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Malnutrition status in patients of very advanced age with nonvalvular atrial fibrillation and its impact on clinical outcomes

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KEYWORDS
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Abstract *Background and aims:* Malnutrition is associated with adverse outcomes in patients with chronic disease. We screened malnutrition among patients of very advanced age with nonvalvular atrial fibrillation (AF) by malnutrition scores and investigated the associations between malnutrition and clinical outcomes.
Methods and results: This retrospective observational study included 461 patients aged ≥80 years with nonvalvular AF. Malnutrition was screened using the Controlling Nutritional Status (CONUT), Prognostic Nutritional Index (PNI), and Geriatric Nutritional Risk Index (GNRI) scores. The primary endpoints were composite events, including thromboembolic events and all-cause death. Malnutrition was present in 62.9%, 5.0%, and 21.9% of patients according to the CONUT, PNI, and GNRI scores, respectively. During a median 27-month follow-up, 130 (28.2%) patients had composite events. Kaplan–Meier curves revealed that patients with moderate to severe malnutrition had the worst clinical outcomes (log-rank $P < 0.05$ for all scores). Multivariate Cox proportional hazards analysis showed that moderate to severe malnutrition was an independent predictor of composite events [hazard ratio (HR): 2.051, 95% confidence interval (95%CI): 1.143–3.679, $P = 0.016$ for CONUT score; HR: 3.374, 95%CI: 1.898–5.998, $P < 0.001$ for PNI score; HR: 2.254, 95%CI: 1.381–3.679, $P = 0.001$ for GNRI score]. Addition of the CONUT or GNRI score to a baseline prediction model for composite events significantly improved the net reclassification improvement and integrated discrimination improvement (all $P < 0.05$).
Conclusion: Moderate to severe malnutrition was an independent predictor of adverse outcomes among patients of very advanced age with nonvalvular AF. Screening for malnutrition might provide useful information regarding prognosis and risk stratification.

Acronyms: AF, Atrial fibrillation; CAD, Coronary artery disease; CHA_2DS_2-VASc, Congestive heart failure, hypertension, Age ≥75 years (double), diabetes, stroke (double), vascular disease, Age 65–74 years, sex (female); CI, Confidence interval; CONUT, Controlling nutritional status; eGFR, Estimated glomerular filtration rate; GNRI, Geriatric nutritional risk index; HAS-BLED, Hypertension, abnormal renal/liver function (1 point each), stroke, bleeding history or predisposition, liable INR, elderly (>65 years), drugs/alcohol concomitantly (1 point each); HR, Hazard ratio; Hs-CRP, High-sensitivity C-Reactive protein; IDI, Integrated discrimination index; NRI, Net reclassification index; NT-proBNP, N-terminal pro-B-Type natriuretic peptide; PNI, Prognostic nutritional index.

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Introduction

Atrial fibrillation (AF) is one of the most common arrhythmias among elderly patients. AF prevalence is associated with advancing age, affecting >10.0% of patients aged ≥80 years [1]. Patients with AF have a 5-fold higher risk of ischemic stroke and a nearly 2-fold higher risk of all-cause mortality than patients without AF [2,3]. Patients of advanced age with AF usually have complex comorbidities and malnutrition. However, patients of very advanced age (≥80 years), especially frail or malnourished patients, are often under-represented in large-scale randomized controlled trials. Although comprehensive geriatric assessment of advanced-age patients with AF is recommended in some guidelines [4], studies of the malnutrition status and prognosis of malnutrition for clinical outcomes in older patients with AF are scarce. Malnutrition among advanced-age patients with AF might be overlooked.

Screening advanced-age patients with AF for malnutrition may be beneficial for early detection of patients with a high risk of adverse clinical outcomes, thereby providing them with more individual treatments to improve their prognosis. Various systems and scores have been proposed for evaluation of malnutrition, including subjective assessments such as the Mini Nutritional Assessment [5] and the Subjective Global Assessment [6] as well as objective assessment tools. Among the objective malnutrition assessment tools, the Controlling Nutritional Status (CONUT) score, Prognostic Nutritional Index (PNI), and Geriatric Nutritional Risk Index (GNRI) have been widely used for screening malnutrition in clinical practice [7–9]. Recent studies have demonstrated that malnutrition identified by the CONUT, PNI, or GNRI score is an independent predictor of poor clinical outcomes in patients with heart failure (HF), myocardial infarction, and peripheral artery disease [10–13].

In the present study, we screened malnutrition by three objective malnutrition scores (CONUT, PNI, and GNRI scores) in patients of very advanced age with nonvalvular AF and investigated the impact of malnutrition on adverse clinical outcomes.

Methods

Study population

Patients with nonvalvular AF aged ≥80 years discharged from our hospital from January 2010 to December 2015 were included in this retrospective observational study. A research physician reviewed the medical records to identify eligible patients. The diagnosis of nonvalvular AF was based on current or past 12-lead electrocardiography or 24-h Holter monitoring. The exclusion criteria were rheumatic valvular disease, the presence of an artificial valvular prosthesis, acute or chronic infection, malignant tumors, severe comorbidities with a life expectancy of <1 month, and in-hospital death. Patients whose malnutrition scores (CONUT, PNI, or GNRI score) could not be calculated were also excluded. Demographics, medical history, medications prescribed at discharge, laboratory data, and echocardiographic parameters were retrospectively collected from our electronic clinical information system. The first laboratory test and echocardiographic data obtained at the time of admission were collected and analyzed. Hypertension was defined as systolic blood pressure of ≥140 mmHg, or diastolic blood pressure of ≥90 mmHg, or current use of medications prescribed for hypertension. Coronary artery disease (CAD) was defined as the presence of imaging evidence with stenosis of ≥50% of the diameter in at least one major coronary artery or documentation of myocardial infarction or cardiac revascularization. Diabetes mellitus was defined as a fasting serum glucose level of ≥7.0 mmol/L, or a random serum glucose level of ≥11.0 mmol/L or current use of hypoglycemic medications. HF was defined according to the recommendations of the European Society of Cardiology [14]: typical symptoms and signs associated with HF, an elevated concentration of N-terminal pro-B-type natriuretic peptide (NT-proBNP), and echocardiographic evidence of cardiac dysfunction and cardiac structural abnormalities. The CHA_2DS_2-VASc score and HAS-BLED score were used to evaluate the risks of stroke and bleeding. The estimated glomerular filtration rate (eGFR) was determined by the Modification of Diet in Renal Disease formula. Body mass index was calculated as weight divided by height squared (kg/m^2). The left ventricular mass was calculated according to the Devereux formula [15], and the left ventricular mass index was obtained by dividing the left ventricular mass by the body surface area.

Nutritional status assessment

All patients were screened for malnutrition using three objective malnutrition scores. The CONUT score was calculated using the serum albumin level, total cholesterol level, and lymphocyte count [7]. The patients were divided into four groups according to their CONUT score: normal nutritional status (0–1), mild malnutrition (2–4), moderate malnutrition (5–8), and severe malnutrition (9–12). As previously described [8], the PNI score was calculated using the following formula: PNI = 10 × serum albumin in g/dL + 0.005 × total lymphocyte count in mm^3. The patients were classified into three groups based on their PNI score: normal nutritional status (<35), moderate malnutrition (35–38), and severe malnutrition (>38). The GNRI score was calculated using the following equation: GNRI = 14.89 × serum albumin in g/dL+ 41.7 × (body weight/ideal body weight) [9]. The patients were stratified into four groups according to their GNRI score: normal nutritional status (GNRI>98), mild malnutrition (92–98), moderate malnutrition (82–91), and severe malnutrition (<82). We combined patients with moderate malnutrition and severe malnutrition status for analysis.

The study protocol was approved by the Ethics Committee of Fuwai Hospital and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all patients.

Follow-up and outcomes

Follow-up was conducted through clinic visits or telephone by trained doctors from October 2017 to December 2017. The primary end points were composite events, including thromboembolic events and all-cause death. Thromboembolic events included nonfatal ischemic stroke (focal neurological deficit resulting from a nontraumatic reason identified by computed tomography or magnetic resonance imaging, confirming that the infarct is correlated with clinical syndrome) and systemic embolism (acute vascular occlusion of an extremity or organ as confirmed by imaging or operative report). The follow-up time was calculated from the day of discharge to the first event date or censored at the last visit. Information regarding patients who died was collected from their relatives.

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median and interquartile range (IQR) according to their distributions and were compared with Student's t test or the Mann–Whitney U test as appropriate. Categorical variables are expressed as proportions and were compared by the chi-square test or Fisher's exact test. Considering the small number of advanced-age patients after long-term follow-up, we analyzed the results under the condition of a decreasing follow-up time to 60 months. Survival curves were plotted by Kaplan–Meier methods and compared using the log-rank test. A univariate Cox proportional hazards analysis was performed to identify independent predictors of composite events. Variables with a P value of <0.10 in the univariate analysis were included in the multivariate Cox proportional hazard analysis. Sex was added in multivariate analysis because of its association with clinical prognosis in patients with AF. Hazard ratio (HR) and 95% confidence interval (95% CI) were calculated for the incidence of composite events and all-cause death. The net reclassification index (NRI) and integrated discrimination index (IDI) were calculated to determine whether the prediction model of composite outcomes would improve after adding the CONUT, PNI, and GNRI scores to the risk factors [including age, sex, type of AF, presence of CAD and HF, serum high-sensitivity C-reactive protein (hs-CRP) and NT-proBNP levels, eGFR, and anticoagulation therapy]. Statistical analyses were performed by SPSS version 21.0 (IBM Corp., Armonk, NY, USA), R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria), and GraphPad Prism version 6.0 (GraphPad Software, San Diego, CA, USA). Differences with a two-tailed P value of <0.05 were considered statistically significant.

Results

Characteristics of advanced-age patients with nonvalvular AF

The baseline characteristics of all advanced-age patients with nonvalvular AF are shown in Table 1. In total, 461 patients were included in our study, with a mean age of 82 years (IQR: 80–84 years), and of them, 198 (43.0%) were women. Persistent AF was present in 382 (82.9%) patients. Hypertension was the most common comorbidity (75.7%), followed by CAD (56.4%) and HF (43.8%). The median CHA_2DS_2-VASc score and HAS-BLED score were 4 (IQR: 3–5) and 1 (IQR: 1–2), respectively. Anticoagulation therapy was received by 92 (20.0%) patients at discharge.

Malnutrition status by the CONUT, PNI, and GNRI scores

The median CONUT score was 2 (IQR: 1–3), the median PNI score was 47.25 (IQR: 44.15–50.88), and the median GNRI score was 105.32 (IQR: 98.69–111.09) (Fig. 1). Based on the CONUT and GNRI scores, 245 (53.1%) and 51 (11.1%) patients had mild malnutrition, respectively. Based on the CONUT, PNI, and GNRI scores, 45 (9.8%), 23 (5.0%), and 50 (10.8%) patients had moderate to severe malnutrition, respectively (Table 1). The malnutrition scores were significantly correlated with one another (CONUT vs. PNI: $r = -0.635$, $P < 0.001$; CONUT vs. GNRI: $r = -0.343$, $P < 0.001$; PNI vs. GNRI: $r = 0.591$, $P < 0.001$). However, only 22 (4.7%) patients were identified as having malnutrition by all 3 malnutrition scores, and 158 (34.3%) patients were not identified as having malnutrition by any of these scores (Fig. 2a). Sixteen (3.5%) patients were identified as having moderate to severe malnutrition according to the three scores (Fig. 2b).

Follow-up data and clinical features of patients experiencing composite events

During a median follow-up of 27 months (IQR: 15–42 months), 130 (28.2%) patients developed composite events and 88 (19.1%) patients died. Thirty-eight (8.2%) patients were lost to follow-up. The patients with composite events had higher rates of malnutrition as identified by the CONUT, PNI, and GNRI scores than those without malnutrition. Furthermore, the patients with composite events had a higher prevalence of persistent AF, a higher prevalence of CAD and HF, and higher CHA_2DS_2-VASc and HAS-BLED scores than those without composite events. The serum concentrations of hs-CRP, creatinine, and NT-proBNP were higher and the eGFR was lower in patients with composite events than in those without these events. Anticoagulation therapy was received less frequently among patients with the events than among those without these events, while no difference was observed in the prescription of antiplatelet agents, statins, β-blockers, and digitalis between patients with composite events and those without these events (Table 1).

Predictors of composite events

The univariate Cox proportional regression analysis demonstrated that older age, type of AF, presence of CAD and HF, higher serum levels of hs-CRP and NT-proBNP, reduced eGFR, no use of anticoagulation therapy, and presence of moderate to severe malnutrition (evaluated by the CONUT, PNI, and GNRI scores) were significantly

Table 1 Baseline characteristics of all patients.

	Overall (n = 461)	No Composite events (n = 331)	Composite events (n = 130)	P
Age, years	82 (80–84)	82 (80–84)	82 (81–84)	0.098
Females, n (%)	198 (43.0)	139 (42.0)	59 (45.4)	0.531
Body mass index, kg/m^2	24.51 (22.49–27.01)	24.65 (22.67–27.21)	24.19 (21.88–26.71)	0.122
SBP, mmHg	130 (120–145)	130 (120–143)	130 (119–150)	0.909
DBP, mmHg	72 (70–80)	75 (70–80)	70 (64–82)	0.319
Heart rate, beats/min	70 (60–83)	70 (60–83)	73 (60–83)	0.843
Persistent AF, n (%)	382 (82.9)	262 (79.2)	120 (92.3)	0.001
CAD, n (%)	260 (56.4)	170 (51.4)	93 (69.2)	0.001
Heart failure, n (%)	202 (43.8)	127 (38.4)	75 (57.7)	<0.001
Hypertension, n (%)	349 (75.7)	252 (76.1)	97 (74.6)	0.719
Diabetes mellitus, n (%)	134 (29.1)	92 (27.8)	42 (32.3)	0.362
Stroke or TIA, n (%)	75 (16.3)	49 (14.8)	26 (20.0)	0.206
CHA_2DS_2-VASc	4 (3–5)	4 (3–5)	5 (4–6)	0.002
HAS-BLED	1 (1–2)	1 (1–2)	2 (1–2)	0.004
Hs-CRP, mg/L	2.66 (1.38–8.76)	2.49 (1.23–6.80)	3.67 (2.21–10.61)	<0.001
Creatinine, μmol/L	89.31 (76.68–111.07)	88.46 (76.48–105.00)	94.43 (77.25–124.84)	0.009
eGFR, ml/(min·1.73 m^2)	62.33 (50.12–74.01)	63.83 (52.80–75.43)	54.57 (42.90–71.91)	<0.001
<60 ml/(min·1.73 m^2), n (%)	202 (43.8)	129 (39.0)	73 (56.2)	0.001
NT-proBNP, fmol/ml	1349.55(868.75–1887.40)	1349.55 (807.50–1655.50)	1428.45 (10433.83–2442.80)	<0.001
CONUT				
Normal, n (%)	171 (37.1)	131 (39.6)	40 (30.8)	0.003
Mild, n (%)	245 (53.1)	177 (53.5)	68 (52.3)	
Moderate to severe, n (%)	45 (9.8)	23 (6.9)	22 (16.9)	
PNI				
Normal, n (%)	438 (95.0)	325 (98.2)	113 (86.9)	<0.001
Moderate to severe, n (%)	23 (5.0)	6 (1.8)	17 (13.1)	
GNRI				
Normal, n (%)	360 (78.1)	276 (83.4)	84 (64.6)	<0.001
Mild, n (%)	51 (11.1)	30 (9.1)	21 (16.2)	
Moderate to severe, n (%)	50 (10.8)	25 (7.6)	25 (19.2)	
Medications at discharge, n (%)				
Anticoagulants	92 (20.0)	84 (25.4)	8 (6.2)	<0.001
Antiplatelet agents	253 (54.9)	175 (52.9)	78 (60.0)	0.177
Statins	252 (60.9)	171 (59.8)	81 (63.3)	0.515
ACEI	69 (16.7)	44 (15.4)	25 (19.5)	0.319
ARB	118 (28.5)	82 (28.7)	36 (28.1)	0.909
CCB	180 (43.5)	130 (45.5)	50 (39.1)	0.239
β-Blockers	288 (62.5)	213 (64.4)	75 (57.7)	0.200
Digitalis	55 (11.9)	35 (10.6)	20 (15.4)	0.154
Echocardiographic data				
Left atrial size, mm	42 (39–47)	42 (38–47)	43 (40–47)	0.236
LVEDD, mm	47 (44–51)	47 (44–51)	49 (44–52)	0.041
LVEF, %	61 (56–65)	61 (57–66)	60 (55–65)	0.022
LVMI, g/m^2	88.45 (74.94–103.62)	86.66 (73.94–99.93)	90.75 (77.96–112.60)	0.004

ACEI, angiotensin-converting enzyme inhibitors; AF, atrial fibrillation; ARB, angiotensin receptor blocker; CAD, coronary artery disease; CCB, calcium channel blocker; CONUT, Controlling Nutritional Status; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; GNRI, Geriatric Nutritional Risk Index; Hs-CRP, high-sensitivity C-reactive protein; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVMI, left ventricular mass index; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PNI, Prognostic Nutritional Index; SBP, systolic blood pressure; TIA, transient ischemic attack.

associated with a higher incidence of composite events. After adjusting for age, sex, type of AF, presence of CAD and HF, serum hs-CRP and NT-proBNP levels, eGFR, and use of anticoagulation therapy in the multivariate Cox proportional hazard regression analysis, moderate to severe malnutrition as identified by the CONUT score remained an independent predictor of composite events and all-cause death (HR: 2.051, 95%CI: 1.143–3.679, P = 0.016 for composite events; HR: 3.688, 95%CI: 1.856–7.326, P <0.001 for all-cause death). This was also true for moderate to severe malnutrition as evaluated by the PNI or GNRI score after adjusting for the same factors (Table 2). The Kaplan–Meier curves showed that patients with moderate to severe malnutrition as assessed by the three objective malnutrition scores had the worst clinical outcomes, including a higher incidence of composite events and all-cause death (log-rank test, P < 0.05 for all) (Fig. 3).

Improvement of prediction model for composite events by addition of CONUT, PNI, and GNRI scores

Addition of the CONUT or GNRI score to the baseline model (including age, sex, type of AF, presence of CAD and HF, serum hs-CRP and NT-proBNP levels, eGFR, and use of anticoagulation therapy) significantly improved the model

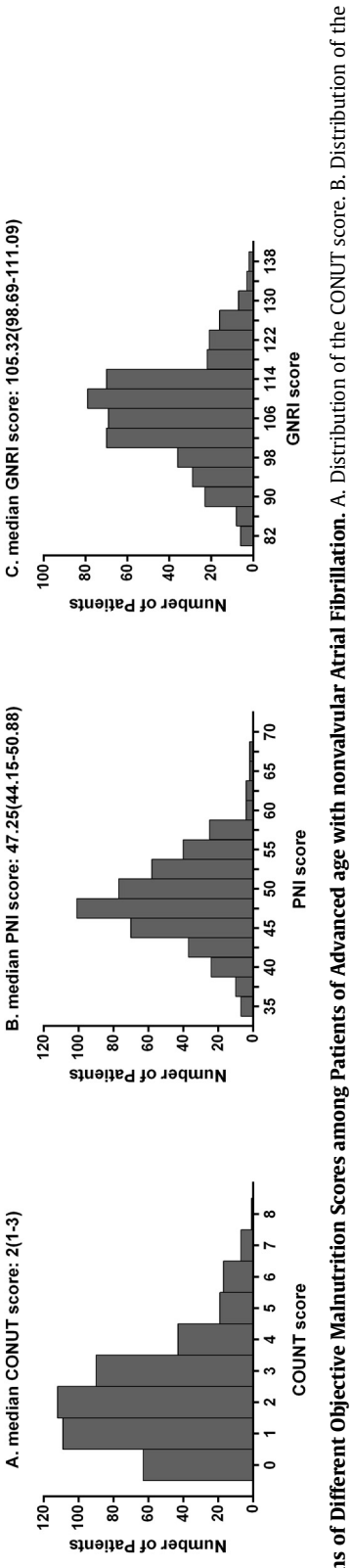

Figure 1 Distributions of Different Objective Malnutrition Scores among Patients of Advanced age with nonvalvular Atrial Fibrillation. A. Distribution of the CONUT score. B. Distribution of the PNI score. C. Distribution of the GNRI score.

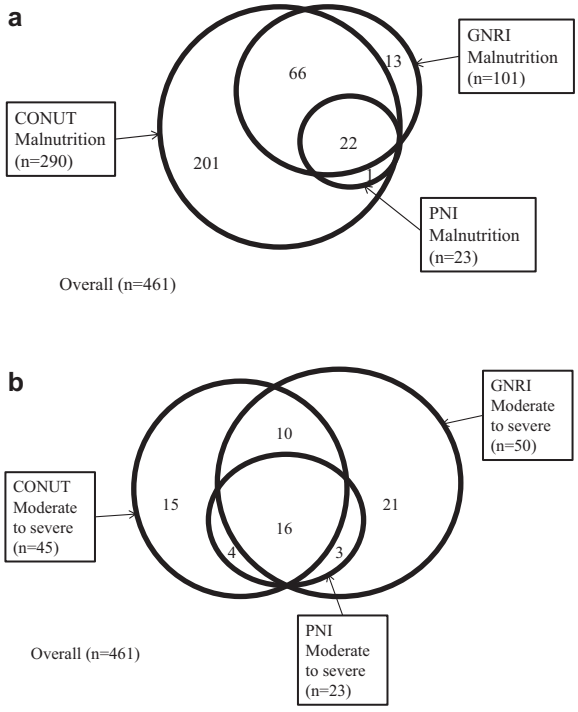

Figure 2 a. Malnourished Patients as Identified by the CONUT, PNI, and GNRI Scores. b. Moderate to Severe Malnutrition as Identified by the CONUT, PNI, and GNRI Scores.

performance for prediction of composite events [NRI of CONUT score: 0.582 (0.218−0.638), P = 0.013; NRI of GNRI score: 0.779 (0.412−0.817), P < 0.001; IDI of CONUT score: 0.012 (0.001−0.042), P = 0.020; IDI of GNRI score: 0.041 (0.013−0.138), P < 0.001]. No significant improvement was observed after adding the PNI score to the same baseline model for prediction of composite events [NRI: 0.289 (−0.355−0.853), P = 0.432; IDI: 0.052 (−0.001−0.219), P = 0.066] (Table 3).

Discussion

In the present study, we screened the malnutrition status of patients of very advanced age having nonvalvular AF by using three malnutrition scores and demonstrated the prognostic impact of the malnutrition status on clinical outcomes. Advanced-age patients with nonvalvular AF who had moderate to severe malnutrition as determined by the CONUT, PNI, and GNRI scores had the worst clinical outcomes. Moderate to severe malnutrition was significantly associated with composite events and all-cause death independent of traditional risk factors such as age, sex, medications, and comorbidities. Adding the CONUT or GNRI score to the basic prediction model significantly improved the model performance for composite events. The present study indicates that malnutrition evaluation should be taken into consideration for patients of very advanced age with nonvalvular AF.

Malnutrition is a common status in older patients with chronic disease. The prevalence of malnutrition varies among different study populations. In a large cohort of

Table 2 Univariate and multivariate Cox proportional hazard analysis of predicting composite events and all-cause death.

	HR	95% CI	P
Univariate analysis			
Age (years)	1.069	(1.013–1.129)	0.016
Females	1.151	(0.815–1.626)	0.426
Body mass index	0.970	(0.925–1.017)	0.206
AF type	0.532	(0.278–1.018)	0.057
CAD	1.835	(1.264–2.664)	0.001
Heart failure	1.743	(1.230–2.470)	0.002
Hypertension	0.877	(0.591–1.303)	0.516
Diabetes mellitus	1.202	(0.832–1.736)	0.327
Stroke or TIA	1.298	(0.844–1.995)	0.234
Hs-CRP (mg/L)	1.058	(1.022–1.095)	0.001
eGFR [ml/(min·1.73 m^2)]	0.983	(0.973–0.992)	<0.001
NT-proBNP (per 100 fmol/ml)	1.023	(1.012–1.033)	<0.001
Anticoagulant therapy	0.270	(0.132–0.553)	<0.001
Nutritional status			
CONUT			
Mild vs. normal	1.298	(0.878–1.918)	0.191
Moderate to severe vs. normal	3.180	(1.885–5.362)	<0.001
PNI			
Moderate to severe vs. normal	4.541	(2.719–7.584)	<0.001
GNRI			
Mild vs. normal	1.918	(1.189–3.095)	0.008
Moderate to severe vs. normal	2.893	(1.850–4.525)	<0.001
Multivariate analysis for composite events[a]			
CONUT			
Mild vs. normal	1.161	(0.778–1.731)	0.465
Moderate to severe vs. normal	2.051	(1.143–3.679)	0.016
PNI			
Moderate to severe vs. normal	3.374	(1.898–5.998)	<0.001
GNRI			
Mild vs. normal	1.542	(0.934–2.543)	0.090
Moderate to severe vs. normal	2.254	(1.381–3.679)	0.001
Multivariate analysis for all-cause death[a]			
CONUT			
Mild vs. normal	1.374	(0.824–2.290)	0.223
Moderate to severe vs. normal	3.688	(1.856–7.326)	<0.001
PNI			
Moderate to severe vs. normal	5.509	(2.887–10.514)	<0.001
GNRI			
Mild to normal	1.565	(0.834–2.935)	0.163
Moderate to severe vs. normal	3.604	(2.094–6.204)	<0.001

AF, atrial fibrillation; CAD, coronary artery disease; CI: confidence interval; CONUT, Controlling Nutritional Status; eGFR, estimated glomerular filtration rate; GNRI, Geriatric Nutritional Risk Index; HR: hazard ratio; Hs-CRP, high-sensitivity C-reactive protein; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PNI, Prognostic Nutritional Index; TIA, transient ischemic attack.

[a] Hazard ratios were adjusted for age, sex, AF type (paroxysmal vs. non-paroxysmal), the presence of CAD and HF, serum Hs-CRP and NT-proBNP levels, eGFR, and anticoagulation therapy.

outpatients with HF, Sez et al. [11] revealed that the prevalence of malnutrition as identified using three malnutrition scores (CONUT, PNI, and GNRI scores) was relatively high, 57%. In an observational study, Wada et al. [16] reported that malnutrition was present in 21.2%–28.3% of consecutive patients with CAD undergoing percutaneous coronary intervention. Sun et al. [17] also showed that the prevalence of malnutrition was as high as 80% among advanced-age patients with hypertension. However, few studies have focused on malnutrition in patients with AF. To the best of our knowledge, only one study conducted by Díez-Manglano et al. [18] evaluated the malnutrition status in 282 patients with AF using the CONUT score and showed that 87.2% of these patients were at risk of malnutrition. Our study included 461 advanced-age patients with nonvalvular AF, and 3 different objective malnutrition scores were applied to screen their malnutrition status. In total, 65.7% of patients were identified as having malnutrition by at least one malnutrition score, indicating that malnutrition was not uncommon among these older patients with AF.

Relatively low concordance among the CONUT, PNI, and GNRI scores for malnutrition was observed in our study. This might be explained by the incorporation of different variables in the three scores. The CONUT score is calculated from the serum albumin level, lymphocyte count, and total cholesterol level; in contrast, the PNI score includes only the serum albumin level and the lymphocyte count, and the GNRI score includes the serum albumin level, measured body weight, and ideal body weight. More patients were identified as having malnutrition by the CONUT score than by the PNI and GNRI scores. This may be a result of the low serum total cholesterol concentrations caused by statin therapy in our study. The CONUT score may overestimate the prevalence of malnutrition among patients taking statins. The PNI score identified far fewer malnourished patients than did the CONUT and GNRI scores because the PNI score does not incorporate cholesterol or anthropometric factors, both of which may be related to the nutrition status. In addition, the PNI score does not include a mild malnutrition category; only moderate to severe malnutrition statuses are assessed. Therefore, the overall prevalence of malnutrition as identified by the PNI score might be underestimated, and the prediction efficacy may be weakened. In the study by Sez et al. [11], the rate of malnourished patients identified by the PNI score was also lower than that identified by the CONUT and GNRI scores. The GNRI score includes both anthropometric factors and serum markers and is a multidimensional evaluation score that is less strongly influenced by statin therapy. Thus, the GNRI score may be a more suitable objective tool with which to screen the malnutrition status in our study.

Moderate to severe malnutrition was significantly associated with adverse clinical outcomes in advanced-age patients with nonvalvular AF in the present study, regardless of the malnutrition evaluation tools used. These results are in accordance with the only other malnutrition study conducted in patients with AF, which showed that a higher nutritional risk as determined by the CONUT score was correlated with the short-, medium-, and long-term mortality rates of hospitalized patients with AF [18]. Our study further showed that adding the malnutrition scores (CONUT or GNRI score) to the baseline model with traditional risk factors could significantly improve the ability of the model to predict composite events. Previous studies also confirmed improvement in the model's ability to predict poor clinical outcomes after adding malnutrition scores to traditional predictors in patients with cardiovascular disease such as CAD and HF [19,11].

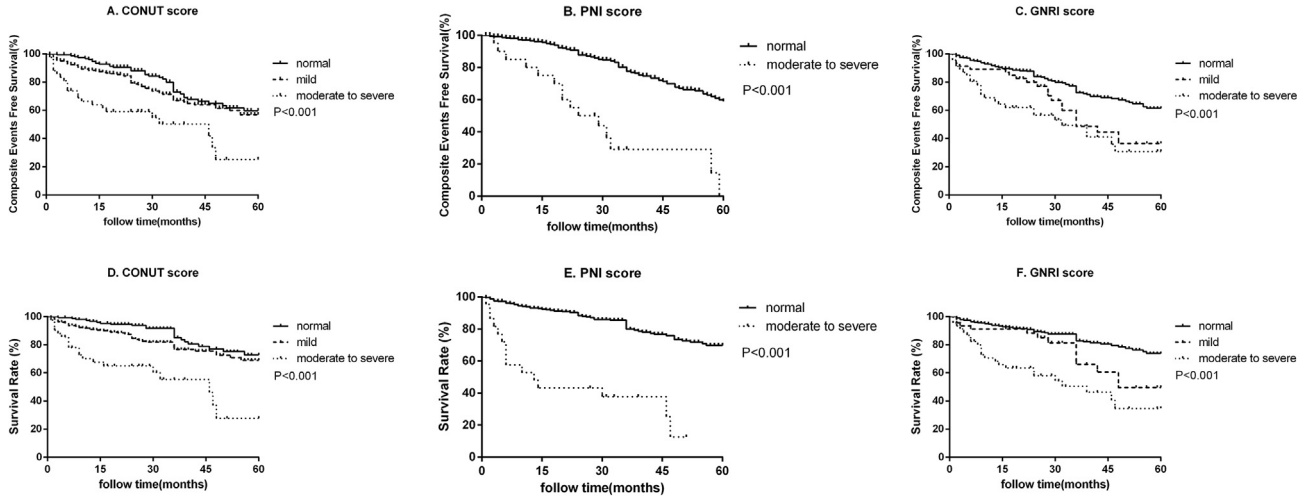

Figure 3 Kaplan–Meier Curves for Composite Events and All-cause Death among Patients with Different Nutrition Status Based on Different Objective Malnutrition Scores. Kaplan–Meier curves for composite events based on the CONUT (A), PNI (B), and GNRI (C) scores. Kaplan–Meier curves for all-cause death based on the CONUT (D), PNI (E), and GNRI (F) scores.

Table 3 Evaluation of prediction models for composite events.

	NRI (95% CI)	P	IDI (95% CI)	P
Baseline model	ref		ref	
+CONUT score	0.582 (0.218–0.638)	0.013	0.012 (0.001–0.042)	0.02
+PNI	0.289 (−0.355–0.853)	0.432	0.052 (−0.001–0.219)	0.066
+GNRI	0.779 (0.412–0.817)	<0.001	0.041 (0.013–0.138)	<0.001

Baseline model includes age, sex, type of atrial fibrillation, coronary artery disease, heart failure, serum high-sensitivity C-reactive protein and N-terminal pro-B-type natriuretic peptide level, the estimated glomerular filtration rate, and anticoagulation therapy.
CI: confidence interval; CONUT, Controlling Nutritional Status; GNRI, Geriatric Nutritional Risk Index; IDI: integrated discrimination improvement; NRI: net reclassification improvement; PNI, Prognostic Nutritional Index.

Screening for malnutrition in patients of very advanced age having nonvalvular AF and performing early interventions for malnutrition, especially for patients with moderate to severe malnutrition, may be of high importance for their prognosis. Reinders et al. [20] demonstrated that oral nutritional supplements and dietary counseling positively affected the energy intake and body weight of older adults at risk of malnutrition. Ogawa et al. [21] showed that sufficient dietary intake in older patients after cardiac surgery was associated with better functional recovery at discharge. Some clinical trials have also demonstrated that micronutrient supplementation might improve left ventricular function and quality of life in patients with chronic HF [22,23]. Similar effects may be achieved when nutritional treatment is administered to patients with AF. Further studies are required to investigate whether nutrition interventions can improve clinical outcomes in patients of very advanced age with nonvalvular AF.

The correlation of the malnutrition status with adverse clinical outcomes among older patients with nonvalvular AF may be partly explained by the vicious circle between malnutrition and chronic disease [24]. Malnutrition is not only a marker of disease severity but also a contributor of disease progression [25]. Long-term chronic disease, including AF, results in malnutrition, which accelerates the progression of the chronic disease [26,27]. AF is accompanied by an enhanced inflammatory response [28], which could contribute to hypoalbuminemia by promoting protein degradation and suppressing protein synthesis [29,30]. Anorexia could also be induced by chronic inflammation, leading to the loss of essential vitamins and amino acids that are necessary for normal immune cell function [31]. The lymphocyte count decreases, and as a result, the immune system becomes impaired. Hypoalbuminemia and a lower lymphocyte count are associated with adverse outcomes in patients with chronic disease [32,33]. Furthermore, the “cholesterol paradox” or “obesity paradox” has been reported in patients with AF, suggesting that underweight patients with AF have increased risks of thromboembolism and all-cause death [34]. Moreover, frailty may be another potential factor conferring adverse outcomes in patients with malnutrition. Izawa et al. [35] indicated that a poor nutrition status could be a useful predictor of physical performance, such as handgrip strength and gait speed, among older patients with cardiovascular disease. In a large-scale cross-sectional study of advanced-age patients, Zhang et al. [36] reported a significant association between the nutritional status (as evaluated by the GNRI score) and low muscle mass. Frailty has a negative impact on cardiovascular events and all-cause mortality in advanced-age patients with

cardiovascular disease [37,38]. A nutritional imbalance could lead to muscle dysfunction, restricting the physical activity of older patients and contributing to worse clinical outcomes. Although we did not evaluate the degree of frailty in our patients, a possible link between malnutrition and frailty may exist.

Limitations

This study has several limitations. First, it was a single-center observational study that included a small number of hospitalized patients. The malnutrition status of advanced-age patients with nonvalvular AF does not precisely reflect the malnutrition status in the overall population of patients with AF. The associations shown in our study do not allow us to make definitive conclusions. Second, given that only a small proportion of elderly patients received anticoagulation therapy, only the composite events were analyzed, and bleeding events could not be further analyzed. Third, the nutritional status was assessed only at admission; changes in nutritional status and their association with clinical outcomes could not be assessed. We did not investigate whether interventions performed to improve the malnutrition status could benefit clinical outcomes as well. Investigation of the effects of nutritional interventions on composite events in these older patients might be worthwhile.

Conclusions

In conclusion, moderate to severe malnutrition was an independent predictor of adverse outcomes among patients of very advanced age with nonvalvular AF. Screening of the nutritional status using objective malnutrition scores can provide useful information regarding prognosis and risk stratification for advanced-age patients with nonvalvular AF.

Conflicts of interest

None.

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