Assessment of Transthyretin Combined With Mini Nutritional Assessment on Admission Provides Useful Prognostic Information in Patients With Acute Decompensated Heart Failure

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SUMMARY

Decreased Transthyretin (TTR) can be observed in heart failure patients with malnutrition evaluated by the Mini Nutritional Assessment (MNA). This study investigated whether a combination of different nutritional assessment methods would be useful for assessing prognosis in patients with acute decompensated heart failure (ADHF).

This prospective study included 52 patients with ADHF (mean age, 71.1 ± 14.7 years; men 55.8%) who were admitted to our hospital between June 2012 and August 2013. On admission, nutritional status was evaluated according to levels of TTR and the MNA. Of 52 patients, 28 (53.8%) had TTR < 15 mg/dL, 39 (75.0%) had malnutrition or were at risk of malnutrition (MNA score ≤ 23.5), and 21 (40.4%) were categorized into group L (MNA score ≤ 23.5 and TTR < 15 mg/dL). Readmission due to worsening heart failure occurred in 12 patients (23.1%), and there were 4 (7.7%) all-cause deaths. The 1-year event-free survival rates in group L and the remaining patients (group O) were 27.7% and 85.6%, respectively ($P = 0.001$). Using Cox multivariate analysis, group L also had a poorer prognosis (hazard ratio 4.35, 95% confidence interval 1.26–17.74, $P = 0.020$).

MNA revealed that 75% of patients with ADHF had malnutrition or were at risk of malnutrition. The combination of low MNA and low TTR on admission can predict the prognosis of patients with ADHF. (Int Heart J 2015; 56: 226-233)

Key words: Controlling nutritional status, Geriatric nutritional risk index, Malnutrition, Prealbumin, Prognosis

Japan is an aging society that is facing an increasing number of patients with heart failure (HF); this number is expected to increase still further.[1)] The Japanese cardiac registry of HF has shown that the rate of all-cause mortality within 1 year after discharge is 9.7%, while the readmission rate has reached 24.3%.[2)]

Many patients with chronic HF have a poor nutritional status, which is associated with a poor prognosis,[3-5)] similarly such as insufficient left ventricular ejection fraction (LVEF), medication, rehabilitation,[6)] and self-care.[7,8)] Malnutrition in HF patients causes body fluid accumulation and infection and exacerbates their general physical condition, resulting in a further deterioration in their nutritional status. Patients may be caught in a vicious circle, starting with malnutrition, progressing to cardiac cachexia, and ending with an extremely poor prognosis.[9)] Accordingly, the improvement of nutritional status at early stages, along with current HF management, can play a crucial role in preventing deterioration of HF and improving a patient's prognosis. Evidence of cardiac rehabilitation has been shown in patients with heart disease.[10-13)] However, there is little evidence of nutritional management in HF patients and the most appropriate nutritional assessment has not yet been established.

Malnutrition screening includes history taking, body measurements, weight changes, and biochemical and other clinical tests. Serum albumin[14)] and transthyretin (TTR)[15,16)] are the most widely used biochemical determinants of nutritional status. The Controlling Nutritional Status (CONUT) tool,[17)] the Geriatric Nutritional Risk Index (GNRI),[18)] and the Mini Nutritional Assessment (MNA®),[19)] which are recently-developed nutritional assessments based on multiple indices, assess nutritional deficits. Many studies have reported their usefulness in predicting the prognosis in patients with HF.[4,5,15,20,21)] Bonilla, *et al*[5)] assessed patients with chronic HF according to the MNA® and found that 12.8% of patients were malnourished and 60.2% of patients were at risk of malnutrition, while only 27.0% had normal nutritional status. "At risk of malnutrition" includes the possibility of malnutrition that is necessary to be extracted.

TTR levels are reduced in both malnutrition and in non-malnutrition, although patients with HF seem to have a reduced TTR that corresponds well to their level of malnutrition. Lower TTR can be observed in HF patients with malnutrition determined using the MNA®.[5)] We focused on this point, and

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Received for publication August 3, 2014. Revised and accepted October 9, 2014.

Released in advance online on J-STAGE February 27, 2015.

expected to observe severe malnutrition if an HF patient who was malnourished or at risk by MNA had low TTR. Thus, we assumed these patients had a poor prognosis.

Nowadays, many HF patients are at high risk of future malnutrition; thus, aggressive management is required in the early stages to prevent exacerbation of their clinical condition or deterioration of their nutritional status.

It is difficult for nutritional screening using only 1 index to provide a precise assessment in patients with acute decompensated HF (ADHF). Here, we investigated the hypothesis that the combination of 2 different nutritional assessments, MNA® and TTR, could predict the prognosis of patients with ADHF at an early stage.

Methods

Subjects: This prospective study evaluated 60 ADHF patients with MNA® and TTR data who were admitted to the St. Marianna University School of Medicine Hospital in Kawasaki, Japan, between June 2012 and August 2013. All patients underwent physical examinations, blood tests, and echocardiography on admission; the European Society of Cardiology's criteria were used for the diagnosis of HF.[6)]

Data collection: On admission, the patients' present conditions, medical history, medications, and comorbidities were identified; then, physical measurements and blood tests were performed. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Renal function was evaluated using cystatin C (Cys-C). The estimated glomerular filtration rate (eGFR) was calculated as follows: men, eGFRcys (mL/minute/1.73m^2) = (104 × Cys-C$^{-1.019}$ × 0.996^{age}) - 8; women, eGFRcys (mL/minute/1.73m^2) = (104 × Cys-C$^{-1.019}$ × 0.996^{age} × 0.929) - 8.[22)]

Nutritional evaluation: Serum TTR concentrations, serum albumin, peripheral blood total lymphocyte counts, and total cholesterol were measured on admission as serum markers associated with nutritional status, and all parameters were assessed using the MNA®,[19)] CONUT,[4,17)] and GNRI[18,20)] nutritional assessment tools.

The MNA® consists of 18 selected questions that are divided into screening and assessment items. The questionnaires were answered by the patient, family members, or relatives, the answers were scored, and then the patients were stratified into the following 3 categories: well nourished, ≥ 24 points; at risk of malnutrition, 17–23.5 points; malnutrition, < 17 points.[19)] In addition, based on TTR levels, the patients were assigned to either the high TTR (≥ 15 mg/dL) or the low TTR (< 15 mg/dL) group.[15,16)] Patients with low MNA (≤ 23.5 points) and low TTR were then classified as group L and the remaining patients were classified as group O. The CONUT scores stratified the patients into 4 levels of nutritional status: good nutritional status, mild, moderate, or severe nutritional impairment.[17)] The GNRI scores divided the patients into good nutritional status (≥ 92 points) or mild to severe nutritional impairment (< 92 points).[18,20)]

All nutritional assessments were performed within 48 hours of hospitalization.

Echocardiography: All echocardiographic measurements were obtained using a commercially available sector scanner (Aplio®, Toshiba, Tokyo) by 3 experienced technicians who were blinded to the study details. LVEF was calculated according to the modified Simpson's method. Patients with LVEF ≥ 40% were classified as HF preserved LVEF (HFpEF) and patients with LVEF < 40% were classified as HF with reduced LVEF (HFrEF).[20,23,24)]

Outcomes: The primary endpoint was all cause death or readmission due to worsening HF during the observation period, which was defined as an "event".

Statistics: The quantitative data obtained are expressed as the mean ± standard deviation. The Shapiro–Wilk test was used to evaluate normal distributions, whereas the Kolmogorov–Smirnov Lilliefors test was used to examine consistency with a uniform distribution. Comparisons between 2 groups were made using the *t*-test when the distribution was normal and the Wilcoxon test otherwise. In the comparisons between the 3 MNA® nutritional assessment groups, analysis of variance was used when the distribution was normal and the Kruskal–Wallis test otherwise. The χ^2 test was used to assess categorical variables. Event-free survival curves for each category of nutritional assessment were calculated using the Kaplan–Meier method, and the derived data were compared using the log-rank test. Multivariate analysis using Cox's hazard models investigated independent prognostic factors. In addition to age and sex, event-related variables identified by univariate analysis ($P < 0.100$) were included. However, the MNA® scores, nutritional assessment based on MNA®, and serum TTR concentrations were excluded as contributing to the composition of group L. Study results are expressed as hazard ratios and 95% confidence intervals. The cutoff points of analyses were at the occurrence of an event, at the time point when no further follow-up survey was conducted, or on August 31, 2013. A value of $P < 0.05$ was regarded as statistically significant. JMP® version 10.0.2 (SAS Institute Inc., Cary, NC, USA) was used for all statistical analyses.

Ethics: This study was approved by the Ethics Committee of Saint Marianna University School of Medicine (approval number 2123, UMIN ID 000008835). Informed consent was obtained from all study patients after providing oral and written explanations.

Results

Patient characteristics: Of the 60 subjects initially evaluated, we excluded 8 (4 due to missing data from blood tests on admission, one the underlying cause of HF was unknown, and 3 because of cancer), leaving a total of 52 subjects (Figure 1).

Patients' characteristics are listed in Table I. The mean age of the subjects was 71.1 ± 14.7 years, and 55.8% were male ($n = 29$). Ischemic cardiomyopathy was present in 38.5% ($n = 20$). LVEF was 38.9 ± 16.0%, 44.2% ($n = 23$) of the patients had HFpEF, and 48.1% ($n = 25$) were class IV according to the New York Heart Association functional classification. Among the comorbidities and previous conditions, the most common was hypertension, present in 53.8% of cases ($n = 28$), followed by coronary artery disease in 46.2% ($n = 24$), and diabetes in 36.5% ($n = 19$). BMI was 24.1 ± 3.4 kg/m^2. Systolic blood pressure on admission was high at 154.0 ± 40.0 mmHg. Hemoglobin levels indicated slight anemia (11.3 ± 2.4 g/dL) and C-reactive protein (CRP) indicated slight inflammation (2.3 ± 2.8 mg/dL). Cys-C was elevated at 1.4 ± 0.8 mg/L, and

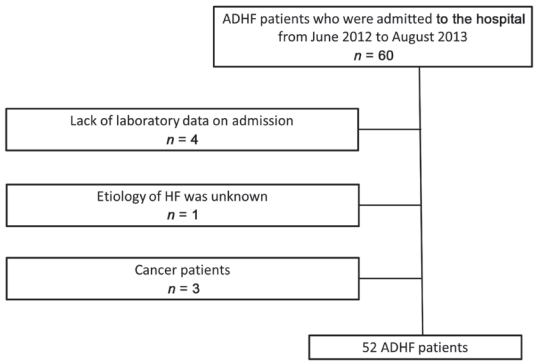

Figure 1. Recruitment of patients with acute decompensated heart failure at St. Marianna University School of Medicine Hospital.

eGFRcys indicated mild renal dysfunction (55.2 ± 25.6 mL/minute/1.73 m^2). Medications taken prior to admission included angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers and diuretics, each taken by 51.9% of patients (n = 27), while beta-blockers were taken by 59.6% (n = 31).

There were 21 patients in group L, 40.4% of the total, representing both low TTR levels and a low MNA® score. In group L, Log NT-pro BNP and CRP were significantly higher, and total lymphocyte and total cholesterol, LDL cholesterol, and albumin were significantly lower than in group O.

Nutritional assessment: The nutritional statuses of the patients are listed in Table II. The overall mean serum TTR concentration was 15.6 ± 6.9 mg/dL and the overall mean MNA® score was 20.4 ± 4.8. The MNA® on admission revealed that 25% of patients were well nourished (n = 13), 51.9% were at risk of

Table I. Patients' Baseline Characteristics

	Overall (n = 52)	Group L (n = 21)	Group O (n = 31)	P
Male gender, n (%)	29 (55.8)	11 (52.4)	18 (58.1)	0.686
Age (years)	71.1 ± 14.7	73.2 ± 14.6	69.6 ± 14.8	0.398
BMI (kg/m^2)	24.1 ± 3.4	23.6 ± 5.5	24.5 ± 5.1	0.547
sBP (mmHg)	154.0 ± 40.0	151.9 ± 39.6	155.4 ± 40.8	0.763
Ejection Fraction (%)	39.0 ± 16.3	40.2 ± 14.4	38.2 ± 17.6	0.674
HFpEF, n (%)	23 (44.2)	10 (47.6)	13 (41.9)	0.686
Log NT-pro BNP	3.6 ± 0.6	3.8 ± 0.4	3.5 ± 0.7	0.045
NYHA classification, n (%)				0.027
III	27 (51.9)	7 (33.3)	20 (64.5)	
IV	25 (48.1)	14 (66.7)	11 (35.5)	
Prior HF hospitalization, n (%)	18 (34.6)	7 (33.3)	11 (35.5)	0.873
Etiology of HF, n (%)				0.117
Ischemic cardiomyopathy	20 (38.5)	7 (33.3)	13 (41.9)	
Hypertensive heart disease	7 (13.5)	4 (19.1)	3 (9.7)	
Dilated cardiomyopathy	13 (25.0)	5 (23.8)	8 (25.8)	
Hypertrophic cardiomyopathy	1 (1.9)	1 (4.8)	0 (0.0)	
Valvular heart disease	11 (21.2)	4 (19.1)	7 (22.6)	
Medication before administration, n (%)				
ACE-I or ARB	27 (51.9)	12 (57.1)	15 (48.4)	0.535
Mineralocorticoid receptor antagonists	35 (67.3)	13 (61.9)	22 (71.0)	0.494
Beta blocker	31 (59.6)	12 (57.1)	19 (61.3)	0.765
Diuretics	27 (51.9)	11 (52.4)	16 (51.6)	0.957
Statin	40 (76.9)	18 (85.7)	22 (71.0)	0.216
Comorbidity, n (%)				
Hypertension	28 (53.8)	13 (61.9)	15 (48.4)	0.337
Dyslipidemia	13 (25.0)	3 (14.3)	10 (32.3)	0.142
Diabetes	19 (36.5)	9 (42.9)	10 (32.3)	0.436
Coronary artery disease	24 (46.2)	9 (42.9)	15 (48.4)	0.695
Atrial fibrillation	15 (28.8)	6 (28.6)	9 (29.0)	0.971
Chronic obstructive pulmonary disease	3 (5.8)	1 (4.8)	2 (6.5)	0.798
Cerebral artery diseases	9 (17.3)	5 (23.8)	4 (12.9)	0.308
Hemodialysis	2 (3.8)	1 (4.7)	1 (3.2)	0.778
Hemoglobin (g/dL)	11.3 ± 2.4	10.6 ± 2.0	11.7 ± 2.6	0.111
Sodium (mEq/L)	137.6 ± 5.8	137.0 ± 6.5	138.0 ± 5.3	0.554
Total lymphocyte count (/mm^3)	985.0 ± 589.9	774.5 ± 307.1	1127.5 ± 690.4	0.021
Total cholesterol (mg/dL)	154.6 ± 44.6	134.2 ± 33.4	168.4 ± 46.4	0.003
LDL cholesterol (mg/dL)	92.8 ± 36.7	77.4 ± 29.0	103.3 ± 38.0	0.011
Albumin (g/dL)	3.3 ± 0.5	3.0 ± 0.4	3.5 ± 0.4	< 0.001
CRP (mg/dL)	2.3 ± 2.8	3.8 ± 3.1	1.2 ± 2.2	0.002
Cystatin C (mg/L)	1.4 ± 0.8	1.5 ± 0.6	1.4 ± 0.9	0.173
eGFR (mL/minute/1.73 m^2)	55.2 ± 25.6	49.1 ± 17.8	59.3 ± 29.4	0.156

Results are expressed as mean ± SD. Group L is both MNA score ≤ 23.5 and TTR < 15 mg/dL, Group O includes other patients. Event was defined as all cause death or readmission due to worsening HF during the observation period. BMI indicates body mass index; HF, heart failure; sBP, systolic blood pressure; HFpEF, heart failure with preserved ejection fraction; NT-pro BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blockers; LDL, low density lipoprotein; HDL, high-density lipoprotein; CRP, C-reactive protein; and eGFR: estimated glomerular filtration rate. NT-pro BNP was log-transformed, because it was found to have a log-normal distribution.

Table II. Patients' Nutritional Status

	Overall (n = 52)	Group L (n = 21)	Group O (n = 31)	P
TTR (mg/dL)	15.6 ± 6.9	10.4 ± 2.6	19.2 ± 6.7	< 0.001
Low TTR, n (%)	28 (53.8)	21 (100.0)	7 (22.6)	< 0.001
MNA score	20.4 ± 4.8	17.6 ± 3.8	22.4 ± 4.5	< 0.001
MNA classification, n (%)				< 0.001
Well nourished	13 (25.0)	0 (0.0)	13 (41.9)	
At risk	27 (51.9)	12 (57.1)	15 (48.4)	
Malnutrition	12 (23.1)	9 (42.9)	3 (9.7)	
Low MNA, n (%)	39 (75.0)	21 (100.0)	18 (58.1)	< 0.001
CONUT score	5.0 ± 2.7	7.0 ± 2.1	3.7 ± 2.3	< 0.001
CONUT classification, n (%)				0.002
Well nourished	5 (9.6)	0 (0.0)	5 (16.1)	
Mild	19 (36.5)	3 (14.3)	16 (51.2)	
Moderate	23 (44.2)	14 (66.7)	9 (29.0)	
Severe	5 (9.6)	4 (19.0)	1 (3.2)	
GNRI score	94.7 ± 13.7	89.3 ± 13.2	98.3 ± 13.0	0.019
GNRI < 92, n (%)	27 (51.9)	14 (66.7)	13 (41.9)	0.080

TTR indicates transthyretin; MNA, Mini Nutritional Assessment; CONUT, Controlling Nutritional Status; and GNRI, Geriatric Nutritional Risk Index. Low TTR is a serum TTR concentration < 15 mg/dL, low MNA is MNA score < 23.5. Group L contains patients with both low TTR and low MNA.

malnutrition (n = 27), and 23.1% suffered from malnutrition (n = 12), with 75% of all patients exhibiting either malnutrition or being at risk of malnutrition. There was no difference in the proportion of patients with low TTR between these 3 MNA® groups (P = 0.210, Figure 2). According to the CONUT, 53.8% (n = 28) of the patients exhibited moderate or worse nutritional impairment, and the GNRI score was < 92 in 51.9% (n = 27). In group L, the CONUT score was higher, and the serum TTR level, MNA score, and GNRI score were significantly lower than in group O.

Although the MNA® score was not significantly correlated with serum TTR concentration (r = 0.234, P = 0.095) (Figure 3A), there were significant correlations between the MNA® score and CONUT score (r = -0.358, P = 0.009) (Figure 3B) and between the MNA® score and GNRI score (r = 0.444, P = 0.001) (Figure 3C).

Negative correlations were found between TTR and log CRP (r = -0.428, P = 0.002; Figure 4A) and between serum albumin and log N-terminal pro-brain natriuretic peptide (NT-pro BNP; r = -0.364, P = 0.008), respectively (Figure 4B). The MNA® score was not significantly correlated with log NT-pro BNP or log CRP (Figure 4C); however, the CONUT score was positively correlated with log NT-pro BNP (r = 0.394, P = 0.004) and log CRP (r = 0.328, P = 0.018), respectively (Figure 4D). A negative correlation was found between the GNRI score and log NT-pro BNP (r = -0.410, P = 0.003; Figure 4E).

Presence of events and nutritional markers: Events occurred in 16 subjects (30.8%). There were 12 readmissions due to worsening HF and 4 all-cause deaths, including 1 due to a cardiovascular event. Patients in group L more often had an event than those in group O (52.4% [n = 11] versus 16.1% [n = 5], P = 0.006).

MNA®, TTR, and event-free survival rate: The mean follow-up period was 10.1 months. The event-free survival rates after 12 months by the Kaplan–Meier method were 83.3% for the well-nourished, 67.5% for those at risk of malnutrition, and 51.3% for those with malnutrition according to MNA® (P = 0.039). Other event-free survival rates by group were as follows: high MNA® 83.3% and low MNA® 57.3% (P = 0.119); high TTR 81.7% and low TTR 47.2% (P = 0.060); group O 85.6% and group L 27.7% (P = 0.001) (Figure 5).

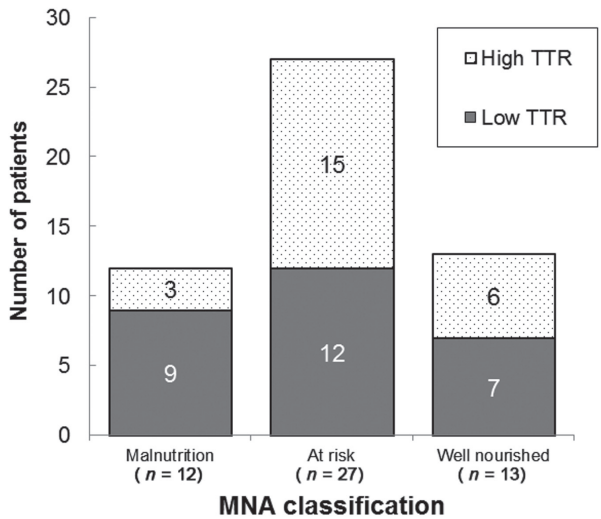

Figure 2. MNA classification and Low TTR. Nutritional assessment on admission by MNA: 23.1% patients with malnutrition, 51.9% patients at risk of malnutrition, and 25% patients with a good state of nutrition. There was no significant difference in the proportion of low TTR among the 3 groups (P = 0.210). MNA indicates Mini Nutritional Assessment; and TTR, transthyretin.

On univariate analysis, a significantly poorer prognosis was observed for patients with HFpEF (hazard ratio [HR] 3.22; 95% confidence interval [CI] 1.17–10.26, P = 0.023), high log CRP (HR 1.36; 95% CI 1.02–1.88, P = 0.037), or a low MNA® score (HR 0.88; 95% CI 0.80–0.98, P = 0.019). Moreover, a significantly poorer prognosis was observed for patients with malnutrition, according to MNA®, compared to those who were well nourished (HR 5.89; 95% CI 1.34–40.30, P = 0.018), and for group L compared to group O (HR 5.69; 95%

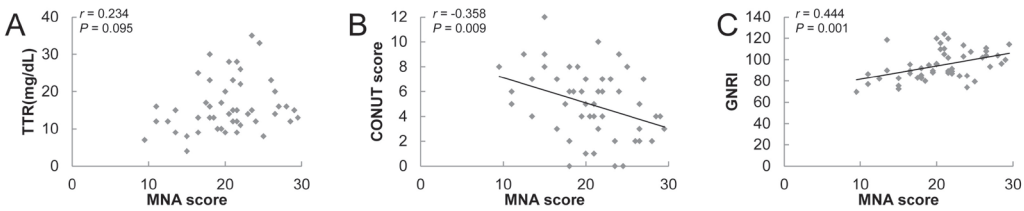

Figure 3. Correlation of each indicator and MNA score. **A:** CONUT score and MNA score showed a significant negative correlation. **B:** GNRI and MNA score showed a significant positive correlation. **C:** TTR and MNA score showed a trend towards a positive correlation, but it was not significant. CONUT indicates Controlling Nutritional Status; and GNRI, Geriatric Nutritional Risk Index. Other abbreviations as in Figure 2.

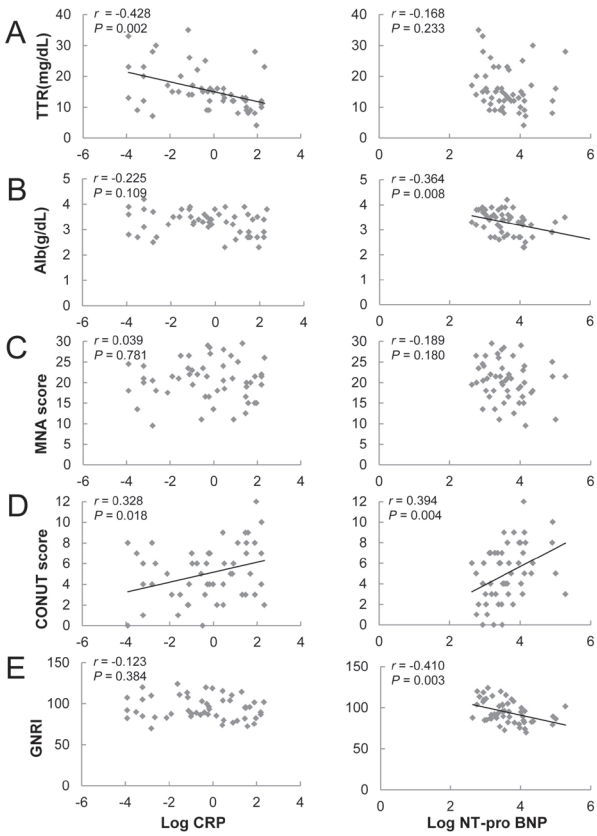

Figure 4. Correlations of each nutritional marker with log NT-pro BNP and log CRP. **A:** TTR and log CRP showed a significant negative correlation. **B:** Albumin and NT-pro BNP showed a significant negative correlation. **C:** MNA score was not significantly correlated with either index. **D:** CONUT score showed a significant positive correlation with both log CRP and log NT-pro BNP. **E:** GNRI and log NT-pro BNP showed a significant negative correlation. NT-pro BNP indicates N-terminal pro-brain natriuretic peptide; and CRP, C-reactive protein. Other abbreviations as in Figures 2 and 3.

CI 2.01–18.62, $P = 0.001$).

Multivariate analysis showed that group L (HR 4.35; 95% CI 1.26–17.74, $P = 0.020$) was the only independent prognostic factor (Table III).

Discussion

Nutritional status of heart failure patients and usefulness of nutritional markers: The causes of malnutrition in patients with chronic HF include lack of appetite in right-sided HF and malabsorption in intestinal edema,[25] as well as cardiac cachexia, a state of hypercatabolism that includes increased blood catecholamine concentrations, renin–angiotensin system activity, and blood cytokine levels.[26] Another factor is that elderly people, who make up a large proportion of HF patients, are generally more likely to experience malnutrition.[27,28] However, since HF presents with a complex pathology, it is often difficult to interpret nutritional evaluations.

It is well known that hyperalbuminemia is related with poor outcome in ADHF,[29,30] although inflammation and fluid retention reduce serum protein levels in the acute phase of hospitalization (Figure 4). Our study results demonstrated that CONUT and GNRI, including serum albumin, reflected the patients' nutritional status (Figure 3); thus, it might be difficult to use CONUT and GNRI to assess nutrition in ADHF. Lourenco, *et al*[15,31] reported TTR as a useful prognostic factor in acute HF; however, TTR generally decreases in nutritional disorders, liver disorders, and protein synthesis disorders in the liver caused by inflammation. Accordingly, TTR, albumin, CONUT score, and GNRI were affected by several factors that were not associated with nutritional status, suggesting that the assessment methods using these indicators might not provide precise nutritional status in ADHF.

MNA® does not use serological markers. It basically focuses on questions about the clinical course, and is characterized by the inclusion of mental status evaluations.[19] Unlike serum markers, MNA® is unlikely to be influenced by inflammatory reactions or body congestion that occur in the acute stage (Figure 4). Thus, it is thought that MNA® can evaluate nutritional status even in acute HF. In the present study, many subjects were found to be in a state of malnutrition or at risk of malnutrition according to the MNA® on admission; this finding was similar to those of Bonilla-Palomas, *et al*[5] in hospitalized HF patients before discharge. These results indicate that MNA® is a useful nutritional marker, even in patients with ADHF, and that detecting the patients with malnutrition or at risk of malnutrition at the time of admission is important for planning nutritional management interventions for these patients.

In the present study, patients younger than 65 years old were also included. Although the MNA is mainly used in elderly patients, earlier studies have reported the use of this assessment in younger study populations.[32,33]

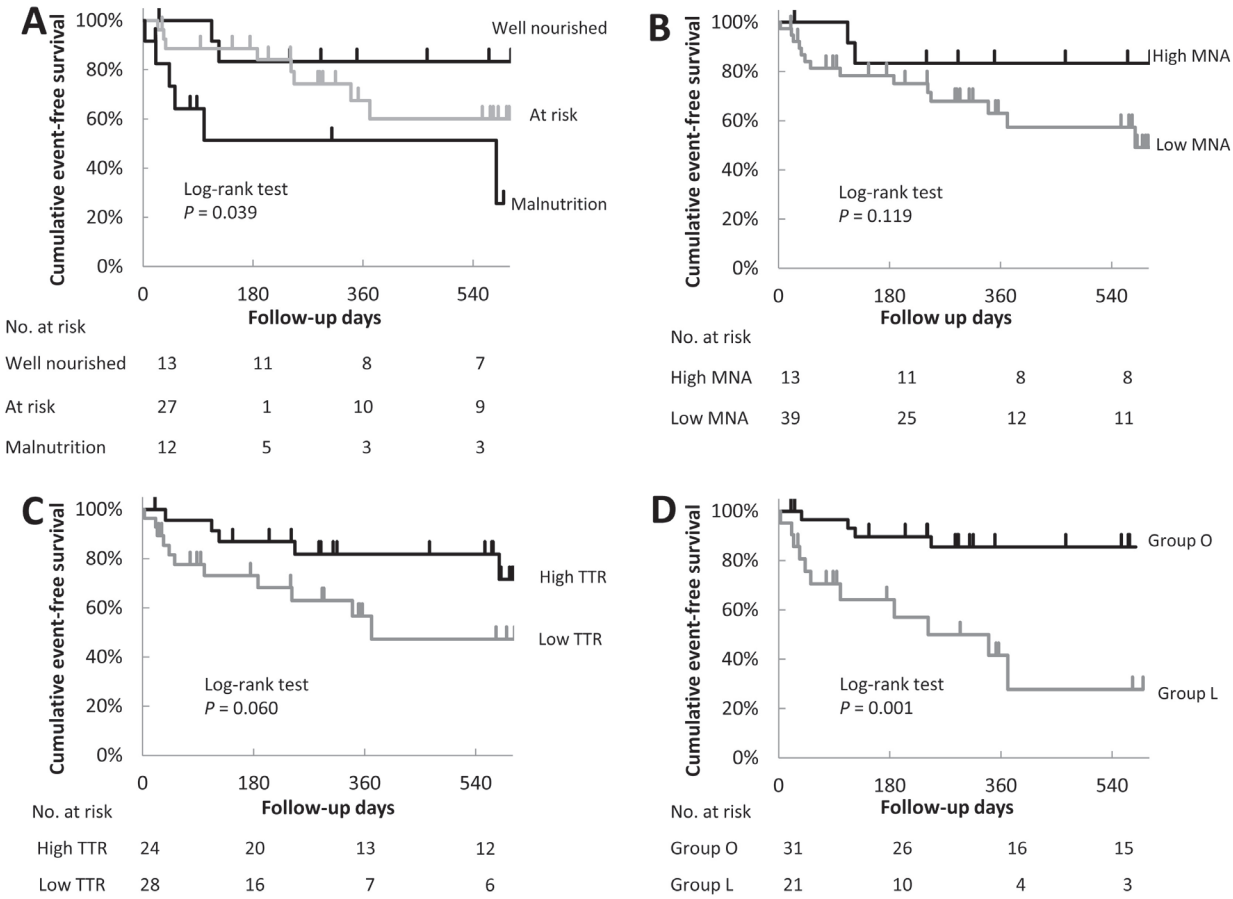

Figure 5. Kaplan–Meier analysis for the event-free survival. **A:** MNA classification. **B:** high MNA versus low MNA. **C:** high TTR versus low TTR. **D:** Group O versus group L. Group L contains patients with low TTR levels and a low MNA score. Malnutrition (HR 5.89; 95%CI 1.34–40.30; $P = 0.018$) and group L (HR 5.69; 95%CI 2.01–18.62; $P = 0.001$) were found to be independent prognostic factors in the univariate analysis. On multivariate analysis, groupβ L was an independent predictor of the event-free survival. HR indicates hazard ratio; and CI, confidence interval. Other abbreviations as in Figure 2.

Table III. Independent Predictors of Readmission due to Worsening Heart Failure or All-Cause Mortality

	Univariate analysis			Multivariate analysis		
	HR	95% CI	*P*	HR	95% CI	*P*
Male gender	0.38	0.14-1.05	0.061	0.51	0.13-2.16	0.348
Age (years)	1.03	0.99-1.07	0.129	1.00	0.96-1.05	0.958
Log NT-pro BNP	0.98	0.42-2.09	0.969			
NYHA classification	1.44	0.52-3.95	0.474			
Prior HF hospitalization	1.85	0.68-5.05	0.225			
HFpEF	3.22	1.17-10.26	0.023	3.69	0.93-17.03	0.063
Total lymphocyte count	0.99	0.99-1.00	0.412			
Total cholesterol	1.00	0.99-1.01	0.616			
LDL cholesterol	1.00	0.99-1.01	0.535			
Albumin	0.43	0.14-1.36	0.149			
Log CRP	1.36	1.02-1.88	0.037	1.34	0.93-1.93	0.062
MNA score	0.88	0.80-0.98	0.019			
MNA classification			0.059			
Well nourished	1.00	-	-			
At risk	2.27	0.57-15.09	0.265			
Malnutrition	5.89	1.34-40.30	0.018			
Low MNA	3.07	0.85-19.61	0.091			
TTR (mg/dL)	0.93	0.84-1.01	0.079			
Low TTR	2.67	0.96-8.53	0.059			
Group L	5.69	2.01-18.62	0.001	4.35	1.26-17.74	0.020

CRP was log-transformed, because it was found to have a log-normal distribution. Abbreviations as in Tables I and II.

Combining low MNA and low TTR: Because the present study demonstrated that malnutrition by MNA® was the only independent prognostic factor, we focused on ADHF patients with an MNA® score < 23.5 on admission. Further, we found there was a trend towards more patients with low MNA® in the event group. The survival curve for patients at risk of malnutrition was between the curves of patients who were well nourished and those with malnutrition, as in previous studies.[5,34] Thus, the status "at risk of malnutrition" can be interpreted as 1) a state of malnutrition that lacks sufficient evidence, and 2) having the possibility of falling into a state of malnutrition in the future. Since a large number of subjects were classified overall as at risk of malnutrition (51.9%), this means not only that there are many patients who could decline into malnutrition, but also that there may be more patients suffering from malnutrition than were actually found in the evaluations. Stated differently, this is the group that could benefit most from the early discovery of malnutrition and intervention with nutritional management.

TTR, also called prealbumin, is a rapid turnover protein with a short half-life of about 2 days, compared to the 20 days of albumin. Thus, blood TTR concentrations can serve as a marker for current hepatocyte protein synthesis.[16] If protein intake falls below 60% of the required amount, 14 days later blood TTR concentration declines,[35] which often makes this a simple marker for nutritional status. However, TTR is a marker indicating the deterioration of general condition caused by various influences, including malnutrition and inflammation.[15,31] As TTR does not reflect only nutritional status, it should be combined with other nutritional evaluations for differentiation.

Similarly to previous studies that found low TTR in malnutrition patients,[5] our results showed low TTR in 75% of subjects with malnutrition. Moreover, group L, which included 53.8% of the low MNA® subjects, was found by multivariate analysis to be an independent prognostic factor. By combining low TTR with low MNA®, it could be possible to determine reduced TTR that is due to malnutrition. Additionally, in low MNA® patients, using low TTR to help interpret low MNA® can screen patients who are at higher risk of malnutrition and can also detect patients with a poor prognosis among those at risk of malnutrition, as a majority of subjects were. These observations could aid early intervention with nutritional management and help improve prognosis.

In this study HFpEF was an independent prognostic factor (Table III), a finding that is inconsistent with a previous study.[6] Age was significantly higher in HFpEF patients (HFpEF 77.3 ± 11.0 years old versus HFrEF 66.1 ± 15.5 years old) so it could have affected the prognosis in HFpEF patients. Furthermore, it is possible that there were some diseases that could not be found in this study.

Study limitations: There are several limitations to this study. 1) It did not evaluate the differences in the etiology and type of HF. 2) The evaluations of prognostic predictive value and variables for multivariate analysis were also limited. A further study with a larger population will be required to assess the prediction of events. In the Cox regression analysis, neither albumin nor TTR was an independent prognostic factor as shown in Table III. Unlike the evaluation of MNA, low TTR and hypoalbuminemia are caused by a variety of factors, such as inflammation, HF severity, and malnutrition. More data is needed. 3) The follow-up periods were short to moderate. Further study is required for long-term observation. 4) Nutritional evaluations were performed only once at the time of admission. 5) MNA® evaluations were often difficult in severe cases, because of artificial respiration management, impaired consciousness, and other reasons. 6) Among the patients with malnutrition, it was unclear how many had cardiac cachexia. 7) Because there are differences in physique between Asian and Western people, the recommended cut-off value for calf circumference in Asian subjects was 28 cm in a previous study.[36] MNA® includes estimation by calf circumference using a cut-off of 31 cm. Additionally, we were unable to perform evaluations related to activities of daily living.

Conclusions: According to MNA®, 75% of patients with ADHF had malnutrition or were at risk of malnutrition. This study demonstrated that the combination of low MNA® and low TTR on admission can predict the prognosis in patients with ADHF. Such nutritional screening could demonstrate a need for early intervention, contributing to an improvement in the prognoses of these patients.

Acknowledgments

We would like to thank the staff of the HF team at St. Marianna University School of Medicine Hospital for their help with the patient recruitment. We also would like to thank Dr. Ryo Kamijima, Dr. Masaki Izumo, and the echocardiography staff of the Department of Cardiology, and Ms. Yukiko Kawashima and the nutrition support team members of St. Marianna University School of Medicine Hospital for their contributions.

Disclosure

Conflict of interest: None to declare.

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