

Impact of Malnutrition in Patients With Heart Failure and Secondary Mitral Regurgitation

The COAPT Trial



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ABSTRACT

BACKGROUND Although malnutrition is associated with poor prognosis in several diseases, its prognostic impact in patients with heart failure (HF) and secondary mitral regurgitation (SMR) is not understood.

OBJECTIVES The purpose of this study was to assess the prevalence and impact of malnutrition in HF patients with severe SMR randomized to transcatheter edge-to-edge repair (TEER) with the MitraClip plus guideline-directed medical therapy (GDMT) vs GDMT alone in the COAPT trial.

METHODS Baseline malnutrition risk was calculated using the validated geriatric nutritional risk index (GNRI) score. Patients were categorized as having "malnutrition" (GNRI ≤ 98) vs "no malnutrition" (GNRI > 98). Outcomes were assessed through 4 years. The primary endpoint of interest was all-cause mortality.

RESULTS Among 552 patients, median baseline GNRI was 109 (IQR: 101-116); 94 (17.0%) had malnutrition. All-cause mortality at 4 years was greater in patients with vs those without malnutrition (68.3% vs 52.8%; $P = 0.001$). Using multivariable analysis, both baseline malnutrition (adjusted-HR [adj-HR]: 1.37; 95% CI: 1.03-1.82; $P = 0.03$) and randomization to TEER plus GDMT compared with GDMT alone (adj-HR: 0.65; 95% CI: 0.51-0.82; $P = 0.0003$) were independent predictors of 4-year mortality. In contrast, GNRI was unrelated to the 4-year rate of heart failure hospitalization (HFH), although TEER treatment reduced HFH (adj-HR: 0.46; 95% CI: 0.36-0.56). The reductions in death (adj- $P_{\text{interaction}} = 0.46$) and HFH (adj- $P_{\text{interaction}} = 0.67$) with TEER were consistent in patients with and without malnutrition.

CONCLUSIONS Malnutrition was present in 1 of 6 patients with HF and severe SMR enrolled in COAPT and was independently associated with increased 4-year mortality (but not HFH). TEER reduced mortality and HFH in patients with and without malnutrition. (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation [The COAPT Trial] and COAPT CAS [COAPT]; [NCT01626079](https://clinicaltrials.gov/ct2/show/study/NCT01626079)) (J Am Coll Cardiol 2023;82:128-138) © 2023 by the American College of Cardiology Foundation.



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Malnutrition is common in heart failure (HF), affecting up to 62% of patients,¹ and is associated with an increased risk of mortality.² Malnutrition may also be a driver of disease progression in HF as part of a vicious cycle associated with cytokine activation, autonomic dysfunction, and cachexia.³ As a result, the presence of malnutrition is associated with worsening HF and higher mortality. Screening patients with HF for malnutrition may, therefore, identify those at higher risk of adverse outcomes who might benefit from tailored treatments to prevent HF deterioration and to improve prognosis. For that purpose, the geriatric nutritional risk index (GNRI) was developed as a simple tool that has been validated to assess the risk of malnutrition in different medical and surgical patient populations.⁴ Among the available scores, GNRI has been reported to have the strongest association with mortality risk in HF cohorts.^{5–7}

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Recently, the pivotal COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; [NCT01626079](#)) trial showed that transcatheter edge-to-edge repair (TEER) with the MitraClip system (Abbott; hereafter referred to as “percutaneous edge-to-edge mitral valve repair system”) is safe and improves prognosis, functional status, and quality of life in selected patients with HF and secondary mitral regurgitation (SMR).^{8–11} Although malnutrition identifies patients with HF at higher risk of adverse events, the impact of baseline nutritional status on TEER outcomes has not been described. Thus, the objectives of this analysis from the COAPT trial were to assess: 1) the prevalence of malnutrition in HF patients with severe SMR; and 2) its prognostic impact in patients randomized to TEER plus guideline-directed medical therapy (GDMT) and GDMT alone.

METHODS

STUDY DESIGN. Details of the study design and results of the COAPT trial have been published previously.¹² In brief, COAPT was a multicenter, randomized, open-label clinical trial of TEER with the percutaneous edge-to-edge mitral valve repair

system in HF patients with moderate-to-severe or severe (3+ or 4+) SMR who remained symptomatic despite maximally tolerated GDMT and cardiac resynchronization therapy when applicable. The severity of mitral regurgitation was graded according to American Society of Echocardiography guidelines¹³ and has been previously described in detail.¹⁴ Inclusion criteria included left ventricular ejection fraction (LVEF) between 20% and 50%, left ventricular end-systolic diameter ≤ 70 mm, and absence of severe pulmonary hypertension or symptomatic moderate or severe right ventricular dysfunction. Eligible patients were randomized in a 1:1 ratio to either TEER in addition to GDMT or GDMT alone. Institutional review board/ethics committee approval was obtained from all sites that participated in the COAPT trial, and all patients signed informed consent. Abbott sponsored the trial and provided funding to the Cardiovascular Research Foundation (New York, New York) for statistical support for the present analysis. The investigators had unrestricted access to the data and accept responsibility for the integrity of the present report.

STUDY ENDPOINTS. Baseline malnutrition was assessed for each patient using the GNRI. The GNRI was calculated using the following formula: $1.489 \times \text{serum albumin (g/L)} + 41.7 \times (\text{body weight in kilograms/ideal body weight})$.⁴ The ideal body weight was derived using the following formula: $22 \times \text{square of height in meters}$, according to previous studies.¹⁵ A score >98 was considered normal; scores of 92 to 98, 82 to 91, and <82 reflect mild, moderate, and severe malnutrition respectively. For the present study, we categorized patients as having “malnutrition” (GNRI ≤ 98) vs “no malnutrition” (GNRI >98).

The primary outcome of interest for this analysis was the 4-year rate of all-cause mortality. Secondary outcomes included cardiovascular and HF-related mortality, and heart failure-related hospitalization (HFH). Outcomes were evaluated according to baseline malnutrition status and using randomization to TEER plus GDMT vs GDMT alone. The impact of malnutrition for each endpoint was further assessed in each treatment group separately.

ABBREVIATIONS AND ACRONYMS

adj = adjusted

BMI = body mass index

GDMT = guideline directed medical therapy

GNRI = geriatric nutritional risk index

HF = heart failure

HFH = heart failure hospitalization

LVEF = left ventricular ejection fraction

SMR = secondary mitral regurgitation

TEER = transcatheter edge-to-edge repair

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

STATISTICAL ANALYSIS. All analyses were performed in the intention-to-treat population. Categorical variables are reported as counts and corresponding proportions and were compared with the chi-square test or the Fisher exact test, as appropriate. Continuous variables are reported as mean \pm SD or median (IQR) and were compared with the 2-sided parametric Student's *t*-test or the nonparametric Wilcoxon rank sum test according to their distribution. Cumulative mortality rates were estimated using the Kaplan-Meier method and compared using the log-rank test. HRs and 95% CIs were determined using Cox proportional hazards regression. Multivariable Cox proportional hazards regression was performed to explore the independent association between baseline malnutrition and 4-year all-cause mortality and HFH. The following covariates with known historical relationship with adverse outcomes in patients with HF for which there was <10% missing data and no major issues with collinearity were selected: treatment, age, sex, chronic kidney disease, and chronic obstructive pulmonary disease. Nonlinear relationship between baseline malnutrition and the risk of all-cause death were explored using penalized splines with 3 degrees of freedom (knots at 33% and 67%). A 2-sided *P* value <0.05 was considered statistically significant. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

PREVALENCE OF MALNUTRITION. Among 614 patients enrolled in the COAPT trial, 552 patients (89.9%) had sufficient data to calculate baseline GNRI. Median GNRI was 109 (IQR: 101-116); malnutrition (ie, GNRI \leq 98) was present in 94 (17.0%) patients. Mild, moderate, or severe malnutrition was present in 61, 26, and 7 patients, respectively. The distribution of GNRI was similar between the groups randomized to TEER plus GDMT (mean: 109.7 \pm 12.7) and GDMT alone (mean: 109.7 \pm 13.7; *P* = 0.99) (Figure 1, Supplemental Figure 1). A higher prevalence of malnutrition was observed in patients with LVEF <40% vs \geq 40% (20.3% vs 8.7%, respectively; *P* = 0.006) and in patients with body mass index (BMI) \leq 25 vs >25 kg/m² (36.9% vs 3.4%, respectively; *P* < 0.0001).

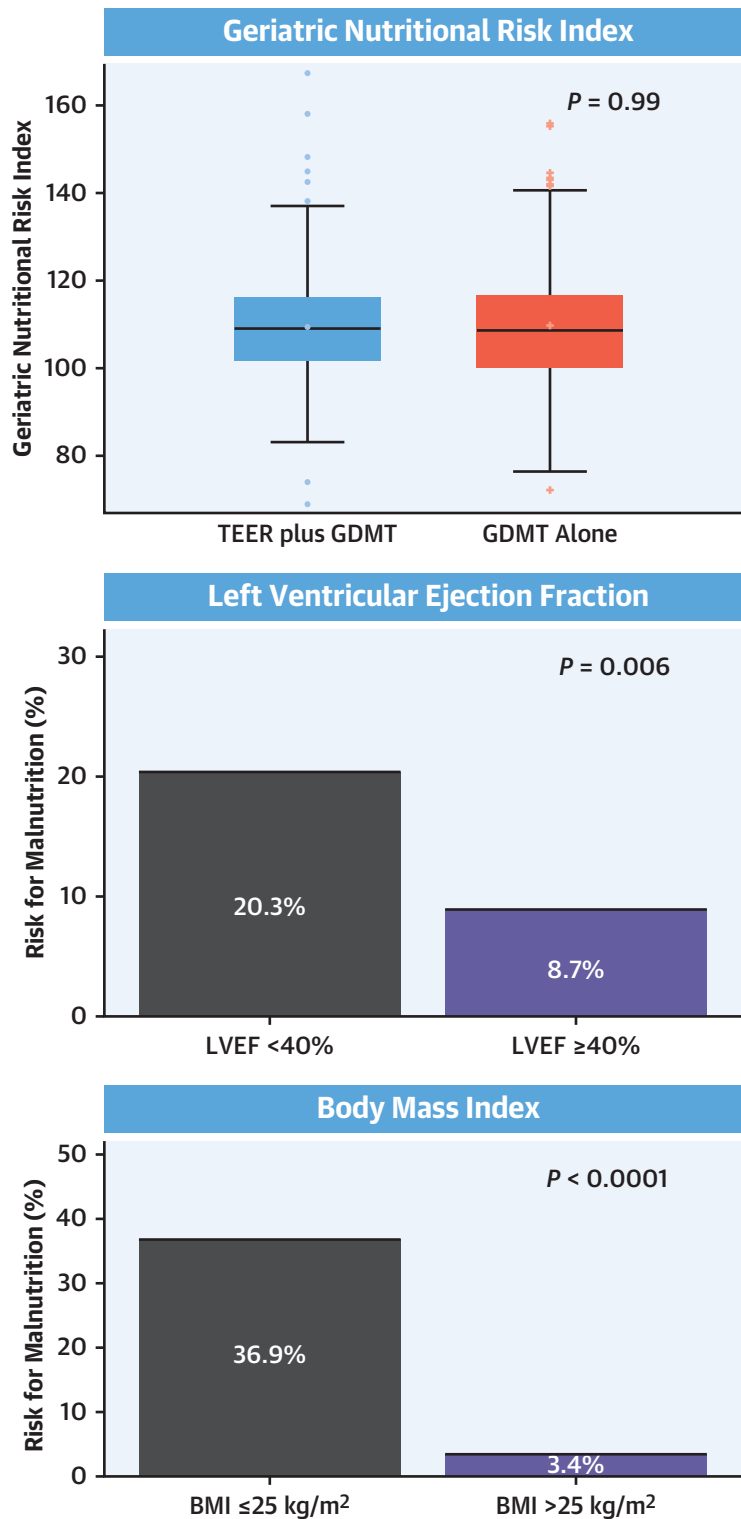
BASELINE CLINICAL AND ECHOCARDIOGRAPHIC CHARACTERISTICS. Baseline clinical characteristics according to the presence of malnutrition are listed in Table 1. Compared with patients with better nutritional status, those having malnutrition were older,

had lower BMI and hemoglobin levels, and higher levels of brain natriuretic peptide. Although comorbidities such as hypertension, diabetes mellitus, coronary artery disease, chronic kidney disease, chronic obstructive pulmonary disease, and atrial fibrillation were similar between the 2 groups, patients with malnutrition had higher mean Society of Thoracic Surgeons repair and replacement risk scores. As shown in Table 2, there were no significant differences in echocardiographic measurements between patients with and without malnutrition. Baseline characteristics according to the different grades of malnutrition (none vs mild vs moderate/severe) were consistent with the main analyses (Supplemental Tables 1 and 2).

IMPACT OF MALNUTRITION ON MORTALITY. As shown in Table 3, at 4 years all-cause mortality had occurred in 284 patients (55.5%), with a significantly higher rate in patients with malnutrition compared with those without malnutrition (68.3% vs 52.8%; *P* = 0.001). Similar findings were observed for deaths adjudicated as cardiovascular (59.9% vs 45.5%; *P* = 0.006) and deaths related to HF (48.6% vs 28.8%; *P* = 0.0001). Stratifying the population by treatment arm (TEER plus GDMT vs GDMT alone) according to nutritional status, the 4-year Kaplan-Meier estimated rates of all-cause death, cardiovascular death, and death related to HF were higher in patients with malnutrition treated with GDMT alone. In contrast, no impact of malnutrition was detected on the outcomes of patients undergoing TEER plus GDMT, although the interaction between malnutrition status, treatment, and mortality was not significant (*P*_{interaction} = 0.79) (Central Illustration). Similar findings were observed at 1-year landmark Kaplan-Meier analyses and when categorizing malnutrition status as none vs mild vs moderate/severe (Supplemental Figure 2, Supplemental Table 3).

By multivariable analysis, malnutrition was found to be an independent predictor of 4-year all-cause death in the overall population (adjusted-HR [adj-HR]: 1.37; 95% CI: 1.03-1.82; *P* = 0.03) and in patients treated with GDMT alone (adj-HR: 1.57; 95% CI: 1.08-2.28; *P* = 0.02), but not in those treated with TEER plus GDMT (adj-HR: 1.16; 95% CI: 0.73-1.84; *P* = 0.52), although again the adjusted interaction between malnutrition status, treatment, and mortality was not significant (adj-*P*_{interaction} = 0.46) (Central Illustration). The relationships between GNRI as a continuous variable and 4-year mortality in patients treated with GDMT alone and TEER plus GDMT are shown in Figure 2.

FIGURE 1 Prevalence of Malnutrition in Patients With HF and Severe SMR



(Top) Distribution of the geriatric nutritional risk index in patients randomized to TEER plus GDMT and GDMT alone. The box plots display the IQR with the median represented by the horizontal line within the box. Boundaries of the whiskers are based on the 1.5 IQR value. Individual points represent the mean value (in the box plot) or outliers (beyond the whiskers). **(Middle)** Prevalence of malnutrition according to LVEF with a cut-off of 40%. **(Bottom)** Prevalence of malnutrition according to BMI with a cut-off of 25 kg/m². BMI = body mass index; GDMT = guideline-directed medical therapy; HF = heart failure; LVEF = left ventricular ejection fraction; SMR = secondary mitral regurgitation; TEER = transcatheter edge-to-edge repair.

TABLE 1 Baseline Characteristics According to the Presence of Malnutrition

	Overall (N = 552)	No Malnutrition (n = 458)	Malnutrition (n = 94)	P Value
Age, y	72.1 ± 11.3	71.5 ± 11.7	75.1 ± 8.9	0.006
Women	201 (36.4)	165 (36.0)	36 (38.3)	0.68
BMI, kg/m ²	27.1 ± 5.9	28.2 ± 5.8	22.0 ± 2.5	<0.0001
Diabetes	207 (37.5)	179 (39.1)	28 (29.8)	0.09
Hypertension	443 (80.3)	372 (81.2)	71 (75.5)	0.21
Ischemic cardiomyopathy	333 (60.3)	271 (59.2)	62 (66.0)	0.22
Coronary artery disease	399 (72.3)	326 (71.2)	73 (77.7)	0.20
Chronic kidney disease ^a	418 (76.6)	344 (76.1)	74 (78.7)	0.59
COPD	126 (22.8)	101 (22.1)	25 (26.6)	0.34
History of AF or flutter	301 (54.5)	251 (54.8)	50 (53.2)	0.77
NYHA functional class III-IV	337 (61.2)	271 (59.3)	66 (70.2)	0.05
STS replacement score, %	8.2 ± 5.9	7.7 ± 5.5	10.5 ± 7.0	<0.0001
STS repair score, %	5.8 ± 5.6	5.3 ± 4.7	8.2 ± 8.3	<0.0001
Hemoglobin, g/dL	12.5 ± 6.9	12.5 ± 5.6	12.4 ± 11.2	0.86
Serum creatinine, mg/dL	1.8 ± 1.1	1.7 ± 1.0	1.9 ± 1.4	0.15
eGFR, mL/min/1.73 m ²	46.2 ± 21.7	46.4 ± 20.9	45.4 ± 25.6	0.70
BNP, pg/mL	646 (348-1,219)	559 (314-1,042)	1,350 (657-2,663)	<0.0001
Serum albumin, g/dL	3.9 ± 0.4	4.0 ± 0.4	3.4 ± 0.5	<0.0001

Values are mean ± SD, n (%), or median (IQR). ^aGlomerular filtration rate <60 mL/min/1.73 m².
AF = atrial fibrillation; BMI = body mass index; BNP = brain natriuretic peptide; COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; STS = Society of Thoracic Surgeons.

IMPACT OF MALNUTRITION ON HFH. As shown in **Table 3**, at 4 years HFH had occurred in 313 patients (67.0%), with similar rates in patients with malnutrition vs those without malnutrition (70.2% vs 66.4%; $P = 0.66$). Malnutrition had a similar effect on HFH in patients treated with TEER plus GDMT and GDMT alone ($P_{\text{interaction}} = 0.74$) (**Figure 3**). Similar

findings were observed at 1-year landmark Kaplan-Meier analyses and when categorizing malnutrition status as none vs mild vs moderate/severe (**Supplemental Figure 3, Supplemental Table 3**).

Using multivariable analysis, malnutrition was not an independent predictor of 4-year HFH in the overall population (adj-HR: 1.00; 95% CI: 0.74-1.35; $P = 0.98$), in patients treated with GDMT alone (adj-HR: 1.05; 95% CI: 0.72-1.53; $P = 0.81$), and in those treated with TEER plus GDMT (adj-HR: 0.87; 95% CI: 0.52-1.47; $P = 0.61$; adj- $P_{\text{interaction}} = 0.67$) (**Figure 3**).

Conversely, malnutrition was associated with an increased rate of noncardiovascular hospitalizations, with a consistent association in patients treated using TEER plus GDMT and GDMT alone ($P_{\text{interaction}} = 0.23$) (**Table 3**). Using multivariable analysis, malnutrition was an independent predictor of 4-year noncardiovascular hospitalizations in the overall population (adj-HR: 1.41; 95% CI: 1.05-1.88; $P = 0.02$), and in patients treated with TEER plus GDMT (adj-HR: 1.76; 95% CI: 1.14-2.73; $P = 0.01$), but not in those treated with GDMT alone (adj-HR: 1.24; 95% CI: 0.84-1.84; $P = 0.28$), although the interaction between malnutrition and treatment for the 4-year risk of noncardiovascular hospitalizations was negative (adj- $P_{\text{interaction}} = 0.28$).

IMPACT OF TREATMENT ON CLINICAL OUTCOMES. Randomization to TEER plus GDMT compared with GDMT alone was an independent predictor of reduced 4-year all-cause mortality (adj-HR: 0.65; 95% CI: 0.51-0.82; $P = 0.0003$). The prognostic benefit conferred using TEER with the percutaneous edge-to-edge mitral valve repair system plus GDMT in reducing mortality was consistently observed in patients with (adj-HR: 0.55; 95% CI: 0.32-0.94) and without (adj-HR: 0.67; 95% CI: 0.51-0.88) malnutrition (adj- $P_{\text{interaction}} = 0.46$) (**Central Illustration**). Randomization to TEER plus GDMT compared with GDMT alone was an independent predictor of reduced 4-year HFH (adj-HR: 0.46; 95% CI: 0.36-0.56; $P < 0.0001$), with consistent effects both in patients with (adj-HR: 0.39; 95% CI: 0.21-0.73) and without (adj-HR: 0.47; 95% CI: 0.36-0.60) malnutrition (adj- $P_{\text{interaction}} = 0.67$) (**Figure 3**).

DISCUSSION

The major findings of the present analysis from the COAPT trial are: 1) malnutrition was relatively common, being present in 17.0% of HF patients with severe SMR; 2) presence of malnutrition was independently associated with greater 4-year rates of mortality and noncardiovascular hospitalizations, but

TABLE 2 Baseline Echocardiographic Measures According to the Presence of Malnutrition

	Overall (N = 552)	No Malnutrition (n = 458)	Malnutrition (n = 94)	P Value
Mitral regurgitation				0.20
Moderate-to-severe, 3+	286 (51.8)	243 (53.1)	43 (45.7)	
Severe, 4+	266 (48.2)	215 (46.9)	51 (54.3)	
EROA by PISA, cm ²	0.41 ± 0.15	0.41 ± 0.15	0.40 ± 0.17	0.46
Regurgitant volume, mL	59.9 ± 22.3	60.2 ± 21.9	58.1 ± 24.2	0.42
LVEF, %	31.4 ± 9.5	31.7 ± 9.5	30.0 ± 9.9	0.14
LV GLS, %	-11.86 ± 3.45	-11.99 ± 3.41	-11.26 ± 3.58	0.07
LVEDVi, mL/m ²	100.8 ± 33.8	102.1 ± 34.9	95.0 ± 27.7	0.07
LA volume, mL	90.0 ± 39.4	90.0 ± 36.5	90.0 ± 51.8	0.34
RVSP, mm Hg	44.4 ± 13.8	44.1 ± 13.4	46.1 ± 15.3	0.22
Tricuspid regurgitation ≥3+	6 (1.1)	5 (1.1)	1 (1.1)	0.97
RV fractional change area, %	31.91 ± 9.05	31.87 ± 8.70	32.09 ± 10.44	0.85
RV free wall GLS, %	-17.62 ± 4.86	-17.81 ± 4.69	-16.82 ± 5.50	0.12

Values are n (%) or mean ± SD.
EROA = effective regurgitant orifice area; GLS = global longitudinal strain; LA = left atrium; LV = left ventricle; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; PISA = proximal isovelocity surface area; RV = right ventricle; RVSP = right ventricular systolic pressure.

not HFH; and 3) TEER with the percutaneous edge-to-edge mitral valve repair system reduced both mortality and HFH independently of baseline malnutrition status.

Malnutrition is common in patients with chronic HF, having been reported in 16% to 62%.¹ This wide range of prevalence might be explained by differences in severity of HF between studies and assessment of malnutrition with varying risk instruments. HF is characterized by fluid retention and chronic inflammation that affect anthropometric parameters (eg, BMI) and serum markers (eg, albumin). For this reason, the adoption of a single index alone cannot provide a comprehensive and accurate evaluation of nutritional status. The GNRI is a multidimensional tool that takes into account both anthropometric factors (the ratio of body weight to ideal body weight) and serum markers (albumin level). Using GNRI in prior studies has identified malnutrition in 14% to 19% of patients with chronic HF,¹⁶ consistent with the 17.0% rate observed in the COAPT population. As seen in COAPT, the risk of malnutrition was increased in patients with a lower LVEF (20.3% vs 8.7% in patients with LVEF <40% vs ≥40%, respectively). Similarly, lower BMI, which is a parameter of the multidimensional GNRI, was associated with a higher prevalence of malnutrition. However, BMI is not an ideal measure of body size and composition in patients with HF who, even when overweight, may still be malnourished.⁵

Malnutrition has been strongly related to increased mortality in prior HF studies.^{5,6} Several disorders of the metabolic system can cause and progress malnutrition. Chronic HF is associated with increased production of catabolic cytokines and greater muscle catabolism and appetite suppression, which collectively result in lower BMI and albumin levels. Both of these parameters are considered in the GNRI formula, and decreasing levels indicate more advanced stages of malnutrition. In the COAPT trial, patients treated with GDMT alone with baseline malnutrition had increased rates of 4-year mortality. This relationship appeared to be attenuated in patients treated with TEER plus GDMT, although the lack of interaction between treatment, malnutrition status, and mortality and similar-appearing spline curves suggest that TEER treatment does not eliminate the deleterious effects of malnutrition. No association was found between malnutrition and the 4-year risk of HFH, although malnutrition was associated with an increased risk of noncardiovascular hospitalizations. Nonetheless, TEER with the percutaneous edge-to-edge mitral valve repair system reduced the 4-year

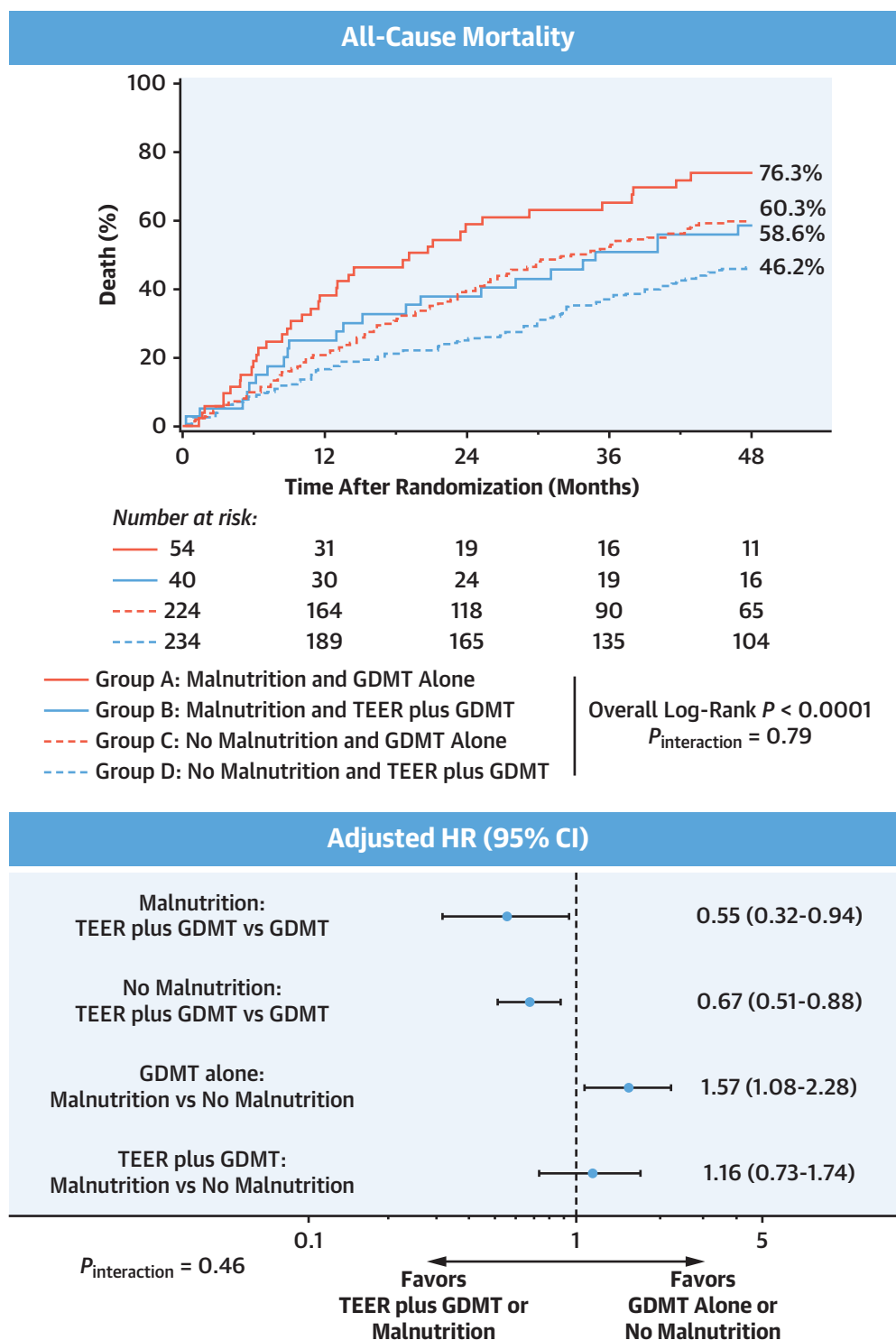
TABLE 3 Clinical Outcomes at 4 Years According to the Presence of Malnutrition

	Overall (N = 552)	No Malnutrition (n = 458)	Malnutrition (n = 94)	P Value
All patients				
All-cause mortality	284 (55.5)	223 (52.8)	61 (68.3)	0.001
Cardiovascular death	228 (47.9)	180 (45.5)	48 (59.9)	0.006
Cardiovascular death related to HF	133 (32.1)	98 (28.8)	35 (48.6)	0.0001
All-cause hospitalization	463 (90.0)	379 (88.9)	84 (95.1)	0.05
HFH	313 (67.0)	261 (66.4)	52 (70.2)	0.66
Noncardiovascular hospitalization	292 (66.2)	233 (63.4)	59 (79.8)	0.003
TEER plus GDMT				
All-cause mortality	125 (48.0)	102 (46.2)	23 (58.6)	0.09
Cardiovascular death	101 (41.3)	84 (40.1)	17 (48.2)	0.28
Cardiovascular death related to HF	53 (25.1)	43 (23.7)	10 (33.5)	0.21
All-cause hospitalization	221 (85.4)	186 (84.3)	35 (91.5)	0.03
HFH	128 (54.5)	111 (54.7)	17 (53.7)	0.79
Noncardiovascular hospitalization	143 (61.6)	117 (59.0)	26 (77.9)	0.006
GDMT alone				
All-cause mortality	159 (63.5)	121 (60.3)	38 (76.3)	0.009
Cardiovascular death	127 (55.0)	96 (51.6)	31 (69.3)	0.01
Cardiovascular death related to HF	80 (39.7)	55 (34.6)	25 (60.5)	0.0004
All-cause hospitalization	242 (94.7)	193 (93.6)	49 (97.8)	0.94
HFH	185 (80.6)	150 (79.9)	35 (84.4)	0.77
Noncardiovascular hospitalization	149 (71.8)	116 (69.0)	33 (82.3)	0.18

Values are n (%).
GDMT = guideline-directed medical therapy; HF = heart failure; HFH = heart failure hospitalization; TEER = transcatheter edge-to-edge.

rates of death and HFH consistently both in patients with and without malnutrition. Thus, malnutrition should not be considered a deterrent for percutaneous edge-to-edge mitral valve repair system treatment when evaluating HF patients with SMR.

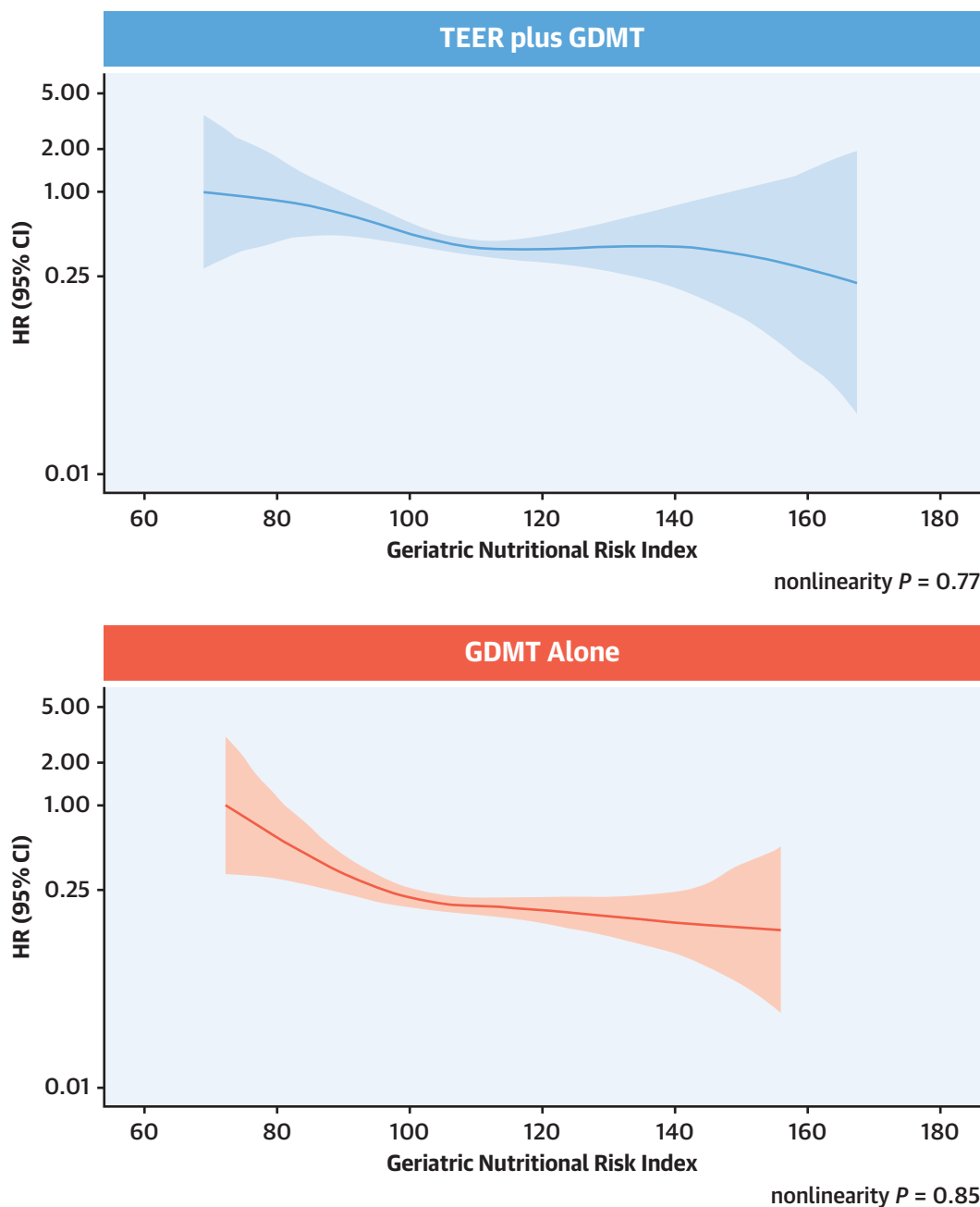
Despite the prevalence and prognostic significance of malnutrition in patients with HF, this condition is not adequately recognized and addressed by current American and European guidelines.^{17,18} Proactive screening for malnutrition in HF patients with SMR is essential. This strategy can identify an important prognostic risk factor and a potential new therapeutic target in chronic HF. Improving nutritional status may attenuate catabolism and disease progression. Multidisciplinary interventions, including education, support, nutritional counseling, dietary modification, and oral supplements have been shown to improve clinical status, body composition, quality of life, and rates of HFH.¹⁹⁻²¹ Beyond direct nutritional interventions, HF therapies may indirectly reverse malnutrition by interrupting the inflammatory and neurohormonal states that leads to cardiac cachexia. In this regard, TEER with the percutaneous edge-to-edge mitral valve repair system for SMR confers a significant prognostic benefit independent from

CENTRAL ILLUSTRATION 4-Year Mortality by Treatment Group and Baseline Malnutrition

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(Top) Cumulative incidence of all-cause death in patients with and without malnutrition who were randomized to TEER with the percutaneous edge-to-edge mitral valve repair system plus GDMT vs GDMT alone. **(Bottom)** The HRs for 4-year all-cause mortality. **Both panels** show the unadjusted (**top**) and adjusted (**bottom**) interaction testing between malnutrition and treatment. GDMT = guideline-directed medical therapy; TEER = transcatheter edge-to-edge repair.

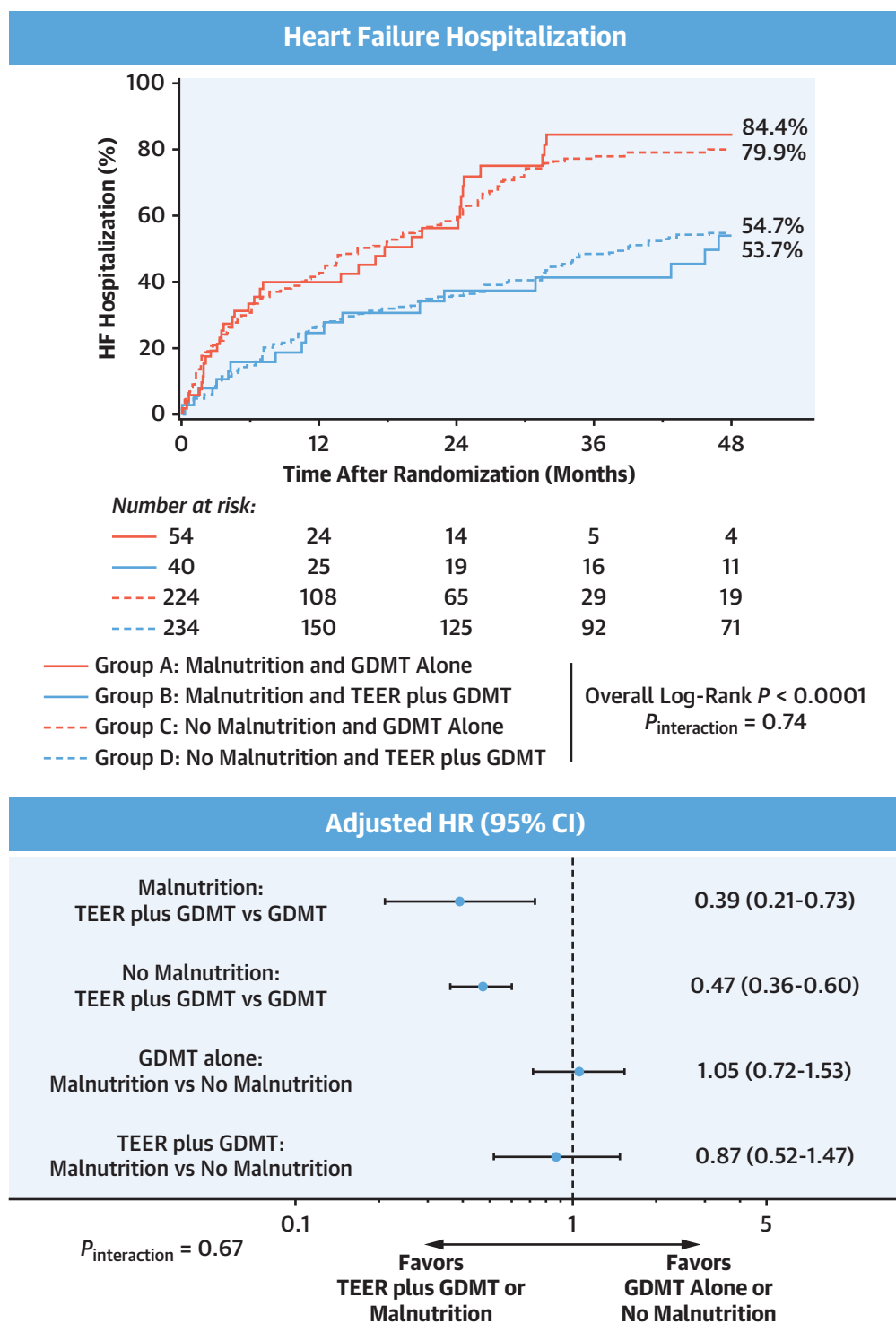
FIGURE 2 Association Between Malnutrition and 4-Year All-Cause Death



The GNRI was modeled as a continuous variable using spline curves in patients randomized to TEER plus GDMT (**Top**) and to GDMT alone (**Bottom**). Penalized splines were realized with 3 degrees of freedom (knots at 33% and 67%). GNRI = geriatric nutritional risk index; other abbreviations as in [Figure 1](#).

nutritional status, thus in part mitigating the detrimental effects of malnutrition. Given the progressive nature of malnutrition and its role in HF worsening, these data further support the expeditious performance of TEER in appropriate patients

with severe mitral regurgitation fulfilling COAPT criteria. Further studies are needed to validate these results, to explore the impact of malnutrition in COAPT-ineligible patients, and to investigate changes in GNRI after TEER.

FIGURE 3 4-Year HFH by Treatment Group and Baseline Malnutrition

(Top) Cumulative incidence of HFH in patients with and without malnutrition who were randomized to TEER with the percutaneous edge-to-edge mitral valve repair system plus GDMT vs GDMT alone. **(Bottom)** The HRs for 4-year heart failure hospitalization. **Both panels** show the unadjusted (**top**) and adjusted (**bottom**) results of interaction testing between malnutrition and treatment. HFH = heart failure hospitalization; other abbreviations as in [Figure 1](#).

STUDY LIMITATIONS. First, malnutrition was not a prespecified subgroup for analysis. Despite being well-balanced between groups and the identification of malnutrition as an independent risk factor for death and noncardiovascular hospitalization, the potential for unmeasured cofounders remains. The present study outcomes should thus be considered hypothesis generating. Second, the findings of this study apply only to patients similar to those enrolled in the COAPT trial. Whether malnutrition impacts outcomes after TEER in patients excluded from COAPT (eg, with end-stage left ventricular dysfunction or severe right-sided heart disease) or with degenerative mitral regurgitation needs further investigation. Additional studies are warranted to evaluate the impact of TEER in such patients. Third, the results demonstrating survival benefit with TEER independent of malnutrition status are specific to treatment with the percutaneous edge-to-edge mitral valve repair system. Future studies are required to establish whether emerging transcatheter mitral valve repair and replacement devices are as safe and effective in patients with malnutrition. Fourth, few patients enrolled in COAPT had GNRI-defined moderate or severe malnutrition, although the 4-year risks of most adverse events tended to be worse in such patients. Further studies are required to examine the prognosis of HF patients with SMR and severe malnutrition treated with TEER plus GDMT vs GDMT alone. Fifth, the detailed reasons for noncardiovascular hospitalizations were not categorized, precluding at this time a more in-depth understanding of the relationship between malnutrition and this event. Sixth, malnutrition is a frequent component of scores measuring the presence and severity of frailty. Whether malnutrition explains much of prognostic risk of frailty could not be assessed in COAPT because other parameters of frailty were not specifically evaluated. Finally, albumin levels were available in a limited number of patients during follow-up and thus changes in GNRI could not be assessed.

CONCLUSIONS

Malnutrition was present in 1 in 6 HF patients with severe SMR enrolled in the COAPT trial and was an independent predictor of both 4-year mortality and noncardiovascular hospitalizations (but not HFH). As such, malnutrition should be recognized as a major adverse prognostic factor in this patient population. TEER with the percutaneous edge-to-edge mitral valve repair system improved survival and freedom

from HFH independent of baseline malnutrition status. As such, malnutrition should not be considered a reason to exclude HF patients with severe SMR from the potential benefits of TEER, and TEER should be performed in appropriate patients meeting COAPT criteria as early as possible before severe malnutrition and cardiac cachexia develop.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND

PROCEDURAL SKILLS: Malnutrition is a major adverse prognostic factor in patients with severe SMR and HF but should not deter TEER with the MitraClip device, which can improve survival and reduce hospitalization for HF.

TRANSLATIONAL OUTLOOK: Further studies are needed to validate these results, to investigate the impact of malnutrition in patients ineligible for the COAPT trial, and to determine the impact of TEER on nutritional status.

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KEY WORDS COAPT Trial, geriatric nutritional risk index, malnutrition, mitral regurgitation, transcatheter edge-to-edge repair

APPENDIX For supplemental tables and figures, please see the online version of this paper.