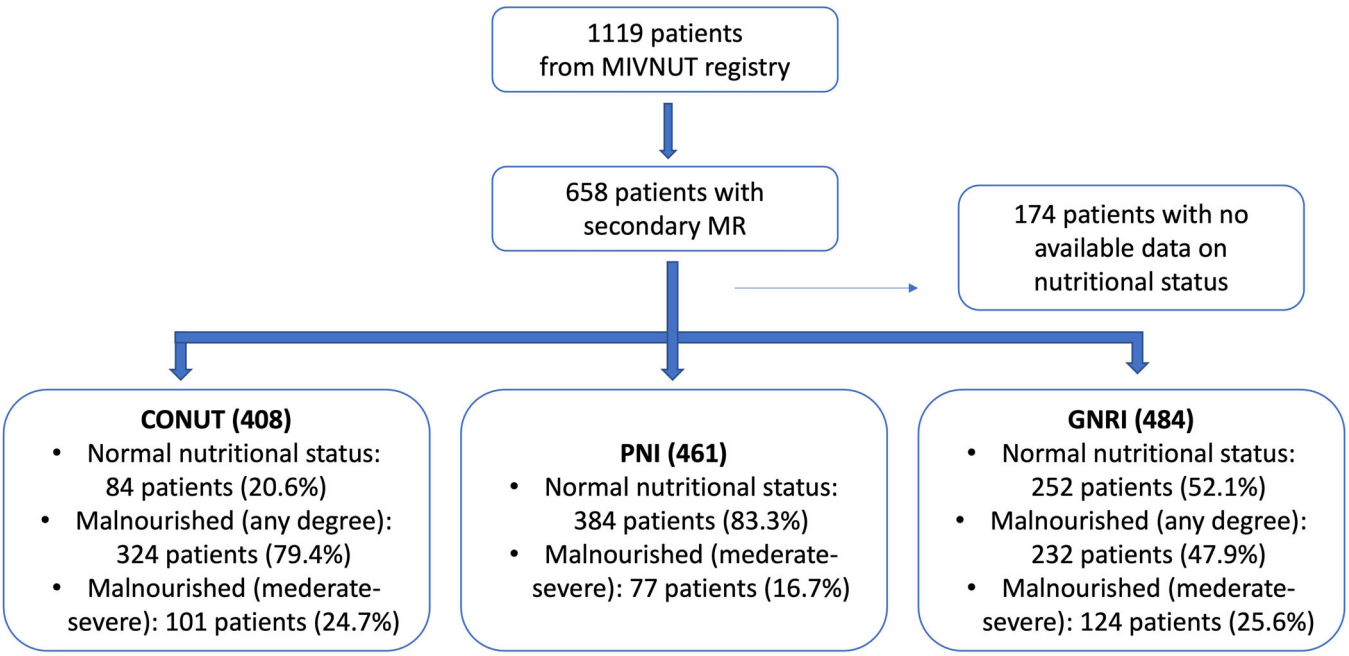


FIGURE 1 MIVNUT registry population and available data for malnutrition screening scores in patients with SMR submitted to TEER. CONUT, controlling nutritional status index; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 1 Baseline characteristics and short-term outcomes of percutaneous mitral valve repair population according to moderate-severe malnutrition evaluated with CONUT, PNI, and GNRI.

Variables	CONUT normal nutritional status-mild malnutrition	CONUT moderate-severe malnutrition	*p* Value	PNI normal nutritional status	PNI moderate-severe malnutrition	*p* Value	GNRI normal nutritional status-mild malnutrition	GNRI moderate-severe malnutrition	*p* Value
Clinical and demographic characteristics									
Age, years	71.33 ± 9.70	72.53 ± 8.65	0.269	71.73 ± 9.77	72.88 ± 8.89	0.339	71.67 ± 9.75	72.02 ± 9.75	0.729
Female sex, *n* (%)	83 (27.04%)	24 (23.76%)	0.516	102 (26.56%)	20 (25.97%)	0.915	90 (25.00%)	35 (28.22%)	0.479
BMI < 18.5 kg/m^2	7 (2.29%)	4 (3.96%)	0.369	6 (1.57%)	7 (9.09%)	<0.001	1 (0.28%)	12 (9.83%)	<0.001
Smoker, *n* (%)	236 (76.87%)	73 (72.28%)	0.350	290 (75.52%)	58 (75.32%)	0.971	271 (75.28%)	89 (71.77%)	0.475
Arterial hypertension, *n* (%)	203 (66.12%)	77 (76.23%)	0.057	258 (67.18%)	58 (75.32%)	0.160	241 (66.94%)	90 (72.58%)	0.244
Diabetes, *n* (%)	109 (35.50%)	40 (39.60%)	0.458	142 (36.98%)	28 (36.36%)	0.919	140 (38.89%)	39 (31.45%)	0.139
Dyslipidemia, *n* (%)	188 (61.24%)	55 (54.45%)	0.228	240 (62.50%)	40 (51.95%)	0.084	222 (61.67%)	64 (51.61%)	0.050
Ischemic heart disease, *n* (%)	184 (59.93%)	67 (67.00%)	0.207	237 (61.88%)	49 (63.63%)	0.772	223 (61.94%)	76 (61.78%)	0.975
Peripheral artery disease, *n* (%)	49 (17.07%)	20 (21.74%)	0.313	60 (17.69%)	15 (21.43%)	0.463	54 (16.98%)	25 (21.92%)	0.241
Previous stroke/TIA, *n* (%)	33 (10.75%)	12 (11.88%)	0.753	46 (11.98%)	6 (7.79%)	0.289	43 (11.94%)	10 (8.06%)	0.233
COPD, *n* (%)	62 (20.46%)	17 (16.83%)	0.426	76 (19.94%)	14 (18.67%)	0.799	75 (21.01%)	23 (18.85%)	0.610
Atrial fibrillation, *n* (%)	175 (57.00%)	57 (56.43%)	0.920	221 (57.55%)	43 (55.84%)	0.782	210 (58.33%)	69 (55.64%)	0.601
Dialysis, *n* (%)	5 (0.17%)	7 (7.37%)	0.006	11 (3.02%)	4 (5.55%)	0.281	7 (2.05%)	9 (7.63%)	0.004
NYHA III–IV, *n* (%)	266 (86.92%)	93 (92.08%)	0.164	330 (86.16%)	74 (96.10%)	0.015	311 (86.63%)	116 (93.53%)	0.038
EuroScore2	5.76 ± 7.15	10.09 ± 10.51	<0.001	6.44 ± 8.06	10.79 ± 10.30	<0.001	6.09 ± 6.89	10.77 ± 11.50	<0.001
STS score	3.20 ± 3.81	6.61 ± 6.98	<0.001	3.63 ± 4.25	7.18 ± 7.20	<0.001	3.51 ± 3.98	6.44 ± 6.73	<0.001
Laboratory and echocardiographic findings									
LVEF ≤ 40%, *n* (%)	255 (84.16%)	86 (85.15%)	0.812	320 (84.21%)	62 (81.58%)	0.570	303 (84.64%)	100 (82.64%)	0.604
PAPs ≥55 mmHg, *n* (%)	57 (21.19%)	27 (29.03%)	0.122	85 (24.78%)	18 (27.69%)	0.620	78 (23.93%)	32 ((30.48%)	0.181
Creatinine ≥1.5 mg/dL	109 (35.73%)	40 (40.00%)	0.443	150 (39.26%)	31 (40.79%)	0.804	139 (38.82%)	55 (44.71%)	0.251
Hemoglobin <12 g/dL, *n* (%)	106 (35.10%)	63 (63.00%)	<0.001	152 (40.10%)	48 (63.16%)	<0.001	137 (38.59%)	73 (59.35%)	<0.001
Background therapy									
B-blocker, *n* (%)	263 (86.23%)	81 (81.00%)	0.205	332 (86.91%)	57 (75.00%)	0.008	414 (87.70%)	96 (70.05%)	0.009
ACE-I/ARB/ARNI, *n* (%)	210 (68.85%)	57 (57.00%)	0.030	262 (68.58%)	40 (52.63%)	0.007	248 (69.27%)	68 (55.28%)	0.005
Furosemide >50 mg/die, *n* (%)	172 (60.71%)	62 (63.91%)	0.663	220 (62.32%)	47 (61.19%)	0.537	210 (63.25%)	75 (65.22%)	0.706
Antialdosteronic, *n* (%)	185 (60.66%)	51 (51.00%)	0.089	222 (58.12%)	37 (48.68%)	0.130	215 (60. 06%)	61 (49.59%)	0.043
ICD, *n* (%)	130 (42.90%)	32 (31.68%)	0.046	162 (43.08%)	21 (28.00%)	0.015	165 (46.74%)	39 (32.23%)	0.005
CRT, *n* (%)	76 (24.75%)	18 (17.82%)	0.151	95 (24.74%)	16 (20.78%)	0.458	98 (27.22%)	25 (20.16%)	0.119

(Continues)

TABLE 1 (Continued)

Variables	CONUT normal nutritional status-mild malnutrition	CONUT moderate-severe malnutrition	*p* Value	PNI normal nutritional status	PNI moderate-severe malnutrition	*p* Value	GNRI normal nutritional status-mild malnutrition	GNRI moderate-severe malnutrition	*p* Value
Outcome									
Procedural success	292 (95.11%)	93 (92.08)	0.251	362 (94.27%)	71 (92.21%	0.489	340 (94.44%)	114 (91.93%)	0.318
In-hospital mortality	6 (2.07%)	4 (4.21%)	0.255	6 (1.66%)	5 (6.94%)	0.009	4 (1.17%)	7 (5.98%)	0.003

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; ARNI, angiotensin receptor/neprilysin inhibitors; BMI, body mass index; CONUT, controlling nutritional status; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EuroScore2, European System for Cardiac Operative Risk Evaluation 2; GNRI, geriatric nutritional risk index; ICD, implantable cardioverter defibrillator; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAP, pulmonary artery pressure; PNI, prognostic nutritional index; STS score, Society of Thoracic Surgery Risk score; TIA, transient ischemic attack.

1.44–3.30], HR: 2.03 [95% CI: 1.30–3.17], HR: 1.92 [95% CI: 1.33–2.79] for CONUT, PNI, and GNRI scores, respectively; Table 2 and Supporting Information S1: Tables 3, 4 and 5).

The combined secondary endpoint of all-cause mortality and HF rehospitalization occurred in 306 patients (46.5%) during the follow-up. Patients with moderate-severe malnutrition had a higher risk of the composite endpoint (unadjusted HR: 1.56 [95% CI: 1.20–2.28], HR: 1.55 [95% CI: 1.01–2.19], HR: 1.36 [95% CI: 1.02–1.80] and adjusted HR: 1.65 [95% CI: 1.18–2.31], HR: 1.57 [95% CI: 1.06–2.31], HR: 1.43 [95% CI: 1.04–1.96] for CONUT, PNI, and GNRI scores, respectively; Table 2, Supporting Information S1: Tables 6, 7, 8 and 9).

The presence of at least one of these scores indicating moderate-severe malnutrition was associated with mortality and with the composite of mortality and HF rehospitalization (Figure 3); when considering patients with available data for all three scores, there were no significant differences if moderate-severe malnutrition was identified by one, two, or all scores used (Figure 4).

4 | DISCUSSION

The main findings of our study are the following:

1) Malnutrition is common in patients with SMR undergoing TEER, with moderate to severe malnutrition observed in 24.7%, 16.7%, and 25.6% of the MIVNUT population, using the CONUT, PNI, and GNRI scores, respectively.
2) Moderate-severe malnutrition was independently associated with poor prognosis regardless of different scores used, with a twofold increased risk of mortality and a 50% increased risk of the composite outcome including all-cause death and HF hospitalization.

4.1 | Prevalence of moderate-severe malnutrition

The prevalence of moderate-severe malnutrition among patients with severe secondary MR undergoing TEER from the MIVNUT registry ranged from 16.7% to 25.6% using different nutritional scores. Concordance among scores for mild degrees of malnutrition was rather poor (any degree of malnutrition was present in 79.4% of patients according to the CONUT score, 16.7% using PNI, and 47.9% with GNRI). These divergences reflect different variables used for calculating the scores. Indeed, serum albumin is the only element considered in all the scores, and low values are notably associated with malnutrition. Some confounding factors (e.g., hepatic disease and congestion, protein-losing gastrointestinal or renal disease that cause a fall in albumin levels) should be considered as well (Central illustration 1).

The CONUT score was developed by Ulibarri as a screening tool for the nutritional status among hospitalized patients.[18] It is based on variables reflecting protein and lipid metabolism as well as immune function measured from blood tests. The majority of patients in the current study had ischemic heart disease, which is one of the main underlying etiologies of HF with reduced ejection fraction and SMR. Statins are commonly prescribed in this population; thus, low plasma cholesterol could be related to the normal response to statin therapy rather than to compromised nutritional status. Thus, this could have led to an overestimation of the prevalence of malnutrition. The results of this subanalysis in patients with SMR are similar to those previously obtained by our research group across the entire population enrolled in the MIVNUT registry, encompassing both patients with primary and secondary MR.[6] Other studies assessing CONUT score in patients with HF have also found a high prevalence of moderate-severe malnutrition, up to 44%.[19]

PNI is obtained from biochemical parameters, including albumin and lymphocyte count. The inflammatory response is often over-activated in patients with advanced HF.[2,20] PNI identified fewer patients as malnourished if compared with other scores. Importantly, it does not foresee the existence of mild malnutrition, so it might underestimate the overall prevalence of malnutrition. Studies on HF have demonstrated a variable prevalence of moderate-severe malnutrition using PNI, ranging from 8% to 60%.[2,19]

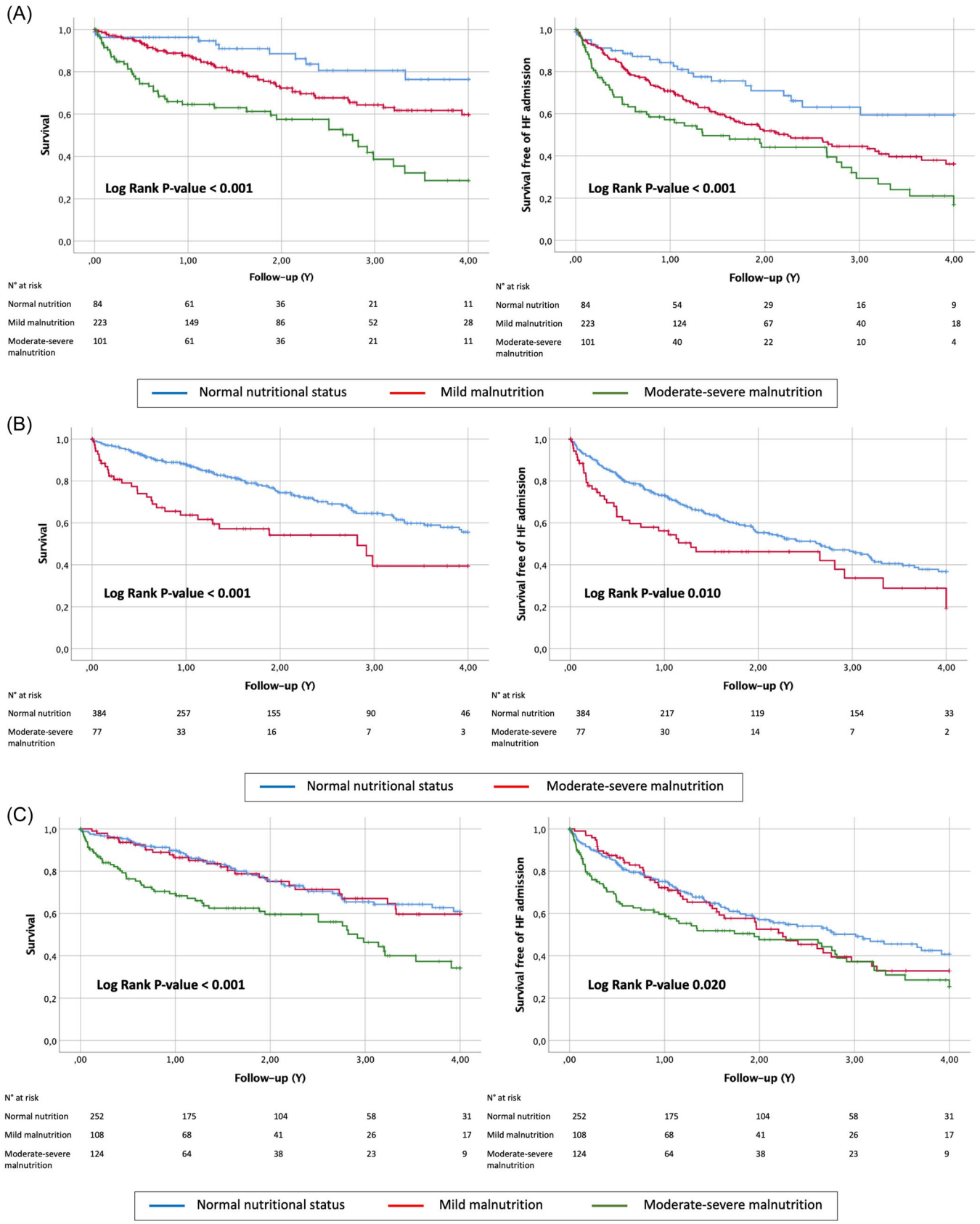


FIGURE 2 Primary and secondary outcomes according to nutritional status defined by CONUT (A), PNI (B), and GNRI (C) in patients with SMR submitted to TEER. CONUT, controlling nutritional status index; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair. [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Univariate and multivariable analysis for the primary and secondary outcomes: moderate-severe versus no(-mild) malnutrition according to CONUT, PNI, and GNRI.

	Univariate analysis		Multivariable analysis[a]	
Outcomes	**HR (95% CI)**	***p* Value**	**HR (95% CI)**	***p* Value**
CONUT moderate-severe				
- All-cause death	2.46 (1.69–3.58)	<0.001	2.18 (1.44–3.30)	<0.001
- Composite of all-cause mortality and HF rehospitalization	1.56 (1.20–2.28)	0.002	1.65 (1.18–2.31)	0.003
PNI moderate-severe				
- All-cause death	2.18 (1.46–3.26)	<0.001	2.03 (1.30–3.17)	0.002
- Composite of all-cause mortality and HF rehospitalization	1.55 (1.01–2.19)	0.014	1.57 (1.06–2.31)	0.024
GNRI moderate-severe				
- All-cause death	1.97 (1.41–2.74)	<0.001	1.92 (1.33–2.79)	0.001
- Composite of all-cause mortality and HF rehospitalization	1.36 (1.02–1.80)	0.037	1.43 (1.04–1.96)	0.027

Abbreviations: CONUT, controlling nutritional status; GNRI, geriatric nutritional risk index; HF, heart failure; PNI, prognostic nutritional index.
[a]The model includes age, sex, diabetes, ischemic heart disease, NYHA III–IV, EuroScore2, LVFE ≤ 40%, PAPs ≥55 mmHg, creatinine ≥1.5 mg/dL, hemoglobin <12 g/dL, ACE-I/ARB/ARNI, furosemide >50 mg/die, and procedural success.

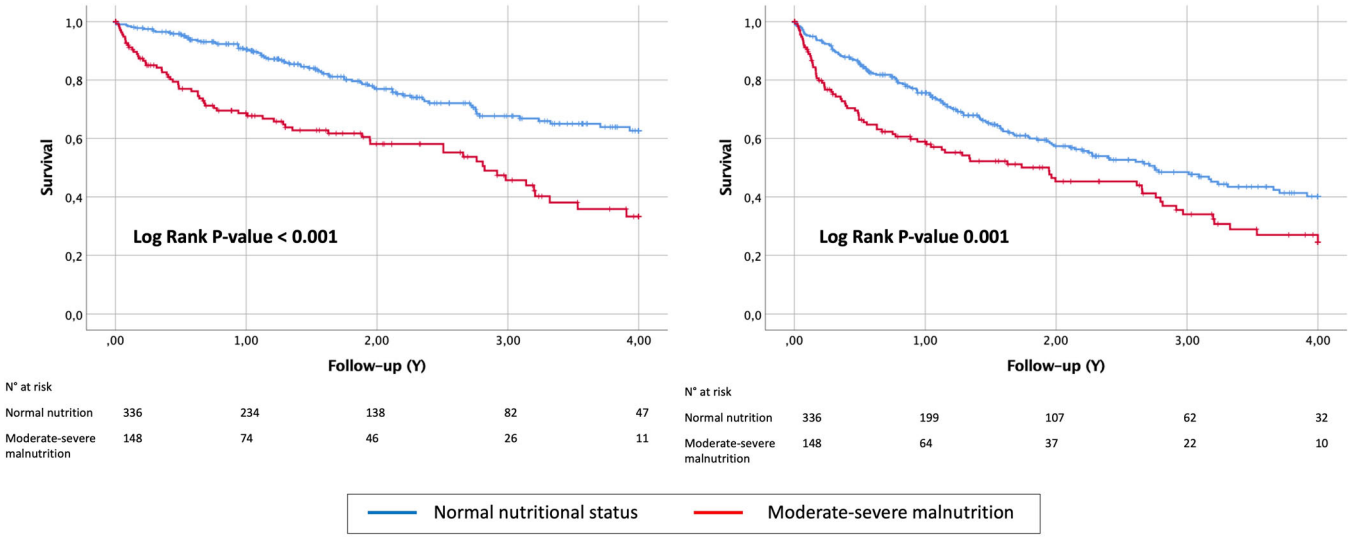


FIGURE 3 Primary and secondary outcomes in patients with SMR submitted to TEER in which at least one score among CONUT, PNI, and GNRI identified moderate-severe malnutrition or not. CONUT, controlling nutritional status index; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair. [Color figure can be viewed at wileyonlinelibrary.com]

GNRI takes into account both anthropometric factors (the ratio of body weight to ideal body weight) and serum markers (albumin level). The prevalence of malnutrition assessed using the GNRI is lower than observed in our population.[2,21] Scotti et al.[14] evaluated the prevalence of malnutrition using GNRI in patients enrolled in the COAPT trial, a selected population with HF and SMR. Only 17.0% of patients in the COAPT trial were malnourished, and only 6.0% exhibited moderate to severe malnutrition. Such divergent results compared to ours are partially explained by the fact that in Scotti's study, the formula used to compute GNRI does not approximate the body weight to an ideal body weight ratio to 1 in cases where BMI is greater than 22. In literature, conflicting data exist, and other studies published malnutrition prevalence data using GNRI without making adjustments for patients with higher BMI.[2,8] We decided, in accordance with the formula originally proposed by Bouillanne et al.[16] and Buzby et al.,[15] and with data presented by other

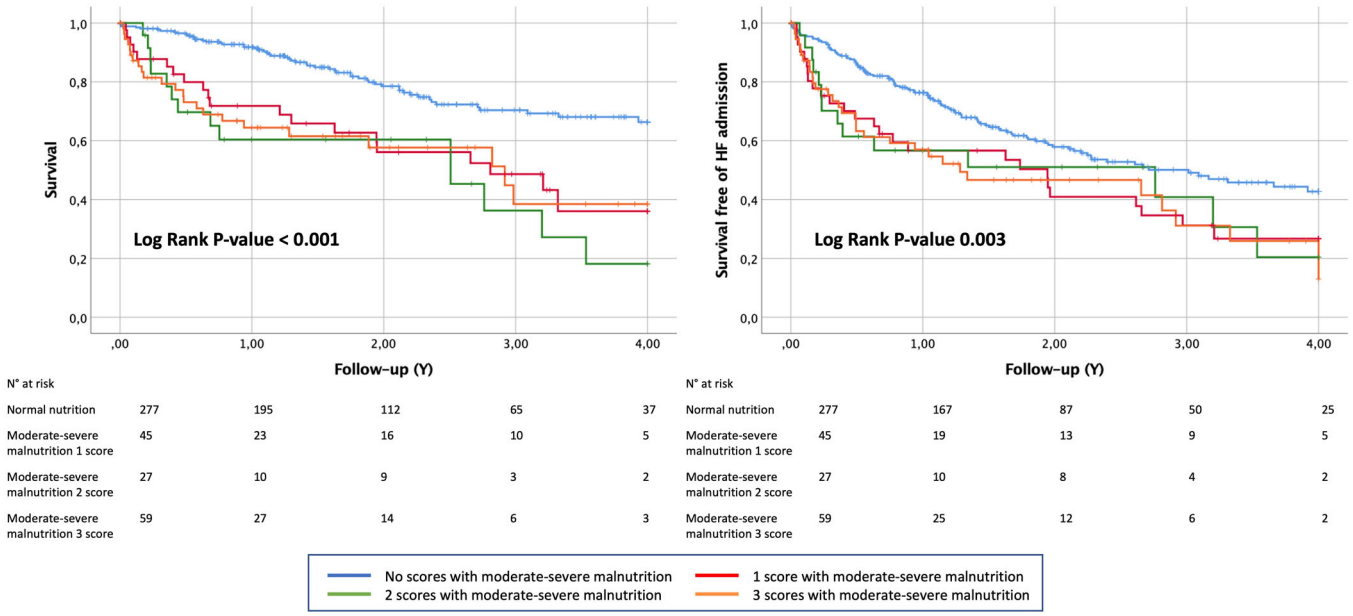


FIGURE 4 Primary and secondary outcomes in patients with SMR submitted to TEER with available data of all CONUT, PNI, and GNRI divided considering the number of scores indicating moderate-severe malnutrition. CONUT, controlling nutritional status index; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair. [Color figure can be viewed at wileyonlinelibrary.com]

authors,[4,17,21,22] to consider the correction BMI/22 = 1 if BMI was above 22 kg/m^2.[23,24] This adjustment reduces the risk of underestimating the prevalence of malnutrition among overweight or obese patients, it is known that these patients can also have malnutrition, especially among those affected by HF where fluid retention can mask weight loss or exaggerate BMI values. Also, the higher prevalence of malnutrition assessed by GNRI in our population as compared to COAPT could be due to the less selected population, including patients with advanced HF.

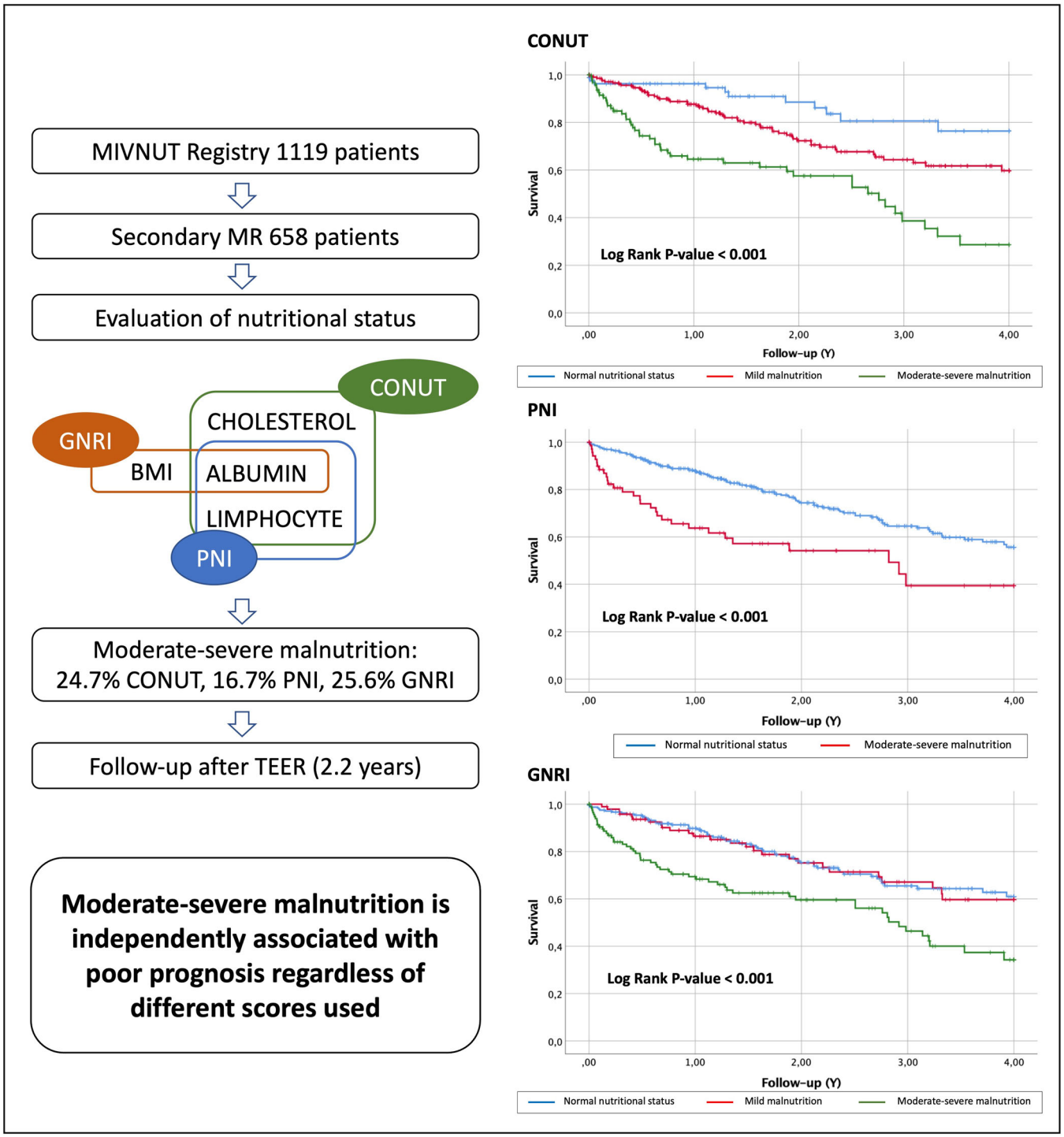
Interestingly, BMI was not differently distributed among all nutritional scores. GNRI is obviously related with BMI as it is one of the variables used in its calculation formula. PNI is calculated using serum albumin level and total lymphocyte count, with low serum albumin being the main parameter influencing the presence or not of malnutrition within this score. Low serum albumin levels are notably associated with advanced malnutrition, including sarcopenia and cachexia, hence a correlation between PNI and BMI is reasonable. Surprisingly, although incorporating serum albumin levels, the CONUT score did not exhibit a significant correlation with BMI. As mentioned before, cholesterol levels may be an important confounding factor, potentially overestimating malnutrition prevalence in patients receiving statin therapy and weakening the correlation with body weight.

4.2 | Outcome

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 during follow-up.[25] Malnutrition has been associated with an increased risk of mortality and HF rehospitalization after TEER; we[6] first showed that the CONUT score was a predictor of adverse events among patients with primary or secondary MR undergoing TEER. Similar results were obtained in the subanalysis of the COAPT trial, where all-cause mortality at 4 years was higher in patients with malnutrition compared to those without malnutrition (68.3% vs. 52.8%; $p = 0.001$).[14] In this study, we evaluated different nutritional scores in a real-world population with SMR undergoing M-TEER.

Several malnutrition screening tools can be used to assess nutritional status but without consensus regarding the best tool. In our analysis, moderate-severe malnutrition assessed with different scores (e.g., CONUT, PNI, and/or GNRI) was significantly associated with worse clinical outcomes, namely mortality and the composite of mortality and HF readmissions in patients with SMR undergoing TEER.

Importantly, we focused on patients with secondary MR. Patients with SMR are typically patients with HF and left ventricular dysfunction. Concomitant malnutrition can be observed in these patients with severe HF. Indeed, patients with advanced HF more frequently present loss of appetite, malabsorption, and catabolic state, resulting in loss of body mass and cachexia.[20] Malnutrition may also be a driver of disease progression as part of a vicious cycle associated with chronic inflammation, improper activation of oxidative processes leading to more tissue damage, wasting syndrome, hypoalbuminemia, and cachexia.[26] Our study showed that patients with moderate-severe malnutrition had worse symptoms with higher NYHA



CENTRAL ILLUSTRATION 1 Study design and survival curves according to nutritional status defined by CONUT, PNI, and GNRI in patients with SMR submitted to TEER. CONUT, controlling nutritional status index; GNRI, geriatric nutritional risk index; PNI, prognostic nutritional index; SMR, secondary mitral regurgitation; TEER, transcatheter edge-to-edge repair. [Color figure can be viewed at wileyonlinelibrary.com]

functional class. However, after adjusting for variables related to severe HF, the prognostic impact of malnutrition was confirmed.

Malnutrition per se should not be a contraindication for referring patients to TEER. The subanalysis of the COAPT trial revealed that the prognostic benefit conferred by TEER, reducing death and hospitalization for HF, remained consistent in patients with and without malnutrition.[14] In our population, procedural success was similar regardless of nutritional status. A significant reduction in MR after TEER is associated with an improvement in NYHA class and quality of life. On the other hand, identifying patients with a higher

risk of adverse outcomes due to malnutrition is relevant in order to manage it and finally ameliorate outcomes. Indeed, malnutrition is a modifiable factor; nutritional interventions have been associated with better clinical outcomes in malnourished patients with HF and with severe aortic stenosis undergoing transcatheter aortic valve replacement by reducing hospital length and readmission.[27–29] Thus, malnutrition could be a potential target to improve outcomes even in a population with SMR before or in parallel with TEER. Nutritional assessment to differentiate malnourished and non-malnourished patients should be the first step. Treatment by using multidisciplinary interventions, including education, support, nutritional counseling, dietary modification, and oral supplements, should be the second step[30] to improve patient outcomes.

According to our findings, we may speculate that both CONUT, PNI, and GNRI are useful tools to identify patients at high risk of adverse events who may benefit from tailored nutritional treatments to prevent deterioration of clinical conditions and improve the prognosis of patients with SMR and HF before or in concomitance with TEER.

5 | LIMITATIONS

This is an observational multicenter retrospective study with all the limitations associated with its nature. Selection bias might be introduced by the lack of data about nutritional status in 26.4% of patients with SMR. Also, a type 2 error could have affected the results due to the low number of events after stratifications.

Acquiring more data concerning the frailty and the residual functional capacity of elderly and comorbid patients, such as those included in this study, could provide important insights for the risk stratification assessment. Additional information regarding anthropometric factors such as sarcopenia (e.g., muscle strength, muscle mass, arm and calf circumferences, percentile of tricipital skinfold), general conditions (e.g., residential status, psychological problems, mobility), dietary habits (e.g., number of meals, food and fluid intake, autonomy in feeding), and subjective self-perception of health and nutrition would surely be useful. Unfortunately, within the framework of a multicentric international registry like MIVNUT, those data are not available for analysis.

Finally, follow-up data regarding BMI, serum albumin, cholesterol levels, and lymphocyte count were not available in the MIVNUT database to assess whether TEER may be associated with changes in nutritional status.

6 | CONCLUSIONS

Moderate-severe malnutrition is common in patients with SMR undergoing TEER, being observed in 16.7%–25.6% of the MIVNUT population, using different nutritional scores. It was independently associated with an increased risk of all-cause death and all-cause death or HF hospitalization.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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